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AUTHOR INDEX

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VOLUME 39, NUMBER 10

MAY 17, 1974

Electrocyclic Effects in Solvolysis. I.[1] Aryl Participation and Cyclopropyl Ring Opening in the Solvolysis of *exo*-3,3-Diaryltricyclo[3.2.1.$0^{2,4}$]oct-8-yl Tosylates[2]

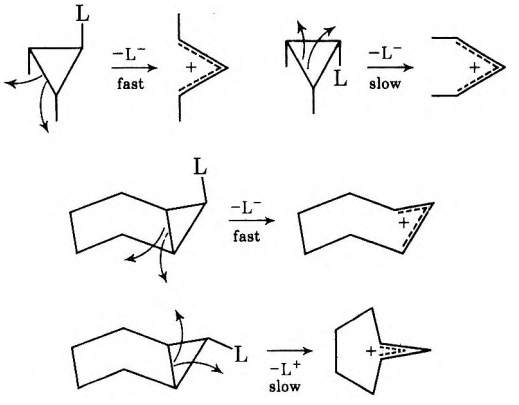
James W. Wilt,* Thomas P. Malloy,[3] Pradip K. Mookerjee, and Daniel R. Sullivan

Department of Chemistry, Loyola University, Chicago, Illinois 60626

Received October 17, 1973

To seek a unique combination of anchimeric participation and electrocyclic ring opening in solvolysis reactions, a number of tosylates of the title were prepared and characterized. The anti-8 tosylates indeed do undergo hydrolysis and acetolysis with concomitant 1,4-aryl migration by the Ar_1-5 route and cyclopropyl ring opening to afford novel 3,*syn*-8-diarylbicyclo[3.2.1]oct-3-en-2-ols. The structures of these products were established by various means, among them ozonation to *cis*-2-arylcyclopentane-*cis*-1,3-dicarboxylic acids (*cis*-2-arylnorcamphoric acids). Although ~ 7000-fold as fast in solvolysis as their nonphenyl analogs (evidence for anchimeric participation), the anti-8 tosylates exhibit a low ρ value (−1.68 for hydrolysis and −1.3 for acetolysis) among themselves. This fact, together with the slight rate retardation caused by the introduction of a C-6,7 double bond, indicates considerable concertedness in the aryl migration and cyclopropyl ring opening processes. An example of a syn-8 tosylate of the title was found to rearrange differently, following a combination of paths most closely related to that reported for *syn*-7-norbornenyl tosylate. Because this path does not involve aryl participation in the slow step, this syn-8 tosylate was essentially equal in rate to its nonphenyl analog.

Electrocyclic ring opening in cyclopropyl substrates can lead to rapid solvolysis when the leaving group is suitably positioned. Literature support abounds for disrotatory opening of the ring and a faster solvolysis rate for trans leaving groups in monocyclic cases and for endo leaving groups in bicyclic cases (eq 1).[4] Similarly, suitably positioned aryl groups can accelerate solvolysis *via* anchimeric participation, a phenomenon of long-standing interest (eq 2).[5] It was our aim to seek examples wherein these two accelerative effects might be combined. Such a combination could afford novel rearrangements and shed further light on the nature of the two effects mentioned.



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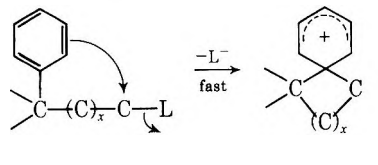
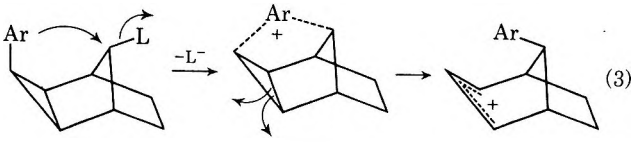


(2)

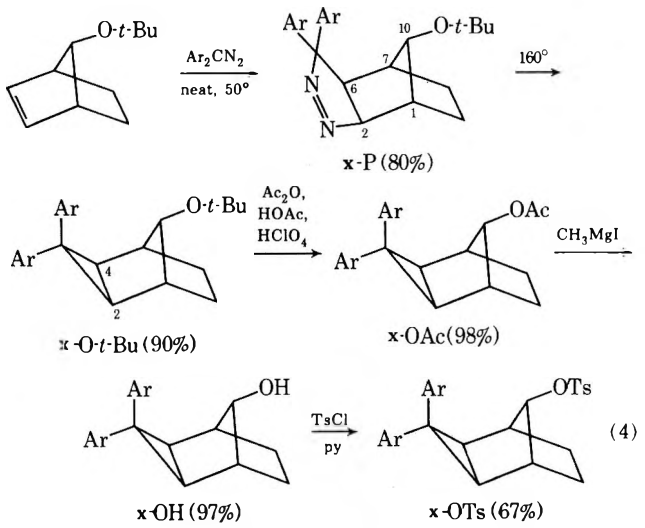
The *exo*-tricyclo[3.2.1.$0^{2,4}$]octane system seemed ideal for the purpose desired. With an aryl group at C-3 and an anti leaving group at C-8 it seemed possible that aryl participation during solvolysis would be sterically propitious. The disrotatory opening of the cyclopropyl portion of the tricycle would also be favorable because the migrating aryl group is properly placed for displacement. Moreover, the bicyclic ion finally formed would be allylic in nature and presumably less strained than the parent species (eq 3).



(3)

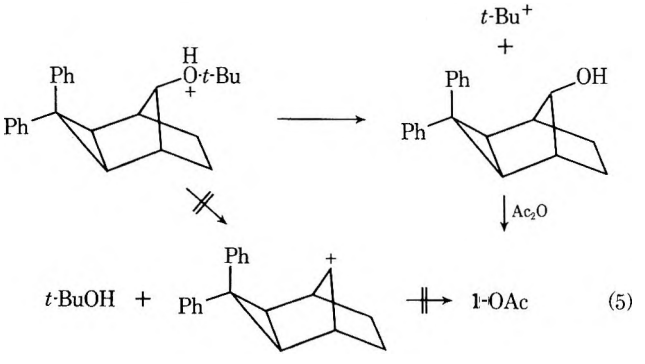
Results

Preparations. The compound initially chosen to exemplify eq 3 was exo-3,3-diphenyltricyclo[3.2.1.$0^{2,4}$]oct-*anti*-8-yl tosylate (1-OTs). Its synthesis, together with those of related compounds, is given in eq 4. The 1,3-dipolar cycloaddition of diphenyldiazomethane to *anti*-7-*tert*-butoxynorbornene proceeded best in excess olefin as solvent, although dioxane was occasionally used. With some diaryldiazomethanes, however, dioxane seemed to retard the cycloaddition. The cycloaddition proceeded totally exo to produce pyrazoline 1-P.[6] The methine proton H-2 adjacent to the azo function was a doublet in the nmr spec-



Ar = Ph, x = 1
Ar = *p*-anisyl, x = 2
Ar = *p*-tolyl, x = 3
Ar = *p*-chlorophenyl, x = 4

trum, giving evidence for coupling to H-6 but not to H-1. This would be expected from the dihedral angles of these various H–H interactions in an exo adduct. Heating **1-P** at 160° until the evolution of nitrogen ceased led in high yield to one product, the tricyclic ether **1-O-*t*-Bu**. The orientation of the cyclopropyl moiety was clearly still exo because the identical hydrogens H-2,4 were a singlet ($W_{1/2}$ = 2 Hz) in the nmr spectrum. Again, the unfavorable angle relationship between these hydrogens and those at the bridgehead precluded coupling.[9] In contrast, in those isomers where the cyclopropyl moiety is endo, a favorable angle relationship exists with the bridgehead hydrogens, and H-2,4 appear as a triplet.[8,11] The subsequent conversions to ester **1-OAc**, alcohol **1-OH**, and tosylate **1-OTs** were standard procedures and details are relegated to the Experimental Section. The cleavage of **1-O-*t*-Bu** to **1-OAc** must involve oxygen–*tert*-butyl bond cleavage and not oxygen–C-8 bond cleavage (eq 5), because the spectral

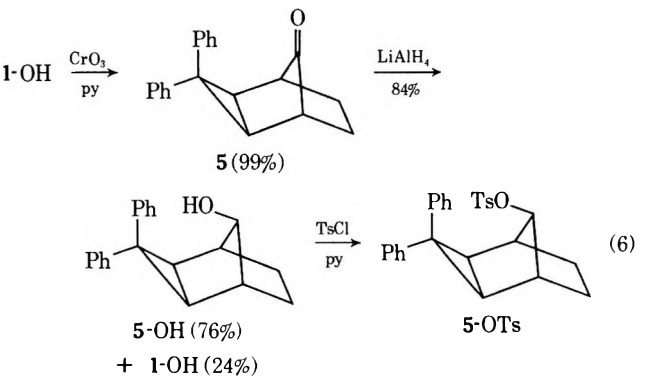


(would rearrange as in eq 3)

characteristics of **1-OAc** were clearly related to those of **1-O-*t*-Bu**. From data presented later, formation of a cationic center at C-8 in this cleavage would have led to skeletal rearrangement as in eq 3.[12]

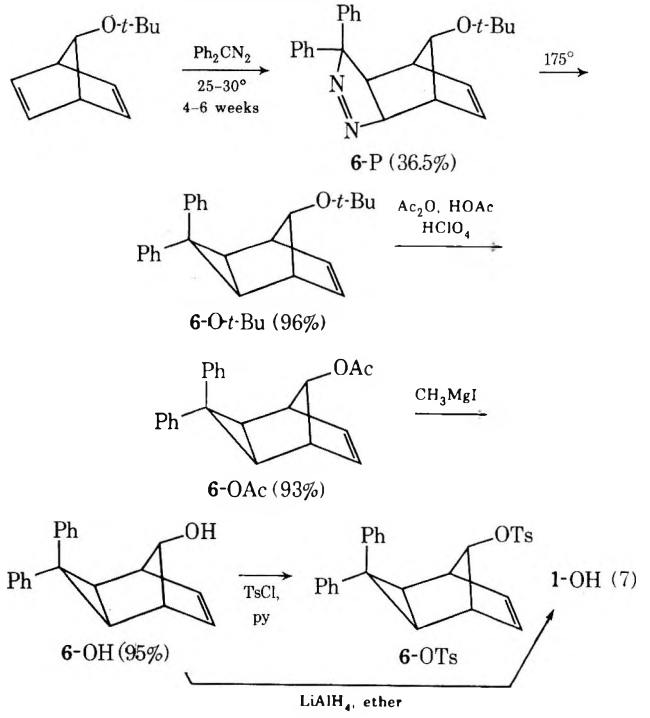
Exactly analogous characterizations applied to the preparation of the related tosylates **2-OTs**, **3-OTs**, and **4-OTs** by the same sequence, which differed only in the use of the appropriate diaryldiazomethane. With **2-P** and **3-P** the use of dioxane solvent in the cycloaddition was deleterious. Yields of adduct were *ca.* 20% in its presence but *ca.* 80% without it.

Oxidation of **1-OH** with chromium trioxide in pyridine gave the corresponding ketone **5**, from which the syn alcohol **5-OH** and tosylate **5-OTs** were easily prepared (eq 6). Ketone **5** was characterized by its carbonyl stretch in the



infrared spectrum at 1769 cm^{-1} (2% in CCl_4) and its H-2,4 (cyclopropane) singlet resonance at δ 1.95 in the nmr spectrum. Reduction of **5** with lithium aluminum hydride yielded a mixture of **5-OH** and **1-OH** (76:24, respectively). Attack by hydride from the less hindered side of the carbonyl was anticipated, and recrystallization allowed the ready isolation of the very sterically crowded **5-OH**.[13] The syn assignment to **5-OH** was made on the basis of its –CHOH– resonances. The methine proton was a broad multiplet centered at δ 3.50 while the hydroxyl proton was a broad singlet at δ 0.47, a large upfield shift ascribable to the shielding influence of the proximate π face of the phenyl group at C-3. In **1-OH** the corresponding chemical shifts were δ 3.37 for the methine proton and δ 1.23 for the hydroxyl proton. The difference in chemical shift for these methine protons ($\Delta\delta$ = 0.13) was doubled in their respective tosylates: **1-OTs**, H-8, δ 3.95; **5-OTs**, H-8, δ 4.20 ($\Delta\delta$ = 0.25). These differences can be understood in terms of a shielding effect caused by the nearby phenyl group and/or the well-known distinction of axial *vs.* equatorial protons. In **1-OH** (OTs) H-8 is axial in the boat cyclohexane portion of the tricycle. In **5-OH** (OTs) it is equatorial.

Addition of diphenyldiazomethane to 7-*tert*-butoxynorbornadiene led to all possible monoadducts, of which **6-P** is relevant to the present study (eq 7).[8,11] The addition was best performed in diene solvent (dioxane was poor) at

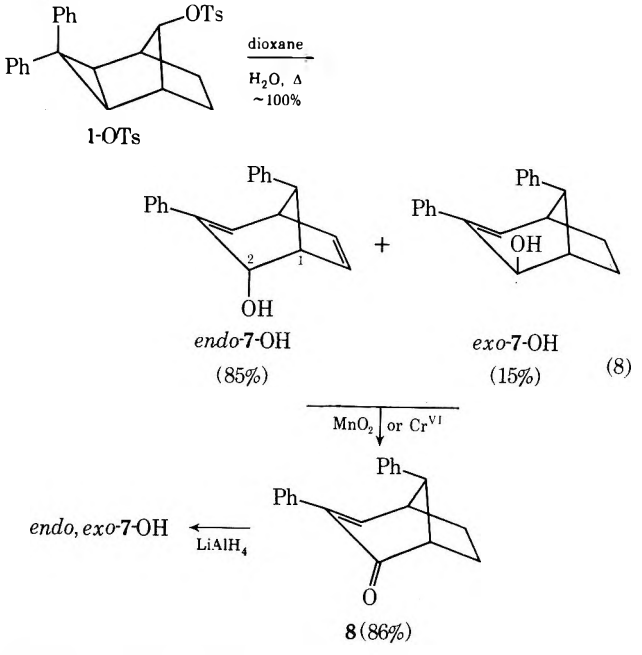


25° over a 4-week time period. Conversion of 6-P *via* the same sequence used for 1-P led to the unsaturated analog 6-OTs. The evidence for the correspondence of the two sequences rested upon the reduction of 6-OH to 1-OH by means of lithium aluminum hydride.[15] Detailed description of the spectral evidence for the intermediate products in eq 7 will be reserved for the more germane paper.

Kinetic Studies. Solvolyses of 1-OTs–4-OTs were performed both in dioxane–water (80:20 v/v) and in dry acetic acid. Tosylate 5-OTs was studied only in aqueous dioxane. The dioxane solvent contained 2,6-lutidine and the acetic acid contained sodium acetate. Good first-order kinetics by titrimetry were observed for all cases. A least-squares computer program[16] was used to calculate the rate constants and activation parameters. The values obtained are collected in Tables I and II.

From the data in Table I a Hammett–Brown $\rho\sigma^+$ correlation was obtained. Each r = 0.99. In 80% dioxane at 112°, ρ = −1.68 ± 0.03. In acetic acid at 110.5°, ρ = −1.30 ± 0.03. In addition, the syn/anti rate ratio k(5-OTs)/k(1-OTs) is 1.35 at 112° in aqueous dioxane. The influence of the double bond in 6-OTs on the reaction can also be determined; k(6-OTs)/k(1-OTs) = 0.92 at 112° in aqueous dioxane and 0.27 at 110.5° in acetic acid.

Solvolysis Products. Reaction of 1-OTs in aqueous dioxane led quantitatively to only two products, which subsequent investigation showed to be a mixture of epimeric alcohols 7-OH (eq 8). From nmr data, the alcohols were



present in a ratio of 85:15. The major component was assigned the endo configuration both from the nmr data (see below) and from chemical findings. When the alcohol mixture was oxidized with activated manganese dioxide or Sarett's reagent a single ketone 8 was obtained. Reduction of 8 with lithium aluminum hydride produced 7-OH once more, but with an epimeric ratio of 61.5:38.5. Such reduction in bicyclo[3.2.1]oct-3-en-2-one gave 90% endo alcohol (exo attack by hydride),[17] so the major product from this reduction in the present case is very probably *endo*-7-OH also. The major reduction product correlated spectrally with the major solvolysis product. Hence the endo assignment was given to it as well. The nmr evidence for assignment is somewhat ambiguous. Exo protons in nmr spectra of such bicyclic systems are known to resonate downfield relative to endo protons.[18] In the major solvolysis product the -CHOH- methine proton showed δ 4.25, whereas in the minor product this proton was at δ 4.60. On this basis,

Table I
Titrimetric Rate Constants for Solvolysis of *exo*-3,3-Diaryltricyclo[3.2.1.0^{2,4}]oct-8-yl Tosylates

Tosylate	Solvent	Temp, °C[a]	10^5k, sec^{-1}
1-OTs	Dioxane–water[b]	112.0	1.55 ± 0.04
		120.0	3.09 ± 0.03
		130.0	9.61 ± 0.08
2-OTs	Dioxane–water	87.0	2.72 ± 0.03
		100.0	9.64 ± 0.13
		110.0	25.0 ± 1.2
3-OTs	Dioxane–water	100.0	1.69 ± 0.06
		112.0	5.36 ± 0.16
		120.0	11.3 ± 0.50
4-OTs	Dioxane–water	112.0	0.961 ± 0.01
		120.5	2.26 ± 0.05
		130.0	4.66 ± 0.11
5-OTs	Dioxane–water	112.0	2.09 ± 0.03
		122.5	5.57 ± 0.10
		133.0	15.2 ± 0.05
6-OTs	Dioxane–water	112.0	1.43 ± 0.02
1-OTs	Acetic acid[c]	110.5	7.31 ± 0.07
2-OTs	Acetic acid	110.5	78.2 ± 0.50
3-OTs	Acetic acid	110.0	6.50 ± 0.06
		110.5	19.9 ± 0.70
		122.0	67.4 ± 0.90
4-OTs	Acetic acid	110.5	5.57 ± 0.12
6-OTs	Acetic acid	100.0	0.725 ± 0.04
		110.5	1.97 ± 0.03[d]
		112.0	2.43 ± 0.01
		122.0	7.31 ± 0.07

[a] ±0.2°. [b] Dioxane–water (80:20 v/v). The solutions were 0.03 *M* in tosylate and 0.04 *M* in 2,6-lutidine. [c] Purified, anhydrous acetic acid. The solutions were 0.03 *M* in tosylate and 0.04 *M* in sodium acetate. [d] Calculated by computer from activation parameter values by means of the Eyring equation.

Table II
Activation Parameters for Solvolysis of *exo*-3,3-Diaryltricyclo[3.2.1.0^{2,4}]oct-8-yl Tosylates

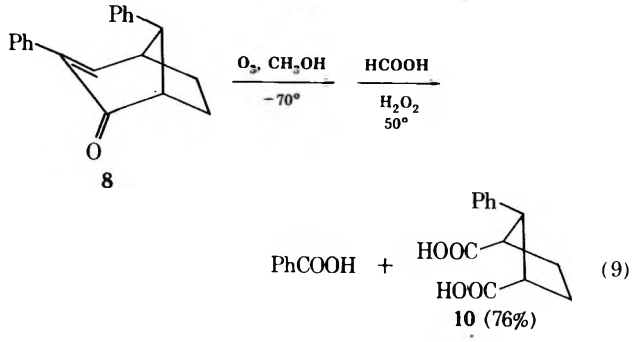
Tosylate	Solvent	ΔH^*, kcal mol^{-1}	ΔS^*, eu
1-OTs	Dioxane–water	26.5 ± 0.3	−12.3 ± 0.7
2-OTs	Dioxane–water	25.6 ± 0.3	−8.6 ± 0.8
3-OTs	Dioxane–water	26.2 ± 0.4	−10.6 ± 1.1
4-OTs	Dioxane–water	26.9 ± 0.2	−12.3 ± 0.4
5-OTs	Dioxane–water	28.7 ± 1.0	−6.0 ± 2.5
3-OTs	Acetic acid	30.3 ± 0.4	3.3 ± 1.3
6-OTs	Acetic acid	30.6 ± 0.8	−0.5 ± 2.1

the major product should be *exo*-7-OH. However, the coupling constant J of this proton with the bridgehead proton ($J_{1,2}$) was ~5 Hz in the minor product and ~10 Hz in the major. These values are in better keeping with *endo*-7-OH as the major product because the dihedral angle relationship is more favorable in this case.[20] The anomalous chemical shift for the methine proton in *endo*-7-OH can, in fact, be rationalized in terms of shielding by the overhanging phenyl group at C-8.

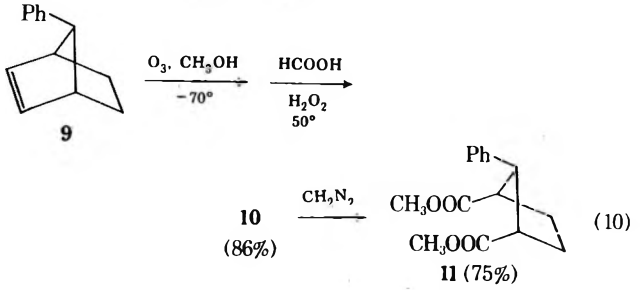
The allylic alcohol nature of 7-OH was attested by its ready oxidation to 8 with manganese dioxide, a reagent generally recognized as specific for such alcohols. Ketone 8 was clearly an α,β-unsaturated ketone from its spectra, λ 6.03 μ (carbonyl stretch) and λ_{max} (ethanol) 265 nm (ϵ 4460). A parent peak, m/e 274, was observed in its mass spectrum. Mass spectral fragments from 1-OTs included the *geminal* diphenyl moieties Ph_2C^+-C≡CH and Ph_2C^+-CH=CH· at m/e 191 and 192, respectively. Alcohol 7-OH, conversely, gave the *separated* phenyl moieties $PhCH{=}CHCH_2^+$ and $CH_2{=}CHC^+(OH)C(Ph){=}CH_2$ at m/e 117 and 159 (base peak), respectively. Such data prompted the structures given in eq 8.

Because an alternative synthesis of 7-OH was not accomplished, its degradation was carried out instead. Oxi-

dation of 7-OH or ketone 8 with potassium permanganate, osmium tetroxide–sodium periodate, potassium permanganate–sodium periodate, or nitric acid either gave benzoic acid (overoxidation) or returned the reactant (underoxidation). Action of ozone on ketone 8, followed by performic acid,[21] was successful, however, and both benzoic acid and *cis*-2-phenylcyclopentane-*cis*-1,3-dicarboxylic acid (*cis*-2-phenylnorcamphoric acid, 10) were isolated (eq 9). The acids formed upon ozonation were converted to

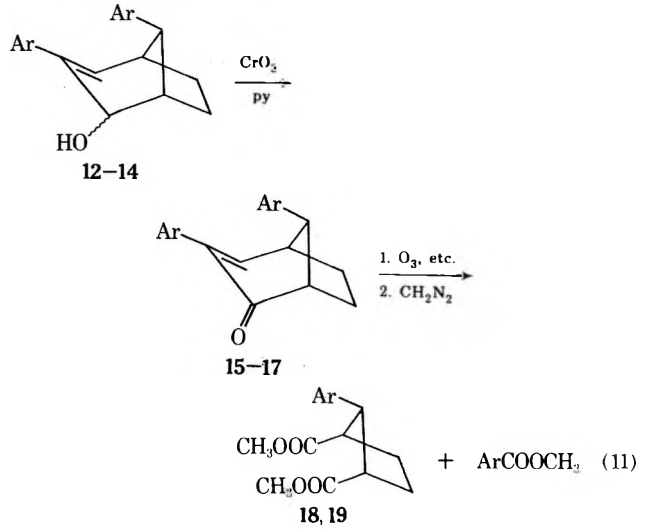


their methyl esters with diazomethane. The methyl benzoate was identical with a known sample. Dimethyl *cis*-2-phenylnorcamphorate (11) was identical with a sample prepared by analogous ozonation of alkene 9 (eq 10), an



easily prepared monoreduction product of the known 7-phenylnorbornadiene. Ester 11 showed in its nmr spectrum a sharp singlet at δ 3.27 for the *equivalent* methyl protons and a triplet (J = 7 Hz) at δ 3.90 for the benzylic proton. Both these spectral features and the mode of synthesis from 9 indicated an all-cis nature for 11 (and 10). On the basis of its allylic nature, separated phenyl groups, and degradation products, the structure of 7-OH shown throughout the foregoing is considered to be established.

Solvolysis products from tosylates 2-OTs, 3-OTs, and 4-OTs were analogous alcohols 12, 13, and 14. The spectra

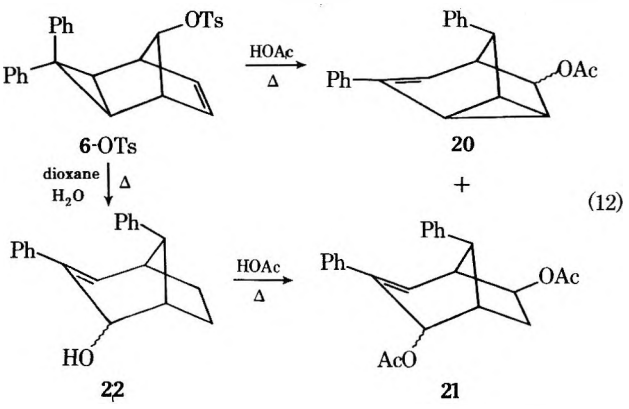


12, 15, Ar = *p*-anisyl
13, 16, 18, Ar = *p*-tolyl
14, 17, 19, Ar = *p*-chlorophenyl

of these products were similar to those of 7-OH. Again an endo:exo ratio of 80:20 was uniformly found. Oxidation of the alcohols led to ketones 15–17, the last two of which were successfully ozonized to aromatic and *cis*-2-arylnorcamphoric acids. The acids were identified as before as the methyl esters 18 and 19 (eq 11). Esters 18 and 19 showed a clear para pattern in the aromatic region of the nmr spectrum, indicating that the rearranged aryl group maintained its initial para substituent. Ketone 15 yielded methyl *p*-anisate upon ozonation, but the norcamphoric acid product was apparently further oxidized[22] because no other aromatic product was detected.

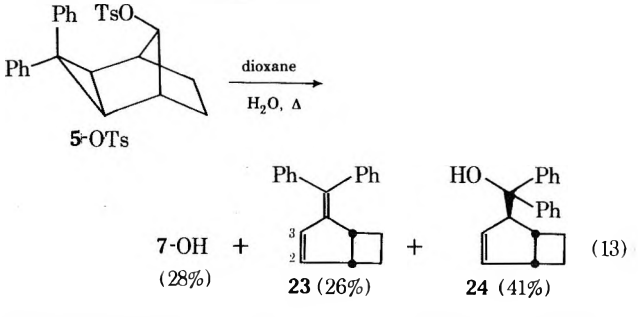
Acetolysis products were obtained only from 3-OTs as a check on the course of this process. The product was an epimeric mixture of acetates 13-OAc (*ca.* 70% endo, 30% exo), which gave alcohol 13 upon hydrolysis. Clearly, acetolysis and hydrolysis in aqueous dioxane follow the same path.

Several products resulted from the solvolysis of the unsaturated tosylate 6-OTs.[8] The characterization of these products will be given in a later paper. Their structures are given in eq 12 to show that the same path is also fol-

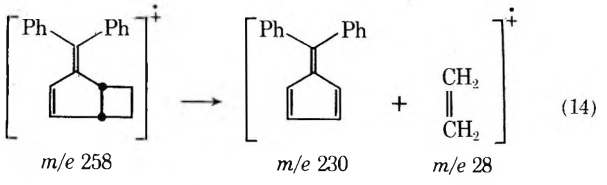


lowed by this tosylate. The acetolysis and hydrolysis studies of 6-OTs were connected *via* the conversion of the epimeric alcohols 22, obtained upon hydrolysis, to the acetates 21, which were among the acetolysis products.

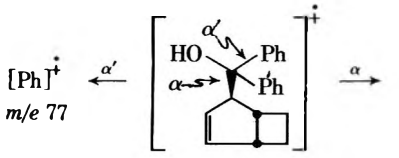
The syn tosylate 5-OTs underwent solvolysis in aqueous dioxane to produce alcohol 7-OH (as did 1-OTs) and two structurally different substances, a hydrocarbon 23 and a related alcohol 24 (eq 13). The alcohol 7-OH was 88%



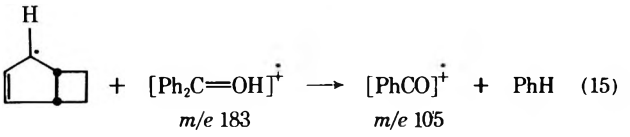
endo and 12% exo. Ketone 8 was formed upon oxidation. Thus this product was identical with the 7-OH obtained from 1-OTs (see earlier). Hydrocarbon 23 was assigned its structure upon spectral and chemical evidence. Its mass spectrum was exceptionally simple, with fragments at m/e 258 (parent), 230, and 28. The last two fragments are



probably diphenylfulvene and ethylene obtained by a cycloreversion process (eq 14). The uv spectrum of **23** showed λ_{max} (ethanol) at 242 (ϵ 9650) and 294 nm (ϵ 21,800), which is similar to that reported[23] for 1,1-diphenyl-1,3-butadiene, λ_{max} (cyclohexane) 236 (ϵ 15,800) and 287 nm (ϵ 23,400). Two vinyl protons at δ 6.38 and 6.06 were observed in the nmr spectrum. The downfield proton (H-3) was a doublet, split by its neighbor H-2. This latter proton was a multiplet, split both by H-3 and the bridgehead H-1. The multiplet sharpened to a doublet upon decoupling H-1 from H-2. Ozonation of **23** produced benzhydryl ether,[24] indicating that the phenyl groups were still geminal in **23**. Alcohol **24** showed strong tertiary alcohol absorptions at 2.83 and 8.6 μ. Its nmr spectrum was complex, but vinyl protons were evident at δ 6.08 and 5.50. The hydroxyl proton was a clear singlet at δ 1.90. The mass spectrum showed no parent peak (usually not found for tertiary alcohols[25]) but rather gave fragments at *m/e* 183, 105, 91, and 77. Most of these fragments may be rationalized as shown in eq 15. Attempted dehydration of **24**



24



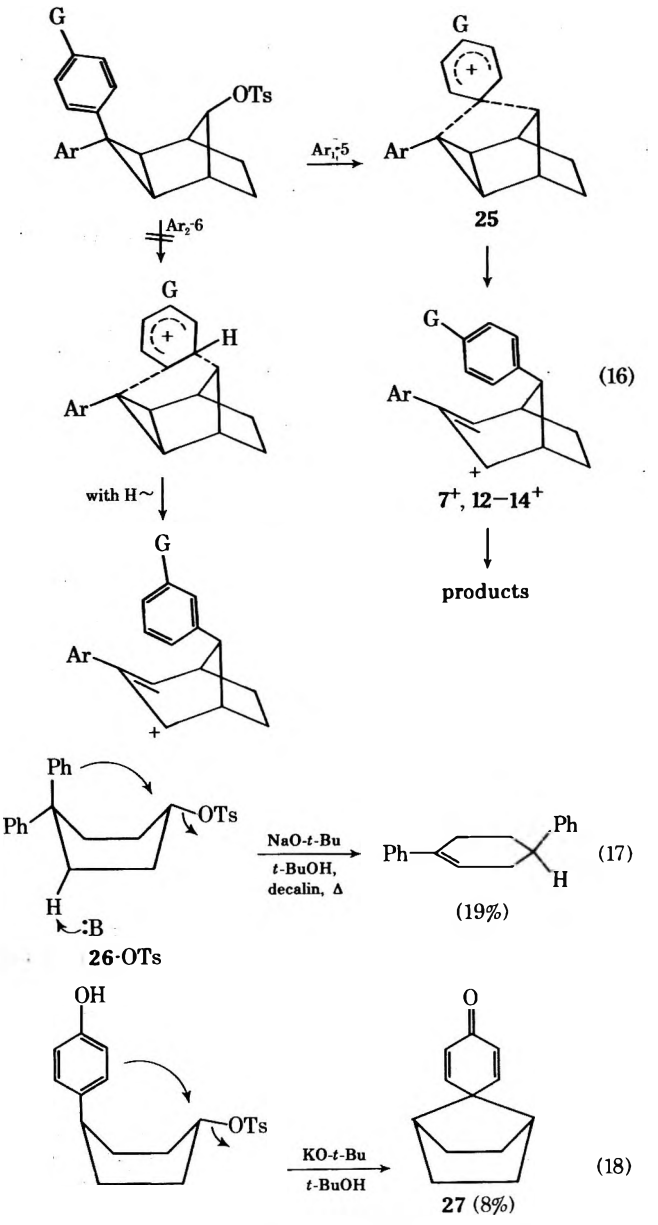
(15)

to **23** either was ineffective (iodine in benzene at reflux) or gave polymer (98% formic acid at 80°). The cis ring juncture in **24** (and **23**) is assumed from the proposed origin of these products (see Discussion).

Discussion

The structure of the solvolysis products from **1**-OTs through **4**-OTs indicates without question that transannular aryl migration and cyclopropyl ring opening have indeed been combined in one process. The site retention of para substituents in the migrated aryl group of **3**-OTs and **4**-OTs (and most probably **2**-OTs as well) further demonstrates that the transannular aryl migration is Ar_1-5 in nature and not Ar_2-6 (eq 16).[26] The allylic ion so formed (7^+) would then produce the observed epimeric alcohol (or acetate) mixture. Because the syn aryl group at C-8 would sterically hinder solvent capture from the normally favored exo direction, it is not surprising that endo capture is favored instead (*ca.* 80:20).

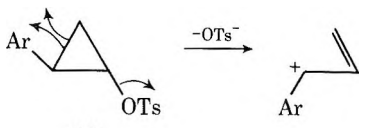
The transannular aryl shift observed in these reactions (a 1,4 aryl migration) is not common. Two reports indicate that under certain conditions, however, such a 1,4-aryl shift can occur. In the first (eq 17) the phenyl group was induced to migrate by the incipient formation of a double bond.[27] Acetolysis of **26**-OTs or deamination of **26**-NH_2 gave no such rearrangement.[27] In another report, the *p*-hydroxyphenyl group (as the phenoxide) performed a transannular displacement under similar conditions (eq 18).[28] Isolation of a spirodienone such as **27** (and others reported as well[29]) lends support to phenonium ion **25** as an intermediate in the present solvolyses. Furthermore, the tetracyclic parent system in **25**, commonly known as "deltacyclane," has no particular strain disfavorability and considerable investigation of the system has been reported.[30] If ion **25** is involved, the cyclopropyl ring opening must be *subsequent* to the aryl participation.



(16) (17) (18)

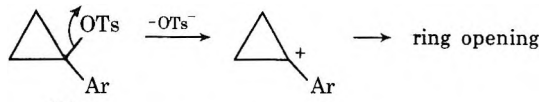
Contrariwise, two experimental facts argue that the cyclopropyl ring opening must be *simultaneous* with the aryl participation. First, the ρ value for the process (-1.68 for hydrolysis and -1.30 for acetolysis) is too small for a process involving phenonium ion intermediacy. Second, an additional double bond, as in **6**-OTs, was mildly rate retarding. Concerning the ρ value, it is informative to note some values associated with the following processes where cationic charge in a transition state is dispersed either into an aromatic ring or into an incipient allyl system.[4] In the cases of **28** and **30**, disrotatory opening of the ring is facile to expel a trans leaving group. The small ρ values indicate that in the transition state little charge is dispersed into the aromatic ring. With **29** and **31**, however, the large ρ values implicate benzylic-type ions in the transition states, and little cyclopropyl ring opening occurs in these transition states.[31]

Also, processes long accepted as involving phenonium ion intermediates have ρ values higher than -1.3 or -1.7. Acetolysis of neophyl substrates, $ArC(CH_3)_2CH_2OBs$, for example, has $\rho = -2.96$ (75°);[32] that of $ArCH_2CH_2OTs$ has $\rho = -2.4$ (115°) for the k_Δ portion of the process;[33] and that of **32** has $\rho = -3.26$ (77.6°).[34] All these reactions involve Ar_1-3 participation, whereas the present rearrangement involves Ar_1-5. Here the situation is less clear. Indeed, smaller ρ values are known for Ar_1-5 participation



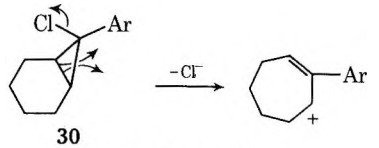
28

$\rho = -1.75$ (108°)



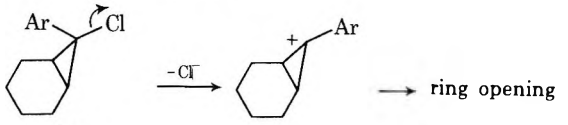
29

$\rho = -4.31$ (108°)



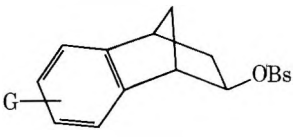
30

$\rho = -2.0$ (100°)



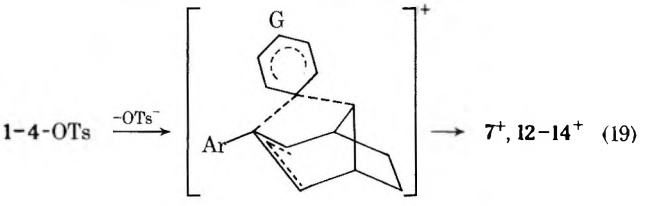
31

$\rho = -4.2$ (100°)



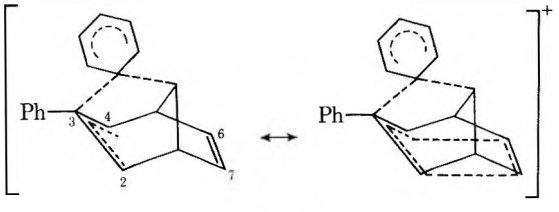
32

in *nonrigid* systems.[35] The tricyclic system used in this present work has, in our opinion, a geometry more akin to the Ar_1-3 cases in that no rotation to a proper conformer must be achieved to allow the participation (and thusly disfavor participation entropically). Rather, the aryl groups in 1-OTs through 4-OTs are always situated properly for participation. From the ρ values it is therefore believed that *ions like* **25** *are not involved in these rearrangements but rather that ions like* **33** *are involved instead* (eq 19). Disrotatory cyclopropyl ring opening accompanies the migration of the aryl group as it moves transannularly to displace the anti tosylate function (much as incipient double-bond formation accompanied the aryl migration in 26-OTs[27]). The cationic charge so created is then spread between the half-migrated aromatic ring and the developing allylic system, resulting in low ρ values.



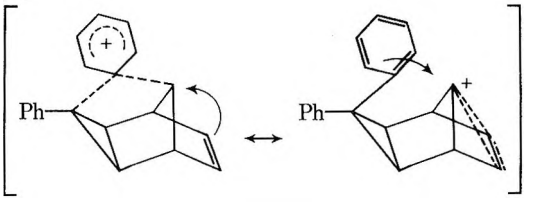
33

The effect of the additional double bond in 6-OTs on the rearrangement if species **33** indeed be involved should be somewhat rate retarding. This follows because the process would now involve **34** and thereby incur some of the disadvantage associated with antiaromaticity.[36] The bicyclo[3.2.1]octadienyl cation has been classified as a bishomocyclopentadienyl cation and as such it should be destabilized by conjugation.[37] Because ion **34** is clearly related to the parent [3.2.1] ion, some of this destabilization should be present in **34** as well. The effect should be small, nonetheless, because the cant of the C-2,3,4 portion of **34** would decrease the possibility for effective overlap with the π system at C-6,7. Such seems to be the case, with the ratios for solvolysis rate constants k(6-OTs)/k(1-OTs) = 0.92 (112°, hydrolysis) and 0.27 (110.5°, acetolysis).



34

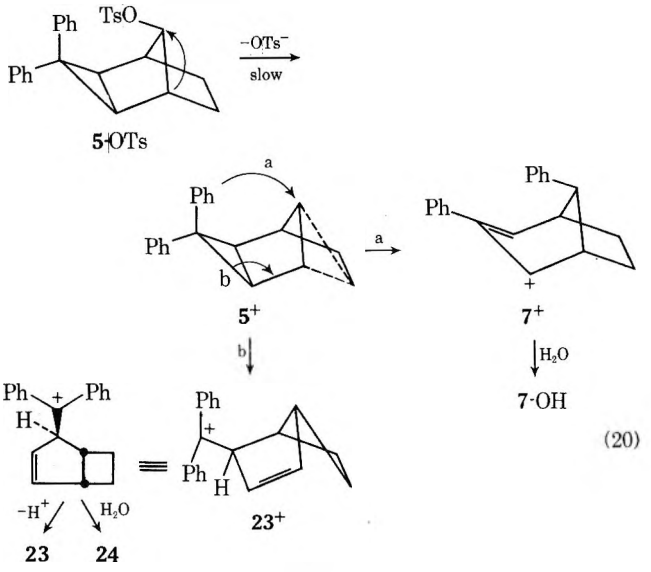
Conversely, if phenonium ions like **25** were involved in these reactions, some acceleration in rate could be expected because additional stabilization as in **35** is possible.

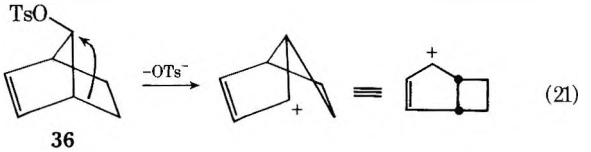


35

Normally, an additional double bond speeds solvolysis in 7-norbornenyl substrates by factors of 100–1000.[38] Although the relationship of such compounds to 6-OTs may not be exact, the slight deceleration in the rate of 6-OTs is in better keeping with an intermediate like **34** rather than **35**.

The products formed from the solvolysis of the syn tosylate 5-OTs can be accommodated by eq 20. This equation is based upon the similar behavior of *syn*-7-norbornenyl tosylate (**36**), reported some years ago (eq 21).[39]



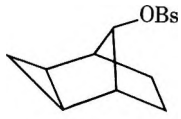


36 (21)

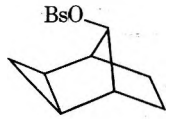
Whereas **36** can form an allylic ion directly upon the displacement of the tosylate leaving group by the σ bond as illustrated, 5-OTs cannot. As a consequence, ion 5^+ (shown in eq 20 as a delocalized ion for convenience) can be partitioned along two paths, each of which is roughly comparable in ease. Path a involves a reoccurrence of the transannular phenyl migration and produces ion 7^+ on the way to the alcohol product 7-OH.[40] Path b involves a cyclopropylcarbinyl-allylcarbinyl rearrangement and more

resembles the behavior shown by **36**. The ring bond in the cyclopropyl portion of 5^+ has considerable p character and its realignment to form ion 23^+ is a plausible occurrence. Once ion 23^+ results, deprotonation to hydrocarbon **23** and solvent capture to alcohol **24** are understandable. This view necessitates the role of intermediate, not just transition state, for 5^+.

The reactivities of **1**-OTs and **5**-OTs can be compared to those of nonphenyl analogs **37** and **38**, studied earlier by

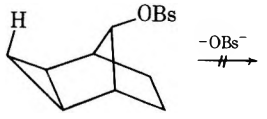


37

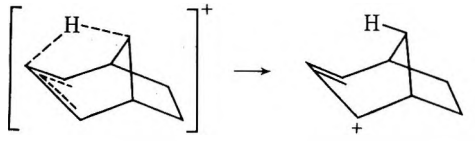


38

Haywood-Farmer and Pincock.[14] Some pertinent data are collected in Table III. Although uncertainties exist in the use of extrapolated rate constants, it is nevertheless clear that the presence of phenyl groups in **1**-OTs greatly increased its solvolytic reactivity (7000-fold) relative to the nonphenyl analog **37**. Such was not the case with **5**-OTs *vis-à-vis* **38** (no change). This great difference can be understood in terms of the pathways given earlier. In **1**-OTs aryl participation coupled with cyclopropyl ring opening caused the increased rate. Apparently a hydride shift in **37** akin to the aryl shift in **1**-OTs, shown in eq 22, does

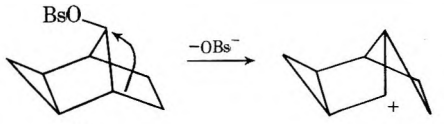


37



(22)

not occur.[41] In **38** a solvolytic pathway suggested by the earlier workers[14] was a σ shift (eq 23), although a steric



(23)

38

acceleration caused by the 3-CH_2 group was an alternative suggestion. Because no products from either **37** or **38** were identified,[14] it is difficult to compare the course of their solvolysis with those of **1**-OTs and **5**-OTs. However, at least with **5**-OTs the pathway shown in eq 20 does mirror that suggested for **38** in eq 23. Moreover, phenyl groups at C-3 should not influence this process greatly because the σ shifts in these equations do not involve them.

Lastly, the carbonyl stretching frequency of ketone **5** (1769 cm^{-1}, 2% in CCl_4) may be used to estimate an acetolysis rate constant for **1**-OTs (or **5**-OTs), provided no anchimeric assistance is involved. Use of Foote's correlation[42] gave for these cases log $k_{rel} = -6.3$, a value that is comparable to that of 7-norbornyl tosylate itself (log $k_{rel} = -7.0$) and much slower than that of cyclohexyl tosylate (log $k_{rel} = 0.0$). On this basis, both **1**-OTs and **5**-OTs are clearly assisted in their solvolysis, because each is much faster than is 7-norbornyl tosylate. In fact, the only unassisted case seems to be **37**.

Experimental Section[43]

Synthesis of Reactants. ***anti*-10-*tert*-Butoxy-*exo*-5,5-diaryl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-3-enes (Diaryldiazomethane-*anti*-7-*tert*-Butoxynorbornene Adducts 1-P-4-P).** The appropriate diaryldiazomethane[44] (73 mmol) was added in small portions to a stirred excess of *anti*-7-*tert*-butoxynorbornene[15] (63.8 g, 0.39 mol) at 25°. The reaction material was heated at 50° for 18 hr and then briefly at 80°. The mixture was then cooled and the vessel was scratched to precipitate the adduct as a white solid (80–85% yield). Analytical samples were recrystallized several times from methanol.[45] The melting points follow: **1**-P, 167.5–169° dec; **2**-P, 168–169° dec; **3**-P, 141–142° dec; and **4**-P, 143–144° dec.

The yellow filtrate from these reactions contained some dissolved adduct and colored by-products. No attempt was made to separate these components. Rather, the filtrate was recycled for further preparations. After four or five cycles the norbornene was recovered by vacuum distillation for reuse.

***anti*-8-*tert*-Butoxy-*exo*-3,3-diaryltricyclo[3.2.1.$0^{2,4}$]octanes (1-O-*t*-Bu-4-O-*t*-Bu).** The selected adduct above (29.3 mmol) was heated without solvent in a wax bath at 160°. Evolution of nitrogen was essentially quantitative after 30 min. The cooled product (87–93% yield) was purified by recrystallization from methanol.[45] The melting points follow: 1-O-*t*-Bu, 119.5–121°; 2-O-*t*-Bu, 131–132°; 3-O-*t*-Bu, 133–134°; 4-O-*t*-Bu, 98–99°.

***anti*-8-Acetoxy-*exo*-3,3-diaryltricyclo[3.2.1.$0^{2,4}$]octanes (1-OAc-4-OAc).** The proper ether above (18.2 mmol) was dissolved in glacial acetic acid (18 ml) containing acetic anhydride (3.5 ml). To this solution in an ice bath *at 0°* was added perchloric acid (70%, 0.85 ml) with rapid swirling of the material. *Caution: locally high concentration of the perchloric acid should be avoided by rapid swirling. Vigorous exotherms can result otherwise.* The colored solution was swirled in the ice bath for an additional 1 min after the addition and then poured onto crushed ice (500 g). The solid so formed was collected and dried (80–87% yield). The compound was recrystallized from methanol.[45] The melting points follow: 1-OAc, 153–155°; 2-OAc, 136–136.5°; 3-OAc, 94–95°; 4-OAc, 157–158°.

***exo*-3,3-Diaryltricyclo[3.2.1.$0^{2,4}$]octan-*anti*-8-ols (1-OH-4-OH).** The appropriate acetate above (7.2 mmol) in ether (100 ml) was added to methylmagnesium iodide (30 mmol) in ether (50 ml). After reaction at 25° for 4 hr, the mixture was hydrolyzed with water (12 ml) and the ether phase was separated. Upon removal of the ether, the residual alcohol (87–91% yield) was purified by recrystallization from hexane.[45] The melting points follow: 1-OH, 154.5–155°; 2-OH, 108–109.5°; 3-OH, 109–110°; 4-OH, 179–180°.

Tosylates of these alcohols (and others in this study) were prepared in the usual way using *p*-toluenesulfonyl chloride in pyridine[46] (63–67% yield). Analytical samples were prepared by recrystallization from benzene–hexane mixtures.[45] The melting points follow: 1-OTs, 140–141°; 2-OTs, 147–148°; 3-OTs, 126–127°; 4-OTs, 129–130°; 5-OTs, 186–188°; 6-OTs, 156–157° dec.

***exo*-3,3-Diphenyltricyclo[3.2.1.$0^{2,4}$]octan-8-one (5).** Alcohol 1-OH (1.64 g, 5.93 mmol) in pyridine (15 ml) was added to a solution of chromium trioxide (5.73 g) in pyridine (57 ml) at 25° with stirring. After 12 hr the solution was treated with water and extracted with ether. The dried ether extracts were evaporated to afford crude **5** as a yellow solid (1.63 g, 99%), which was purified by recrystallization from cyclohexane. The pure ketone was colorless: mp 152–154°; λ (KBr) 5.70, 6.70, 6.92, 8.83, 12.45, 13.10–13.31, 14.21–14.30 μ; nmr δ 7.42 (m, ArH), 2.30 (broad m, H-1,5), 1.95 (s, H-2,4), 1.70 (broad s, H-6,7).

Table III
Comparison Data for Selected Tricyclooctyl Arenesulfonates

Sulfonate	k, sec^{-1} (°C)	k_{rel}
37	8.4×10^{-9} (100)[a]	
37-OTs	1.1×10^{-8} (110.5)[b]	1
1-OTs	7.31×10^{-5} (110.5)[c]	7000
38	7.0×10^{-5} (100)[a]	
38-OTs	2.0×10^{-6} (112)[d]	1
5-OTs	2.09×10^{-6} (112)[c]	1

[a] Reference 14. The rate constants were determined in 0.1 *N* NaOAc–HOAc solvent. [b] Extrapolated value corrected for the temperature difference and the OBs/OTs rate ratio of 3, using the values $\Delta H^* = 29.4$ kcal mol^{-1} and $\Delta S^* = -17.1$ eu.[14] [c] This work, Table I. [d] Extrapolated value corrected for the temperature difference, the OBs/OTs rate ratio of **3**, and the change in solvent from NaOAc–HOAc to aqueous dioxane (from Table I a factor of 0.25 was chosen). The activation values used for **38** were $\Delta H^* = 27.1$ kcal mol^{-1} and $\Delta S^* = -5.4$ eu.[14]

Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.54; H, 6.77.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]octan-*syn*-8-ol (5-OH).** Ketone **5** (1.60 g, 5.84 mmol) was reduced with lithium aluminum hydride (3.5 g) in ether (50 ml) in the standard fashion. Upon processing the reaction, a white solid, 1.35 g (84%), mp 101–130°, was obtained. Spectral analysis indicated that this product was a mixture of syn and anti alcohols. After five recrystallizations from hexane the syn alcohol **5**-OH was obtained pure: mp 132.5–134°; λ (KBr) 2.82, 3.40, 8.60, 9.27, 13.05, 13.29, 14.10, 14.33 μ; nmr δ 7.12–7.80 (m, ArH), 3.48 (broad s, H-8), 2.53 (broad s, H-1,5), 1.73 (s, H-2,4), 1.62 (dd, exo H-6,7), 1.25 (dd, endo H-6,7), 0.47 (broad s, OH).

Anal. Calcd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.87; H, 7.42.

The tosylate was prepared as mentioned above.[45]

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]oct-6-en-*anti*-8-yl tosylate (6-OTs)** was prepared from the alcohol (mp 126.5–127°)[8] as mentioned above.[45]

Reduction of this alcohol with lithium aluminum hydride in ether at 25° for 6 hr gave alcohol **1**-OH in quantitative yield, as established by identical spectra and mixture melting point.

Solvolysis Studies. Kinetics. Dioxane[47] and acetic acid[48] were purified as reported. Solutions were made 0.03 *M* in tosylate, either in aqueous dioxane (80:20 v/v dioxane–water) or in anhydrous acetic acid. The former solutions contained 0.04 *M* redistilled 2,6-lutidine and the latter solutions contained 0.04 *M* sodium acetate. Ampoules sealed under nitrogen were employed and the reactions were followed as described previously for aqueous dioxane studies.[1b] Acetolysis was followed by back-titration of unreacted sodium acetate with standardized *p*-toluenesulfonic acid in anhydrous acetic acid. Crystal violet was the indicator. Infinity titers were within 2% of the theoretical values. Good first-order kinetics were observed with rate constants obtained by a least-squares WAT IV computer program. Activation parameters were similarly calculated from the Eyring equation. See Table I for values.

Solvolysis Studies. Products. Larger scale solvolyses were performed in the same solvents and at the same concentrations as those used above. About 10 mmol of reactant in aqueous dioxane was heated in a pressure bottle under nitrogen at an appropriate temperature for 12 half-lives. The material was poured onto ice and extracted with hexane (ether was used for 4-OTs). The extracts were dried and evaporated. The white solid (*ca.* 100% yield) was determined to be a mixture of *endo*- and *exo*-**3**-*syn*-**8-diarylbicyclo[3.2.1]oct-3-en-2-ols.** Spectral analysis was used to establish the endo:exo ratio. Analytical samples were obtained by recrystallization from aqueous methanol, although this fractionated the product considerably (by nmr) and gave essentially pure endo alcohols.[45] The melting points follow: **7**-OH, 118.5–119.5°; **12**, 130–132°; **13**, 125–126°; **14**, 136–137°.

The endo–exo mixture (mp 102–109°) obtained from the solvolysis of **1**-OTs was analyzed spectrally using the H-2 resonances in the mixture: δ 4.25 for the endo epimer and δ 4.60 for the exo. Certain differences elsewhere in both the nmr and ir spectra were of course also present.[49]

Acetolysis of 3-OTs (0.6 g, 1.3 mmol) was performed in dry acetic acid (50 ml), 0.04 *M* in sodium acetate, at 120° for 14 hr. The material was added to ice water and treated with enough sodium carbonate to neutralize most of the acetic acid. Extraction with ether followed. Removal of solvent from the dried, combined extracts afforded the endo and exo acetates **13**-OAc; 0.38 g (92%); mp 130–134°; λ (KBr) 5.80 μ; nmr δ 5.82 (d, H-2 of endo epimer, J = 6 Hz), 5.44 (d, H-2 of exo epimer, J = 3 Hz). The endo:exo ratio was 7:3. Reaction of this material with ethereal methylmagnesium iodide gave alcohol **13** (83%, identical with that obtained by solvolysis in aqueous dioxane).

Solvolysis products from 5-OTs were isolated by chromatography on alumina (100 g). Elution with 10% benzene–hexane gave **23**, mp 64–64.5°.[45] Use of 1:1 benzene–chloroform gave **24**. Elution with 1:1 ether–chloroform produced **7**-OH. Alcohol **24** was an oil, pure upon elution. Oxidation of the **7**-OH isolated from **5**-OTs with chromium trioxide in pyridine gave ketone **8** just as described later for this oxidation of **7**-OH obtained from **1**-OTs. Treatment of alcohol **24** with a trace of iodine in benzene under reflux produced no change. Reaction of **24** with 98% formic acid at 80° for 3 hr gave a yellow product, mp 197–230°. This material was apparently a polymer but it was not investigated further.

Structural Studies on Solvolysis Products. Oxidation to Ketones. Reaction of the appropriate diarylbicyclooctenol endo–exo mixture (0.73 mmol) with activated manganese dioxide[50] (2.5 g) was carried out at 25° for 12 hr in pentane (50 ml). Removal of the excess oxidant and solvent left a white solid (83–86%), shown to be the corresponding **3**,*syn*-**8-diarylbicyclo[3.2.1]oct-3-en-2-one.** The products from **7**-OH and **13**, ketones **8** and **16**, respectively,[45] had melting points of 107.5–108.5 and 92–93.5°. Larger scale oxidations (*ca.* 2-g scale) were better achieved with chromium trioxide in pyridine. Such oxidation of alcohols **12** and **14** gave the di-*p*-anisyl ketone **15**, mp 135–137°, λ (KBr) 6.01 μ, and the di-*p*-chlorophenyl ketone **17**, mp 138–140.5°, λ (KBr) 5.96 μ, respectively. These two ketones were not purified further, but were used in ozonation studies directly (see later). Treatment of ketone **8** with lithium aluminum hydride in ether in the usual manner produced **7**-OH (72% yield). From its nmr spectrum, the alcohol was still richer in the endo epimer (61.5%).

Ozonation. At −70° the appropriate ketone **8** or **16** (1.8 mmol) in methanol (100 ml) was treated with ozone generated from a Model LOA 2 Corona Generator (Purification Sciences, Inc.), using an oxygen flow rate of 5 ft^3/hr for 12 min. Methanol was removed under reduced pressure at 25°. Formic acid (6 ml) and hydrogen peroxide (30%, 3 ml) were then added to the yellowish-green material. The solution was warmed slowly to 60° on a water bath (Caution: a vigorous reaction may commence).[21] After 30 min the now colorless reaction mixture was poured into cold water and extracted thoroughly with ether. The ether extracts were combined, dried, and treated with excess diazomethane. Upon removal of the remaining diazomethane and ether by rotary evaporation, the residue was chromatographed on alumina (25 g). Elution with either 1:4 benzene–hexane or 1% ether in hexane produced the appropriate aromatic methyl ester. These were identified by comparison with authentic samples. Elution with benzene or 1:4 chloroform–benzene yielded the appropriate dimethyl *cis*-2-arylnorcamphorate (75–80% yield), which was recrystallized from pentane. Esters **11** and **18** had melting points of 66–67.5 and 58–60°,[45] respectively. The aromatic protons in **18** exhibited a singlet resonance in its nmr spectrum. Such is the case for *p*-, but not *m*-, xylene.[51] (see Discussion).

The ozonation of ketone **8** was also processed without the diazomethane. Removal of the ether from the reaction extracts gave an approximately 1:1 mixture of benzoic and *cis*-2-phenylnorcamphoric acids. The former was identical with a known sample and the latter was identical with a sample prepared by ozonation of *syn*-7-phenylnorbornene (see later).

Ozonation of ketones **15** and **17** gave methyl *p*-anisate and methyl *p*-chlorobenzoate, respectively. However, no norcamphorate ester was found among the products from **15**.[22] **Dimethyl *cis*-2-*p*-chlorophenylnorcamphorate (19)** was obtained from ketone **17**, but it was not extensively purified: nmr δ 7.4–7.0 (m, AA′BB′ ArH), 3.98 (t, H-2, J = 8 Hz), 3.40 (s, OMe), 1.8–2.8 (m, all other H's). The aromatic pattern was clearly para (see Discussion).

Ozonation of hydrocarbon **23** (50 mg) was performed as described above, except that methylene chloride was the solvent and the formic acid was omitted. The oily residue from the ether extracts was taken up in ethanol (3 ml) and chilled overnight. A precipate of **benzhydryl ether** (10 mg, mp 107–109°) formed. It was identical with an authentic sample.[52]

***syn*-7-Phenylnorbornene (9).** 7-Phenylnorbornadiene[53] (27.6 g, 0.164 mol) in 95% ethanol (150 ml) containing suspended palladium on charcoal (5%, 0.4 g) was hydrogenated at ambient temperature and 35.5 psig. After 10 min 1 equiv of hydrogen had been taken up. The catalyst was filtered off and the solvent was removed by atmospheric distillation. Vacuum distillation then gave olefin **9** in 88% yield, bp 95–96° (0.75 mm), $n^{25.5}$D 1.5492, δ 5.77 (t, vinyl H's).[45] The product contained about 1% of the anti epimer (δ 6.17, t, vinyl H's) and about 5% of the starting diene. Reaction of the diene with lithium aluminum hydride in ether under reflux for 12 hr gave only 6.7% reduction and the product was a 1:1 mixture of syn and anti epimers. Reduction of the diene with diimide gave a mixture also: 33.8% of syn and anti epimers in the ratio of 82.5:17.5; 39.4% of 7-phenylnorbornane; and 25.8% of recovered diene. This poor result contrasts with other reports.[54] No problem was found using palladium on charcoal for the hydrogenation. It has been reported[55] that such a catalyst is inferior to (more expensive) platinum catalysts in such reductions.

***cis*-2-Phenylnorcamphoric Acid (10).** Olefin **9** (0.5 g, 2.9 mmol) was ozonized as described earlier. After the self-sustaining reaction with formic acid and hydrogen peroxide was completed, the solution was refluxed for 30 min and then evaporated. The solid residue (0.59 g, 86%) was recrystallized from pentane–ether to give acid **10** as a colorless solid, mp 232.5–235.5° dec.[45] The

acid was identical with that produced from ketone **8**, as were the methyl esters.

Acknowledgment. The authors thank Drs. Henry F. Dabek, Jr., and John L. Huston for the mass spectra.

Registry No.—**1**-P, 50522,48-0; **1**-O-*t*-Bu, 50522-49-1; **1**-OAc, 50522-50-4; **1**-OH, 29266-06-6; **1**-OTs, 29266-07-7; **2**-P, 50522-52-6; **2**-O-*t*-Bu, 50522-53-7; **2**-OAc, 50484-72-5; **2**-OH, 50522-54-8; **2**-OTs, 50522-55-9; **3**, 50522-56-0; **3**-P, 51096-42-5; **3**-O-*t*-Bu, 50522-58-2; **3**-OAc, 50522-59-3; **3**-OH, 50522-60-6; **3**-OTs, 50522-61-7; **4**-P, 50522-62-8; **4**-O-*t*-Bu, 50522-63-9; **4**-OAc, 50522-64-0; **4**-OH, 50522-65-1; **4**-OTs, 50522-66-2; **5**, 29302-44-1; **5**-OH, 29266-08-8; **5**-OTs, 29302-43-0; **6**-OTs, 50522-70-8; *endo*-**7**-OH, 50522-71-9; *exo*-**7**-OH, 50522-72-0; **8**, 29283-01-0; **9**, 29266-12-4; **10**, 29266-10-2; **11**, 50522-76-4; *endo*-**12**, 50522-77-5; *exo*-**12**, 50522-78-6; *endo*-**13**, 50522-79-7; *exo*-**13**, 50522-80-0; *endo*-**14**, 50522-81-1; *exo*-**14**, 50522-82-2; **15**, 50522-83-3; **16**, 50522-84-4; **17**, 50522-85-5; **18**, 50522-86-6; **19**, 50522-87-7; **23**, 29283-02-1; **24**, 29283-03-2; **37**, 2040-61-1; **37**-OTs, 50522-91-3; **38**, 24218-05-1; **38**-OTs, 50522-93-5.

Supplementary Material Available. Melting point, combustion analytical data, significant ir, complete nmr, and pertinent mass spectral data (asterisked compounds) for **1**-P-**4**-P, **1**-O-*t*-Bu-**4**-O-*t*-Bu, **1**-OAc-**4**-OAc, **1**-OH-**4**-OH, **1**-OTs*-**6**-OTs (melting point and analysis only), **7**-OH,* **8**,* **9**–**14**, **16**, **18**, **23**, and **24** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1327.

References and Notes

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(6) Exo addition to norbornenes is, of course, commonplace. Even *syn*-7-*tert*-butoxynorbornene adds phenyl azide exclusively exo.[7] Such additions are more complex in norbornadienes, however. The parent hydrocarbon undergoes exo addition exclusively with diphenyldiazomethane,[1b] but 7-*tert*-butoxynorbornadiene affords both exo and endo adducts with both diphenyldiazomethane[8] and phenyl azide.[7]

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(13) Reduction of exo-tricyclo[3.2.1.$0^{2,4}$]octan-8-one with lithium aluminum hydride gave only the syn alcohol.[14] It is curious that ketone **5**, which is more crowded at the carbonyl site, underwent a less stereoselective reduction.

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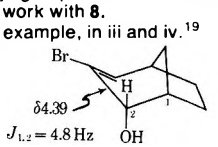

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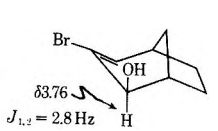

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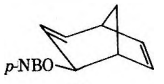

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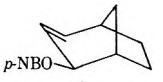

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p-NBO = p-$NO_2C_6H_4CO_2$-

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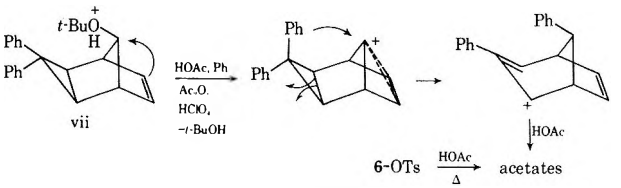

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Bridged Polycyclic Compounds. LXXX. Rearrangements in the Dibenzobicyclooctadiene Systems. Higher Energy Carbocations[1]

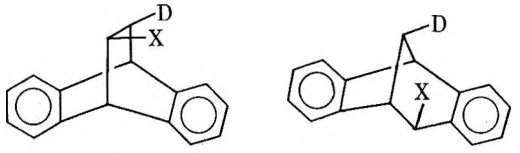
Stanley J. Cristol* and Ronald J. Bopp

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received September 14, 1973

Treatment of 2-deuterio-2-dibenzobicyclo[2.2.2]octadienyl acetate (9) with acetic acid–sulfuric acid leads to equilibration with 1-deuterio-2-dibenzobicyclo[2.2.2]octadienol (10). Similar treatment of 1,*cis*-3-dideuterio-2-dibenzobicyclo[2.2.2]octadienyl acetate (13) gives both 1,*trans*-3-dideuterio-2-dibenzobicyclo[2.2.2]octadienyl acetate (14) and the 2,*trans*-3-dideuterio ester (15), with the former being produced two or three times as fast as the latter. These results demonstrate the existence of 2-dibenzobicyclo[2.2.2]octadienyl cation (6) and 1-protonated dibenzotricyclo[3.3.0.0^{2,8}]octadiene (7) as high-energy carbocations available in such rearranging systems.

Some time ago[2] we reported that acetolysis of the *p*-toluenesulfonate of *cis*-3-deuterio-2-dibenzobicyclo[2.2.2]octadienol (1-OTs) led stereospecifically (*i.e.*, with clean anti migration) to *syn*-8-deuterio-*exo*-2-dibenzobicyclo[3.2.1]octadienyl acetate (2-OAc), which was in turn cleanly transformed (through the endo epimer of 2-OAc) in acetic acid containing perchloric acid to *cis*-3-deuterio-2-dibenzobicyclo[2.2.2]octadienyl acetate (1-OAc). The *trans*-3-deuterio acetate 3-OAc was absent from the latter reaction mixture.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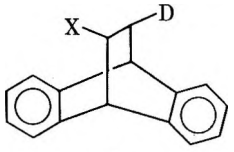
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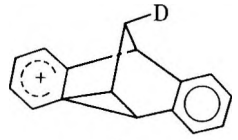
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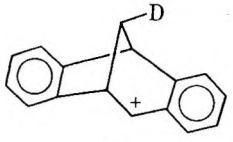
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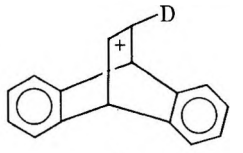
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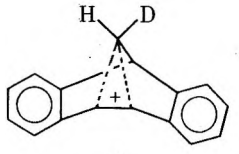
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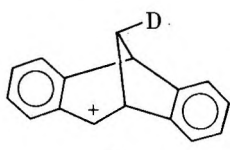
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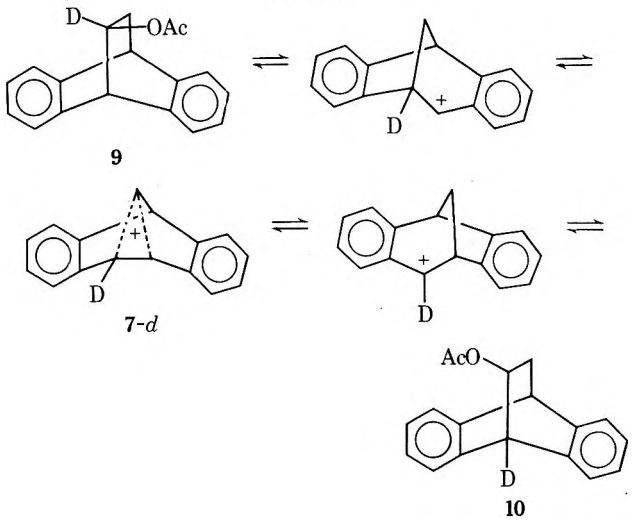
These data were consistent with the intervention of some combination of the phenyl-bridged nonclassical ion (4) or some variant thereof[2,3] and that of the benzylic ion 5 or with that of the latter alone, including a geitonodesmic reaction.[3,4] The absence of 3-OAc made it clear that neither 2-dibenzobicyclo[2.2.2]octadienyl cation (6) nor the bridged ion 7 (1-deuterated dibenzotricyclo[3.3.0.0^{2,8}]octadiene) intervenes in these reactions (7 could be an intermediate or a transition state on the reaction coordinate between 5 and 8). Thus 6 and 7 are obviously of higher energy than 4 and/or 5, and the lower energy pathways involving the latter ions (or analogs) are transversed in these and in many similar reactions.[5] Species analogous to 7 have been shown to be involved as *low-energy* intermediates in reactions of bicyclo[3.2.1]octanyl systems,[6] but as discussed earlier,[7] geometric constraints not present in the latter system are present in 7.

When tetradeuterioacetic acid was added to dibenzobicyclooctatriene at 86° (catalyzed by 1 *M* D_2SO_4), the predominant kinetic product was the cis deuterio ester 1-OAc-d_3,[2] but the trans epimer 3 was also formed. Thus, when 10% of the olefin had been consumed, the ratio of 1-OAc-d_3 to 3-OAc-d_3 was approximately 86:14. By the time (10 hr) the addition was essentially complete, the ratio of 1 to 3 had dropped to 7:3. The isomerization of 1 to 3 obviously utilized one or both of the higher energy reaction channels described above (6 or 7), and it seemed of interest to determine which was utilized. We report now that processes involving both 6 and 7 occur at competitive rates.

Our first experiment was designed to test for the possible intervention of 7. To this end, we prepared 2-deuterio-2-dibenzobicyclo[2.2.2]octadienyl acetate (9). If 6 were the sole intermediate between 1-OAc and 3-OAc, then, in the time for the 1 $\rightleftharpoons$ 3 equilibration, *dl*-9 would act as if it were inert, as its equivalent rearrangement would be degenerate. On the other hand, intervention of 7 (as either an intermediate or a transition state) would lead to scrambling of deuterium between C-2 and C-1, a process readily followed by pmr intensity measurements. (The C-1 proton absorbs at δ 4.50 and that at C-2 at δ 5.05.) This process is shown in Scheme I (in which we have omitted the intermediate phenyl-bridged cations analogous to 4). Bridge migration *via* 7, in the 1 to 3 rearrangement, is thus analogous to that *via* 7-*d* in the 9 to 10 rearrangement.

When 9 was heated in a 1.4 *M* sulfuric acid solution in acetic acid at 85°, it was found to rearrange toward its

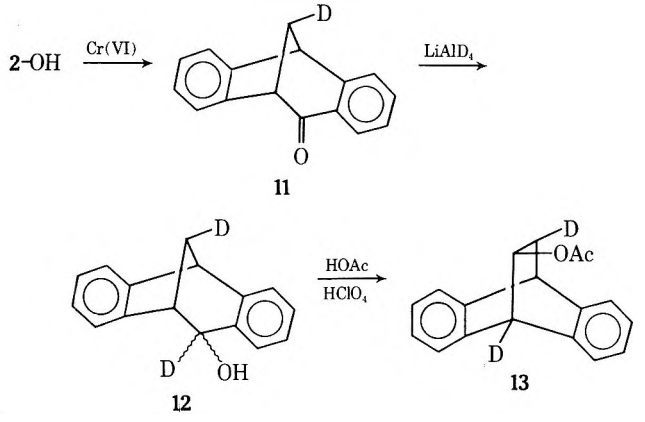
Scheme I



equilibrium mixture with **10**. Thus, after 28 hr, the ratio of **9** to **10** was 72:28, while after 74 hr, it was 61:39. While these results clearly implicated the cation **7**, comparative studies with **1**-OAc rearranging to **3**-OAc under similar conditions indicated that cis–trans equilibration is almost complete (52:48) after only about 30 hr. Thus the possibility of the competition of the open secondary cation **6** with **7** in these rearrangements still remained.

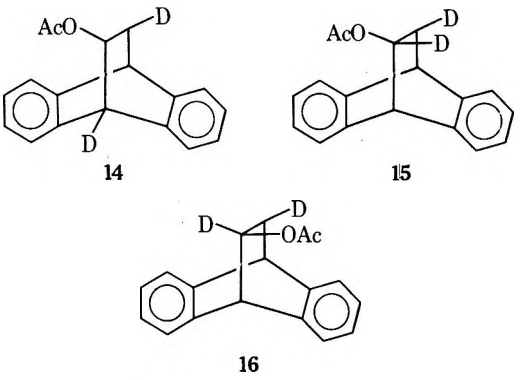
To investigate this possibility, we prepared the doubly labeled compound **13** as shown in Scheme II. With this

Scheme II



compound it is possible to note cis–trans isomerization *via* the open secondary cation **6**, which would lead to **14**, as well as that *via* cation **7** (a process analogous to that of Scheme I), which would give **15**, The reaction can be followed by watching the doublet intensity at δ 5.05 (J = 9 Hz) due to the C-2 proton in compound **13** change on the one hand to a doublet (J = 3 Hz) at the same frequency for the simple cis–trans isomerization giving **14**, or reduce in total intensity at δ 5.05 to give a new singlet at δ 4.50 (C-1 proton in**15**). Accompanying the **13** → **14** or **15** transformation is a reduction in the δ 2.25 intensity and appearance of a new multiplet at δ 1.42 as the proton trans to the acetoxy group is transformed to one cis to the acetoxy group.[2,8] The formation of **16** from **14** *via* Scheme I would complicate the arithmetic in any precise treatment of data, but cause no interference in our interpretations.

Compound **13** was heated at 85° for 30 hr in an acetic acid solution containing 1 *M* sulfuric acid, and the acetate was recovered. The pmr spectrum of the product was considerably changed from that of **13**. The ratio of the δ 2.25 to 1.42 peak intensities in the product was 53:47, indicating that the cis–trans isomerization was over 90% com-

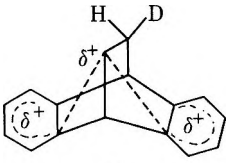


plete (*ca.* 4 half-lives). On the other hand, the ratio of intensities at δ 5.05 and 4.50 was 71:29 (approximately 1 half-life for the deuterium scrambling between C-2 and C-1). Accompanying these phenomena was a decline in the J = 9 Hz doublet at δ 5.05 and a buildup of a doublet with J = 3 Hz at δ 5.05 as anticipated;[9] the δ 4.17 doublet remained unchanged in the experiment.

After 75 hr, the transformation measured by δ 5.05 to 4.50 peak intensities was 56:44 (*ca.* 3 half-lives) while those of the J = 9 to 3 and δ 2.25 to 1.42 were 50:50, to the best of our ability to estimate them.[9]

Recognizing that mechanisms involving either **6** or **7** lead to cis–trans isomerization, while only that involving **7** leads to proton–deuteron scrambling, we find the interesting result that these processes occur at quite similar rates, the secondary cation **6** being formed perhaps two or three times as rapidly as the bridged cation **7**. Although these cations are needed to explain the results described in this paper, we emphasize that they are in fact higher energy species than those (**4** and **5**) utilized[4] in the normal interconversion of [2.2.2] and [3.2.1] systems. They are nevertheless formed under conditions where repeated ionizations are caused to occur. While it is practicable to conduct experiments in which the rates of ionization to **4** or **5** could be measured by labeled acetate exchange and compared with cis–trans isomerization rates, in order to get a measure of the energy difference between **4** and/or **5** and **6** and **7**, we do not now contemplate such experiments.

A referee has noted that the simple cis to trans isomerization, which we have proposed is due to the intermediacy of **6**, may equally well be explained by assuming that the phenonium ion **4** is "inverted" to its mirror image by displacement of the electron pair at the spiro carbon atom by an electron pair from the π system of the opposed benzene ring. The "inverted" **4** would have the same relationship to **3** that **4** has to **1**.[10] The transition state **17** for this interconversion differs conceptually from **6** in that σ bonding is assumed in **17**, while the cationic center in **6** would interact with the benzene rings only by π interaction. It is not clear to us how **6** and **17** can be distinguished experimentally.



The referee has also objected to our conclusion that **6** and **7** are higher in energy than **4** and **5**. He points out that this conclusion may be incorrect if they are *intermediates* which lie in a deep energy well surrounded by high energy barriers separating them from **4** and/or **5**. We see no reason to assume that this is more valid than the usual

assumption[11] that reactive cationic intermediates are not significantly different in energy content from the transition states which separate them from their products.

Experimental Section

Preparation of 2-Deuterio-2-dibenzobicyclo[2.2.2]octadienol. 2-Dibenzobicyclo[2.2.2]octadienone[12] (440 mg, 2.0 mmol) in 10 ml of ether was added dropwise to 58.4 mg (1.4 mmol) of lithium aluminum deuteride in 30 ml of ether. The mixture was heated at reflux overnight. Water (5 ml) was added slowly and then 6 *M* hydrochloric acid was added to dissolve the precipitated salts. The mixture was extracted with ether. The ether layer was washed with aqueous sodium bicarbonate until neutral, dried (magnesium sulfate), and concentrated. The resulting solid (430 mg, 95% yield) was shown by pmr to be the desired deuterated alcohol, mp 138–140° (lit.[12] undeuterated mp 140–141°). The pmr spectrum (deuteriochloroform) exhibited peaks at δ 4.25 (s, 1 H, H-1), 4.14 (t, 1 H, J = 2.5 Hz, H-4), 2.17 (d of d, 1 H, J = 2.5, 13.0 Hz, H-3 trans to OH), 1.20 (d of d, 1 H, J = 2.5, 13.0 Hz, H-3 cis to OH), 6.8–7.4 (m, 8 H, aromatic), 1.52 (s, 1 H, hydroxyl proton). The pmr spectrum was consistent with that previously reported[8] for the undeuterated analog.

Equilibration of 2-Deuterio-2-dibenzobicyclo[2.2.2]octadienol with 1.4 *M* Sulfuric Acid in Acetic Acid. 2-Deuterio-2-dibenzobicyclo[2:2.2]octadienol (150 mg, 0.67 mmol) was dissolved in 2.7 ml of acetic acid which contained 0.2 ml of sulfuric acid (1.4 *M*). Transformation to **9** occurs in a very short time under these conditions. The mixture was allowed to react for 28 hr at 85 ± 1°. The mixture was poured into 15 ml of water and extracted with ether. The ether layer was washed with aqueous sodium bicarbonate until neutral, dried over anhydrous magnesium sulfate, and concentrated. The pmr spectrum (deuteriochloroform) of the resulting oil (*ca.* 120 mg, 71%) showed a ratio of intensity at δ 4.5 (H at C-1) to that at δ 5.0 (H at C-2) of 71:29. When the reaction was run for 74 hr (278 mg of alcohol, 5 ml of acetic acid, and 0.37 ml of sulfuric acid), the per cent of protium at C-2 was 39 ± 5%. Note that 50% exchange is complete equilibration. The triplet at δ 4.1–4.2 (H at C-4) did not change character or intensity.

Preparation of *syn*-8-Deuterio-2-dibenzobicyclo[3.2.1]octadienone (11). *syn*-8-Deuterio-2-dibenzobicyclo[3.2.1]octadienol (2-OH,[2] 1.95 g, 8.7 mmol) in 30 ml of ether was added to 14 ml of 0.6 *M* chromic acid and allowed to react for 12 hr at room temperature. The chromic acid solution was prepared by dissolving 50 g of sodium dichromate dihydrate in 37.5 ml of concentrated sulfuric acid and diluting to 250 ml with water. The mixture was extracted with ether. The ether was washed with aqueous sodium bicarbonate until neutral, treated with charcoal, dried ($MgSO_4$), and concentrated. The solid was recrystallized from methanol to give 1.17 g (62%) of **11**, mp 112–115°, mmp with authentic[13] undeuterated ketone 114–115°. The pmr spectrum was consistent with that reported[14] for the undeuterated analog, with absorption by the syn proton absent.

Reduction of *syn*-8-Deuterio-2-dibenzobicyclo[3.2.1]octadienone with Lithium Aluminum Deuteride. *syn*-8-Deuterio-2-dibenzobicyclo[3.2.1]octadienone (**11**, 1.14 g, 5.0 mmol) in 20 ml of ether was added dropwise to 108 mg (2.57 mmol) of lithium aluminum deuteride in 20 ml of ether. The mixture was allowed to stand for 12 hr, after which 5 ml of water was added, followed by 6 *M* hydrochloric acid to dissolve the salts. The mixture was extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated. The remaining solid, 1.16 g (100%), had a broad melting point range from 80 to 140°, with the majority of material melting at 131–132°. The ir (carbon tetrachloride) showed an alcohol band at 3550 cm^{-1}. The pmr spectrum was consistent with that of a mixture of *endo*- and *exo*-2,*syn*-8-dideuterio-2-dibenzobicyclo[3.2.1]octadienols (**12**). The pmr spectrum (carbon tetrachloride) exhibited major peaks at δ 6.90–7.45 (m, 8 H, aromatic), 3.99 (d, 1 H, J = 4.5 Hz, H-5), 3.47 (d, ~1 H, J = 5.0 Hz, H-1), 2.57 (t, ~1 H, J = 5.0 Hz, H-8 anti), and 1.70 (s, 1 H, hydroxyl), all attributable to the endo isomer. The exo isomer differed only by having H-1 absorbance at δ 3.29 and H-8 anti at δ 2.34. By integration of the 3.29 and 3.47 peaks the exo:endo ratio was estimated to be 12:88. No peak at δ 4.48 (proton H-2 in the undeuterated alcohol) was present in this spectrum.

Preparation of 1,*cis*-3-Dideuterio-2-dibenzobicyclo[2.2.2]octadienyl Acetate (13). The mixture of alcohols **12** (613 mg, 2.74 mmol) was dissolved in 35 ml of 1 *M* perchloric acid in acetic acid and allowed to stand for 12 hr at 22°. The mixture was poured into 100 ml of water and extracted with ether. The ether layer was washed three times with 50-ml portions of water and with aqueous sodium bicarbonate until neutral, dried ($MgSO_4$), treated with charcoal, and concentrated. The resulting solid had a melting point of 95–99°. After recrystallization from petroleum ether (bp 60–80°), 560 mg (77%) of product was obtained, mp 98–100°, mmp with authentic undeuterated acetate 98–100°. The pmr spectrum (carbon tetrachloride) was consistent with the structure 1,*cis*-3-dideuterio-2-dibenzobicyclo[2.2.2]octadienyl acetate (**13**) and exhibited peaks at δ 6.90–7.35 (m, 8 H, aromatic), 5.02 (d, 1 H, J = 9.0 Hz, H-2), 4.17 (d, 1 H, J = 2.5 Hz, H-4), 2.23 (d of d, 1 H, J = 2.5, 9.0 Hz, H-3 trans to acetate), and 1.75 (s, 3 H, acetate methyl).

Equilibration of 1,*cis*-3-Dideuterio-2-dibenzobicyclo[2.2.2]octadienyl Acetate (13) with 1 *M* Sulfuric Acid in Acetic Acid. A portion of the sample of **13** described above (252 mg, 0.95 mmol) was dissolved in 10 ml of 1 *M* sulfuric acid in acetic acid and allowed to stand at 85.5 ± 0.1° for 30 hr. The solution was poured into 75 ml of water and extracted with ether. The ether layer was washed several times with 50-ml portions of water, washed with aqueous sodium bicarbonate until neutral, dried ($MgSO_4$), treated three times with charcoal, and concentrated. The pmr spectrum of the resulting oil is described in the discussion section, as is that of a sample allowed to react for 75 hr.

Acknowledgment. The authors are indebted to the National Science Foundation for generous support of this research.

Registry No.—2-OH, 21438-91-5; **11**, 50894-30-9; *endo*-**12**, 50894-31-0; *exo*-**12**, 50894-32-1; **13**, 50640-89-6; 2-deuterio-2-dibenzobicyclo[2.2.2]octadienol, 50641-11-7; 2-dibenzobicyclo[2.2.2]octadienone, 6372-63-0.

References and Notes

(1) Paper LXXIX: S. J. Cristol and H. W. Mueller, *J. Amer. Chem. Soc.*, **95**, 8489 (1973).
(2) S. J. Cristol, R. J. Bopp, and A. E Johnson, *J. Org. Chem.*, **34**, 3574 (1969).
(3) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Amer. Chem. Soc.*, **87**, 2879 (1965).
(4) We are accumulating evidence for the intervention of both **4** and **5** cations in these reactions (R. S. Beckley, Ph.D. Thesis, University of Colorado, 1970; M. C. Kochansky, Ph.D. Thesis, University of Colorado, 1971).
(5) See references listed in ref 2.
(6) (a) H. L. Goering and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1397 (1961); (b) J. A. Berson and P. Reynolds-Warnhoff, *ibid.*, **84**, 682 (1962); **86**, 595 (1964).
(7) See footnote 15 in ref 3.
(8) S. J. Cristol, T. W. Russell, J. R. Mohrig, and K. Schwarzenbach, *J. Org. Chem.*, **31**, 581 (1966).
(9) At the time this work was carried out, our nmr capabilities were not good enough for complete resolution of these peaks for instrumental integrations. Inspection of the traces suggests that the center doublet was somewhat less intense than the outside doublet. Similarly, integrations on other peak intensities are only reproducible to ±5% and thus the half-life estimates given are quite approximate.
(10) For a similar proposal of nonclassical ion–nonclassical ion rearrangement, see T. Svensson and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2336 (1972).
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The 1-Methyl-3-phospholanol System. Synthesis and Stereochemistry[1]

Louis D. Quin* and Ronald C. Stocks

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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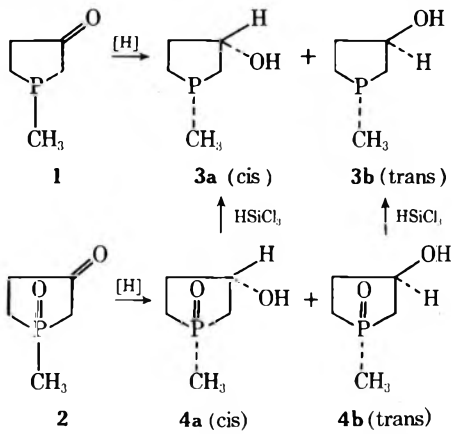
1-Methyl-3-phospholanol (cis, trans) has been prepared by reduction of 1-methyl-3-phospholanone with several agents, preferably lithium aluminum hydride, as well as by P-deoxygenation of the alcohol mixture formed on catalytic hydrogenation of 1-methyl-3-phospholanone 1-oxide. The phospholanol mixture is easily analyzed by the well-separated (13 Hz) PCH_3 nmr signals; the downfield signal is attributed to the cis isomer, which predominated (84%) from the various reductions of the phospholanone. The route *via* the phospholanone oxide gave predominantly the trans alcohol (63%). The conformational equilibrium for the cis isomer appears to be dominated by the diaxial conformer. Addition of methylmagnesium iodide to the phospholanone follows a similar steric path, and gives mostly the cis isomer.

It is now well established by X-ray studies[2] that the replacement of carbon by trivalent phosphorus in a six-membered ring does not alter the chair shape of the ring greatly, in spite of the longer C–P bonds and smaller C–P–C angle. However, the conformational tendency of an exocyclic substituent on phosphorus is quite different from that when on carbon.[3,4] For example, in 1-methylphosphorinane, there is a predominance of the axial methyl conformer at room temperature,[4] and in both the cis and trans forms of 1-methyl-4-phosphorinanol the hydroxy group is largely equatorial and the methyl group is either axial (cis) or equatorial (trans).[3,5] No prior consideration has been given to the conformational consequences of replacing a carbon in cyclopentane with phosphorus, however, mostly because of the lack of access to suitable model compounds for such studies. We recently prepared 1-methyl-3-phospholanone[6] and its 1-oxide,[7] and recognized that these compounds would be useful starting points for stereochemical study of the phospholane ring, in that cis and trans isomers would result from additions to the carbonyl group. The isomer ratio as well as nmr spectral properties could be expected to provide stereochemical information, and this is shown to be true in this paper.

Synthesis of 3-Phospholanols. These alcohols can be approached by two paths from the ketones available. The

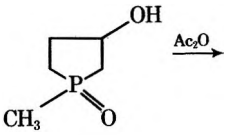


1 3a (cis) 3b (trans)

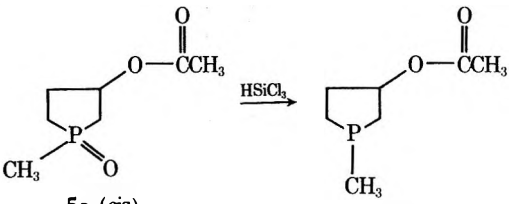
2 4a (cis) 4b (trans)

reduction of ketophospholane 1 proceeded especially well (84%) with lithium aluminum hydride; yields were distinctly inferior with two other systems tried (sodium–ethanol, 13%; aluminum isopropoxide, 54%), although these experiments were performed only once.

The high enolic character[6,7] of β-keto oxide 2 interfered with hydride reduction (sodium borohydride or lithium aluminum hydride). However, catalytic hydrogenation proceeded smoothly to give a mixture of alcohols 4a and 4b. These compounds were very difficult to work with in that they were extremely hygroscopic. They could be acetylated, however, and, though still hygroscopic, the acetates were more readily handled. The acetates were reduced with trichlorosilane to the corresponding phosphines (6a and 6b).



4a (cis)
4b (trans)



5a (cis)
5b (trans)

6a (cis)
6b (trans)

Deoxygenation of the alcohol oxides 4a and 4b occurred in 37% yield. As will be noted later, the ratio of alcohols 3a and 3b is quite different from that obtained by reduction of the ketophosphine, a point which would have utility if the pure isomers were desired. That a separation of the isomer mixture is feasible was demonstrated by subjecting a 1:1 cis–trans mixture to fractional distillation with a spinning-band column. The first fraction was the cis isomer in 95% or greater purity; the pot residue was about 85% trans. The separation was not further perfected, however.

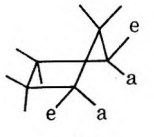
Structure Assignment. The ^1H nmr spectrum (neat) of the 3-phospholanol mixture contained two sharp, well-separated PCH_3 doublets (3a, δ 1.71; 3b, δ 1.49), which permitted easy analysis of the mixture. The signals are of additional importance, however, in that their chemical-shift difference is attributable to the orientation of the methyl and hydroxyl groups. The hydroxyl group is well known to deshield cis methyl groups.[8] This effect also prevails in the 1-methyl-4-phosphorinanols.[9] Accordingly, structure 3a is assigned to that compound with the more deshielded PCH_3.

The ^{31}P nmr signals of the isomers are sufficiently well separated (1.5 ppm) that under conditions of proton decoupling they may be used to analyze a mixture. The trans isomer has the more upfield signal (3b, δ ^{31}P +40.3; 3a, δ +38.8), but the structural significance of this order of signals is not yet apparent.

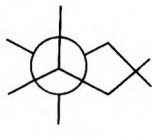
The 3-phospholanols were found to experience a strong upfield shift of all ^1H nmr signals on addition of benzene.

The most readily observed signal was that for PCH_3, where it was seen that the signal associated with the cis compound (**3a**) was less susceptible to this effect than that of the trans. This allowed a greater spread to develop between the PCH_3 signals of the isomer mixture. Thus, in a 40% benzene solution, **3a** had $\delta(PCH_3)$ 1.30, while **3b** had δ 0.95. The difference (21 Hz) is substantially greater than seen for the neat sample (13 Hz). The same effect holds for the 1-methyl-4-phosphorinanols,[9] although the shifts are much smaller since the complexed solvent (at OH[10]) is more removed from the PCH_3 group. The geometry of the complex would also be quite different.

Conformational Aspects. The conformation of the five-membered ring is usually discussed in terms of an envelope (A) or twist envelope (B) shape, shown in Newman projection. These forms are flexible, and pseudo-rotation,



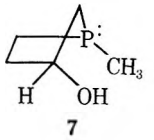
A



B

which is rapid, causes puckering at all ring positions. Similar shapes appear to be adopted by heterocyclic rings, including some heterosubstituted phospholanes (1,3,2-dioxa-,[11] 1,3,2-dithia-,[12] 1,3,2-oxathia-,[12a,13] 1,3,2-oxaza[14]). Models show that it is reasonable to depict the parent phospholane ring in the same manner. For convenience, substituents occupying the a positions in structure A will be referred to as axial, and those in the e positions as equatorial.

One nmr property of the 3-phospholanols is of particular importance in a conformational sense: the large difference (13 Hz) in chemical shifts for the PCH_3 groups in the cis and trans form [$\Delta\delta(PCH_3)$], as caused by hydroxyl deshielding, is in the range commonly found for 1,3-methyl and hydroxyl when fixed rigidly in the diaxial relation.[15] In the flexible 3-methylcyclopentanol system, the difference between isomers is only 4 Hz[16] (with cis downfield). The implication is clear that in the *cis*-3-phospholanol system the CH_3 and OH groups are, on the average, closer together than they are in *cis*-3-methylcyclopentanol. This may be expressed by envelope structure **7**, or twist envelope **8**; presumably these predominate in the conformational equilibrium with other puckered structures (*e.g.*, **9** and **10**).



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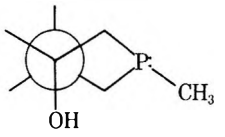

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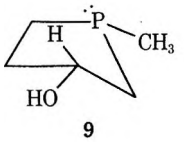

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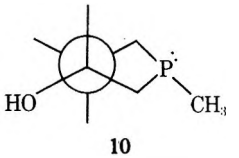
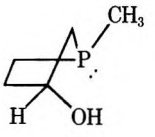


10

Indeed, the size of $\Delta\delta(PCH_3)$ suggests that the *cis*-3-phospholanol may exist exclusively as **7** (or **8**), with no ring flexing, but this view would require a stronger defense than can now be developed.

In the isomeric *trans*-1-methyl-3-phospholanol, either the hydroxy group or the methyl group may be axial, and the other equatorial, as represented by **11** and **12**. No information is available on the conformational preference in this compound.



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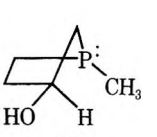


12

The importance of the diaxial conformation **7** (or **8**) for the cis isomer suggests that nonbonded 1,3 interactions must play only a small role in the phospholane system, and this is supported by the fact that the cis and trans phospholanols are of nearly equal concentration (51 and 49%, respectively) in the mixture formed on equilibration at 135° *via* pyramidal inversion at phosphorus. This low energy difference between cis and trans forms is paralleled in the cyclopentane system; in 1,3-dimethylcyclopentane, cis is more stable than trans by 0.53 kcal/mol[17] and, for 3-methylcyclopentanol, $\Delta G°$ for cis $\rightleftharpoons$ trans is -0.2 kcal/mol.[18] Carbon-13 shifts for these same 1,3-disubstituted cyclopentanes also reveal the absence of strong steric interaction.[19] The spectra for an isomer pair are very similar, comparable carbons differing at most by only 1.9 ppm. In the cyclohexane system, the more severe 1,3-nonbonded interactions involving an axial substituent can cause differences of about 5 ppm at the ring carbons involved. The ^{31}P shifts for the corresponding phospholane derivatives reveal the same situation to hold true. For the 1-methyl-3-phospholanols, $\Delta\delta(^{31}P)$ is 1.5 ppm and, for the 1,3-dimethylphospholanes, it is 0.4 ppm;[20] in isomeric *P*-methylphosphorinane derivatives, $\Delta\delta(^{31}P)$ can be several parts per million (6 ppm in the 4-hydroxy compounds[9] and 7 ppm in the 4-hydroxy-4-*tert*-butyl compounds[3]).

That diaxial structures such as **7** or **8** can have special importance in phospholanes is not out of keeping with the character of phosphorus in six-membered rings. It has already been noted[3,4] that 1,3 interactions of PCH_3 are markedly reduced in this system, and an axial orientation is not disfavored at room temperature. Since 1,3 interactions are generally weaker in five-membered rings, it follows that structure **7** (or **8**) may be quite stable. It perhaps is relevant also that the known[21] preference of the hydroxy group for axial orientation in cyclopentanol is maintained in this structure. It is also relevant that in some of the five-membered cyclic phosphite derivatives[11-13] the substituent on phosphorus seems to adopt the axial position. However, the lone pairs on the heteroatoms attached to phosphorus, which may play a role in controlling the structure, are absent in the phospholane system.

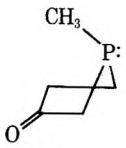
Stereochemistry of Phospholanol Formation. When 3-methyl-[18] or 3-*tert*-butylcyclopentanone[22] are reduced under kinetically controlled conditions, the alcohol mixture formed is richer in the cis isomer. Equilibration, however, leads to a slight predominance of trans in each case (*tert*-butyl, 52%; methyl 57%). That the cis isomer forms faster has been explained by hindrance provided by the substituent on that face of the ring to which it is attached, making it more favorable for hydrogen to be delivered from the opposite side. When 1-methyl-3-phospholanone is reduced, the cis isomer also predominates, but to an extent much larger than that seen for the cyclopentanones. Data are compared in Table I. That these percentages for **3a** and **3b** result from kinetic control is indicated by the adjustment of the cis–trans composition to nearly 1:1 on equilibration at 135° *via* pyramidal inversion at phosphorus. At least at this temperature, which is not greatly different from that of the aluminum isopropoxide reduction (80–90°), it is seen that there is little energy difference between the two isomers.

Table I
Per Cent Cis Alcohol Formed in Various Reductions

Compd	$LiAlH_4$	Na–ROH	$Al(O\text{-}i\text{-}C_3H_7)_3$
3-Methylcyclopentanone[18]	60	53[a]	*b*
3-*tert*-Butylcyclopentanone[22]	60	56[c]	59
1-Methyl-3-phospholanone[d]	81	79[c]	80

[a] R = H. [b] Conditions used allowed equilibration to occur. [c] R = C_2H_5. [d] Nmr analysis, by integration of CH_3 doublets.

The significantly higher content of cis product from the phospholanone may be taken to indicate that approach to the carbonyl is more hindered than in the 3-alkyl cyclopentanones. This is consistent with the concept that a P substituent on the phospholane ring experiences only weak nonbonded interactions when axially oriented, allowing contributions from structures such as **13** to be important relative to the equatorially substituted form, **14**.



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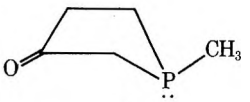
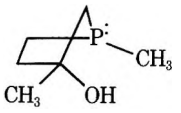
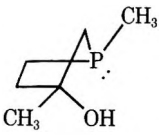


14

In some preliminary work[23] on the addition of Grignard reagents to ketone **1**, we have found that methylmagnesium iodide gives predominantly the cis alcohol (88.2%). This was established again with the aid of the cis deshielding of PCH_3 by hydroxyl (in benzene, major isomer, δ 1.25; minor, δ 0.91). The mixture showed only one CCH_3 signal, implying that this group has the same orientation in both isomers. Structures **15** and **16** (or twist



15 (cis)

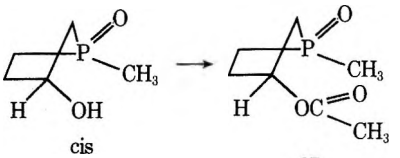


16 (trans)

forms) accommodate these facts, and are in keeping with the concept of low preference by PCH_3 for a particular location. Again, the proportion of cis isomer formed exceeded that from addition to 3-*tert*-butylcyclopentanone, which gave 51% cis alcohol. A steric block to one face of the phospholanone ring is indicated, as proposed to explain the large amount of cis product on reduction.

Stereochemistry of Reduction of 1-Methyl-3-phospholanone 1-Oxide. Catalytic hydrogenation of ketone **2** gave an alcohol mixture again readily analyzed by well-separated PCH_3 signals ($\Delta\delta$ 10 Hz). The cis structure (**4a**) was assigned to the isomer with the downfield PCH_3 signal. This time, however, the trans isomer predominated (60:40); this was confirmed by deoxygenation with trichlorosilane, which gave the phospholanols in the same ratio. Little can be said about the significance of the steric result with the oxide, since it is not known if the keto or the enol form is the species undergoing reduction.

Acetylation of the alcohol oxide mixture gave the isomeric acetates **5a** and **5b**, again recognized from their differing PCH_3 signals. However, the signals were reversed in position from the alcohols, the more intense now being downfield. This suggests that the acetate group has a specific shielding effect on the PCH_3 of the cis compound, moving the signal from δ 2.30 in the alcohol to 2.16 in the acetate. The trans signal was but slightly affected, shifting from δ 2.17 to 2.22. If the shielding effect can be associated with anisotropy of the ester carbonyl group, then only the cis isomer should allow positioning of the two groups in the appropriate relation, as expressed by conformer **17**. Instances of such shielding of methyl by acetoxy



cis

17

groups are found among rigid five-membered rings with diaxial geometry, as in the D ring of steroids.[15a]

The shielding by acetate is found also in the corresponding phosphines **6a** and **6b**. The ratio of isomers, as seen by the nmr spectrum, was the same as in the starting oxide mixture. The major isomer (60%) was downfield (δ 1.58), as was the major isomer in the oxide mixture. Since this is the trans isomer, the shielding by acetate in the cis isomer is demonstrated.

Experimental Section[24]

Synthesis of 1-Methyl-3-phospholanol (3) from 1-Methyl-3-phospholanone 1-Oxide (2). A mixture of 8.5 g (64.4 mmol) of ketone **2**, 1 g of Raney nickel, and 100 ml of 95% ethanol was hydrogenated in a Parr apparatus (48 hr at 50 psi). Norit was added and the mixture was filtered through Celite. The filtrate was evaporated to dryness, providing crude *cis*- and *trans*-1-methyl-3-phospholanol 1-oxide (**4**): nmr ($CDCl_3$) δ 2.17 (d, $^2J_{PH}$ = 12.8 Hz, cis PCH_3, 35%), 2.30 (d, $^2J_{PH}$ = 13.8 Hz, trans PCH_3, 65%), 2.3–3.1 (6 H, m), 4.6–5.4 (CHOH, m). The product was extremely hygroscopic.

The alcohol mixture was dissolved in 200 ml of benzene containing 15 ml of triethylamine. The solution was chilled to 0° and treated with 17.4 g (12.8 mmol) of trichlorosilane in 60 ml of benzene over a 30-min period. The reaction was completed with 2 hr of reflux. The mixture was chilled again for hydrolysis with 10 *N* NaOH, added to obtain complete dissolution of the initially precipitated solid. The benzene layer was recovered, and the aqueous layer was extracted with benzene. The combined benzene solutions were dried ($MgSO_4$) and distilled to give 2.8 g (37%) of 1-methyl-3-phospholanol (**3**, cis:trans 37:63): bp 93–95° (17 mm); nmr (neat) δ 1.49 (d, $^2J_{PH}$ = 2.8 Hz, trans PCH_3), 1.71 (d, $^2J_{PH}$ = 2.5 Hz, cis PCH_3), 1.82–2.9 (6 H, m), 4.7–5.3 (CHOH, m); nmr (40% in benzene) δ 0.98 (trans PCH_3) and 1.30 (cis PCH_3); $\delta(^{31}P)$ +38.8 (cis) and +40.3 (trans); ir (neat) ν_{OH} 3250 cm^{-1}.

The methiodide of the alcohol mixture was prepared in benzene and recrystallized from methanol–ether.

Anal. Calcd for $C_6H_{14}IOP$: C, 27.69; H, 5.43; P, 11.91. Found: C, 27.85; H, 5.57; P, 11.72.

Reduction of 1-Methyl-3-phospholanone (1) with Lithium Aluminum Hydride. A slurry of 0.30 g (7.9 mmol) of lithium aluminum hydride in 20 ml of tetrahydrofuran at reflux was treated dropwise (20 min) with a solution of 1.26 g (10.9 mmol) of ketone **1** in 20 ml of THF. The mixture was then refluxed for 4 hr, chilled in an ice bath, and hydrolyzed cautiously with 1 ml of water, followed by 1 ml of 15% NaOH and more water (6 ml). The mixture was filtered. The filtrate was washed with 30 ml of saturated NaCl solution, then dried ($MgSO_4$) and distilled to give 1.07 g (83.6%) at 96–97° (15 mm). The product contained by ^1H nmr analysis 81% *cis*- and 19% *trans*-1-methyl-3-phospholanol (**3**).

Reduction of 1-Methyl-3-phospholanone (1) with Aluminum Isopropoxide. A mixture of 3.0 g (14.7 mmol) of aluminum isopropoxide and 120 ml of isopropyl alcohol at reflux was treated dropwise (30 min) with a solution of 1.45 g (12.5 mmol) of ketone **1** in 20 ml of isopropyl alcohol. The mixture was refluxed for 12 hr, and then 20 ml of solvent was removed by distillation. This distillate gave a strong positive test for acetone with 2,4-dinitrophenylhydrazine. The reaction was continued, with occasional removal of distillate for the acetone test. When the test was negative, the reaction was terminated and the volume was reduced to about 30 ml by distillation. The mixture was cooled and stirred with 1 ml of water for 1 hr, and then overnight with 30 ml of 1 *N* NaOH. The mixture was extracted with one 200-ml and two 50-ml portions of benzene. The benzene extract was dried

($MgSO_4$) and distilled to give 0.80 g (54%) of 4 at 96–100° (16 mm) (by ^1H nmr, 80% cis, 20% trans).

Reduction of 1-Methyl-3-phospholanone (1) with Sodium and Ethanol. Sodium sand (2.0 g, 87 mmol) in 100 ml of toluene at 5–10° was treated with 3.36 g (29.2 mmol) of ketone 1 in 4.0 g (87 mmol) of absolute ethanol at such a rate as to keep the temperature below 10°. After 2.5 hr at 10°, 15 ml of water was cautiously added. The toluene layer was removed, and the aqueous layer was extracted with two 40-ml portions of benzene. The organic fractions were combined and dried ($MgSO_4$); distillation gave 0.41 g (12.7%) of 4 containing a trace of starting ketone 1. The ^1H nmr spectrum showed the composition 79% *cis*- and 21% *trans*-1-methyl-3-phospholanol (3).

Thermal Equilibration of 1-Methyl-3-phospholanol Isomers. A neat specimen (78.7% cis, 21.3% trans) was heated in an oil bath maintained at 135°. The specimen was then placed in benzene and its ^1H nmr spectrum was recorded for determination of the isomer composition by the PCH_3 signal size. After 35 hr, the composition was 67% cis, 33% trans. After an additional 107 hr, the composition of the dark material was 51% cis, 49% trans. Further heating caused tar formation, and the experiment was terminated.

1-Methyl-3-acetoxyphospholane 1-Oxide (5) and 1-Methyl-3-acetoxyphospholane (6). Ten grams (75.8 mmol) of 1-methyl-3-phospholanone 1-oxide (2) was hydrogenated as above. The product was dissolved in 35 ml of pyridine, cooled to 0°, and treated with 5.86 g (74.7 mmol) of acetyl chloride. After 2 hr, the mixture was warmed to room temperature and the precipitated pyridine hydrochloride was filtered off. The filtrate was evaporated to dryness, placed in 30 ml of 1 *N* HCl, and extracted with six 50-ml portions of $CHCl_3$. The extracts were dried ($MgSO_4$) and distilled, giving 6.6 g (50.5%) at 126–128° (0.17 mm) which solidified on standing. The product was a mixture of cis (34%) and trans (66%) isomers: nmr ($CDCl_3$) δ 2.16 (d, $^2J_{PH}$ = 13.5 Hz, cis PCH_3), 2.22 (d, $^2J_{PH}$ = 13.5 Hz, trans PCH_3), 2.38–3.12 (complex m, ring CH_2), 2.51 and 2.54 (s, CH_3CO), 5.34–6.25 (complex m, OCH). The oxide mixture is very hygroscopic and difficult to purify. Analytical results are only partly satisfactory.

Anal. Calcd for $C_7H_{13}O_3P$: C, 47.71; H, 7.44. Found: C, 46.91; H, 7.75.

The oxide mixture was deoxygenated as described previously with trichlorosilane–triethylamine. Distillation gave 3.46 g (82.8%) of colorless liquid at 105–110° (12 mm); nmr ($CDCl_3$) δ 1.44 (d, $^2J_{PH}$ = 2.92 Hz, PCH_3 of cis isomer, 34%), 1.58 (d, $^2J_{PH}$ = 2.80 Hz, PCH_3 of trans isomer, 66%), 1.79–2.92 (complex m, ring CH_2), 2.44 and 2.45 (s, CH_3CO), 5.84 (m, OCH); ir (neat) $\nu_{C=O}$ 1740, ν_{CO} 1240 cm^{-1}. Various attempts to form quaternary salts for analysis of the isomer mixture have so far given only intractable oils.

Registry No.—1, 49849-35-6; 2, 21229-61-8; 3a, 51015-54-4; 3b, 51015-55-5; 3 methiodide, 51015-53-3; 4a, 51015-58-8; 4b, 51015-59-9; 5a, 51015-60-2; 5b, 51015-61-3; 6a, 51015-62-4; 6b, 51015-63-5.

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(1) Taken from the Ph.D. Dissertation of R. C. Stocks, 1973. Supported by Public Health Service Research Grant CA-05507 from the National Cancer Institute. The National Science Foundation provided funds toward the purchase of the Bruker spectrometer (Grant No. GP 10301).
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The Stereochemical Elucidation of the Birch Reduction Product of [2.2]Paracyclophane[1a]

James L. Marshall* and Ban-Huat Song[1b]

Department of Chemistry, North Texas State University, Denton, Texas 76203

Received December 5, 1973

The tetrahydro Birch reduction product of [2.2]paracyclophane is shown to be the *dl* stereoisomer (**2b**), with the olefins of the upper deck only partially overlapping with the olefins of the lower deck. This stereochemical elucidation is accomplished primarily by means of a complete proton nmr analysis of the tetraepoxide derivative **3**. The *dl* stereochemistry is in agreement with CNDO calculations performed on likely carbanion intermediates.

It has been recently shown[2,3] that the Birch reduction of [2.2]paracyclophane (**1**) gives the tetrahydro product **2** in which reduction has gone 2,5 in each deck. Although the structure elucidation of each deck of **2** was straightforward,[2,3] it was not possible to establish the overall stereochemistry of **2**, *i.e.*, whether the product was meso (**2a**) with each olefin in the upper deck overlying a corresponding olefin in the lower deck, or was *dl* (**2b**) with the olefins

Table I
Proton Nmr Parameters of the ABC Pattern Observed for 3[a,b]

δ_A[c]	δ_B	δ_C	J_{AB}[d]	J_{AC}	J_{BC}
3.03	2.49	1.95	6.79 ± 0.06	1.35 ± 0.06	−16.99 ± 0.06

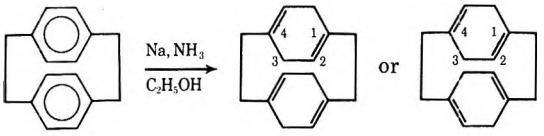
[a] For the partial structure which was assigned for these parameters, see 4. [b] The RMS error for this analysis was 0.09 Hz Probable errors as generated by the analysis are included in Table I. [c] In parts per million. [d] In hertz.

Table II
Proton Nmr Parameters of the AA'BB' Pattern Observed for 3[a]

δ_A[b]	δ_B	$J_{AA'}$[c]	$J_{BB'}$	$J_{AB'} = J_{A'B}$	$J_{AB} = J_{A'B'}$
2.34	1.35	12.11 ± 0.09	1.56 ± 0.08	6.48 ± 0.09	−14.94 ± 0.10

[a] The RMS error for this analysis was 0.10 Hz. Probable errors as generated by the iterative method are included in the Table. [b] In parts per million. [c] In hertz.

partially overlapping, or was a mixture of both isomers **2a** and **2b**. This paper describes the successful determination of the geometrical structure of 2 and discusses the probable mechanism for the reduction reaction.

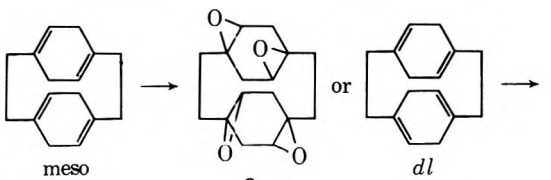


1 2a 2b

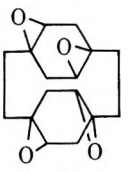
Structure Elucidation. The first step in elucidating the geometrical structure of 2 was to determine that 2 was only one isomer. The carbon magnetic resonance spectrum of 2 exhibited two olefin signals (at δ_{TMS} 137.4 and 125.6) and two aliphatic signals (at δ_{TMS} 44.0 and 38.0), consistent with either **2a** or **2b**. Since the carbon chemical shifts in **2a** and **2b** should be quite different for the respective methylene (C-3 and C-6) and olefin (C-2 and C-5) carbons,[4] it was evident that one isomer was preponderant.

It was reasoned that, if the geometry of 2 were meso (**2a**), then the two olefin pairs would be in a position ready for a [2 + 2] intramolecular cycloaddition.[5] However, photolysis of 2 under a variety of conditions resulted either in recovered starting material or in an untractable tar. Thus, indirect evidence was obtained that the geometry of 2 was *dl* (**2b**).

Next, a proton nmr study was conducted. Since the proton nmr of 2 could not differentiate between the two possible isomers **2a** or **2b** (see Experimental Section), a derivative of 2 was sought that would be amenable to a complete nmr analysis. It was found that epoxidation of 2 with excess peracid under carefully controlled conditions resulted in an isolable tetraepoxide derivative **3**, whose proton nmr was remarkably soluble for such a large mole-



meso 3a *dl*
2a 2b



3b

cule. The 100-MHz spectrum of **3** exhibited an ABC pattern with an AA'BB' pattern partially overlapping (see Figure 1). The ABC pattern was easily recognized as being generated by four equivalent systems in the two

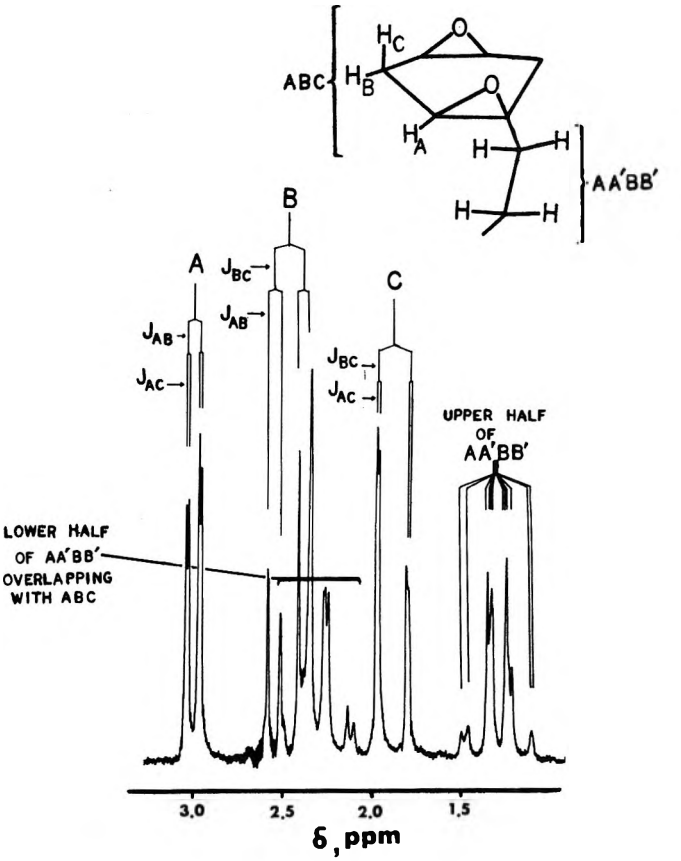
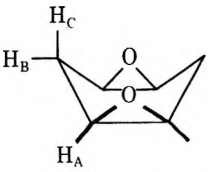


Figure 1. 100-MHz pmr spectrum of 3.

puckered rings, with $|J_{BC}| > |J_{AB}| > |J_{AC}|$, corresponding to an approximately eclipsing H_A-H_B pair and an approximately orthogonal H_A-H_C pair (see 4). The AA'BB' pat-



4

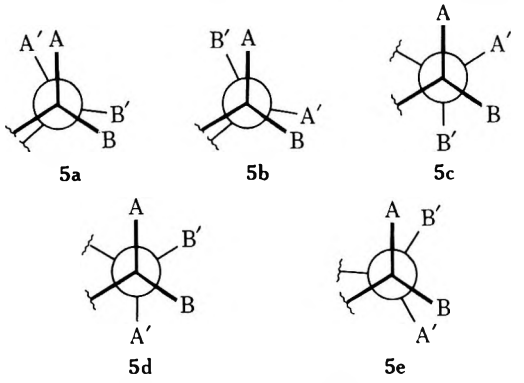
tern, caused by two equivalent $-CH_2CH_2-$ bridges, was partially obscured by the ABC pattern, but, since more than one complete half of the AA'BB' pattern was openly visible and since an AA'BB' pattern is perfectly bilateral,[6] a complete analysis of this pattern was possible. The ABC and AA'BB' patterns were analyzed separately by the iterative method[7] to give the parameters listed in Tables I and II. Recombination of the computed ABC and AA'BB' patterns gave the simulated spectrum shown in Figure 2.[8]

Table III
CNDO Calculations of the Radical Anions 12a and 12b with Varying Degrees of Puckering of the 1,4-Cyclohexadiene Ring[a]

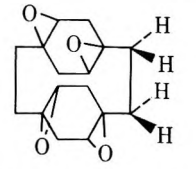
	Degree of Puckering, θ			
	0°	10°	20°	30°
12a (meso)	−0.0155	−0.1051	−0.1173	−0.1039
	(−9.72)	(−65.92)	(−73.57)	(−65.17)
12b (*dl*)	0.0000	−0.1076	−0.1228	−0.1117
	(0.00)	(−67.49)	(−77.02)	(−70.06)

[a] Values are given in atomic units (kilocalories in parentheses).

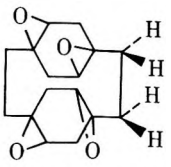
Although analysis of the ABC parameters gave in a straightforward manner the geometry of the involved nuclei (see **4**) and was independent of the stereochemistry of the overall compound, a corresponding analysis of the AA′BB′ parameters was more complex and proved ultimately to involve the overall stereochemistry and conformation of the complete molecule **3**. First in this analysis of the AA′BB′ parameters was the realization that the $-CH_2CH_2-$ bridge must be in a particular conformation. A consideration of the four possible eclipsed and staggered conformations (see the Newman projections **5a–d**)[9] clearly



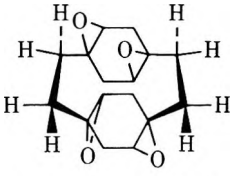
favored **5d**, in which A and A′, which were diaxial, coupled with a large J value. The quite different values of $J_{BB'}$ and of $J_{A'B}$ indicated that this staggered conformation was actually skewed somewhat (**5e**) so that the dihedral angle of H_B and $H_{B'}$ approached 90° while the dihedral angle of H_A and $H_{B'}$ and of $H_{A'}$ and H_B approached 0°.[10] Of all the possible overall structures and conformers of **3** (see **6a–f**), the only choice fitting this particular AA′BB′ disposition was **6f**, the *dl* isomer with the two $-CH_2CH_2-$ bridges staggered so as to give the molecule D_2 symmetry; all other possibilities (**6a–e**) could be ruled out. Structures **6a** and **6d** were eliminated because they would have the eclipsed arrangement of the AA′BB′ nuclei. Structure **6b** would not fit any of the AA′BB′ arrangements, since with all of its protons having different chemical shifts an ABCD pattern would result. Structure **6e** would have *two different* AA′BB′ patterns (the protons being disposed differently about the epoxide in the two bridges, the chemical shifts of the protons in the two bridges would differ). Finally, structure **6c** could be removed as a possibility because H_A and H_B would be diaxial (*i.e.*, **5c**).[11] Thus, the only remaining possibility was **6f**, the D_2 conformer of the *dl* staggered isomer.[12]


meso, eclipsed, C_{2h}

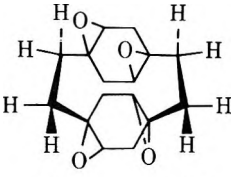
6a


dl, eclipsed, D_2

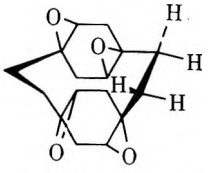
6d


meso, staggered, C_i

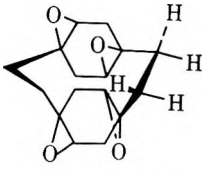
6b


dl, staggered, C_2

6e


meso, staggered, C_2

6c


dl, staggered, D_2

6f

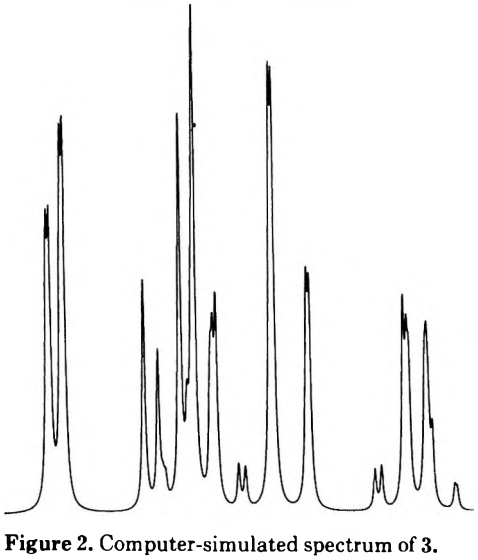
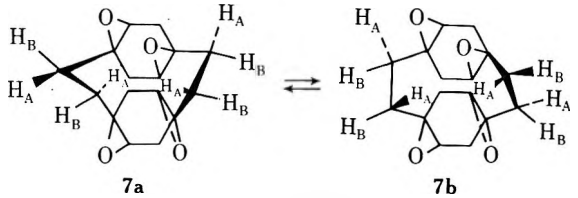


Figure 2. Computer-simulated spectrum of **3**.

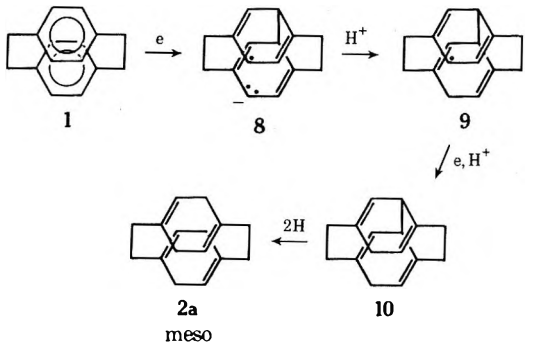
A brief consideration was made of the possibility of rapidly equilibrating conformers (*e.g.*, **7a** ⇄ **7b**),[13a] but this possible complication was ruled out by three compelling arguments. (1) The time-averaged spectrum of two rapid-



7a **7b**

ly equilibrating conformers would never have a large apparent J approximating J_{180}; at best the largest apparent J would be $J = \frac{1}{2}J_{60} + \frac{1}{2}J_{180}$. In fact, $J_{AA'}$ (see Table II) was clearly approximating J_{180}.[13b] (2) A time-averaged spectrum of two conformers would give rise to a higher order of identity in the parameters; for example, equilibrating **7a** and **7b** would give an apparent AA′BB′ system in which $J_{AA'} = J_{BB'}$, $J_{A'B} = J_{AB'}$, and $J_{AB} =$

Scheme I



$J_{A'B'}$. (3) It was observed that the proton nmr spectrum of 3 was unchanged down to −50°.

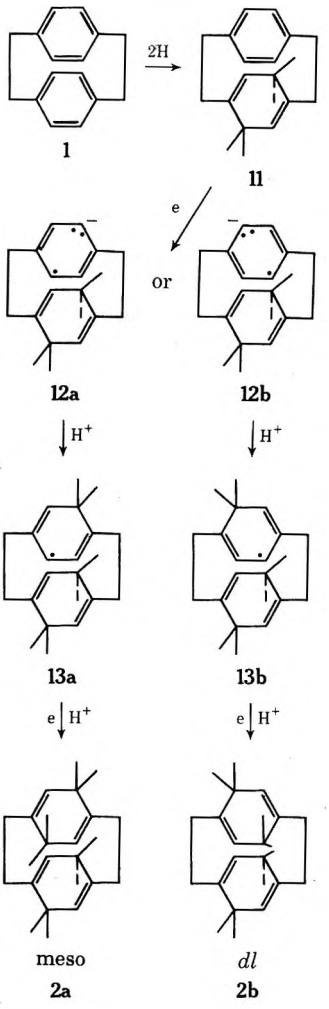
Thus, the proton nmr study of the tetraepoxide 3 indicated that the correct structure was *dl* (**3b**), thereby giving conclusive evidence that the structure of the Birch reduction production of [2.2]paracyclophane is *dl* (**2b**).

Two points are worthy of further discussion concerning the nmr analysis of **3**. First, the $J_{AA'}$ value corresponding to a diaxial arrangement of A and A′ (**5d**) is at first sight perhaps surprisingly large for two nuclei which are in fact somewhat skewed (**5e**).[14] However, there is evidence[15] that an electronegative substituent *vicinal* to a proton involved in vicinal coupling *increases* the J value. Thus, the observed $J_{AA'}$ is actually just about right for the proposed conformation.[16]

The second matter deserving comment concerns precisely in what D_2 conformation (**7a** or **7b**) the tetraepoxide **3** exists. Although it appeared certain that the isomer and conformer was the D_2 staggered *dl* structure, it was not immediately obvious whether the conformer was **7a**, with H_A of the $-CH_2CH_2-$ bridge lying away from the epoxide ring, or **7b**, with H_A lying over the face of the epoxide ring. It was frustrating to realize that in fact the complete nmr analysis, though resolving a number of vital questions, could not choose between two quite different conformers. The chemical shifts of H_A and H_B were left as the only means to decide between **7a** and **7b**, but unfortunately the literature is not settled concerning the magnetic anisotropy of the epoxide ring.[17,18] A tentative assignment, however, was made in favor of **7b** by means of the following argument. First, H_B (of AA′BB′) was assigned as the upfield proton at δ 1.35, because its geometrical relationship with the epoxide in either **7a** or **7b** was the same as H_C (of ABC) with the similar chemical shift of δ 1.95; *viz.*, these protons eclipsed the C–O bond of the epoxide ring.[19] Next, it was recognized that in **7a** the H_A proton (of AA′BB′) was in a geometrical relationship similar to that of H_B (of ABC) with the epoxide groups. It was further reasoned that, since H_B (of ABC) next to two epoxides is deshielded somewhat from H_C, then H_A (of AA′BB′) of **7a**, which is next to only one epoxide, should be deshielded but somewhat less. As a matter of fact, H_A (of AA′BB′) is deshielded much *more* than H_B (of ABC). On the other hand, in the other conformer **7b**, H_A (of AA′BB′) is quite close to the face of the epoxide ring, which might explain the large downfield shift. It was concluded, therefore, that the correct conformer was **7b** with H_A (of AA′BB′) over the face of the epoxide with the recognition that this conclusion rested upon the assumption that the face of the epoxide was a deshielding region.

Mechanism. Proposed mechanisms for the Birch reduction of [2.2]paracyclophane (**1**) involving classical formulations lead to faulty conclusions, *i.e.*, that the meso product **2a** should be produced. A reasonable mechanism involving such classical formulations with σ-bond participation between the two decks during the stepwise reduction of **1** is outlined in Scheme I. According to this scheme, an electron is first added to **1** to give the radical anion **8** with a σ bridge between the two decks. A proton is then added at the carbanion to give the radical **9**. A subsequent addition of an electron and a proton gives the bridged intermediate **10**; at this point, the geometry of the ultimate product has been determined to be meso. Addition of two more electrons and two more protons would reduce the σ bridge to give the final meso product **2a**.

Scheme II



A theoretical approach not involving such σ-bridge participation, however, is in agreement with the assigned structure **2b**. The most reasonable mechanism is outlined in Scheme II. According to this scheme, first one ring is reduced to give **11**. Then reduction of the second ring commences by the usual addition of an electron to give the radical anion **12**. At this point it is necessary to inquire whether C-2 or C-3 has the higher electron density[20] (represented by **12a** and **12b**, respectively), because the next step in the mechanism—the addition of a proton to give **13**—fixes irrevocably the geometry of the final product. Thus, a study was conducted on the anion **12** to see if theoretical considerations would support the contention that **12b** (which would ultimately lead to the observed final product **2b**) is more important than **12a**. This study involved the CNDO/2 calculations[21] of the relative stabilities of **12a** and **12b**, in which the upper deck was held flat and the lower deck was puckered. The degree of this puckering was varied from θ = 0° to 30° (θ was the dihedral angle of the two planes defined by the CH–CH_2–CH bonds and the two olefin bonds of the lower deck). Table III reports the results. The data suggest that the bottom

deck is puckered with $\theta \cong 20°$ and that in this conformation the *dl* radical anion **12b** is in fact more significant than the meso radical anion **12a**.[22]

Experimental Section

Melting points were determined by a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 237 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Jeolco JNM-MH-60 (Minimar) and a Jeolco JNM-PS-100, with tetramethylsilane as an internal reference. Elemental analyses were performed by C. F. Geiger, Ontario, Calif.

[2.2]Paracyclophane (1) was obtained from Aldrich Chemical Co., Milwaukee, Wis.

***dl*-Tricyclo[8.2.2^{1,10}.2^{4,7}]hexadeca-4,10,1(13),7(16)-tetraene (2b) (Tetrahydro[2.2]paracyclophane).** To a 1000-ml, three-necked flask cooled in a Dry Ice–acetone mixture and purged with nitrogen was added 1.424 g (0.00684 mol) of [2.2]paracyclophane (1), 400 ml of anhydrous tetrahydrofuran, 200 ml of distilled liquid ammonia, and 10.0 ml of anhydrous ethanol. Over a period of 1.5 hr, 2.3 g of sodium was added in small pieces while 10.0 ml more of anhydrous ethanol was added dropwise. The blue color persisted for 0.5 hr and the reaction mixture was quenched by the careful addition of 30 ml of water. After 20 min of stirring, the reaction mixture was allowed to warm to room temperature and to stand overnight. The organic layer was separated and the aqueous layer was extracted with 100 ml of ether. The combined organic layers were dried (anhydrous magnesium sulfate) and concentrated to give 1.393 g of crude **2b**. Sublimation of the product (100°, 30 mm) gave 1.316 g (93%) of **2b**: mp 121.0–123.5°; ir ($CHCl_3$) 794 cm^{-1}; proton nmr ($CDCl_3$) δ 2.3 (m, 16, methylene) and 5.3 (m, 4, olefin); carbon nmr δ_{TMS} 137.4, 125.6, 44.0, 38.0; mass spectrum *m/e* 212 (P).

Anal. Calcd for $C_{16}H_{20}$: C, 90.50; H, 9.49. Found: C, 90.44; H, 9.52.

Attempted Photolysis of 2. Photolysis of **2** by a number of different methods[23-26] resulted in either an untractable tar, unreacted starting material, or a mixture of both. Sublimation of the product gave no volatile material except unreacted **2**, with trace amounts (<5%) of [2.2]paracyclophane (**1**). Nineteen runs were executed.

Tetraepoxide of 2b (3b). Over a period of 1.5 hr, a solution of 2.20 g (0.0128 mol of 85% assay) of *m*-chloroperbenzoic acid in 50 ml of chloroform was added dropwise to a vigorously stirring mixture of 0.500 g (0.00235 mol) of **2b** in 15 ml of chloroform. The mixture was stirred and refluxed for 3 hr and then worked up in the usual manner.[27] The crude product was crystallized from carbon tetrachloride to give 0.420 g (65%) of white crystals, mp 287.0–289.5° dec, mass spectrum *m/e* 276 (P), nmr (see Tables I and II).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.32; H, 7.31.

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Registry No.—**1**, 1633-22-3; **2b**, 50921-78-3; **3b**, 50978-09-1.

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(8) To confirm the nmr parameters of Tables I and II, the spectrum of **3** was recorded and simulated also at 60 MHz. In this way several other possible combinations of the nmr parameters were conclusively ruled out.
(9) There are other degenerate possibilities with the A's and B's interchanged with no change in the bilateral AA′BB′ pattern. All possibilities, however, must have two hydrogens of equal chemical shift on vicinal carbons; there is no conformation of **3a** or **3b** (see **6a–f**) in which chemically equivalent protons are geminal.
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(11) These arguments hold when all the conformers **5a–d** are skewed. The critical feature of this analysis is that the largest vicinal coupling constant is of protons with the *same* chemical shift ($J_{AA'}$) and that the corresponding $J_{BB'}$ is very small. This realization eliminated all meso possibilities.
(12) Even when **6f** is skewed, the point group is still D_2.
(13) (a) In passing from **7a** to **7b**, the labels have been reversed; *e.g.*, the protons labeled as H_A in **7a** become labeled as H_B in **7b**. This is done so that the H_A's are always diaxial. (b) S. Sternhell, *Quart Rev., Chem. Soc.*, **23**, 236 (1969).
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(19) Because H_C (of ABC) eclipses two epoxides while H_B (of AA′BB′) eclipses one epoxide, this assignment presumes that the epoxide in this geometrical arrangement has little effect or is slightly deshielding. This assumption, however, is reasonable, because, if the anisotropic effect of the epoxide in this arrangement of the AA′BB′ protons were shielding, then H_B (of AA′BB′) should be downfield and must be accordingly assigned as the downfield signal at δ 2.34, which is an incredibly lowfield signal for a *shielded* proton.
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Synthesis of 2,9β-Dimethyl-6,7-benzomorphan[1]

Tokuro Oh-ishi,[2] Arthur E. Jacobson, Raymond S. Wilson, Herman J. C. Yeh, and Everette L. May*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20034

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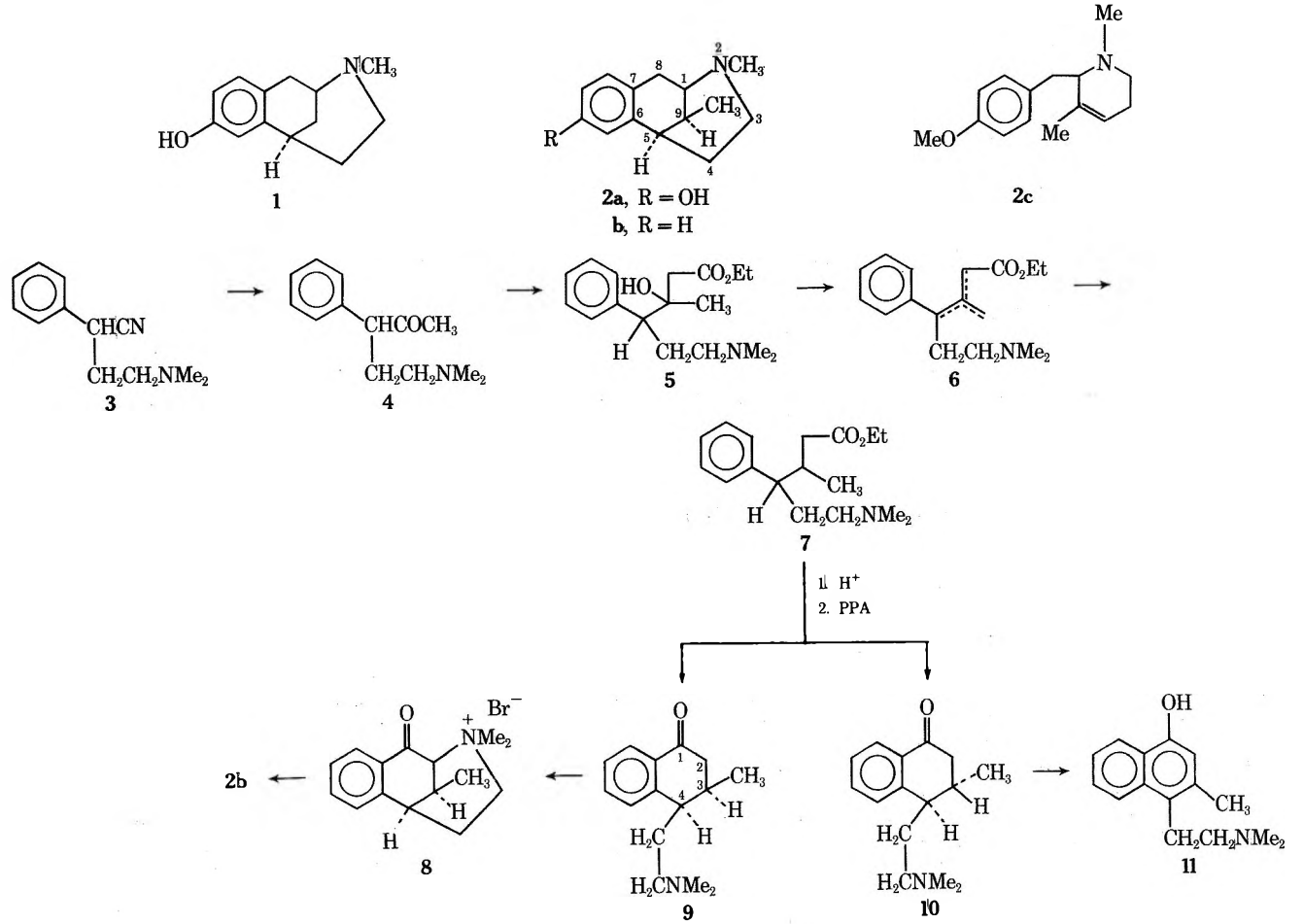
2,9β-Dimethyl-6,7-benzomorphan (**2b**) has been synthesized in 12 steps from phenylacetonitrile. The structure and configuration of **2b** and α-tetralone precursors **8** and **9** were deduced mainly from nmr data. Quaternization-rate studies with **2b** also indicated the 9β-methyl[1b] configuration. A diastereomeric (to **9**) α-tetralone, **10**, gave, instead of the expected 2,9α-dimethyl-6,7-benzomorphan, 4-(2-dimethylaminoethyl)-3-methyl-1-naphthol (**11**), obtained also as a by-product in the preparation of **8**. Compound **2b** has appreciable analgesic activity.

2′-Hydroxy-2-methyl-6,7-benzomorphan (**1**, without a quaternary carbon)[3] and its optical isomers are analgesics of moderate activity which possess, as well, properties of antagonism to narcotics.[4] Because of the demonstrated enhancing effect of a 9-methyl substituent on the analgesic activity of 2,5-dimethyl-2′-hydroxy-6,7-benzomorphan[5] we wished to examine the 9-methyl homolog (**2a**) of **1**. Attempts to synthesize **2a** by cyclization[6] of the appropriate tetrahydropyridine [in this case 1,3-dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine (**2c**)],[7] the usual route to 6,7-benzomorphans, failed. A 12-step sequence for the deoxy congener, **2b**, of **2a** has been developed and is described below.



Reformatsky product, **5**, was obtained in 50% overall yield by dimethylaminoethylation of phenylacetonitrile ($NaNH_2$), Grignard reaction (MeMgI) on the resultant **3**, and reaction of **4** with $BrZnCH_2CO_2Et$. Dehydration of **5** (*p*-TsOH-H_2O, refluxing C_6H_6, 1 week) afforded a mixture of olefins (90%) whose nmr spectrum did not rule out any of the structures indicated by **6** and which was reduced quantitatively to a mixture of diastereoisomers (**7**) with Pd. Hydrolysis of **7** with 6 *N* HCl and cyclization of the acid with polyphosphoric acid (PPA) at 100–110° gave a mixture of tetralones in 71% yield, separated as their HBr salts into **9** and **10** (4:1 ratio).

Bromination of **9** in acetic acid and neutralization of the resultant HBr salt with NH_4OH gave benzomorphan methobromide (**8**, 58%) and a low yield of the 1-naphthol **11**. Similar treatment of **10** gave no benzomorphan, simply aromatization to **11** (61%). Benzomorphan **2b** resulted (in 90% yield) from extrusion of MeBr from **8** (triethylene glycol, 195–200°) and subsequent Wolff–Kishner reduction.

The C-9 methyl protons of **2b** displayed their chemical shift at δ 1.32 (d, J = 7 Hz), typical of the 9β-methyl[1b] protons of 6,7-benzomorphans; the 9α-methyl signals are

known to appear about 0.8 ppm.[8] Further, the rate of formation of the methiodide **2b** approximated that of the 9β series. Thus, less than 15% of the base had reacted with methyl iodide during 24 hr (the 9α series generally shows 90–100% reaction in 24 hr).[8] The nmr spectrum of 8 indicated a definite downfield shift of the methyl group (δ 1.56) from that in **2b**, as might be expected from the deshielding effect of the ammonium cation, owing to its proximity to this methyl.

As **9** (not **10**) gave **8**, **9** must be the cis compound; only the cis isomer can cyclize to a 9β-methyl benzomorphan. The nmr data for **9** did not prove its cis stereochemistry. The spectrum of **9** shows a methyl group at δ 1.08 (d, J = 7 Hz). Decoupling of this C-3 methyl group from the C-3 proton clearly showed the C-3 proton as a doublet at δ 2.40. The coupling constant observed due to the coupling of the C-3 and C-4 protons (J = 4 Hz) is indicative of the axial–equatorial arrangement of these protons. It is noteworthy that the C-2 protons in **9** (and **10**) did not appear in the original spectra. These protons were found to rapidly exchange with deuterium (from the D_2O solvent used). The internal standard used, sodium 3-trimethylsilylpropionate-*2,2,3,3-d*$_4$ (TSP), was found to catalyze the exchange reaction. With sodium 3-trimethylsilylpropanesulfonate as the internal standard, or a fast spectral recording of **9** containing TSP, the C-2 protons centered at δ 2.64 (m) were clearly evident.[9]

Compound **2b** appears to be as active as codeine in preliminary animal testing.

Experimental Section

Melting points (Hershberg) are corrected. Infrared data are from a Perkin-Elmer 257, mass spectra from an Hitachi RMU-6E double-focusing spectrometer at 80 eV. Nmr spectra, at 60 MHz, were obtained on a Varian A-60 (TMS or TSP at δ 0.0 ppm as internal standard, D_2O as solvent unless otherwise specified); 100-MHz nmr spectra and decoupling experiments were done on a Varian HA-100. Spin decoupling was obtained in the conventional manner. A second radiofrequency field was obtained by side-band modulation using a Hewlett-Packard oscillator.

Ethyl 6-Dimethylamino-3-methyl-4-phenylhexanoate (Diastereoisomers, 7). To phenylacetonitrile (75 g, 0.64 mol), 50 g (0.47 mol) of $Me_2NCH_2CH_2Cl$, and 200 ml of C_6H_6 was added portionwise (stirring, below 40°) 20 g (0.54 mol) of $NaNH_2$. The mixture was refluxed for 1 hr and cooled. After addition of ice–H_2O the C_6H_6 layer was extracted with 10% HCl. The acid extracts were washed with C_6H_6, made alkaline with NH_4OH, and extracted with C_6H_6. Washing (H_2O), drying,[10] and evaporating the C_6H_6 gave 80.5 g (92%) of **3**, bp 100–107° (0.2 mm),[11] ir (neat) 2240 cm^{-1} (CN).

To the Grignard reagent (1.3 mol) prepared from 180 g of MeI, 31.2 g of Mg, and 350 ml of ether was added 80.5 g (0.43 mol) of **3** in 350 ml of toluene. Ether was distilled until vapor temperature was 100°; refluxing was continued for 7 hr. After cooling, NH_4Cl and H_2O were added. The organic layer was washed with H_2O, then refluxed for 30 min with 20% HCl. The acid layer was separated, made alkaline with NH_4OH, and extracted with ether. The ether was washed with H_2O, dried,[10] and evaporated to give 86.3 g (79.5%) of **4**, bp 89–90° (0.3 mm),[12] ir (neat) 1715 cm^{-1} (C=O).

To 67 g (1.0 mol) of Zn dust was added a small amount of $BrCH_2CO_2Et$ in methylal. Addition of a few iodine crystals initiated a vigorous reaction. Additional (total 114 g, 0.7 mol) $BrCH_2CO_2Et$ in 350 ml of methylal was added dropwise so as to maintain gentle refluxing. The mixture was refluxed for an additional 30 min. To this $BrZnCH_2CO_2Et$ solution was added 23.3 g of **4** in 50 ml of methylal while keeping the temperature below 30°. The mixture was stirred at room temperature for 1 hr, then refluxed for 3 hr and poured into 10% H_2SO_4. The acid layer was washed with C_6H_6, made basic with NH_4OH, and extracted with C_6H_6. The extract was washed with H_2O, dried,[10] and distilled to give 24.3 g (73%) of **ethyl 6-dimethylamino-3-hydroxy-3-methyl-4-phenylhexanoate (5)**: bp 153–155° (0.8 mm); M^+ m/e 293; ir (neat) 3500 (OH), 1730. 1715 cm^{-1} (sh, C=O).

Ester **5** (24.3 g, 0.08 mol), 31.6 g (0.17 mol) of *p*-TsOH·H_2O, and 300 ml of C_6H_6 were refluxed (H_2O separator) for 1 week, made alkaline with dilute NH_4OH, washed with H_2O, dried,[10] and evaporated to dryness, giving 20.7 g (91%) of **6**: bp 120–128° (0.3 mm); M^+ m/e 275; ir (neat) 1740, 1715, 1450 cm^{-1} (m).

6 (21.2 g), 100 ml of CH_3OH, and 5 g of Pd/C absorbed 1 molar equiv of H_2 during 3.5 hr to give a 95% yield of **7** (two diastereoisomers as shown by tlc): bp 127–133° (0.3 mm); M^+ m/e 277; ir (neat) 1735 cm^{-1}.

Cyclization (PPA) of 7. The **7** mixture (20.2 g) and 200 ml of 6 *N* HCl were refluxed for 4 hr and evaporated to dryness *in vacuo*. The residue and 200 g of PPA were kept at 100–110° for 3 hr. Ice–H_2O was added to the cooled mixture, which was then made alkaline with 40% KOH (or KOH pellets). The resultant oil was dissolved in ether, washed with H_2O, and dried.[10] Evaporation of the ether gave a fluorescent oil (13.8 g) which was distilled, yield 11.9 g (71%), bp 115–127° (0.2 mm). Treatment (in acetone) with 33% HBr–acetic acid gave crystals which were filtered and recrystallized from ethanol, giving 9.7 g (42%) of prisms of **cis-4-(2-dimethylaminoethyl)-3-methyl-3,4-dihydro-1(2*H*)-naphthalenone (9 HBr)**: mp 197–199°; M^+ m/e 231; ir (Nujol) 2650–2400, 1665 cm^{-1}; nmr (D_2O) δ 2.90 [s, $^+N(CH_3)_2$], 7.35–7.98 (m, aromatic, 4 H).

Anal. Calcd for $C_{15}H_{22}BrNO$: C, 57.7; H, 7.1; Br, 25.6; N, 4.5. Found: C, 57.5; H, 7.1; Br, 26.2; N, 4.2.

The filtrate from the 9.7 g of **9** HBr was evaporated to dryness. The residue crystallized from acetone, giving 2.3 g (10%) of thin plates of **10** HBr (trans isomer): mp 149–152°; M^+ m/e 231; ir (Nujol) 2700–2450, 1685 (sh), 1675 cm^{-1}; nmr δ 1.02 (d, J = 7 Hz, C-3 CH_3), 2.48 (m, C-2, 2 H), 3.0 [s, $^+N(CH_3)_2$], 7.3–8.04 (m, aromatic, 4 H), decoupled from C-3 CH_3 2.52 (d, J = 3 Hz, C-3 H).

Anal. Calcd for $C_{15}H_{22}BrNO$: C, 57.7; H, 7.1; Br, 25.6; N, 4.5. Found: C, 57.8; H, 7.2; Br, 26.2; N, 4.4.

2,9β-Dimethyl-8-oxo-6,7-benzomorphan Methobromide (8).[1b] The hydrobromide (9.7 g, 0.03 mol) of **9** in 50 ml of refluxing acetic acid was treated during 20 min with 5 g (0.03 mol) of bromine in 20 ml of acetic acid. After refluxing for an additional 10 min, the solution was evaporated to dryness *in vacuo* to give a syrup which was dissolved in 100 ml of ice–H_2O and neutralized by slow addition of 12 *M* NH_4OH (*ca.* 4 ml) under cooling. Extraction with ether, washing (H_2O), drying,[10] and evaporation of the ether gave an oil which was dissolved in CH_3OH. Brief refluxing and evaporation to dryness gave crystals which were recrystallized from absolute C_2H_5OH to give 8 (5.6 g, 58%) as prisms: mp 221–222° dec (with frothing); ir (Nujol) 1680 cm^{-1}; nmr δ 1.56 (d, J = 7.5 Hz, C-9 CH_3), 3.05 and 3.44 [s, $N(CH_3)_2$], 4.08 (m, C-1 H), 7.45–8.10 (m, aromatic, 4 H).

Anal. Calcd for $C_{15}H_{20}BrNO$: C, 58.1; H, 6.5; Br, 25.8; N, 4.5. Found: C, 58.3; H, 6.5; Br, 25.8; N, 4.3.

The filtrate contained a mixture of **8** and **11** HBr (see below).

4-(2-Dimethylaminoethyl)-3-methyl-1-naphthol (11) Hydrobromide. As described in the preparation of **8**, 1.0 g of **10** HBr gave (after heating the base of the bromo ketone in acetone) 630 mg (61%) of the HBr salt of **11**, mp 262° dec, ir (Nujol) 3280 cm^{-1} (OH). The nmr spectrum was consistent with structure **11**.

Anal. Calcd for $C_{15}H_{20}BrNO$: C, 58.1; H, 6.5; N, 4.5. Found: C, 58.1; H, 6.2; N, 4.3.

2,9β-Dimethyl-8-oxo-6,7-benzomorphan Hydrochloride.[1b] Triethylene glycol (36 ml) and 3.6 g of **8** were kept at 195–200° for 20 min, treated with H_2O, and made basic with 12 *M* NH_4OH, giving an oil which was dissolved in ether. The ether was washed with water, dried,[10] and evaporated. The resultant oil was distilled (bp *ca.* 115°, bath temperature 150°), yield 2.2 g (89%), mp 74–77° (yellow rods from hexane). The HCl salt (from *i*-PrOH–HCl) melted at 225–229° dec, ir (Nujol) 1680 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.8; H, 7.2; Cl, 14.1; N, 5.6. Found: C, 66.6; H, 7.1; Cl, 14.1; N, 5.5.

2,9β-Dimethyl-6,7-benzomorphan (2b) Hydrochloride. Hydrazine–H_2O (2.5 ml), 2.2 g of the 8-oxo base above, 2.5 g of KOH, and 50 ml of triethylene glycol were heated at 170–180° as low-boiling substances were distilled. Then the mixture was kept at 195–205° for 4 hr, diluted with H_2O, and extracted with ether. The ether was washed with H_2O, dried, and evaporated, giving an oil, **2b**, which was distilled evaporatively at 0.2 mm (bath temperature 140°). The 1.8 g of colorless oil was converted to the hydrochloride with MeOH–HCl. Evaporation of solvent and crystallization of the residue from *i*-PrOH gave needles (1.6 g, 66%): mp 251–255° dec; M^+ m/e 201; nmr (base, $CDCl_3$) δ 2.34 (s, NCH_3), 7.0–7.3 (m, aromatic, 4 H).

Anal. Calcd for $C_{14}H_{20}ClN$: C, 70.7; H, 8.5; Cl, 14.9; N, 5.9. Found: C, 70.7; H, 8.5; Cl, 14.7; N, 5.7.

This compound underwent quaternization with methyl iodide at a very slow rate, less than 15% of base having reacted at room temperature after 24 hr.[8]

Registry No.—**2b** HCl, 50599-89-8; **3**, 50599-78-5; **4**, 50599-79-6; **5**, 50599-80-9; **6**, 50679-04-4; **7** isomer A, 50599-87-6; **7** isomer B, 50599-88-7; **8**, 50599-86-5; **9**, 50599-84-3; **9** HBr, 50599-85-4; **10** HBr, 50599-83-2; **11** HBr, 50599-81-0; phenylacetonitrile, 140-29-4; 2-dimethylaminoethyl chloride, 107-99-3; 2,9β-dimethyl-8-oxo-6,7-benzomorphan, 51096-41-4; 2,9β-dimethyl-8-oxo-6,7-benzomorphan hydrochloride, 50599-82-1.

References and Notes

(1) (a) Chemical Abstracts name: 3,11β-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine. (b) The β designation relates to the hydroaromatic ring.
(2) Visiting Associate of Tanabe Laboratories, Tokyo, Japan.
(3) K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 405 (1969).
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(5) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).
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(9) R. S. Wilson, H. J. C. Yeh, T. Oh-ishi, and A. E. Jacobson, unpublished results.
(10) Over Na_2SO_4.
(11) E. Tagman, E. Sury, and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).
(12) W. Wilson, *J. Chem. Soc.*, 6 (1952), prepared **4** in 57% yield from $PhCH_2COMe$, $NaNH_2$, and $Me_2NCH_2CH_2Cl$.

Structure and Chemistry of the Aldehyde Ammonias. II. Phenylacetaldimines, Styrylamines, and 2,4,6-Tribenzyl-1,3,5-hexahydrotriazines

Arnold T. Nielsen,* Ronald L. Atkins,[1] John DiPol, and Donald W. Moore

Organic Chemistry Branch, Chemistry Division, Code 6056, Michelson Laboratory, Naval Weapons Center, China Lake, California 93555

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Reaction of phenylacetaldehyde, hydratropaldehyde, and diphenylacetaldehyde with ammonia in methanol or ether at −15° leads to 2,4,6-tribenzyl-1,3,5-hexahydrotriazines **2a–c**. Two of these products had been described by others as hydratropaldimine and diphenylacetaldimine. The platinum-catalyzed hydrogenation of 2,2-diphenyl-1-nitroethene gave 2,2-diphenylethenamine, not diphenylacetaldimine as previously reported. Oxidation of triazines **2a** and **2b** with *tert*-butyl hypochlorite gave 2,4,6-tribenzyl-1,3,5-triazabicyclo[3.1.0]hexanes **3a** and **3b**. The stereochemistry of triazines **2a–c** and oxidation products **3a** and **3b** was established from ^1H and ^{13}C nmr spectra. Thermolysis of triazines **2a–c** in aprotic solvents was followed by nmr spectroscopy; the principal initial products are ammonia and *N,N'*-distyryl-1,1-diamino-2-phenylethanes (**5a–c**). Prolonged heating of triazine **2c** or 2,2-diphenylethenamine gave bis(2,2-diphenylethen)amine (**6c**). 5,5-Diphenyl-2-(diphenylmethyl)-3-oxazoline (**14**) was isolated as a minor product of the reaction of diphenylacetaldehyde with methanolic ammonia.

Accounts of the synthesis of unsubstituted aldimines, RCH=NH, from aldehydes and ammonia are found in the literature.[2-13] However, recent reexamination of some of these reports has established that unsubstituted aldimines of this type cannot be isolated as stable free bases.[14-16] Rather, their self-reaction occurs extremely rapidly, leading to other products such as 2,4,6-trisubstituted 1,3,5-hexahydrotriazines and diimines, $(RCH{=}N)_2CHR$.[7,14-19] Unsubstituted aldimines often are described as reaction intermediates, *e.g.*, in photolysis of azides and primary aliphatic amines, and in reduction of oximes.[20-23]

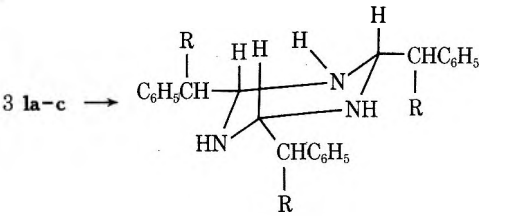
Reactions of hydratropaldehyde and diphenylacetaldehyde with ammonia have been reported by several workers to produce white crystalline solids described as monomeric aldimines **1b** and **1c**, respectively.[6,10,12,13]

$$C_6H_5CH(R)CHO + NH_3 \longrightarrow C_6H_5CH(R)CH{=}NH + H_2O$$

1a, R = H
b, R = CH_3
c, R = C_6H_5

Aldimine **1c** has erroneously been described as a product of hydrogenation of 2,2-diphenyl-1-nitroethene.[9] An unstable solid ammonia derivative of phenylacetaldehyde has been reported, but it could not be purified and its molecular formula was not established.[24] Enamine 2-phenyl-2-methylethenamine has been described as the product of reaction of hydratropaldehyde with ammonia in ethyl acetate solvent;[25] Witkop describes it as imine **1b**.[12]

In the present work the reactions of phenylacetaldehyde, hydratropaldehyde, and diphenylacetaldehyde with ammonia at low temperature were found to produce 2,4,6-tribenzyl-1,3,5-hexahydrotriazines **2a–c**, not aldimines **1a–c** nor the corresponding enamines. These reac-



2a, R = H
b, R = CH_3
c, R = C_6H_5

tions were usually conducted in methanol or ether solvent with a slight excess of ammonia at *ca.* −15° for a few days. Isolated products are white, crystalline solids obtained in variable yields (Table I). Only **2a**, derived from phenylacetaldehyde, forms a stable hydrate ($3H_2O$). Anhydrous **2a** was prepared and its trihydrate formation is reversible. These results agree with previous findings that 2,4,6-tris(*n*-alkyl)-1,3,5-hexahydrotriazines derived from *n*-alkanals form stable trihydrates whereas a 2,4,6-triisopropyl derivative obtained from the α-substituted isobutyraldehyde does not.[14] Repetition of earlier work said to produce **1b** and **1c** or the corresponding enamines gave

Table I
2,4,6-Tribenzyl-1,3,5-hexahydrotriazines

Compd	R	Yield, %[a]	Mp, °C[b]	Molecular formula
2a	H		62–69	$C_{24}H_{27}N_3$
2a·$3H_2O$	H	9.6[c]	60–64	$C_{24}H_{27}N_3 \cdot 3H_2O$
2b	CH_3	79	111–112[d]	$C_{27}H_{33}N_3$
2b′	CH_3		144–150[e]	$C_{27}H_{33}N_3$
2c	C_6H_5	34	82–88[f]	$C_{42}H_{39}N_3$
2c′	C_6H_5		105–110[e]	$C_{42}H_{39}N_3$

[a] Yield of isolated form having melting point listed. [b] Capillary melting points of analytical samples; melting occurs with decomposition and depends on the method of determination (Kofler or capillary) and on the rate of heating.[6] [c] An additional 90% yield of crude product was isolated, mp 45–60°. [d] Lit. mp 114° for sample recrystallized from ethanol (rapid heating); mp 104–105° (slow heating rate);[6] mp 110–112° (crude product), 114–115° after recrystallization from ethanol;[10] mp 98–105°, 95–112°, 96–102° on crude samples prepared in different solvents;[12] mp 100–105° on sample recrystallized from ethanol.[12] [e] Polymorph obtained by heating **2b** or **2c** in methanolic potassium hydroxide; for **2b′** lit. mp 143–145°, 143–147°,[10] 135–137°.[12] [f] Lit. mp 75–82°, 88–89°, 89°, 91° on samples prepared in different solvents.[12,13]

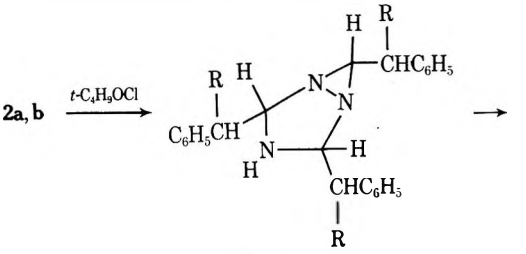
products identical with those described in Table I.[6,10,12,13,25,26]

Structures **2a–c** are supported by the following: molecular formula, spectral data, and chemical behavior. Molecular weights determined by vapor phase osmometry on chloroform or benzene solutions of anhydrous samples indicate a trimeric aldimine structure. Surprisingly, previous workers[6,10,12,13] did not report molecular weight determinations for their products of reaction of aldehydes with ammonia—with the exception of 2-phenyl-2-methylethenamine.[25,26] The infrared spectra determined on pure samples of **2a–c** in Nujol mulls or freshly prepared carbon tetrachloride or chloroform solutions reveal strong NH bands (3270 cm^{-1}) but no C=N bands. However, solutions of **2c** are unstable and in chloroform a C=N band (1670 cm^{-1}) appears rapidly on standing at room temperature; after *ca.* 15 min the 1670-cm^{-1} band is replaced by an enamine C=CN band at 1640 cm^{-1}. The presence of C=N bands at 1661, 1664, and 1668 cm^{-1} in chloroform solutions of diphenylacetaldehyde and hydratropaldehyde ammonias was used by Witkop as evidence to support aldimine structures **1b** and **1c**.[12]

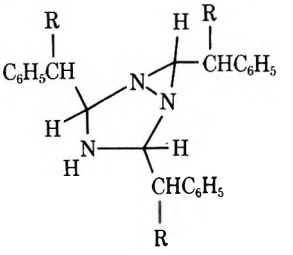
The ^1H and ^{13}C nmr spectra of **2a–c** in various solvents support the assigned structures, including stereochemistry. A broad NH signal is observed which is shifted to the HOD region by addition of D_2O (three protons). The simple proton spectra of **2a** and **2c**, revealing a single ring CH signal, indicate an all-equatorial configuration of the 2,4,6 substituents in agreement with previous results for 2,4,6-trialkyl-1,3,5-hexahydrotriazines.[14] The ^{13}C nmr spectra of **2a** and **2c** are in agreement with this assignment, revealing single peaks for ring and benzyl carbons. Although compound **2b** would also be expected to have all-equatorial 2,4,6-ring substituents, the multiplicity of the observed ^1H and ^{13}C nmr peaks shows the sample to be a mixture of three, possibly four epimers. It is the first reported 1,3,5-hexahydrotriazine having chiral ring substituents. Several all-equatorial **2b** diastereoisomers having similar properties are possible, since epimerization in the ring substituent cannot occur under the reaction conditions. Even more vigorous reaction conditions fail to effect epimerization (*vide infra*).

Interesting and unique behavior is exhibited by triazines **2b** and **2c** in refluxing methanolic potassium hydroxide. A higher melting form **2b′** is produced, mp 144–150°, in agreement with previous findings (Table I).[10,12] Its properties, except for melting point, appear indistinguishable from those of the lower melting form. Interconversion of the two forms occurs readily. Dissolving it in chloroform, followed by solvent removal, leads to recovered low-melting **2b**. Triazine **2c** in refluxing methanolic potassium hydroxide produces a higher melting isomer **2c′**, mp 105–110°. Triazine **2a** is decomposed rapidly by this treatment. It is suggested that forms **2b,b′** and **2c,c′** are polymorph pairs, distinguished possibly by configurations of one or more NH groups in the crystal.[27] The polymorph pairs **2b,b′** appear not to differ in epimer composition. Isomerization by epimerization at the benzyl carbon cannot be involved in the interconversion **2b** ⇄ **2b′** since heating **2b** in methanol-*O*-*d*-KOD produced **2b′** (after washing with water) having no CD bonds (ir and ^1H nmr spectra). The thermal stability order in hot methanolic potassium hydroxide is **2b** > **2c** > **2a** (in contrast to the stability order in aprotic solvents, where **2a** is more stable than **2c**). The stability of **2b** and **2c** in hot methanolic potassium hydroxide contrasts with the instability of these substances in hot neutral solvents. This result suggests that the facile thermolysis of **2a–c** in solutions containing no added base is autocatalytic and/or catalyzed by solvent (alcohol) acting as an acid; this catalysis would be repressed in strongly basic media.

Additional evidence supporting the structure of triazines **2a** and **2b** was obtained by *tert*-butyl hypochlorite oxidation to 2,4,6-tribenzyl-1,3,5-triazabicyclo[3.1.0]hexanes **3a** and **3b** with C-2, C-4 trans stereochemistry. These



cis-**3a**, R = H
cis-**3b**, R = CH_3



trans-**3a**, R = H
trans-**3b**, R = CH_3

NH_3 ↑ NH_2Cl

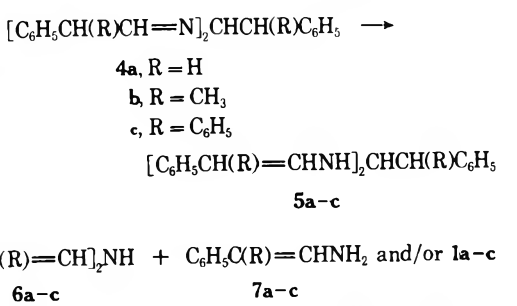
$C_6H_5CH(R)CHO$

products were also obtained by the Schmitz reaction from the required aldehyde and chloramine.[28] Attempts to prepare 2,4,6-tris(diphenylmethyl)-1,3,5-triazabicyclo[3.1.0]hexane (**3c**, R = C_6H_5) from **2c** by oxidation or from diphenylacetaldehyde by the Schmitz reaction were unsuccessful. The C-2, C-4 groups in **3a** and **3b** were observed to have trans stereochemistry; this fact is evident from the ^1H and ^{13}C nmr spectra of these compounds, which reveal separate signals for the C-2,4,6 carbons and their attached protons. Cis isomers **3a** and **3b** are the expected initial products from all-equatorial **2a** and **2b**. These are unstable intermediates, however, since it has been established that the cis → trans epimerization of

2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes occurs rapidly and completely in the reaction medium in those examples where the 2,4,6 substituents are large.[14,29] The ^1H and ^{13}C spectra of *trans*-**3b** indicate that it, like its precursor **2b**, is a mixture of three or four epimers owing to the chiral ring substituents.

Triazines **2a–c** are relatively unstable materials with properties similar to those of known 2,4,6-trialkyl-1,3,5-hexahydrotriazines.[14] They may be stored at −15° for extended periods, but at room temperature they evolve ammonia to produce brown, amorphous solids.[6] The thermal stability order of the anhydrous compounds or their solutions is **2b** > **2a** > **2c**.

Heating **2a–c** under reflux in aprotic solvents such as chloroform, benzene, or toluene produces ammonia (1 molar equivalent in *ca.* 1–1.5 hr); removal of the solvent after this period of heating yields oils believed to contain principally bis enamines **5a–c** (tautomers of diimines **4a–c**) and polymers thereof. Prolonged heating of **2c** gave

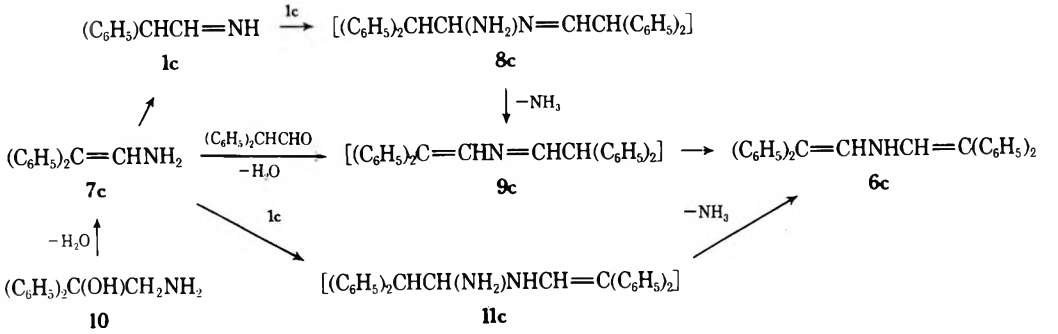


bis(2,2-diphenylethen)amine (**6c**, R = C_6H_5) by cleavage of **5c**. (This result was interpreted by Witkop as a dimerization reaction of imine **1c**.[12]) 2,2-Diphenylethenamine **7c** and/or imine **1c** would be expected as the other products of **5c** cleavage, but **7c** should readily tautomerize to the corresponding imine (**1c**) and ultimately be consumed in a repeating chain sequence: **7** → **1** → **2** → **4** → **5** → **6** + **7**. Bis(2-methyl-3-phenylethen)amine (**6b**, R = CH_3, mp 120°) has been reported to form from **2b** (our assignment) in methanolic formic acid;[25] we have been unable to repeat this experiment, however. Behavior contrasting to that of **2a–c** is observed with 2,4,6-trialkyl-1,3,5-hexahydrotriazines during thermolysis in refluxing cyclohexane; the products are not enamines but diimines (high yields of **4**; C_6H_5 = alkyl; R = H or alkyl).[14] Phenyl conjugation favors enamine tautomers **5**, **6**, and **7** over imine tautomers **4** and **1**.

Evidence for intermediates **4a–c** and **5a–c** was obtained by following changes in the proton nmr spectra.[30] Transient formation of diimines **4a–c** occurs on heating dilute chloroform, benzene, or toluene solutions of **2a–c** at 60–70° for short periods (10–30 min). Weak signals appear at *ca.* δ 4.4, 5.3, and 5.4 assigned to =NCHN= protons in **4a**, **4b**, and **4c**, respectively, by analogy with the nmr spectra of known diimines [$(RCH{=}N)_2CHR$, R = alkyl].[14] These signals disappear during longer periods of heating (1–3 hr at 60–70°) with formation of relatively high concentrations of new products believed to be **5a–c** [strong signals near δ 6.5–6.7 (=CH) and 4.2–5.0 (HNCHNH)]. Removal of solvent from the solution containing principally **5c** gave an oil [λ_{max} 285 nm (ε 20,800) in methylcyclohexane; a band near 360 nm is absent; 2,2-diphenylethenamine (**7c**) has λ_{max} 283 nm (ε 15,000) and **6c** has λ_{max} 362 nm (ε 30,000)]. Formation of acetophenone on ozonolysis of cyclohexane solutions of **2b** (our assignment) agrees with structures **5b**, **6b**, or **7b** and suggests decomposition of **2b** into one or more of these products during the reaction.[25] Prolonged heating of **2a–c** yields products in which nonvinylic benzylic protons are absent and only phenyl and vinyl =CH signals are present in their nmr spectra (principally **6a–c**, **7a–c**, and polymers).

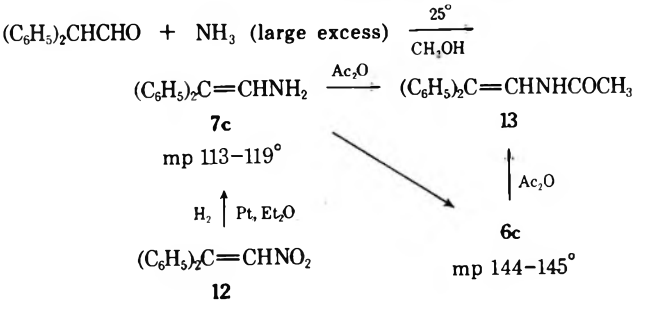
Bis(2,2-diphenylethen)amine (**6c**), a thermolysis product of **2c**, is encountered as a product of several other reactions. For example, reaction of diphenylacetaldehyde with aqueous or methanolic ammonia (slight excess) at *ca.* 25° deposits crystals of **6c** (mp 144–145°) in 18–50% yield;[10,13,31] however, at −15° triazine **2c** is formed. The formation of **6c** at the higher reaction temperature could be interpreted as a decomposition reaction of initially formed **2c** (**2c** → **4c** → **5c** → **6c**). Alternatively, it could involve dimerization of **1c** to diamine **8c**, followed by deamination of the latter. Reaction of diphenylacetaldehyde with 2,2-diphenylethenamine (**7c**) yields **6c**; however, this result is obscured by the fact that **7c** alone also forms **6c** under similar conditions. Enamine imine **9c** could be an intermediate in these transformations.

2,2-Diphenylethenamine (**7c**), by heating in ethanol or without solvent, or by treatment with ethereal hydrogen bromide at 25°, yields ammonia and **6c**.[12,13,30] Heating 2,2-diphenyl-2-hydroxy-1-aminoethane (**10**, a **7c** precursor) in refluxing benzene with phosphorus pentoxide leads to **6c** in 76% yield.[32] These reactions are believed to involve the tautomeric imine **1c**, either by its dimerization to **8c**, or reaction with **7c** to yield diamine **11c**. Bis enamine **6c**



was discovered by Lipp, who obtained it as a product of aluminum amalgam reduction of 1,1-diphenyl-2-nitroethane (**12**).[33]

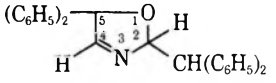
2,2-Diphenylethenamine (**7c**, mp 113–119°) was prepared by passing a large excess of ammonia gas into methanolic diphenylacetaldehyde solution at 25° for 12 hr.[13] Its molecular formula and spectra support the struc-



ture assignment. Earlier claims of preparation of **7c** appear to be erroneous. A compound described by Krabbe as **7c** has a reported melting point much higher than that of authentic **7c**.[10,26] Its reaction with acetic anhydride gave *N*-acetyl-2,2-diphenylethenamine (**13**), which result was taken as evidence of precursor structure **7c**.[26] However, we have found that bis enamine **6c** reacts with acetic anhydride (as does authentic **7c**) to produce **13**. It is concluded that Krabbe's compound is **6c** not **7c**.

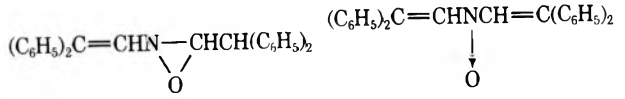
Hydrogenation of 2,2-diphenyl-1-nitroethene (**12**) in ether solvent with platinum catalyst has been reported to yield diphenylacetaldimine (**1c**).[9] We have repeated this experiment and find this product to be enamine **7c**, formed in nearly quantitative yield. A report of the preparation of 2-phenyl-2-methylethenamine [C_6H_5-$C(CH_3)$=$CHNH_2$, **7b**] by reaction of hydratropaldehyde with ammonia is also believed to be erroneous.[25] The product is triazine **2b**.

A new product of reaction of diphenylacetaldehyde with ammonia was encountered in the present study. Reaction with methanolic ammonia by the procedure of Curtin[13] gave, in addition to 2,2-diphenylethenamine (**7c**, 69% yield), a white, crystalline material, $C_{28}H_{23}NO$, mp 125–127°, in *ca.* 5% yield. Spectral data and chemical behavior support the assigned structure, 5,5-diphenyl-2-(diphenylmethyl)-3-oxazoline (**14**), a new derivative of the rarely encountered 3-oxazoline ring system.[34-36] The infrared

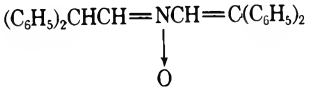


14

spectrum reveals absence of NH and C=O bands; a weak C=N band appears at 1630 cm^{-1} (Nujol). Styrene-derived structures **15**–**17** cannot be considered, since strong ultraviolet absorption near 300 nm is absent. The ^1H nmr



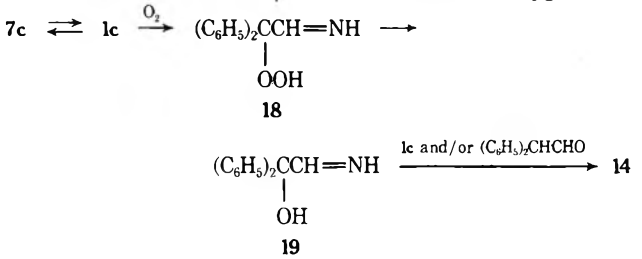
15 **16**



17

spectrum is in agreement with a CH=NCHCH grouping; the C-2 ring proton signal appears as a split doublet (δ 6.44, J = 5 Hz) owing to additional long-range coupling with the C-4 vinyl proton (δ 7.78, d, J = 2.5 Hz); the exocyclic benzyl proton appears as a doublet at δ 4.48 (J = 5 Hz). The proton-coupled and decoupled ^{13}C nmr spectra also support structure **14**. In the proton-coupled spectrum the C-4 vinyl ring carbon (δ 163.5) appears as a doublet, the C-2 ring carbon (δ 107.4) appears as a singlet with weak splitting indicating a quaternary carbon with adjacent CH, and the C-5 ring carbon appears as a singlet (δ 95.3). The exocyclic benzyl carbon appears as a doublet (δ 56.1). Acid hydrolysis of **14** gave diphenylacetaldehyde.

One possible route to oxazoline **14** could proceed by oxidation of imine tautomer **1c**. Reaction of oxygen with

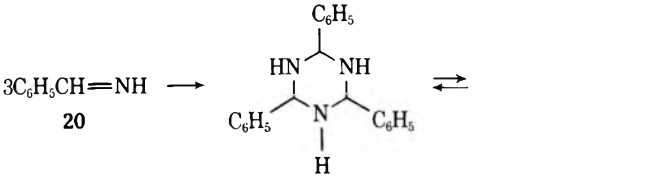


18

19

phenylacetaldehyde-derived Schiff bases occurs rapidly in solution without added catalyst to produce C-2 hydroperoxy derivatives.[12] Decomposition of hydroperoxide **18** could yield hydroxyimine **19**, a reaction facilitated in alcohol solvents;[37] a covalent hydrate or amminate of **19** [$(C_6H_5)_2C(OH)CH(OH)NH_2$ or $(C_6H_5)_2C(OH)CH(NH_2)_2$] could also be an intermediate. The reaction of β-amino alcohols with aldehydes or of α-hydroxy ketones with ammonia yields 3-oxazolines.[34-36]

A product obtained by ammonolysis of hydrobenzamide (**22**) in liquid ammonia which has been described as benzaldimine (**20**) is possibly 2,4,6-triphenyl-1,3,5-hexahydrotriazine (**21**).[7] It loses ammonia readily to regenerate hydrobenzamide, as does **21**, a very unstable substance said to form from benzaldehyde in methanolic ammonia at −10°.[38] Owing to their instabilities, these materials have been poorly characterized and their molecular weights could not be accurately determined.[7,38] Attempts to prepare benzaldimine from its salts gave hydrobenzamide.[17]



20 **21**

$(C_6H_5CH{=}N)_2CHC_6H_5 + NH_3$

22

It is concluded from our studies of the aldehyde ammonias that unsubstituted aldimines (RCH=NH; R = alkyl, aryl), although able to exist at low concentrations in solution or the vapor phase, are too reactive to permit isolation of the pure free bases. We have examined the reaction of three phenylacetaldehydes with ammonia and isolated several products; none have the aldimine structures previously reported.

Experimental Section[39]

Aldehydes. Phenylacetaldehyde, hydratropaldehyde, and diphenylacetaldehyde were commercial samples, reagent grade, distilled immediately before use.

2,4,6-Tribenzyl-1,3,5-hexahydrotriazine Trihydrate (2a-3H$_2$O). Phenylacetaldehyde (50.0 g, 0.416 mol) was added dropwise with stirring to 50 ml of 9 *M* methanolic ammonia during 15 min (reaction temperature of 2–5° maintained during addition by ice-bath cooling). The clear solution was stored at −15° for 4 days, then treated with 1.5 ml of water and 5 ml of ether. After storage at −15° for 3 weeks, crystals were removed by filtration and washed successively with cold aqueous methanol and isopentane to yield 4.8 g (9.6%) of **2a** trihydrate as chunky, white prisms: mp 60–64° dec; ir (Nujol) 3250 cm^{-1} (broad) OH and NH, C=O and C=N bands absent; ^1H nmr (C_5D_5N) δ 7.00 (15, m, C_6H_5), 3.67 (3, t, J = 6 Hz, CH), 2.55 (6, d, J = 6 Hz, CH_2), 3.0–4.0 [9, broad s, NH and H_2O, disappeared on addition of D_2O to produce a signal at δ 5.17 (9, s, OH)]. Elemental analysis for nitrogen was determined by dissolving a rapidly weighed sample in a mixture of 1 *N* hydrochloric acid (excess) and ethanol and titrating with 1 *N* sodium hydroxide.

Anal. Calcd for $C_{24}H_{27}N_3 \cdot 3H_2O$: N, 10.21. Found: N, 10.0.

The filtrate remaining from removal of the first crop (excluding washings) was diluted with 250 ml of cold 15 *M* aqueous ammonia. After storage at 0° for 3 months there was obtained 45 g (90%) of crude **2a** trihydrate as slightly gummy, chunky, white crystals, mp 40–65° dec, which could not be recrystallized without decomposition. In another procedure anhydrous ammonia was bubbled into a solution of phenylacetaldehyde (**2g**) in 20 ml of ether for 1 hr at 0°. After storage at −15° for 2 months there was obtained 0.54 g (27%) of crude **2a** trihydrate, mp 45–65° dec.

2,4,6-Tribenzyl-1,3,5-hexahydrotriazine (2a). Triazine **2a** trihydrate (2.0 g) was added to 10 ml of benzene at room temperature. Water which separated (0.25 ml) was removed and the benzene solution was dried briefly with Drierite. Filtration, followed by rapid removal of solvent under reduced pressure at 25°, gave

1.6 g (90%) of anhydrous **2a**, mp 61–67° dec. Recrystallization from hexane gave prisms (50% recovery): mp 62–69° dec; ir (Nujol) 3200 cm^{-1} (sharp, NH), C=O and C=N bands absent; ^1H nmr ($CDCl_3$) δ 7.10 (15, s, C_6H_5), 3.72 (3, t, J = 6 Hz, CH), 2.67 (6, d, J = 6 Hz, CH_2), 1.20 (3, s, broad, NH); ^{13}C nmr ($CDCl_3$) δ 136.1 (C-1, C_6H_5), 128.8 (C-2, C_6H_5), 127.8 (C-3, C_6H_5), 125.9 (C-4, C_6H_5), 70.2 (CH), 42.1 (CH_2).

Anal. Calcd for $C_{24}H_{27}N_3$: N, 11.76; mol wt, 357.5. Found: N, 11.2 (titration); mol wt, 380.

2,4,6-Tris(1-phenylethyl)-1,3,5-hexahydrotriazine (Low-Melting Form 2b). Hydratropaldehyde (20 g, 0.149 mol) was added during 15 min to 20 ml (0.18 mol) of 9 *M* methanolic ammonia keeping the temperature at 5–7° by ice-bath cooling. Storage at −15° for 3 days gave white crystals, removed by filtration and washed with cold methanol to yield **2b**: 15.7 g (79%); mp 114–120° (capillary), 111–112° (Kofler); melting occurs with decomposition (gas evolution); *cf.* Table I for literature melting point; ir (Nujol) 3280 cm^{-1} (NH), C=N and C=O bands absent; ir (CCl_4 solution) 3270 cm^{-1} (NH, sharp), C=N and C=O absent; ^1H nmr (C_6D_6) δ 7.15 (15, m, C_6H_5), 3.77, 3.75, 3.70 (3, three doublets, NCHN, $J \simeq 7$ Hz), 2.4–3.0 (3, m, $CH_3CHC_6H_5$), 1.62, 1.55, 1.40, 1.35 (9, four doublets, $J \sim 7$ Hz, CH_3CH), 0.82 (3, broad s, NH); ^{13}C nmr ($CDCl_3$) δ 141.9 (C-1, C_6H_5), 127.6 (C-2, C_6H_5), 127.3, 126.9, 125.7, 125.3 (C-3 and C-4 C_6H_5), 74.8, 74.6, 73.9 (more intense, CH), 43.7, 43.6, 43.1 (CH_2), 16.6, 16.0, 15.7 (CH_3).

Anal. Calcd for $C_{27}H_{33}N_3$: C, 81.16; H, 8.33; N, 10.52, mol wt, 399.56. Found: C, 81.42; H, 8.35; N, 10.52; mol wt, 390.

A 1.0-g (2.5 mmol) sample of **2b** in 100 ml of dry benzene was heated under reflux for 1 hr with a stream of nitrogen passing through the liquid. The exit gas, having a strong ammonia odor, was bubbled through 1 *N* hydrochloric acid solution; titration with 1 *N* sodium hydroxide indicated that 2.5 mmol of ammonia had evolved. Concentration under reduced pressure to remove solvent gave 0.95 g of a yellow oil; crystallization from heptane gave 0.02 g of recovered **2b**, but no other crystalline product could be isolated; ir (neat film) 3250 (NH, sharp, weak), 1640 cm^{-1} (C=CN); ^1H nmr ($CDCl_3$) δ 7.15 (m, C_6H_5), 4.46 (d, $J \cong 7$ Hz, HNCHNH), 3.4–3.9 (m, $C_6H_5CHCH_3$), 2.47 (s, CH_3C=, weak), 1.1–1.4 (several doublets, J = 7 Hz, CH_3CH).

2,4,6-Tris(1-phenylethyl)-1,3,5-hexahydrotriazine (High-Melting Form 2b′). A 2.5-g sample of low-melting **2b** was heated with stirring under reflux with 100 ml of 20% methanolic potassium hydroxide for 2 hr. The mixture was chilled at 0°, filtered, and washed with hot ethanol to yield 1.7 g (68%) of **2b′**, rectangular prisms, mp 136–144° dec; *cf.* Table I for literature melting point. The infrared, ^1H nmr, and ^{13}C nmr spectra of the product were virtually identical with spectra of low-melting **2b**.

Anal. Calcd for $C_{27}H_{33}N_3$: C, 81.16; H, 8.33; N, 10.52; mol wt, 399.56. Found: C, 81.27; H, 8.30; N, 10.49; mol wt, 378.

A 0.50-g sample of **2b** was heated under reflux with stirring for 2 hr with 20 ml of methanol-*O*-*d* (99% assay) containing 6.0 g of potassium hydroxide-*O*-*d*. The solution was chilled and filtered and the product was washed with water and methanol to yield 0.43 g (86%) of **2b′**, mp 144–150°; the infrared, ^1H nmr, and ^{13}C nmr spectra of the product were virtually identical with those of low-melting **2b**. Evaporation of a chloroform solution of **2b′** gave **2b** in quantitative recovery, mp 109–116° dec.

2,4,6-Tris(diphenylmethyl)-1,3,5-hexahydrotriazine (2c). Diphenylacetaldehyde (4.0 g, 0.0207 mol) was added during 8 min to 40 ml of a saturated solution of ammonia in ether (temperature maintained at 0–2°). After storage at −15° for 2 days white crystals were removed by filtration and washed with ether, 1.36 g (34%), mp 82–88° dec (A second crop precipitated from the filtrate after storage at −15° for 4 additional days, 0.45 g, mp 68–70° dec.): ir (Nujol) 3270 cm^{-1} (NH), C=O and C=N bands absent; ir ($CHCl_3$) 3350 (NH), 1670 cm^{-1} (C=N), band forms very rapidly (A = 0.10 after 0.5 min, 0.25 after 3 min); after 15 min the 1670-cm^{-1} band had virtually disappeared with the formation of a strong C=CN band at 1640 cm^{-1} (A = 0.44) which was virtually absent initially; nmr spectra were determined rapidly; ^1H nmr ($CDCl_3$) δ 7.58 (30, s, C_6H_5), 4.62, 4.18 [6, AB q, J = 6 Hz, ring CH at δ 4.62 (slight broadening), $(C_6H_5)_2CH$ at δ 4.18], 1.4 (3, broad s, NH; signal disappears on addition of D_2O); ^{13}C nmr ($CDCl_3$) δ 140.7 (C-1, C_6H_5), 128.4 (C-2, C_6H_5), 127.9 (C-3, C_6H_5), 126.1 (C-4, C_6H_5), 72.9 (NCN), 56.1 (CHC_6H_5).

Anal. Calcd for $C_{42}H_{39}N_3$: N, 7.17; mol wt, 585.8. Found: N, 7.03 (titration); mol wt, 553 (osmometry, C_6H_6).

In an alternate procedure 10 g of diphenylacetaldehyde was added to 20 ml of 9 *M* methanolic ammonia (temperature at 0–5° during the addition). After storage at −15° for 1 day a few drops of water was added to the clear solution and storage at −15° was continued for 2 weeks. A precipitate which formed was filtered off and washed with cold methanol to yield 8.64 g (87%) of crude **2c**, mp 63–78° dec; the material decomposed on attempted recrystallization. The filtrate after standing at room temperature for 2 weeks deposited crystals of oxazoline 14, 0.20 g, mp 123–125° (*vide infra*).

A 0.10-g sample of triazine **2c** was heated under reflux with 20% methanolic potassium hydroxide for 2 hr. Chilling at 0°, followed by filtration and washing of the precipitate with methanol, gave 0.80 g (80%) of crystalline isomer **2c′**, mp 105–110° dec; its infrared and nmr spectra were virtually identical with those of **2c**.

2,4,6-Tribenzyl-1,3,5-triazabicyclo[3.1.0]hexane (*trans*-3a). Procedure A. Phenylacetaldehyde (6.0 g, 0.050 mol) was added dropwise, with stirring during 5 min, to a methanolic solution of chloramine (prepared by addition, during 10 min, of 3.0 ml of *tert*-butyl hypochlorite to 25 ml of 9 *M* methanolic ammonia containing 3 ml of *tert*-butyl alcohol keeping the reaction temperature at −35°); a reaction temperature of −35 to −37° was maintained by an ethylene dichloride–Dry Ice bath. Stirring magnetically was continued (flask capped with a calcium chloride tube) maintaining the temperature at −30 to −37° for 2.25 hr and at ambient temperature for 3 hr. The mixture, which contained a voluminous precipitate, was concentrated *in vacuo* to near dryness and the residue was extracted three times with hot chloroform. The cooled extracts were filtered and the filtrate was concentrated to dryness; the pale yellow solid residue was crystallized from 1:1 benzene–hexane to yield 2.9 g (49%) of *trans*-**3a**, mp 163–168°; a second crop of crude material was recovered from the filtrate, 1.0 g, mp 130–155°. Several recrystallizations from cyclohexane gave long needles: mp 172–175°; ir (KBr) 3130 cm^{-1} (NH); ^1H nmr ($CDCl_3$) δ 7.42 (15, s, C_6H_5), 4.46, 4.37 (2, apparent triplets, $J \cong 5$ Hz, ring CH at C-4 and C-6), 2.9 (6, two nearly superimposed apparent triplets, $J \cong 5$ and 5.5 Hz, CH_2), 2.22 (1, apparent triplet, $J \cong 5.5$ Hz, ring CH at C-2); ^{13}C nmr ($CDCl_3$, the multiplicities of the proton-coupled spectra are given in parentheses) δ 138.8, 137.8, 136.9 (s, C-1 C_6H_5), 129.8, 129.1, 128.3, 128.2, 126.8, 128.4 (d, C-2,3,4 C_6H_5), 80.8, 76.9 (d, ring C-2,4), 52.5 (d, ring C-6), 41.1, 37.6, 36.0 (t, CH_2).

Procedure B. To 2,4,6-tribenzyl-1,3,5-hexahydrotriazine (**2a**, 0.715 g, 2 mmol), 0.11 g of sodium carbonate, and 30 ml of methanol at −35° (Dry Ice–ethylene dichloride bath) was added, with stirring, *tert*-butyl hypochlorite (0.22 g, 2 mmol). The mixture was stirred at −35° for 1.8 hr and at ambient temperature for 2 hr. The mixture was concentrated to dryness under reduced pressure and the residue was extracted with hot benzene. The extract was filtered and concentrated to dryness and the residue was crystallized from hexane to yield 0.14 g of crystals, mp 75–141°; recrystallizations from cyclohexane gave needles, 30 mg, mp 172–175°. This material was identical with the product obtained by procedure A, above (mixture melting point, ir, nmr).

Anal. Calcd for $C_{24}H_{25}N_3$: C, 81.09; H, 7.09; N, 11.82; mol wt, 355.46. Found: 81.04; H, 6.92; N, 11.63; mol wt, 356.

2,4,6-Tris(1-phenylethyl)-1,3,5-triazabicyclo[3.1.0]hexane (*trans*-3b). Procedure A. Hydratropaldehyde (6.71 g, 0.05 mol) was treated with chloramine using the procedure described for preparation of *trans*-**3a** to yield 0.35 g of crude product, mp 110–130°. Recrystallization from hexane gave 0.17 g, mp 148–154°. Further recrystallization gave prisms: mp 161–164°; ir (KBr) 3150 cm^{-1} (NH); ^1H nmr ($CDCl_3$) δ 7.26 (15, broad m, C_6H_5), 3.9–4.4 (2, m, C-4,6 ring CH), 2.0–3.0 (4, m, C-2 ring CH and CH_3CH), 1.0–1.6 (9, nine major doublets, $J \cong 7$ Hz, CH_3); ^{13}C nmr ($CDCl_3$) δ 144.0, 143.2, 142.9 (C-1, C_6H_5), 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 127.3, 127.1, 126.5, 126.4, 126.2, 126.1 (C-2,3,4 C_6H_5), 85.1, 84.2, 82.8, 82.6, 82.3, 81.2 (ring C-2,4), 58.4, 58.1 (ring C-6), 45.0, 44.7, 44.2, 43.2, 42.7, 41.8, 41.4, 41.1, 40.8 (CH_3CH), 21.2, 20.8, 20.3, 19.9, 19.5, 17.8, 17.5, 16.6, 15.8 (CH_3).

Procedure B. 2,4,6-Tris(1-phenylethyl)-1,3,5-hexahydrotriazine (**2b**, 0.80 g) was oxidized with *tert*-butyl hypochlorite by the procedure employed with **2a** to yield 14 mg of crude product, mp 115–144°. Recrystallizations from hexane gave *trans*-**3b**, mp 161–165°, identical with the product obtained by procedure A (ir, nmr, mixture melting point).

Anal. Calcd for $C_{27}H_{31}N_3$: C, 81.57; H, 7.86; N, 10.57; mol wt, 397.54. Found: C, 81.61; H, 7.80; N, 10.46; mol wt, 394.

Attempts to prepare 2,4,6-tris(diphenylmethyl)-1,3,5-triazabicyclo[3.1.0]hexane (**3c**) from diphenylacetaldehyde by the procedures employed for preparing **3a** and **3b** were unsuccessful. Procedures A and B both gave small amounts (2–5%) of diphenylacetamide, mp 167–169° (prisms from cyclohexane), as the only isolated crystalline product (lit.[40] mp 167.5–169°), ir (Nujol) 1630 cm^{-1}

(C=O, strong, amide); elemental analyses and molecular weight data agree with the molecular formula $C_{14}H_{13}NO$.

Bis(2,2-diphenylethen)amine (6c). Procedure A. 2,4,6-Tris(diphenylmethyl)-1,3,5-hexahydrotriazine (**2c**, 0.50 g, 0.854 mmol) in 50 ml of benzene was heated under reflux for 1.3 hr while nitrogen was passed through the solution. The exit gas containing ammonia was passed through 1 *N* hydrochloric acid solution to yield 1.0 mequiv of ammonia (0.72 mequiv formed in 45 min); assay determined by titration with 1 *N* sodium hydroxide. The solution was concentrated to dryness to yield pale yellow crystals, mp 100–135° dec. Recrystallization from methanol gave 0.14 g (44%) of **6c**: mp 143–144° (lit.[33] mp 142–146°); ir (Nujol) 3300 (NH), 1625 cm^{-1} (C=CN); ^1H nmr ($CDCl_3$) δ 7.32 (20, m, C_6H_5), 6.90 (2, s, CH=); ^{13}C nmr ($CDCl_3$) δ 141.2 (C-1, C_6H_5), 138.1 (C-1, C_6H_5), 129.8, 128.9, 128.3 (C-2,3 C_6H_5), 128.0, 126.8, 125.1 (C-4, C_6H_5 and CH=), 116.0 [quaternary C, $(C_6H_5)_2C$=]; ^{13}C assignments were based on peak intensities, multiplicities observed in the proton-coupled spectra, and/or relaxation times; uv (ethanol) λ_{max} 362 nm (ϵ_{max} 30,000).

Procedure B. 2,2-Diphenylethenamine[13] (0.20 g, 1 mmol) and diphenylacetaldehyde (0.20 g, 1 mmol) were dissolved in 10 ml of methanol by warming on the steam bath. The cooled solution was diluted with water until turbid. Chilling at 0° gave 15 mg of **6c**, mp 140–144°.

Procedure C. 2,2-Diphenylethenamine (0.10 g) in 10 ml of 95% ethanol was warmed on the steam bath until a clear solution was obtained. After standing at room temperature for 40 hr and at 0° for 6 hr there was obtained 10 mg of **6c**, mp 145–147°.

Procedure D. 2,2-Diphenylethenamine (0.10 g) was heated, without solvent, on the steam bath for 1 hr. Ammonia was evolved vigorously during the heating. Recrystallization of the product from methanol gave 35 mg of **6c**, mp 144–149°. After **6c** itself was heated for 1 hr the compound was unchanged.

Procedure E. Phenylacetaldehyde (5 g) and 9 *M* methanolic ammonia (10 ml) were added to 400 ml of methanol. After standing at room temperature for 1 week the solution was concentrated to dryness and the residue was recrystallized from ethanol to yield 0.85 g (18%) of **6c**, mp 145–148°.

Anal. Calcd for $C_{28}H_{23}N$: C, 90.04; H, 6.21; N, 3.75; mol wt, 373.47. Found: C, 90.07; H, 6.10; N, 3.70; mol wt, 375.

2,2-Diphenyl-1-nitroethene (12) was prepared from 1,1-diphenylethene (Aldrich) by the procedure of Bordwell and Garbisch[41] as crystals from hexane, mp 85–87° (lit.[41] mp 85–86°).

2,2-Diphenylethenamine (7c). Procedure A. 2,2-Diphenyl-1-nitroethene (**12**, 1.0 g, 4.45 mmol) in 50 ml of ether was shaken with platinum oxide catalyst (0.37 g) and hydrogen in a Parr apparatus (33 psi, 25°) for 45 min (3 molar equiv of hydrogen absorbed). Filtration of the catalyst followed by concentration of the filtrate gave 0.70 g of white solid which was triturated with cold ether and isopentane to yield 0.42 g (48%) of **7c** as white prisms, mp 122–129° (Kofl), identical with that prepared by procedure B (ir, nmr, mixture melting point) (lit.[13] mp 116–125° dec).

Procedure B. The procedure of Curtin was employed with modifications.[13] Diphenylacetaldehyde (19.6 g, 0.1 mol) was added to 9 *M* methanolic ammonia (150 ml) during 20 min with ice-bath cooling (reaction temperature below 5°). Ammonia was bubbled into the solution for 12 hr (20–22°). Chilling at 0° deposited crystals which were removed by filtration and washed with cold methanol, 13.5 g (69%) of **7c**, mp 100–128°. Recrystallization from ethanol gave long prisms: mp 119–127°; ir (KBr) 3270, 3350 (NH), 1630 cm^{-1} (C=CN); ^1H nmr ($CDCl_3$) δ 7.38, 7.18 (10, two singlets, C_6H_5), 6.70 (1, broad m, =CH, sharpens to singlet on addition of D_2O), 3.44 (2, broad m, NH_2, disappears on addition of D_2O).

Anal. Calcd for $C_{14}H_{13}N$: C, 86.11; H, 6.71; N, 7.17; mol wt, 195.25. Found: C, 85.90; H, 6.69; N, 7.00; mol wt, 201.

***N*-Acetyl-2,2-diphenylethenamine (13).** Bis(2,2-diphenylethen)amine (**6c**, 0.20 g) in 20 ml of acetic anhydride was heated on the steam bath for 16 hr. Concentration to dryness gave an oil which was recrystallized from benzene–heptane to yield 35 mg (28%) of **13**, prisms, mp 158–163° (Kofl) (lit. mp 162–163°,[26] 162–164°,[13] 166°[32]).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; mol wt, 237.29. Found: C, 80.79; H, 6.17; N, 5.99; mol wt, 226.

5,5-Diphenyl-2-(diphenylmethyl)-3-oxazoline (14). The filtrate remaining after removal of the first crop of 2,2-diphenylethenamine (**7c**) (from reaction of diphenylacetaldehyde with ammonia, procedure B, above) was concentrated to a small volume to yield a gummy solid, which on standing overnight produced 0.72 g of prisms, mp 125–128°; additional material was obtained in a similar manner from the mother liquors remaining from recrystallization of **7c**, 0.34 g, mp 124–127°; total yield of high-purity **14**, 1.04 g (5.4%). Recrystallization from ethanol gave needles: mp 125–127°; ir (Nujol) 1630 cm^{-1} (C=N, weak), NH band absent; uv (methylcyclohexane) λ_{max} 218 nm (ϵ 23,900), 260 (5050); ^1H nmr ($CDCl_3$) δ 7.78 (1, d, $J \cong 2.5$ Hz, CH= at C-4), 6.7–7.5 (20, m, C_6H_5), 6.44 (1, dd, $J \cong 5$ and 2.5 Hz, CH at C-2), 4.48 [1, d, $J \cong 5$ Hz, $CHCH(C_6H_5)_2$]; ^{13}C nmr ($CDCl_3$) δ 163.5 (C-4 oxazoline ring), 141.2, 140.8, 140.6, 140.3 (C-1, C_6H_5), 129.4, 128.5, 128.2, 128.0, 127.8, 127.6, 127.0, 126.5, 126.2 (C-2,3,4, C_6H_5), 107.4 (C-2 oxazoline ring), 95.3 (C-5 oxazoline ring), 56.1 (C_6H_5CH).

Anal. Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60; mol wt, 389.47. Found: 86.38; H, 5.97; N, 3.58; mol wt, 389 (mass spectrum), 380 (osmometry).

A sample of **14** dissolved in hot methanol was treated with 1 *N* hydrochloric acid to adjust the pH of the solution to 4.0. After standing at 25° for 24 hr the solution was made slightly alkaline by addition of 1 *N* sodium hydroxide solution. Concentration gave an oil (wet), which was dissolved in benzene and treated with Drierite. Filtration, followed by concentration to dryness, gave a pale yellow oil: ir 1700 cm^{-1} (C=O, aldehyde); ^1H nmr ($CDCl_3$) δ 9.77 (s, CHO aldehyde); diphenylacetaldehyde spectra reveal the same aldehyde peaks (ir and ^1H nmr).

Registry No.—**2a**, 51003-90-8; **2b**, 51003-91-9; **2c**, 51003-92-0; *trans*-**3a**, 51003-11-3; *trans*-**3b**, 51003-93-1; **6c**, 985-09-1; **7c**, 947-90-0; **12**, 5670-69-9; **13**, 1722-89-0; **14**, 51002-92-7; phenylacetaldehyde, 122-78-1; hydratropaldehyde, 93-53-8; diphenylacetaldehyde, 947-91-1.

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Bicyclic Enamines. VIII. Mechanistic Studies of Rearrangements in a Quinuclidine System[1]

Karl-Henrik Hasselgren, Jörgen Dolby, M. M. Al Holly, Magnus Elander, and J. Lars G. Nilsson*[2]

Faculty of Pharmacy, University of Uppsala, S-751 23 Uppsala, Sweden

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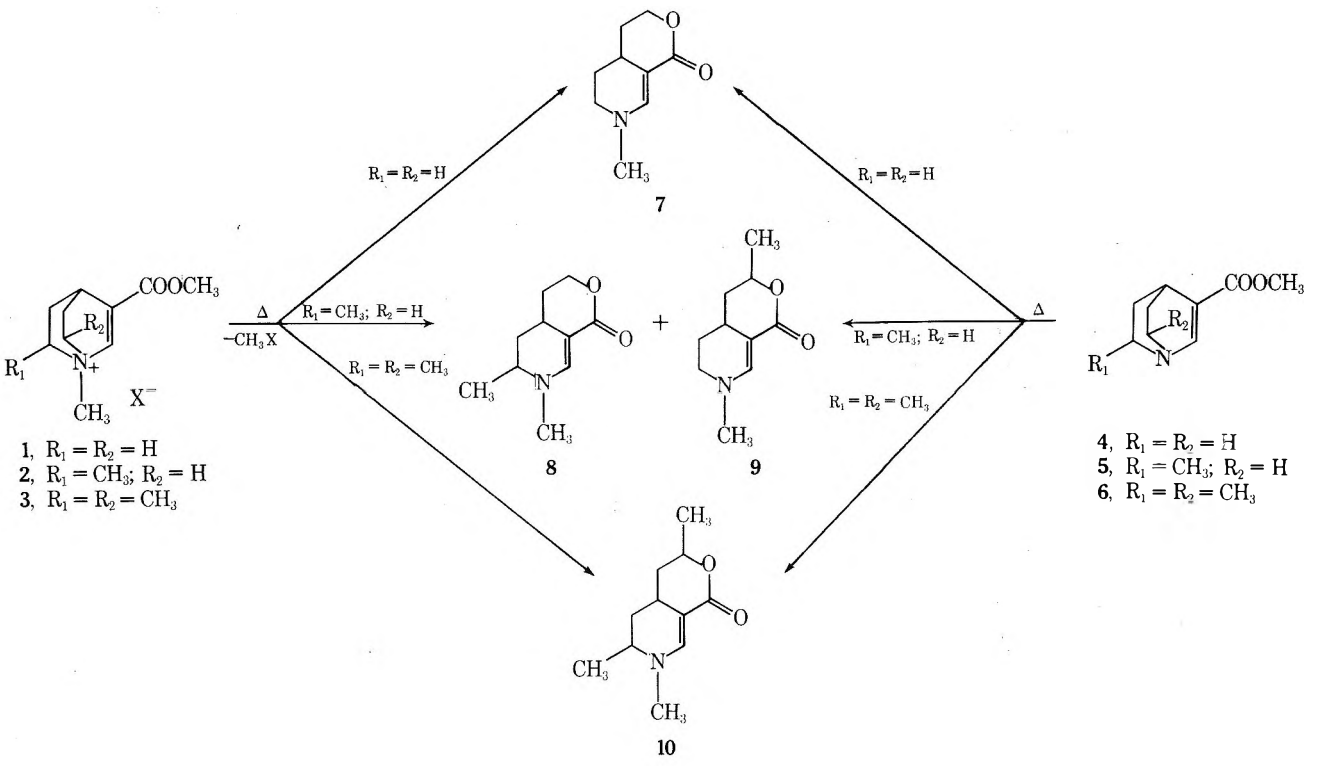
When an unsaturated quaternary quinuclidine-3-carboxylic acid ester of type **1** (X = I^-) is heated to about 150° for 1 min or less, it rearranges in very good yield to a lactone of type **7**. The same lactone is formed from the corresponding base **4**, although prolonged heating at higher temperature is required (200° for 30 min). We have shown that these conversions are multistep reactions initiated by the attack of a nucleophile, which can either be the counterion of the quaternary salts **1–3** or another base molecule in the rearrangement of the bases **4–6**.

Recently we reported[3,4] that the unsaturated quinuclidine-3-carboxylic acid esters **1** and **2**, when heated, were converted into tetrahydronicotinic acid lactones. We have now extended this work to all the esters **1–6** and studied the mechanism for their conversion into lactones **7–10**.

In a preliminary report[3] several mechanisms were considered for the thermal conversions of Scheme I, and it was concluded that the intermediate **11** (Scheme II) was formed by successive sigmatropic rearrangements. Further studies have shown that this proposal was in error, and evidence now indicates that, contrary to the preliminary report, the rearrangements probably occur by attack of the counterion of the quaternary salt. Rearrangement of the tertiary bases probably occurs *via* a related mechanism.

In our early studies on this problem we observed that bases **4** and **5** gave lactones in a manner similar to that of quaternary salts **1** and **2** (Scheme I). This indicated to us that the bases and the quaternary salts were converted *via* the same mechanism, and in a preliminary report[3] we proposed that the lactone **7** was formed *via* sigmatropic rearrangements. However, we later found that the nitrogen substituent of compounds of type **1** influenced the ease of rearrangement to lactones. We could thus demonstrate that *N*-allyl- and *N*-propargylquinuclidine-3-carboxylic acid esters gave the corresponding lactones when

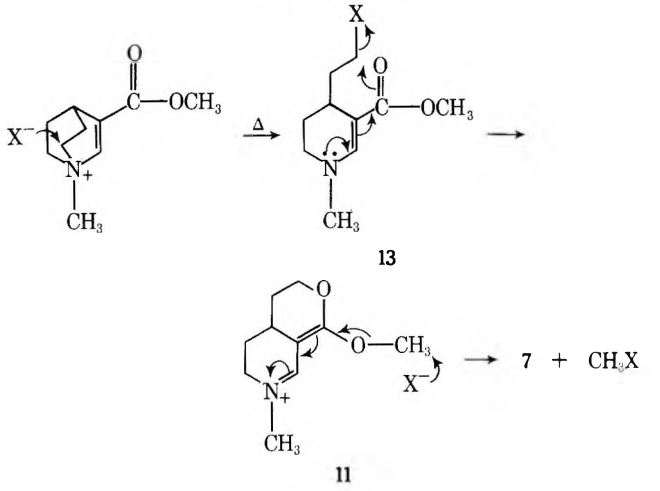
Scheme I



1, $R_1 = R_2 = H$
2, $R_1 = CH_3$; $R_2 = H$
3, $R_1 = R_2 = CH_3$

4, $R_1 = R_2 = H$
5, $R_1 = CH_3$; $R_2 = H$
6, $R_1 = R_2 = CH_3$

Scheme II



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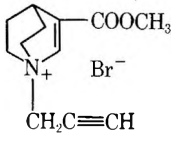
the compounds were stored at room temperature for a few weeks, while the *N*-methyl derivative **1** rearranged only when heated above 100°. This prompted us to investigate the mechanism further.

Results and Discussion

To study the effect of various negative ions on the rearrangement, salts with counterions of different nucleophilicity were prepared and heated to 150° for 10 min. We found that **1** with X = I^- as well as **12** with X = Br^-, the



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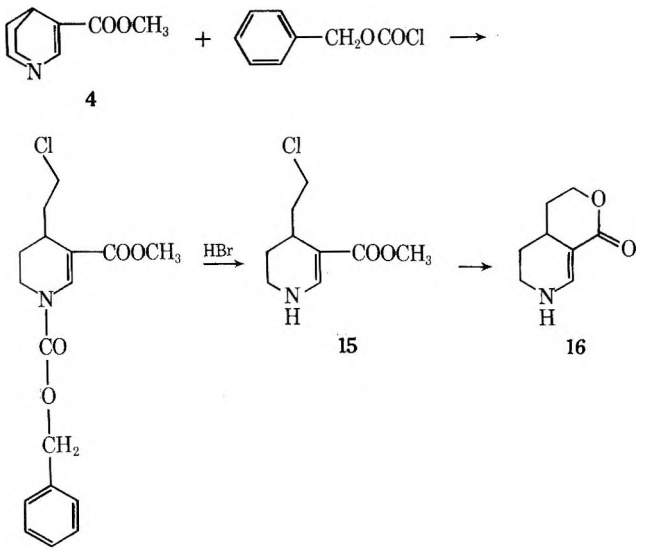
hydrochloride of **4**[5] and the hydriodide of **5** smoothly rearranged to the corresponding lactones. However, the quaternary salt **1** with X = NO_3^- or ClO_4^- as well as the hydrotosylate of **4** and the hydroperchlorate of **5** did not rearrange. This indicates that the counterion is involved in the mechanism and that it must have a certain nucleophilicity either to react with **1** and form the intermediate **13** or with the hypothetical intermediate **11** in the terminating step of the reaction sequence.

The occurrence of **11** as an intermediate is supported by the observation that the alkyl halide formed is derived from the ester function of **1**, since ethyl iodide could be isolated during the rearrangement of the corresponding ethyl ester.

To get further mechanistic evidence, it was necessary to determine if an ester of type **13** in Scheme II can undergo the proposed ring closure to a lactone. We therefore carried out the reaction sequence depicted in Scheme III. The unsaturated quinuclidine ester **4** was treated with benzyloxycarbonyl chloride which opened the bicyclic structure[6] and gave the carbamate **14**. This was then treated with anhydrous HBr in acetic acid to remove the benzyloxycarbonyl group affording the ester **15**, which at room temperature spontaneously underwent ring closure to the lactone **16**. This shows that conversion of **13** into **11** is a highly favored reaction and that the intermediate **11** is unstable and spontaneously converted into the lactone at room temperature.

The experiments with counterions of different nucleophilicity as well as the reactions outlined in Scheme III support a mechanism involving an attack by the counterion as a primary step. We therefore propose, contrary to our previous report,[3] that the quaternary salts **1**–**3** form lactones **7**–**10** according to this mechanism.

Scheme III



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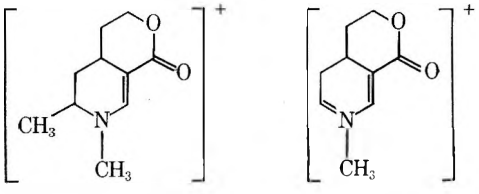
To determine if other parallel mechanisms were operating, several additional experiments were carried out. Rearrangements *via* mechanisms involving formation of a radical or a carbonium ion intermediate[3] should be facilitated by alkyl substituents at the migrating carbon. We therefore decided to study the rearrangement of the C_6-methyl substituted ester **2**. If the conversion of **2** occurred *via* these mechanisms, compound **9** would probably be the main product since an unpaired electron[7,8] or a positive charge[7] reside preferably on a secondary carbon. Rearrangement of **2** yielded a mixture of two products present in a ratio of 4:1.

Crystallization gave the pure main product. The ir and uv spectra indicate that the compound is an enamino lactone.[9] The nmr spectrum is consistent with the lactone **8**. It shows, among other signals, a multiplet at 4.4–4.1 ppm (2 H) due to the $-CH_2O-$ protons of the lactone ring and a doublet at 1.29 ppm (3 H) corresponding to the C_6-methyl protons. Structure **8** was also confirmed by the mass spectrum which shows a molecular ion at *m/e* 181 (rel intensity 100%) and a diagnostically valuable peak at *m/e* 166 (53%) due to an α cleavage[10] to fragment **8a**. Other fragments are presented in the Experimental Section.

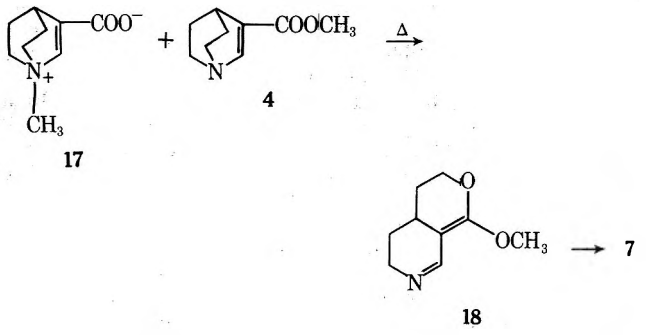


8, *m/e* 181 **8a**, *m/e* 166

The mass spectrum of the minor component is very similar to that of **8**. It shows the ion at *m/e* 181 (79%) but the peak at *m/e* 166 has only an intensity of 8%, indicating that the 6 position of the molecule is unsubstituted. The mass spectrum is therefore consistent with structure **9**. This structure is also supported by the observation that the mass spectra of **7**, **8** and **16**, all with the structure $-CH_2OCO-$ in the lactone ring, have a peak at M − 31, whereas this fragment is not formed from the lactones **9** and **10** which have a methyl-substituted lactone ring. The appearance of compound **9** as a minor conversion product from **2**, as well as from **5**, indicates that a radical or a carbonium ion mechanism is not involved to a major extent in the rearrangements depicted in Scheme I.

As indicated in Scheme I, bases **4**–**6** are rearranged to lactones. Thus, we observed that the base **4** was converted

Scheme IV



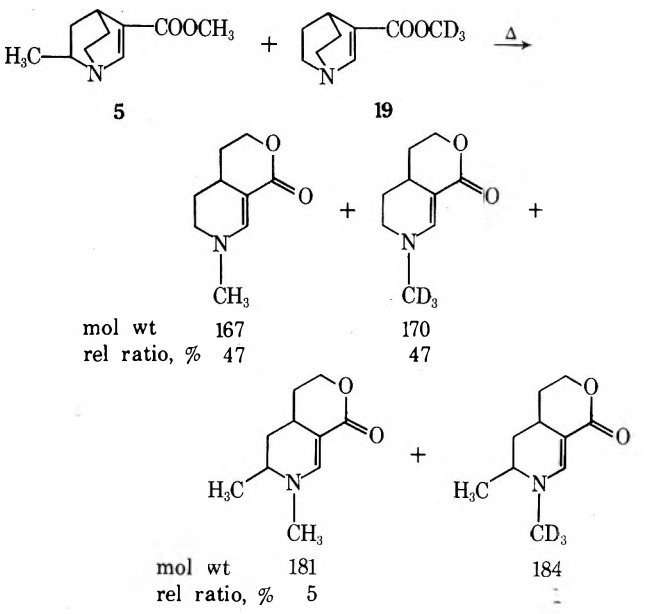
into **7** in 75% yield when heated for 30 min at 200° (Scheme IV). Similar to the rearrangement of the quaternary compound **2**, the C_6-methyl substituted base **5**, upon heating gave a mixture of the lactones **8** and **9** in a ratio of 4:1. Under the conditions used for the rearrangement of the quaternary compounds **1** and **2** no reaction occurred. It is also of interest to note here that the hydrotosylate of **4** (above) gave lactone **7** when heated at 200° for 30 min. The same lactone was also formed from betaine **17** under these conditions. In these cases, no reaction occurred at 150° for 10 min.

For the tertiary base **4**, successive sigmatropic rearrangements to the intermediate **18** was considered as a possibility. To form the lactone **7**, the methyl group of **18** would migrate from the oxygen to the nitrogen. To test this possibility of intramolecular methyl migration we heated an equimolecular mixture of the two bases **5** and **19** at 200° for 30 min (Scheme V). The reaction mixture was analyzed by mass spectrometry and this revealed the presence of all the four possible lactones (Scheme V) showing that an intermolecular reaction had taken place.

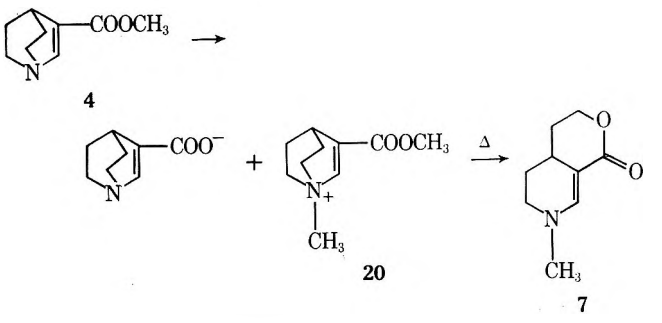
We have previously shown[3] that the lactones **9** (from **2** or **5**) and **10** (from **3** or **6**) cannot be formed *via* sigmatropic rearrangements. It therefore seems reasonable to exclude the sigmatropic rearrangements from the discussion.

An alternative mechanism for the lactone formation from the ester **4** is outlined in Scheme VI. The basic nitrogen in one molecule is attacking the ester methyl group of another molecule forming the quaternary salt **20**. The cation of this ion pair is then rearranged to the lactone according to Scheme II, and the nucleophilic species involved in the reaction is probably the carboxylate ion of **20**. This is supported by the observation given above, that the betaine **17** is rearranged to **7** at 200° for 30 min. The carboxylate ion can thus function as a nculeophile in this reaction. Similarly, we could also show that the perchlorate of **1** (X = ClO_4^-) is rearranged at 150° for 10 min if small amounts of the base **4** are added. Under these conditions neither the pure base nor the pure perchlorate is rearranged to the lactone. We therefore propose that the bases **4**–**6** are converted into the lactones **7**–**10** by the reaction presented in Scheme VI, a sequence closely related to the mechanism proposed in Scheme II for the rearrangement of the quaternary salts **1**–**3**.

Scheme V



Scheme VI



Experimental Section

General Comments. Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Ir spectra were run on a Perkin-Elmer 457 spectrophotometer. Uv spectra were measured on a Perkin-Elmer 402 spectrophotometer and a Zeiss PMQ II Spectralphotometer. Nmr spectra were measured with a Varian Associates A-60 instrument using $CDCl_3$ solutions. Chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra were recorded using an LKB 9000 apparatus at 70 eV. Microanalysis were performed in the laboratories of Dr. A. Bernhardt Mülheim, Germany. Methyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide (**1**) and methyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (**4**) were prepared as previously described.[4]

3-Ethoxycarbonyl-3-hydroxyquinuclidine. 3-Cyano-3-hydroxyquinuclidine[5] was hydrolyzed, and the acid was esterified with ethanol by the methods used in the preparation of 3-methoxycarbonyl-3-hydroxyquinuclidine.[5] This yielded the title compound in 77% yield; mp 117–119° (from chloroform–pentane). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.60; N, 7.03. Found: C, 60.2; H, 8.63; N, 7.20.

Ethyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate hydrochloride was prepared by $SOCl_2$ treatment[5] of the above hydroxy ester; yield 69%, mp 149–151° dec (from acetone). *Anal.* Calcd for $C_{10}H_{15}NO_2 \cdot HCl$: C, 55.2; H, 7.41; N, 6.44. Found: C, 54.8; H, 7.69; N, 6.32.

Ethyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide was prepared from the above ester as described for **1**,[4] mp 128–129° dec. *Anal.* Calcd for $C_{11}H_{18}INO_2$: C, 40.9; H, 5.57; N, 4.33 Found: C, 40.8; H, 5.59; N, 4.45. Rearrangement of this compound gave the lactone **7** with concomitant evolution of ethyl iodide.

Methyl 1,6-dimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide (2) was prepared from methyl 6-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate **5**[11] as described for **1**;[4] yield 77%; mp 134–135° dec (from acetone); ir (KBr) 1730 (C=O) and 1660 cm^{-1} (C=C); uv (EtOH) 221 nm (ϵ 16,400); nmr δ 7.75 (s, 1 H, vinylic), 3.90 and 3.80 (s, 3 H each, NCH_3 and $-COOCH_3$), 1.77 (d, J = 6.5 Hz, 3 H, CCH_3). *Anal.* Calcd for $C_{11}H_{18}INO_2$: C, 40.9; H, 5.60; N, 4.35. Found: C, 40.7; H, 5.58; N, 4.33.

Methyl 1-allyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide was prepared as described for **1**,[4] mp 95–96° dec. *Anal.* Calcd for $C_{12}H_{18}INO_2$: C, 43.0; H, 5.41; N, 4.18. Found: C, 43.0; H, 5.25; N, 4.31.

Methyl 1-propynyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate bromide (12) was also prepared as described for **1**,[4] mp 123–124° dec. *Anal.* Calcd for $C_{12}H_{16}BrNO_2$: C, 50.4; H, 5.64; N, 4.90. Found: C, 50.8; H, 5.55; N, 4.71.

Methyl 1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (1) as Nitrate or Perchlorate. The iodide **1** was dissolved in

methanol and stirred with 1 equiv of silver nitrate or silver perchlorate over night at room temperature. Filtration and evaporation of the solvent yielded the crystalline salts, mp 102–103° (nitrate) (from methanol) and 138–139° (perchlorate) (from methanol–ether). The nitrate was very hygroscopic, but the perchlorate could be subjected to elementary analysis. *Anal.* Calcd for $C_{10}H_{16}ClNO_6$: C, 42.7; H, 5.74; N, 4.97. Found: C, 42.8; H, 5.75; N, 4.88.

Methyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (1) hydrotosylate was obtained by precipitating the salt from an ether solution of **4**, mp 118–120° (from ethanol–ether). *Anal.* Calcd for $C_{16}H_{21}NO_5S$: C, 56.7; H, 6.24; N, 4.13. Found: C, 56.6; H, 6.26; N, 4.09.

Methyl 1-Benzyloxycarbonyl-4-(2-chloroethyl)-1,4,5,6-tetrahydronicotinate (14). Compound **4** was treated with benzyloxycarbonyl chloride using the procedure described for quinuclidine and phenyl chloroformate by Hobson and McCluskey.[6] This yielded the title compound in 78% yield as an oil which could not be distilled: ir (film) 1720, 1690, 1630 cm^{-1} (C=O and C=C); nmr ($CDCl_3$) δ 7.96 (s, 1 H, vinylic), 7.20 (s, 5 H, ArH), 5.20 (s, 2 H, $ArCH_2O$–), and 3.58 ppm (s, 3 H, OCH_3). The peaks due to other protons were not well resolved. *Anal.* Calcd for $C_{17}H_{20}NO_4Cl$: 60.5; H, 5.97; N, 4.15. Found: C, 60.3; H, 5.95; N, 4.02.

Methyl 4-(2-Chloroethyl)-1,4,5,6-tetrahydronicotinate (15). Compound **14** was dissolved in glacial acetic acid containing 30% anhydrous HBr, and this was left at room temperature for 4 hr. The hydrobromide was then precipitated as an oil by addition of anhydrous ether. The compound was very hydroscopic and could not be obtained in solid form; ir (film) 1730 cm^{-1} (C=O). *Anal.* Calcd for $C_9H_{14}ClNO_2 \cdot HBr \cdot H_2O$: C, 35.7; H, 5.66; N, 4.60. Found: C, 35.4; H, 5.61; N, 4.30. Attempts to convert the hydrobromide into the free base yielded the lactone **16** within a few hours at room temperature. Compound **16** was identified by melting point and spectroscopic comparisons with an authentic sample.[12]

1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate 17. A solution of methyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide[3] (0.7 g) in water (2 ml) was applied to a hydroxyl saturated ion-exchange column (Dowex 1-X8, 50–100 mesh) (10 g). The column was eluted with water and the fraction containing **12** as indicated by a Uvicord II uv absorptiometer was collected and evaporated to yield the carboxylate **12** in 91% yield as a crystalline material, mp 260° dec (from ethanol). *Anal.* Calcd for $C_9H_{13}NO_2 \cdot H_2O$: C, 58.4; H, 8.16; N, 7.56. Found: C, 58.5; H, 7.82; N, 7.47.

3-Cyano-3-hydroxy-6,8-dimethylquinuclidine. This compound was prepared from 6,8-dimethyl-3-quinuclidinone[13] according to Grob and Renk;[5] yield 89%, mp 152–154° (from ethyl acetate). The compound showed a tendency to lose HCN, and it was therefore identified by its ir, and mass spectra: ir (KBr) 2230 cm^{-1} (C≡N); mass spectrum *m/e* (rel intensity) 180 (3, $M\cdot^+$), 165 (3), 153 (2), 125 (50), 110 (63), 83 (22), 70 (25), 68 (24), 57 (20), 56 (100), 55 (25).

3-Methoxycarbonyl-3-hydroxy-6,8-dimethylquinuclidine was prepared from the above hydroxynitrile as described for 3-methoxycarbonyl-3-hydroxyquinuclidine;[5] yield 87%, mp 136–137° (from carbon tetrachloride). *Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 8.98; N, 6.57. Found: C, 61.7; H, 8.78; N, 6.45.

Methyl 6,8-dimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate (6) was prepared from the above hydroxy ester using $SOCl_2$;[5] yield 70%, mp 36–38°. *Anal.* Calcd for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.78; N, 7.18. Found: C, 67.4; H, 8.65; N, 7.03.

Methyl 1,6,8-Trimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide (3) was prepared from the above ester as described for **1**;[4] yield 88%; mp 153–154° dec (from acetone–ether); ir (KBr) 1730 (C=O) and 1655 cm^{-1} (C=C); uv (EtOH) 221 nm (ϵ 17,300). *Anal.* Calcd for $C_{12}H_{20}INO_2$: C, 42.7; H, 5.98; N, 4.15. Found: C, 42.6; H, 5.60; N, 3.81.

Azabicyclo[2.2.2]oct-2-ene-3-carboxylic Acid Hydrochloride. An aqueous solution of **4** hydrochloride (250 mg; 1.2 mol) was converted into its acid, using a basic ion-exchange Dowex-1 column (2 × 100 cm), and the acid was eluted with 2 *N* HCl (100 ml). Evaporation gave colorless crystals: mp 193–194° dec (from methanol); 250 mg (98% yield); ir (KBr) at 3380 (+NH), 3050 (C=CH), 1700 (C=O), and 1600 cm^{-1} (C=C). *Anal.* Calcd for $C_8H_{11}NO_2 \cdot HCl$: C, 50.7; H, 6.38; N, 7.46. Found: C, 50.9; H, 6.61; N, 7.41.

Methyl-d_3 1-Azabicyclo[2.2.2]oct-2-ene-3-carboxylate (19). A solution of the above acid (190 mg, 1 mmol) was dissolved in CD_3OD (1 ml), and dry HCl gas was passed through for a few minutes. The reaction mixture was then kept at room temperature for 60 hr. The excess CD_3OD was evaporated under vacuum yielding a white solid residue (189 mg, 99%): mp 178–179° (from MeOH); ir (KBr) at 3380 (+NH), 3020 (C=CH), 2160 and 2060 (CD), 1710 (C=O), 1300 and 1290 ($COCD_3$), and 740 cm^{-1} (C=CH). The free base was obtained as an oil, purified by a thick layer chromatography on silica gel G [ether–methanol, (8:2)]: ir (film) at 3030 (C=CH), 2240, 2180, and 2070 (C—D), 1710 (C=O), 1605 (C=C), 1290 and 1270 cm^{-1} ($COCD_3$). Mass spectrum showed a molecular ion peak at *m/e* 170.

General Procedure for the Rearrangements. The quaternary compounds were rearranged to the lactones when heated without solvent to 150° for 1 min.[3] To ensure complete reaction some compounds were heated for 10 min. Under these conditions, tertiary bases **4–6** were unchanged. These compounds could be rearranged by prolonged heating at higher temperature, usually 30 min at 200°, and purified by column chromatography as previously described.[4] The lactones formed were crystallized from ethyl acetate and were obtained in 70–90% yield. The lactones were identified by elementary analysis and ir and uv spectra. An extensive investigation of the spectral properties of lactones of type **7** and related compounds have been described in a previous paper.[9] The rearrangement of a few special compounds will be discussed below in detail.

Rearrangement of 1,6-Dimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate Iodide (2). The rearrangement was carried out as described above. Gas chromatography (Aerograph 1700 with a 6 ft × ⅛ in. i.d. glass column filled with 5% SE-30 on Gas-Chrom P, 100–120 mesh. Flow rate (25 ml of N_2/min, temp 160°) of the crystalline material obtained indicated the presence of two compounds in a ratio of 4:1. Recrystallization from ether gave the pure main product (73% yield), mp 82–84°. The structure elucidation was based on the data presented: ir (KBr) 1670 and 1590 cm^{-1} (C=O and C=C);[9] uv (EtOH) 305 nm (ϵ 21,400); nmr δ 7.55 (1 H, d, J = 2 Hz, C=CH), 4.4–4.1 (2 H, m, CH_2O–), 2.96 ppm (3 H, s, NCH_3), and 1.29 ppm (3 H, d, J = 6.5 Hz, CCH_3); mass spectrum *m/e* (rel intensity %) 181 (100 $M\cdot^+$), 166 (53), 150 (11), 137 (27), 122 (33), 109 (30), 108 (45), 94 (24), 44 (34), 42 (54). These data are consistent with structure **8**. Using combined glc–mass spectrometry, a mass spectrum was obtained on the minor product. This shows *m/e* (rel intensity %) 181 (79 $M\cdot^+$), 166 (8), 137 (20), 136 (18), 122 (35), 109 (28), 108 (19), 94 (35), 44 (100). This is consistent with structure **9**. The same compounds (**8** and **9**) were obtained in the same ratio (4:1) when **5** was heated at 200° for 30 min.

4-(2-Hydroxyethyl)-1,4,5,6-tetrahydro-1-propynylnicotinic Acid Lactone. This compound was obtained in 82% yield by rearrangement of methyl 1-propynyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate bromide: mp 121–122°; uv (EtOH) 300 nm (ϵ 22,500); ir (KBr) 3210 (C=CH), 2110 (C=C), 1660 and 1580 cm^{-1} (C=O and C=C). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.1, H, 6.85; N, 7.33. Found: C, 69.3; H, 6.55; N, 7.09.

1-Allyl-4-(2-hydroxyethyl)-1,4,5,6-tetrahydronicotinic Acid Lactone. This compound was obtained in 80% yield by rearrangement of methyl 1-allyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide: mp 95–97°; uv (EtOH) 304 nm (ϵ 24,800); ir (KBr) 1670, 1640, and 1575 cm^{-1} (C=O and C=C). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.82; N, 7.25. Found: C, 68.6; H, 7.58; N, 7.33.

Rearrangement of 1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate 17. This compound was heated in a sealed ampoule at 200° for 30 min. The dark product was purified by column chromatography as previously described.[4] The compound thus obtained (75% yield) had identical spectral properties and melting point as an authentic sample[4] of **7**.

Rearrangement of Methyl 1,6,8-Trimethyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate Iodide (3). The reaction was carried out as described above. The product was obtained in 64% yield; mp 124–126° (from ether); ir (KBr) 1670 and 1595 cm^{-1} (C=O and C=C);[9] uv (EtOH) 308 nm (ϵ 24,100); nmr δ 7.62 (s, 1 H, vinylic) 4.8–4.1 (m, 1 H, =CHO–), 3.9–3.2 (m, 1 H, =CHN=), 2.97 (s, 3 H, NCH_3), 2.3–1.7 (m, 2 H, aliphatic ring protons), 1.38 and 1.27 ppm (d, 3 H each, J = 4 Hz, $>NCHCH_3$ and $-OCHCH_3$); mass spectrum (prominent peaks) *m/e* (rel intensity %) 196 (16), 195 (100 $M\cdot^+$), 180 (41), 151 (35), 150 (25), 138 (24), 136 (100), 108 (63), 94 (26), 42 (54). *Anal.* Calcd for $C_{11}H_{17}NO_2$: C, 67.6; H, 8.78; N, 7.18. Found: C, 67.5; H, 8.54; N, 7.17. These data are consistent with the lactone **10**. The same compound was obtained from **6** when this was heated at 200° for 30 min.

Rearrangement of a Mixture of 5 and 19 (Scheme V). A mix-

ture of equimolecular amounts (10 mg) of 5 and 19 was heated in a sealed tube under N_2 at 200° for 30 min. The lactone fraction was separated from unreacted starting material by tlc and analyzed by mass spectrometry. The mass spectrum showed four molecular ion peaks at *m/e* 167, 170, 181, and 184 (relative ratio: 47:47:4.7:1.3) indicating the presence of the four lactones presented in Scheme V.

Rearrangement of Methyl 1-Methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate Perchlorate (1, X^- = ClO_4^-) in the Presence of Methyl 1-Azabicyclo[2.2.2]oct-2-ene-3-carboxylate (4). A mixture of 136 mg of 1 (X^- = ClO_4^-) and 81 mg of 4 was heated at 150° for 10 min. It was then treated with 3 ml of ether which after evaporation afforded 28 mg of 4. Treatment of the crystalline residue with 5 ml of ethyl acetate, evaporation of the solvent, and recrystallization from ethyl acetate afforded 20 mg of 7. Recrystallization of the residue from methanol yielded 85 mg of 1 (X^- = ClO_4^-). Under the above conditions, separate heating of 1 (X^- = ClO_4^-) and 4 afforded only unchanged starting material.

Registry No.—1 iodide, 33402-77-6; 1 nitrate, 50790-74-4; 1 perchlorate, 50790-75-5; 1 hydrotosylate, 50790-76-6; 2 iodide, 33816-58-9; 3 iodide, 50790-77-7; 4, 31539-88-5; 5, 50790-78-8; 6, 50790-79-9; 8, 33689-31-5; 9, 50790-80-2; 10, 50790-81-3; 12, 35593-77-2; 14, 50790-82-4; 15, 50790-83-5; 17, 35645-77-3; 19, 50790-84-6; 3-ethoxycarbonyl-3-hydroxyquinuclidine, 6238-31-9; 3-cyano-3-hydroxyquinuclidine, 6238-30-8; ethyl 1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate HCl, 50790-85-7; ethyl 1-methyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide, 50790-86-8; methyl 1-allyl-1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate iodide, 50883-30-2; 3-cyano-3-hydroxy-6,8-dimethylquinuclidine, 50790-87-9; 6,8-dimethyl-3-quinuclidinone, 50790-88-0; 3-methoxycarbonyl-3-hydroxy-6,8-dimethylquinuclidine, 50790-89-1; azabicyclo[2.2.2]oct-2-ene-3-carboxylic acid HCl, 50790-90-4; 4-(2-hydroxyethyl)-1,4,5,6-tetrahydro-1-propynylnicotinic acid lactone, 50790-91-5; 1-allyl-4-(2-hydroxyethyl)-1,4,5,6-tetrahydronicotinic acid lactone, 50790-92-6.

References and Notes

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(2) Correspondence should be addressed to AB Hassle, Fack, S-431 20 Mölndal, Sweden.
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1-Imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole. Reactions with Electrophiles[1]

R. D. Haugwitz,* B. V. Maurer, and V. L. Narayanan

The Squibb Institute for Medical Research, Princeton, New Jersey 08540

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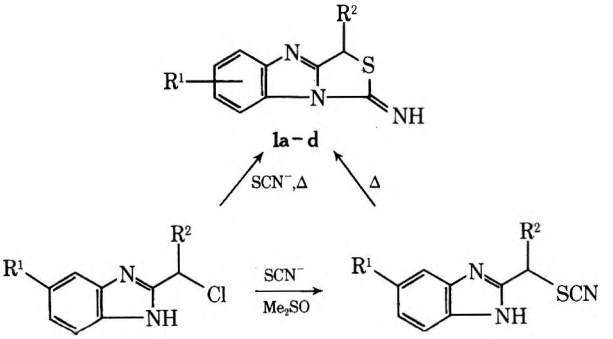
Intramolecular cyclization of 2-thiocyanoalkylbenzimidazole yielded the novel 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (1). Reaction of 1 with isocyanates gave exclusively the monoureas, 4. Treatment of 1 with strong electrophiles (acid chlorides, tosyl chloride, and halocarbonates) furnished the derivatives 8.

In a recent communication,[2] we reported a simple synthesis of the novel 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole ring system (1) by the intermolecular cyclization of 2-thiocyanoalkylbenzimidazoles, 2 (Scheme I). Our interest in medicinal aspects of compounds derived from benzimidazole[3] prompted a study of the parent compound, **1a**.

Initially, we sought solely to investigate reaction of the 1-imino group of **1a** with electrophiles. Treatment of **1a** with isocyanates yielded only the ureas, **4a-c**, rather than the enureas, **5**, that would be expected based on the results obtained by Chupp[4] with imines derived from cyclohexanone. Our efforts to synthesize the thioureas corresponding to 4 failed.

The product that resulted from heating of **1a** with acetic anhydride had an nmr spectrum that showed two methyl signals at δ 2.30 and 2.65 (DMSO-d_6) and a one-proton signal at δ 6.66 that was suggestive of a vinyl grouping. To distinguish between the two possible structures **6** and **8a**, we undertook the acid hydrolysis of this product. Whereas **6** should yield the enamino ketone **7**, hydrolysis of **8a** should furnish the cyclic thiocarbamate **9**. The nmr and ir data of the product obtained on the hydrolysis were identical with those of **9**, which was derived by acid treatment of **1a**, thus establishing the enamide structure **8a**. The postulated intermediate in this reaction, monoacetate **10**, was eventually isolated in 30% yield after we had acetylated **1a** with acetic anhydride for 3 min and quenched the reaction with water. However, even under these conditions, most of the starting material had already been converted to the diacetate **8a**. In analogous fashion we prepared enamides **8b** and **8c**, encarbamates **8d** and **8e**, and ensulfonamide **8f**. The product of hydrolysis of **1a**, namely **9** when acetylated with acetic anhydride gave the enamide **11**. Finally, monourea **4a**, when treated

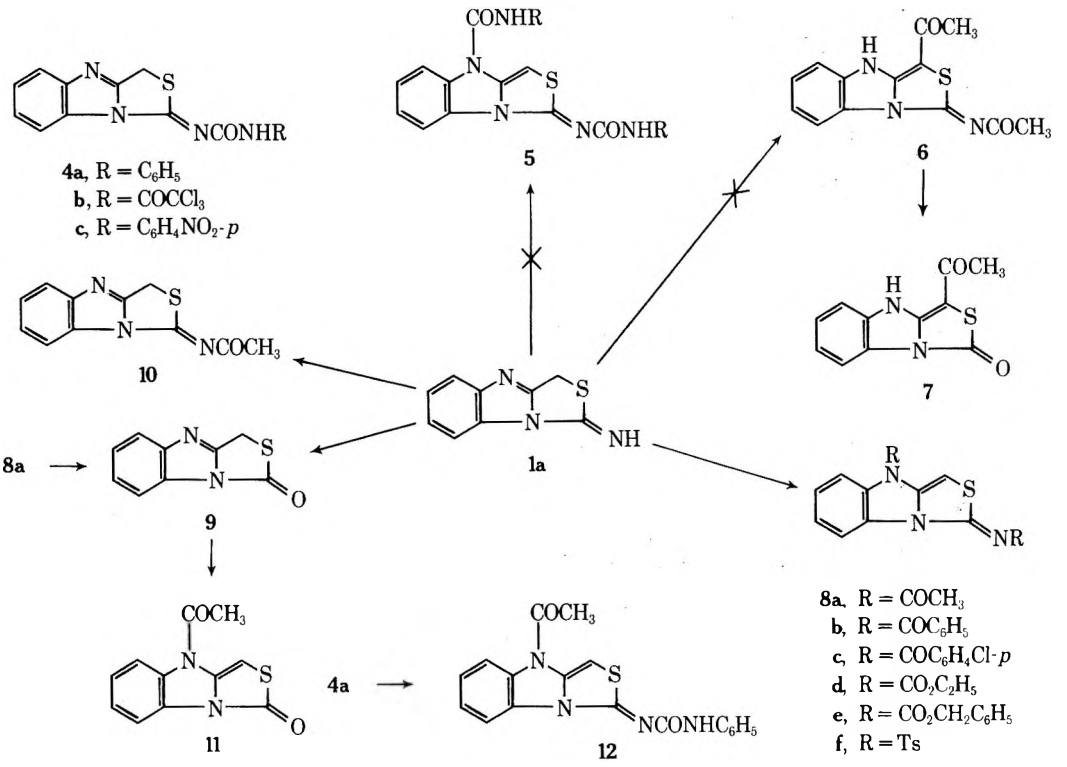
Scheme I



3a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = Me$
c, $R^1 = Cl$; $R^2 = H$
d, $R^1 = Me$; $R^2 = H$

2a, c

Scheme II

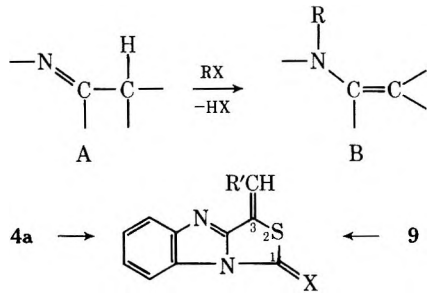


with acetic anhydride, yielded the urea enamide **12** (Scheme II). Similar "enacylamine" formations have been reported.[5-9]

It is suggested then that azomethines of type A, bearing a labile hydrogen (*i.e.*, enolizable imines), will, when exposed to very reactive electrophiles such as acid chlorides, acid anhydrides, tosyl chloride, and halocarbonates, yield substituted enamines, B. In the absence of the requisite α hydrogen, addition products or their displacement products[10] will be formed.

Lastly, derivatization of C_3 was achieved when **4a** or **9** was treated with the requisite aldehyde to furnish ylidenes **13a-d** (Scheme III).

Scheme III



13a, X = NCONHC$_6$H$_5$; R′ = C$_6$H$_5$

b, X = NCONHC$_6$H$_5$; R′ = 

c, X = NCONHC$_6$H$_5$; R′ = 

d, X = O; R′ = 

Experimental Section

Melting points were determined in capillary tubes on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Proton nmr spectra were obtained on a Varian A-60 instrument. Signals are described as singlet (s) or multiplet (m). For chromatography, neutral alumina (Woelm activity IV) was used.

2-Chloromethylbenzimidazoles (3). These derivatives were prepared according to known methods: **3a**,[11a] **3b**,[11b] **3c**,[11c] and **3d**.[11d]

Thiocyanic Acid (2-Benzimidazolyl)methyl Ester (2a). A solution of 8.4 g of ammonium thiocyanate and 9 g of 2-chloromethylbenzimidazole in 68 ml of dimethyl sulfoxide was stirred for about 15 min at room temperature. Water was added until no further precipitate formed, then the solid was filtered out and washed with water. Precipitation twice from dimethyl sulfoxide–water furnished, after drying, 4.2 g (41%) of the pure **2a**, mp 153–154°.

Anal. Calcd for $C_9H_7N_3S$: C, 57.20; H, 3.37; N, 22.23. Found: C, 57.10; H, 3.86; N, 21.96.

Thiocyanic Acid (5-Chloro-2-benzimidazolyl)methyl Ester (2c). A solution of 25 g of ammonium thiocyanate and 9.8 g of 5-chloro-2-chloromethylbenzimidazole in 125 ml of dimethyl sulfoxide was kept at 0° for 6 hr. Water was added, then the solid was filtered out and dried. Crystallization from chloroform–petroleum ether (bp 30–60°) yielded 4 g (38%) of **2c**, mp 125–128°.

Anal. Calcd for $C_9H_6ClN_3S$: C, 48.33; H, 2.70; N, 18.78. Found: C, 48.28; H, 2.98; N, 18.50.

1-Imino-1*H*-3*H*-thiazolo[3,4-*a*]benzimadazole (1a). Method A. A mixture of 1 g of 2-chloromethylbenzimidazole, 2 g of ammonium thiocyanate, and 30 ml of methanol was refluxed for 1 hr. The solvent was evaporated, then water was added to the residue and the solid was filtered off to yield 0.96 g (42%) of product, which was crystallized from methanol, mp 169–170°, mass spectrum *m/e* 189 (M^+).

Method B. A solution of 4.2 g of **2a** in 200 ml of methanol was refluxed for 1 hr. Water was added to the cooled solution until complete precipitation had been achieved. Recrystallization from methanol yielded 2 g (40%) of **1a**.

Anal. Calcd for $C_9H_7N_3S$: C, 57.12; H, 3.73; N, 22.20. Found: C, 57.23; H, 3.96; N, 22.20.

1-Imino-3-methyl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (1b). The preparation of **1b** was analogous to that of **1a**, method A (23%, after chromatography); **1b** had mp 117–118° (petroleum ether).

Anal. Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.47; N, 20.67. Found: C, 59.25; H, 4.46; N, 20.46.

6- (and 7-) Chloro-1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (1c). A mixture of 10 g of 2-chloromethyl-5-chlorobenzimidazole and 8 g of ammonium thiocyanate in 200 ml of dimethylformamide was heated for 3.5 hr at 50°. The mixture was allowed to stand overnight at room temperature. The solid that formed was filtered off and crystallized twice from ethyl ether to yield 6 g (59%) of pure **1c**, mp 156–158°.

Anal. Calcd for $C_9H_6ClN_3S$: C, 48.33; H, 2.70; N, 18.78. Found: C, 48.55; H, 2.96; N, 18.70.

Fractional crystallization from ether furnished two distinct crystal forms, bars and rosettes, which were separated by Pasteur's technique and recrystallized from ether. The rosettes had mp 158–159° (6 isomer); the bars had mp 161–162° (7 isomer).

6- (and 7-) Methyl-1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (1d). The preparation of **1d** was analogous to that of **1c** (19%); **1d** had mp 152–153° (ether).

Anal. Calcd for $C_{10}H_9N_3S$: C, 59.10; H, 4.47; N, 20.67. Found: C, 59.08; H, 4.78; N, 20.48.

1-Phenyl-3-(1*H*,3*H*-thiazolo[3,4-*a*]benzimidazol-1-ylidene)-urea (4a). A mixture of 5.7 g of **1a**, 10 ml of phenyl isocyanate, and 50 ml of ethyl acetate was refluxed for 1 hr. The solvent was evaporated, and the resulting residue was crystallized twice from benzene to yield 4 g (43%) of **4a**, mp 160° (melts, solidifies, melts again at 195–197°).

1-(1*H*,3*H*-Thiazolo[3,4-*a*]benzimidazol-3-ylidene)-3-(trichloroacetyl)urea (4b). The preparation of **4b** was analogous to that of **4a** (33%); **4b** had mp 180–182° (DMSO-water).

1-(*p*-Nitrophenyl)-3-(1*H*,3*H*-thiazolo[3,4-*a*]benzimidazol-3-ylidene)urea (4c). The preparation of **4c** was analogous to that of **4a** (50%); **4c** had mp 260–262° (pyridine).

9-Acetyl-3-(acetylimino)-3*H*,9*H*-thiazolo[3,4-*a*]benzimidazole (8a). A mixture of 5 g of **1a**, 5 g of anhydrous sodium acetate, and 20 ml of acetic anhydride was heated on a steam bath for 0.25 hr. On cooling a solid separated, and was filtered off and washed with water. Crystallization from chloroform yielded 3 g (87%) of pure **8a**, mp 258–261°.

9-Benzoyl-3-(benzoylimino)-3*H*,9*H*-thiazolo[3,4-*a*]benzimidazole (8b). To a solution of 1.9 g of **1a** in 250 ml of ethyl acetate and 10 ml of pyridine, there was added 3.1 g of benzoyl chloride. The mixture was refluxed for 0.5 hr and was then filtered hot. The residue obtained after evaporation of the solvent was filtered, washed with water, and crystallized from ethyl acetate to furnish 2 g (50%) of **8b**, mp 232–234°.

9-(*p*-Chlorobenzoyl)-3(*p*-chlorobenzoylimino)-3*H*,9*H*-thiazolo[3,4-*a*]benzimidazole (8c). To a solution of 3.6 g of **1a** in 10 ml of triethylamine and 250 ml of ethyl acetate there was added, dropwise, 7 ml of *p*-chlorobenzoyl chloride. The mixture was then refluxed for 20 min. The resulting solid was filtered off, washed with water, and crystallized from pyridine to yield 6 g (65%) of **8c**, mp 220°.

1-(Carboxyimino)-1*H*,4*H*-thiazolo[3,4-*a*]benzimidazole-4-carboxylic Acid Diethyl Ester (8d). A mixture of 5 g of **1a** and 50 ml of freshly distilled chloroethyl carbonate was refluxed for 1.5 hr. The cooled mixture was filtered and the remaining solid was washed with 10% NaOH and water. The dried solid was crystallized once from ethyl acetate and then twice from benzene to furnish 1.2 g (27%) of **8d**, mp 162–163°.

1-(Carboxyimino)-1*H*,4*H*-thiazolo[3,4-*a*]benzimidazole-4-carboxylic Acid Dibenzyl Ester (8e). The preparation of **8e** was analogous to that of **8d** (25%); **8e** had mp 168–170°.

4-(*p*-Tolylsulfonyl)-1-[(*p*-tolylsulfonyl)imino]-1*H*,4*H*-thiazolo[3,4-*a*]benzimidazole (8f). A mixture of 3.78 g of **1a**, 8 g of *p*-toluenesulfonyl chloride, 8 ml of pyridine, and 300 ml of benzene was stirred at room temperature for 2 days. The benzene solution was decanted and evaporated. After treatment of the benzene residue with excess $NaHCO_3$ solution, the remaining solid was filtered off, then was crystallized twice from acetone to furnish 2 g (20%) of **8f**, mp 197–198°.

1*H*,3*H*-Thiazolo[3,4-*a*]benzimidazol-3-one (9). To 195 ml of hot, concentrated hydrochloric acid (90°) there was added 7.8 g of **1a**. The mixture was kept on a steam bath for 10 min. The solution was cooled and brought to pH 5 with concentrated ammonia. The resulting precipitate was filtered and crystallized twice from ethyl acetate to yield 2.8 g (38%) of **9**, mp 212–224°.

1-(Acetylimino)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (10). A mixture of 0.5 g of **1a** and 20 ml of acetic anhydride was heated on a steam bath for about 1.5 min until the solid just dissolved. Water was added, and the resulting solid was filtered off, dried, and chromatographed on neutral Alumina (Woelm, activity IV). Elution with petroleum ether–ether (1:1) yielded the product, which was crystallized from petroleum ether–ether to yield 0.2 g (30%) of **10**, mp 195–197°.

4-Acetyl-1*H*,4*H*-thiazolo[3,4-*a*]benzimidazol-1-one (11). The preparation of **11** was analogous to that of **8a** (65%); **11** had mp 179–182° (ethyl acetate).

1-(4-Acetyl-1*H*,4*H*-thiazolo[3,4-*a*]benzimidazol-1-ylidene)-3-phenylurea (12). A mixture of 2.8 g of **4a** and 35 ml of acetic anhydride was heated on a steam bath for 15 min. The solid that formed was filtered out and crystallized from ethyl acetate to give 2.5 g (77%) of **12**, mp 153–155°.

1-(3-Benzylidene-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazol-1-ylidene)-3-phenylurea (13a). A mixture of 2.0 g of **8a** and 1.5 ml of benzaldehyde was refluxed for 3 min. After the reaction mixture had cooled, methanol was added. The resulting yellow solid was crystallized from chloroform–ether to yield 1.0 g (63%) of **13a**, mp 221–224°.

1-(3-Furfurylidene-1*H*,3*H*-thiazolo[1,2-*c*]benzimidazol-1-ylidene)-3-phenylurea (13b). The preparation of **13b** was analogous to that of **13a** (33%); **13b** had mp 230–234° (chloroform–ether).

1-Phenyl-3-[3-(2-thenylidene)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazol-1-ylideneurea (13c). The preparation of **13c** was analogous to that of **13a** (42%); **13c** had mp 256–258° (ether).

3-Thenylidene-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazol-1-one (13d). A solution of 2 g of **9** in 5 ml of 2-thiophenecarboxaldehyde was refluxed for 5 min. After the mixture had cooled, it was triturated with a few milliliters of methanol. The resulting yellow solid was filtered off and crystallized from chloroform to yield 1 g (35%) of **13d**, mp 211–212°.

Acknowledgment. We thank Drs. A. I. Cohen and M. Puar and Mrs. B. Toeplitz for the spectral data, and Mr. J. Alicino and his staff for the microanalyses.

Registry No.—**1a**, 34580-85-3; **1b**, 34580-83-1; **1c** 6 isomer, 34580-81-9; **1c** 7 isomer, 34580-80-8; **1d** 6 isomer, 34580-79-5; **1d** 7 isomer, 34580-78-4; **2a**, 34091-38-8; **2c**, 34091-37-7; **4a**, 37506-42-6; **4b**, 37506-43-7; **4c**, 37601-96-0; **8a**, 37506-45-9; **8b**, 37506-46-0; **8c**, 51065-52-2; **8d**, 37506-48-2; **8e**, 51065-53-3; **8f**, 51065-54-4; **9**, 34580-84-2; **10**, 37506-44-8; **11**, 51065-55-5; **12**, 37506-47-1; **13a**, 51065-56-6; **13b**, 51065-57-7; **13c**, 51065-58-8; **13d**, 51065-59-9; 2-chloromethylbenzimidazole, 4857-04-9; 5-chloro-2-chloromethylbenzimidazole, 20443-38-3.

Supplementary Material Available. Analytical data for compounds **4a–c** and **8–13** and pertinent spectral data (ir and nmr) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1359.

References and Notes

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Thermal Rearrangements of 2-Azido- and 2,3-Diazido-1,4-quinol Diacetates[1,2]

Dan S. Pearce, Mei-Sie Lee, and Harold W. Moore*

Department of Chemistry, University of California, Irvine, California 92664

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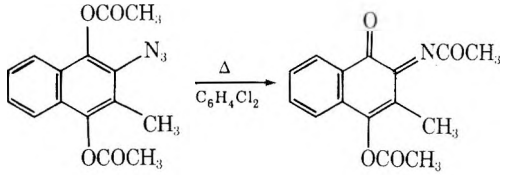
The thermal rearrangements of various 1,4-diacetoxy-2-azidobenzenes (**3a–c**) to *N*-acyl-*o*-quinoneimines (**4**) and of 1,4-diacetoxy-2,3-diazidobenzenes (**3f–h**) to *trans,trans*-1,4-diacetoxy-*cis,cis*-1,4-dicyano-1,3-butadienes (**21**) are reported. The scopes and mechanisms of these transformations are discussed. In addition, further synthetic utility of the pyrolytic cleavage of 1,4-diacetoxy-2,3-diazidoaryls is illustrated by the conversion of 1,4-diacetoxy-2,3-diazidonaphthalene (**3e**) to a mixture of *cis*- and *trans*-1,2-diacetoxy-1,2-dicyanobenzocylobutene (**22, 23**) and 1,4-diacetoxy-3-cyanoisoquinoline (**24**).

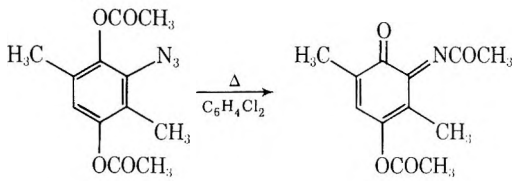
The general availability of azidoquinones[3] and their ease of conversion to reduced hydroquinone derivatives provide a convenient and facile route to a large variety of highly substituted aryl azides. Reported here is the synthesis and an investigation of the thermal chemistry of two such series of compounds. Specifically, the pyrolytic rearrangement of the 1,4-diacetoxy-2-azidobenzenes (**3a–c**) to the corresponding *N*-acyl quinoneimines (**4a–c**) and the thermally induced cleavage of 1,4-diacetoxy-2,3-diazidobenzenes (**3f–h**) to 1,4-diacetoxy-1,4-dicyano-1,3-butadienes (**21a–c**) are reported. The former transformation is without precedent in aryl azide chemistry, while the latter finds direct analogy in the previously reported thermal cleavage of o-diazidobenzenes to *cis,cis*-1,4-dicyano-1,3-butadienes.[4] To our knowledge, the only other report in the literature concerning the chemistry of 1,4-dioxygenated aryl azides is the observation that azidohydroquinones thermally disproportionate to the corresponding aminoquinones.[5]

Synthesis of Azidohydroquinone Diacetates. All of the azidohydroquinone diacetates (**3a–h**) reported here were conveniently prepared in reasonable yield by the simple sodium dithionite reduction of the corresponding azidoquinones (**1a–h**) followed by their acylation with acetic anhydride–pyridine. The hydroquinones (**2a–h**) were not isolated, but were converted *in situ* to the diacetates (**3a–h**) (Scheme I). The syntheses of all of the starting azidoquinones, with the exception of **1f** and **1g** (Experimental Section) have been previously reported.[3,6]

Thermolysis of 1,4-Diacetoxy-2-azidobenzenes. Thermal decomposition of the monoazidohydroquinone diacetates (**3a–c**) in refluxing *o*-dichlorobenzene (180°) or chlorobenzene (132°) resulted in their facile transformation to the corresponding *N*-acyl-1,2-quinoneimines (**4a–c**). The reactions were most conveniently accomplished by slowly adding a solution of the azide to the refluxing solvent. In most cases this resulted in an instantaneous reaction upon

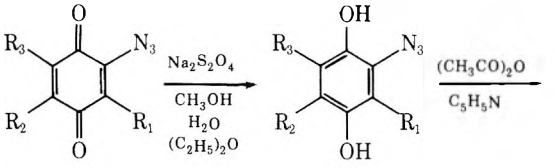


3a **4a** (89%)



3b **4b** (45%)

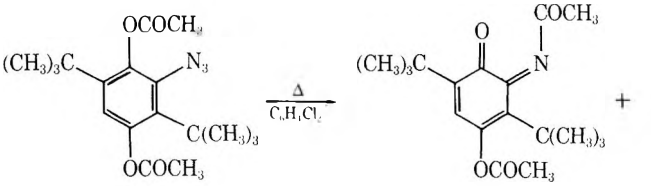
Scheme I



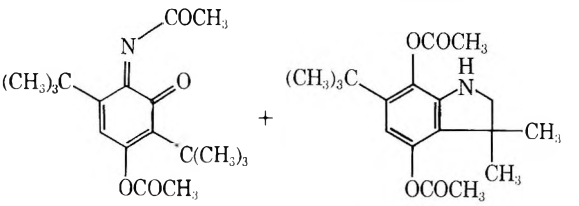
1 **2** **3**

	R_1	R_2	R_3	Yield, %
3a	CH_3	$-CH=CHCH=$	$CH-$	66
b	CH_3	H	CH_3	92
c	$C(CH_3)_3$	H	$C(CH_3)_3$	44
d	C_6H_5	H	C_6H_5	84
e	N_3	$-CH=CHCH=$	$CH-$	69
f	N_3	$-CH_2CH_2CH_2-$	CH_2-	64
g	N_3	C_6H_5	H	63
h	N_3	CH_3	CH_3	72

contact. The yields of the products were appreciably enhanced when the reactions were run in this manner as compared to simply refluxing a preformed solution of the azide.



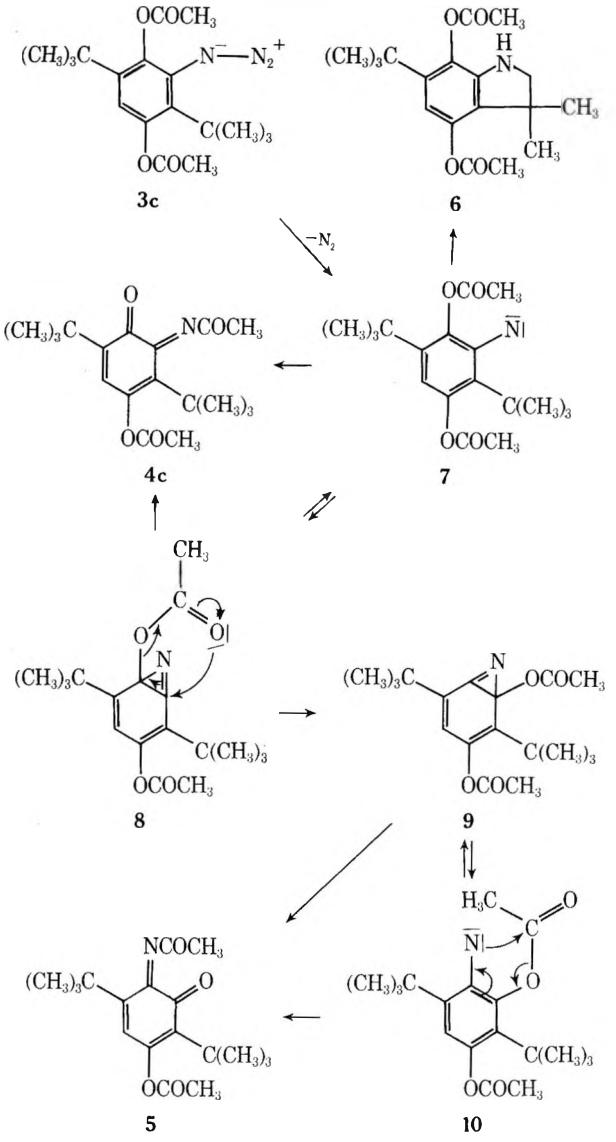
3c **4c** (69%)



5 (17%) **6** (1.5%)

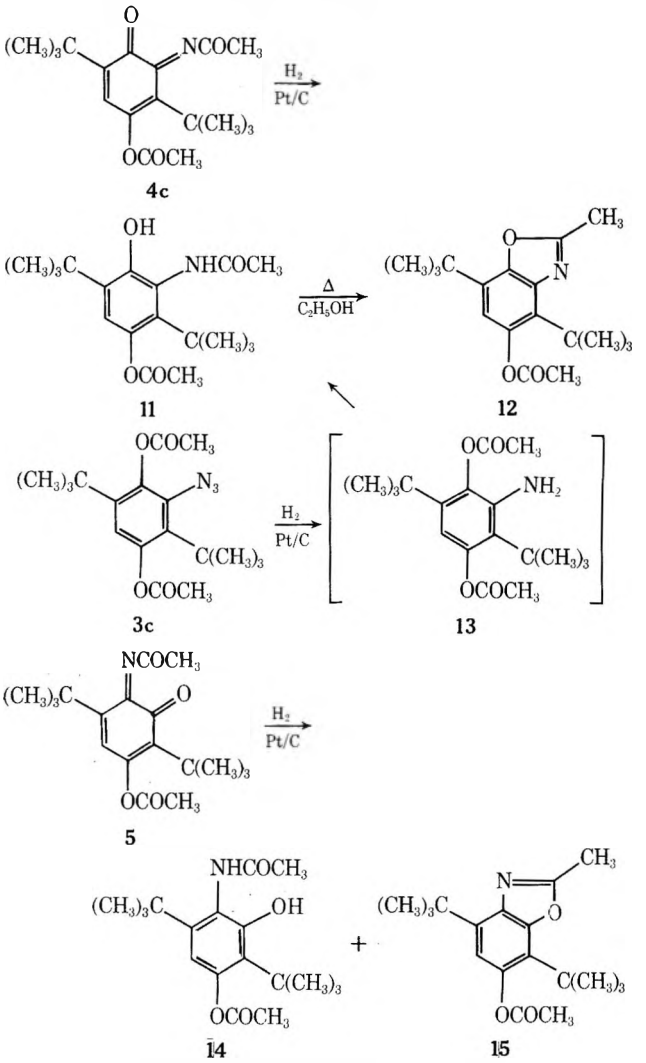
N-Acyl-1,2-quinoneimines of the type presented here constitute a previously unreported class of compounds and would be most difficult to prepare by other known methods. Their potential utility as o-quinone precursors is under investigation.

Scheme II



It should be noted that two additional products were isolated from the decomposition reaction of the azide **3c**. In addition to the major and anticipated product, **4c**, a minor isomeric quinoneimine, tentatively identified as **5**, and the ring-closed dihydroindole **6** were obtained. The quinoneimine **5** could arise *via* the azirine **8** while **6** most certainly is generated from an insertion reaction of a nitrene precursor (**7**). Whether the penultimate precursors of the isomeric quinoneimines, **4c** and **5**, are the respective azirines or nitrenes is not known. However, the fact that both isomers are formed suggests the conversion of **8** to **9** *via* the interesting indicated sigmatropic shift represented in Scheme II. These azirines could collapse directly to the quinoneimines or equilibrate with the respective nitrenes, which could then give the products *via* acyl migration.

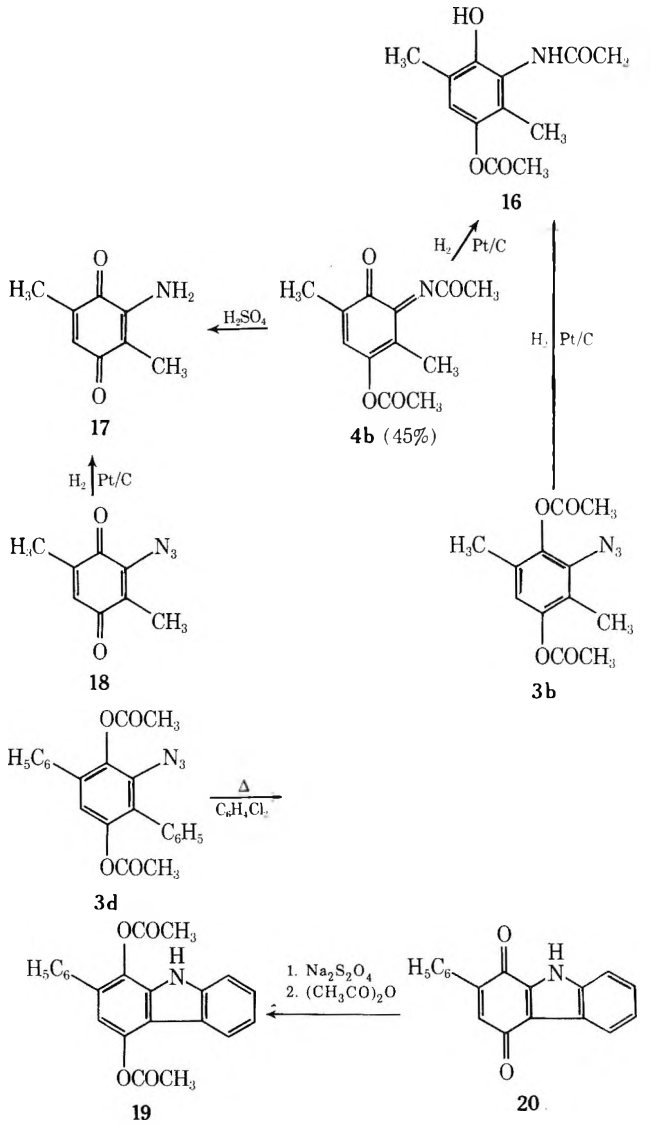
The structures of the products reported above are based upon both spectral and chemical properties. The quinoneimines all show characteristic ir absorptions for both carbonyl and imine double bonds. Their nmr spectra (Experimental Section) are also in strict agreement with their indicated formulations. Compound **4a** was chemically identified by its acid hydrolysis to the known aminoquinone, 2-amino-3-methyl-1,4-naphthoquinone.[5] Catalytic reduction of **4c** gave the phenol **11**, which was readily converted to the benzoxazole **12** in refluxing ethanol or in acetic anhydride–pyridine at 0–5°. The structural relationship of the various substituents of **4c** was established by the independent synthesis of **11** and **12** starting with 1,4-diacetoxy-2-azido-3,6-di-*tert*-butylbenzene (**3c**). Reduction of this azide with molecular hydrogen (Pt/C) gave **11** *via* the precursor **13**. The phenol **11**, in turn, was converted to the benzoxazole **12** as described above. The quinoneimine **5** was converted to **14** and **15** upon catalytic reduction. However, since these same compounds were not prepared by an independent route and since the spectral properties of **5**, **14**, and **15** do not unambiguously establish the orientation of the various substituents, the exact isomeric relationship of **4c** to **5** remains somewhat clouded.



Like **4a** and **4c**, the structure of **4b** was also well documented. The phenol, 2-acetamido-4-acetoxy-3,6-dimethylphenol (**16**), was obtained from both the quinoneimine **4b** and the azide **3b** by catalytic reduction. In addition, hydrolysis of **4b** in concentrated sulfuric acid gave 2-amino-3,6-dimethyl-1,4 benzoquinone (**17**), which was identical in all respects with the aminoquinone obtained by catalytic reduction of 2-azido-3,6-dimethyl-1,4-benzoquinone[3] (**18**).

Thermal decomposition of 1,4-diacetoxy-2-azido-3,6-diphenylbenzene (**3d**) in refluxing *o*-dichlorobenzene took a different course from that described above in that no quinoneimine was isolated. The only product identified was the carbazole **19**, obtained in 61% yield. The same heterocyclic compound was prepared in an independent manner by reductive acylation of the known indolequinone **20**,[7] thus firmly documenting its constitution.

The formation of **19** from the azide **3d** is suggestive of a nitrenoid intermediate.[8] This, along with the fact that the



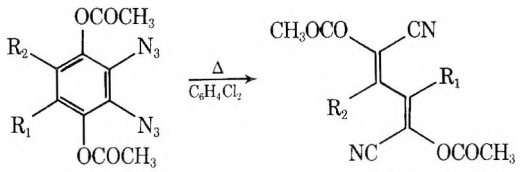
dihydroindole **6** is also generated from the azide **3c**, implies that monovalent nitrogen intermediates may be precursors to the quinoneimines **4a–c**. See, for example, Scheme II. However, the detailed mechanistic pathways for these transformations await further study. It is worthy of note that the formation of the quinoneimines does involve an acyl migration, a process rarely observed in the pyrolytic decomposition of organic azides.[9]

Thermolysis of 1,4-Diacetoxy-2,3-diazidobenzenes. Unlike the monoazides, 1,4-diacetoxy-2,3-diazidobenzenes (**3f–h**) (Scheme III) smoothly undergo a thermally induced ring cleavage in refluxing *o*-dichlorobenzene to give the 1,4-diacetoxy-1,4-dicyano-1,3-butadienes, respectively (**21a–c**). The stereochemistry of these dienes was not determined. However, based upon the unique report of Hall and Patterson[4] that simpler *o*-diazidobenzenes thermally cleave to *cis,cis*-1,4-dicyano-1,3-butadienes, it is assumed that a completely analogous transformation occurs here.

The fact that a large variety of substituted quinones are commercially and synthetically available and that they are easily converted to the corresponding *o*-diazidobenzenes provides a convenient source of highly substituted *trans,trans*-1,4-diacetoxy-*cis,cis*-1,4-dicyano-1,3-butadienes *via* the route described here. The highly functionalized dienes **21a–c**, which can be regarded as the acylated cyanohydrins of bis(ketenes), are masked 1,4-dicarbonyl moieties and may find corresponding synthetic utility.

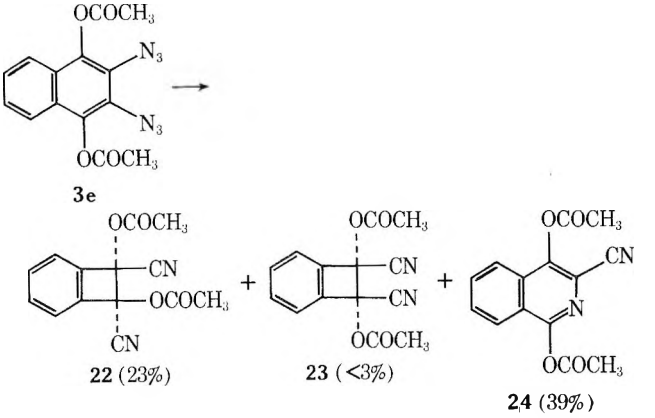
The spectral properties of the dienes **21a–c** are in agreement with their proposed structures (Experimental Section).

Scheme III

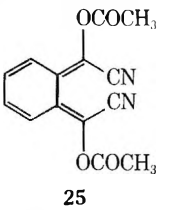


	R_1	R_2	Yield, %
21a	$-CH_2CH_2CH_2-$		77
b	C_6H_5	H	72
c	CH_3	CH_3	94

As yet, nothing is known of their chemical properties except that they are very poor Diels–Alder dienes, as one might expect since they are 1,4 tetrasubstituted. Molecular models, in fact, show a serious steric interaction between the linear cyano substituents when the dienes are in the s-cis conformation. Synthetic advantage was taken of the propensity of these dienes to avoid the planar s-cis conformation. Thermal decomposition of 1,4-diacetoxy-2,3-diazidonaphthalene (**3e**) would give a quinodimethane (**25**) in which the exocyclic diene system is obliged to reside in a planar s-cis conformation. Electronically as well as sterically, such a compound is favored to undergo electrocyclic ring closure and thus provide a direct route to the benzocyclobutene ring system. Indeed, such a transformation was observed. Decomposition of the diazidonaphthalene **3e** gave a mixture of the isomeric benzocyclobutenes **22** and **23** along with the unexpected isoquinoline **24**.



The stereochemical constitutions of **22** and **23** were not unambiguously established. However, from orbital symmetry considerations one would predict the major, if not the exclusive, isomer to be the trans, *i.e.*, **22**, which would arise *via* a conrotatory ring closure of the intermediate quinodimethane **25**.[10] Also, the ultraviolet absorption



spectra of **22** and **23** are in good agreement with their respectively assigned structures and stereochemistry. That is, an acetonitrile solution of **22** showed absorptions at 257 (2.74), 263 (2.89), and 270 nm (2.85) as compared to a solution of the cis isomer **23**, which absorbed at 257 (2.81), 263 (2.97), and 270 nm (2.90). Note that the extinction coefficients for the cis isomer are slightly larger than those for the trans. This observation, along with the characteris-

tic position of the three absorptions, are in strict accord with other 1,2-dioxygenated benzocyclobutenes.[11] For example, *trans*-1,2-dimethyl-1,2-dihydroxybenzocyclobutene absorbs at 258 (2.96), 265 (3.15), and 270.5 nm (3.09) while the cis isomer absorbs at 258 (3.02), 264 (3.18), and 270.5 nm (3.14).

In addition to its spectral characteristics (Experimental Section), the constitution of the isoquinoline **24** has its foundation on the fact that it undergoes hydrolytic (HI) conversion to the known 4-hydroxy-1-2*H*-isoquinolone.[12]

The formation of 1,4-diacetoxy-3-cyanoisoquinoline (**24**) from **3e** is most intriguing and must result from a very deep-seated rearrangement. An attractive possibility for such a mechanism is based upon the well-documented and fascinating gas-phase equilibration of phenylnitrenes and α-pyridylcarbenes.[13] In the case at hand, the nitrene **26** would rearrange to the azidocarbene **30** which, upon nitrogen loss, would give **24** (Scheme IV).

The rearrangements and cleavage reactions described in this paper illustrate further the synthetic utility of azidoquinones and related compounds. These compounds are readily available and constitute a synthetically versatile class of reagents. Depending upon their substitution pattern and, as illustrated here, their oxidation state, they can be converted to γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides,[3] 2-cyano-4-cyclopentene-1,3-diones,[7] cyanoketenes,[14] azepine-2,5-diones,[15] diacyl cyanides,[6,16] 3-cyano-2-azaquinones,[16] aminoquinones,[5] indolequinones,[17] 2-alkenyl-2,3-dihydroindole-4,7-diones,[1] and, now, 4-acetoxy-1,2-quinone-2-(*N*-acetyl)imines (**4**) and *trans,trans*-1,4-diacetoxy-*cis,cis*-1,4-dicyano-1,3-butadienes (**21**).

Experimental Section

General Procedure for the Preparation of 1,4-Diacetoxy-2-azido- (or 2,3-diazido-) benzenes (3). A suspension or solution of the corresponding azidoquinone **1** (0.5 mmol) in approximately 50–100 ml of diethyl ether and 10–20 ml of methanol was stirred at ambient temperature under an atmosphere of nitrogen. Excess aqueous sodium dithionite solution was then added and the two-phase mixture was vigorously stirred until the color stopped fading (10–30 min). The organic layer was separated and the aqueous layer was washed several times with ether. The combined organic layers were then dried and the solvent was removed *in vacuo* at temperatures below 30°. The resulting residue was dissolved in acetic anhydride–pyridine (4:1) and allowed to stand at room temperature or below for 5–20 hr. The reaction solution was then poured into ice and water and the resulting diacetates **3** were collected by filtration. Recrystallization from ethanol gave the pure samples.

1,4-Diacetoxy-2-azido-3-methylnaphthalene (3a). The title compound was prepared in 66% yield by the general procedure. Characteristic properties of **3a** follow: mp 145–146 dec; ir (Nujol) 2120, 1760 cm^{-1}; nmr ($CDCl_3$) δ 2.20 (s, 3), 2.49 (s, 6), 7.5 (m, 4).

Anal. Calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.20; H, 4.50; N, 13.90.

1,4-Diacetoxy-2-azido-3,6-dimethylbenzene (3b). The title compound was prepared in 92% isolated yield as described above and showed the following characteristic properties: mp 81–83°; ir (Nujol) 2114, 1764 cm^{-1}; nmr ($CDCl_3$) δ 2.03 (s, 3), 2.09 (s, 3), 2.26 (s, 3), 2.34 (s, 3), 6.75 (s, 1).

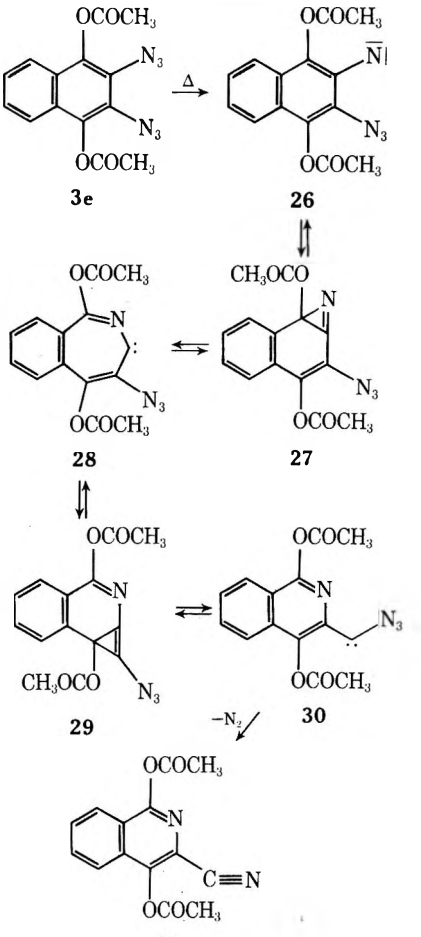
Anal. Calcd for $C_{12}H_{13}N_3O_4$: C, 54.74; H, 4.94; N, 15.96. Found: C, 54.56; H, 4.94; N, 15.93.

1,4-Diacetoxy-2-azido-3,6-di-*tert*-butylbenzene (3c). The title compound was prepared in 44% isolated yield as described above and showed the following characteristic properties: mp 134–136°; ir (Nujol) 2105, 1773, 1754 cm^{-1}; nmr ($CDCl_3$) δ 1.31 (s, 9), 1.47 (s, 9), 2.24 (s, 3), 2.40 (s, 3), 6.78 (s, 1).

Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.24; H, 7.20; N, 12.10. Found: C, 62.18; H, 7.15; N, 12.14.

1,4-Diacetoxy-2-azido-3,6-diphenylbenzene (3d). The title compound was prepared in 84% isolated yield as described above and showed the following characteristic properties: mp 149–151°; ir (Nujol) 2123, 1783, 1767 cm^{-1}; nmr ($CDCl_3$) δ 1.87 (s, 3), 2.04 (s, 3), 7.0 (s, 1), 7.55–7.18 (m, 10).

Scheme IV



Anal. Calcd for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.39; N, 10.85. Found: C, 67.95; H, 4.56; N, 10.56.

1,4-Diacetoxy-2,3-diazidonaphthalene (3e). The title compound was prepared in 69% isolated yield as described above and showed the following characteristic properties: mp 134–135° dec; ir (Nujol) 2120, 1770 cm^{-1}; nmr ($CDCl_3$) δ 2.48 (s, 6), 7.4–7.8 (m, 4).

Anal. Calcd for $C_{14}H_{10}N_6O_4$: C, 51.53; H, 3.09; N, 25.76. Found: C, 51.47; H, 3.11; N, 25.76.

1,4-Diacetoxy-2,3-diazido-5,6,7,8-tetrahydronaphthalene (3f). The title compound was prepared in 64% isolated yield as described above and showed the following characteristic properties: mp 107–109 dec; nmr ($CDCl_3$) δ 1.5–1.7 (m, 4), 2.3–2.6 (m, 4), 2.32 (s, 6).

Anal. Calcd for $C_{14}H_{14}N_6O_4$: C, 50.91; H, 4.27; N, 25.45. Found: C, 50.99; H, 4.22; N, 25.38.

1,4-Diacetoxy-2,3-diazido-5-phenylbenzene (3g). The title compound was prepared in 63% isolated yield as described above and showed the following characteristic properties: mp 79–81°; ir (Nujol) 2120, 1760, 1560 cm^{-1}; nmr ($CDCl_3$) δ 2.05 (s, 3), 2.31 (s, 3), 6.96 (s, 1), 7.37 (s, 5).

Anal. Calcd for $C_{16}H_{12}N_6O_4$: C, 54.54; H, 3.43; N, 23.85. Found: C, 54.58; H, 3.41; N, 23.88.

1,4-Diacetoxy-2,3-diazido-5,6-dimethylbenzene (3h). The title compound was prepared in 72% isolated yield as described above and showed the following characteristic properties: mp 101–101.5° dec; ir (Nujol) 2120, 1760 cm^{-1}; nmr ($CDCl_3$) δ 2.01 (s, 6), 2.33 (s, 6).

Anal. Calcd for $C_{12}H_{12}N_6O_4$: C, 47.37; H, 3.96; N, 27.63. Found: C, 47.40; H, 3.91; N, 27.61.

2,3-Diazido-5,6,7,8-tetrahydro-1,4-naphthoquinone (1f). A solution of 4 g of sodium azide in 10 ml of water was added to a well-stirred solution of 3.0 g (13 mmol) of 2,3-dichloro-5,6,7,8-tetrahydro-1,4-naphthoquinone[18] in 50 ml of dichloromethane–methanol (1:1). The two-phase mixture was stirred at room temperature for 12 hr and then diluted with water. The organic layer was collected and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The resultant deep red semisolid was recrystallized (methanol) to give the diazide as deep maroon crystals, mp 75–77° dec.

This diazide showed the following characteristic spectral properties: ir (Nujol) 2120, 1650, 1560 cm^{-1}; nmr ($CDCl_3$) δ 1.77 (m, 4), 2.44 (m, 4).

Anal. Calcd for $C_{10}H_8N_6O_2$: C, 49.18; H, 3.30; N, 34.42. Found: C, 49.26; H, 3.42; N, 34.50.

2,3-Diazido-5-phenyl-1,4-benzoquinone (1g). A solution of 5 g of sodium azide in 25 ml of water was added to a well-stirred solution of 5.0 g (20 mmol) of 2,3-dichloro-5-phenyl-1,4-benzoquinone in 200 ml of ethanol–dichloromethane (1:1). The two-phase mixture was stirred at room temperature for 2 hr, at which time it had become a deep purple color. Water was added and the organic layer was collected. It was dried and the solvent was removed *in vacuo*. The residue was recrystallized from ethanol–dichloromethane to give the diazide as lustrous purple crystals, mp 115–117° dec. This diazide showed the following characteristic spectral properties: ir (Nujol) 2100, 1640, 1575 cm^{-1}; nmr ($CDCl_3$) δ 6.65 (s, 1), 7.31 (s, 5).

Anal. Calcd for $C_{12}H_6N_6O_2$: C, 54.05; H, 2.43; N, 31.51. Found: C, 54.28; H, 2.34; N, 31.51.

4-Acetoxy-3-methyl-1,2-naphthoquinone-2-(*N*-acetyl)imine (4a). A solution of 0.50 g (1.7 mmol) of 1,4-diacetoxy-2-azido-3-methylnaphthalene (**3a**) in 5 ml of warm o-dichlorobenzene was slowly added to 10 ml of gently refluxing o-dichlorobenzene. Nitrogen gas was immediately evolved and the solution became a honey-yellow color. The solvent was removed *in vacuo* and the resulting yellow solid was recrystallized (dichloromethane–cyclohexane) to give, in two crops, 0.41 g (89%) of the imine **4a** as deep yellow needles, mp 175–178° dec.

Characteristic spectral properties of **4a** follow: ir (Nujol) 1760, 1690, 1670, 1630, 1590 cm^{-1}; nmr ($CDCl_3$) δ 1.98 (s, 3), 2.31 (s, 3), 2.43 (s, 3), 7.2–8.2 (m, 4).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.46; H, 4.76; N, 5.20. Found: C, 66.41; H, 4.83; N, 5.16.

2-Amino-3-methyl-1,4-naphthoquinone. The imine **4a** (0.10 g) was slowly added to 5 ml of cold concentrated sulfuric acid, resulting in a pale red solution. The solution was warmed to room temperature, stirred for 1 hr further, and then poured over ice. Recrystallization of the resulting precipitate (ethanol) gave 50 mg of 2-amino-3-methyl-1,4-naphthoquinone, mp 165–167°, which was identical with that prepared independently by catalytic reduction of 2-azido-3-methyl-1,4-naphthoquinone.

4-Acetoxy-3,6-dimethyl-1,2-benzoquinone-2-(*N*-acetyl)imine (4b). A suspension of 2.2 g (8.2 mmol) of 1,4-diacetoxy-2-azido-3,6-dimethylbenzene (**3b**) in 5 ml of chlorobenzene was slowly (1 min) dropped into 10 ml of refluxing o-dichlorobenzene and the solution was refluxed for an additional 40 min. The solvent was then removed *in vacuo* and the residue was chromatographed on 70 g of silica gel. Elution with chloroform gave 1.2 g of recovered starting material (**3b**) and 410 mg (45% yield based upon reacted azide) of the quinoneimine **4b**, mp 112–113°. Characteristic spectral properties for **4b** follow: ir (Nujol) 1751, 1681, 1653, 1613 cm^{-1}; nmr ($CDCl_3$) δ 1.91 (br, 6), 2.30 (s, 3), 2.26 (s, 3), 6.73 (q, 1, J = 1.2 Hz).

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.53; N, 5.95. Found: C, 61.18; H, 5.53, N, 5.95.

2-Amino-3,6-dimethyl-1,4-benzoquinone. A sample of 118 mg (0.5 mmol) of **4b** was slowly added to 3 ml of cold concentrated sulfuric acid. The color immediately changed from orange to purple and after 5 min of continued stirring the solution was poured into ice–water. The resulting mixture was extracted with dichloromethane, and the solvent was removed *in vacuo*. The residue was chromatographed on 15 g of silica gel using chloroform as the eluent, giving 25 mg (33%) of 2-amino-3,6-dimethyl-1,4-benzoquinone and 30 mg (31%) of 2-(*N*-acyl)-2-amino-3,6-dimethyl-1,4-benzoquinone.

The purple crystalline aminoquinone, mp 183° (sublimed), was identical with the product obtained upon catalytic reduction of 2-azido-3,6-dimethyl-1,4-benzoquinone. The *N*-acyl derivative, mp 157–159°, showed the following characteristic spectral and analytical properties: ir (Nujol) 3279, 1681, 1656, 1631 cm^{-1}; nmr ($CDCl_3$) δ 1.91 (s, 3), 2.03 (d, 3, J = 1.2 Hz), 2.20 (s, 3), 6.60 (q, 1, J = 1.2 Hz), 7.67 (br, 1).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.69; N, 7.25. Found: C, 62.07; H, 5.68; N, 7.22.

Thermolysis of 1,4-Diacetoxy-2-azido-3,6-di-*tert*-butylbenzene. Formation of 4-Acetoxy-3,6-di-*tert*-butyl-1,2-benzoquinone-2-(*N*-acetyl)imine (4c), 5-Acetoxy-3,6-di-*tert*-butyl-1,2-benzoquinone-2-(*N*-acetyl)imine (5), and 4,7-Diacetoxy-6-*tert*-butyl-3,3-dimethyl-2,3*H*-indole (6). A suspension of 2.3 g (6.62 mmol) of the azide **3c** in 5 ml of o-dichlorobenzene was slowly added (1 min) to 10 ml of refluxing o-dichlorobenzene. The solution was refluxed for 10 min, at which time all starting material had been consumed (tlc, silica gel, CH_2Cl_2). Nmr analysis of the reaction mixture showed only absorptions corresponding to **4c** and **5** in a ratio of 4.1:1.0, respectively.

The solvent was then removed with a stream of nitrogen and the orange residue was recrystallized from chloroform–ether to give 280 mg of the quinoneimine **5**. From the mother liquor, a total of 1.54 g of **4c** (contaminated with some **5**) and 30 mg of the dihydroindole **6** were isolated by fractional crystallization. Characteristic properties of these compounds follow. Quinoneimine **4c**: mp 102–104° (4% contamination of isomer **5** present); ir (Nujol) 1757, 1681, 1664, 1610 cm^{-1}; nmr ($CDCl_3$) δ 1.19 (s, 9), 1.37 (s, 9), 2.27 (s, 6), 6.50 (s, 1). *Anal.* Calcd for $C_{18}H_{25}NO_4$: C, 67.71; H, 7.83; N, 4.38. Found: C, 67.70; H, 7.90; N, 4.44. Quinoneimine **5**: mp 148–153°; ir (Nujol) 1761, 1686, 1661, 1613 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (s, 9), 1.28 (s, 9), 2.27 (s, 6), 6.24 (s, 1). *Anal.* Found: C, 67.49; H, 7.80; N, 4.32. Dihydroindole **6**: mp 200–201°; ir (Nujol) 2597, 1764 cm^{-1}; nmr ($CDCl_3$) δ 1.31 (s, 6), 1.36 (s, 9), 2.25 (s, 6), 3.70 (s, 2), 6.75 (s, 1), 10.85 (s, 1, disappears completely with D_2O added in 3.5 days). *Anal.* Found: C, 67.64; H, 7.85; N, 4.33.

Catalytic Reduction of 4-Acetoxy-3,6-di-*tert*-butyl-1,2-benzoquinone-2-(*N*-acetyl)imine (4c). A solution of 957 mg (3 mmol) of **4c** in 100 ml of diethyl ether was hydrogenated in the presence of 200 mg of 5% Pt/C at ambient temperature under 37 psi for 4 min. The catalyst and solvent were removed, leaving a slightly colored oily residue. This residue was dissolved in low-boiling petroleum ether and cooled to give 400 mg of 4-acetoxy-2-(*N*-acetyl)-3,6-di-*tert*-butylphenol (**11**), mp 145–148°. Five careful recrystallizations from dichloromethane–petroleum ether gave the analytical sample, mp 157–158°. Characteristic spectral properties follow: ir (Nujol) 3333, 3247, 1742, 1669 cm^{-1}; nmr ($CDCl_3$) δ 1.43 (s, 9), 1.52 (s, 9), 2.17 (s, 3), 2.25 (s, 3), 2.72 (s, 1), 6.85 (s, 1), 7.47 (s, 1).

Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.28; H, 8.41; N, 4.36. Found: C, 67.26; H, 8.28; N, 4.35.

From the above mother liquor 410 mg of the oxazole derivative **12** was isolated, mp 92–95°. Five recrystallizations (ether–petroleum ether) gave the analytical sample, mp 93–95°. Characteristic spectral properties of **12** follow: ir (Nujol) 1757, 1608 cm^{-1}; nmr ($CDCl_3$) δ 1.52 (s, 9), 1.68 (s, 9), 2.28 (s, 3), 2.59 (s, 3), 6.70 (s, 1).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.28; H, 8.25; N, 4.62. Found: C, 71.36; H, 8.22; N, 4.48.

Conversion of the Phenol 11 to the Benzoxazole 12. A solution of 40 mg of **11** in 5 ml of 95% ethanol was refluxed for 3 hr. Evaporation of the solvent gave 35 mg of **12**, which was identical in all respects with the compound described above. The same transformation was accomplished in 84% yield when **11** was treated with acetic anhydride–pyridine at 0–5° for 2 days.

Catalytic Reduction of 1,4-Diacetoxy-2-azido-3,6-di-*tert*-butylbenzene (3c). A solution of 347 mg of **3c** in 100 ml of diethyl ether was hydrogenated in the presence of 100 mg of 5% Pt/C at ambient temperature at 36 psi for 20 min. From the reaction solution, 80 mg of the phenol **11** was isolated. If the hydrogenation was allowed to go for 4.75 hr, a 12% yield of **11** and a 69.3% yield of **12** were obtained; after 40 hr only the oxazole was isolated (89%).

Catalytic Reduction of 5-Acetoxy-3,6-di-*tert*-butyl-1,2-benzoquinone-2-(*N*-acetyl)imine (5). A suspension of 200 mg of **5** in 50 ml of 95% ethanol was hydrogenated in the presence of 100 mg of 5% Pt/C at ambient temperature under 36 psi for 15 min. Filtration and removal of the solvent at room temperature gave a residue which upon recrystallization from dichloromethane–petroleum ether gave 100 mg of 5-acetoxy-2-(*N*-acetyl)-3,6-di-*tert*-butylphenol (**14**). Recrystallization again gave the pure sample, mp 148–151°. Characteristic spectral properties of **14** follow: ir (Nujol) 3571, 3236, 1742, 1656 cm^{-1}; nmr ($CDCl_3$) δ 1.46 (s, 9), 1.56 (s, 9), 1.62 (s, 1, exchangeable), 2.25 (s, 3), 2.27 (s, 3), 6.50 (s, 1), 7.63 (s, 1, exchangable).

The mother liquor from the above yielded 50 mg of the benzoaxazole **15**. Recrystallization from diethyl ether gave the analytical sample: mp 100–101°; ir (Nujol) 1757, 1608 cm^{-1}; nmr ($CDCl_3$) δ 1.58 (s, 9), 1.60 (s, 9), 2.30 (s, 3), 2.59 (s, 3), 6.47 (s, 1).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.28; H, 8.25; N, 4.62. Found: C, 71.39; H, 8.26; N, 4.71.

Catalytic Reduction of 4-Acetoxy-3,6-dimethyl-1,2-benzoquinone-2-(*N*-acetyl)imine (4b). Formation of 4-Acetoxy-2-(*N*-acetyl)-3,6-dimethylphenol (16). A solution of 100 mg (0.425 mmol) of **4b** in 50 ml of diethyl ether was hydrogenated at ambient temperature in the presence of 100 mg of 5% Pt/C at 36 psi.

After approximately 5 min the reaction mixture was filtered and the solvent was removed *in vacuo*. Recrystallization of the residue gave 80 mg (79%) of the phenol **16**: mp 185–186°; ir (Nujol) 3413, 3226, 1742, 1667 cm^{-1}; nmr ($CDCl_3$) δ 1.87 (s, 3), 2.12 (s, 3), 2.20 (s, 3), 2.27 (s, 3), 6.75 (s, 1), 7.62 (s, 1, exchangeable), 7.73 (s, 1, exchangable).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.32; N, 5.90. Found: C, 60.81: H, 6.32; N, 5.82.

Catalytic Reduction of 1,4-Diacetoxy-2-azido-3,6-dimethylbenzene (3b). Formation of 4-Acetoxy-2-(*N*-acetyl)-3,6-dimethylphenol (16). The phenol **16** was obtained in 93% yield by catalytic reduction of **3b** under the same above-described conditions.

1,4-Diacetoxy-2-phenylcarbazole (19). A suspension of 3.87 g (10 mmol) of 1,4-diacetoxy-2-azido-3,6-diphenylbenzene (**3d**) in 10 ml of o-dichlorobenzene was slowly dropped (2 min) into 10 ml of refluxing o-dichlorobenzene. Refluxing was continued for an additional 40 min. Most of the solvent was removed by passing a stream of nitrogen over the surface of the reaction solution. Then chloroform–ether (1:1) was added which caused precipitation of 1.76 g of nearly pure carbazole **19**. The solvent from the mother liquor was removed *in vacuo* and the residue was chromatographed on 200 g of silica gel using methylene chloride as the solvent. This yielded 620 mg more of **19**, bringing the total yield to 61%. Recrystallization from methylene chloride–petroleum ether gave the analytical sample: mp 219–220°; ir (Nujol) 3401, 1757 cm^{-1}; nmr ($CDCl_3$) δ 2.08 (s, 3), 2.48 (s, 3), 7.07–8.09 (m, 10), 8.26 (s, 1, exchangeable).

Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.73; N, 3.89. Found: C, 73.42; H, 4.73; N, 3.81.

The same carbazole (**19**) was prepared by dithionite reduction of the quinone **20** followed by acetic anhydride–pyridine acylation of the resulting hydroquinone; all operations were done under known standard conditions.

A red crystalline compound was also isolated from the above chromatography. Recrystallization twice from ethyl acetate–ether–petroleum ether gave a sample melting at 203–205°. Spectral properties follow: ir (Nujol) 1767, 1751, 1724, 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.83 (s, 3), 1.95 (s, 3), 2.61 (s, 3), 6.85 (s, 1), 7.50 (m, 17), 8.30 (m, 2).

Anal. Found: C, 76.11; H, 4.89; N, 4.01.

***trans,trans*-1,4-Diacetoxy-*cis,cis*-1,4-dicyano-2,3-tetramethylene-1,3-butadiene (21a).** A solution of 0.416 g (1.26 mmol) of 1,4-diacetoxy-2,3-diazido-5,6,7,8-tetrahydronaphthalene (**3f**) in 3 ml of warm o-dichlorobenzene was added dropwise in 3 ml of gently refluxing o-dichlorobenzene. A pink color formed which faded to a yellow orange. After 10 min of further refluxing, the solution was cooled and the solvent was removed *in vacuo*. Recrystallization of the resulting residue from benzene–carbon tetrachloride gave 0.26 g (77%) of the diene **21a**, mp 153–155°. Characteristic spectral properties of **21a** follow: ir (Nujol) 2220, 1775, 1640 cm^{-1}; nmr ($CDCl_3$) δ 1.5–3.0 (m, 8), 2.26 (s, 6); mass spectrum *m/e* (rel intensity) 232 (2), 190 (16), 43 (100); uv (acetonitrile) 208 (4.81), 246 nm (3.88).

Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.25; H, 5.05; N, 10.24.

***trans,trans*-1,4-Diacetoxy-*cis,cis*-1,4-dicyano-2-phenyl-1,3-butadiene (21b).** A solution of 1.5 g (4.25 mmol) of 1,4-diacetoxy-2,3-diazido-5-phenylbenzene in 3 ml of warm o-dichlorobenzene was added dropwise to 25 ml of gently refluxing decalin. The solution turned a deep red and then lightened to an orange color. The solution was then refluxed for an additional 5 min and cooled. The resulting precipitate was washed with hexane to give 0.9 g (72%) of the diene **21b**, mp 82–86°. Recrystallization from carbon tetrachloride gave the analytical sample, which showed the following characteristic properties: mp 89–90°; ir (Nujol) 2220, 1770, 1630, 1590 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (s, 3), 2.23 (s, 3), 7.4 (m, 6); mass spectrum *m/e* (rel intensity) 254 (1), 212 (5), 43 (100); uv (acetonitrile) λ_{max} 270 nm (4.24).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: 64.91; H, 4.14; N, 9.51.

***trans,trans*-1,4-Diacetoxy-*cis,cis*-1,4-dicyano-2,3-dimethyl-1,3-butadiene (21c).** A solution of 2.0 g (6.6 mmol) of 1,4-diacetoxy-2,3-diazido-5,6-dimethylbenzene in 10 ml of o-dichlorobenzene was added dropwise to 10 ml of gently refluxing o-dichlorobenzene. A red color developed which faded to a pale yellow. The solution was diluted with 20 ml of hexane and cooled to −10° to give 1.47 g (94%) of diene **21c** as a white, crystalline solid, mp 125–127°. Characteristic spectral properties for **21c** follow: ir (Nujol) 2240, 1770, 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (s, 6), 2.25 (s, 6); uv (acetonitrile) λ_{max} 206 nm (4.25).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.17. Found: C, 58.12; H, 4.79; N, 11.29.

Thermolysis of 1,4-Diacetoxy-2,3-diazidonaphthalene (3e). Formation of the 1,2-Diacetoxy-1,2-dicyanobenzocyclobutenes (22 and 23) and 1,4-Diacetoxy-3-cyanoisoquinoline (24). A solution of 2.0 g (6.1 mmol) of the diazide **3e** in 10 ml of warm o-dichlorobenzene was added over a 2-min period to 10 ml of gently refluxing o-dichlorobenzene. The solution became deep red and then litened to amber. The solvent was removed *in vacuo* and the yellow solid was dissolved in 20 ml of hot benzene. Upon cooling a precipitate formed and was collected by filtration to give 0.64 g (39%) of the 1,4-diacetoxy-3-cyanoisoquinoline (**24**) as a yellow solid. This sample was chromatographed (silica gel) and then recrystallized from benzene to give the analytical sample, mp 183–186°. Characteristic spectral properties of **24** follow: ir (Nujol) 1780, 1670, 1640, 1600, 1580 cm^{-1}; nmr ($CDCl_3$) δ 2.61 (s, 3), 2.65 (s, 3), 7.6–8.2 (m, 4); uv (acetonitrile) 231 (4.43), 253 (4.18), 262 (4.20), 304 nm (4.03).

Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.33; H, 3.76; N, 10.38.

The above benzene mother liquor was chromatographed over 150 g of silica gel. Elution with dichloromethane–pentane (1:1) gave 0.38 g (23%) of the *trans*-1,2-diacetoxy-1,2-dicyanobenzocyclobutene (**22**), mp 144–147°. Recrystallization from benzene–carbon tetrachloride gave the analytical sample, mp 147–148°, as a white, crystalline compound. Characteristic spectral properties of **22** follow: ir (Nujol)[19] 1770, 1760 cm^{-1}; nmr ($CDCl_3$) δ 2.29 (s, 6), 7.76 (s, 4); uv (acetonitrile) 257 (2.74), 2.63 (2.89), 270 nm (2.85); mass spectrum *m/e* (rel intensity) 186 (1.7), 114 (0.5), 102 (0.5), 44 (1.7), 43 (100), 42 (1.5).

Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.14; H, 3.74; N, 10.37.

From the above chromatography another fraction was collected upon elution with dichloromethane. The tan solid obtained was recrystallized from benzene–carbon tetrachloride to give 50 mg (3%) of *cis*-1,2-diacetoxy-1,2-dicyanobenzocyclobutene (**23**), mp 160–161° dec. Characteristic spectral properties of **23** follow: ir (Nujol)[19] 1755 cm^{-1}; nmr ($CDCl_3$) δ 2.20 (s, 6), 7.6–7.7 (m, 4); uv (acetonitrile) 257 (2.81), 263 (2.97), 270 nm (2.93); mass spectrum *m/e* (rel intensity) 186 (4.3), 114 (0.8), 102 (1.2), 44 (6), 43 (100), 42 (3).

Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.19; H, 3.84; N, 10.36.

4-Hydroxy-1(2*H*)-isoquinolone. A solution of 0.4 g (1.5 mmol) of 1,4-diacetoxy-3-cyanoisoquinoline (**24**) in 3 ml of 47% HI was refluxed for 5 hr, and 10 ml of distilled water containing 0.1 g of sodium thiosulfate was added. Cooling gave a brown solid which, when recrystallized from dilute sodium thiosulfate, gave 0.15 g (62%) of 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline as a yellow, crystalline solid which was identical with an authentic sample prepared by an alternate route.[12]

Registry No.—**1f**, 51021-93-3; **1g**, 51021-94-4; **3a**, 51021-95-5; **3b**, 51021-96-6; **3e**, 51021-97-7; **3d**, 51021-98-8; **3e**, 51021-99-9; **3f**, 51022-00-5; **3g**, 51022-01-6; **3h**, 51022-02-7; **4a**, 51022-03-8; **4b**, 51022-04-9; **4c**, 51022-05-0; **5**, 51022-06-1; **6**, 51022-07-2; **11**, 51022-08-3; **12**, 51022-09-4; **14**, 51022-10-7; **15**, 51022-11-8; **16**, 51022-12-9; **19**, 51022-13-0; **21a**, 51021-74-0; **21b**, 51021-75-1; **21c**, 51021-76-2; **22**, 51021-77-3; **23**, 51021-78-4; **24**, 51022-14-1; *N*-acetyl-2-amino-3,6-dimethyl-1,4-benzoquinone, 51022-15-2.

References and Notes

(1) This is paper XIV in a series concerning the chemistry of azidoquinones and related compounds. For paper XIII see P. Germeraad, W. Weyler, Jr., and H. W. Moore, *J. Org. Chem.*, **39**, 781 (1974).

(2) The authors are grateful to the National Science Foundation for financial support of this project.

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(19) No C≡N absorption was detected for this compound. This is not unexpected, particularly for acetoxy cyanohydrins. See L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1959, p 266.

A Synthetic Approach to Aporphine Alkaloids. A New Tetracyclic Benzodiazepine Derivative from the Benzyne Cyclization of a Bromophenolic 1-Benzyltetrahydroisoquinoline

Richard J. Spangler,* Donald C. Boop, and Jong Ho Kim

Department of Chemistry, University of Idaho, Moscow, Idaho 83843

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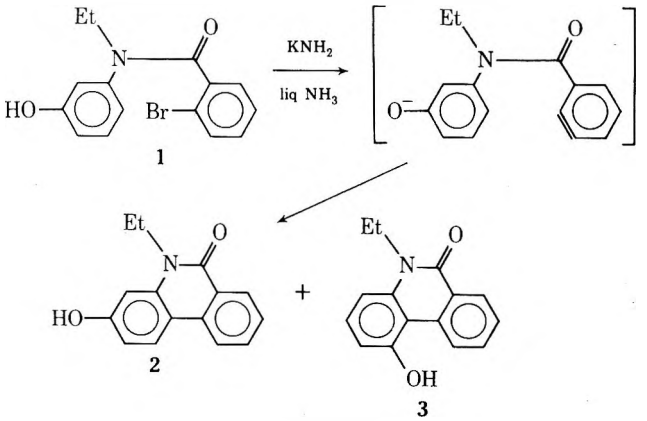
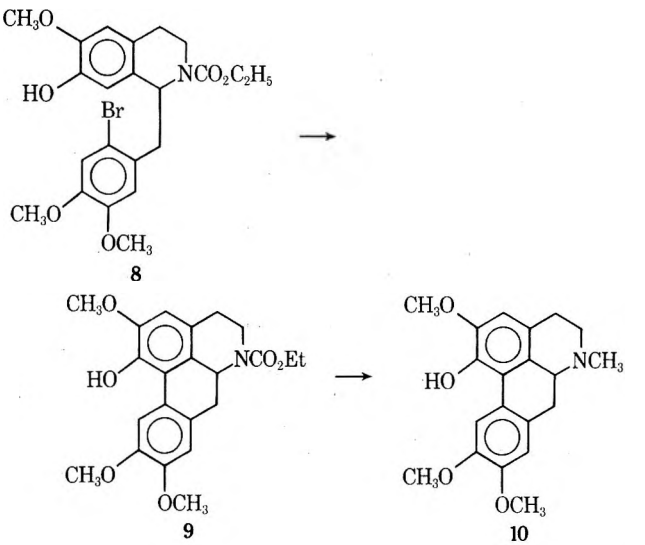
The synthesis of aporphine alkaloids by the benzyne reaction of bromophenolic 1-benzyltetrahydroisoquinolines containing a carbethoxy protecting group on the isoquinoline nitrogen was examined. The benzyne reaction of 1-(2′-bromo-4′,5′-dimethoxybenzyl)-2-carbethoxy-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (8) gave a new tetracyclic benzylisoquinoline derivative, **17**, in good yield. Aryl–aryl coupling *via* intramolecular attack of phenoxide on the intermediate aryne to give the *N*-carbethoxynoraporphine **9** was not observed. This process provides a useful new synthesis of certain benzodiazepines.

It is well established that a variety of nucleophiles readily add to benzyne. When the nucleophile is part of a side chain attached to the benzyne, the intramolecular nucleophilic addition results in ring closure; numerous demonstrations of this process have been described.[1] For example, Hey, Leonard, and Rees have shown that, when the nucleophile is the ambident phenoxide ion, its intramolecular nucleophilic addition results in an aryl–aryl coupling reaction (**1** → **2** + **3**).[2] Several groups[3-8] have recently investigated the application of this aryl–aryl coupling process to the synthesis of aporphine alkaloids[9] (*e.g.*, **5**) from 1-benzyltetrahydroisoquinoline precursors (*e.g.*, **4**) as shown in Scheme I, path a. In every case except one in which the yield of aporphine **5** is reported as "about 30% as estimated by tlc,"[6] only minor amounts of aporphine are obtained.[10] Competing with aporphine formation is the formation of morphinandienones (*e.g.*, **6**) *via* para attack of the phenoxide on the aryne (Scheme I, path b), the formation of indolizine derivatives (*e.g.*, **7**) by the attack of the nucleophilic isoquinoline nitrogen on the aryne (Scheme I, path c), and the formation of primary aromatic amines by the addition of ammonia to the aryne. In most cases the major cyclized products are the indolizine derivatives **7**; in fact this general method provides a useful synthesis of indolizine derivatives.[11,12] Thus, if this process is to be a useful synthesis of aporphine alkaloids, the isoquinoline nitrogen must be protected during the cyclization reaction. In this paper we wish to describe the results of the reaction of urethane **8** with potassium amide–liquid ammonia; in **8** the isoquinoline nitrogen is no longer nucleophilic, indolizine formation is thus prevented, and we anticipated that synthetically useful yields of aporphine alkaloid precursors such as **9** might be obtained. After cyclization the *N*-carbethoxy noraporphines (*e.g.*, **9**) can be readily converted to the desired aporphine alkaloids (*e.g.*, **10**); this last step has also been used in other recent aporphine syntheses.[9b,f]

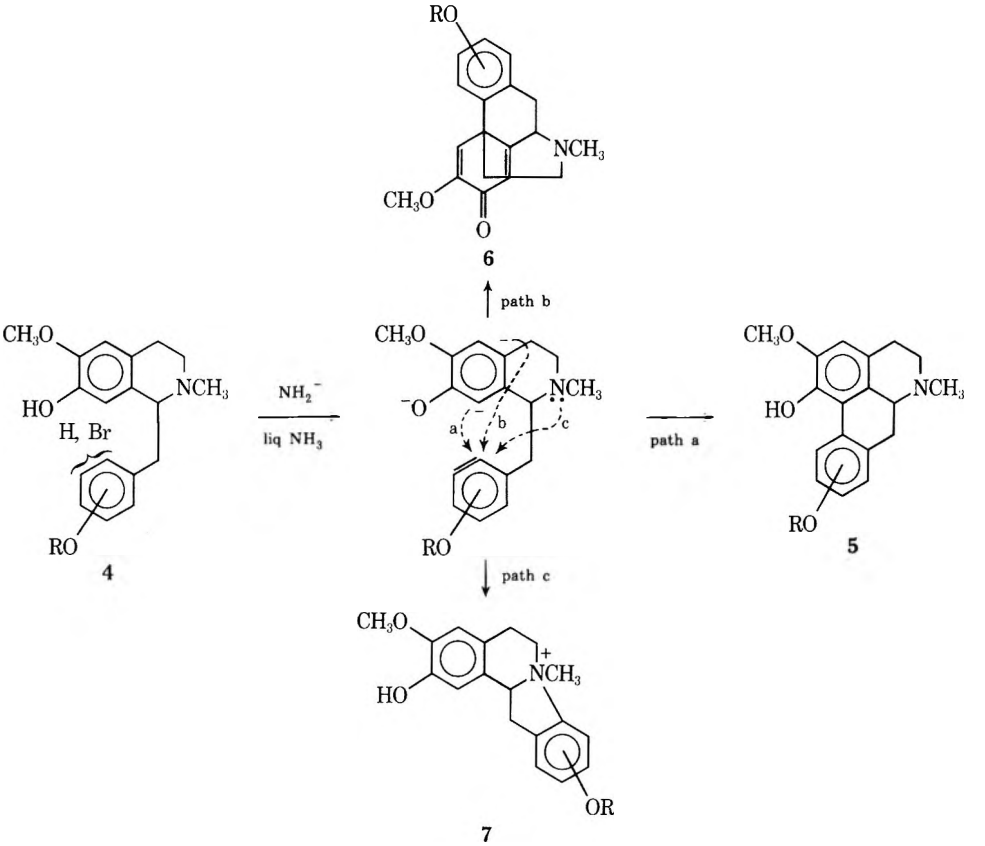




Results and Discussion

The required precursor **8** was synthesized as outlined in Scheme II. Thus heating the β-phenethylamine **11**[13] with the phenylacetic ester **12**[14] at 140–150° gave the amide **13** (70% yield), which was then readily converted to the hy-

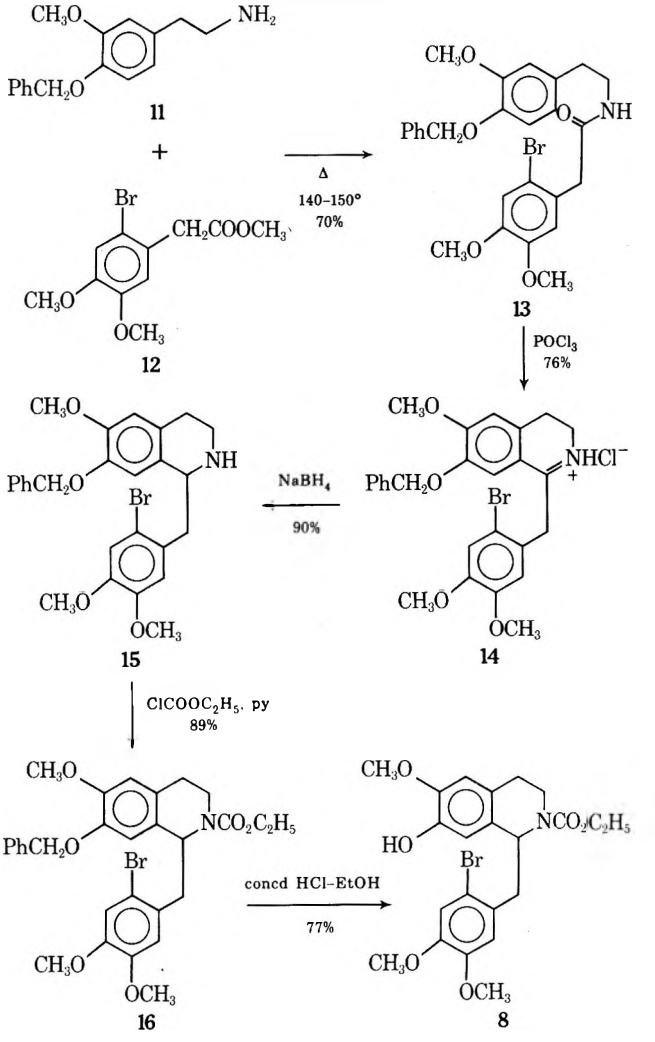
Scheme I

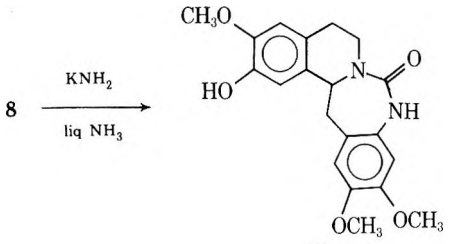


drochloride salt **14** in 76% yield upon treatment with phosphoryl chloride. Conversion of **14** to the tetrahydroisoquinoline **15** with sodium borohydride proceeded in 90% yield; treatment of **15** with ethyl chloroformate and pyridine gave the urethane **16** (90% yield), which was in turn debenzylated with concentrated hydrochloric acid to give the desired bromophenol **8** in 77% yield. The good yields obtained in this sequence further enhance the attractiveness of **8** as an aporphine precursor. All the compounds in Scheme II were fully characterized spectrally. Especially noteworthy are the nmr spectra of compounds **16** and **8**. The benzyl ether **16** shows a complex multiplet instead of the expected triplet for the urethane methyl group and a broadened singlet for the methylene protons of the benzyl ether group. Urethane **8** shows a quintet centered at δ 1.10 rather than the expected triplet for the urethane methyl group. We attribute these effects to the existence of **16** and **8** in more than one conformation. The quintet at δ 1.10 in the spectrum of **8** can be attributed to the existence of two conformations, resulting in two overlapping triplets which appear as a quintet. The peak areas of the quintet show that the two conformers of **8** are present in a ratio of about 1:3. Dalton and coworkers have described in detail the conformational analysis of similar tetrahydroisoquinolines.[15,16]

The reaction of **8** with potassium amide in liquid ammonia did not give the expected aporphine derivative **9** but instead gave a 74% yield of the white, crystalline urea **17**, which was obtained nearly pure directly from the reaction mixture. After removal of urea **17** from the reaction mixture the residue was examined for the presence of the aporphine derivative **9**. None of the aporphine derivative **9** could be detected by comparing the tlc behavior and nmr spectrum of the residue with those of an authentic sample of **9**. Authentic **9** was prepared by the ultraviolet irradiation of **8** and sodium hydroxide in aqueous methanol. We have described the preparation of a number of aporphine alkaloids by this method.[9c,17]

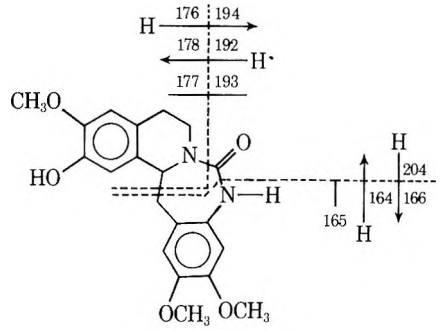
Scheme II





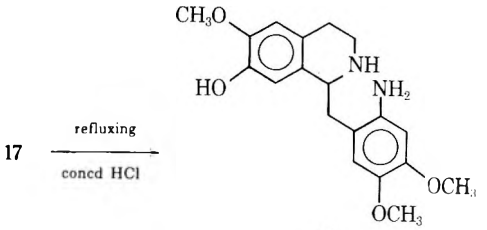
17

The structure assignment of **17** follows from its spectral properties and its acid hydrolysis product. The complete high-resolution mass spectrum of **17** was especially helpful. Thus the elemental composition of **17** was established as $C_{20}H_{22}N_2O_5$, also in accord with the elemental analysis. The most useful fragmentations were those resulting in cleavage of the doubly benzylic carbon–carbon bond and one of the carbonyl to nitrogen linkages of the urea group. These fragments, which are shown below, are clearly indicative of the cyclic urea structure of **17**. Fragmentations leading to $M\cdot^+ - CH_3$, $M\cdot^+ - CO$, $M\cdot^+ - CHO$, $M\cdot^+ - CONH_2$, and secondary fragmentations account for the majority of the remaining peaks. The nmr spectrum of **17** shows the six methylene protons as a mul-



17

tiplet at δ 2.49–3.81, the benzylic methine proton as a multiplet at δ 5.00, the three methoxy groups at δ 3.83, 3.85, and 3.91, the NH proton as a very broad peak at δ 5.56, the phenolic proton slightly broadened at δ 6.44, and the four aromatic protons as singlets at δ 6.33, 6.57, 6.67, and 6.79. The nmr spectrum also shows that the ethyl group present in the urethane **8** is not present in **17**. The infrared spectrum is likewise consistent with structure **17**, showing multiple OH and NH absorptions in the 3100–3500-cm^{-1} region and a carbonyl stretching band at 1660 cm^{-1} which is consistent with the presence of a urea group.[18] Acid hydrolysis of **17** gave the benzylisoquinoline **18**, which was identical with a sample of **18** prepared by



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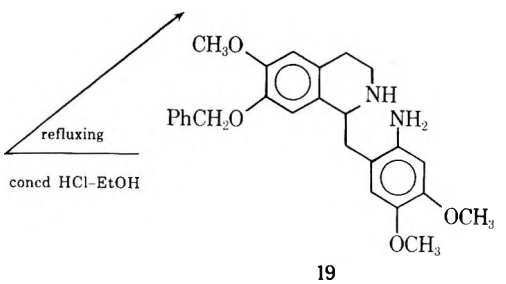

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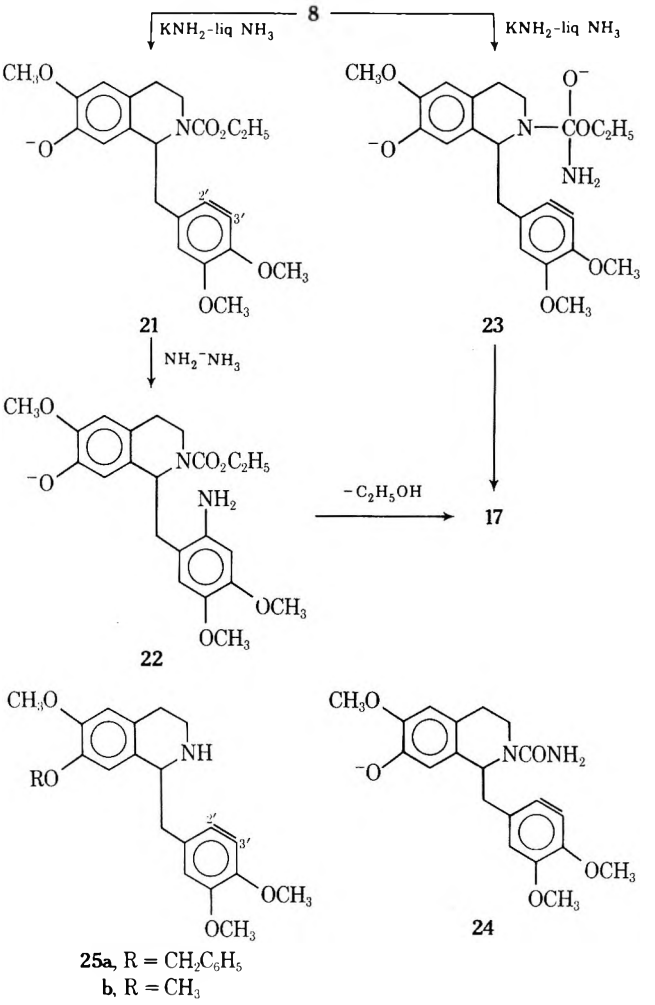
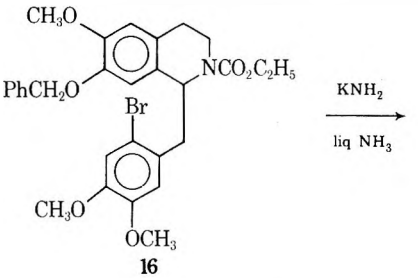
Scheme III



the debenzylation of the known **19**.[12] The benzyl ether **19** was prepared by the action of sodium amide–liquid ammonia on **15**, as described by Kametani and Ogasawara;[12] the ir and nmr spectra of **19** were identical with the reference spectra provided to us by these workers.

Thus even in the presence of the *N*-carbethoxy blocking group aryl–aryl coupling *via* intramolecular attack of the phenoxide ion on the intermediate aryne is not a facile process and the desired aporphine derivative **9** is not obtained; the phenoxide ion apparently plays no active role in the formation of urea **17**. To test this latter hypothesis we also allowed the benzyl ether **16** to react with potassi-



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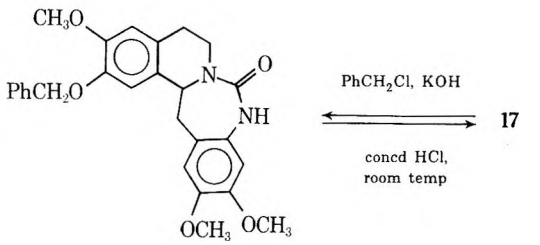
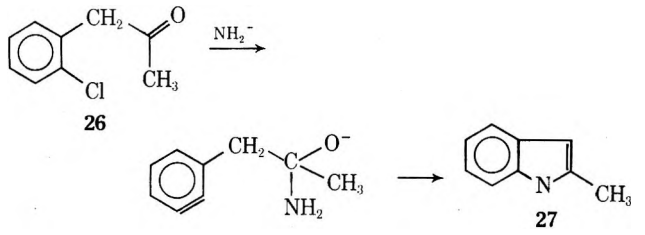


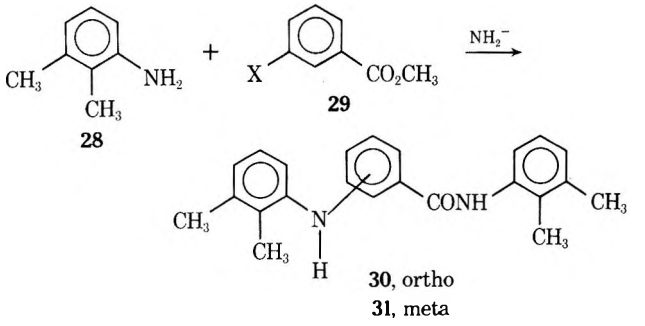
20

um amide in liquid ammonia. The reaction proceeded smoothly and gave a 75% yield of the benzyl ether **20**. Debenzylation of **20** with hydrochloric acid gave **17** and benzylation of **17** gave **20**. These interconversions and its spectral properties (see Experimental Section) secure our structure assignment of **20**. The cyclic ureas **17** and **20** constitute a new class of tetracyclic benzodiazepine derivatives. This cyclization reaction provides a useful new synthesis of certain benzodiazepines.

Two routes to the unexpected ring closure product **17** can be envisioned (Scheme III).[19] One involves the addition of amide ion to the aryne intermediate **21**, producing **22**, which then closes to **17** with loss of ethanol. The addition of amide ion to the 2′ position rather than the 3′ position of the benzyl group of **21** is in accord with Hoffmann's discussion of substituent effects[20] and the observation that the related aryne **25a** undergoes addition of amide ion at the 2′ position.[12] The other route involves the formation of **23**, which then closes to **17**. Urea **24** is a less likely intermediate in that Bunnett, *et al.*, has shown that carboxamides (or carboxamide anions) are usually poor nucleophiles toward arynes.[21] Analogy for the type of ring closure described here is found in the potassium amide initiated closure of o-chlorophenylacetone (**26**) to 2-methylindole (**27**)[19] and in the benzyne reaction of 2,3-



xylidine (**28**) with methyl *m*-halobenzoates (**29**) to give the benzamides **30** and **31**.[22]



The failure of this reaction to produce the desired aporphine derivative **9** cannot be due to the low nucleophilicity of phenoxide ion *vs.* external amide ion toward arynes in that Hey, Leonard, and Rees have provided several examples of the efficient intramolecular attack of phenoxide on an aryne.[2] Failure is most likely due to the fact that the primary amino group in intermediate **23** is a much better nucleophile than the phenoxide anion and therefore adds much more rapidly to the aryne.[23] Analogously external oxygen nucleophiles (including phenoxide) cannot compete with potassium amide–liquid ammonia for benzyne.[24] The conformation of **21** and/or **23** may play a smaller role in determining the mode of cyclization. Conformation has been discussed with regard to similar aryne cyclizations[24] and could also be in part responsible for the 68% yield of indolizine derivative obtained from the aryne **25b**.[12] Conformation is known to be important in the synthesis of aporphine alkaloids by the Pschorr cyclization reaction.[25]

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed at the University of Idaho with a Perkin-Elmer 240 elemental analyzer. Infrared (ir) spectra were determined with a Perkin-Elmer 621 or 237B spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained in $CDCl_3$ with TMS as internal standard using a Varian Model A-60 or HA-100 spectrometer. Ultraviolet (uv) spectra were taken with a Perkin-Elmer Model 202 spectrometer. Low-resolution mass spectra were obtained at 70 eV using a Hitachi Perkin-Elmer RMU-6E mass spectrometer. The high-resolution mass spectra were obtained at Stanford University using a MAT 711 mass spectrometer, and at Cornell University. Column chromatography employed either neutral aluminum oxide, activity grade I (M. Woelm, Eschwege, Germany) or silica gel (30–70 mesh ASTM; E. Merck, Darmstadt, Germany). Analytical thin layer chromatography (tlc) employed precoated sheets of aluminum oxide (F-254, neutral, Type T. 0.20 mm thick) or silica gel (F-254, 0.25 mm thick) on aluminum (E. Merck, Darmstadt, Germany).

***N*-(4-Benzyloxy-3-methoxy-β-phenethyl)-2-(2′-bromo-4′,5′-dimethoxyphenyl)acetamide (13).** A stirred mixture of 4-benzyloxy-3-methoxy-β-phenethylamine (**11**,[13] 24.5 g, 88.5 mmol) and methyl 2-bromo-4,5-dimethoxyphenylacetate (**12**,[14] 30.4 g, 118.5 mmol) was heated at 140–150° in an oil bath for 12 hr. The dark brown solid which formed upon cooling the mixture was recrystallized from benzene–*n*-hexane to give light tan crystals of acetamide **13** (31.7 g, 69.7%): mp 158–160° (lit.[12] mp 160–162°); ir (film) 3280, 3040, 2900, 1640, 1585, 1568, 1535, 1500, 1450, 1430, 1410, 1375, 1330, 1250, 1215, 1160, 1140, 1030, 1010, 965, 915. 850, 825, 800, 765, 740, and 695 cm^{-1}; nmr δ 2.71 (t, 2 H, J = 7 Hz, $\mathbf{CH_2CH_2}$NHCO–), 3.23–3.73 (m, 2 H, $CH_2\mathbf{CH_2}$NH), 3.58 (s, 2 H, NHCO$\mathbf{CH_2}$), 3.85 (s, 9 H, OCH_3), 5.14 (s, 2 H, $O\mathbf{CH_2}C_6H_5$), 5.60 (broad s, 1 H. NH). 6.47–6.95 (m, 4 H, ArH), 7.02 (s, 1 H. ArH), and 7.39 (s, 5 H, $OCH_2\mathbf{C_6H_5}$); mass spectrum m/e (rel intensity) 515 (2), 513 (2), 434 (3), 424 (<1), 422 (<1), 240 (40), 231 (10), 229 (10). 194 (2), 151 (6), 150 (7), 149 (21). 137 (23), 134 (6). and 91 (100).

7-Benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Hydrochloride Monohydrate (14·H_2O). Acetamide **13** (39.6 g, 77.1 mmol) was dissolved with heating in 500 ml of dry benzene, and phosphoryl chloride (50.0 ml, 0.574 mol) was slowly added. After the mixture was refluxed for 4 hr, the benzene was evaporated, giving a dark oil which crystallized upon stirring and cooling externally in an NaCl–ice bath. The yellow crystals of crude isoquinoline hydrochloride were washed with hot *n*-hexane (3 × 100 ml) and recrystallized from 95% ethanol, giving **14**·H_2O (32.2 g, 76.0%) as pale yellow needles: mp 207–210° dec (lit.[12] mp 217–218° dec); ir (film) 2900 (broad), 1640, 1600, 1550. 1450, 1430, 1410, 1370, 1330, 1295, 1290, 1270, 1210, 1150, 1100. 1070, 1030, 975, 860, 805, 750. and 695 cm^{-1}; nmr δ 3.12 (t, 2 H, J = 7 Hz, 4-H_2), 3.80–4.50 (m, 3 H, 3-H_2 and $^+$C=NH), 3.85 (s, 6 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.74 (broad s, 2 H, methylene protons of 1-benzyl group), 5.10 (s, 2H, $O\mathbf{CH_2}C_6H_5$), 6.89 (s, 1 H, ArH), 7.02 (s, 1 H, ArH), 7.09 (s, 1 H, ArH), and 7.37 (s, 6 H, $OCH_2\mathbf{C_6H_5}$ and one ArH); mass spectrum m/e (rel intensity) 497 (<1), 495 (<1), 416 (44), 326 (15), 325 (58), 324 (21), 310 (16), 296 (23). 295 (11), 294 (26), 282 (7), 281 (5), 280 (8), 267 (6), 266 (9), 265 (6), 231 (<1), 229 (4), and 91 (100).

7-Benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (15).[12] Sodium borohydride (2.50 g, 65.8 mmol) was added portionwise at room temperature to a stirred solution of 7-benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride monohydrate (**14**·H_2O, 3.38 g. 6.14 mmol) in methanol (40 ml) and water (5 ml). Stirring was maintained for 0.5 hr followed by refluxing for an additional 1 hr. Evaporation of the methanol gave a white, solid residue which was suspended in water (30 ml) and then extracted with chloroform (5 × 20 ml). The chloroform extracts were washed with water (15 ml), dried (K_2CO_3). and evaporated, giving a clear pale yellow gum (3.2 g), which was then dissolved in a minimal amount of hot 95% ethanol. The solution was cooled and crystallization was induced by scratching the vessel wall, giving 2.77 g (90.6%) of colorless bromotetrahydroisoquinoline **15**: mp 120–120.5°; ir (KBr) 3410 (broad), 2920, 2830, 1600, 1510, 1463, 1455, 1438, 1425, 1381, 1373, 1324, 1301, 1257, 1216, 1165, 1120, 1022, 985, 951, 855, 800, 780, 730, 692, and 600 cm^{-1}; nmr δ 1.63 (broad s, 1 H, NH), 2.50–3.50 (m, 6 H, 3-H_2, 4-H_2, methylene protons of 1-benzyl group), 3.80 (s, 3 H, OCH_3). 3.82

(s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.00–4.34 (m, 1 H, 1-H), 5.09 (s, 2 H, $OCH_2C_6H_5$), 6.61 (s, 1 H, ArH), 6.73 (s, 1 H, ArH), 6.77 (s, 1 H, ArH), 7.03 (s, 1 H, ArH), and 7.20–7.56 (m, 5 H, $OCH_2C_6H_5$); mass spectrum *m/e* (rel intensity) 499 (<1), 498 (<1), 497 (<1), 496 (<1), 417 (2), 416 (5), 326 (1), 268 (100), 231 (2), 229 (2), 177 (23), 176 (9), 148 (14), and 91 (15).

7-Benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-2-carbethoxy-1,2,3,4-tetrahydro-6-methoxyisoquinoline (16). A solution of the isoquinoline **15** (2.5 g, 5.02 mmol) and pyridine (5.0 ml) in chloroform (60 ml) was chilled in ice water and stirred while ethyl chloroformate (5.0 ml, 63 mmol) was added dropwise. Upon completion of the addition, the solution was stirred for 10 min more at room temperature, heated for 5 min on a steam bath, and evaporated, giving an opaque, pale yellow residue. The residue was suspended in water (300 ml), extracted with ether (4 × 50 ml), and washed successively with 1.2 *N* hydrochloric acid (50 ml), 5% sodium bicarbonate (50 ml), and water (50 ml). Drying (Na_2SO_4) and evaporation of the ether gave a pale yellow gum (3.16 g) which was crystallized from 95% ethanol, giving white crystals of the carbethoxyisoquinoline **16** (2.55 g, 89.3%): mp 113–114°; ir (KBr) 2940, 2910, 2840, 1692, 1605, 1505, 1465, 1440, 1425, 1382, 1330, 1310, 1260, 1240, 1228, 1218, 1200, 1165, 1116, 1100, 1095, 1027, 990, 970, 950, 855, 800, 759, 740, and 698 cm^{-1}; nmr δ 0.78–1.39 (m, 3 H, $COOCH_2CH_3$), 2.45–4.40 (m, 8 H, 3-H_2, 4-H_2, methylene of 1-benzyl group, $COOCH_2CH_3$), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.07 (broad s, 2 H, $OCH_2C_6H_5$), 5.32 (m, 1 H, 1-H), 6.33–6.83 (m, 2 H, ArH), 6.64 (s, 1 H, ArH), 7.02 (s, 1 H, ArH), and 7.38 (s, 5 H, $OCH_2C_6H_5$); mass spectrum *m/e* (rel intensity) 571 (<1), 569 (<1), 340 (100), 312 (10), 249 (6), 231 (3), 229 (3), 221 (8), 220 (4), 205 (3), 204 (3), 177 (7), 176 (10), 148 (7), and 91 (30).

Anal. Calcd for $C_{29}H_{32}BrNO_6$: C, 61.05; H, 5.66; N, 2.46. Found: C, 60.86; H, 5.51; N, 2.39.

1-(2′-Bromo-4′,5′-dimethoxybenzyl)-2-carbethoxy-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (8). A mixture of the benzyloxyisoquinoline **16** (1.0 g, 1.8 mmol) and concentrated hydrochloric acid–95% ethanol (10 ml, 1:1 v/v) was refluxed for 2 hr and the ethanol was then removed by rotary evaporation. The remaining aqueous layer was extracted with chloroform (3 × 50 ml). The extracts were washed with water (100 ml), dried (Na_2SO_4), and evaporated, leaving a pale yellow gum which yielded a white solid upon addition of ether. Recrystallization from ethanol–ether gave colorless needles of isoquinoline **8** (0.65 g, 77%) which were dried overnight at 60° (0.02 mm): mp 123–126°; ir (KBr) 3580, 3350 (broad), 2970, 2935, 2840, 1670, 1645, 1600, 1510, 1483, 1465, 1445, 1382, 1336, 1311, 1262, 1238, 1220, 1167, 1105, 1030, 1000, 983, 970, 951, 872, 860, 808, and 765 cm^{-1}; uv λ_{max} (MeOH) 290 nm (ϵ 7000), 233 (14,400) and 211 (43,700); nmr δ 1.10 (apparent quintet, 3 H, distance between peaks = 7 Hz, $COOCH_2CH_3$), 2.42–4.48 (m, 8 H, 3-H_2, 4-H_2, $COOCH_2CH_3$, methylene protons of 1-benzyl group), 3.75 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3,83 (s, 3 H, OCH_3), 4.76–6.07 (broad m, 2 H, 1-H, ArOH), 6.17, 6.53, 6.79, and 6.96 (all s, 4 H, ArH); mass spectrum *m/e* (rel intensity) 481 (<1), 479 (<1), 434 (<1), 406 (<1), 399 (<1), 398 (<1), 250 (100), 235 (3), 231 (4), 229 (4), 222 (36), 206 (5), 191 (9), 178 (23), 177 (6), 176 (8), 163 (17), and 162 (8).

Anal. Calcd for $C_{22}H_{26}BrNO_6$: C, 55.01; H, 5.46; N, 2.92. Found: C, 55.03; H, 5.48; N, 2.97.

***N*-Carbethoxy-1-hydroxy-2,9,10-trimethoxynoraporphine (9).** A stirred solution of the bromophenolic isoquinoline **8** (203 mg, 0.423 mmol), sodium hydroxide (200 mg, 5.0 mmol), methanol (9 ml), and water (1 ml) in a quartz vessel was purged with nitrogen for 15 min and irradiated under nitrogen for 24 hr with an Ultraviolet Products Model PCQ-X1 low-pressure mercury lamp. The methanol was removed on a rotary evaporator and the brown aqueous solution was diluted with 5% aqueous sodium hydroxide solution (40 ml). After the basic solution was made ammoniacal with an excess of ammonium chloride, the resulting suspension was extracted with ether (10 × 25 ml). The extracts were washed with water (2 × 10 ml), dried (Na_2SO_4), and evaporated, yielding an orange-yellow film (141 mg) containing the noraporphine **9**. The crude noraporphine was purified by column chromatography on neutral alumina (50 g), using ether [fractions 1–130 (each 2.5 ml)] and chloroform [fractions 131–134 (each 50 ml)]. Fractions 90–134 were combined and evaporated, giving a solid yellow film (35 mg) which was recrystallized twice from methanol, yielding the noraporphine **9** as pale yellow granules (13 mg, 7.7%): mp 108–109°; analytical tlc on neutral alumina using ether–chloroform–methanol (70:20:1 v/v/v) gave a single spot, R_f 0.73; ir ($CHCl_3$) 3520, 3035, 3000, 2965, 2940, 2915, 2850, 1675, 1605, 1580, 1510, 1440, 1390, 1340, 1300, 1280, 1255, 1180, 1155, 1120, 1110, 1090, 1025, 1010, 1000, 960, 945, 870, 855, 825, and 725 cm^{-1}; uv λ_{max} (MeOH) 306 nm (ϵ 23,300), 281 (20,000), and 224 (47,800); nmr δ 1.30 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.50–3.27 (m, 4 H, 4-H_2, 5-H_2), 3.50 (m, 2 H, 7-H_2), 4.07 (s, 9 H, OCH_3), 4.24 (quartet, 2 H, J = 7 Hz, $COOCH_2CH_3$), 4.50–5.00 (m, 1 H, 6a-H), 6.18 (s, 1 H, ArOH), 6.61 (s, 1 H, 8-H), 6.79 (s, 1 H, 3-H), and 8.15 (s, 1 H, 11-H); mass spectrum *m/e* (rel intensity) 399 (70), 371 (3), 370 (8), 354 (4), 311 (3), 310 (9), 298 (30), 297 (100), 283 (11), 268 (6), and 267 (13); high-resolution mass spectrum, *m/e* 399.1677 (calcd for $C_{22}H_{25}NO_6$, *m/e* 399.1682).

Cyclization of Bromophenolic Isoquinoline 8 with Potassium Amide in Liquid Ammonia. A three-necked, 100-ml, round-bottomed flask equipped with a magnetic stirrer and surrounded by a pan was fitted with a Dry Ice condenser, a three-way stopcock gas inlet, and a glass stopper. The outlet of the Dry Ice condenser was protected by a potassium hydroxide drying tower. After the apparatus had been flamed dry under a stream of dry nitrogen gas and had cooled to room temperature, the condenser and pan were filled with Dry Ice and acetone. The nitrogen flow was discontinued and anhydrous ammonia gas (through KOH) was condensed into the flask until about 50 ml of liquid ammonia was collected. A gentle nitrogen flow and stirring was maintained while small pieces of potassium metal (391 mg, 10.0 mmol) were added to the liquid ammonia until a deep blue color persisted. *Ca.* 1 mg of ferric nitrate hydrate was then added to the liquid ammonia followed by the addition of the remaining potassium metal in small portions. About 15 min was required for the addition. After all the blue color had turned to a gray (*ca.* 3 hr later) the bromophenolic isoquinoline **8** (480 mg, 1.00 mmol) was added as a powder to the stirred potassium amide suspension; anhydrous ether was used to wash the last traces of powder into the flask. The Dry Ice pan was removed and the reaction mixture was refluxed for 3 hr. The excess potassium amide was destroyed by cautiously adding crystalline ammonium chloride (10 g). Replacement of the Dry Ice condenser with a water-cooled condenser permitted the liquid ammonia to evaporate, leaving a white residue to which water (30 ml) was added. Extraction of the mixture with chloroform (5 × 50 ml) gave a yellow solution which was washed with water (30 ml). Because crystals began forming on the sides of the flask after standing for a few minutes, the chloroform extracts were not dried but the solution was evaporated directly, giving a peach-colored, chalky solid (430 mg). The crude product was recrystallized twice by suspending the solid in refluxing chloroform (15 ml) and slowly adding 95% ethanol until all the solid dissolved. The solution was filtered hot and the filtrate was slowly evaporated on a steam bath until leaflets began to appear. After cooling, the colorless leaflets were collected by filtration to give 274 mg (74.0%) of **17**, mp 261–262° dec. A second recrystallization afforded 198 mg (53.5%) of **17**: mp 262–264° dec; ir ($CHCl_3$) 3540, 3410, 3320, 3220, 3100, 2930, 2840, 1660, 1605, 1525, 1518, 1440, 1420, 1272, 1237, 1120, 1088, 1015, and 841 cm^{-1}; uv λ_{max} (MeOH) 291 nm (ϵ 11,700), 247 (sh, 13,200), and 217 (42,400); nmr (TMS external standard) δ 2.49–3.81 (m, 6 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.00 (m, 1 H, methine proton), 5.56 (broad s, 1 H, NH), 6.33 (s, 1 H, ArH), 6.44 (s, 1 H, ArOH), 6.57 (s, 1 H, ArH), 6.67 (s, 1 H, ArH), and 6.79 (s, 1 H, ArH); mass spectrum *m/e* (rel intensity, formula) 370.15381 (74.2, $C_{20}H_{22}N_2O_5$), 369.14526 (4.2, $C_{20}H_{21}N_2O_5$), 355.12915 (2.6, $C_{19}H_{19}N_2O_5$), 354.13184 (1.2, $C_{20}H_{20}NO_5$), 342.15820 (6.6, $C_{19}H_{22}N_2O_4$), 341.15063 (1.2, $C_{19}H_{21}N_2O_4$), 326.13892 (2.9, $C_{19}H_{20}NO_4$), 204.06676 (1.7, $C_{11}H_{10}NO_3$), 194.07817 (12.3, $C_{10}H_{12}NO_3$), 193.07384 (86.7, $C_{10}H_{11}NO_3$), 192.06538 (9.5, $C_{10}H_{10}NO_3$), 178.08698 (100.0, $C_{10}H_{12}NO_2$), 178.05066 (14.1, $C_9H_8NO_3$), 177.07816 (21.4, $C_{10}H_{11}NO_2$), 176.07149 (35.5, $C_{10}H_{10}NO_2$), 166.08705 (14.6, $C_9H_{12}NO_2$), 165.07938 (1.0, $C_9H_{11}NO_2$), 164.06973 (5.5, $C_9H_{10}NO_2$), 163.06322 (23.7, $C_9H_9NO_2$), 162.05560 (7.8, $C_9H_8NO_2$), and 150.05641 (5.0, $C_8H_8NO_2$).

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 6.00; N, 7.56. Found: C, 64.73; H, 6.06; N, 7.44.

Evaporation of the filtrates from compound **17** gave a black residue. A comparison of the nmr spectrum and tlc [neutral alumina; ether–chloroform–methanol (70:20:1 v/v/v)] of the black residue with those of the authentic noraporphine **9** showed that no noraporphine **9** was present in the residue.

Cyclization of Bromobenzyloxyisoquinoline 16 with Potassium Amide in Liquid Ammonia. Dropwise addition of a solution of bromoisoquinoline **16** (570 mg, 1.00 mmol) in dry tetrahydrofuran (5 ml) to a stirred suspension of potassium amide [prepared as above from potassium metal (391 mg, 10.0 mmol)] in liquid

ammonia (50 ml) produced a milky gray mixture which was refluxed for 3 hr under nitrogen. Cautious addition of solid ammonium chloride followed by evaporation of the liquid ammonia and tetrahydrofuran gave a white residue. Water (30 ml) was then added and the mixture was extracted with chloroform (5 × 50 ml). The extracts were washed with water (30 ml) and concentrated to 50 ml on a rotary evaporator. Addition of ether (100 ml) gave white crystals, which were filtered and dried at 110°, giving cyclic urea **20** (344 mg, 74.8%), mp 268–270° dec. Two recrystallizations from chloroform–petroleum ether (bp 30–60°) yielded 300 mg (65.2%) of colorless **20**: mp 271–272° dec; ir ($CHCl_3$) 3400, 3200, 2995, 2930, 2910, 2835, 1665, 1605, 1510, 1440, 1423, 1375, 1335, 1259, 1242, 1227, 1120, 1080, 1010, and 860 cm^{-1}; uv λ_{max} (MeOH) 288 nm (ϵ 5100), 248 (sh, 6800), and 208 (41,000); nmr δ 2.20–3.81 (m, 6 H, $CH_2CHNCH_2CH_2$), 3.84 (s, 6 H, OCH_3), 3.92 (s, 3 H, OCH_3), 5.00 (m, 1 H, methine proton), 5.14 (s, 2 H, $OCH_2C_6H_5$), 6.38 (s, 1 H, ArH), 6.53 (s, 1 H, ArH), 6.73 (s, 2 H, ArH), and 7.40 (s, 5 H, $OCH_2C_6H_5$) (the expected broad NH signal could not be detected because of limited sample solubility); mass spectrum *m/e* (rel intensity) 460 (80), 459 (5), 458 (5), 445 (5), 442 (2), 432 (10), 369 (20), 341 (2), 326 (7), 268 (48), 267 (32), 266 (23), 194 (10), 193 (76), 192 (19), 178 (27), 177 (37), 176 (56), 166 (25), 150 (9), 148 (28), and 91 (100).

Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.41; H, 6.13; N, 6.08. Found: C, 70.16; H, 5.93; N, 6.03.

Interconversion of Cyclic Ureas 17 and 20. A mixture of compound **17** (37 mg, 0.10 mmol), potassium hydroxide (17 mg, 0.30 mmol), benzyl chloride (28 mg, 0.22 mmol), water (1 drop), and 95% ethanol (2 ml) was refluxed for 15 hr. The white solid which formed was filtered, washed successively with 95% EtOH, water, and absolute ether, dried in air, and recrystallized from chloroform–petroleum ether to give **20** (26 mg, 57%), mp 270–271.5° dec, identical (ir, mass spectrum, tlc, mixture melting point) with that obtained above.

Stirring a mixture of compound **20** (30 mg, 0.065 mmol) in concentrated hydrochloric acid (10 ml) for 20 hr at room temperature under nitrogen produced a white precipitate, which was filtered, washed with water, and dried at 120° to give **17** (16 mg, 67%), mp 260–261°. The properties of this compound (tlc, mass spectrum, mixture melting point) were identical with that of compound **17** obtained from the reaction of **8** with potassium amide in liquid ammonia.

Acid Hydrolysis of Cyclic Urea 17. A mixture of compound **17** (100 mg, 0.271 mmol), water (2 ml), and concentrated hydrochloric acid (6 ml) were refluxed under nitrogen for 10 hr until all of the solid went into solution and no starting material remained, as shown by analytical tlc. After filtration, the cooled solution was diluted with water (20 ml) and washed with ether (3 × 50 ml). The acidic aqueous layer was made basic (pH ~10) with cold 6 *N* ammonium hydroxide and the resulting dark purple-black solution was extracted with ether (3 × 50 ml). The clear extracts were dried (Na_2SO_4) and evaporated, giving a pale yellow solid (31 mg) which was shown by tlc on alumina using chloroform–methanol (10:1 v/v) to be a complex mixture of products which were not identified.

The aqueous layer was then extracted with chloroform (8 × 30 ml). The black extracts were washed with water (20 ml), dried (Na_2SO_4), and evaporated, giving the aminoisoquinoline **18** as a black-green solid (50 mg, 54%): ir ($CHCl_3$) 3555, 3450 (broad sh), 3360 (broad), 3005, 2960 (sh), 2940, 2910 (sh), 2840, 1725 (broad), 1620, 1600, 1510, 1480, 1465, 1450, 1415, 1370, 1330, 1265, 1175, 1170, 1160, 1135, 1105, 1025, 1000, 865, 825, and 730 cm^{-1} (broad); nmr δ 2.40–3.46 (m, 6 H, 3-H_2, 4-H_2, and methylene protons of 1-benzyl group), 3.74 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.00–4.70 (m, 5 H, 1-H, NH, NH_2, ArOH), 6.30 (s, 1 H, ArH), 6.54 (s, 2 H, ArH), and 6.77 (s, 1 H, ArH); mass spectrum *m/e* (rel intensity) 382 (<1), 356 (<1), 355 (<1), 354 (<1), 344 (<1), 343 (<1), 342 (<1), 326 (<1), 325 (<1), 324 (<1), 313 (<1), 296 (<1), 295 (<1), 178 (100), 177 (9), 176 (3), 167 (10), 166 (7), 163 (11), and 162 (7).

The spectral data and tlc [R_f 0.12, neutral alumina, chloroform–methanol (10:1 v/v)] of compound **18** obtained here by hydrolysis of cyclic urea **17** were identical with that of aminoisoquinoline **18** prepared by debenzylation of the known **19** as described below.

1-(2′-Amino-4′,5′-dimethoxybenzyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxyisoquinoline (19). This compound was prepared as described in the literature[12] by the dropwise addition of a solution of 7-benzyloxy-1-(2′-bromo-4′,5′-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**15**, 1.00 g, 2.01 mmol) in dry tetrahydrofuran (6 ml) to a stirred suspension of sodium amide [prepared from sodium metal (2.00 g, 87.0 mmol)] in liquid ammonia (50 ml) under nitrogen. After 4 hr of refluxing with stirring, the reaction mixture was cautiously treated with solid ammonium chloride (10.0 g). The dark brown residue which remained after the liquid ammonia evaporated was mixed with ice water (30 ml) and extracted with chloroform (6 × 40 ml). The extracts were washed with water (2 × 10 ml), dried (K_2CO_3), and evaporated, giving a dark brown solid (733 mg), which was chromatographed on a column of neutral alumina (60 g) using chloroform [fractions 1–40 (10 ml each)] and chloroform–methanol (100:1 v/v) [fractions 41–66 (10 ml each)].

Evaporation of fractions 41–66 gave a brown yellow film (160 mg) which was shown by nmr to be mostly the desssired aminoisoquinoline **19**. Elution of the column with methanol (320 ml) gave a deep orange solid (186 mg) which was also shown to be mostly **19**. The combined residues of **19** were crystallized four times from 95% ethanol to give a constant-melting, tan-white solid (92 mg, 11%): mp 114–115° (lit.[12] mp 163–164°);[26] ir ($CHCl_3$) 3390 (broad), 3030, 3005, 2960, 2940, 2915, 2875, 2840, 1610, 1515, 1470, 1450, 1415, 1375, 1350, 1325, 1290, 1260, 1255, 1175, 1170, 1165, 1110, 1005, 855, 750, 695, and 655 cm^{-1}; nmr[26] δ 2.45–3.60 (m, 9 H, 3-H_2, 4-H_2, methylene protons of 1-benzyl group, NH, NH_2), 3.75 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.05 (t, 1 H, J = 7 Hz, 1-H), 5.05 (s, 2 H, $OCH_2C_6H_5$), 6.27 (s, 1 H, ArH), 6.55 (s, 1 H, ArH), 6.58 (s, 1 H, ArH), 6.66 (s, 1 H, ArH), and 7.10–7.58 (m, 5 H, $OCH_2C_6H_5$); mass spectrum *m/e* (rel intensity) 446 (1, impurity), 434 (1), 433 (1), 432 (1), 268 (100), 267 (5), 178 (6), 177 (17) 176 (9), 167 (8), 166 (8), 148 (10), and 91 (8).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.12; H, 6.89; N, 6.35.

1-(2′-Amino-4′,5′-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (18). A solution of the aminobenzyloxyisoquinoline **19** (43 mg, 0.10 mmol) in 2 ml of concentrated hydrochloric acid–ethanol (1:1 v/v) was refluxed under nitrogen for 1 hr and cooled, and the ethanol was removed with a rotary evaporator. The residual yellow liquid was diluted with 6 *N* hydrochloric acid (3 ml) and washed with ether (3 × 5 ml) to remove benzyl impurities. The aqueous layer was made basic with 10% ammonium hydroxide and extracted with chloroform (6 × 10 ml). The combined $CHCl_3$ extracts were washed with water (5 ml), dried (Na_2SO_4), and evaporated, giving a pale yellow solid film of the hydroxyisoquinoline **18** (32 mg, 94%), whose properties (tlc, nmr, ir, mass spectrum) were identical with those of the sample of **18** obtained by the hydrolysis of cyclic urea **17**.

Acknowledgments. We are indebted to the Research Corporation for a Frederick Gardner Cottrell grant in support of this research. We thank Professors Carl Djerassi, Stanford University, and Fred W. McLafferty, Cornell University, for providing high-resolution mass spectra, and Professor Tetsuji Kametani, Tohoku University, for providing reference spectra of compound **19**.

Registry No.—**8**, 51015-09-9; **9**, 51015-10-2; **11**, 22231-61-4; **12**, 4697-57-8; **13**, 18883-64-2; **14**, 17138-37-3; **15**, 47706-25-2; **16**, 51015-11-3; **17**, 51015-12-4; **18**, 51015-13-5; **19**, 51015-14-6; **20**, 51015-15-7.

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C-Glycosyl Nucleosides. V. A Novel One-Step Asymmetric Synthesis of C-Nucleoside Analogs[1]

Haruo Ogura* and Hiroshi Takahashi

School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan

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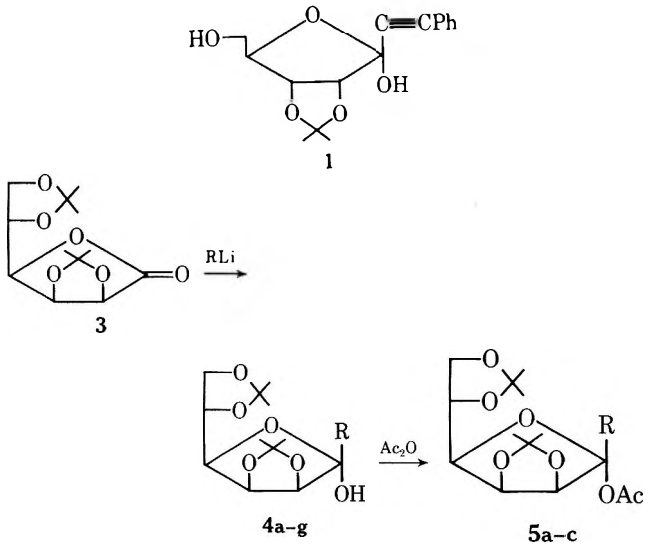
Reaction of lithiated heterocycles such as pyridine, benzothiazole, imidazole, benzimidazole, and sydnone with sugar lactones, 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (**3**) or 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**7**), afforded a variety of 1-(2-substituted heterocyclic)-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (**4**) or 1-(2-substituted heterocyclic)-2,3-*O*-isopropylidene-β-D-ribofuranose (**8**). Attempted dehydroxygenation of the anomeric hydroxyl group failed. These C-nucleoside analogs were reduced with sodium borohydride to gulitols and ribitols. The configuration of gulitols, which had a π-electron ring system, was determined with CD and ORD spectra to confirm their absolute configuration. It was concluded that a similar Cotton effect is observed in furanose-type and gulitol-type nucleosides.

Synthetic studies on the nucleoside antibiotic, pyrazomycin, have been reported by Tronchet and Perret.[2] On the other hand, Townsend and his collaborators synthesized its analogous N-nucleoside[3] and pyrazolopyrimidine nucleosides.[4] Several synthetic routes directed to C-nucleosides have also been reported by Fox and Ohrui.[5] In the previous paper,[6] we reported the reaction of ethynyl compounds with lactones, and the resulting compound had been expected as an intermediate for the preparation of the carbon-linked nucleoside. In another paper,[7] we reported the ethynylation of glucosyl bromide with ethynylmagnesium bromide, although we could not obtain the desired carbon-linked nucleoside. The attempted 1,3-dipolar cycloaddition reaction of 1-ethynylphenyl-2,3-*O*-isopropylidene-α-D-ribofuranose (**1**) and *N*-benzylsydnone failed.

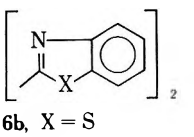
The present paper concerns itself with a direct reaction of some lithiated heterocycles with sugar lactones to yield a carbon-linked nucleoside. The reaction of 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (**3**) or 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**7**) with various lithiated heterocycles gave gulofuranosyl derivatives (**4a–g**) or ribofuranosyl derivatives (**8b,c**).

By application of the reported method[6] of ethynylation with lactones to the reaction of heterocycles with sugar lactones, it has been possible to obtain heterocyclic sugar lactols. Treatment of **3** with *n*-butyllithium and α-bromopyridine, benzothiazole, or 1-benzylbenzimidazole gave 1-substituted 2,3:5,6-di-*O*-isopropylidenegulonolactols (**4a–c**) in a good yield (74, 56, and 40%, respectively, Chart I). The ir spectra of these compounds showed hydroxyl bands in the 3200–3380-cm^{-1} region, and no lactonic band at around 1780 cm^{-1}. Gulonolactols (**4a–c**) were acetylated with acetic anhydride in pyridine to yield their acetyl derivatives (**5a–c**). This result was similar to those of ethynyl derivatives.[6] In the case of 1-benzylbenzimidazole, the lithiation does occur at the 2 position similar to that of benzothiazole,[8] and this fact was confirmed from the nmr spectra of **4b**. Micetich[9] reported that lith-

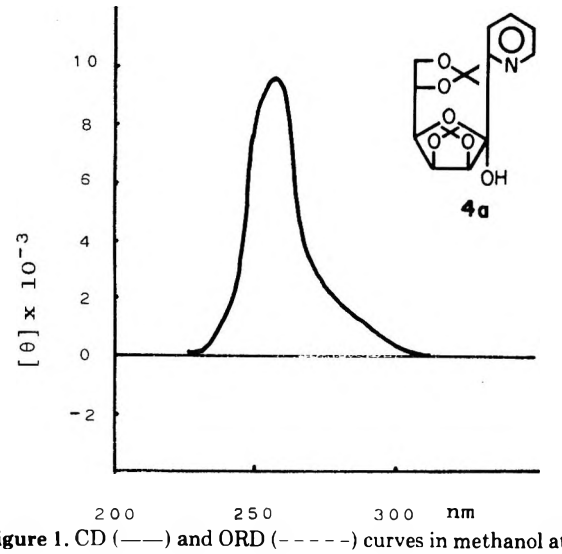
Chart I



a, R = pyrid-2-yl
b, R = benzothiazol-2-yl
c, R = 1-benzylbenzimidazol-2-yl
d, R = benzimidazol-2-yl
e, R = 1-benzylimidazol-2-yl
f, R = 1-benzylimidazol-5-yl
g, R = benzylsydnon-4-yl



6b, X = S
c, X = $NCH_2C_6H_5$



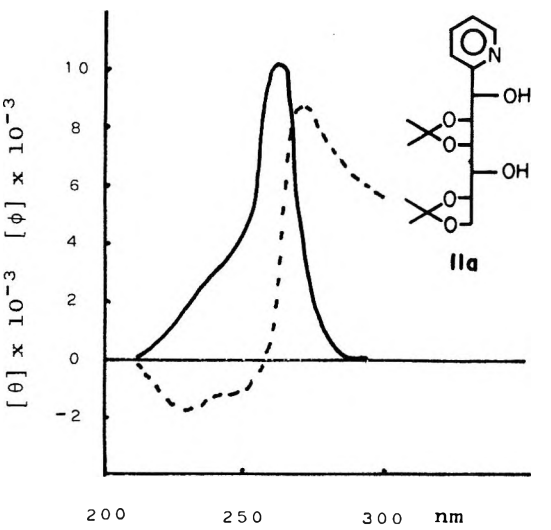
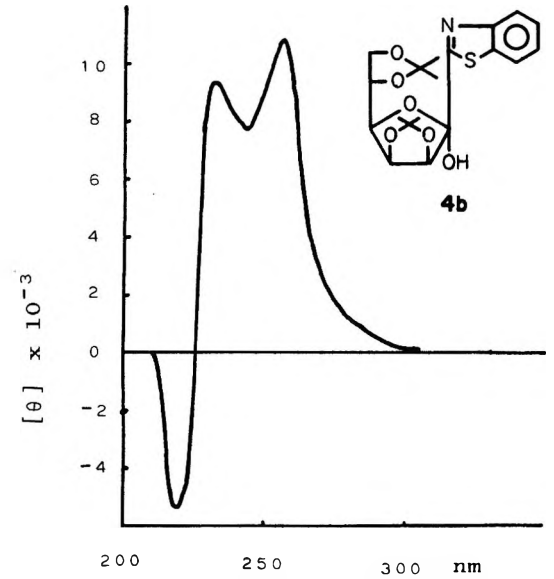


Figure 1. CD (——) and ORD (- - - - -) curves in methanol at 28°.



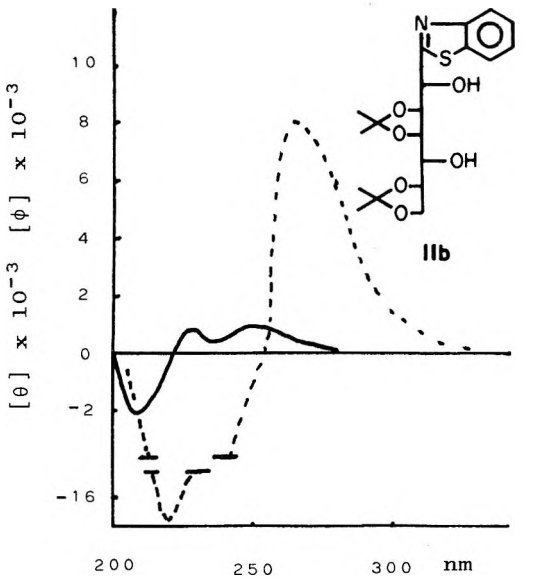
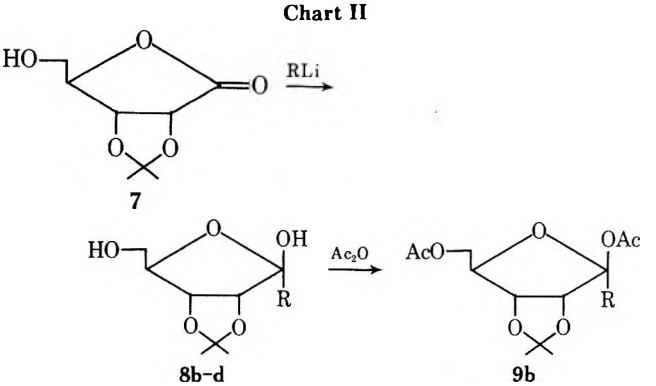


Figure 2. CD (——) and ORD (- - - - -) curves in methanol at 28°.

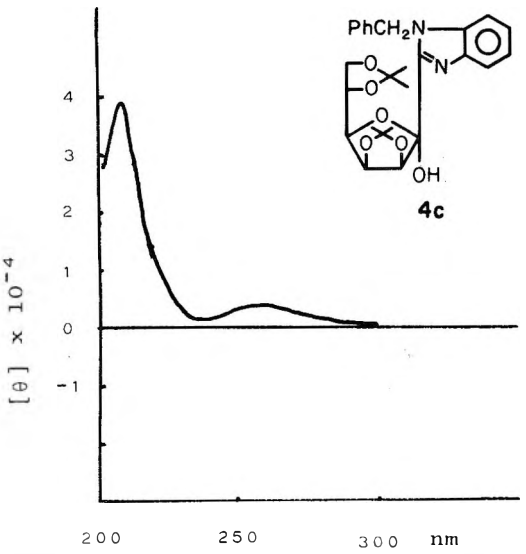
iation of isothiazoles and thiadiazoles gave the 5-lithio compounds. The lithiation of 1-benzylbenzimidazole by *n*-butyllithium at the 2 position is supported by the formation of 1,1′-dimethyl-2,2′-bibenzimidazole from the lithiation of 1-methylbenzimidazole.[10] On the other hand, treatment of 1-benzylimidazole under the same condition as above afforded 30% of 2-substituted compound **4e** and 12% of 5-substituted compound **4f**. The nmr spectrum of 2-substituted benzylimidazole (**4e**) showed a pair of doublets at δ 6.77 and 6.98 ppm (J = 5 Hz) corresponding to H-4 and H-5, respectively, in the imidazole ring. On the other hand, 5-substituted compound **4f** showed a pair of singlets at δ 7.10 and 7.92 ppm, corresponding to H-4 and H-2, respectively. Shirley and Alley[11] reported that lithiation of 1-substituted imidazole with *n*-butyllithium resulted in lithiation at the 2 position, and did not give a 5-substituted compound. The direct lithiation[12] of benzothiazole or 1-benzylbenzimidazole gave only the bis compounds **6b** and **6c**, respectively.

A similar reaction of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**7**) (Chart II) with benzothiazole of 1-benzylbenzimidazole gave 1-(benzothiazol-2-yl)-2,3-*O*-isopropylidene-β-D-ribofuranose (**8b**) and 1-(1-benzylbenzimidazol-2-yl)-2,3-*O*-isopropylidene-β-D-ribofuranose (**8c**), and **8b** was acetylated to the 1,5-di-*O*-acetyl derivative (**9b**) in a usual manner. The reaction of sugar lactones with lithiated heterocycles progressed stereospecifically and isomeric lactols were not detected by thin layer and gas chromatography. Reductive elimination of 1-benzylbenzimidazol-2-yl derivatives (**4c**, **8c**) over palladium on charcoal in a hydrogen atmosphere afforded the corresponding benzimidazolyl derivatives (**4d**, **8d**) in a good yield (70 and 65%, respectively).

Chart II



b, R = benzothiazol-2-yl
c, R = 1-benzylbenzimidazol-2-yl
d, R = benzimidazol-2-yl



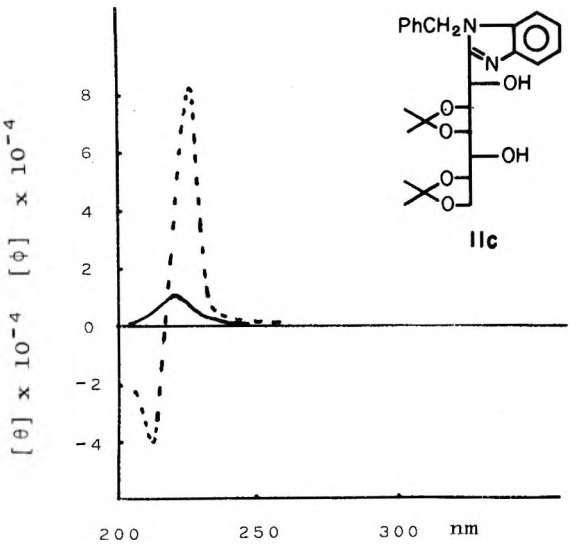
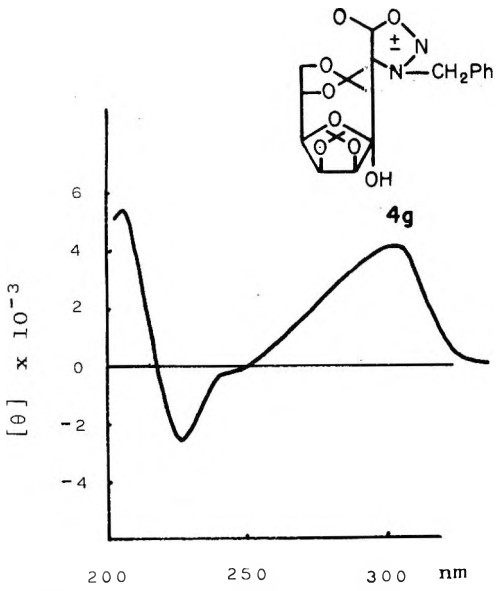


Figure 3. CD (——) and ORD (- - - - -) curves in methanol at 28°.



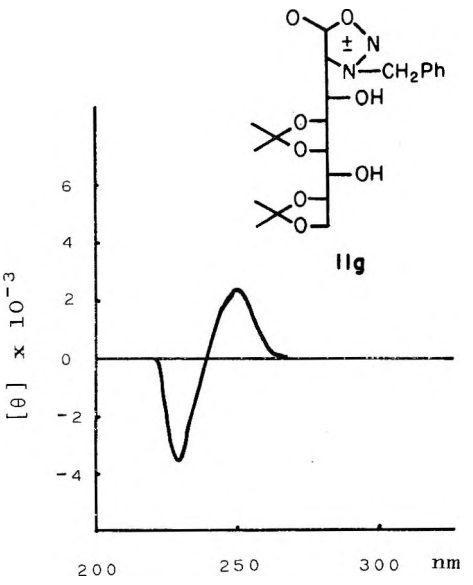


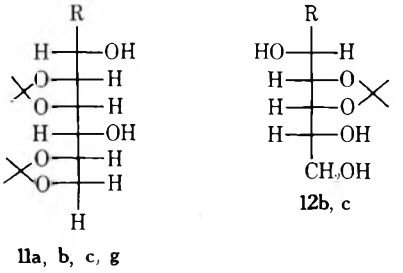
Figure 4. CD (——) and ORD (- - - - -) curves in methanol at 28°.

Chilton and Krahn,[13] and Moffatt, *et al.*,[14] already reported the relationship between the absolute configuration at the C-1 position of sugar heterocycles, such as benzimidazole, quinoxaline, flavazole, and anhydroosazone derivatives, and the Cotton effect of the ORD. Satoh, *et al.*,[15] also reported that the absolute configuration of 1-nitroheptitols was determined by ORD and CD. Snatzke and his coworkers[16] had reported the CD spectra of benzothiazole and benzothiazoline derivatives on aldoses and its acetates. Previously, we also reported[12] the Cotton effect and the structural relation of 1,2-dideoxy-4,5:7,8-di-*O*-isopropylidene-1-phenyl-L-glycero-D-galacto-oct-1-ynitol and 1,2-dideoxy-4,5-*O*-isopropylidene-1-phenyl-D-allohept-1-ynitol. Moreover, the ethynylation reaction of sugar lactones **3** and **7** with lithiated ethynyl compounds using *n*-butyllithium or by the direct lithiation resulted in the attack of the reagent from the less hindered face to form the β-C-nucleoside.[6,12]

The stereochemistry of the gulofuranosyl derivatives **4a–g** and ribofuranosyl derivatives **8b–d** was confirmed by the Cotton effect of CD curves of ring-opened alcohols, which were formed by sodium borohydride reduction.

As shown in Figures 1–3, the positive Cotton effect was observed from CD and ORD curves of gulofuranosyl compounds (**4a–c**) and 2,3:5,6-di-*O*-isopropylidene-1-(2-substituted)hexane-L-glycero-D-galacto-1,2,3,4,5,6-hexol (**11a,b,c,g**) (Chart III). From this result, gulofuranosyl

Chart III



compounds and L-glycerohexol compounds should have the β configuration at the 1 position; therefore compounds **4a,c,g** and **11a,c,g** should have *S* chirality at the 1 position and *R* chirality for **4b** and **11b.**

On the other hand, the negative Cotton effect was observed in the ribonosyl compounds **8b,c** and 2,3-*O*-isopropylidene-1-(2-substituted)pentane-D-altro-1,2,3,4,5-pentol (**12b,c**) (Figures 4–6). From these results, ribonosyl compounds and D-altropentol should have the β configuration

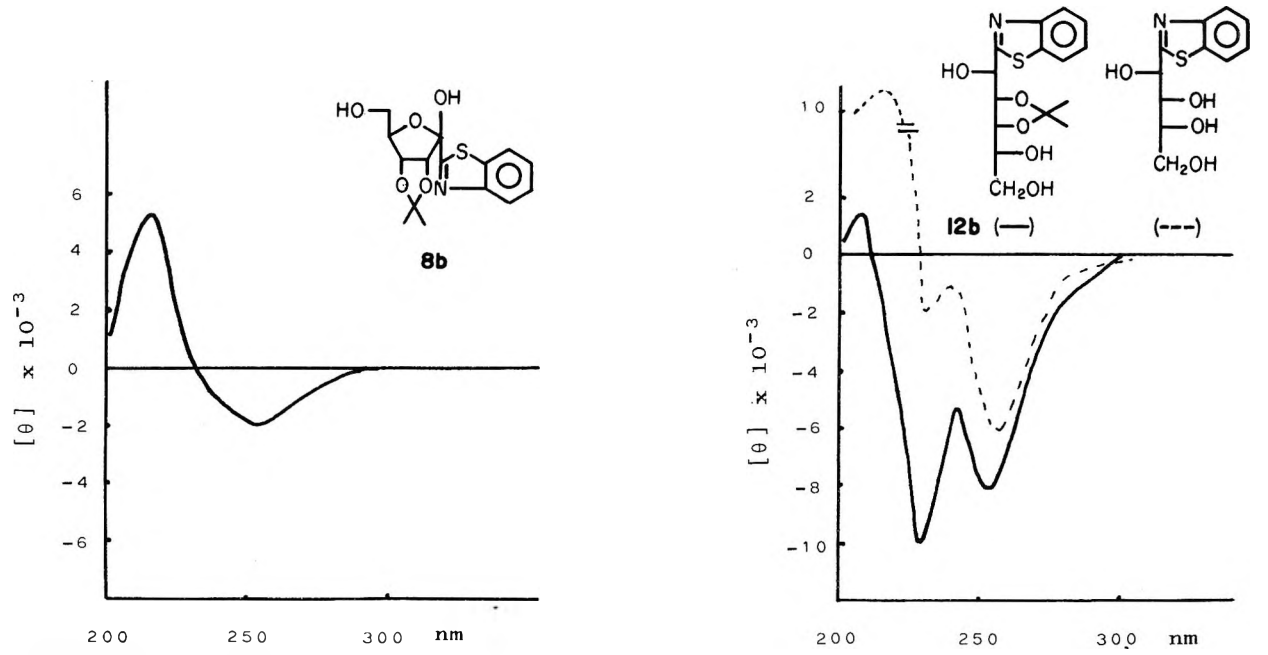


Figure 5. CD curves in methanol at 30°.

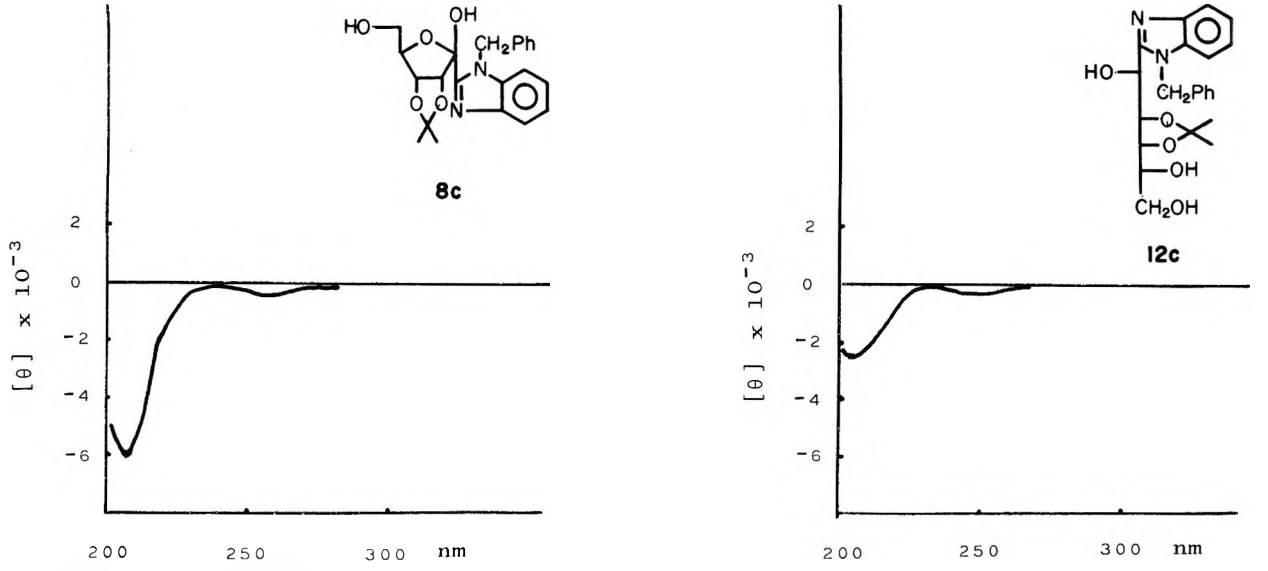


Figure 6. CD curves in methanol at 30°.

at the 1 position; therefore compounds **8c** and **12c** should have the *R* chirality at the 1 position and *S* chirality for compounds **8b** and **12b**.

In conclusion, asymmetric synthesis of C-nucleoside analogs was effected *via* lithiated heterocycles by a one-step synthesis. The absolute configuration of the products was confirmed from the Cotton effect. Ethynylation of isopropylidenegulonolactone (3) or -ribonolactone (7) afforded lactols which have the same chirality at the anomeric position.[6,12] This conclusion differs from the results of C-nucleoside analogs, in which gulofuranosyl derivatives (4) obtained had the same stereochemistry with ethynyl derivatives: *S* chirality (**4a,c,g**) and *R* chirality (**4b**) at the anomeric position. However, ribofuranosyl derivatives (8) have *R* chirality (**8c,d**) and *S* chirality (**8b**) at the anomeric position.

Attempted elimination of the anomeric hydroxyl group failed. When 1-benzylbenzimidazolylgulonolactol (**4c**) was treated with formic acid in trimethylamine or sodium carbonate in formic acid, only 1-benzylbenzimidazole was obtained. Treatment of **4c** with thionyl chloride–pyridine or phosphoryl chloride–pyridine also resulted in cleavage of the carbon–carbon bond to form 1-benzylbenzimidazole and sugar lactone (3). Hydrogenolysis of **4c** with lithium aluminum hydride–aluminum chloride at room temperature gave many products on tlc, and the desired product was not obtained.

Experimental Section[17]

Reaction of 1-Phenylethynyl-2,3-*O*-isopropylidene-α-D-ribofuranose (1) with Benzylsydnone. A solution of **1** (160 mg, 0.55 mmol) and benzylsydnone or *N*-nitrosobenzylglycine (106 mg, 0.55 mmol) in acetic anhydride (10 ml) was heated under reflux for 8 hr. When cooled, the reaction mixture was poured into ice-water and extracted with chloroform. Evaporation of dried chloroform solution left a brown syrup, which was chromatographed over silica gel and eluted with hexane–benzene. There was obtained 70 mg (26%) of an unidentified compound (2) as colorless needles: mp 125–127°; ir (KBr) 2180 (C≡C), 1380, 1370 (CH_3), 1590, 765 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 4.47 (2 H, dd, $=CH_2$), 4.78 (1 H, d, H-1), 1.38, 1.58 ppm (6 H, s, isopropylidene).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; *m/e* 256.110. Found: C, 74.95; H, 6.30; *m/e* 256.108 (M^+).

General Procedure for Preparation of 2,3:5,6-Di-*O*-isopropylidene-β-L-gulofuranosyl Derivatives (4a–c, e–g) (Table I) and 2,3-*O*-Isopropylidene-β-D-ribofuranosyl Derivatives (8b,c)

Table I
2,3 : 5,6-Di-*O*-isopropylidene-β-L-gulofuranosyl Derivatives (4a–g)

Compd	R	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mass, *m/e* (M⁺) Calcd	Mass, *m/e* (M⁺) Found
4a	Pyrid-2-yl	74[a]	86–87	$C_{17}H_{23}NO_6$	60.52	6.87	4.15	60.69	6.48	3.89	322.129	322.129[c]
4b	Benzothiazol-2-yl	56	170–171	$C_{19}H_{23}NO_6S$	58.01	5.89	3.56	58.10	5.96	3.47	393.123	393.125
4c	1-Benzylbenzimidazol-2-yl	40	155–156	$C_{26}H_{30}N_2O_6$	66.93	6.48	6.01	66.68	6.68	6.10	466.210	466.210
4d	Benzimidazol-2-yl	70	175–176	$C_{19}H_{24}N_2O_6$	60.63	6.43	7.44	60.94	6.50	7.47	376.163	376.163
4e	1-Benzylimidazol-2-yl	30	87–88	$C_{22}H_{28}N_2O_6$							416.195	416.193
4f	1-Benzylimidazol-5-yl	12	199 dec	$C_{22}H_{28}N_2O_6$	63.44	6.78	6.73	63.15	6.95	6.69	416.195	416.196
4g	Benzylsydnon-4-yl	29 32[b]	157–158	$C_{21}H_{26}N_2O_8$	58.06	6.03	6.45	57.71	6.06	6.23	434.169	434.165

[a] From α-bromopyridine. [b] From 3-benzyl-4-bromosyndnone. [c] $(M - CH_3)^+$.

Table II
2,3-*O*-Isopropylidene-β-D-ribofuranosyl Derivatives (8b–d and 9b)

Compd	R	Yield, %	Mp, °C	Formula	Mass, *m/e* (M⁺) Calcd	Mass, *m/e* (M⁺) Found
8b	Benzothiazol-2-yl	23	110–111	$C_{15}H_{17}NO_5S$	323.083	323.083
8c	1-Benzylbenzimidazol-2-yl	25	175–176	$C_{22}H_{23}N_2O_5$	396.169	396.169
8d	Benzimidazol-2-yl	65	173–174	$C_{15}H_{18}N_2O_5$	306.122	306.123
9b	1,5-Di-*O*-acetyl **8a**	32	166–167	$C_{19}H_{21}NO_7S$	407.104	407.104

Table III
1-*O*-Acetyl-2,3 : 5,6-Di-*O*-isopropylidene-β-L-gulofuranosyl Derivatives (5a–c)

Compd	R	Yield, %	Mp, °C	Formula	Mass, *m/e* (M⁺) Calcd	Mass, *m/e* (M⁺) Found
5a	Pyrid-2-yl	24	147–148 dec	$C_{19}H_{25}NO_7$	379.163	379.165
5b	Benzothiazol-2-yl	36	163–164	$C_{21}H_{25}NO_7S$	435.135	435.129
5c	1-Benzylbenzimidazol-2-yl	24	176–177	$C_{28}H_{32}N_2O_7$	493.197	493.198[a]

[a] $(M - CH_3)^+$.

Table IV
β-L-Gulitols (11a–c, g) and β-D-Ribitols (12b,c)

Compd	R	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mass, *m/e* (M⁺) Calcd	Mass, *m/e* (M⁺) Found
11a	Pyrid-2-yl	54	84–85	$C_{17}H_{25}NO_6$	60.16	4.13	7.43	59.82	3.94	7.59	339.168	339.168
11b	Benzothiazol-2-yl	57	97–98	$C_{19}H_{25}NO_6S$	57.71	6.37	3.54	57.65	6.65	3.25	395.140	395.140
11c	1-Benzylbenzimidazol-2-yl	40	178–179	$C_{23}H_{32}N_2O_6$	66.65	6.88	5.98	66.43	7.09	5.72	468.222	468.225
11g	Benzylsydnon-4-yl	42	148–149	$C_{21}H_{28}N_2O_8$	57.79	6.47	6.42	57.81	6.62	6.38	421.161	421.158
12b	Benzothiazol-2-yl	70	64–65	$C_{15}H_{19}NO_5S$	55.37	5.89	4.30	55.35	5.87	4.32	325.098	325.098
12c	1-Benzylbenzimidazol-2-yl	54	76–78	$C_{22}H_{26}N_2O_5$	66.32	6.58	7.03	66.33	6.59	7.01	398.183	398.184

Table V
Acetates of 11b and 12b

Compd	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mass, *m/e* Calcd	Mass, *m/e* Found
Acetyl β-L-gulitol	15	95–96	$C_{23}H_{29}NO_8S$	57.61	6.10	2.92	57.72	6.33	2.66	479.161	479.161 (M⁺)
Acetyl β-D-ribitol	30	129–130	$C_{21}H_{25}NO_8S$	55.87	5.58	3.10	55.90	5.70	3.16	436.107	436.106 $(M - CH_3)^+$

(Table II). To an ether solution of *n*-butyllithium prepared from lithium (0.2 g, 0.03 mol) and *n*-butyl bromide (2.5 g, 0.02 mol), the heterocyclic compound (0.01 mol) in ether (5–10 ml) was added slowly during 20–30 min at below −70°. After the reaction solution was stirred for 2 hr at room temperature, 2,3:5,6-di-*O*-isopropylidene-γ-L-gulonolactone (**3**, 2.5 g, 0.01 mol) in freshly distilled tetrahydrofuran (10–20 ml) was added dropwise into the cooled reaction solution, and the stirring was continued for 2–3 hr. The reaction mixture was then allowed to stand overnight at room temperature. The reaction mixture was treated with saturated ammonium chloride solution and extracted with ether (150 ml). The organic layer was washed with water and dried over magnesium sulfate. The extracts were concentrated under reduced pressure to give **4a–c,e–g.**

Acetylation of 4a–c (Table III). The compounds **4a–c** were acetylated with acetic anhydride (4 ml) and pyridine (5 ml). The reaction solution was stirred for 20–30 hr at room temperature and poured into ice–water. The solution was extracted with chloroform and the organic layer was washed with saturated sodium bicarbonate solution and water. The extract was dried and concentrated under reduced pressure.

Reductive Elimination of Benzyl Group from 4c and 8c (Tables I and II). A methanol (60 ml) solution of **4c** or **8c** (0.01 mol) was hydrogenated over 5% palladium on charcoal. After the reaction; the filtered solution was concentrated under reduced pressure to give 1-(2-benzimidazolyl)-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (**4d**) or 1-(2-benzimidazolyl)-2,3-*O*-isopropylidene-β-D-ribofuranose (**8d**).

Reduction of 4a–c,g with Sodium Borohydride (Table IV). The compound (**4a–c,g**, 0.01 mol) was dissolved in methanol (10 ml), and sodium borohydride (0.15 g) was added. After the reaction solution was stirred for 2–24 hr at room temperature, excess reagent was decomposed with ethyl acetate and water, and the organic layer was washed with 0.1 *N* hydrochloric acid and water, dried, and evaporated to give **11a–c,g.**

Reduction of 8b,c with Sodium Borohydride (Table IV). After a similar procedure as above, the obtained syrup was chromatographed over silica gel with hexane–chloroform (85:15) and the desired product was isolated as an oily product.

Acetylation of 11b and 12b (Table V). The compound (**11b, 12b**) was acetylated with acetic anhydride in pyridine, and the acetate was obtained after chromatography and recrystallization from chloroform–ether.

Attempted Elimination of Tertiary Hydroxyl Group. A. With

Formic Acid. A solution of **4c** (50 mg) in 5 ml of trimethylammonium formate [bp 92° (18 mm)] was stirred for 2 hr at room temperature and left overnight. This solution was gently refluxed in an oil bath for 3 hr until the reaction mixture was colored dark brown. When cooled, the separated crystals were collected and recrystallized from hexane–chloroform to colorless needles, mp 195–196°. This was treated with 1 *N* sodium hydroxide form 1-benzylbenzimidazole, mp and mmp with authentic sample 115°.

B. With Phosphoryl Chloride or Thionyl Chloride in Pyridine. To a solution of **4c** (400 mg) in pyridine or pyridine–chloroform, phosphoryl chloride (5 ml) or thionyl chloride (4 ml) was added at 0–5°. After the reaction mixture was stirred for 1 hr at room temperature, it was poured into ice–water. Extraction of the reaction mixture with benzene afforded 1-benzylbenzimidazole.

C. With Lithium Aluminum Hydride–Aluminum Chloride. To an ether solution of **4c** (450 mg), lithium aluminum hydride (50 mg) and aluminum chloride (25 mg) were added under stirring at 0–5°. After stirring overnight at room temperature, the reaction mixture was treated with ethyl acetate and then with 0.1 *N* hydrochloric acid. Evaporation of the dried ether solution left a brownish syrup, which showed four spots on tlc (R_f 0.79, 0.45, 0.30, and 0.14), and the main spot (R_f 0.45) was found to be 1-benzylbenzimidazole.

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Registry No.—**1**, 32257-18-4; **3**, 7306-64-1; **4a**, 51057-41-1; **4b**, 51057-42-2; **4c**, 51057-43-3; **4d**, 51057-44-4; **4e**, 51057-45-5; **4f**, 51057-46-6; **4g**, 51108-10-2; **5a**, 51057-47-7; **5b**, 51057-48-8; **5c**, 51057-49-9; **8b**, 51057-50-2; **8c**, 51057-51-3; **8d**, 51057-52-4; **9b**, 51057-53-5; **11a**, 51057-54-6; **11b**, 51057-55-7; **11b** acetate, 51057-56-8; **11c**, 51057-57-9; **11g**, 51057-58-0; **12b**, 51057-59-1; **12b** acetate, 51057-60-4; **12c**, 51057-61-5; benzylsydnone, 16844-42-1; α-bromopyridine, 109-04-6; 3-benzyl-4-bromosydnone, 4918-27-8.

References and Notes

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(17) All melting points were measured on a Mettler FP-1 melting point apparatus and are uncorrected. Gas chromatography was performed with a JGC-810 gas chromatograph and an OV-1 column was used at 180°. CD and ORD curves were obtained on a Japan Spectroscopic Model J-20 recording polarimeter. Test solutions were prepared by dissolving about 2 mg of the sample in 1.5 ml of methanol, and quartz cells with an optical path of 1, 0.2, and 0.1 mm were used. Nmr spectra were measured with a Varian T-60 spectrometer and tetramethylsilane was used as an internal reference. Mass spectra were determined with a JEOL-01S spectrometer by a direct inlet system at 75 eV.

Synthesis of Macrolide Antibiotics. I.[1] Stereospecific Addition of Methyllithium and Methylmagnesium Iodide to Methyl α-D-*xylo*-Hexopyranosid-4-ulose Derivatives. Determination of the Configuration at the Branching Carbon Atom by Carbon-13 Nuclear Magnetic Resonance Spectroscopy

Momčilo Miljković,* Miodrag Gligorijević, Toshio Satoh, and Dušan Miljković

Department of Biological Chemistry, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pennsylvania 17033

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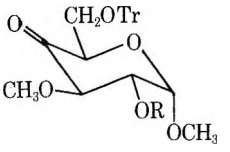
Methyllithium (LiBr-free) adds stereospecifically to methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (**1**) and methyl 3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (**2**) in an ethereal solution at −80° to give methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**9**) and methyl 3-*O*-methyl-4-*C*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**11**), respectively. Methylmagnesium iodide adds to the oxo sugars **1** and **2** in an ethereal solution at −80° again stereospecifically, giving methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**8**) and methyl 3-*O*-methyl-4-*C*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**10**), which are, however, the C-4 epimers of the branched-chain sugars **9** and **11**. The stereochemistry of the addition of Grignard reagent to the oxo sugars **1** and **2** depended upon the reaction temperature, the solvent, and the nature of the halogen atom. Carbon-13 nmr spectroscopy was used for unequivocal configurational assignments at the branching-carbon atom in branched-chain sugars **8**–**11**. A rationalization of the observed stereospecificity was proposed.

In the course of our studies directed toward the stereoselective synthesis of the 14-membered lactone ring of erythromycins A and B from appropriate sugar derivatives, it was necessary to introduce an axial methyl group at the C-4 carbon atom of a methyl D-*xylo*-hexopyranosid-4-ulose derivative and to develop a simple but reliable method for configurational assignment of the thus obtained branching carbon atom.[2]

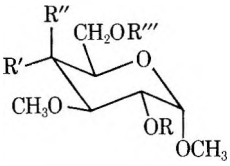
It is well known that the addition of Grignard reagents and organolithium compounds to carbonyl groups in carbohydrates is highly stereoselective[4] yielding in certain cases products epimeric at the quaternary carbon atom,[5,6] whereas in other instances branched-chain sugars with the same configuration at the branching carbon atom[7] are obtained. Since a clear rationalization of these findings[8] does not exist, many stereochemical "anomalies"[4] re-

ported in the literature have led to the conclusion that the steric course of the addition of Grignard reagents and/or alkyl- (or aryl-) lithium to oxo sugars cannot be reliably predicted.[9]

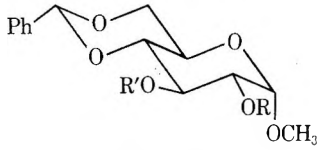
We now wish to report the results of our studies on the addition of methylmagnesium halides and methyllithium to the methyl α-D-*xylo*-hexopyranosid-4-uloses **1** and **2**, and on the application of the carbon-13 nmr spectroscopy for configurational assignments at the thus created branching carbon atom.



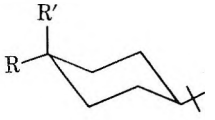
1, R = CH_3
2, R = CH_3SO_2



3, R = CH_3SO_2; R′ = OH; R″ = R‴ = H
4, R = CH_3; R′ = OH; R″ = H; R‴ = Tr
5, R = CH_3SO_2; R′ = OH; R″ = H; R‴ = Tr
6, R = H; R′ = CH_3; R″ = OH; R‴ = Tr
7, R = H; R′ = OH; R″ = CH_3; R‴ = Tr
8, R = R′ = CH_3; R″ = OH; R‴ = Tr
9, R = R″ = CH_3; R′ = OH; R‴ = Tr
10, R = CH_3SO_2; R′ = CH_3; R″ = OH; R‴ = Tr
11, R = CH_3SO_2; R′ = OH; R″ = CH_3; R‴ = Tr



12, R = CH_3SO_2; R′ = H
13, R = CH_3SO_2; R′ = CH_3



14, R = H; R′ = OH
15, R = OH; R′ = H
16, R = CH_3; R′ = OH
17, R = OH; R′ = CH_3

Methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (**1**) and methyl 3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (**2**) were synthesized by the oxidation of methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**4**) and methyl 3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**5**) with dimethyl sulfoxide–acetic anhydride at 50–60°.

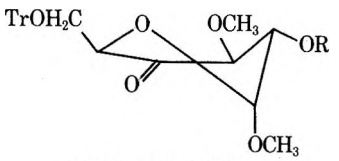
Reaction of the oxo sugars **1** and **2** with an ethereal solution of methyllithium (LiBr-free) at −80° afforded, in each case, only one product: methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**9**, from **1**) and methyl 3-*O*-methyl-4-*C*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**11**, from **2**).

Reaction of the oxo sugars **1** and **2** with an ethereal solution of methylmagnesium iodide at −80° again proceeded stereospecifically, but the products obtained were the C-4 epimers of the branched-chain sugars **9** and **11**. Thus, **1** gave methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**8**), whereas **2** gave methyl 3-*O*-methyl-4-*C*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**10**).

In contrast to the above results, methylmagnesium iodide and methyllithium added nonstereospecifically and at a considerably slower rate to 4-*tert*-butylcyclohexanone at −80°, yielding in each case a mixture of both C-1 epimers: *cis*-4-*tert*-butyl-1-methylcyclohexan-*r*-1-ol (**16**) and *trans*-4-*tert*-butyl-1-methylcyclohexan-*r*-1-ol (**17**). The isomer with the equatorial methyl group (**16**) was the predominant product in both reactions.

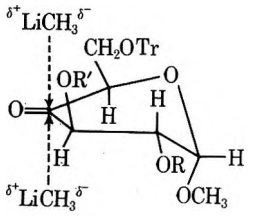
The stereochemistry of the addition of Grignard reagent to the oxo sugars **1** and **2** depended upon the reaction temperature, the solvent,[15] and the nature of the halogen atom. Thus, treating an ethereal solution of **1** and/or **2** with methylmagnesium iodide at −80° afforded **8** and/or **10** as the only isolable products. At reflux, both C-4 epimers, **8** and **9** (from **1**) and **6**, **7**, and **10** (from **2**),[16] were obtained, but the isomers having the methyl group in the equatorial orientation (**6**, **7** and **10**) predominated in *ca.* 6:1 ratio. The dependence of the stereochemistry of the addition reaction upon the nature of the halogen atom and of the solvent was demonstrated in the following way: refluxing a 10:1 ether–tetrahydrofuran solution of **2** with methylmagnesium chloride gave a 1:1 mixture of C-4 epimers **6** and **7**,[17] whereas methylmagnesium iodide under the same experimental conditions gave a mixture of C-4 epimers **6** and **7**, in which the axial isomer predominated by a ratio of 2.3:1.

The stereospecificity of the addition reaction of methyllithium to the C-4 carbonyl carbon atom in the oxo sugars **1** and **2** at −80° can be rationalized in the following way. It is well known from studies of the conformational equilibrium of α-halocyclohexanones[18-21] that conformations in which the halogen atom is axially oriented are strongly favored in solvents of low dielectric constant. This tendency of halogen atoms to assume the axial rather than equatorial orientation was attributed to the strong electrostatic repulsions of the nearly coplanar and equally oriented C=O and C–halogen dipoles in conformations in which the halogen atom is equatorially oriented. A similar situation probably exists in the case of the oxo sugars **1** and **2**. If so, then the C1 conformation of **1** and **2** wherein the C-3 methoxy group is equatorially oriented should be destabilized in solvents of low dielectric constant (*e.g.*, ether), owing to an electrostatic repulsion of the nearly coplanar and equally oriented C=O and C–O dipoles. Consequently, the oxo sugars **1** and **2**, will, at −80°, most likely adopt either a half-chair conformation **18** or a conformation which is between the C1 and a half-chair conformation (**18**). The adoption of any conformation other than C1 by **1** and/or **2** prior to the reaction with methyllithium will then be responsible for pure axial addition of methyllithium to the C-4 carbonyl carbon atom, since the severe electrostatic and nonbonding steric interactions between an electronegative methyl group (from CH_3Li) approaching the C-4 carbonyl carbon atom from the "equatorial" direction and the C-1 methoxy group will impede the equatorial addition of methyllithium. Furthermore, in case of an axial attack of methyllithium to the C-4 carbonyl carbon atom, not only will the severe "1,4-diaxial" interactions in the transition state **19** be avoided, but also the two relatively strong nonbonding steric interactions between the two axial hydrogens at C-3 and C-5 with an equatorially approaching methyl group will be replaced by one weaker 1,3-nonbonding interaction between the axially incoming methyl group and the C-2 axial hydrogen atom. This rationalization is strongly supported by the fact that methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-*xylo*-hexopyranosid-4-ulose (**20**), *i.e.*, a D-hexopyranosid-4-ulose of the *β series*, where such "1,4-diaxial" electrostatic and nonbonding steric interactions do not exist, reacts with an ethereal solution of methyllithium at −80°, yielding both C-4 epimers, **23** and **24**. It is interesting to



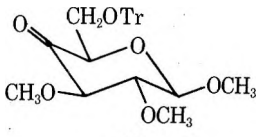
18, R = CH_3, CH_3SO_2

axial approach



equatorial approach

19, R = CH_3, CH_3SO_2; R′ = CH_3



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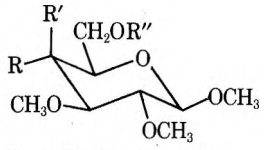
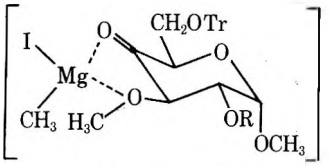


21, R = OH; R′ = R″ = H

22, R = OH; R′ = H; R″ = Tr

23, R = CH_3; R′ = OH; R″ = Tr

24, R = OH; R′ = CH_3; R″ = Tr



25, R = CH_3; CH_3SO_2

note that a similar explanation was proposed[22] for the observation[23,24] that 4-chlorocyclohexanone and cyclohexanones with other electronegative substituents at C-4 give unusually high proportions of axial (cis) alcohols on reduction with complex hydrides.

The reversal of stereochemistry of the addition of the Grignard reagent to the oxo sugars 1 and 2 can be rationalized as a consequence of "chelation" of the magnesium atom of the Grignard reagent with the C-4 carbonyl oxygen and the C-3 oxygen atom.[15b,25,26] Thus, the formation of the cyclic five-membered ring intermediate 25 forces the oxo sugars 1 and 2 to adopt the C1 conformation prior to the addition of the methyl group to the C-4 carbonyl carbon. The solvent dependence of stereochemistry of the addition of Grignard reagent to the oxo sugars 1 and 2 strongly supports this view.

Various methods have been used thus far in carbohydrate chemistry for making unequivocal configurational assignments to a branching-carbon atom in branched-chain sugars,[27] and the conclusions often had to be supported by chemical evidence.

Table I

Branched-chain sugar	Chemical shift, ppm[a]	Methyl group at C-4
6	21.9	e
7	15.4	a
8	21.8	e
9	15.5	a
10	21.8	e
11	15.3	a

[a] Downfield from TMS.

The observations on methylcyclohexanes[28,29] that the carbon-13 chemical shift of an axial methyl group is 6 ppm toward a higher field than that of an equatorial methyl group prompted us to investigate the possibility of utilizing the carbon-13 resonance of the C-4 methyl group for determination of the configuration at the branching carbon atom in sugars 6–11.[2]

Table I lists carbon-13 chemical shifts of the C-4 methyl groups in the branched-chain sugars 6–11.

The identification of the C-4 methyl group in carbon-13 nmr spectra of the branched-chain sugars 6–11 was straightforward, since it was the only sp^3 carbon atom not attached to an oxygen atom. This was in accord with a previous finding[30] that the carbon-13 resonance of the C-6 methyl group of methyl α-L-rhamnopyranoside is shifted strongly upfield relative to the carbon-13 resonances of the other carbon atoms.

The carbon-13 chemical shift of the equatorial and axial methyl group in the branched-chain sugars 6–11 had a fairly constant value: 21.8 ppm for the equatorial and 15.4 ppm for the axial methyl group (average values). The upfield shift of the axial methyl group in 7, 9, and 11, relative to the carbon-13 chemical shifts of the equatorial methyl group in 6, 8 and 10, is 6.4 ppm. This was in good agreement with the chemical-shift difference of an axial and equatorial methyl group found in the 4-*tert*-butyl-1-methylcyclohexanols (6.0 ppm). Table II lists the carbon-13 chemical shifts of the two isomeric 4-*tert*-butyl-1-methylcyclohexanols (16 and 17). Our spectral assignments are compared with reported spectral assignments made for carbon-13 resonances of *cis*- and *trans*-4-*tert*-butylcyclohexanols (14 and 15).[31] [The conversion $\delta_C(TMS) = 192.8 - \delta_C(CS_2)$ was used in order to express the carbon-13 resonances for 14 and 15 in parts per million downfield from TMS.]

Experimental Section

General. The silica gel used for all column chromatography was E. Merck (Darmstadt, Germany) silica gel, grain size <0.08 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267. The proton nmr spectra were recorded

Table II

Substituted cyclohexanol	Chemical shift, ppm C-1	C-2, C-6	C-4	C-3, C-5	(e)CH_3	(a)CH_3
cis-4-*tert*-Butyl-1-methylcyclohexanol (**16**)[a]	68.9	39.4	47.7	22.7	31.4	
trans-4-*tert*-Butyl-1-methylcyclohexanol (**17**)[b]	71.0	41.0	47.9	25.0		25.4
cis-4-*tert*-Butylcyclohexanol (**14**)[c]	65.0	33.3	48.2	21.0		
trans-4-*tert*-Butylcyclohexanol (**15**)[d]	70.4	35.7	47.3	25.7		

[a] Quaternary carbon atom from *tert*-butyl group, 32.4 ppm; methyl groups from *tert*-butyl group, 27.7 ppm. [b] Quaternary carbon atom from *tert*-butyl group, 32.3 ppm; methyl groups from *tert*-butyl group, 27.7 ppm. [c] Quaternary carbon atom from *tert*-butyl group, 32.4 ppm; methyl groups from *tert*-butyl group. 27.4 ppm. [d] Quaternary carbon atom from *tert*-butyl group, 32.1 ppm; methyl groups from *tert*-butyl group, 27.5 ppm.

with Varian T-60 and HR-220 spectrometers using tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in parts per million. The proton noise decoupled carbon-13 nmr spectra were recorded with a TNM PS-100 FT spectrometer. The spectra were obtained using 5000-Hz sweep with 8K data points. The pulse width was 7.0 μsec and pulse repetition rate was 1.5 sec.

Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (1). Methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**4**,[32] 1.000 g, 2.16 mmol) was dissolved in 10:7 dimethyl sulfoxide–acetic anhydride (17 ml) and heated at 65° for 2 hr. The residual syrup, obtained after evaporation of solvents *in vacuo*, was dissolved in ether (50 ml) and washed with saturated aqueous NaCl solution. The ether extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*, yielding a white, amorphous solid (830 mg, yield 83%). An analytical sample was obtained by chromatographing crude **1** (250 mg) on silica gel (30 g). Elution with 120:60:1 hexane–acetone–water gave pure **1** (212 mg) as an amorphous solid, $[\alpha]^{27}D$ +123° (*c* 0.6, $CHCl_3$), ir ($CHCl_3$) 1735 cm^{-1} (C=O stretch). *Anal.* Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.45; H, 6.23.

Reaction of Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (1) with Methyllithium (LiBr-Free) in an Ethereal Solution at −80°. To an ethereal solution (10 ml) of **1** (76 mg, 0.16 mmol), cooled to −80°, an ethereal solution (0.5 ml, 2 *M*) of methyllithium (LiBr-free) was added and the reaction mixture was stirred for 1.5 hr at −80°. Water was then added (10 ml), the ethereal layer was separated, and the water solution was extracted with three 30-ml portions of of ether. The combined ethereal extracts were washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The white, amorphous crude product (77 mg) was chromatographed on silica gel (15 g). Elution with 95:5 benzene–2-propanol afforded pure methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**9**, 53 mg, 70%), which after recrystallization from isopropyl ether showed mp 119°: $[\alpha]^{27}D$ +51° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3580 and 3520 cm^{-1} (broad peaks, OH); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 4.80 (d, $J_{1,2}$ = 4.2 Hz, 1, H-1), 0.99 (s, 3, C-4-methyl group). *Anal.* Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 73.00; H, 7.27.

Reaction of Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (1) with Methylmagnesium Iodide in an Ethereal Solution at −80°. An ethereal solution (5 ml) of methylmagnesium iodide (50 mg of Mg + 0.3 ml of MeI) cooled to −80° was added to an ethereal solution (10 ml) of pure **1** (50 mg, 0.11 mmol) precooled to −80°. The reaction was monitored by tlc using the solvent system 95:5 benzene–2-propanol. After the reaction mixture was stirred for 2.5 hr at −80°, a few milliliters of methanol was added and then 1 *N* H_2SO_4 (30 ml). After extraction with three 30-ml portions of ether, the combined ethereal extracts were washed with saturated aqueous NaCl solution until neutral and dried over anhydrous Na_2SO_4. A syrup (74 mg) obtained after removal of ether *in vacuo* was chromatographed on silica gel (20 g). Elution with 95:5 benzene–2-propanol gave 49 mg (94%) of pure methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**8**), which after recrystallization from isopropyl ether showed mp 149–149.5°: $[\alpha]^{27}D$ +73° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3570 and 3510 cm^{-1} (broad peaks, OH); nmr ($CDCl_3$) δ 7.7–7.1 (m, 15, triphenylmethyl), 5.00 (d, $J_{1,2}$ = 3.8 Hz, 1, H-1), 1.03 (s, 3, C-4 methyl group). *Anal.* Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.58; H, 6.99.

Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-glucopyranoside (13). A benzene solution (50 ml) containing methyl 4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (**12**,[33] 1.30 g, 3.61 mmol), methyl iodide (6.0 ml, 96.3 mmol), and Ag_2CO_3 (1.3 g, 4.71 mmol) was refluxed for 5 hr. At the end of every hour an additional amount of Ag_2CO_3 (1.3 g, 4.71 mmol) was added. The solid was then filtered off through Celite, and the filtrate was evaporated *in vacuo*. The crude product (1.55 g) was chromatographed on silica gel (85 g). Elution with 155:45 benzene–ethyl acetate afforded pure **13** (1.22 g, 90%). After recrystallization from ether, compound **13** had mp 110–111°; $[\alpha]^{27}D$ +70° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 1367 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); nmr ($CDCl_3$) δ 7.5–7.2 (m, 5, phenyl), 5.53 (s, 1, methine H from benzylidene group), 4.91 (d, $J_{1,2}$ = 3.8 Hz, 1, H-1), 3.57 (s, 3, Me from C-3 methoxy group), 3.41 (s, 3, Me from C-1 methoxy group), 3.23 (s, 3, Me from methylsulfonyl group). *Anal.* Calcd for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92; S, 8.57. Found: C, 51.43; H, 6.01; S, 8.68.

Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-α-D-glucopyranoside (3). A 50% aqueous acetic acid solution (50 ml) containing methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-glucopyranoside (**13**, 1.984 g, 5.3 mmol) was heated at 100° for 1 hr. The solvent was evaporated *in vacuo*, and the crude product (1.864 g) was chromatographed on silica gel (70 g). Elution with 1:1 acetone–hexane afforded 1.410 g (91%) or pure **25** as an oil: $[\alpha]^{27}D$ +95° (*c* 1.5, $CHCl_3$); ir ($CHCl_3$) 3580 (shoulder) and 3420 cm^{-1} (broad peak, OH); nmr ($CDCl_3$) δ 4.93 (d, $J_{1,2}$ = 3.9 Hz, 1, H-1), 3.60 (s, 3, Me from C-3 methoxy group), 3.42 (s, 3, Me from C-1 methoxy group), 3.08 (s, 3, Me from methylsulfonyl group). *Anal.* Calcd for $C_9H_{18}O_8S$: C, 37.76; H, 6.34; S, 11.18. Found: C, 37.63; H, 6.42; S, 11.31.

Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (5). To a pyridine solution (20 ml) of methyl 3-*O*-methyl-2-*O*-methylsulfonyl-α-D-glucopyranoside (**13**, 1.410 g, 5.18 mmol), triphenylmethyl chloride (1.90 g, 6.83 mmol) was added. After standing at room temperature overnight, the solvent was evaporated *in vacuo*. The residue was dissolved in benzene (it does not dissolve completely), and water was added. The benzene layer was separated, and, after drying over anhydrous Na_2SO_4, the benzene was evaporated *in vacuo*. The crude product was chromatographed on silica gel (160 g). Elution with 2:1 hexane–acetone afforded 2.500 g (94%) of pure **5**, in amorphous state: $[\alpha]^{27}D$ +47° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3580 and 3500 (two broad peaks, OH), 1597, 1490, and 1449 (benzene ring stretching frequencies), 1365 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 4.91 (d, $J_{1,2}$ = 3.9 Hz, 1, H-1), 3.57 (s, 3, Me from C-3 methoxy group), 3.40 (s, 3, Me from C-1 methoxy group), 3.04 (s, 3, methyl from methylsulfonyl group). *Anal.* Calcd for $C_{28}H_{32}O_8S$: C, 63.62; H, 6.10; S, 6.07. Found: C, 63.86; H, 6.06; S, 6.00.

Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (2). Methyl 3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**5**, 578 mg, 1.1 mmol) was dissolved in a 2:1 mixture of dimethyl sulfoxide–acetic anhydride (4.5 ml). After the reaction mixture was kept at 60° for 2 hr, the solvents were removed *in vacuo* and the crude product (**2**), because it is very unstable, was not purified, but directly used for reaction with methyllithium.

Reaction of Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (2) with Methyllithium in an Ethereal Solution at −80°. An ethereal solution (20 ml) containing crude **2** (580 mg) was cooled to −80°, whereby the solution became very turbid, and *ca.* 2 *M* ethereal solution (2 ml) of methyllithium was added. After stirring for 1.5 hr at −80°, methanol was added, whereby the solution became clear. After removal of solvents *in vacuo*, the crude product (630 mg) was purified by several chromatographies, on silica gel, using 95:5 benzene–2-propanol and 3:1 hexane–acetone for elution, whereby the pure 3-*O*-methyl-4-C-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**11**, 320 mg, 53%) was obtained as an oil: $[\alpha]^{27}D$ +92° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3580 (shoulder) and 3520 (broad peak) (OH), 1360 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 4.83 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), 4.22 (q, $J_{1,2}$ = 4.0 and $J_{2,3}$ = 10.0 Hz, 1, H-2), 3.87 (broad t, $J_{5,6}$ = 6.4 Hz, 1, H-5), 3.55 (s, 3, Me from C-3 methoxy group), 3.40 (s, 3, Me from C-1 methoxy group), 3.00 (s, 3, Me from methylsulfonyl group), 1.01 (s, 3, C-4 methyl group). *Anal.* Calcd for $C_{29}H_{34}O_8S$: C, 64.19; H, 6.32; S, 5.91. Found: C, 63.99; H, 6.21; S, 5.85.

Reaction of Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (2) with Methylmagnesium Iodide in an Ethereal Solution at −80°. To an ethereal solution (20 ml) of methylmagnesium iodide (200 mg of Mg + 0.5 ml of CH_3I) cooled to −80°, an ethereal solution (15 ml) of **2** (300 mg, 0.57 mmol) was added with stirring. After the reaction mixture had been stirred for 1 hr at −80°, aqueous methanol was added and the reaction product was extracted with ether. The crude product (300 mg), obtained after removal of ether *in vacuo*, was chromatographed on silica gel. Elution with 95:5 benzene–2-propanol afforded pure **10** (166 mg; 53%), which after recrystallization from ether–isopropyl ether showed mp 117.5°: $[\alpha]^{27}D$ +75° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3570 (shoulder) and 3490 (broad peak) (OH), 1365 and 1178 cm^{-1} (asymmetric and symmetric SO_2 stretch); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 5.13 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), 4.86 (q, $J_{1,2}$ = 4.0 and $J_{2,3}$ = 10.0 Hz, 1, H-2), 3.57 (s, 3, Me from C-3 methoxy group), 3.48 (s, 3, Me from C-1 methoxy group), 3.07 (s, 3, Me from methylsulfonyl group), 1.05 (s, 3, C-4 methyl group). *Anal.* Calcd for $C_{29}H_{34}O_8S$: C, 64.19; H, 6.32; S, 5.91. Found: C, 63.98; H, 6.44; S, 5.81.

Reaction of Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (1) with Methylmagnesium Io-

dide in an Ethereal Solution at Reflux. To a refluxing ethereal solution (10 ml) of methylmagnesium iodide (50 mg of Mg + 0.5 ml of CH_3I), an ethereal solution (10 ml) of **1** (116 mg, 0.25 mmol) was added dropwise during 7 min. After refluxing for 20 min the reaction mixture was diluted with ether, and the ethereal solution was washed with saturated aqueous NaCl solution, aqueous K_2CO_3–$NaHSO_3$ solution, and again with saturated aqueous NaCl solution. The ethereal phase was dried over anhydrous Na_2SO_4, and ether was evaporated *in vacuo*. The semicrystalline residue (117 mg) was chromatographed on silica gel (15 g). Elution with 95:5 benzene–2-propanol gave tlc-homogenous product (83 mg) which according to the nmr spectrum was a *ca.* 6:1 mixture of **8** and **9**, **8** being the predominant product.

Reaction of Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (1) with Methylmagnesium Chloride in a 40:1 Ether–Tetrahydrofuran Solution at Reflux. To an ethereal solution (20 ml) of **1** (200 mg, 0.43 mmol) a 3 *M* solution of methylmagnesium chloride in tetrahydrofuran (0.5 ml, *ca.* 2 mmol) was added, whereby a white precipitate appeared. After the reaction mixture was refluxed for 2 hr, it was kept at room temperature overnight. Methanol (10 ml) was then added (the white precipitate dissolved) and the solvents were evaporated *in vacuo*. The residue was dissolved in ether–1 *N* HCl mixture, and the ethereal layer was separated. The aqueous phase was extracted three times with ether, the combined ethereal extracts were washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4, and the ether was removed *in vacuo*. The crude product (203 mg) was a 1.3:1 mixture of **8** and **9**, **8** being the predominant product.

Reaction of Methyl-3-*O*-Methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (2) with Methylmagnesium Chloride in Refluxing 10:1 Ether–Tetrahydrofuran Solution. To an ethereal solution (20 ml) of **2** (346 mg, 0.66 mmol) a 3 *M* solution of methylmagnesium chloride (2.00 ml, 6 mmol) in tetrahydrofuran was added and the reaction mixture was refluxed for 4 hr. The excess of methylmagnesium chloride was destroyed by addition of ethyl acetate and the reaction mixture was poured into water (80 ml) containing 2 ml of concentrated HCl. The aqueous layer was extracted with ether, the combined ethereal extracts were washed with water and dried over anhydrous Na_2SO_4, and ether was removed *in vacuo*. The residue (280 mg) was chromatographed on silica gel. Elution with 95:5 benzene–2-propanol gave a product (140 mg) homogenous on tlc, but which, according to the nmr spectrum, was a 1:1 mixture of **6** and **7**.

Reaction of Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (2) with Methylmagnesium Iodide in an Ethereal Solution at Reflux. To an ethereal solution (20 ml) of methylmagnesium iodide (200 mg of Mg + 0.5 ml of CH_3I), an ethereal solution (20 ml) of **2** (600 mg, 1.14 mmol) was added at reflux. After refluxing for 1.5 hr, water was added until no undissolved material remained. The ethereal layer was separated and the aqueous phase was extracted with ether, the combined ethereal extracts were dried over anhydrous Na_2SO_4, and ether was evaporated *in vacuo*. The residue (470 mg) was chromatographed on silica gel. The elution with 95:5 benzene–2-propanol afforded two fractions. The first fraction (159 mg, 25%). after rechromatography on silica gel (25 g) and recrystallization from isopropyl ether, was identified (mixture melting point, ir and nmr spectra) as **10**, whereas from the second fraction (155 mg, 29%), which was according to the nmr spectrum a 2.8:1 mixture of C-4 epimers **6** and **7**, after rechromatography on silica gel (25 g) and recrystallization from isopropyl ether was isolated pure methyl 3-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**6**): mp 125–126°; $[\alpha]^{27}D$ +30° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 3570 and 3510 cm^{-1} (broad peak) (OH); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 4.90 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), 3.60 (s, 3. Me from C-3 methoxy group), 3.51 (s, 3, Me from C-1 methoxy group), 1.02 (s. 3, C-4 methyl group). *Anal.* Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.44; H, 7.05.

Reaction of Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (2) with Methylmagnesium Iodide in 10:1 Ether–Tetrahydrofuran Solution at Reflux. To a 5:1 ether–tetrahydrofuran solution (22 ml) of methylmagnesium iodide (200 mg of Mg + 0.5 ml of CH_3I), an ethereal solution (10 ml) of **2** (350 mg, 0.66 mmol) was added. After the reaction mixture was heated under reflux for 1 hr, water was added and the water phase was extracted with ether. The combined ethereal extracts were dried over anhydrous Na_2SO_4 and ether was evaporated *in vacuo*. The crude product (300 mg) was chromatographed on silica gel. Elution with 95:5 benzene–2-propanol afforded a tlc-homogenous product (148 mg) which was, according to the nmr spectrum, a mixture of **6** and **7** in the ratio 1:2.3.

Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-β-D-glucopyranoside (22). A pyridine solution (60 ml) containing methyl 2,3-di-*O*-methyl-β-D-glucopyranoside (**21**,[36] 3.778 g, 17 mmol) and triphenylmethyl chloride (6.000 g, 21.5 mmol) was kept at room temperature for 2 days. The residue obtained after removal of pyridine *in vacuo* was dissolved in water, the solution was extracted three times with benzene (50 ml), the combined benzene extracts were washed successively with water, 1 *N* sulfuric acid, and again with water and dried over anhydrous Na_2SO_4, and benzene was evaporated *in vacuo*. The residue (9.778 g) was chromatographed twice on silica gel (250 g). Elution with 3:1 hexane–acetone afforded pure **22** (6.621 g, 83%) as a white, amorphous substance: $[\alpha]^{27}D$ −39° (c 1.0, $CHCl_3$); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 4.23 (m, 1, H-1), 3.63, 3.56, and 3.55 (three s, 9, Me from C-1, C-2, and C-3 methoxy groups). *Anal.* Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.59; H, 7.03.

Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-β-D-*xylo*-hexopyranosid-4-ulose (20). To a dimethyl sulfoxide solution (17 ml) of methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-glucopyranoside (**22**, 1.750 g, 3.8 mmol), acetic anhydride (10 ml) was added with stirring and the reaction mixture was kept at 55–60° for 2 hr. The solvents were then evaporated *in vacuo* to a syrup (maintaining the bath temperature below 40°). The syrup was dissolved in ether (50 ml) and the ethereal solution was washed with saturated aqueous NaCl solution. The ethereal phase was dried over anhydrous Na_2SO_4 and ether was removed *in vacuo*. The crude product (1.746 g) was chromatographed on silica gel (150 g). Elution with 120:60:1 hexane–acetone–water gave pure **20** (1.260 g, 70%), which was recrystallized from isopropyl ether as needles: mp 100–102°; ir ($CHCl_3$) 1740 cm^{-1} (C=O stretch); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 4.63 (d, $J_{1,2}$ = 6.0 Hz, 1, H-1), 3.53 and 3.51 (two s, 9, Me from C-1, C-2, and C-3 methoxy group).

Reaction of Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-β-D-*xylo*-hexopyranosid-4-ulose (20) with Methylmagnesium Iodide in an Ethereal Solution at −80°. To an ethereal solution (15 ml) of methylmagnesium iodide (100 mg of Mg + 1 ml of CH_3I) cooled to −80° an ethereal solution (5 ml) of **20** (190 mg, 0.41 mmol), precooled to −80°, was added, whereby a white precipitate separated. After stirring for 3 hr at −80°, water was added, the ethereal layer was separated, the aqueous phase was extracted with ether, the combined ethereal extracts were dried over anhydrous Na_2SO_4, and ether was evaporated *in vacuo*. The crude product (155 mg, 76%) was according to the nmr spectrum only one isomer. After chromatography on silica gel (50 g) and elution with 2:1 benzene–ether, pure methyl 2,3-di-*O*-methyl-4-C-methyl-6-*O*-triphenylmethyl-β-D-galactopyranoside (**23**) was obtained as an amorphous solid: $[\alpha]^{27}D$ −13° (c 1.0, $CHCl_3$); nmr ($CDCl_3$) δ 7.6–7.1 (m, 15, triphenylmethyl), 4.16 (d, $J_{1,2}$ = 8.0 Hz, 1, H-1), 3.60 and 3.55 (two s, 9, Me from C-1, C-2, and C-3 methoxy group), 1.01 (s, 3, C-4 methyl group). *Anal.* Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 73.04; H, 7.40.

Reaction of Methyl 2,3-Di-*O*-methyl-6-*O*-triphenylmethyl-β-D-*xylo*-hexopyranosid-4-ulose (20) with Methyllithium (LiBr-Free) in an Ethereal Solution at −80°. To an ethereal solution (10 ml) of **20** (243 mg, 0.53 mmol) cooled to −80° a 2 *M* ethereal solution (1 ml) of methyllithium was added. After the reaction mixture was stirred at −80° for 4.5 hr, water was added, the ethereal layer was separated, and the aqueous layer was extracted with three 30-ml portions of ether. The combined ethereal extracts were washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The crude product (236 mg) obtained after removal of ether *in vacuo* was according to the nmr spectrum at 3:1 mixture of **23** and **24**, **24** being the predominant product. *Anal.* Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.67; H, 7.16.

Reaction of 4-*tert*-Butylcyclohexanone with Methylmagnesium Iodide in an Ethereal Solution at −80°. To an ethereal solution (15 ml) of methylmagnesium iodide (144 mg of Mg + 0.5 ml of CH_3I) cooled to −80° an ethereal solution (5 ml) of 4-*tert*-butylcyclohexanone (460 mg, 3 mmol) precooled to −80° was added (during cooling of the ethereal solution of ketone to −80°, the ketone crystallized out so that the suspension was added). After stirring for 6 hr at −80°, water was added, the undissolved solid was dissolved by adding 1 *N* HCl, and the aqueous phase was extracted with three 70-ml portions of ether. Combined ethereal extracts were successively washed with saturated aqueous NaCl solution, saturated aqueous NaCl solution which contained

K_2CO_3 and $NaHSO_3$, and again with saturated aqueous NaCl solution. The ethereal extract was dried over anhydrous Na_2SO_4, and the ether was evaporated *in vacuo*. The crystalline residue (447 mg) was chromatographed on silica gel (40 g). Elution with 7:3 benzene–ethyl acetate gave three fractions; the first fraction (110 mg) was starting material, the second fraction (170 mg, 33%) was pure **16**, whereas the third fraction (103 mg, 20%) was pure **17**. The ratio of **16**:**17** was hence 1.7:1.

Reaction of 4-*tert*-Butylcyclohexanone with Methyllithium in an Ethereal Solution at −80°. To an ethereal solution (20 ml) of 4-*tert*-butylcyclohexanone (308 mg, 2 mmol) cooled to −80°, a 2 *M* ethereal solution (1.4 ml, 2.8 mmol) of methyllithium was added. After stirring for 2 hr at −80°, water was added, the ethereal layer was separated, and the aqueous phase was extracted with ether. The combined ethereal extracts were washed with water and dried over anhydrous Na_2SO_4. The crude crystalline product (274 mg) was chromatographed on silica gel (15 g). Elution with 17:3 benzene–ethyl acetate gave three fractions; the first fraction (66 mg) was the unreacted starting material, the second fraction (132 mg, 40%) was pure **16**, whereas the third fraction (37 mg, 11%) was pure **17**. The ratio **16**:**17** was therefore 3.6:1.

Acknowledgment. We are greatly indebted to Professor L. M. Jackman for recording carbon-13 nmr spectra.

Registry No.—**1**, 51016-07-0; **2**, 51016-08-1; **3**, 51016-09-2; **4**, 51016-10-5; **5**, 51016-11-6; **6**, 51016-12-7; **7**, 51016-13-8; **8**, 51016-14-9; **9**, 51016-15-0; **10**, 51016-16-1; **11**, 51016-17-2; **12**, 51016-18-3; **13**, 51016-19-4; **14**, 937-05-3; **15**, 21862-63-5; **16**, 16980-55-5; **17**, 16980-56-6; **20**, 51016-20-7; **21**, 10227-29-9; **22**, 51016-21-8; **23**, 51016-22-9; **24**, 51016-23-0; methyllithium, 917-54-4; methylmagnesium iodide, 917-64-6; methylmagnesium chloride, 676-58-4; 4-*tert*-butylcyclohexanone, 98-53-3.

References and Notes

(1) This work was supported, in part, by Grant CA 15483 from the National Institutes of Health.

(2) After the preparation of this manuscript, a paper was published dealing with the configurational assignment by carbon-13 nmr spectroscopy of quaternary centers in carbohydrates cortaining C-1,3 dithianyl branched chains: G. Lukacs, A. M. Sepulchre, A. Gateau-Olesker, G. Vass, S. D. Gero, R. D. Guthrie, W. Voelter, and E. Breitmaier, *Tetrahedron Lett.*, 5163 (1972). In an earlier paper Sepulchre, *et al.*,[3] made a configurational assignment at the branching carbon atom of branched-chain sugars based on carbon-13 nmr spectroscopy together with circular dichroism studies, but without disclosing any details; the data were listed as unpublished results.

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(16) In addition to **10**, methyl 3-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**6**) and methyl 3-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**7**) were obtained as hydrolysis products of **10** and **11**.

(17) The branched-chain sugars **10** and **11** could not be isolated.

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Photochemistry of 1-Aryl-1,2-propanediones. Intermediacy of an Enol in the Photocyclization of 1-(*o*-Tolyl)-1,2-propanedione[1]

Yoshiro Ogata* and Katsuhiko Takagi

Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

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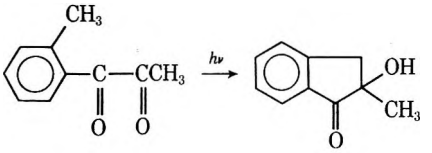
An enol (4), a precursor for photocyclization of 1-(*o*-tolyl)-1,2-propanedione (1) to 2-hydroxy-2-methylindanone (2), was trapped in the photolysis of 1 in the presence of an equivalent amount of dimethyl acetylenedicarboxylate as its cyclic adduct (3). The obtained adduct 3 was thermally unstable and decomposed at 180° to a mixture of the product (2), the starting diketone (1), and dimethyl acetylenedicarboxylate. This fact suggests that the photocyclization of 1 to 2 may proceed *via* an enol (4) formed by 1,5-hydrogen migration, but not the apparent 1,6 shift. Further, this is in accordance with the fact that a methylene analog to 1, α-(o-tolyl)acetone, gives the corresponding reduction product, but not the corresponding indene.

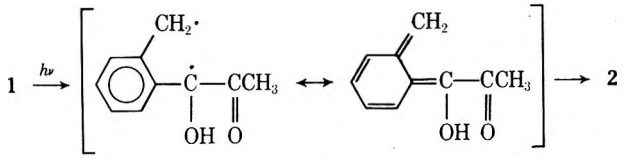
Photocyclization of 1-(o-tolyl)-1,2-propanedione (1) to 2-hydroxy-2-methylindanone (2) was reported by Bishop and Hamer.[2] It is ambiguous in the photocyclization which of the carbonyl oxygens initially abstracts a methyl hydrogen atom.



1 2

While 1,6-hydrogen migration from ortho methyl to the excited acetyl carbonyl oxygen can lead directly to the product (2), 1,6-hydrogen migration in general is not common in cases where the 1,5-hydrogen shift can operate.[3] The 1,6 shift seems to be limited to carbonyl systems which have no γ-hydrogen or have a δ-hydrogen atom activated by alkoxy or other groups.[4,5] A more common 1,5 shift to give enol (*e.g.*, the enol 4) followed by a 1,2 shift produces the overall effect of a 1,6 shift. However, Bishop and Hamer have discarded the intervention of enol 4 at any stage of the reaction since no deuterium incorporation into the product (2) occurs in photolysis in methanol-*O*-*d*.[1a]

We have reexamined the question of the intermediacy of the enol 4 in the photocyclization and wish to present some evidence for an initial 1,5-hydrogen transfer to aroyl carbonyl oxygen leading to the enol.



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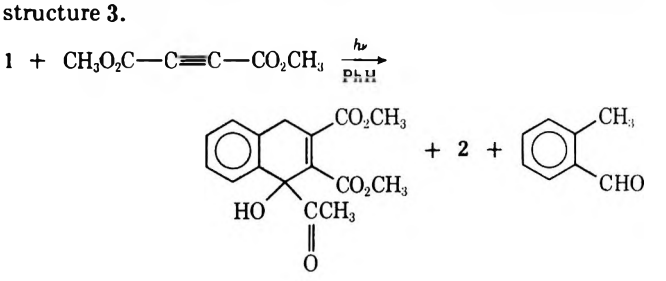
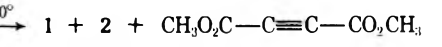
A solution of 1 (3.5 mmol) and dimethyl acetylenedicarboxylate (3.6 mmol) in benzene (120 ml) was irradiated for 6 hr under a nitrogen atmosphere. The reaction mixture was condensed *in vacuo* and the products were separated by silica gel chromatography, yielding unreacted starting diketone (trace), dimethyl acetylenedicarboxylate (trace), 2-tolualdehyde (14.5%), an adduct (3, 5.7%), and 2 (51.7%). An adduct (3) was isolated as a viscous, pale yellow oil which could not be crystallized. The infrared absorption of this material clearly showed the presence of hydroxyl (3400 cm^{-1}) and two sorts of carbonyl (1710 and 1680 cm^{-1}), but the absence of the acetylenic triple bond (2200 cm^{-1}). In addition, its nmr spectrum showed two carbomethoxy methyl (6 H, τ 6.23), an acetyl methyl (3 H, τ 7.78), and a broad hydroxylic proton (1 H, τ 1.20) which is exchangeable with D_2O. The mass spectrum of the material (M^+ 304) as well as the nmr peaks and the integration of the nmr bands (see Experimental Section) was consistent with the molecular formula $C_{16}H_{16}O_6$ and structure 3.

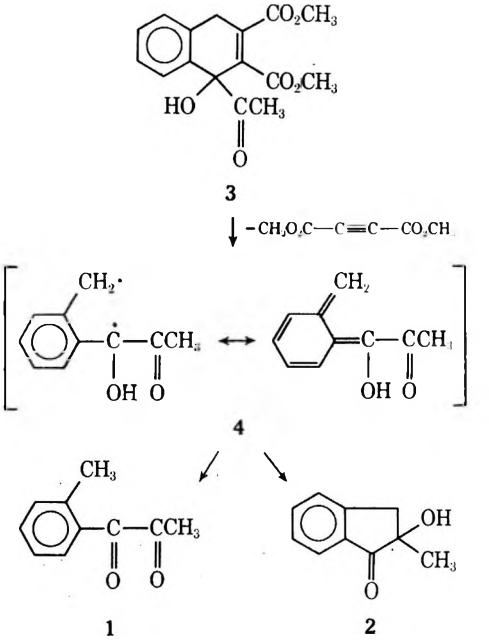


3

Interestingly, compound 3 is thermally unstable. Thus, the adduct 3 decomposed on passing through a glc column at 180° to yield the two starting materials 1 and dimethyl acetylenedicarboxylate and the cyclization product 2 (molar ratio of two products 1:2 was 2:3). Adduct 3 itself could not be detected by the glc method on account of the thermal instability.



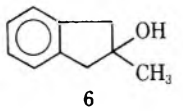
The observation is important because it demonstrates that an enol (or its resonance structure, diradical 4) expected from the pyrolysis of 3 can either cyclize or return to 1.



3 4 1 2

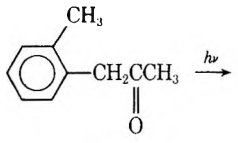
The above thermal reaction of **3** to **2** correlates with the photochemical process of **1** to **2**, since it shows the possibility of 1,6-cyclization of a 1,4-diradical or enol (**4**) which may be formed by 1,5-hydrogen transfer from ortho methyl to aroyl carbonyl oxygen. However, this cannot preclude the possibility of a competitive pathway, a direct 1,6-hydrogen shift (*via* a seven-membered transition state).

Finally, an attempt to photocyclize a monoketone analog, α-(*o*-tolyl)acetone (**5**), to the corresponding indene (**6**) for the examination of the possibility of 1,6-hydrogen abstraction was made. Irradiation of a 2-propanol solution (0.09 *M*) of α-(o-tolyl)acetone (**5**) yielded mainly 1,2-di(o-tolyl)ethane (**7**, 29.3%) and a pinacol (**8**, 14%), but the corresponding indene was absent. Failure to observe cyclization to **6** in spite of the proximity of ortho methyl and



6

acetyl oxygen suggests that there is little tendency for a 1,6 shift.



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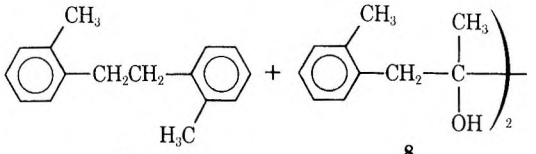
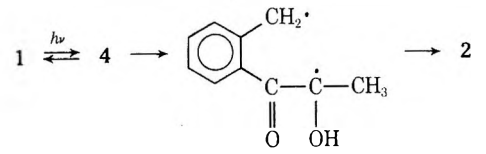


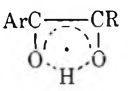
7 **8**

In summary, a 1,4 diradical or its resonance form **4** may be converted to a 1,5 diradical (**9**) by 1,2-hydrogen shift and then cyclization to **2**. Indeed, such 1,2-hydrogen shift was reported for α-diketone radical[6] (**9**).



9

The pathway *via* 1,5 shift seems to be inconsistent with the fact that no deuterium incorporation into **2** is observed in methanol-*O*-*d*. However, an assumption of the stabilization of **4** *via* hydrogen bonding (**10**) can account for this phenomenon.



10

Experimental Section

Infrared spectra were determined with a Perkin-Elmer grating infrared spectrophotometer, Model 337. The nmr spectra were determined with a Japan Electron Optic Laboratory Co. C60 HL nmr instrument. Mass spectra were determined with a Hitachi RMS-4 mass spectrometer. Gas chromatograms were recorded with a Yanaco GCG-550F gas chromatograph with a flame ionization detector (a 2 m × 2.5 mm column packed with 5% SE-30 on Chromosorb at 100–250°). The irradiation was carried out using a Halos 300-W high-pressure Hg lamp which emits over 300-nm light through a Pyrex filter.

Materials. 1-(o-Tolyl)-1,2-propanedione (**1**) was prepared by a method similar to Hartung's procedure,[7] bp 128–137° (20 mm). α-(2-Toyl)acetone (**5**) was prepared by the reaction of α-(*o*-tolyl)-acetyl chloride with methylzinc iodide in ethyl acetate as a pale yellow oil: bp 110–113° (14–15 mm) [lit.[8] bp 122° (23 mm)]; nmr (CCl_4) τ 2.94 (s, 4 H, phenyl), 6.32 (s, 2 H, methylene), 7.80 (s, 3 H, $COCH_3$), and 8.02 (s, 3 H, tolyl methyl).

Reaction of 1 with Dimethyl Acetylenedicarboxylate. A benzene solution (120 ml) of an equimolar mixture of **1** (567 mg) and dimethyl acetylenedicarboxylate (513 mg) was irradiated for 6 hr until the yellow color of the solution had disappeared. The concentrated reaction mixture was chromatographed on a 15 × 300 mm column, slurry packed in benzene–5% acetone as an eluent. Fractions 5–10 (each 5 g) were a mixture of dimethyl acetylenedicarboxylate and the starting diketone (trace). Fractions 38–40 were 2-tolualdehyde (61 mg). Fractions 41–44 yielded a viscous, pale yellow oil, an adduct (**3**, 61 mg). Thin layer chromatography on Kiesel Gel G (Merck) with benzene–5% acetone showed one spot at R_f 0.24. The adduct **3** had the following spectra: ir ν_{max} (liquid film) 3400, 3050, 2940, 1710, 1680, 1425, 1340, 1275, 1150, and 740 cm^{-1}; nmr (CCl_4) τ 1.20 (s, 1 H), 2–3 (m, 4 H), 5.98 (s, 2 H), 6.23 (s, 6 H), and 7.78 (s, 3 H); mass spectrum *m/e* (rel intensity) 28 (100), 39 (25), 43 (50), 44 (25), 45 (20), 65 (20), 77 (20), 91 (64), 105 (20), 115 (20), 118 (60), 119 (66), 129 (15), 133 (20), 136 (50), 145 (63), 160 (25), 161 (22), 213 (10), 221 (25), 245 (17), 262 (5), and 304 (10). The adduct (**3**) was completely decomposed in a glc column (SE-30 on Chromosorb) at 180° as the injection temperature to yield **1** and **2** (**2**:**1** = 1.5 based on their relative peak area) as well as dimethyl acetylenedicarboxylate (column temperature 100–250°). Fractions 55–70 were 2-hydroxy-2-methylindanone (**2**, 293 mg), mp 53–54.5°. The indanone **2** had the following spectra: ν_{max} (KBr) 3400, 2960, 2910, 1715, 1145, and 730 cm^{-1}; λ_{max} (MeOH) 245 and 290 nm; nmr (CCl_4) τ 2.5 (m, 4 H), 6.0 (s, 1 H), 6.84 (s, 2 H), 8.63 (s, 3 H); mass spectrum *m/e* (rel intensity) 43 (100), 50 (40), 64 (15), 65 (15), 76 (13), 91 (42), 105 (13), 120 (30), 146 (13), and 162 (25).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 73.5; H, 6.22.

Photolysis of α-(*o*-Tolyl)acetone (5). A 2-propanol solution (30 ml) of the ketone (507 mg) was irradiated for 10 hr in a quartz vessel without a Pyrex filter under N_2 atmosphere, giving three isolated products. The first eluted product was di(2-tolyl)ethane (**7**, 29.3%): mp 66°; nmr (CCl_4) τ 2.94 (s, 8 H), 7.20 (s, 4 H), and 7.74 (s, 6 H). Although the second product was unidentified yet, it was not a hydroxylic compound (*e.g.*, indene **6**), because its nmr spectrum shows the absence of an acetyl group and a hydroxyl group which was confirmed by no signal change by addition of D_2O in a range of τ −10 to 10. The third eluted product was a pale yellow liquid (a pinacol, **8**, 14%): nmr (CCl_4) τ 2.93 (s, 8 H), 5.60 (s, 2 H, OH exchangeable with D_2O), 7.10 (s, 4 H), 7.70 (s, 6 H), and 8.82 (s, 6 H); ν_{max} (liquid film) 3400, 1700, 1150, and 740 cm^{-1}; mol wt (mass spectrum) 298 (M^+) (calcd for $C_{20}H_{26}O_2$, 298).

Registry No.—**1**, 25412-56-0; **2**, 25412-59-3; **3**, 51051-99-1; **5**, 51052-00-7; **7**, 952-80-7; dimethyl acetylenedicarboxylate, 762-42-5.

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Photoisomerization of Phenyl Alkyl Ethers. II. The Mechanism for the Formation of Meta Alkylphenols

John J. Houser,* Mao-Ching Chen, and San Susan Wang

Department of Chemistry, The University of Akron, Akron, Ohio 44325

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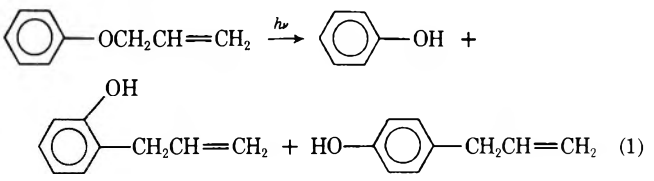
In the photoisomerization of anisole to the three isomeric cresols, evidence is presented for a common precursor to *m*- and *p*-cresol. The intermediate is presumed to be 4-methylcyclohexa-2,5-dienone, which subsequently is photoisomerized to 6-methylbicyclo[3.1.0]hex-3-en-2-one. This, on further irradiation, isomerized to *m*-cresol. Strong evidence for this mechanism is provided by the irradiation of 2,4,6-trideuterioanisole, and the isolation from the photolysate of a dideuterio-*m*-cresol showing the predicted location of the deuterons.

The photo-Claisen rearrangement (eq 1) serves as a model for the photoisomerization of most diaryl, aryl allyl, and aryl benzyl ethers.[1-4] As we previously reported,[5] however, the photoisomerization of phenyl alkyl ethers exhibits the complication that meta alkylphenols are formed, in addition to the ortho and para isomers predicted by eq 1. It is the purpose of this paper to describe the



probable mechanism by which meta alkylphenols are formed. The most significant aspect of the proposed mechanism is that it requires an unhindered 2,5-cyclohexadienone to aromatize slowly enough that a prior photoisomerization can occur.

Results and Discussion

Characteristics of the Reaction. The photoisomerization of phenyl alkyl ethers is best carried out in methanol, ethanol, or 2-propanol. Other solvents, such as cyclohexane, cyclohexene, and *tert*-butyl alcohol, have also been used, but these lead to decreased yields of the desired phenols and an increased yield of tar (Table I).

A 450-W Hanovia medium-pressure mercury arc in a quartz dipping well was used in these studies. Experiments with Corex, Vycor, and Pyrex sleeves lead us to conclude that the wavelength at which the yield is maximized is about 220 nm. Quantum yields were not measured, owing to the difficulty of isolating wavelengths in this region of the spectrum, but Table II gives the absolute yields of the phenolic products from four phenyl alkyl ethers, irradiated for 24 hr as 0.10 *M* solutions in methanol.

That the photoisomerization is unimolecular may be seen from the absence of "crossover" products in the photolysate of a mixture of phenetole and *p*-methylanisole.[5] At present, by analogy to Pinhey's work[2] on phenyl allyl ethers, we are inclined toward a mechanism whereby initially formed alkyl and phenoxy radicals combine within a solvent cage to produce 2,4- and 2,5-cyclohexadienones, but we cannot yet rule out a concerted pathway from the ether to the cyclohexadienones. It is certain, however, that photochemical interconversion of alkylphenols is not intervening, since, when *o*-, *m*-, and *p*-cresol were irradiated separately in methanol under the usual conditions, no products except the original cresol and tar were obtained.

Formation of Meta Alkylphenol. There are two plausible mechanisms by which meta alkylphenols could be formed in these reactions, and these are illustrated in Schemes I and II. In the first scheme, a "direct attack" of the alkyl radical at the meta position of the phenoxy radical yields a diradical (1) which is transformed into meta alkylphenol by the (formal) transfer of a hydrogen from the meta carbon to the oxygen. Scheme II involves the photoisomerization of an initially formed 4-alkylcyclohexa-2,5-dienone (2) to a 6-alkylbicyclo[3.1.0]hex-3-en-2-one (3)—a process with ample precedent in the literature.[6]

The latter mechanism, we feel, is favored by evidence, derived from the photolysis of anisole, which links the for-

Table I
Solvent Effect on Photolysis of Anisole[a]

Solvent	Conversion to phenolic products, %	Phenol, %	*o*-Cresol, %	*m*-Cresol, %	*p*-Cresol, %
Methanol	30.1	11.50	10.99	3.65	3.96
Ethanol	31.2	12.65	10.40	2.45	5.70
2-Propanol	19.0	8.10	7.53	0.83	2.54
tert-Butyl alcohol	22.7	7.58	9.29	1.40	4.44
Cyclohexane	0.65	0.10	0.33	0.17	0.05
Cyclohexene	0.95	0.16	0.53	0.08	0.19

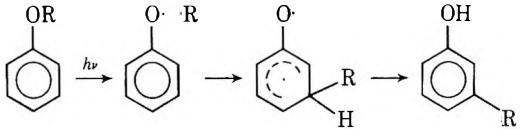
[a] Initial concentration of anisole 0.10 *M*; irradiated for 24 hr with a 450-W medium-pressure Hg lamp.

Table II
Per Cent Yield of Photoproduct after 24 Hr[a]

Registry no.	Starting ether	Phenol	Ortho isomer	Meta isomer	Para isomer
100-66-3	PhOMe	2.81	2.38	0.28	1.61
103-73-1	PhOEt	2.85	2.19	0.44	1.97
2741-16-4	PhOPr-*i*	9.10	2.06	0.77	2.32
6669-13-2	PhOBu-*t*	41.30	7.40	1.11	9.81

[a] Initial concentration of starting ether was 1.35 *M*; irradiated for 24 hr with a 450-W medium-pressure Hg lamp.

Scheme I
Formation of Meta Alkylphenol *via* "Direct Attack" Mechanism



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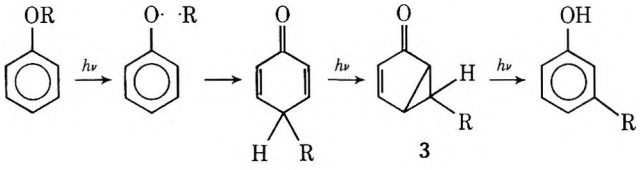
Scheme II
Formation of Meta Alkylphenol *via* a Secondary Photolysis



2 3

mation of meta and para alkylphenols. The first piece of evidence is found in the concentration dependence of the relative yields of *m*- and *p*-cresol (Table III).

While the relative yields of phenol, *o*-cresol, and *m*-plus *p*-cresol are invariant, within experimental error, *m*-cresol increases in yield at the expense of *p*-cresol when the more dilute solution of anisole is irradiated. This suggests that *m*- and *p*-cresol have a common precursor. In the absence of knowledge of the mechanism by which the cyclohexadienones are formed, however, the concentration effect on the meta to para ratio cannot be explained. This aspect is currently under investigation.[7]

Secondly, Stern–Volmer plots were obtained for the quenching of the anisole photolysis by *cis*-dichloroethylene (Figure 1). The plots for *m*- and *p*-cresol formation are nearly coincident ($k_q\tau$ = 169 and 176 l. mol^{-1}, respectively) and are clearly separated from the *o*-cresol plot ($k_q\tau$ = 270 l. mol^{-1}). It is not as yet clear which entity or entities in the reaction scheme are being quenched, anisole or an anisole eximer being the most likely candidates. A common precursor for *m*- and *p*-cresol is clearly implied, however.[8]

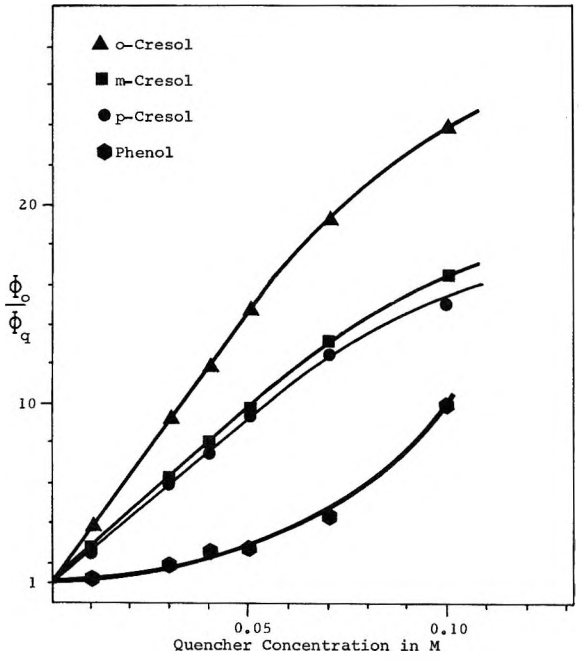


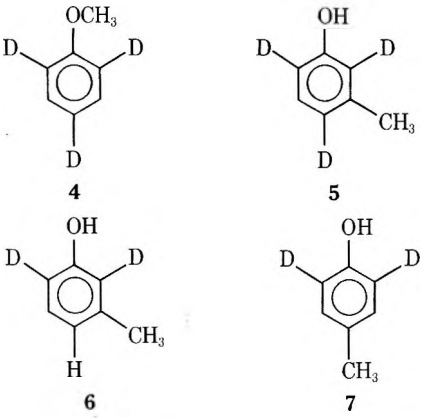
Figure 1. Stern–Volmer plots for the quenching of the anisole photoisomerization by *cis*-dichloroethylene, initial anisole concentration 0.10 *M* in methanol.

Table III
Composition of the Phenolic Photoproduct from the Irradiation of Anisole at two Different Initial Concentrations[a]

Product	Per cent formed at 1.35 *M*[b]	Per cent formed at 0.10 *M*[c]
Phenol	39.7	38.2
o-Cresol	33.6	36.5
m-Cresol	4.0 } 26.7	12.1 } 25.3
p-Cresol	22.7 }	13.2 }

[a] For 24 hr in methanol. [b] Absolute yield of phenolic photoproduct was 7.08%. [c] Absolute yield of phenolic photoproduct was 30.1%.

Labeling Studies. In order to distinguish between Schemes I and II, 2,4,6-trideuterioanisole (4) was prepared and photolyzed in methanol under the usual conditions. The phenolic products were partially separated by preparative gas chromatography, and the *m*-cresol fraction was collected. The aromatic region of a 300-MHz nmr spectrum of this fraction appears in Figure 2. If the mechanism of formation of *m*-cresol from anisole is as outlined in Scheme I, the deuterated *m*-cresol isolated will be 5. If Scheme II is correct, 6 will be the expected deuterated



4 5 6 7

m-cresol. Figure 3 shows the aromatic region of a 300-MHz spectrum of a mixture of undeuterated *m*- and *p*-cresol. Using the chemical shifts and coupling constants obtained from Figures 2 and 3 and from 60-MHz spectra, the 300-MHz spectra of 6 and 7 were simulated on an IBM 350/70 computer, using the LAOCOON III program and a suitable plotting program. The presumed genesis of Figure 2, then, is given in Figure 4. The small peaks in the δ 7.1–7.2 region in Figure 2 are considered to be due to impurities. Figure 4A is the simulated spectrum of a mixture of 17.5% *m*-cresol, 48.8% 6, 3.5% *p*-cresol, and 30.2% 7. The presence of 5 in the mixture would simply add to the intensity of the peak at δ 7.028. While the correspondence of relative areas between Figures 2 and 4A is not perfect, owing to some impurities in the collected sample, we can say that 5 cannot be present to the extent of more than a few per cent.

Tautomerization *vs.* Photoisomerization. A remarkable feature of this reaction, as outlined in Scheme II, is that a 4-alkyl-2,5-cyclohexadienone (2), unsubstituted in the 2 and 6 positions, is capable of being photoisomerized before it can tautomerize to a 4-alkylphenol. In a series of papers, Miller[9] has shown that, in 4-alkyl-2,5-cyclohexadienones substituted with bulky alkyl groups in the 2, 3, and 6 positions, photoisomerization to the bicyclo[3.1.0]hex-3-en-2-one proceeds to the virtual exclusion of tautomerization. This phenomenon, however, does not appear to have been reported for less hindered systems.

On the assumption that tautomerization should be subject to acid and base catalysis, anisole was photolyzed

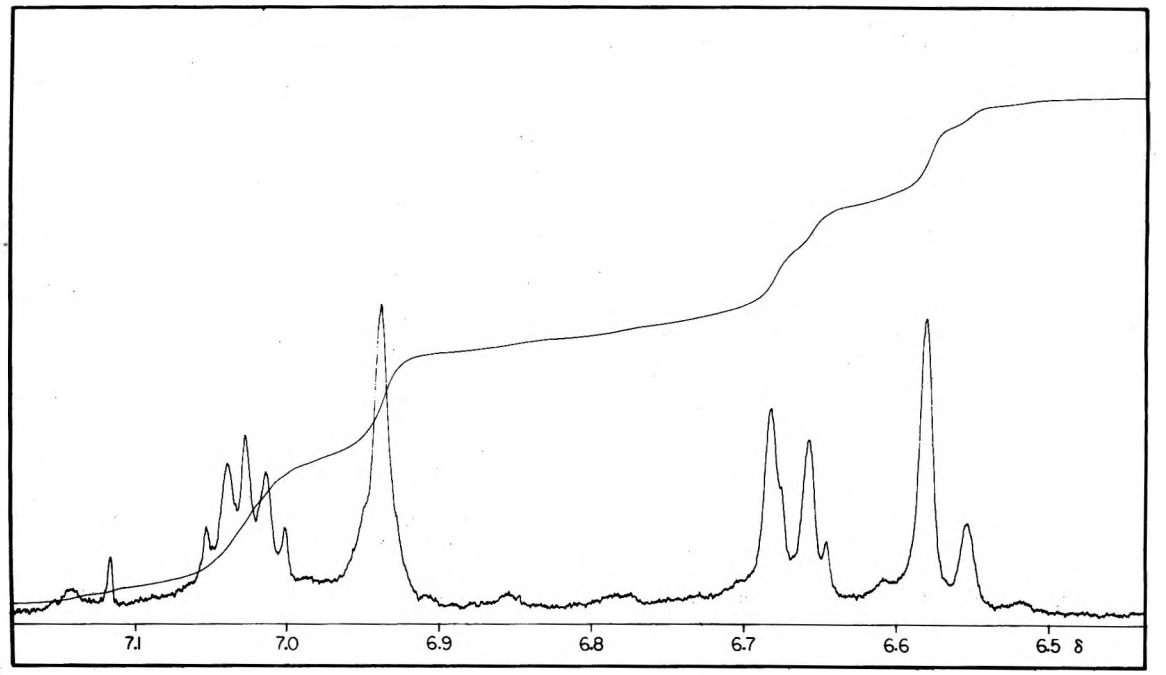


Figure 2. Partial 300-MHz spectrum of the *m*-cresol fraction from the photolysate of 2,4,6-trideuterioanisole, solvent $CDCl_3$.

in methanol containing minute amounts of HCl or $NaOCH_3$. As expected, in both cases, *m*-cresol formation was completely eliminated and *p*-cresol formation increased. Conversely, if C–H bond breaking at C-4 were retarded, *m*-cresol formation should increase as photoisomerization competed more successfully with tautomerization. To this end, 4-deuterioanisole was irradiated under the usual conditions, and the photolysate was examined by gas chromatography. It was observed that the yield of *m*-cresol had been increased by a factor of 2 to 3, while that of *p*-cresol had been correspondingly reduced. Though these data are only semiquantitative, they are completely in accord with the operation of a primary kinetic isotope effect on the tautomerization of the 2,5-cyclohexadienone.

Irradiation of Phenyl Ether. As stated at the outset, the photolysis of phenyl ether, phenyl benzyl ether, and phenyl allyl ether have been reported to yield ortho- and para-substituted phenols, but none of the meta isomer. Because we had observed both that meta alkylphenols tend to be formed in smaller amounts than the ortho and para isomers and that on most gas chromatographic columns meta and para alkylphenols cannot be separated from each other, we irradiated phenyl ether in methanol, and separated the photolysate on a column which had a demonstrated ability to separate the three phenylphenols.

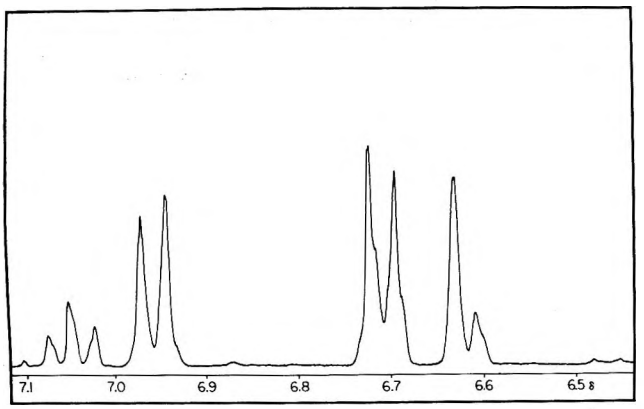


Figure 3. Partial 300-MHz spectrum of a mixture of *m*- and *p*-cresol in $CDCl_3$.

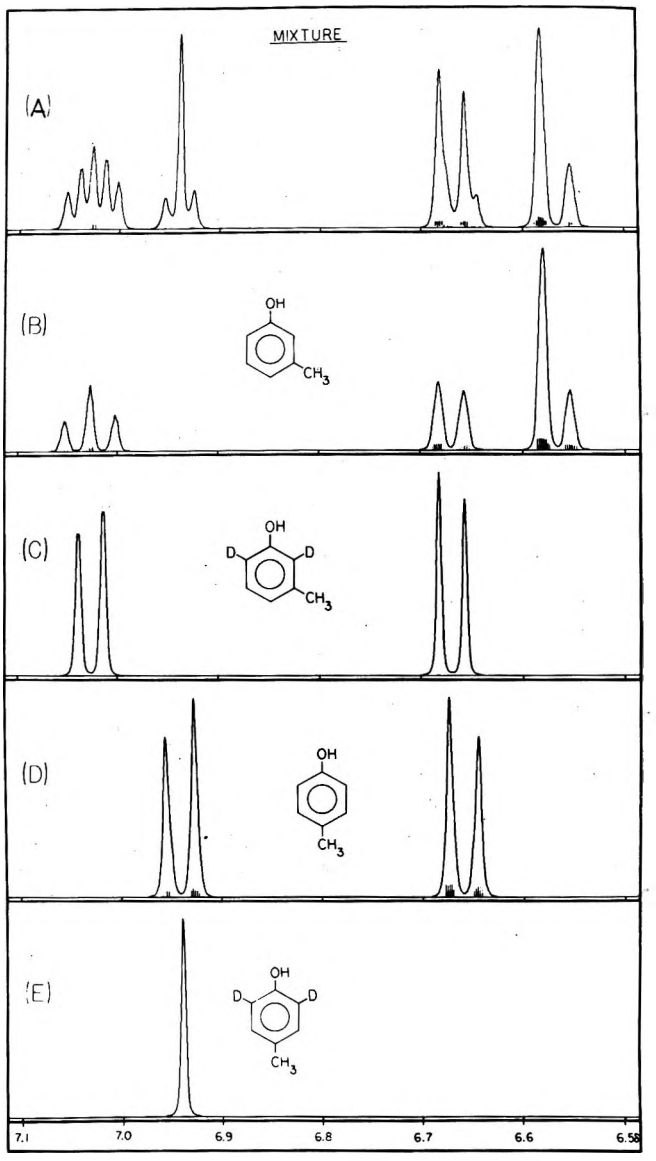


Figure 4. Computer simulation of the 300-MHz spectra of several cresols from the photolysate of 2,4,6-trideuterioanisole in methanol.

In this experiment, *m*-phenylphenol could not be detected in the photolysate. We conclude, then, that a phenyl, benzyl, or allyl group in the 4 position of a 2,5-cyclohexadienone promotes tautomerization by electron withdrawal, rendering the C-4 proton more acidic.

Experimental Section

Materials. Anisole, phenetole, *p*-methylanisole, phenyl ether, phenol, *cis*-dichloroethylene, and all solvents were obtained commercially as reagent or Spectrograde materials, and were used as received. All alkylated phenols were commercial materials, and were recrystallized or vacuum distilled before use.

Isopropyl phenyl ether and *tert*-butyl phenyl ether were prepared by the dicyclohexylcarbodiimide-promoted condensation of phenol with the corresponding alcohol according to the method of Vowinkel[10] and purified by vacuum distillation. Isopropyl phenyl ether had bp 62° (12 Torr); nmr τ 8.75 (doublet, J = 6.2 Hz, rel area 6), 5.55 (septet, J = 6.2 Hz, rel area 1), and 3.0 (multiplet, rel area 5). *tert*-Butyl phenyl ether had bp 68–69° (11 Torr); nmr τ 8.7 (singlet, rel area 1) and 3.0 (multiplet, rel area 5).

Sodium 2,4,6-trideuteriophenoxide was prepared by dissolving sodium phenoxide, freshly prepared from phenol and sodium hydroxide, in D_2O with a small chip of sodium added to ensure basicity. The solution was refluxed overnight, and the D_2O was distilled off *in vacuo*. Fresh D_2O was then added, the solution was again refluxed for several hours, and the D_2O was distilled off. A final refluxing with D_2O yielded sodium 2,4,6-trideuteriophenoxide which, by nmr analysis, contained only about 9% of undeuterated and partially deuterated phenoxide. To the D_2O solution of this product was added 2 equiv of methyl sulfate, and the resulting mixture was refluxed overnight. The trideuterioanisole was extracted from this solution, washed, dried, and distilled at atmospheric pressure. Its purity was confirmed by ir and nmr spectroscopy.

4-Deuterioanisole was prepared by quenching 4-methoxyphenylmagnesium bromide in D_2O. The product was then extracted with ether, dried, and distilled at atmospheric pressure. The purity of the compound was confirmed by its nmr spectrum.

Irradiation. Photolyses were typically carried out in a 250-ml cylindrical Pyrex irradiation vessel equipped with a nitrogen inlet tube and standard taper joints for a condenser and the water-cooled dipping well. High-purity tank nitrogen was bubbled vigorously through the solution for 30–40 min prior to irradiation, and a slow stream of nitrogen was maintained during the irradiation. Phenolic products were isolated from the photolysate by extraction with dilute base, followed by acidification and ether extraction. The products in all cases were separated and collected by preparative gas chromatography, and were identified by comparison of their ir and nmr spectra with those of authentic samples. In the quenching experiment, the 0.10 *M* solutions of anisole in methanol were sealed in quartz tubes after three freeze–pump–thaw degassing cycles, and were arranged around the dipping well, in contact with it. Because of the long irradiation time (24 hr) the tubes were not continuously rotated, but were moved around the dipping well every few hours. At high quencher concentrations (above 0.07 *M*) a yellow, insoluble material began to be deposited on the walls of the sample tubes, thereby reducing the light input. In the attempted photoisomerization of *o*-, *m*-, and *p*-cresol, these compounds were irradiated separately for 24 hr as 0.05 *M* solutions in methanol.

Gas Chromatographic Separation. Phenol and the isomeric alkylphenols were separated on a 0.25 in. × 20 ft column containing 15% SE-52 and 5% Bentone 34 on 60–80 mesh Gas-Chrom Z, at a column temperature of 160–180°. This column could not separate o-cresol from phenol, however; so the anisole photolysate was analyzed both on the SE-52/Bentone 34 column and on a 0.25 in. × 10 ft column containing 10% SE-30 on 60–80 mesh Chromosorb W, at a column temperature of 105°. For the preparative chromatographic analysis of the trideuterioanisole photolysate, a 0.25 in. × 10 ft column containing 20% Carbowax 2000 on 60–80 mesh Chromosorb W was plced in tandem with the SE-52/Bentone 34 column, and the column temperature was 160°.

Spectroscopic Analysis. Infrared spectra were obtained with a Perkin-Elmer Model 337 spectrophotometer; nmr spectra were obtained with either a Varian A-60 or a Varian HR-300 spectrometer.

Computer Simulation of Nmr Spectra. The chemical shifts (in parts per million from TMS) and coupling constants (in hertz) used in the simulation of the 300-MHz spectrum of *m*-cresol were $\delta_{o'}$, 6.581, δ_o 6.566, δ_m 7.028, δ_p 6.670, δ_{Me} 2.201, $J_{o,o'}$ = 1.4, $J_{o',m}$ = 1.7, $J_{o',p}$ = 1.5, $J_{o,m}$ = 8.0, $J_{o,p}$ = 1.2, $J_{m,p}$ = 7.5, $J_{o',Me}$ = 0.6, $J_{o,Me}$ = 0.6, $J_{m,Me}$ = 0.7, $J_{p,Me}$ = 0.6 Hz. The parameters for the simulation of the *p*-cresol spectrum were δ_o 6.669, δ_m 7.028, δ_{Me} 2.201, $J_{o,m}$ = 8.6, $J_{o,Me}$ = 0.6, $J_{m,Me}$ = 0.7 Hz. The values for $J_{o',m}$, $J_{o,m}$, and $J_{m,p}$ in the case of *m*-cresol are known to be somewhat in error. However, the appearance of the simulated 300-MHz spectrum does not change materially when these coupling constants are varied over a reasonable range. In both the *m*- and *p*-cresol cases, the values of δ_o and δ_p are sensitive to concentration. In plotting the simulations, the nmr Spectra Plot Program III—Variable Peak Height was used as adapted by B. L. Bruner (the University of Kentucky) for use with a Calcomp plotter. To simulate the spectrum of the cresol mixture, the intensities of the spectral lines of the individual components were multiplied by the appropriate factors, and the resulting data were combined and plotted.

Acknowledgments. The authors wish to thank Professor H. James Harwood for assistance in obtaining the 300-MHz spectra, and Professor Henry A. Kuska for assistance in obtaining the spectral simulations.

Registry No.—*m*-Cresol, 108-39-4; *p*-cresol, 106-44-5.

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(7) A possible explanation is autocatalysis of the tautomerization of **2** by the phenolic photoproducts, since the absolute final concentration of phenols in the 1.35 *M* case is roughly three times that in the 0.10 *M* case. A study of the *m*- to *p*-cresol yield ratio as a function of solution acidity is in progress.
(8) (a) We are examining the possibility that more than one excited state of the ether may be involved. When the photolyses of 0.10 *M* methanolic anisole solutions were quenched at 254 nm with *cis*-dichloroethylene, the slope of the Stern–Volmer plot for o-cresol was now lower than those for the *m*- or *p*-cresol plots. These latter were, as above, nearly coincident. Moreover, at 254 nm, the ratio of phenol yield to total cresol yield (1.8) was higher than the ratio observed with the medium-pressure lamp (0.62). (b) A referee has suggested that the fact that the yield of phenol decreases less rapidly with increasing quencher concentration than does the yield of any cresol implies that the dichloroethylene, in addition to quenching excited states, is capturing a methyl radical from the $PhO\cdot\cdot CH_3$ radical pair. We feel that an equally plausible explanation involves the production of phenol from two different excited species which are quenched with different efficiencies. This would also account for the curvature of the Stern–Volmer plot for phenol.
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Purine *N*-Oxides. LVI. Photoisomerization of 1-Hydroxy- to 3-Hydroxyxanthine. Photochemistry of Related 1-Hydroxypurines[1]

Fuk L. Lam, George Bosworth Brown, and James C. Parham*

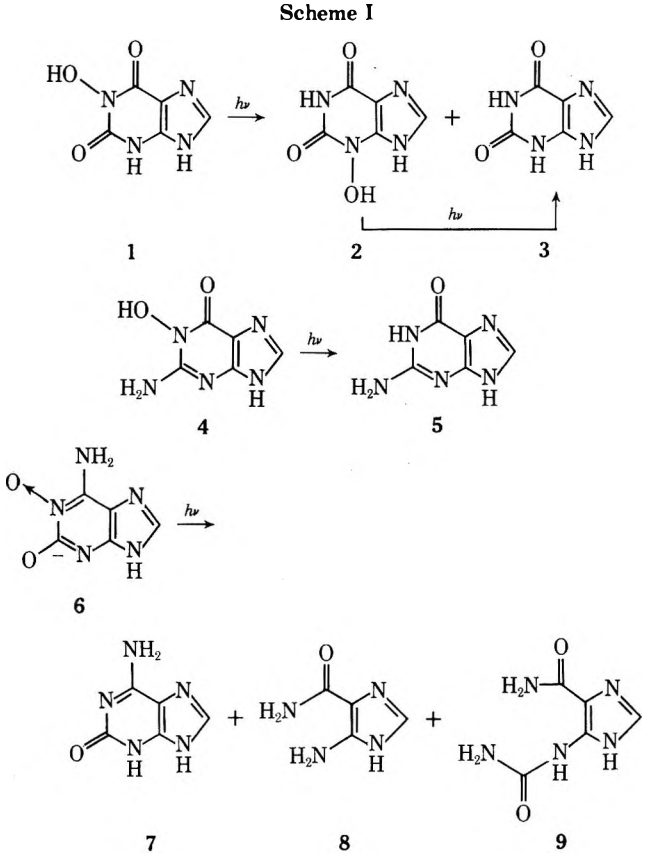
Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received November 29, 1973

Ultraviolet irradiation of solutions of 1-hydroxyxanthine causes extensive photoreduction. Concomitantly, there is some photoisomerization to 3-hydroxyxanthine that is less rapidly photoreduced. This novel rearrangement of a hydroxyl from N-1 to N-3 occurs in either the neutral species of 1-hydroxyxanthine or its anion. Two structurally related purines, 1-hydroxyguanine and 1-hydroxyisoguanine, showed no evidence of comparable photoisomerization of the *N*-hydroxyls. The former undergoes photoreduction only, regardless of the ionic state. Irradiation of the cation of 1-hydroxyisoguanine yielded isoguanine and its 8-hydroxy derivative, while irradiation of the anion induced photoreduction and ring opening to two imidazoles, 4(5)-amino- and 4(5)-ureidoimidazole-5(4)-carboxamides.

Previous studies on the reactions of esters[2] of the oncogen[3] 3-hydroxyxanthine demonstrated that at certain pH's spontaneous reduction to xanthine is one mode of its reactivity. A comparable reduction of 3-hydroxyxanthine, or of 3-acetoxyxanthine, can be accomplished photochemically, either by direct uv irradiation in solution or by irradiation of the dry solid, to produce a free radical that is reduced instantly upon reaction with water.[4] These observations prompted a more detailed study of the photoinduced reactions of N-oxidized purines in solution.[5] Photoreduction and photorearrangements of oxygen from N to C are usually observed.[5-11] We now report that photoreduction of 1-hydroxyxanthine (1) (Scheme I) in solution is accompanied by a novel photoisomerization of the *N*-hydroxyl to form 3-hydroxyxanthine (2). This isomerization is of interest from both chemical and biological respects, since 2 is a potent carcinogen,[3] while 1 is not.[12] The photochemical reactivities of two structurally related derivatives, 1-hydroxyguanine (4) and 1-hydroxyisoguanine (6), are also examined.

Scheme I



Results

Each of the *N*-hydroxypurines was irradiated in deaerated solutions with a Corex filter at pH values selected to maximize the amount of a single ionic species. The pK_a's associated with the protonation and first two ionizations of 3-hydroxyxanthine (2) are 0.35, 6.71, and 9.65.[13] The neutral species of 2 was irradiated at pH 3 and the anion at pH 9; 2 was also irradiated at pH 0, where it is partially protonated. Xanthine (3) was the only uv-absorbing product in each case. The rate of photodecomposition of 2 increased significantly with increased pH. In Figure 1 the rates of the disappearance of 2 and the yields of 3 are plotted for the three pH's as a function of time.

The pK_a's for the protonation and first two ionizations of 1 are 0.85, 6.54, and 9.94.[14] Irradiation of 1 at pH's 0, 3, and 9 induced photoreduction to 3 (14–20%) and rearrangement to 2 (2–7%). Prolonged irradiation of 1 gave 3 only. The amounts of 1, 2, and 3 were determined following irradiation of 1 for various periods of time and the values are plotted as a function of time in Figure 2.

Irradiation of 4 (pK_a's 3.49, 6.73, and 11.51[15]) in solutions at either pH 2 for the cation, or at pH 5.5, where the neutral species should predominate, gave only the photoreduction product, guanine (5) (24–28%). The irradiation of the anion at pH 10 yielded mainly 5 (23%) with traces of two unidentified uv-absorbing compounds and an insoluble precipitate.

Because of its low solubility 1-hydroxyisoguanine (6) could be irradiated in a sufficiently concentrated solution only as its cation at pH's 0–3 or as its monoanion at pH 10 (pK_a's 3.64, 6.41, and 11.48).[14] The irradiation of 6 at pH 3 gave only the reduction product, isoguanine (7, 36%), and a trace of an unknown whose uv absorption suggests an imidazole. The irradiation at pH 0 gave 7 (36%), traces of an unidentified product, and the 8-hydroxy derivative of 7, 6-amino-2,8-dihydroxypurine (1%). The last was identified by comparison of its uv spectra at three pH's with those of an authentic sample.[16] Comparable photooxidation at C-8 under acid conditions was noted previously.[5]

The first ionization of 6 was deduced[13] to occur from the *N*-hydroxyl group, and the species at pH 10 should be the enolate anion shown as 6 (Scheme I). Upon irradiation of the anion three uv-absorbing products were obtained, all in low yield. These include 7 (8%) and two products resulting from ring opening, 4(5)-aminoimidazole-5(4)-carboxamide (8, 3%) and 4(5)-ureidoimidazole-5(4)-carboxamide (9, 8%). The structure of 9, which has not previously been reported, was deduced from its uv, nmr, and mass spectral properties. It was authenticated by comparison of

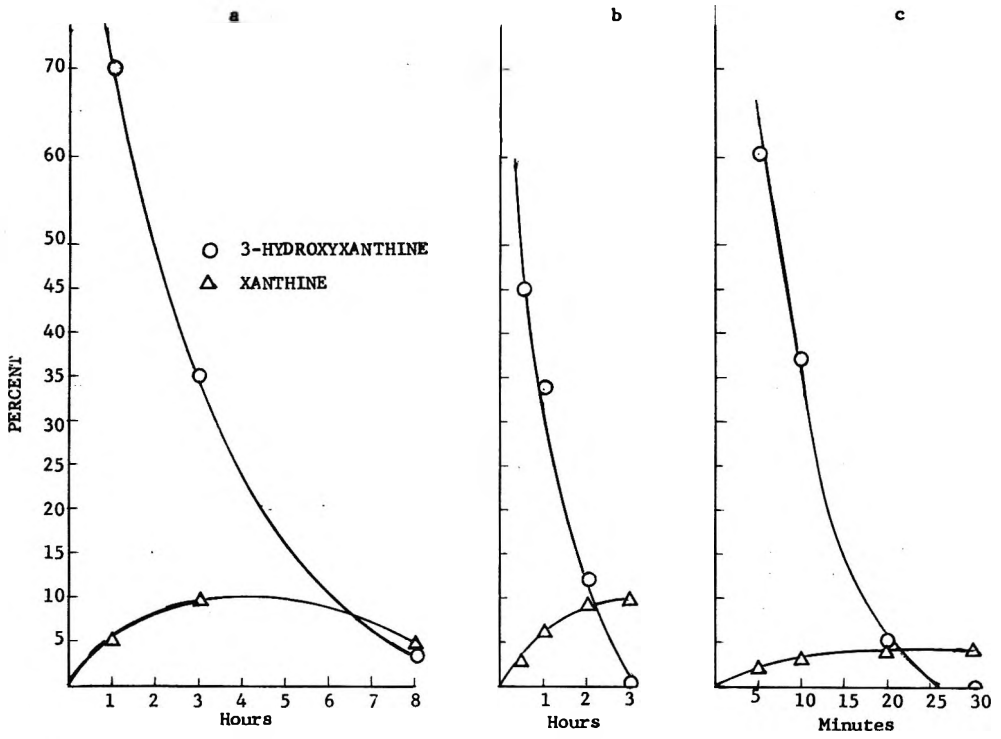


Figure 1. Irradiations of 3-hydroxyxanthine: (a) pH 0; (b) pH 3; (c) pH 9.

these and other properties with those of a sample synthesized from 8 and KCNO.

Discussion

An initial study[5] examined the influence of ionic and tautomeric states on the photochemical reactivity of 1-hydroxyhypoxanthine. That compound, with a single isolated hydroxamate function, was selected for its minimal tautomeric possibilities. Photoreduction was observed both from the neutral *N*-hydroxy species and from its conjugate enolate anion, but was favored when the neutral form predominated. Ionization was a prerequisite for photorearrangement, which was the predominant photoreaction of the anion.

The state of ionization also exerts a strong influence on the photochemistry of the more complex *N*-hydroxyxanthines. The several pK_a's of 1-hydroxy- (1) and 3-hydroxyxanthine (2) have been determined and the sequence of ionization of 3-hydroxyxanthine has been assigned as 3-OH, 9-H, 1-H.[13] This sequence parallels that of the parent xanthine.[17,18] For 1-hydroxyxanthine, ionization of the 1-hydroxyl group is not associated with the first pK_a, but with the second pK_a of 1.[14] These data and the known sequence of xanthine indicate that the ionization

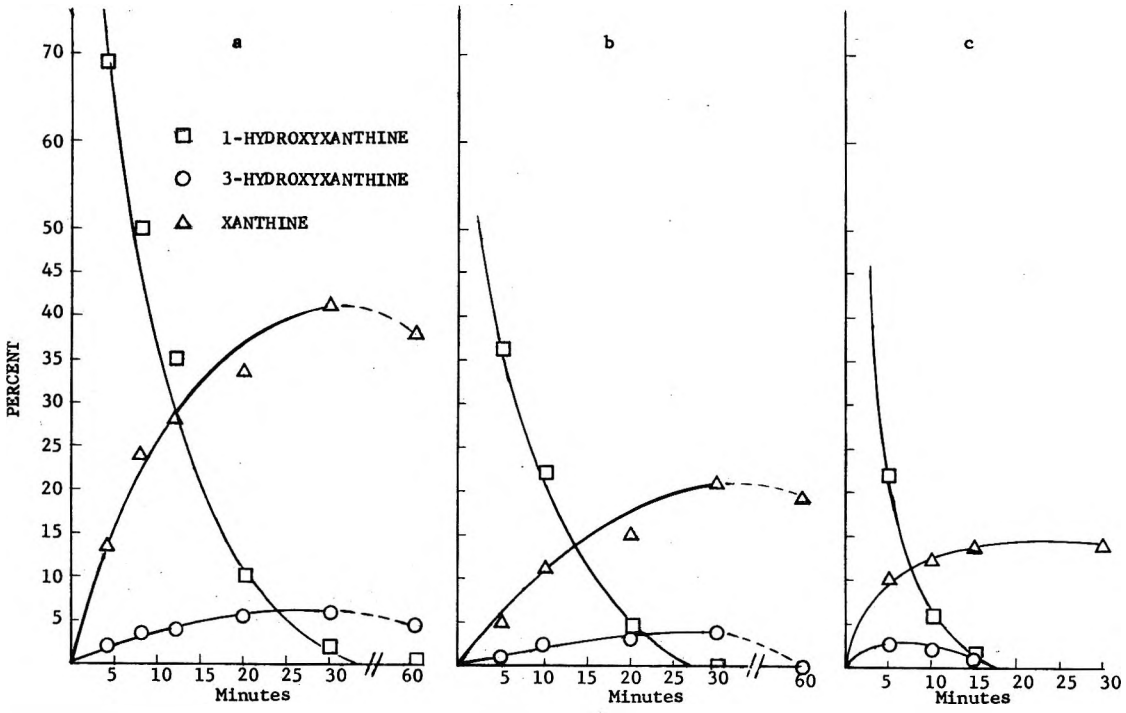


Figure 2. Irradiations of 1-hydroxyxanthine: (a) pH 0; (b) pH 3; (c) pH 9.

sequence of 1 is 3-H, 1-OH, 7,9-H. In general[13] an *N*-hydroxyl substituent lowers all of the ionization pK_a's for a compound. The digression of 1 from the usual ionization sequence, *i.e.*, N-1 ionization following that of N-3, can be attributed to the greater acid-strengthening effect of the 1-hydroxyl group on the pyrimidine moiety. Both 1 and 2 exist as the *N*-hydroxyl form in the neutral species.[13] The monoanions, however, must differ if each ionizes from N_3. The monoanion of 2 contains a nitrone group,[13] comparable to that of 1-hydroxyhypoxanthine, while the monoanion of 1-hydroxyxanthine should have no interaction with the N_1 hydroxyl, leaving it in the nonionized *N*-hydroxy form. Although the closeness of the second pK_a (9.94) of 1, that of the N_1 hydroxyl, makes it impossible to achieve a "pure" monoanion of 1, it is evident from uv spectra that there are different states of ionization of the *N*-hydroxyl groups in the monoanions of 1 and 2.

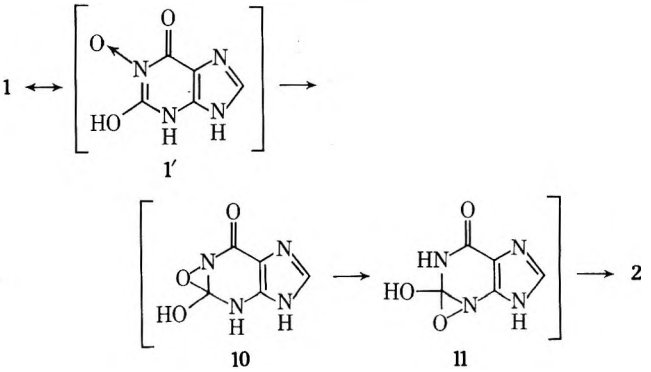
Photolysis of any ionic species of 2 (Figure 1) gave 3 as the only uv-absorbing product. The higher photodecomposition rate and poorer material balance with increasing ionization are analogous to results from the irradiations of 1-hydroxyhypoxanthine. Irradiation of 1, either as the neutral species (pH 3) or primarily as the monoanion (pH 9.0), gave qualitatively similar results (Figure 2), a complete loss of 1 in 30 min and comparable yields of 2 (4 and 2%) and of 3 (20 and 14%). These similarities agree with the deduction that the extent of ionization of the *N*-hydroxyl group is approximately the same for both the neutral species and the monoanion of 1. The small differences in rates of decomposition and yields might initially be attributed to a small degree of ionization of the N_1 hydroxyl at pH 9 to form some dianion. An alternative interpretation is discussed below.

The data for 1-hydroxyhypoxanthine indicated that the pK_a for its *N*-hydroxyl group was lowered 2–3 pH units in the excited state.[5] Therefore, 1 and 2 were each irradiated at pH 0, where ionization of the *N*-hydroxyl function should be suppressed even if the pK_a's of their excited states (pK_a*'s) are shifted to lower values. Should the pK_a*'s be lower than those of the ground states, a difference in the photochemical reactivities at pH 0, compared to those at pH 3, would be expected. The rate of photolysis of 3-hydroxyxanthine was decidedly slower at pH 0 (Figure 1a), but the rate of formation and apparent maximum yield of xanthine were identical with those from the irradiation at pH 3 (Figure 1b). The rate of photolysis of 1 at pH 0 (Figure 2a) was only slightly lower than that at pH 3, but the yield of xanthine at pH 0 (43%) was twice that obtained at pH 3 (21%). This difference suggests that the pK_a of the *N*-hydroxyl proton of 1 is lowered in the excited state, probably to below pH 3. This pK_a* would then be below that of the ground-state N_3-H pK_a (6.54) and consequently in the excited state both N_3 H and N_1 OH should be completely ionized at pH 9. This deduction clarifies the observation that ionization of the N-3 proton has little effect on the photoreactivity of 1. The small differences in the data at pH's 3 and 9 correspond to a completion of ionization of the *N*-hydroxyl at pH 9 and not to the partial ionization indicated by ground-state pK_a's. These data indicate that photoreduction of 1 is favored by the presence of the nonionized *N*-hydroxyl species, predominant at pH 0, but that it can occur to a smaller extent from the ionized form.

The unexpected photoisomerization of 1-hydroxy- to 3-hydroxyxanthine was observed at all pH's studied (Figure 2). The yield of 2 was maximal at pH 0 and decreased with increasing pH. This is partially due to the greater photolability of 2 at higher pH's (Figure 1). The 6% yield of 2 after irradiation of 1 at pH 0 for 30 min (Figure 2a) is essentially a maximum formation of 2 under these conditions, since 2 was not significantly degraded within 30 min under comparable conditions (Figure 1a). By contrast, the 4% of 2 formed after irradiation of 1 for 30 min at pH 3 (Figure 2b) does not represent a maximum yield, since over half of any 2 formed would have been decomposed during this period (Figure 1b). The corrected yield of 2 may be estimated as ~8%. Similarly, the maximum yield of 2 isolated after irradiation of 1 at pH 9 for 5 min was 2.5%, but at that time ~40% of 2 would have been decomposed, and the corrected value of 2 is ~4%. The high photolability of both 1 and 2 at pH 9 reduces the accuracy of this estimated yield, but it is certainly less than that at pH 3.

A plausible mechanism for the rearrangement of an *N*-hydroxyl group from N-1 to N-3 can be suggested based upon mechanisms proposed for other photoisomerizations. Ionization of the *N*-hydroxyl was shown to be necessary for N to C photorearrangement of 1-hydroxyhypoxanthine, and it was postulated that the nitrone component of the anion rearranged *via* an intermediate oxazirane.[5] If 1 to 3 photoisomerization is a comparable intramolecular process, it should also occur preferentially from a nitrone-containing species. It would thus be dependent upon ionization of the *N*-hydroxyl group and should increase with increasing pH, as noted for N to C photorearrangement of 1-hydroxyhypoxanthine. The increased photolability of 2 at higher pH's makes it difficult to evaluate this accurately, but the estimated corrected values for maximum yield of 2 show that ionization of the *N*-hydroxyl of 1 does not enhance its migration. Although little difference was noted in yields of 2 between pH's 0 and 3, the large change in yields of xanthine indicates that in this pH range there is some change in the form of 1 that influences its photochemical reactivity. This was interpreted to indicate that the nonionized *N*-hydroxyl species was present to a greater extent at pH 0 and that 1 must have a pK_a* in this range. The absence of a parallel change in the yield of 2 suggests that formation of 2 is not associated with ionization of 1 in this range. One plausible intramolecular[19] mechanism that is consistent with rearrangement *via* a nitrone intermediate without ionization involves a photoinduced enolization of 1. If 1 is converted to an enol, *e.g.*, 1′ (Scheme II), as a primary photochemical

Scheme II

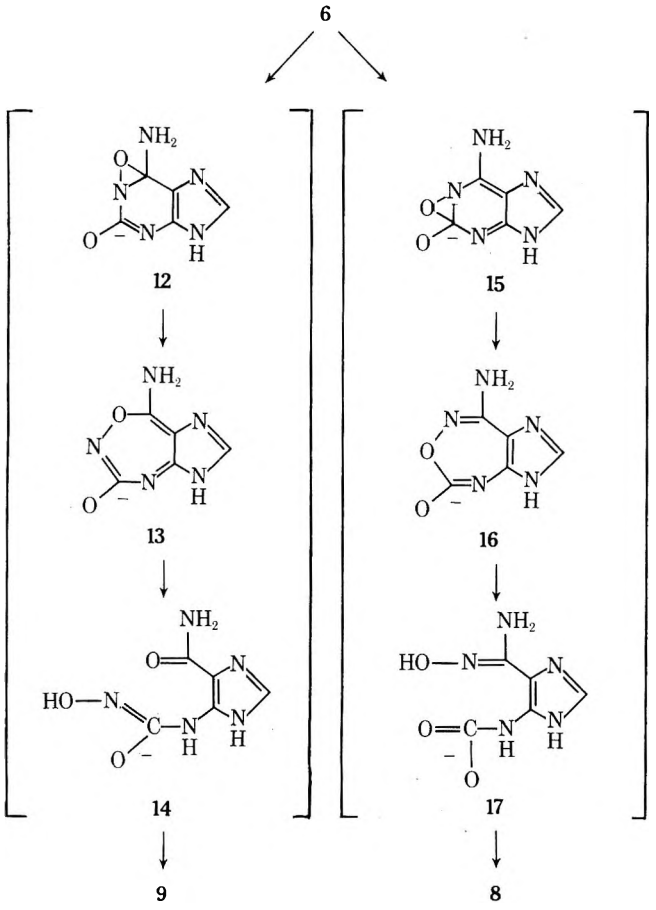


process,[20] the nitrone thus formed could then be photochemically converted to an oxazirane (10) comparable to that proposed for N to C rearrangements.[21] Since the adjacent position is substituted, 10 might then undergo a subsequent rearrangement to the isomeric oxazirane (11) and thence to 2. Sequential oxazirane migrations have been proposed previously in the photochemical isomerizations of *N*-oxides,[22] but this is the first example of a photoinduced allylic N to N migration.

Two other 1-hydroxypurines structurally related to **1**, 1-hydroxyguanine[15] (**4**) and 1-hydroxyisoguanine[14] (**6**), were studied as possible additional examples of such an *N*-hydroxyl rearrangement. Irradiation of **4** at selected pH's yielded none of the known[30] 3-hydroxyguanine, but produced guanine (**5**) as the only, or the predominant, uv-absorbing product.

The possible rearrangement product from 1-hydroxyisoguanine (**6**) would be 3-hydroxyisoguanine. That compound is not reported, but certain of its properties can be predicted by analogy to those of other known purine 3-oxides.[8,9,31] There was no evidence of such a product. The photoproducts obtained from the irradiation of **6** in acidic solution were isoguanine (**7**, 36%) and 6-amino-2,8-dihydroxypurine (1%). Irradiation of the anion produced isoguanine (**7**, 8%), 4(5)-aminoimidazole-5(4)-carboxamide (**8**, 3%), and 4(5)-ureidoimidazole-5(4)-carboxamide (**9**, 8%). Comparable products resulting from ring opening of intermediates have been isolated from irradiations of heterocyclic *N*-oxides.[32] One suggested[33] route for formation of such products involves initial rearrangement of the *N*-oxide to an oxazirane, ring expansion, followed by hydrolytic ring cleavage of the ring-expansion product. Since the first ionization of **6** produces a nitrone-containing enolate anion, the parallels previously noted[5] between the photochemical reactivity of such anions and heterocyclic *N*-oxides should also be applicable to that of **6**. Two isomeric oxaziranes, **12** and **15** (Scheme III), could form from **6**. Ring expansion[21] of these would lead to the isomeric imidazolooxadiazepines, **13** and **16**, respectively. Hydrolysis of these would yield initially the two disubstituted imidazoles, **14** and **17**. The ureido derivative isolated, **9**, can only arise from the *N*-hydroxyureide, **14**, or its precursor, **13**.[35] This suggests that the oxazirane **12** is a requisite intermediate from **6**.

Scheme III



No plausible path from **12**, **13**, or **14** to **8** is obvious, nor does **8** arise experimentally from **7** or **9** under the conditions employed. A facile explanation for the formation of **8** is available from reactions of the isomeric oxazirane, **15**, *via* the path **15** → **16** → **17** → **8**. Following ring opening of **16**, both the formate and amidoxime groups of **17** must hydrolyze to lead to **8**. Thus oxazirane **15** apparently undergoes reactions other than rearrangement to 3-hydroxyisoguanine.[36]

These studies demonstrate that only certain structural systems permit migration of the hydroxyl from N-1 to N-3. Under some conditions oxazirane formation occurs in a direction unfavorable for 1 to 3 migration, as suggested by the formation of **9** from **6** *via* **12** (Scheme III). Even the appropriate oxazirane intermediates can be diverted to other reactions, as shown by the production of **8**. The hydroxyl isomerization apparently requires both carbonyl groups, since replacement of either carbonyl of the pyrimidine moiety prevents rearrangement. No comparable 1 to 3 rearrangement was observed with 1-hydroxyhypoxanthine,[5] nor has any reverse 3 to 1 hydroxyl migration been noted from **2**, although the relative photochemical sensitivities of **1** and **2** would make detection of **1** from **2** difficult. The requisite structural features for the rearrangement have thus far been found only in 1-hydroxyxanthine.

Experimental Section

The uv spectra were determined with a Unicam SP800A recording spectrophotometer and the nmr spectra with a Varian A-60 spectrometer, using TMS as an internal standard. An ISCO UA-2 uv analyzer was used to monitor column eluates, except as noted for values in Figures 1 and 2. The λ_{max} and ϵ values were determined with a Cary 15 spectrophotometer. Elemental analyses were performed by Spang Microanalytical Laboratories. Ann Arbor, Mich. Paper chromatograms were developed, ascending, on Whatman No. 1 paper using the following solvents: (A) CH_3CN–H_2O–28% NH_4OH (7:2:1 v/v); (B) 3% NH_4Cl; (C) 5% Na_2HPO_4–isoamyl alcohol (3:2); and were viewed under uv light (253.7 nm). Samples of **7** and **8** were obtained from Cyclo Chemical Co. for comparison with photoproducts from **6**.

Irradiation Procedures. Samples were irradiated in 1.2×10^{-3} *M* solutions that had been adjusted to pH 3.0 or 9.0 with 1 *N* HCl or 28% NH_4OH; 3 *N* CF_3COOH was used for pH 0. Nitrogen was bubbled through solutions for 2 hr prior to irradiations that were then carried out in an immersion apparatus with a 450-W Hanovia high-pressure mercury lamp with a Corex filter, as described.[5] Aliquots were withdrawn periodically and the photoproducts were analyzed by ion exchange chromatography. For identification the solutions were concentrated *in vacuo* to a small volume when the reactions were complete and the products were separated by chromatography.

Chromatography. Photolysis products were separated with a Bio-Rad AG-50, X8 [H^+], 200–400 mesh column (9 × 220 mm) that was monitored with an ISCO uv analyzer. Yields of reaction products were calculated from their known ϵ_{max} values. The λ_{max} and ϵ_{max} values at pH 0 were determined to be 267 nm (7.0×10^3) for **8** and 255 nm (11.4×10^3) for **9**. The quantities of **1**, **2**, and **3** in the mixture of products following the irradiation of **1** for various times were determined with a standardized AG-50 [H^+] column (9 × 150 mm) that was pumped at 60 ml/hr and was monitored at 240, 260, and 290 nm with a Beckman DB spectrophotometer. The column was eluted with 0.05 *N* HCl, and the products were isolated in the sequence (ml) **2** (85),[37] **1** (185), **3** (340).[37] Linear plots of known concentrations of **1**, **2**, and **3** against their OD values at 260 nm were used as calibration curves to calculate the yields shown in Figures 1 and 2. Values were reproducible within ±5%.

Identification of 3-Hydroxyxanthine (2). This photoproduct from **1** was unambiguously identified by comparisons of it with an authentic sample[13,30] of **2**. The uv absorption at selected pH's of a sample of the photoproduct isolated from a Bio-Rad AG-50 [H^+] column was identical with values reported[13] for **2** at those pH's. The R_f values of both were identical in three solvents: A, (R_f), **1** (0.09), **2** (0.09), **3**, (0.28); B, **1** (0.57), **2** (0.56), **3** (0.34); C, **1** (0.58), **2** (0.60), **3** (0.47). While the R_f values of **1** and **2** are close in all solvents, they are easily distinguished when the paper is viewed

under uv light; **1** appears as a dark purple spot, but **2** has blue fluorescence. The photoproduct also manifested blue fluorescence identical with that of **2** under uv light. The photoproduct and authentic **2** had identical positions of elution from two standardized columns. From the AG-50 [H^+] column both appeared at 85 ml. From a Bio-Rad A-6,[38] 6 × 400 mm column, eluted at 50° with 0.4 *M* ammonium formate (pH 4.7) at 20 ml/hr and monitored with the Beckman DB spectrophotometer, authentic **2** and the photoproduct were eluted at 17.8 ml, **3** at 20 ml, and **1** at 22 ml.

4(5)-Ureidoimidazole-5(4)-carboxamide (9). A solution of 267 mg (3.3 mmol) of KCNO and 198 mg (3.3 mmol) of HOAc in 20 ml of H_2O was added to a solution of 340 mg (3.3 mmol) of **8** in 20 ml of water. The clear solution was stirred at room temperature overnight, the solvent was then evaporated to dryness *in vacuo*, and the brown residue was dissolved in ~40 ml of methanol. After filtration the solvent was removed *in vacuo* and the residue was chromatographed on a 2.4 × 24 cm AG-50 [H^+] column by elution with 1 *N* HCl to yield first **9** (35 mg) and then **8** (150 mg). The crude HCl salt of **9** was neutralized by passing an aqueous solution of it through a Bio-Rad AG-3 [OH^-] column and eluting with H_2O. The eluate was evaporated *in vacuo* to give 30 mg (11%) of pure 4-ureidoimidazole-5-carboxamide: mp 230° dec; nmr (CF_3CO_2H) δ 6.96 (s); nmr (Me_2SO-d_6) a broad, unresolved multiplet centered near δ 7.0 (The addition of D_2O caused collapse to a singlet at δ 7.35. The multiplet integral was seven times that of the singlet.): mass spectra (chemical ionization) *m/e* 170 (M + 1), 153, 127, and 109 (major peaks); uv λ_{max} (H_2O) (pH) 240, 255 (2), 232, 267 (6), and 281 nm (12).

Anal. Calcd for $C_5H_7N_5O_2$: C, 35.51; H, 4.17; N, 41.40. Found: C, 35.35; H, 4.23; N, 41.47.

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Registry No.—**1**, 1932-15-6; **2**, 13479-29-3; **8**, 360-97-4; **9**, 51022-63-0.

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(36) Several possibilities might explain this: (a) 3-hydroxyisoguanine is much more photolabile than might be expected from comparison of the rates of photoreaction of **1** and **2**; (b) ring expansion of the 1,2-oxazirane, **15**, is more facile than conversion to the isomeric 2,3-oxazirane comparable to **11**; or (c) ring expansion of the 2,3-oxazirane is favored over stabilization as 3-hydroxyisoguanine. The latter two are more likely; the third also represents an alternative path to **8**, since the imidazolooxadiazepine from the 2,3-oxazirane might also be expected, after ring opening, to lead to **8**.
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Photocycloaddition in the β-Naphthyl-Substituted Azirine System[1]

Albert Padwa*[2a] and S. I. Wetmore, Jr.[2b]

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

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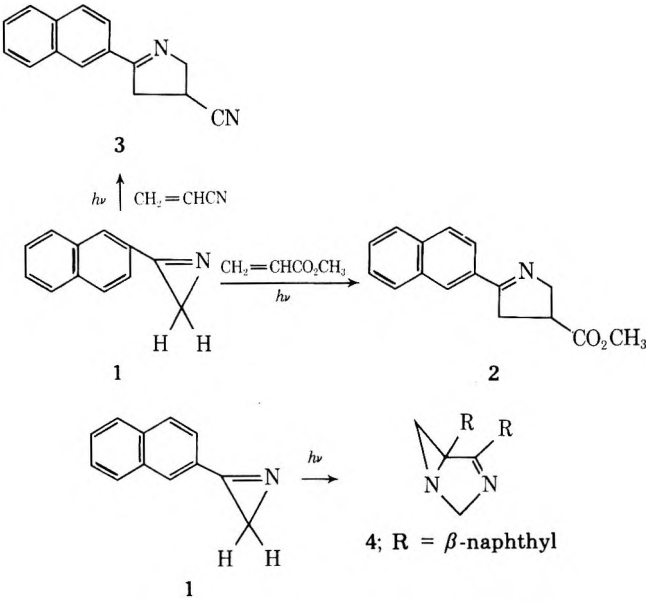
Upon irradiation with ultraviolet light, β-naphthyl-substituted azirines undergo ring opening to give nitrile ylide intermediates which are subsequently trapped with electron-deficient olefins to produce Δ¹-pyrrolines. The regiospecificity of the cycloaddition is discussed in terms of the frontier orbital method. The cycloaddition reaction was shown to proceed from the excited singlet state; the corresponding triplet was demonstrated to be unreactive. Excited singlet lifetimes of a number of substituted naphthylazirines as well as quantum yields for cycloaddition were determined. The rate of opening of the excited azirine ring was found to decrease with increasing methyl substitution. The observed order of photoreactivity is discussed in terms of upper excited singlet states.

In previous papers we reported on the photocycloaddition of arylazirines with electron deficient olefins.[3] The formation of the adducts was interpreted as proceeding by way of irreversible ring opening of the azirine ring to form a nitrile ylide intermediate, which was subsequently trapped by a suitable dipolarophile.[3,4] Irradiation of an arylazirine in the absence of a dipolarophile gave rise to 1,3-diazabicyclo[3.1.0]hex-3-enes as primary photoproducts. The formation of these dimers was attributed to the 1,3-dipolar addition of the initially generated nitrile ylide onto a ground-state azirine molecule. The cleavage of the C-C bond of the azirine ring was also shown to proceed from the n-π* excited singlet state and was rationalized in terms of an electrocyclic transformation by analogy with the cyclopropyl → allyl cation rearrangement.[5] The fact that the singlet state of the azirine was involved was substantiated by our inability to quench or sensitize the cycloaddition with a variety of triplet quenchers and sensitizers.[3]

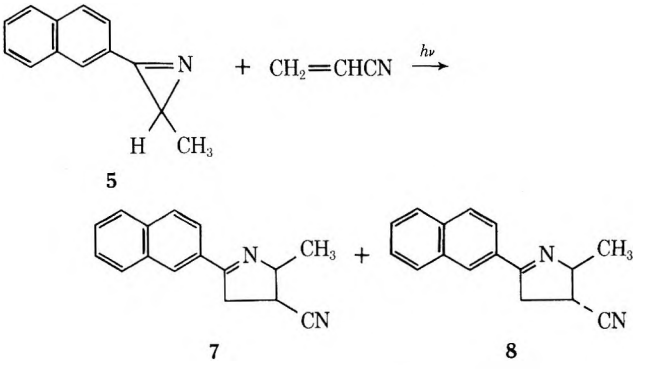
It is well known that a considerable amount of information on the reactivity of singlet excited states of organic molecules can be obtained from a study of molecular fluorescence properties.[6] In order to secure additional information on the reactivity of the excited singlet state(s) involved in the photocycloaddition reaction, we decided to study the photochemistry of a number of substituted naphthylazirines. Marked differences in the photochemistry of phenyl- and naphthyl-substituted ketones are known and have been ascribed to the difference in nature of the lowest excited state involved in the reaction.[7] It is reasonable to assume that in the naphthylazirine excited states, both singlet and triplet, the excitation energy will be heavily localized on the naphthyl portion of the molecule. Concentration of the excitation at one end of the molecule seemed a possible way of modifying the photobehavior of the azirine ring. The present paper reports on the photocycloaddition reaction of a number of naphthyl-substituted azirines and also describes some fluorescence emission data which permit approximation of the rate constants involved in the ring opening step.

Photocycloaddition in the β-Naphthylazirine System. Our initial experiments revealed that naphthyl-substituted azirines were highly photochemically reactive. Thus, direct irradiation of 2-(β-naphthyl)azirine (1) with methyl acrylate and acrylonitrile occurred smoothly and gave rise to good yields of photoadducts 2 and 3.[3] Irradiation of 1 in the presence of electron-rich acyclic or cyclic olefins produced no photoadduct, but instead gave a dimeric material, whose structure was assigned as 4,5-di(β-naphthyl)-1,3-diazabicyclo[3.1.0]hex-3-ene (4).

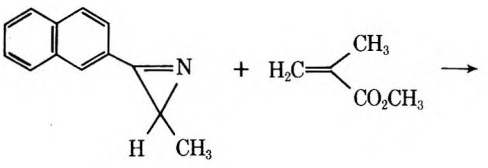
The photochemical cycloaddition reactions of 3-methyl-2-(β-naphthyl)azirine (5) and 3,3-dimethyl-2-(β-naphthyl)-



azirine (6) with electron-deficient olefins were also investigated. Irradiation of a pentane solution of 5 and acrylonitrile produced a 3:1 mixture of *cis*- and *trans*-4-cyano-5-methyl-2-(β-naphthyl)-Δ¹-pyrroline (7 and 8). The structures of photoadducts 7 and 8 are derived from con-



sideration of the nmr data (see Experimental Section), which proved to be remarkably similar to the nmr of the adducts obtained from the photolysis of 3-methyl-2-phenylazirine with acrylonitrile.[3] Similar irradiation of a solution of 5 in pentane which contained an excess of methyl methacrylate proceeded to give a mixture of *cis*- and *trans*-4-carbomethoxy-4,5-dimethyl-2-(β-naphthyl)-Δ¹-pyrroline (9 and 10). The ratio of the two cycloadducts (9:10 = 3:2) was determined by nmr analysis of the singlets associated with the methyl groups in the crude photolysate.



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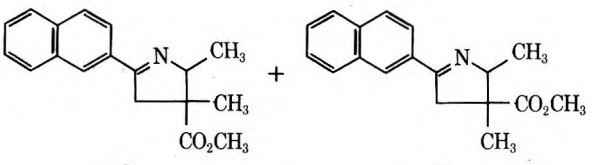
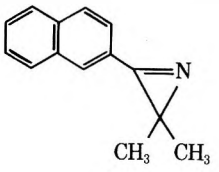
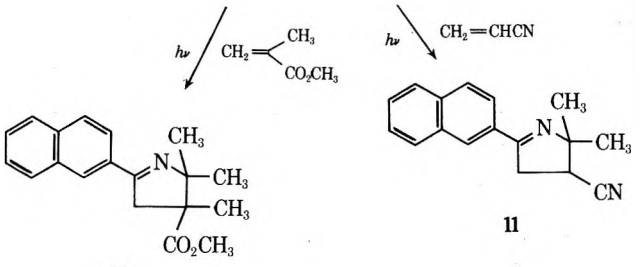


9 10

Photoaddition of 3,3-dimethyl-2-(β-naphthyl)azirine (**6**) with the same two electron-deficient olefins affords Δ¹-pyrrolines **11** and **12**. The configurations of the adducts were readily established by examination of their characteristic nmr spectra (see Experimental Section).



6



12 11

The orientation of the groups in the Δ¹-pyrrolines obtained from the above photoadditions is essentially identical with that observed by Huisgen in related 1,3-dipolar additions.[8,9] The origin of the orientation or regioselectivity in this and related 1,3-dipolar cycloadditions has been one of the major unsolved problems in this area of chemistry. Huisgen has suggested that a subtle interplay of steric and electronic factors controls the regioselectivity in 1,3-dipolar additions.[10] Firestone, on the other hand, has attempted to explain the direction of orientation by estimating the relative energies of two possible diradical intermediates.[11] In a recent report, Houk has successfully employed the frontier orbital method for rationalizing the effect of substituents on rates and regioselectivity of 1,3-dipolar cycloadditions.[12] According to the perturbation model,[12] the relative reactivity of a given 1,3 dipole toward a series of dipolarophiles will be determined primarily by the extent of stabilization afforded the transition state by interaction of the frontier orbitals of the two reactants. When nitrile ylides are used as 1,3 dipoles, the dipole highest occupied (HO) and dipolarophile lowest unoccupied (LU) interaction will be of greatest importance in stabilizing the transition state. The favored cycloadduct will be that formed by union of the atoms with the largest coefficient in the dipole HO and the dipolarophile LU. An electron-deficient olefin has the largest coefficient on the unsubstituted carbon in the lowest unoccupied (LU) orbital while the imine carbon atom of the nitrile ylide has the largest coefficient in the (HO) orbital.[14] With this information, it becomes possible to accommodate the regiochemical data found in the above cycloaddition reactions.

Table I
Quantum Yields, Singlet Lifetimes, and Rates of Reaction in the β-Naphthylazirine System

Azirine	$\Phi_{cycloaddition}$	$\tau_s \times 10^9$, sec	$k_r \times 10^{-8}$, sec
2-(β-Naphthyl)azirine (**1**)	0.37	1.1	3.4
3-Methyl-2-(β-naphthyl)-azirine (**5**)	0.44	2.0	2.2
3,3-Dimethyl-2-(β-naphthyl)azirine (**6**)	0.41	2.5	1.6

Quantum Yield Studies. Quantum yields for adduct formation were determined using benzophenone–benzhydrol actinometry.[15] Degassed and sealed Pyrex tubes containing solutions of the naphthylazirine and the dipolarophile were irradiated along with antinometer tubes in the rotating photochemical assembly. The light from a 450-W Hanovia lamp was filtered through a nickel-cobaltous solution (transmission 300–340 nm). Reactions were carried to low conversions to prevent appreciable light absorption by the products, and yields of products were determined by glpc using internal standards. The quantum yields for cycloaddition at high dipolarophile concentration (see Table I) showed no wavelength dependence. The naphthylazirines proved to be unreactive when irradiated in the presence of acetophenone. In these experiments, the concentrations were adjusted so that acetophenone absorbed more than 98% of the light. The concentration of the naphthylazirine was kept sufficiently low to ensure unimolecular destruction of acetophenone singlet molecules prior to collision with ground-state azirine, yet sufficiently high to guarantee collision of acetophenone triplets with azirine at a rate faster than acetophenone decay.[16] Under these conditions, no photocycloaddition whatsoever was detected. This observation suggests that the excited singlet state of the naphthylazirine is the reacting species.

Absorption and Emission Spectra of the Naphthyl-Substituted Azirines. The ultraviolet absorption spectra of the naphthylazirines studied exhibit strong absorption maxima in the naphthalene region of the spectrum.[17] The fluorescence emission curves for the β-naphthylazirines were essentially identical in shape and wavelength with that of naphthalene.[18] However, the fluorescence quantum efficiencies of these systems were only *ca.* 10% of that of naphthalene. The considerably diminished fluorescence of the naphthylazirine system may be attributed to the shorter lifetime of the excited singlet state of these systems. Most importantly, the fluorescence emission of these azirines was not quenched with added quantities of dipolarophile.

Interpretative Discussion

The first point to be noted from our results is that the photocycloaddition of the naphthyl-substituted azirines still occurs with high quantum efficiency (*i.e.*, $\Phi \sim 0.40$) despite the fact that the excitation energy in the reactant is heavily localized on the naphthyl end of the molecule. Another point which can be made is that the reaction does not proceed *via* T_1, the first excited triplet. The evidence presented above showed that efficient triplet energy transfer from acetophenone to the naphthylazirine occurred, and yet no photocycloaddition was observed. The possibility that the cycloaddition occurs through a T_2 state cannot be totally excluded since acetophenone, with its 74-kcal/mol excitation energy, will not be able to generate the second triplet of naphthalene.[19] It should be pointed out, however, that the singlet excited state of these naphthyl-substituted azirines lies 88 kcal/mol above ground state and therefore should not have sufficient en-

Scheme I

$$A_0 \xrightarrow{h\nu} A^{*1}$$

$$A^{*1} \xrightarrow{k_f} A_0 + h\nu'$$

$$A^{*1} \xrightarrow{k_d} A_0$$

$$A^{*1} \xrightarrow{k_r} NY$$

$$NY + O \xrightarrow{k_1} \text{adduct}$$

$$NY + A_0 \xrightarrow{k_2} \text{dimer}$$

ergy to lead to T_2.[19] Hence, photocycloaddition from S_1 seems the most likely possibility for these systems, but reaction from T_2 cannot be excluded with rigor. Zimmerman and coworkers have also noted the general difficulty in differentiating between the involvement of S_1 and T_2 states in photochemical reactions as a result of their similarities in lifetime and energy.[21,22]

The structural details of the above photocycloaddition reactions are consistent with the mechanism outlined in Scheme I, where A_0 = naphthylazirine, NY = nitrile ylide, and O = dipolarophile. The fact that the fluorescence emission of these systems was not quenched with added quantities of dipolarophile suggests that the opening of the azirine ring to the nitrile ylide (*i.e.*, k_r) is an extremely fast process. One can, in principle, obtain all the desired rate constants of the excited singlet state provided that Φ_r, Φ_f, and one of the rate constants are known. Here k_f is the rate constant of fluorescence, k_r is the rate of opening of the excited azirine ring, and k_d is the sum of all radiationless modes of excited singlet destruction (including any intersystem crossing)

$$\Phi_r = k_r/(k_f + k_d + k_r) \quad (1)$$

$$\Phi_f = k_f/(k_f + k_d + k_r) \quad (2)$$

The above two equations (1 and 2) may be combined to give eq 3. The excited singlet lifetimes of naphthylazirines

$$\Phi_r/k_r = \Phi_f/k_f = \tau_s \quad (3)$$

($\tau_s = \Phi_f/k_f$) were measured by single-photon counting and are shown in Table I. Since the quantum yield for cycloaddition (Φ_a) of the naphthylazirines with the various dipolarophiles used is high (Φ_a = 0.37–0.44), we can estimate that the quantum yield for ring opening (Φ_r) lies somewhere between Φ_a and unit efficiency. The fact that the quantum yield for adduct formation at infinite dipolarophile concentration did not vary significantly as a function of dipolarophile structure indicates that all the nitrile ylides are being efficiently trapped.[23] Consequently, we can estimate Φ_r as being approximately equal to Φ_a. Values of k_r can now be calculated using the measured singlet lifetimes and Φ_r. These are summarized in Table I.

The large magnitude of k_r (*i.e.*, 1.6–3.4 × 10^8 sec) is compatible with a rapid opening of the excited azirine ring to give a nitrile ylide intermediate. The substituent effects noted, although admittedly small, seemingly indicate that methyl groups diminish the rate of ring opening. Moreover, there does not appear to be any correlation of the quantum yields for cycloaddition with the values obtained for k_r. As was pointed out earlier,[24] quantum yields do not necessarily have any relation to excited state reactivity. A correlation of the excited state rate constants with the stability of the photochemically generated nitrile ylide intermediate does not apply in this system either. The precise reasons for this are not known at this time. One possibility worth mentioning is that the reaction leading to the nitrile ylide may proceed from an upper n–π^* excited singlet state. This is not so unreasonable, since Ullman and Singh have already shown that the rearrangements observed with the related 2-aroyl-3-arylazirine system proceeds from a S_2 state.[25,26] If this were the case here, then the photoreactivity of the naphthylazirine system could arise from the equilibrium concentration of the upper n–π^* singlet state. Alternatively, the ring opening reaction might occur from the naphthalene singlet state, which is mostly π–π^* in character but has enough n–π^* character mixed in to cause it to be slightly reactive. At any rate, the photoreactivity of the system would be expected to decrease as the energy gap between the S_1 and S_2 state increases. A similar situation was noted by Wagner in the Norrish Type II reactions of substituted aromatic ketones.[27] If the energy gap of the two excited singlet states increases with methyl substitution, one might expect to see a diminution in the chemical reactivity of the azirine ring as it becomes more heavily substituted. Additional experiment work is required for any further understanding of the problem.

Experimental Section[28]

3-Methyl-2-(β-naphthyl)azirine (5). To a solution of 15 g of sodium azide in 100 ml of acetonitrile cooled in a methanol–ice bath was added a solution of 18.3 g of iodine monochloride in 15 ml of acetonitrile. The mixture was allowed to stir for an additional 30 min while maintaining the temperature at 0°. To this solution was added 13.4 g of β-propenylnaphthalene.[29] The mixture was kept at 0° for 2 hr and was then allowed to warm to room temperature over a 12-hr period. The resultant orange slurry was added to 600 ml of water and extracted with ether. The ether extracts were washed with three 100-ml portions of a 5% sodium thiosulfate solution and then with three 100-ml portions of water. After the organic layer was dried over magnesium sulfate, it was concentrated under reduced pressure to give 25.8 g (96%) of an orange oil which was identified as 1-azido-2-iodo-1-(β-naphthyl)propane: ir (neat) 3.38, 4.76, 6.21, 6.90, 7.91, 9.33, 12.20, and 13.36 μ; nmr ($CDCl_3$) τ 8.13 (3 H, d, J = 7.0 Hz), 5.54 (1 H, m), 5.04 (1 H, d, J = 7.0 Hz), and 1.8–2.6 (7 H, m).

To a stirred and cooled solution of 25.8 g of the above iodine azide adduct in 250 ml of ether was added 15.3 g of potassium *tert*-butoxide over 30 min. The mixture was then allowed to stir at 0° for 1 hr. The slurry was extracted with ether, washed with water, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 15.6 g of an orange oil which was purified by passing it through a column of neutral alumina with benzene. The resulting light yellow oil was identified as 1-azido-1-(β-naphthyl)-1-propene: ir (neat) 3.30, 4.78, 6.03, 7.34, 7.90, 11.60, 12.17, and 13.30 μ; nmr ($CDCl_3$) τ 8.20 (3 H, d, J = 8.0 Hz), 4.35 (1 H, q, J = 8.0 Hz), and 1.8–2.7 (7 H, m).

A 1.0-g sample of the above azide was refluxed for 24 hr in 5 ml of chloroform. After being concentrated under reduced pressure, the residue was sublimed at 75° (0.1 mm) to give 690 mg (80%) of 3-methyl-2-(β-naphthyl)azirine (5): mp 76–77°; ir (KBr) 3.48, 5.79, 7.23, 10.20, 11.01, 11.46, 12.10, 13.23, and 14.16 μ; nmr τ 8.57 (3 H, d, J = 0 Hz), 7.59 (1 H, q, J = 5.0 Hz), and 1.5–2.4 (7 H, m); uv (cyclohexane) 241, 247, 280, 284, 294, and 339 nm (ε 54,500, 55,800, 9,300, 11,200, 9,400, and 1,200); m/e 181 (M^+), 153 (base), 127, 126, and 101.

Anal. Calcd for $C_{13}H_{11}N$: C, 86.16; H, 6.12; N, 7.73. Found: C, 85.92; H, 6.15; N, 7.56.

3,3-Dimethyl-2-(β-naphthyl)azirine (6). In a Carius tube was placed 5.0 g of β-isobutyronaphthone,[30] 3.0 g of unsymmetrical dimethylhydrazine, 0.05 g of *p*-toluenesulfonic acid, and 1.5 g of anhydrous magnesium sulfate. The tube was sealed under reduced pressure and the mixture heated at 110° for 3 days. To the cooled mixture was added 10 ml of ether, and the resulting solids were removed by filtration. Concentration of the solution under reduced pressure gave 7.3 g of a dark oil which was used in the next reaction without further purification.

The above hydrazone (7.3 g) was placed in a flask which contained 5 ml of ethanol and 28 g of methyl iodide. The mixture was heated at reflux for 6 hr after it was cooled in ice and triturated with ether until a dark solid crystallized out. Recrystalliza-

tion from a 9:1 mixture of ethyl acetate–ethanol gave 7.0 g (61%) of a white crystalline solid, mp 164–166°, which was identified as β-isobutyronaphthone-*N,N,N*-trimethylhydrazonium iodide.

To a stirred solution of the above iodide in 350 ml of isopropyl alcohol was added a solution of sodium isopropoxide (prepared from 0.46 g of sodium in 100 ml of isopropyl alcohol). After the addition was complete, the mixture was allowed to stir for an additional hour at 35°. The solvent was removed under reduced pressure and the residue was extracted with ether. Removal of the ether left 3.25 g (84%) of a pale yellow oil which solidified upon standing. Distillation of this material at 75–80° (0.04 mm) gave 3,3-dimethyl-2-(β-naphthyl)azirine (**6**), as a white crystalline solid: mp 30–31°; ir (neat) 3.40, 5.77, 7.27, 8.88, 12.18, and 13.16 μ; nmr ($CDCl_3$) τ 8.46 (6 H, s) and 1.6–2.5 (7 H, m); *m/e* 195 (M^+), 180, 154 (base), 127, and 126.

Anal. Calcd for $C_{14}H_{13}N$: C, 86.11; H, 6.71; N, 7.17. Found: C, 85.92; H, 6.80; N, 7.18.

Photoaddition of 3-Methyl-2-(β-naphthyl)azirine with Acrylonitrile. A solution of 1.2 g of 3-methyl-2-(β-naphthyl)azirine and 7 ml of acrylonitrile in 250 ml of pentane was irradiated for 2 hr using a Corex filter. After filtration of polymeric materials, the reaction mixture was evaporated to yield an off-white solid (62%) which proved to be a 3:1 mixture of stereoisomers. Repeated recrystallization and chromatography failed to separate the isomers. Spectral and elemental analysis of the mixture of *cis*- and *trans*-4-cyano-5-methyl-2-(β-naphthyl)-Δ^1-pyrroline (**7** and **8**) showed the following features: ir (KBr) 3.40, 4.49, 6.21, 7.00, 7.42, 8.88, 9.12, 11.53, 12.00, and 13.40 μ; nmr (cis) τ 8.45 (3 H, d, J = 7 Hz), 6.63 (3 H, m) 5.40 (1 H, m), and 1.7–2.5 (7 H, m); nmr (trans) τ 8.47 (3 H, d, J = 7 Hz), 6.40–7.50 (3 H, m), 5.40 (1 H, m), and 1.7–2.5 (7 H, m); uv (cyclohexane) λ 339 nm (ε 1130), 330 (790), 323 (1130), 306 (sh, 2220), 293 (11,500), 282, (13,500), 273 (10,600), 521 (60,200), 243 (58,500), and 237 (43,700); *m/e* 234 (M^+), 182, 181 (base), 180, 154, 153, and 127. An elemental analysis was obtained on the mixture.

Anal. Calcd for $C_{16}N_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.86; H, 6.06; N, 11.92.

Photoaddition of 3-Methyl-2-(β-naphthyl)azirine with Methyl Methacrylate. A solution of 0.95 g of 3-methyl-2-(β-naphthyl)-azirine and 8 ml of methyl methacrylate in 250 ml of pentane was irradiated for 2 hr using a Cortex filter. After filtering polymeric side products, 1.05 g of an orange oil was obtained, which by nmr ananlysis was shown to be a 3:2 mixture of *cis*- and *trans*-4-carbomethoxy-4,5-dimethyl-2-(β-naphthyl)-Δ^1-pyrrolines (**9** and **10**). The mixture of pyrrolines could not be separated into the individual isomers by distillation or chromatography. Characterization was accomplished by elemental analysis of the picrate of the mixture and from the following spectral properties: ir (neat) 3.38, 5.80, 6.20, 7.71, 8.31, 11.60, 12.11, and 13.35 μ; nmr (major isomer) τ 8.56 (3 H, s), 8.50 (3 H, d, J = 7 Hz), 6.63 (2 H, ABq, J = 17 Hz), 5.64 (1 H, q, J = 7 Hz), and 1.6–2.4 (7 H, m); nmr (minor isomer) τ 8.76 (3 H, d, J = 7 Hz), 8.71 (3 H, s), 6.47 (2 H, ABq, J = 17 Hz), 5.42 (1 H, 2, J = 7 Hz), and 1.6–2.4 (7 H, m); *m/e* 281 (M^+), 229, 228, 181 (base), 180 154, 153, 128, 127, 111, and 69.

Anal. Calcd for $C_{24}H_{22}N_4O_9$: C, 56.47; H, 4.34; N, 10.98. Found: C, 56.38; H, 4.38; N, 10.88.

Photoaddition of 3,3-Dimethyl-2-(β-naphthyl)azirine with Acrylonitrile. A solution of 1.0 g of 3,3-dimethyl-2-(β-naphthyl)-azirine and 7 ml of acrylonitrile in 250 ml of pentane was irradiated for 1 hr using a Corex filter. After filtration of polymeric materials and removal of the solvent under reduced pressure, the resultant oil was triturated with hexane to yield an off-white solid which was recrystallized from ether to give white crystals, mp 107–108°. This material was identified as 4-cyano-5,5-dimethyl-2-(β-naphthyl)-Δ^1-pyrroline (**11**) (71%): ir (KBr) 3.45, 4.47, 6.23, 7.40, 8.16, 8.82, 11.16, 12.17, and 13.40 μ; nmr τ 8.50 (3 H, s), 8.44 (3 H, s), 6.24–7.10 (3 H, m), and 1.7–2.4 (7 H, m); uv (cyclohexane) λ 339 nm (ε 1090), 330 (750), 323 (1070), 305 (sh, 2240), 293 (11,600), 283 (13,800), 273 (10,800), 251 (62,900), 243 (60,900), and 236 (sh, 44,300); *m/e* 248 (M^+), 194 (base), 154, 153, 127, and 81.

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.27; H, 6.59; N, 11.05.

Photoaddition of 3,3-Dimethyl-2-(β-naphthyl)azirine with Methyl Methacrylate. A solution of 1.0 g of 3,3-dimethyl-2-(β-naphthyl)azirine and 7 ml of methyl methacrylate in 250 ml of pentane was irradiated for 1 hr using a Corex filter. After filtration of polymer and removal of the solvent, an orange oil remained. Trituration of this material in hexane gave 0.93 g of an off-white oily solid. Repeated recrystallization from pentane yielded an analytical sample, mp 76–77°, identified as 4-carbomethoxy-2-(β-naphthyl)-4,5,5-trimethyl-Δ^1-pyrroline (**12**) (50%): ir (KBr) 3.42, 5.80, 6.20, 7.77, 9.21, 11.53, 12.09, and 13.32 μ; nmr τ 8.80 (3 H, s), 8.68 (3 H, s), 8.45 (3 H, s), 7.02 (1 H, d, J = 17.5 Hz), 6.20 (3 H, s), 6.01 (1 H, d, J = 17.5 Hz), and 1.6–2.4 (7 H, m); uv (cyclohexane λ 337 nm (ε 900), 328 (780), 322 (900), 306 (sh, 1920), 293 (10,400), 282 (13,200), 273 (10,700), 249 (54,400), 242 (60,400), and 236 (sh, 47,600); *m/e* 295 (M^+), 236, 195 (base), 194, 179, 154, 153, 127, 81, and 69.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H. 7.17; N, 4.74. Found: C, 77.13; H, 7.22; N, 4.72.

Emission Studies. Fluorescence emission studies were made on an Aminco-Bowman spectrophotofluorometer. The spectrofluorometer was equipped with a 1P21 photomultiplier and a high-pressure Xenon lamp, as supplied by the manufacturer. The fluorescence spectra of the azirines were determined in cyclohexane solution at 25°. The values obtained were carefully corrected for any residual solvent emission. No interference due to solvent was found at any time. The concentration of each substrate was 5×10^{-3} *M*. All slits were set at 3 mm and the excitation wavelength (310–356 nm) was chosen so as to yield the highest substrate emission. The shape of the emission envelopes for the naphthyl-substituted azirines were essentially identical with that of naphthalene. The singlet lifetime (τ_s) of the naphthyl-substituted azirines was measured by single-photon counting and was found to be in the order of $1.1–2.5 \times 10^{-9}$ sec.

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Registry No.—**1**, 41413-91-6; **5**, 51051-84-4; **6**, 51051-85-5; **7**, 51051-86-6; **8**, 51051-87-7; **9** picrate, 51051-89-9; **10** picrate, 51051-91-3; **11**, 51051-92-4; **12**, 51051-93-5; β-propenylnaphthalene, 51051-94-6; 1-azido-2-iodo-1-(β-naphthyl)propane, 51051-95-7; 1-azido-1-(β-naphthyl)-1-propene, 51051-96-8; β-isobutyronaphthone, 51051-97-9; β-isobutyronaphthone-*N,N,N*-trimethylhydrazonium iodide, 51051-98-0; acrylonitrile, 75-05-8; methyl methacrylate, 80-62-6.

References and Notes

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Acid-Catalyzed Angular Methyl Migration in a Substituted Octalin[1]

Alan R. Hochstetler

Givaudan Corporation, Clifton, New Jersey 07014

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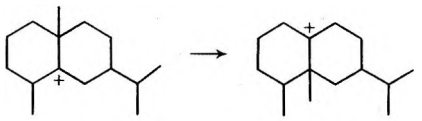
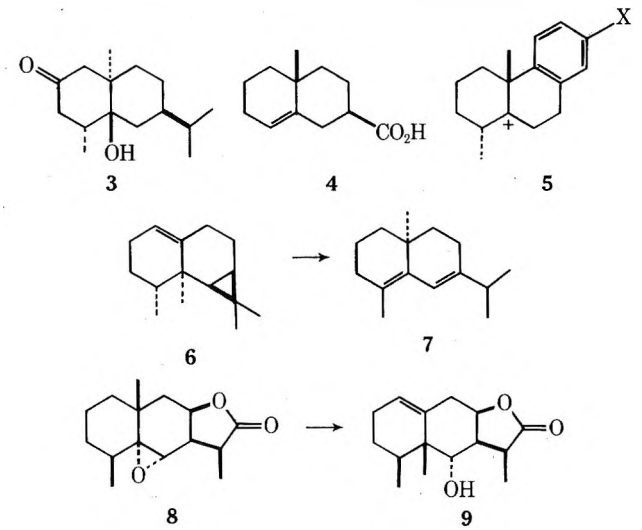
The acid-catalyzed isomerization of optically active 2,2,8,8,10-pentamethyl-1(9)-octalin (**12**) of known absolute configuration affords two major olefin products, **13** and **14**, whose gross structure was determined by a combination of spectral data and chemical transformations of each product to the common derivative, alcohol **17**. The absolute configuration at the chiral angular methyl center in **13** and **14** was determined by the ORD curves of the corresponding trans-fused 1-decalone derivatives **25** and **20**. The isomerization pathway of **12** to **13** and **14** therefore involves a specific spiro[4.5]decalyl cation to key intermediate **29a** which undergoes angular methyl migration. Intermediate **29a** was generated independently and shown to undergo rapid conversion to octalins **13** and **14**.

A vast amount of literature has appeared over the years dealing with the solvolytic and acid-catalyzed rearrangements of a wide variety of organic molecules found in nature.[2] Backbone rearrangements and angular methyl migrations have been well documented in the biosynthetic pathways leading to the multicyclic triterpenes.[3] Similarly, angular methyl migration has long been considered for the derivation of the eremophilane-type sesquiterpenes from the eudesmane skeleton (**1** → **2**).[4]



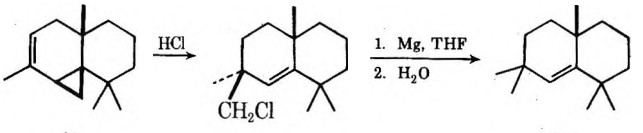
1 **2**

Angular methyl migrations of the above type, however, have been difficult to achieve in decalin systems under laboratory conditions. Attempts to dehydrate ketol **3** with concomitant angular methyl migration failed to afford any methyl-migrated products.[5] The apparent methyl migration observed[6] in the rearrangement of **4** has subsequently been shown to proceed *via* spiro intermediates.[7] Some angular methyl migration has been observed in the rearrangement products arising from cation **5** generated by appropriate solvolysis conditions, although the same cation generated by acid from the corresponding olefin gave only small amounts of such products.[8] Formic acid treatment of **6** has, however, been reported to afford the angular methyl migrated product, diene **7**.[9] Likewise, a recent communication[10] shows that formic acid–acetone treatment of epoxydihydroalantolactone (**8**) gives reasonable yields of the angular methyl migrated product **9**.



3 **4** **5** **6** **7** **8** **9**

Scheme I



10 **11** **12**

Both of the latter two examples which give rise to angular methyl migration products contain more than simple double-bond functionality. We wish to report now a substituted simple octalin system whose acid-catalyzed rearrangement proceeds *via* both a spiro[4.5]decalyl cation system and an angular methyl migration.

Results

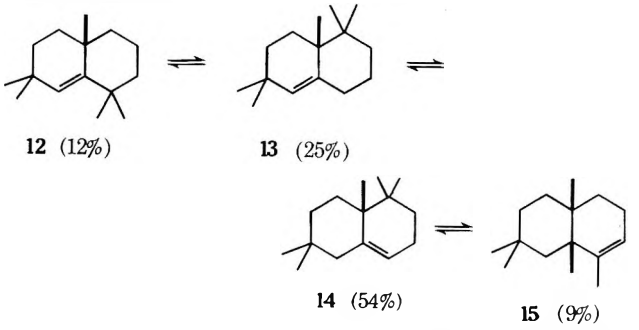
Synthesis of (+)-(*S*)-2,2,8,8,10-Pentamethyl-1(9)-octalin (12). The octalin employed in this study was readily obtained from (−)-thujopsene (**10**) *via* the two-step sequence outlined in Scheme I. Treatment of **10** with hydrogen chloride eventually formed the most stable addition product, neopentyl chloride **11**.[11] Reduction of **11** to the desired octalin **12** was conveniently effected by aqueous treatment of the corresponding Grignard complex. The nmr spectrum of **12** showed five methyl singlets and a sharp vinyl proton singlet at δ 5.13, in full agreement with the assigned structure.

It is important to note that the pentamethyloctalin **12** thus obtained is optically active and possesses the absolute configuration depicted. The absolute stereochemistry

of (−)-thujopsene has previously been established[12] as shown in structure **10**. Since the chemical transformations of **10** to **12** have not involved the chiral center at C-10, the absolute configuration at that center in **12** remains unchanged.

Acid-Catalyzed Isomerization of 12. Treatment of octalin **12** with 20% sulfuric acid in acetic acid at 40° slowly gave an equilibrium mixture of four components in a ratio of 12:25:54:9 in the order of their elution on a Carbowax 20M gas chromatography column. Subjection of pure major (54%) product to the same isomerization conditions afforded a nearly identical mixture of the above four components, thus showing that a true equilibrium had been established. Isomerizations starting from **12** interrupted at partial conversion showed a much higher ratio of the last eluted component with respect to the other two major products than found under equilibrium conditions.

These components were separated *via* spinning-band distillation. The first eluted component was identical with starting octalin **12**. The last eluted component clearly showed four upfield methyl singlets, a vinyl methyl, and a broad vinyl hydrogen absorption in the nmr spectrum. Consideration of the structure of the products of closely related isomerizations,[13,14] in combination with our spectral data, allows us to assign structure **15** for this initial isomerization product.



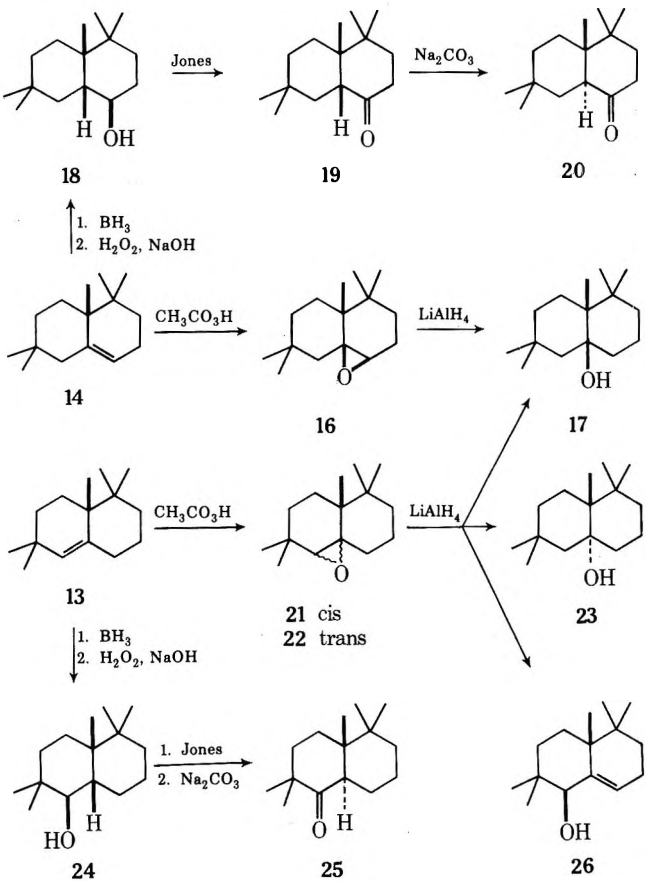
Structure **13** was assigned to the second eluted (25%) component on the basis of its nmr spectrum, which showed five methyl singlets and a vinyl hydrogen singlet only slightly broadened by allylic coupling. Suspicion that the major equilibrium component was the double bond positional isomer **14** of octalin **13** was confirmed *via* conversion of each pure olefin isomer to a common derivative, tertiary alcohol **17**.

Structure Proof of Octalins 13 and 14. As shown in Scheme II, treatment of octalin **14** with peracetic acid afforded a single epoxide isomer **16**. Inspection of molecular models clearly shows that the α face is badly hindered by the α-methyl group at C-7 and therefore β-face epoxidation leading to **16** is expected. Similar results have also been reported for the closely related olefin 7,7,10-trimethyl-1(9)-octalin.[15] Reduction of epoxide **16** with lithium aluminum hydride then gave the tertiary decalol **17**.

In similar fashion the epoxide mixture **21** and **22** was obtained from octalin **13** in an 82:18 ratio as determined directly by gas chromatography and by integration of the proton singlets α to the epoxide in the two isomers. The cis stereochemistry of the major product **21** is again assigned from a consideration of molecular models where β-face attack is less hindered than α-face attack. Reduction of this epoxide mixture with lithium aluminum hydride afforded three products, **17** (44%), **23** (14%), and **26** (42%), which were separated by column chromatography.

Alcohol **17** was identical in all respects with the tertiary alcohol obtained from reduction of epoxide **16** and thereby proves the isomeric relationship between precursor octalins **13** and **14**. Spectral data indicated that the minor

Scheme II



(14%) reduction product was the trans decalol **23** derived from reduction of minor trans epoxide **22**. The remaining product was assigned the allylic alcohol structure **26** from the nmr spectrum. This alcohol presumably arises *via* lithium aluminum alkoxide rearrangement[16] of hindered epoxide **21** in competition with the normal hydride reduction leading to tertiary alcohol **17**.

Since all three product olefins **13**, **14**, and **15** were optically active, we next sought to establish the absolute stereochemistry of the chiral angular methyl center at C-10 in both octalins **13** and **14**. Hydroboration–oxidation[17] of octalin **14** gave the crystalline secondary alcohol **18** as the sole product. The cis stereochemistry arising from β-face attack is again assigned from consideration of molecular models and by analogy to a closely related octalin system.[15] Jones oxidation[18] of **18** gave the cis-fused decalone **19**, which was readily equilibrated in base to the more stable trans-fused decalone **20**.

A similar sequence was followed starting from octalin **13**. A 77:23 mixture of secondary alcohols was obtained. The major isomer in this mixture is assigned structure **24**, again based upon attack from the least hindered β face. This crude decalol mixture was directly oxidized with Jones[18] reagent and the crude ketone mixture thereby obtained was treated with base to give the more stable trans-fused decalone **25**.

With both the gross structure and the relative (trans ring fusion) stereochemistry of both decalones **20** and **25** now established, we next sought to determine their absolute configuration *via* their optical rotatory dispersion curves. Decalone **20** was found to have a strong positive Cotton effect and decalone **25** a strong negative Cotton effect. Since the trans ring fusion avoids the conformational mobility inherent in the cis-fused decalones, the octant rule[19] can be unambiguously applied to decalones **20**

and **25**. Application of the octant rule in the present case clearly predicts the experimentally determined sign of the Cotton effect for both decalones **20** and **25** with the absolute configuration as shown in Scheme II. These findings are also in agreement with the results of related decalone systems studied earlier by Djerassi and coworkers.[20]

Since none of the reactions leading from octalins **13** and **14** to decalones **20** and **25** have involved the chiral center at C-10, the absolute configuration at the angular methyl center for these olefins must also be as shown in Scheme II.

Discussion

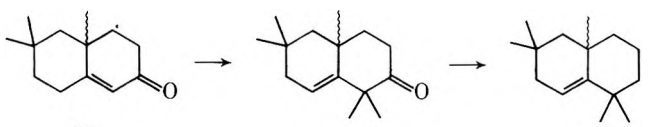
Octalin **12** presents an interesting case for the study of the isomerization pathways available in the 9-decalyl cation system. Scheme III outlines the four isomerization pathways possible from initially formed cation **12a**.

Path A involves β-methyl migration from C-2 to C-9 to afford the cis-fused cation **15a** and the corresponding olefin **15**. Such a product has literature precedent[13,14] in closely related systems and in the case of the 8,8,10-trimethyl-1(9)-octalin isomerization[13] comprises 94% of the equilibrium mixture. In the present case olefin **15** becomes a minor product owing to the additional steric effects of the *gem*-dimethyl group at C-7 with the angular methyl group at C-9. Although spectral data for olefin **15** could also be compatible with the trisubstituted spiro olefins derived from cations **12b** or **12c**, this possibility seems rather unlikely in view of the known[21,22] rapid isomerization of spiro olefins of this type to the octalin systems under mineral acid treatment, and indeed are not even found in the equilibrium mixture.

Path B involves stereospecific contraction of the B ring in cation **12a** to generate the spiro[4.5]decalyl cation **12b**. Subsequent opposite-sense rearrangement gives cation **13a′**, in turn leading to octalins **13′** and **14′**. Such a pathway, however, predicts that the configuration at the chiral angular methyl group is opposite to that experimentally found and is therefore dismissed as a viable pathway.

Path C involves stereospecific contraction of ring A in cation **12a** to generate the alternate spiro[4.5]decalyl cation **12c**. Again, opposite-sense rearrangement would generate the new cation **29a**. Two severe 1,3-diaxial methyl interactions in this cation can be readily alleviated by angular methyl migration to generate cation **13a**. Deprotonation now affords octalins **13** and **14** possessing the correct absolute configuration at C-10.

Additional evidence for the isomerization route of path C was obtained from independent generation of racemic cation **29a** from racemic octalin **29**. This octalin was synthesized by modified Wolff–Kishner reduction of ketone **28**, which in turn was obtained from alkylation of ketone

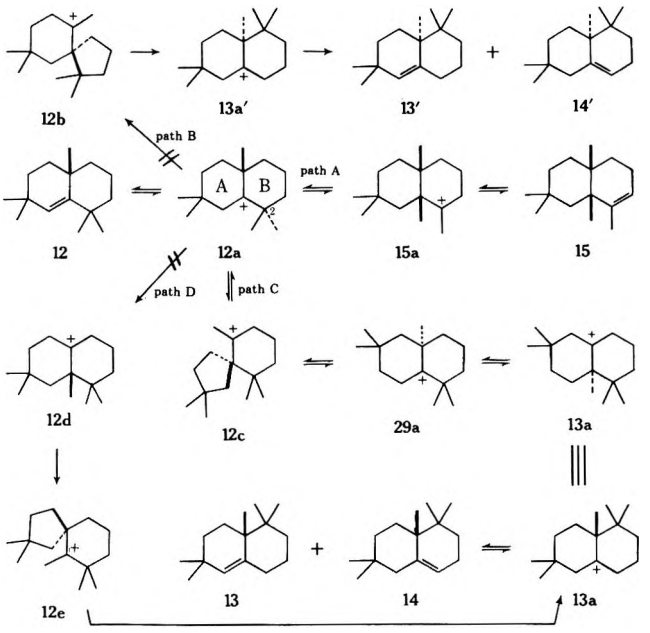


27 28 29

27, the Robinson annelation product of 2,4,4-trimethylcyclohexanone and methyl vinyl ketone.

Treatment of racemic octalin **29** under our standard acid isomerization conditions led to a rapid disappearance of **29** (none observed by glc after 0.5 hr) and the immediate formation of racemic octalins **13** and **14** in a 1:2 ratio. Extended reaction times slowly saw the appearance of racemic octalins **12** and **15** up to the equilibrium percentages. These results show that cation **29a**, once formed, more rapidly undergoes angular methyl migration to energetically favorable cation **13a** than reversion to spiro cation **12c**.

Scheme III



Path D involves initial angular methyl migration to afford cation **12d**. Subsequent formation of cation **12e** by contraction of the A ring in cation **12d** would ultimately lead to cation **13a** of the correct absolute configuration. The net difference between path C and path D is in the sequence of steps; in path C the spiro intermediate precedes angular methyl migration, whereas in path D angular methyl migration precedes the spiro intermediate.

We favor the path C route for two reasons. First, we have already described the independent generation of racemic cation **29a** and shown its ready conversion to racemic olefins **13** and **14**. Second, if path D were operative one would expect to see some evidence for the formation of the two octalins obtainable by loss of a proton from cation **12d** during the course of the isomerization. These octalins do not appear to have any more severe steric interactions than those found in octalin **15**, which is actually present in the equilibrium mixture. The absence of octalin **29** from the equilibrium mixture is, however, expected, since there are two 1,3-diaxial methyl interactions in that olefin.

The rotations of the optically pure product octalins **13**, **14**, and **15** are not known and therefore our observed rotations of these octalins give us no clue to their optical purity. Some decrease in optical activity corresponding to 20% racemization of octalin **12** recovered from the equilibrium mixture was noted. This decrease indicates that octalins **13**, **14**, and **15**, although not optically pure, do retain a high degree of optical purity. The racemization noted is most likely due to a small amount of the path B isomerization pathway affording the enantiomeric olefins **13′** and **14′**.

Experimental Section[23]

Materials. (−)-Thujopsene was readily obtained in 99% purity by careful fractional distillation of Hibawood oil through a 2-ft Goodloe column: bp 67–68° (0.5 mm); n^{20}D 1.5050; $[\alpha]^{25}$D −92.5° (neat).

(+)-2(*S*)-Chloromethyl-2,8,8,10(*S*)-tetramethyl-1(9)-octalin (11). A mixture of (−)-thujopsene (**10**, 816 g, 4 mol), acetic acid (800 ml), and anhydrous calcium chloride (444 g, 4 mol) was heated at 60° for 2 hr. After cooling, the reaction mixture was di-

luted with water (2 l.) and extracted with three 300-ml portions of benzene. The combined organic extracts were washed neutral with water and the solvent was removed under reduced pressure. The residue was fractionally distilled on a 37-cm column packed with glass helices, affording 613 g (64%) of **11**: bp 89–92° (0.5 mm); $n^{20}D$ 1.5030; $[\alpha]^{25}D$ +87° (neat). The ir and nmr spectra were identical with those described in the literature.[11]

(+)-(*S*)-2,2,8,8,10-Pentamethyl-1(9)-octalin (12). Into a nitrogen-purged flask was charged magnesium turnings (101 g, 4.16 mol). Two addition funnels were separately charged with dry tetrahydrofuran (900 ml) and chloride **11** (1,000 g, 4.16 mol). A small amount of tetrahydrofuran (50 ml) was added to the magnesium, followed by chloride **11** (20 ml) and ethyl bromide (2 ml). The reaction mixture was then heated at 50° until reaction began and the remainder of the tetrahydrofuran and the chloride **11** were fed in over 1 hr at 50°; then the mixture was brought to reflux for 18 hr. The reaction mixture was cooled to 5°, 20% sulfuric acid (1000 ml) was added, and the mixture was allowed to stir at 25° for 2 hr. The layers were separated and the organic phase was washed with water and saturated sodium bicarbonate solution. The solvent was removed under reduced pressure and the residue was distilled, affording 651 g (76%) of **12**: bp 52° (0.3 mm); $n^{20}D$ 1.4815; $[\alpha]^{20}D$ +81° (neat); ir (liquid film) 1021, 980, 953, 928, 869, 820, 662 cm^{-1}; nmr ($CDCl_3$) δ 0.93, 0.96, 1.04, 1.07, 1.14 (s, 3 each), 5.13 (s, 1); mass spectrum *m/e* (rel intensity) 206 (M^+, 20), 191 (100), 121 (45), 107 (47), 95 (94), 69 (40), 41 (45). The nmr spectrum agrees with that reported in the literature.[24]

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.44; H, 12.72.

Acid-Catalyzed Isomerization of 12. A mixture of octalin **12** (350 g, 1.70 mol), 98% sulfuric acid (350 g), and acetic acid (1400 g) was agitated at 40° for 24 hr. The mixture was cooled and the organic layer was separated. The acid layer was poured into ice-cold water (3 l.) and extracted with three 200-ml portions of hexane. The combined organic extracts were washed with water and saturated sodium carbonate solution. The solvent was removed under reduced pressure and the residue was flash distilled, affording 336 g (96%) of isomerized olefin mixture, bp 70–80° (0.4 mm). Vpc analysis showed four peaks identified as **12** (12%), **13** (25%), **14** (54%), and **15** (9%) in the order of their elution with relative retention times (based on **12**) of 1:1.7:2.0:2.2. Analysis of the isomerization mixture after 5 hr gave the following: **12** (52%), **13** (6%). **14** (13%), and **15** (29%). Isomerization of a pure sample of **14** under the above conditions for 24 hr gave the following mixture: **12** (9%), **13** (27%), **14** (57%) and **15** (7%).

(+)-(*R*)-2,2,5,5,10-Pentamethyl-1(9)-octalin (13). Spinning-band distillation of the above equilibrium mixture afforded in the first fractions recovered octalin **12**, bp 79–80° (5 mm), $[\alpha]^{25}D$ +50° (neat). The ir and nmr spectra were identical with those of the starting octalin **12**. Continued spinning-band distillation afforded pure **13**: bp 89–90° (5 mm); $n^{20}D$ 1.4932; $[\alpha]^{20}D$ +30.5° (neat); ir (liquid film) 1655, 1160, 1058, 861, 839 cm^{-1}; nmr ($CDCl_3$) δ 0.86, 0.90, 1.08 (s, 3 each), 0.93 (s, 6), 5.11 (s, 1, $W_{1/2}$ = 4 Hz); mass spectrum *m/e* (rel intensity) 206 (M^+, 9), 150 (99), 137 (100), 107 (38), 95 (59), 81 (54), 69 (37), 41 (46).

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.38; H, 12.85.

(−)-(*R*)-4,4,7,7,10-Pentamethyl-1(9)-octalin (14). Continued spinning-band distillation of the above mixture afforded pure octalin **14**: bp 92–93° (5 mm); $n^{20}D$ 1.4941; $[\alpha]^{25}D$ −32° (neat); ir (liquid film) 1658, 1058, 1022, 830, 804 cm^{-1}; nmr ($CDCl_3$) δ 0.77, 0.86, 0.91, 0.93, 1.01 (s, 3 each), 5.25 (s, 1, $W_{1/2}$ = 8 Hz); mass spectrum *m/e* (rel intensity) 206 (M^+, 7), 191 (18), 150 (100), 135 (32), 107 (28), 79 (36), 41 (26).

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.13; H, 12.70.

(−)-*cis*-1,7,7,9(*R*),10(*S*)-Pentamethyl-1-octalin (15). Continued spinning-band distillation of the above equilibrium mixture afforded pure octalin **15**: bp 97–98° (5 mm); $n^{20}D$ 1.4980; $[\alpha]^{25}D$ −35° (neat); ir (liquid film) 1655, 1078, 1054, 1034, 811, 794, 689 cm^{-1}; nmr ($CDCl_3$) δ 0.90, 0.93 (s, 6 each), 2.67 (d, 3, J = 1.5 Hz), 5.30 (m, 1, $W_{1/2}$ = 9 Hz); mass spectrum *m/e* (rel intensity) 206 (M^+, 13), 191 (100), 137 (30), 121 (38), 107 (30), 95 (78), 81 (32), 69 (37), 55 (31), 41 (42).

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.16, H, 12.60.

(+)-*cis*-8(*R*),9(*S*)-Epoxy-2,2,5,5,10(*R*)-pentamethyldecalin (16). To a mixture of pure octalin **14** (8.3 g, 45 mmol), ethylene dichloride (20 ml), and sodium carbonate (8 g) was added 40% peracetic acid (13 g, 70 mmol) at 30° over 10 min. After an additional 3 hr at 30–35°, water (50 ml) was added and the layers were separated. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Distillation afforded 8.5 g (94%) of a colorless liquid: bp 87–89° (0.4 mm); $n^{20}D$ 1.4868; $[\alpha]^{25}D$ +10.5° (neat); ir (liquid film) 1165, 1098, 990, 954, 916, 844, 792, 747 cm^{-1}; nmr ($CDCl_3$) δ 0.76 (s, 3), 0.93 (s, 6), 1.03 (s, 6), 2.80–2.95 (m, 1); mass spectrum *m/e* (rel intensity) 222 (M^+, 24), 207 (36), 189 (23), 166 (30), 151 (30), 140 (45), 123 (71), 109 (58), 95 (56), 83 (47), 81 (62), 69 (61), 67 (45), 55 (81), 43 (61), 41 (100).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.93; H, 11.86.

(−)-*cis*-2,2,5,5,10(*R*)-Pentamethyl-9(*S*)-decalol (17). A mixture of epoxide **16** (3.0 g, 13.5 mmol) and lithium aluminum hydride (1.0 g, 26 mmol) in tetrahydrofuran (20 ml) was refluxed under nitrogen for 42 hr. The mixture was cooled, carefully treated with water (2 ml) and 10% aqueous sodium hydroxide (1.6 ml), and stirred for an additional 2 hr. The mixture was filtered and the solvent was removed under reduced pressure. Short-path distillation afforded 2.6 g (86%) of a colorless oil: bp 85–90° (0.5 mm); $n^{20}D$ 1.4975; $[\alpha]^{25}D$ −9° (neat); ir (liquid film) 3500 (OH), 1070, 1007, 1000, 959, 912, 850 cm^{-1}; nmr ($CDCl_3$) δ 0.79, 0.91, 0.93, 0.99, 1.18 (s, 3 each); mass spectrum *m/e* (rel intensity) 224 (M^+, 1), 191 (12), 150 (68), 140 (66), 111 (31), 95 (61), 69 (88), 55 (72), 43 (71), 41 (100).

Vpc analysis showed the presence of 3% of unreacted **16** and no components other than **17**.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.05; H, 12.49.

(−)-*cis*-4,4,7,7,10(*S*)-Pentamethyl-*cis*-decal-1(*R*)-ol (18). The hydroboration procedure of Brown and coworkers[25] was employed on octalin **14** (9.3 g, 45 mmol) and 60 ml (60 mmol) of 1 *M* diborane in tetrahydrofuran solution at 25° for 4 hr. The mixture was cooled and carefully treated with 10% aqueous sodium hydroxide (30 ml) and 35% hydrogen peroxide (30 ml). The mixture was allowed to stir at 35° for 2 hr, then thoroughly extracted with hexane. The solvent was removed under reduced pressure to give 10 g (99%) of crude decalol **18**, mp 99–103°. A sample was recrystallized from hexane and exhibited the following characteristics: mp 111–112°; $[\alpha]^{25}D$ −2° (c 0.2, $CHCl_3$); ir (KBr pellet) 3310 (OH), 1059, 1030, 1014, 981 cm^{-1}; nmr ($CDCl_3$) δ 0.82, 0.88, 1.06 (s, 3 each), 0.94 (s, 6), 3.65–4.05 (m, 1); mass spectrum *m/e* (rel intensity) 224 (M^+, 1), 124 (32), 70 (100), 57 (37), 55 (35), 41 (50).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.40; H, 12.68.

(+)-(*S*)-4,4,7,7,10-Pentamethyl-*cis*-1-decalone (19). The standard Jones oxidation procedure[18] was employed on 5.0 g (22.3 mmol) of crude hydroboration decalol **18**. Short-path distillation afforded 4.5 g (91%) of colorless ketone **19**: bp 90–95° (0.7 mm); $n^{20}D$ 1.4959; $[\alpha]^{25}D$ +7° (neat); ir (liquid film) 1700 (C=O), 1208, 1120, 1020 cm^{-1}; nmr ($CDCl_3$) δ 0.69, 0.92, 0.96, 1.01, 1.07 (s, 3 each); mass spectrum *m/e* (rel intensity) 222 (M^+, 8), 207 (16), 70 (59), 55 (71), 41 (100). Vpc analysis showed only a single peak.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.70; H, 11.68.

(−)-(*S*)-4,4,7,7,10-Pentamethyl-*trans*-1-decalone (20). A sample of decalone **19** (6.0 g, 27 mmol), sodium carbonate (2 g), methanol (200 ml), and water (40 ml) was allowed to reflux under nitrogen for 18 hr. The mixture was cooled, diluted with water (50 ml), and thoroughly extracted with hexane. The solvent was removed under reduced pressure and the residue was distilled, affording 5.8 g (97%) of colorless ketone **20**: bp 95–98° (0.7 mm); $n^{20}D$ 1.4971; $[\alpha]^{25}D$ −1.5° (neat); ir (liquid film) 1710 (C=O), 1280, 1184, 1148, 1008, 580 cm^{-1}; nmr ($CDCl_3$) δ 0.77, 0.86, 0.92, 0.96, 1.27 (s, 3 each); mass spectrum *m/e* (rel intensity) 222 (M^+, 25), 208 (35), 151 (48), 124 (39), 123 (40), 109 (38), 70 (85), 69 (50), 56 (55), 55 (69), 41 (100); CD (c 0.0108, dioxane) θ_{320} 0, θ_{313} +139, θ_{298} +231, θ_{255} 0, θ_{244} −46, θ_{220} 0; ORD ϕ_{380} +111°, ϕ_{307} +76°, ϕ_{300} 0°, ϕ_{265} −245°, ϕ_{222} −208°. This ketone had the same vpc retention time as the cis-fused ketone **19**, but analysis of the nmr spectra of the two ketones showed that at equilibrium >98% of the mixture was the trans ketone **20**.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.08; H, 11.98.

(−)-*cis*-1(*S*),9(*R*)-Epoxy-2,2,5,5,10(*R*)-pentamethyldecalin (21). The procedure for the epoxidation of octalin **14** was employed with pure octalin **13** (4.1 g, 20 mmol), 40% peracetic acid (8.0 g, 42 mmol), sodium carbonate (5 g), and ethylene dichloride (15 ml). The product was isolated in the same manner and distilled, affording 3.7 g (84%) of colorless oil, bp 80–85° (0.5 mm). The gas chromatogram showed two peaks in an 18:82 ratio. These

peaks were separated by preparative gas chromatography. The major isomer, epoxide **21**, exhibited the following characteristics: $n^{20}D$ 1.4871; $[\alpha]^{25}D$ −1° (neat); ir (liquid film) 1085, 936, 916, 830, 819 cm^{-1}; nmr ($CDCl_3$) δ 0.89, 1.00, 1.02 (s, 3 each), 1.04 (s, 6), 2.60 (s, 1); mass spectrum *m/e* (rel intensity) 222 (M^+, 16), 165 (10), 153 (15), 135 (21), 125 (32), 123 (36), 109 (36), 95 (52), 81 (35), 69 (71), 67 (30), 55 (51), 43 (61), 41 (100).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.98; H, 11.84.

***trans*-1(*R*),9(*S*)-Epoxy-2,2,5,5,10(*R*)-pentamethyldecalin (22).** The minor epoxide isomer obtained above exhibited the following characteristics: $n^{20}D$ 1.4864; ir (liquid film) 961, 920, 854, 820 cm^{-1}; nmr ($CDCl_3$) δ 0.80 (s, 3), 1.02, 1.04 (s, 6 each), 2.31 (s, 1); mass spectrum *m/e* (rel intensity) 222 (M^+, 15), 189 (16), 153 (19), 135 (28), 125 (34), 123 (42), 109 (35), 95 (56), 81 (44), 69 (72), 53 (54), 43 (64), 41 (100).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.87; H, 11.86.

Reduction of Epoxide Mixture 21 and 22. Under a nitrogen atmosphere was charged lithium aluminum hydride (1.5 g, 39 mmol) and anhydrous 1,2-dimethoxyethane (25 ml). Epoxide mixture **21** (82%) and **22** (18%) (2.5 g, 11.2 mmol) was then added and the mixture was allowed to reflux for 24 hr. The mixture was cooled and ether (50 ml) was added followed by the careful addition of water (3 ml) and 10% aqueous sodium hydroxide (2.5 ml). After an additional 2 hr of stirring the mixture was filtered and the solvent was removed under reduced pressure. Analysis of the residue (2.6 g) by gas chromatography showed three products in a 14:44:42 ratio. These components were separated by chromatography on silica gel.

***trans*-2,2,5,5,10(*R*)-Pentamethyl-9(*R*)-decalol (23).** The early fractions above eluted with 1% ether in hexane afforded a pure sample of the minor (14%) component **23**, which exhibited the following characteristics: $n^{20}D$ 1.4935; ir (liquid film) 3610 (nonbonded OH), 3500 (bonded OH), 981, 950, 920, 841 cm^{-1}; nmr ($CDCl_3$) δ 0.79, 0.89, 0.92, 1.14, 1.19 (s, 3 each); mass spectrum *m/e* (rel intensity) 224 (M^+, 2), 191 (8), 150 (49), 140 (63), 111 (34), 95 (59), 69 (83), 55 (68), 43 (74), 41 (100).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.42; H, 12.38.

Later 1% ether in hexane fractions afforded a pure sample of the second (44%) component. This component was identical in all respects with the tertiary alcohol **17** previously obtained from reduction of epoxide **16**.

***cis*-2,2,5,5,10(*R*)-Pentamethyl-8-octal-1(*S*)-ol (26).** Fractions of the above chromatography eluted with 2% ether in hexane afforded pure third (42%) component **26**, which exhibited the following characteristics: $n^{20}D$ 1.4960; ir (liquid film) 3620 (nonbonded OH), 3490 (bonded OH), 1650 (C=C), 1185, 1024, 995, 975, 923, 849, 809 cm^{-1}; nmr ($CDCl_3$) δ 0.76, 0.85, 0.91, 0.98, 1.23 (s, 3 each), 3.58 (s, 1), 5.57 (dd, J = 4, 2.5 Hz); mass spectrum *m/e* (rel intensity) 222 (M^+, 1), 204 (16), 189 (30), 153 (43), 110 (41), 95 (73), 81 (45), 69 (47), 55 (55), 43 (82), 41 (100).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 79.77; H, 12.01.

(−)-*cis*-2,2,5,5,10(*S*)-Pentamethyl-*cis*-decal-1(*R*)-ol (24). A sample of pure octalin **13** (4.1 g, 20 mmol) was treated with 1 *M* diborane in tetrahydrofuran solution (25 ml, 25 mmol) under nitrogen for 18 hr at 25°. The mixture was cooled to 0° and 10% aqueous sodium hydroxide (15 ml) was added, followed by 35% hydrogen peroxide (15 ml). After stirring for 2 hr at 35° the mixture was thoroughly extracted with hexane. The solvent was removed under reduced pressure to afford 4.4 g (98%) of crude crystalline product, mp 85–92°. Integration of the areas of the α to the hydroxyl proton resonances gave a 77:23 ratio of isomers. A sample was recrystallized from hexane at 0° and exhibited the following characteristics: mp 108–109°; $[\alpha]^{25}D$ −3° (*c* 0.2, $CHCl_3$); ir (KBr pellet) 3260 (OH), 1075, 1005, 990, 925 cm^{-1}; nmr ($CDCl_3$) δ 0.78, 0.98, 1.00 (s, 3 each), 0.87 (s, 6), 3.17 (d, 1, J = 10 Hz); mass spectrum *m/e* (rel intensity) 224 (M^+, 16), 209 (12), 206 (7), 139 (57), 109 (21), 95 (35), 82 (100), 69 (50), 55 (44), 43 (70), 41 (56).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.01; C, 12.67.

(−)-(*S*)-2,2,5,5,10-Pentamethyl-*trans*-1-decalone (25). A sample of crude decalol mixture containing 77% of decalol **24** from the preceding hydroboration reaction was subjected to the standard Jones[18] oxidation procedure. The crude ketone mixture (2.5 g) thus obtained was then treated with methanol (75 ml), water (15 ml), and sodium carbonate (0.7 g) at reflux under nitrogen for 20 hr. The mixture was cooled, water (100 ml) was added, and the mixture was thoroughly extracted with hexane. The solvent was removed under reduced pressure and the residue was distilled, affording 2.1 g (84%) of decalone **25**: bp 85–90° (0.5 mm); $n^{20}D$ 1.4916; $[\alpha]^{25}D$ −20° (neat); ir (liquid film) 1698 (C=O), 1110, 932, 827 cm^{-1}; nmr ($CDCl_3$) δ 0.73, 0.82, 1.02, 1.08, 1.15 (s, 3 each), 2.70 (dd, 1, J = 9, 4.5 Hz); mass spectrum *m/e* (rel intensity) 222 (M^+, 17), 207 (16), 153 (39), 126 (43), 120 (40), 82 (81), 69 (53), 55 (57), 41 (100); CD (*c* 0.0107, dioxane) θ_{328} 0, θ_{312} −2340, θ_{303} −4024, θ_{299} −3463, θ_{295} −4024, θ_{270} −1029, θ_{240} 0; ORD ϕ_{317} −2375°, ϕ_{310} −1671°, ϕ_{307} −1818°, ϕ_{297} 0°, ϕ_{273} +2276°.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.20; H, 12.06.

(±)-6,6,10-Trimethyl-1(9)-octal-2-one (27). The general procedure of Ross and Levine[26] was employed. To a mixture of potassium hydroxide (6 g), ethanol (35 ml), ether (250 ml), and 2,4,4-trimethylcyclohexanone[27] (87 g, 0.62 mol) under nitrogen at 0° was added a solution of methyl vinyl ketone (25 g, 0.35 mol) in ether (50 ml) over 1.5 hr. The mixture was allowed to agitate at 0° for 1 hr, then at 25° for 3 hr. Water (100 ml) was added and the mixture was extracted with ether. The organic phase was washed neutral with brine and the residue was distilled, affording 50 g of recovered 2,4,4-trimethylcyclohexanone, bp 65–68° (10 mm), and 36.5 g (54%) of desired octalone **27**: bp 100–103° (0.5 mm); $n^{20}D$ 1.5152; ir (liquid film) 1662 (C=O), 1615 (C=C), 1238, 1190, 863 cm^{-1}; nmr ($CDCl_3$) δ 0.94, 1.17, 1.31 (s, 3 each), 5.76 (d, 1, J = 1.5 Hz); mass spectrum *m/e* (rel intensity) 192 (M^+, 49), 177 (44), 164 (33), 150 (89), 135 (100), 121 (39), 108 (94), 107 (44), 93 (45), 91 (37), 80 (36), 79 (66), 77 (34), 55 (44), 41 (65). The gas chromatogram showed a single peak.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.30; H, 10.36.

(±)-1,1,6,6,10-Pentamethyl-8-octal-2-one (28). To a suspension of 57% sodium hydride in mineral oil (14 g, 0.332 mol) in dry toluene (210 ml) under nitrogen was added *tert*-butyl alcohol (24.6 g, 0.332 mol) at 50° over 0.5 hr. The mixture was held at 50° for 1 hr, then cooled to 35°; octalone **27** (30.5 g, 0.158 mol) was added and the mixture was stirred at 35° for 1.5 hr. Methyl iodide (50 g, 0.352 mol) was then added over 5 min, and the temperature of the exothermic reaction was held to 45° with ice-bath cooling. After heat evolution ceased (0.5 hr), water (50 ml) was added. The layers were separated and the organic phase was washed once with brine (50 ml). The solvent was removed under reduced pressure and the residue was distilled, affording 31.4 g (90%) of distillate, bp 92–105° (0.5 mm). Analysis by gas chromatography showed the presence of four components in the ratio of 25:53:12:8. A sample of the major component, octalone **28**, was obtained pure by preparative gas chromatography and exhibited the following characteristics: $n^{20}D$ 1.4975; ir (liquid film) 1710 (C=O), 1653 (C=C), 1244, 1109, 1024, 822 cm^{-1}; nmr ($CDCl_3$) δ 0.97, 1.01, 1.04 (s, 3 each), 1.26 (s, 6), 1.41 (s, 2), 1.87 (d, 2, J = 4.5 Hz), 1.70–1.95 (m, 2), 2.40–2.65 (m, 2), 5.60 (t, 1, J = 4.5 Hz); mass spectrum *m/e* (rel intensity) 220 (M^+, 53), 205 (59), 164 (53), 149 (40), 121 (100), 109 (43), 107 (66), 93 (40), 91 (41), 55 (48), 43 (49), 41 (81).

Anal. Calcd for $C_{15}H_{24}O$: C. 81.76, H, 10.98. Found: C, 81.48; H, 10.98.

Nmr and mass spectral analysis of the 25% component in the above mixture indicated the introduction of three methyl groups in the alkylation process.

(±)-3,3,8,8,10-Pentamethyl-1(9)-octalin (29). The Wolff-Kishner procedure as modified by Nagata[28] was employed. A mixture of octalone **28** (22 g, 0.1 mol, 60% pure by vpc), 85% hydrazine hydrate (12 g, 0.2 mol), hydrazine dihydrochloride (1 g), and triethylene glycol (105 ml) was heated under nitrogen at 125° for 2 hr. Solid potassium hydroxide (18.5 g, 0.33 mol) was then cautiously added at 125°. The temperature was then raised to 225° over 1.0 hr and the excess hydrazine hydrate was removed by a Dean-Stark trap. Nitrogen evolution began when the temperature reached 175°. The reaction mixture was heated for an additional 10 min at 225° after gas evolution ceased. The mixture was cooled, poured into water (300 ml), and extracted three times with hexane (75 ml). The organic extracts were washed neutral with water and the solvent was removed under reduced pressure. Analysis by gas chromatography showed three components. The two minor components (35%) still retained a carbonyl group and were identical with the minor ketones in the starting material. The major component, octalin **29**, was purified by distillation, affording 11.4 g (55%) of colorless oil: bp 62–64° (0.5 mm); $n^{20}D$ 1.4910; ir (liquid film) 1640, 1148, 1068, 1030, 968, 815, 663 cm^{-1}; nmr ($CDCl_3$) δ 0.91, 0.99, 1.08, 1.12, 1.23 (s, 3 each), 1.32 (s, 2),

Table I

Olefin	T_R[b]	0[a]	0.5[a]	2.0[a]	5.0[a]	18[a]
12	1.0	0	1.3	4.6	6.8	9.0
29	1.5	100	0	0	0	0
13	1.7	0	32.9	30.1	29.4	27.1
14	2.0	0	65.8	59.9	58.6	56.8
15	2.2	0	1.0	3.4	5.2	7.1

[a] Time in hours. [b] Retention time.

1.86 (d, 2, J = 4.5 Hz), 5.45 (t, 1, J = 4.5 Hz); mass spectrum m/e (rel intensity) 206 (M^+, 33), 191 (100), 150 (20), 136 (28), 135 (66), 121 (62), 107 (50), 95 (47), 93 (38), 82 (38), 81 (35), 69 (48), 55 (47), 43 (34), 41 (63).

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.23; H, 12.87.

Acid-Catalyzed Isomerization of Octalin 29. A pure sample of octalin **29** (0.5 g, 2.5 mmol) was treated with acetic acid (4 g) containing sulfuric acid (1 g) at 40°. Samples were removed periodically for analysis by gas chromatography. Table I summarizes the results. The products were separated by preparative gas chromatography and gave ir, nmr, and mass spectra identical with those of the products previously isolated from the equilibration of olefin **12**. The octalins isolated in this experiment were optically inactive, since a racemic octalin (**29**) had been employed as the starting material.

Registry No.—**10**, 470-40-6; **11**, 50562-26-0; **12**, 32540-36-6; **13**, 50562-28-2; **14**, 50562-29-3; **15**, 50512-32-8; **16**, 50562-30-6; **17**, 50562-31-7; **18**, 50562-32-8; **19**, 50562-33-9; **20**, 50562-34-0; **21**, 50562-35-1; **22**, 51096-44-7; **23**, 51096-43-6; **24**, 50562-38-4; **25**, 50562-39-5; **26**, 50562-40-8; **27**, 50562-41-9; **28**, 50562-42-0; **29**, 50562-43-1.

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Synthesis of *cis*-1,2-Dihydroxy-1,2-dihydronaphthalene and *cis*-1,4-Dihydroxy-1,4-dihydronaphthalene

Alan M. Jeffrey,* Herman J. C. Yeh, and Donald M. Jerina

National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

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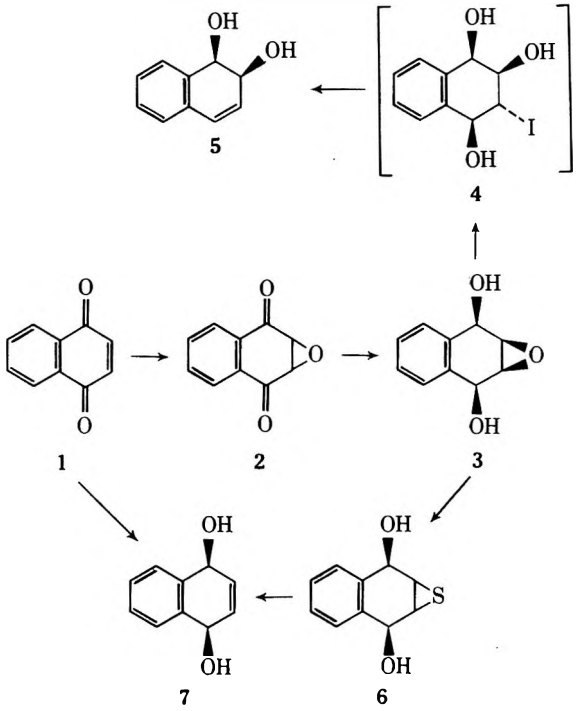
Both of title compounds were prepared from the readily accessible *cis,cis*-1,4-dihydroxy-2,3-epoxy-1,2,3,4-tetrahydronaphthalene. The 1,2-dihydrodiol, a bacterial metabolite of naphthalene, was obtained through the action of sodium iodide and zinc dust in acetic acid on the epoxide. Conversion of the epoxide to the thioepoxide and desulfurization with triphenylphosphine provided the 1,4-dihydrodiol, which was also obtained by direct reduction of *p*-naphthoquinone with diisobutylaluminum hydride.

Although *cis*- and *trans*-1,2-dihydroxy-1,2-dihydroarenes have been known as oxidative metabolites of the aromatic ring for many years,[1] relatively little has been reported on the synthesis of this important class of metabolites. Both *cis*- and *trans*-1,2-dihydroxy-1,2-dihydrobenzene have been prepared by dehalogenation of the corresponding tetrachlorocyclohexanediols.[2] While *cis*-1,2-dihydrodiols at the K regions of polycyclic aromatic hydrocarbons are available through the action of osmium tetroxide,[3] the procedure fails with naphthalene. *trans*-1,2-Dihydrodiols have been prepared by reduction of K region o-quinones with lithium aluminum hydride.[4,5] The hydride reduction produces only pyrocatechol from o-benzoquinone[4] and a mixture of cis and trans isomers is formed from 7,12-dimethylbenz[*a*]anthracene-5,6-quinone.[5] Reduction of certain *p*-quinones such as 1,4-naphthoquinone results in conjugate addition of hydride.[6] The only 1,4-dihydrodiols without substitution at the carbinol position prepared thus far have been by lead tetraacetate oxidation[7] of the 9,10 positions of anthracene and by the lithium aluminum

hydride reduction of 9,10-anthraquinone.[6] An attempt to prepare the 1,4-dihydrodiol of naphthalene from 1,4-dihydronaphthalene *endo*-1,4-oxide was unsuccessful.[8]

Metabolism of naphthalene by bacteria produces the *cis*-1,2-dihydrodiol.[9] Evidence for the 1,4-dihydrodiol has been obtained with mammalian systems.[8] The first chemical syntheses of *cis*-1,2- and 1,4-dihydrodiols of naphthalene (**5** and **7**), the title compounds, are reported here.



Advantage has been taken of the availability of *cis,cis*-1,4-dihydroxy-2,3-epoxy-1,2,3,4-tetrahydronaphthalene (**3**), through epoxidation of **1** to **2** and subsequent reduction with sodium borohydride to **3**,[10] for the synthesis of both compounds. Treatment of **3** with Cornforth's reagent[11] gives an intermediate iodohydrin **4** which potentially could form either **5** or **7**. Only **5** was isolated in 85% yield. The 1*R*,2*S* dihydrodiol, which results from bacterial metabolism of naphthalene,[9] showed the same nmr and mass spectra as **5**. Only the 1*R*,2*S* isomer of **5** is metabolized by microorganisms, thus affording a satisfactory method of obtaining pure 1*S*,2*R* isomer.[12]

Attempted deoxygenation of **3** to **7** with triphenylphosphine, in the presence of hydroquinone at room temperature, was unsuccessful. When the mixture was heated, the only detectable product was α-naphthol. The thioepoxide **6**, however, is readily desulfurized to give a 70% yield of **7** along with 14% of **5**. At first the formation of **5** in this reaction seemed quite unusual. However, careful examination of the nmr spectrum of the sample of **6** used in this preparation revealed signals consistent with the presence of *cis*-1,2-dihydroxy-3,4-thioepoxy-1,2,3,4-tetrahydronaphthalene, which had formed in a competing reaction during preparation of **6** from **3** with potassium thiocyanate.

The previous attempt to prepare **7** by the reduction of **1** with lithium aluminum hydride failed[6] because of the propensity of this reagent to undergo 1,4 addition. Diisobutylaluminum hydride, in contrast, causes 1,2 reductions of similar systems.[13] Treatment of **1** with this reagent produces **7**, although in low yield. Acid-catalyzed dehydration of **7** gives only α-naphthol, at a rate 52 times faster than **5**, which in turn is more unstable than the trans isomer of **5**.[9]

Catalytic hydrogenation of **7**, prepared from **3**, to *cis*-1,4-dihydroxy-1,2,3,4-tetrahydronaphthalene (**8**) gave a product indistinguishable from a sample obtained by catalytic reduction of **1** with copper chromite to which the trans stereochemistry has been assigned.[14] The stereochemistry of **7** was established by reducing the diacetate of **7** with deuterium in the presence of Wilkinson's catalyst, which catalyzes cis addition.[15] Analysis of the nmr spectrum of the 8-*cis*-2,3-d_2, in the presence of shift reagents, showed a single broadened resonance band corresponding to the 2,3 hydrogens. In comparison, **8** showed two bands under similar conditions. These results are only compatible with a stereospecific addition of deuterium to one face of **7**, which must have had cis stereochemistry. Thus, the original assignment of **3**[10] would seem correct, and the diol (**8**) isolated from the catalytic reduction of **1** is possibly the cis isomer.

Experimental Section

Diisobutylaluminum hydride and Wilkinson's catalyst [tris(triphenylphosphine)rhodium(I) chloride] were purchased from Alfa Inorganics, Beverly, Mass., and Eu(fod)$_3$ [europium(III) tris(1,1,1,-2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)] from North Chemical., Inc., Landing, N. J. Mass spectra were measured at 70 eV on a Hitachi RMU7 spectrometer. A Varian HA-100 spectrometer was used for the determinations of nmr spectra in $CDCl_3$ with TMS as internal standard. Chemical shifts are reported in δ units and coupling constants (*J*) in hertz. Compound **7** gave a microanalysis within 0.25% for carbon and hydrogen while the molecular ion of compound **6** was peak matched within 1 mmass unit of the expected value.

***cis,cis*-1,4-Dihydroxy-2,3-epoxy-1,2,3,4-tetrahydronaphthalene (3).** Reduction of **2**[16] to **3** with an excess of sodium borohydride in aqueous ethanol was conducted essentially as described by Rashid and Read.[10] Most of the ethanol was removed before saturation of the solution with sodium chloride and extraction with ethyl acetate. Recrystallization from chloroform gave pure **3**, mp 204° (lit.[10] mp 192–194°).

***cis*-1,2-Dihydroxy-1,2-dihydronaphthalene (5).** To 0.95 g of **3** was added 4.2 g of sodium iodide, 0.2 g of sodium acetate, 8.4 ml of acetic acid, and 4.2 g of zinc dust. The paste was stirred under nitrogen for 3 hr before adding 25 ml of water and adjusting the pH to 7.0 with sodium carbonate. The aqueous phase was extracted three times with equal volumes of ethyl acetate and the combined organic phase was dried with magnesium sulfate. Evaporation of the solvent left 0.72 g (85%) of crude diol which, by nmr, showed no trace of the 1,4 isomer (**7**). The diol was recrystallized from chloroform to give pure **5**, mp 101–102°, which was identical in all respects, except optical activity and melting point, with biosynthetic material.[9]

***cis*-1,4-Dihydroxy-2,3-thioepoxy-1,2,3,4-tetrahydronaphthalene (6).** A solution of 1 g of **3** in 10 ml of ethanol and a five-molar excess of KSCN in 1 ml of water were mixed and stored at 50° for 1 week. The ethanol was evaporated at reduced pressure and 10 ml of water was added. Products were extracted into chloroform (3 × 5 ml) and the combined extracts were dried with magnesium sulfate and concentrated to leave 0.55 g of crude **6**. A sample was purified by dissolving in chloroform, adding benzene, and allowing **6** to crystallize slowly at 4°. **6**, mp 110–113°, had a mass spectrum showing ions at *m/e* (rel intensity) 194 (M^+, 14), 176 (9), 161 (35), 147 (100), 144 (42), and 128 (32). The nmr spectrum of **6** ($H_{2,3}$ = 3.45, $H_{1,4}$ = 5.07 as triplets with an apparent $J_{1,2}$ = 1.8 Hz; aromatic protons δ 7.0–7.8) did not allow assignment of relative stereochemistry between the thioepoxide and the cis diol, but it was assumed to be trans.

***cis*-1,4-Dihydroxy-1,4-dihydronaphthalene (7).** A solution of 0.5 g of crude **6** in dry dimethoxyethane was treated with a three-molar excess of triphenylphosphine at 80° overnight. After removal of the solvent, nmr analysis of the residue showed the presence of **5** and **7** in a ratio of 1:5. The two isomers were separated by applying the residue in ethyl acetate–chloroform (1:1) to a 3 × 25 cm column of silica gel and eluting with the same mixed solvent. The first dihydrodiol to elute was **5**, which was followed immediately by 290 mg (70%) of **7**: mp 106–107° after crystallization from chloroform–benzene (1:1); mass spectrum *m/e* (rel intensity) 162 (M^+, 24), 144 (100), 128 (5), 115 (6); nmr spectrum, $H_{1,4}$ δ 5.0 and $H_{2,3}$ δ 6.12 as doublets, *J* (apparent) = 1.5 Hz, aromatic protons δ 7.2–7.8. Reduction of **1** (1 g) in 50 ml of benzene under nitrogen with 10 ml of 20% diisobutylaluminum hydride in hexane also gave **7** in 20% yield after purification by chromatography as described above.

Assignment of Stereochemistry to 7. Reduction of 7 in ethanol with hydrogen in the presence of 10% Pd on carbon gave 1,4-dihydroxy-1,2,3,4-tetrahydronaphthalene (8), mp 138°. This material was indistinguishable by mp, nmr, and glc (as the diacetate, 3% OV-17, 170°, retained 9.5 min) from a sample prepared by catalytic reduction of 1.[14] The diol 7 (170 mg) was acetylated with acetic anhydride in pyridine and the crude product was then reduced in 8 ml of benzene with deuterium gas in the presence of 10 mg of Wilkinson's catalyst (free diol did not reduce readily). The reaction was complete in 8 days. After removal of the solvent under reduced pressure, the product was deacetylated in 80% ethanol–water containing an excess of sodium hydroxide. The ethanol was removed, water was added, and the pH was adjusted to 7 with acetic acid. Extraction with ethyl acetate provided 8-*cis*-2,3-d_2; incorporation of two atoms of deuterium was confirmed by its mass spectrum.

Saturated $CDCl_3$ solutions (400 μl) of deuterated and normal 8 at 20° were used to determine their nmr spectra in the presence of 3 mg of Eu(fod)$_3$. Normal 8 showed the four protons at the 2 and 3 positions to be split into two separate groups at δ 2.66 and 3.16, presumably due to hydrogens cis and trans to the hydroxyl groups. The benzylic protons moved to δ 6.0 and the aromatic protons split into two groups at δ 7.5–7.6 and 8.1–8.3. The corresponding spectrum of deuterated 8 lacked the absorption at δ 2.66, and when the benzylic protons were irradiated, the signal at δ 3.16 sharpened considerably. This observation confirms the assignment of the chemical shifts in the complex and, together with the cis addition of deuterium, is consistent with the hydroxyl groups in 8 as cis.

Dehydration of the Dihydrodiols 5 and 7. Rates were measured by following the decrease in absorption at 265 nm and the increase at 295 nm for 5 and 7, respectively, in dioxane–water (1:1) which was 0.6 *M* in HCl. The rates at 25° for 5 and 7 are 5.4×10^{-4} and 2.8×10^{-2} sec^{-1}, respectively. Only α-naphthol could be detected by tlc as a product from 7.

Acknowledgment. The authors are very indebted to Dr. P. A. Argabright of the Denver Research Center, Marathon Oil Co., Littleton, Colo., for a sample of 8 prepared by the catalytic reduction of 1. We thank Dr. P. Roller of the National Cancer Institute for obtaining the accurate mass measurement reported.

Registry No.—1, 130-15-4; 3, 25129-70-8; 5, 31966-70-8; 6, 50987-67-2; 7, 51096-10-7; 8, 50987-68-3.

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Formation of a Cyclohexane Ring by Condensation of a Nitro Ketone and an Aldehyde[1a]

Morris E. Lewellyn[1b] and D. Stanley Tarbell*

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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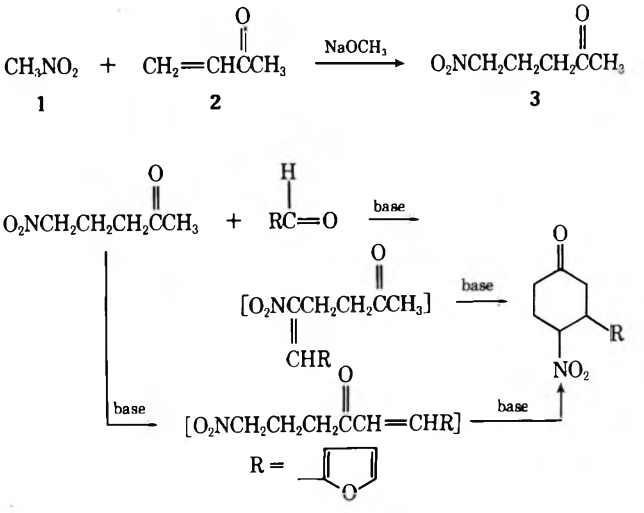
5-Nitro-2-pentanone (3) and furfural were used to study the feasibility of using a condensation reaction to form a cyclohexane ring. The Schiff base of furfural was condensed with the ethylene ketal of 5-nitro-2-pentanone in acetic acid to give 1-(2-furyl)-2-nitro-1-hexen-5-one 5-ethylene ketal (11). The ketal was removed and an intramolecular Michael reaction was effected using an enamine to form 3-(2-furyl)-4-nitrocyclohexanone (21). Practical syntheses of 1-methoxy-5-nitro-2-pentanone (22) and *trans*-2,6-dimethyl-2-heptenal (23) have been developed.

Earlier papers have reported experiments on the preparation and Birch reduction of 2,3-dihydrobenzofurans as possible intermediates for syntheses in the fumagillin series.[2] Corey has recently reported a synthesis of fumagillin, using a Diels–Alder reaction to form the carbocyclic ring.[3]

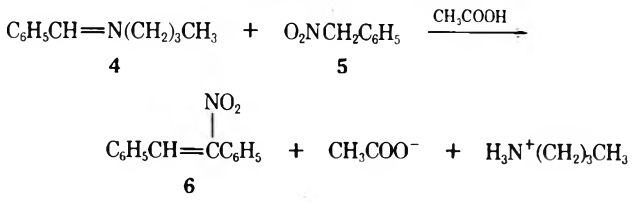
We considered that the cyclohexane ring of fumagillin could be formed by the condensation of a γ-nitro ketone with an aldehyde, which would allow a stereoselective synthesis. To test the feasibility of such a reaction, the condensation of furfural with 5-nitro-2-pentanone (3) was studied; these compounds are accessible and are reasonable models for the proposed syntheses.

5-Nitro-2-pentanone (3) was obtained by a modification of the published procedure.[4] An attempt to cyclize 3 with furfural according to the following scheme gave only tars, probably owing to the high reactivity of α,β-unsaturated nitro compounds.[5] A two-step condensation was therefore



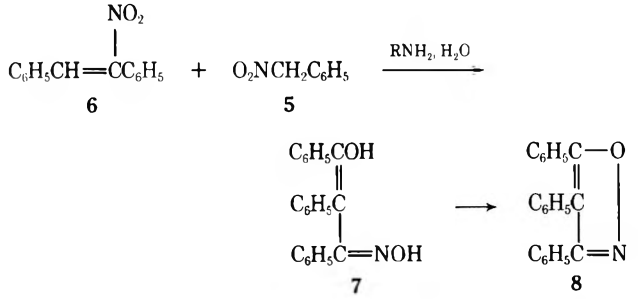
examined; the ethylene ketal of **3** was used, because this has only one active site for condensation. A mild method for the formation of the nitro olefin was then sought.

Robertson has reported a method of making α-nitrostilbene (**6**) by using the Schiff base of an aromatic aldehyde (**4**) with the nitro compound (**5**) in acetic acid.[6]



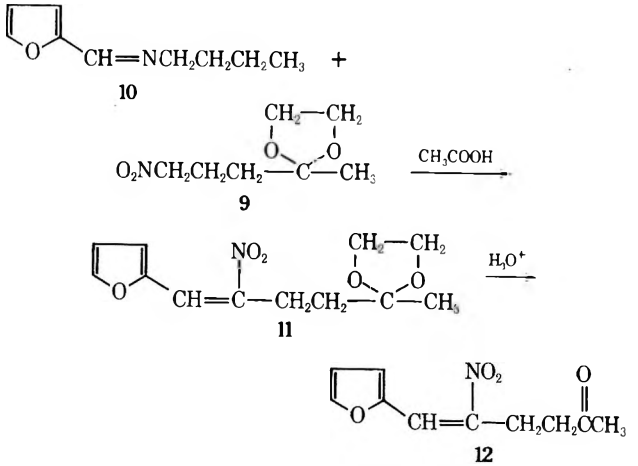
A kinetic study of the Knoevenagel reaction between nitromethane and piperonal, using *n*-butylamine as catalyst, indicated that the Schiff base was the intermediate.[7] It was found that the Schiff base reacted rapidly with nitromethane when catalyzed by *n*-butylammonium acetate, whereas piperonal did not react with nitromethane using the same catalyst.

Worrall found that an α-nitrostilbene will react with another molecule of the nitro alkane to form **7** and **8**.[8] A



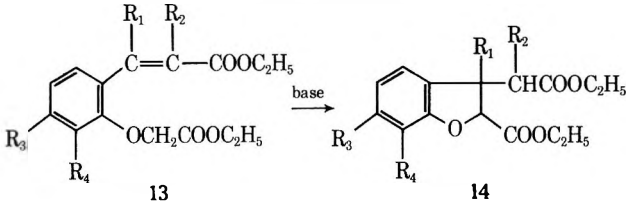
trace of water was necessary for formation of these products. Robertson reasoned that, to eliminate these side products, the water could be removed by forming the Schiff base before reacting with the nitro alkane; then acetic acid was added to remove the amine which is formed when the α-nitrostilbenes were formed.

This method was applied to the ethylene ketal of 5-nitro-2-pentanone (**9**) by treating with the Schiff base of furfural and *n*-butylamine (**10**) in acetic acid at room temperature for 40 hr; this gave a 72% yield of compound **11** in crystalline form, mp 93–95°. The structure **11** was supported by ir, nmr, mass spectral, and elemental analytical data. The ethylene ketal was hydrolyzed in 10%



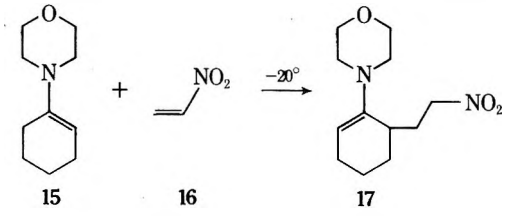
HCl solution to give 1-(2-furyl)-2-nitro-1-hexen-5-one (**12**) in 85% yield, mp 63.5–64.5°; the compound was characterized as above.

The next step was an internal Michael reaction involving the α,β-unsaturated nitro group of the molecule as acceptor and the methyl ketone part as donor. Nitro compounds effectively activate a double bond for such an addition and there are a number of examples of such Michael additions in the literature.[9] An internal Michael reaction has been reported by Koelsch on compounds such as **13** to form compounds of the structure **14**.[10] He found that this cyclization was not subject to the inhibiting effect by substituents on the α- and β-carbon atoms as are intermolecular Michael reactions. The yields obtained indicated that the reaction was essentially complete, with no unfavorable equilibrium apparent.



A variety of conditions was tried to effect the cyclization of **12**. Conditions which were strong enough to abstract the proton from the $CH_3C{=}O$ ($pK_a \cong 20$)[11] resulted in tars, probably owing to the high reactivity of the nitro olefin. A method was then needed which would produce a good nucleophilic center at the methyl carbon and also be mild enough to prevent polymerization of the nitro olefin. An enamine intermediate seemed to fit these qualifications. Enamines have been reported to be efficient nucleophiles in the Michael reaction.[12]

Kuehne and Foley have reported the Michael addition of the enamine **15** to nitroethylene (**16**) to give the product **17** in 80% yield.[13] The weak base morpholine was used



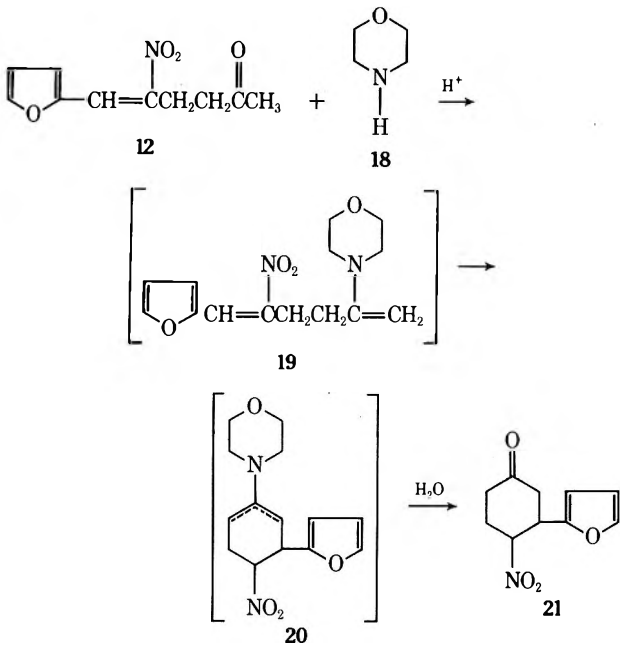
because it was unlikely to cause polymerization of nitroethylene.

Application of Stork's conditions[14] with morpholine to **12** caused the disappearance of the starting ketone and appearance of a peak which was probably the enamine, as shown by vpc analysis. The enamine was then hydrolyzed by refluxing with water and benzene overnight. After work-up, an oil resulted which was purified by column chromatography on silica gel. A crystalline substance (**21**) resulted in 30–40% yield, mp 76–77.5°. The reaction is thought to go through the route shown.

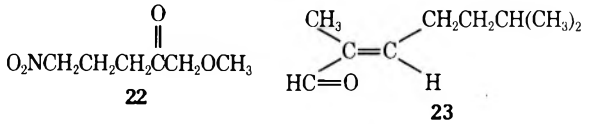
The enamine **19** is formed, which quickly cyclizes under the reaction conditions to the enamine **20**; this is then hydrolyzed to give the product **21**.

The infrared spectrum for 3-(2-furyl)-4-nitrocyclohexanone (**21**) showed absorptions of 1710 cm^{-1} for the carbonyl and 1540 cm^{-1} for the C-NO_2 stretch. The nmr spectrum was consistent with the assigned structure (see Experimental Section). A satisfactory elemental analysis was obtained and the mass spectrum yielded a molecular ion at *m/e* 209. A decoupling experiment showed that the coupling constant for the protons in the 3 and 4 positions of **21** is 8.5 Hz, which is in good agreement with that expected for a trans diaxial configuration for these two protons.[15] This configuration was expected since the diequatorial configuration of the two substituents should be the more stable.

To prepare compounds in the fumagillin series,[16] by the general scheme leading to **21**, 1-methoxy-5-nitro-2-penta-

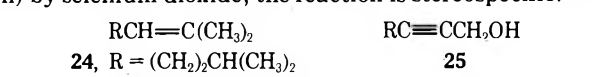


none (**22**) and *trans*-2,6-dimethyl-2-heptenal (**23**, aldehyde group trans to the alkyl groups) would be suitable components. Although the condensation of **22** and **23** was not carried out, both **22** and **23** were synthesized by practical methods, and the procedures will be described briefly, because they represent a considerable amount of experimentation, in which numerous approaches were examined.



Compound **22** was prepared in 50% yield by the addition of nitromethane (in large excess) to methoxymethyl vinyl ketone,[17] with Triton B as base.[18] Numerous attempts to generate the vinyl ketone *in situ* from various precursors, and to add nitromethane in one step, were unsuccessful.[19] The use of other bases[4] for catalyzing the addition of nitromethane to the vinyl ketone was unsatisfactory.

The unsaturated aldehyde **23** was made by oxidizing the unsaturated hydrocarbon **24** (prepared by a Wittig reaction) by selenium dioxide; the reaction is stereospecific.[20]



The procedure of Corey[21] for reduction, iodination, and methylation of propargylic alcohols was unsatisfactory, giving a mixture of the 2- and 3-iodoallylic alcohols. Another procedure,[21] designed to yield the carboxylic acid corresponding to **23**, gave a mixture of cis and trans isomers, separated only with difficulty.

Experimental Section[22]

5-Nitro-2-pentanone (3). 5-Nitro-2-pentanone was made as described except that a 1-hr reflux was used instead of a 10-hr reflux.[4] Starting with 160 g of nitromethane and 25 g of methyl vinyl ketone, a yield of 22.3 g (48%) of the desired product was obtained, bp 76° (0.25 mm) [lit. bp 85° (0.1 mm)].[4] The nmr spectrum gave peaks at δ 2.13 (s, 3 H, O=CCH$_3$), 2.1–2.8 (m, 4 H, CH$_2$CH$_2$C=O), and 4.41 (t, 2 H, O$_2$NCH$_2$).

The ethylene ketal of 5-nitro-2-pentanone (**9**) was prepared by refluxing 22.3 g of the nitro ketone with 30 ml of ethylene glycol, 100 ml of benzene, and a trace of *p*-toluenesulfonic acid for 19 hr with a water separator; the benzene solution was washed several times with a saturated solution of sodium bicarbonate and then with water. The combined water solutions were washed with chloroform and this was added to the benzene solution. The combined organic solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The ketal was used without further purification. The nmr and ir spectra were consistent with the structure of this compound.

Schiff Base of Furfural (10). To a 250-ml round-bottom flask were added 25 g (0.26 mol) of freshly distilled furfural, 19 g (0.26 mol) of *n*-butylamine, and 100 ml of benzene. The flask was fitted with a water separator and allowed to reflux until the proper amount of water had been collected (about 3 hr). The solvent was then removed under reduced pressure and the Schiff base was used without any further purification. The nmr and ir spectra were consistent with the structure of this compound.

1-(2-Furyl)-2-nitro-1-hexen-5-one 5-Ethylene Ketal (11). A procedure similar to that of Robertson was used.[6] To a solution of the ketal of 5-nitro-2-pentanone made above in 30 ml of glacial acetic acid was added 28.3 g of the Schiff base. The flask was purged with nitrogen and the solution was allowed to stir at room temperature under a nitrogen atmosphere. After 40 hr, the crystals in the solution were separated by suction filtration and washed with cold ethanol. More crystals were obtained by pouring the filtrate over cracked ice, separating the crystals, and washing with cold ethanol. The total yield was 31.2 g (72%) of yellow crystals, mp 93–95° (from ethanol). The absorptions in the nmr spectrum are δ 1.40 (s, 3 H, CH$_3$), 1.94 (m, 2 H, CH$_2$), 3.14 (m, 2 H, CH$_2$C=C), 3.99 (s, 4 H, OCH$_2$CH$_2$O), 6.60 (q, 1 H, 4-furan proton), 6.94 (d, 1 H, 3-furan proton), 7.65 (d, 1 H, 5-furan proton), and 7.82 (s, 1 H, CH=C). An ir spectrum gave peaks at 2980 and 2880 (C–H stretch), 1650 (C=C stretch), and 1510 cm^{-1} (nitro). A mass spectrum gave a molecular ion at *m/e* 253.

Anal. Calcd for C$_{12}$H$_{15}$NO$_5$: C, 56.91; H, 5.97. Found: C, 56.70; H, 6.11.

1-(2-Furyl)-2-nitro-1-hexen-5-one (12). The ethylene ketal of 1-(2-furyl)-2-nitro-1-hexen-5-one (**11**, 28.9 g) was refluxed for 1 hr with 100 ml of 10% HCl and 100 ml of benzene. A conventional work-up gave, after removal of solvent, 20.8 g (84%) of yellow needles, mp 63.5–64.5°. The absorptions of the nmr spectrum are δ 2.12 (s, 3 H, CH$_3$), 2.65 (m, 2 H, CH$_2$C=O), 3.18 (m, 2 H, CH$_2$C=C), 6.50 (q, 1 H, 4-furan proton), 6.80 (d, 1 H, 3-furan proton), 7.56 (d, 1 H, 5-furan proton), and 7.71 (s, 1 H, CH=C). The ir spectrum gave peaks at 1700 (carbonyl) and 1510 cm^{-1} (nitro).

Anal. Calcd for C$_{10}$H$_{11}$NO$_4$: C, 57.41; H, 5.30. Found: C, 57.50; H, 5.30.

3-(2-Furyl)-4-nitrocyclohexanone (21). A 250-ml three-neck round-bottom flask was equipped with a water separator with condenser and a nitrogen inlet tube. The system was purged with nitrogen and the reaction was run under a nitrogen atmosphere. To the flask were added 5 g (0.024 mol) of 1-(2-furyl)-2-nitro-1-hexen-5-one (**12**), 65 ml of benzene, 3.1 g (0.036 mol) of morpholine, and a catalytic amount of *p*-toluenesulfonic acid. The solution was refluxed for 20 hr. The enamine was hydrolyzed by adding 50 ml of water to the solution and refluxing overnight. The benzene solution was separated from the water and the water layer was extracted with ether. The ether solution was added to the benzene solution and the combined organic solution was washed with 5% HCl solution, saturated sodium bicarbonate solution, and water. The combined water washings were extracted once with ether and this was added to the organic solution. This solution was then dried over magnesium sulfate and the solvent was removed under reduced pressure, yielding a dark oil.

The oil was purified by chromatography on silica gel (activity grade 1). The solvent used at the start was a 50:50 benzene–hexane mixture. The first fractions collected contained the remainder of the starting ketone. The fractions became less colored and the solvent was gradually changed to 100% benzene. The column itself became quite dark, while the liquid remained a very pale yellow. The solvent was removed under reduced pressure, yielding 2.1 g of crude product. This was further purified by sublimation at 70° (0.05 mm) to yield 1.6 g (32%) of white crystals, mp 76–77.5°. The absorptions of the nmr spectrum are δ 2.54 (m, 4 H, CH$_2$CH$_2$), 2.76 (d, 2 H, CH$_2$C=O), 4.00 (q, 1 H, CHCHNO$_2$), 5.11 (m, 1 H, CHNO$_2$), 6.29 (d, 1 H, 3-furan proton), 6.32 (m, 1 H, 4-furan proton), and 7.39 (m, 1 H, 5-furan proton). The ir spectrum showed peaks at 1710 (carbonyl) and 1540 cm^{-1} (nitro). The mass spectrum gave a molecular ion at *m/e* 209.

Anal. Calcd for C$_{10}$H$_{11}$NO$_3$: C, 57.41; H, 5.30. Found: C, 57.22; H, 5.67.

Methoxymethyl Vinyl Ketone.[17] 1,4-Dimethoxy-2-butanone[23] (10.0 g) was heated and stirred with 12.5 g of sodium benzoate plus a small amount of hydroquinone in a flask fitted with a dis-

tillation head and condenser. The temperature in the distillation head rose to 130° at the end of the distillation. The liquid collected weighed 6.0 g. This was a mixture of methanol, water, and a small amount of starting material, and the desired methoxymethyl vinyl ketone was estimated by nmr to be 2.9–3.0 g. Peaks in the nmr spectrum (crude mixture) for methoxymethyl vinyl ketone are δ 3.36 (s, 3 H, $-OCH_3$), 4.26 (s, 2 H, $-CH_2O-$), 5.86 (d of d, 1 H, C=CH), and 6.38 (m, 2 H, CH_2=C). The liquid was dried over magnesium sulfate for use in the reaction with nitromethane.

1-Methoxy-5-nitro-2-pentanone (22). To a 1-l. round-bottom three-neck flask, fitted with an addition funnel, condenser, and nitrogen inlet, were added 480 g (~100 equiv) of nitromethane, 150 ml of ether, and 8 ml of 40% Triton B in methanol.[18] This was heated to reflux, and a solution containing approximately 7.9 g of methoxymethyl vinyl ketone in ether was added dropwise. The resulting mixture was allowed to reflux for 20 hr. The solution was cooled, the solvent was removed under reduced pressure, and the residue was taken up in chloroform, and this solution was washed with 5% HCl solution, 10% sodium bicarbonate, and water. The solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was distilled, yielding 6.3 g (50%) of a pale yellow liquid, bp 86–89° (0.05 mm). An ir spectrum (liquid film) showed peaks at 1720 (carbonyl) and 1540 cm^{-1} (nitro). The mass spectrum gave a molecular ion at m/e 161. The nmr spectrum was in agreement with structure **22**. An elemental analysis was performed on the semicarbazone, mp 145–146° (from water).

Anal. Calcd for $C_7H_{14}N_4O_4$: C, 38.53; H, 6.47. Found: C, 38.67; H, 6.54.

4-Methylpentanal was prepared in 35% overall yield by the reaction of isoamylmagnesium bromide on ethyl orthoformate, followed by hydrolysis of the acetal, and isolation of the aldehyde as the bisulfite product;[24] the free aldehyde had bp 120–122° (reported[25] bp 124°).

2,6-Dimethyl-2-heptene (24). A three-neck 250-ml round-bottom flask was fitted with a mechanical stirrer, rubber septum, and condenser with nitrogen inlet. The system was purged with nitrogen and a nitrogen atmosphere was maintained throughout the reaction. To the flask was added 43.2 g (0.1 mol) of isopropyltriphenylphosphonium iodide[26] in 100 ml of ether. The suspension was cooled in an ice bath and 0.11 mol of *n*-butyllithium was added by means of a syringe through the rubber septum. The solution was allowed to warm to room temperature and was then stirred at this temperature for 3 hr. The rubber septum was replaced with a dropping funnel and 10 g (0.1 mol) of 4-methylpentanal in 20 ml of ether was added dropwise. This was allowed to stir at room temperature for 48 hr. During this time the triphenylphosphine oxide precipitated out of the solution. The liquid was then separated from the solid by filtration and the solid was washed several times with petroleum ether (bp 30–60°). The solvent was removed from the solution under reduced pressure. The product was distilled to yield 5.2 g (41%), bp 135–136° (lit. bp 142–143°).[27] The nmr spectrum (neat) showed absorptions at δ 0.90 (d, 6 H, CH_3CHCH_3), 1.13–1.54 (m, 3 H, CH_2CH), 1.61 (s, 3 H, methyl trans to alkyl), 1.68 (s, 3 H, methyl cis to alkyl), 2.04 (q, 2 H, $C=CCH_2$), and 5.25 (m, 1 H, C=CH).

trans-**2,6-Dimethyl-2-heptenal (23).** A procedure similar to that of Bhalerao and Rapoport[20] was used. To a 100-ml round-bottom flask were added 5.2 g (0.041 mol) of 2,6-dimethyl-2-heptene, 9.6 g (0.044 mol) of selenium dioxide, and 70 ml of ethanol. The mixture was allowed to reflux for 15 hr. The solvent was removed under reduced pressure and the residue was dissolved in ether. This was then washed with a saturated sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was removed under reduced pressure. The product was distilled to give 2.0 g (35%), bp 82–85° (10 mm). The ir spectrum (CCl_4) showed peaks at 2940 (C–H stretch), 1670 (carbonyl), and 1400 cm^{-1} (C–H bend). The mass spectrum gave a molecular ion at m/e 140.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.39; H, 11.41.

The nmr showed absorptions at δ 0.92 [d, 6 H, $(CH_3)_2CH$], 0.95–1.6 [m, 3 H, $(CH_3)_2CHCH_2$], 1.69 [s, 3 H, $C=C(CH_3)$], 2.32 (q, 2 H, $CH_2C=C$), 6.31 (m, 1 H, HC=C), and 9.20 (s, 1 H, CHO).

Registry No.—**3,** 22020-87-7; **9,** 19639-74-8; **10,** 51004-05-8; **11,** 51004-06-9; **12,** 51004-07-0; **21,** 51004-08-1; **22,** 51004-09-2; **22** semicarbazone, 51021-62-6; **23,** 51004-04-7; **24,** 5557-98-2; furfural, 98-01-1; *n*-butylamine, 109-73-9; methoxymethyl vinyl ketone, 43042-58-6; 1,4-dimethoxy-2-butanone, 25680-86-8; 4-methylpentanal, 1119-16-0; isoamyl bromide, 107-82-4; ethyl orthoformate, 122-51-0; isopropyltriphenylphosphonium iodide, 24470-78-8.

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Vinyl Grignard Reagents. Rearrangement of the Cyclopropylidenephenylmethylmagnesium Bromide

Jean-Luc Derocque* and Freyja-Beate Sundermann

Institut für Organische Chemie, Universität des Saarlandes, 66 Saarbrücken, West Germany

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The reactions of cyclopropylidenephenylmethyl bromide (I-Br), 1-phenyl-2-methylpropenyl bromide (V-Br), and 2-phenylcyclobutenyl bromide (III-Br) with magnesium in diethyl ether (DEE) and tetrahydrofuran (THF), and with organotin hydrides, were investigated. The 2-phenylcyclobutenylmagnesium bromide (III-Mg) was found tc be stable, while the cyclopropylidenephenylmethylmagnesium bromide (I-Mg) yielded the ring-cleavage product 4-phenylbut-3-ynylmagnesium bromide (II-Mg). A radical-like and a four-centered cyclic reaction mechanism are proposed for the ring-cleavage reaction.

Adjacent aryl groups and double bonds are able to stabilize cations, radicals, and anions by delocalization through their π-orbital(s) system. It has been extensively shown in the literature that stabilization of a cation by a cyclopropyl substituent may be greater than that by a vinyl group.[1]

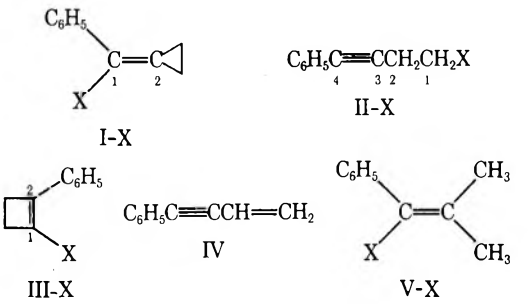
The question of the influence of a cyclopropyl substituent on an adjacent anion, or a carbon–metal bond, has also been raised.[2] From the results published in the literature it can be concluded that stabilization exists and may be observed especially if additional effects, such as conjugative stabilization through phenyl ring(s)[2f,g] or nonconjugative stabilization in the α-cyclopropylvinyl Grignard reagent,[3] are also present. This ability has been attributed to the low-lying vacant MO of the cyclopropyl bond (conjugative stabilization) and to the relatively high s character of bonds from a cyclopropyl substituent, which should raise its electronegativity (nonconjugative stabilization).[2j]

Therefore it seems reasonable to us that the cyclopropylidenephenylmethyl anion (I^-) would be a stable species, as is the case for the corresponding cation.[4] Since intramolecular additions of organometallic compounds to double and triple bonds have often been reported,[2,5] we expected that, if 4-phenylbut-3-ynylmagnesium bromide (II-Mg) would cyclize, the cyclopropylidenephenylmethyl Grignard reagent (I-Mg) would be preferable to the 2-phenylcyclobutenyl Grignard reagent (III-Mg). Although the ring strain for the formation of I-Mg would greatly increase the energy of the transition state, our suggestion was reinforced by the fact that cyclopropylphenylcarbinyl metal species are true intermediates in the rearrangement of homoallylic Grignard reagents.[2f,g] Moreover, in addition to the stabilization of the carbon–metal bond in I-Mg by the phenyl and the cyclopropyl ring, cyclization of II-Mg to the vinylic Grignard reagent I-Mg might be favored to the extent that the energy of the transition state could reflect the greater stability of the sp^2 compared to the sp^3 carbon–metal bond in II-Mg.

However, we observed[6] that 4-phenylbut-3-ynylmagnesium bromide (II-Mg) did not rearrange to any of the cyclic products I-Mg or III-Mg by refluxing in THF.

We aim to discuss here the comparative stability of the vinylic Grignard reagents I-Mg and III-Mg (Scheme I).

Scheme I[a]



[a] In the text the reference number of a compound followed by symbols (Mg for -MgBr, -Br, -H, -D, etc.) or by the radical or the anion signs describes that compound with the corresponding substituent instead of X.

Results and Discussion

Cyclopropylidenephenylmethylmagnesium Bromide and Radical. Cyclopropylidenephenylmethyl bromide (I-Br) was added with a standard (xylene mixture) to a suspension of magnesium (5% excess) preheated at the desired temperature in the solvent (THF or DEE) in a nitrogen atmosphere. After the reaction had started, samples were pipetted out at time intervals and quenched with D_2O. Glc and glc–mass spectral analysis led to the following observations (see Tables I and II and Scheme II). During the formation of the Grignard reagent I-Mg, four other products are formed along with I-Mg: cyclopropylidenephenylmethane (I-H), 4-phenylbut-3-ynylmagnesium bromide (II-Mg), 1-phenylbutyne (II-H), and 1-phenylbut-3-enyne (IV).

After it has been generated in the medium, the concentration of I-Mg decreases while the concentrations of 4-phenylbut-3-ynylmagnesium bromide (II-Mg) and cyclopropylidenephenylmethane increase, showing that I-Mg undergoes two competitive reactions: a ring cleavage rearrangement to form II-Mg and a hydrogen–metal exchange reaction with the solvent or other species present in the medium, yielding the hydrocarbon I-H. A further slow decrease of the deuterium incorporation in the II-H–II-D mixture shows that 4-phenylbut-3-ynylmagnesium bromide (II-Mg) abstracts hydrogen to give the corresponding

Scheme II

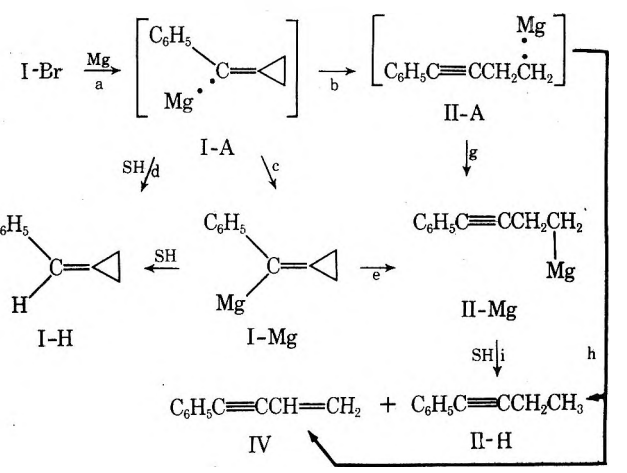


Table I
Distribution[a] of the Products Formed during the Generation of the Grignard Reagent I-Mg and after 20–25-hr Reaction Time

Run	Solvent	Temp, °C	Time	% I-Mg	% I-H	% II-Mg	% II-Hg	% IV	% of the ring cleavage
1	THF	66	*c*	34	25	30	4	7	41
			b	0	25	12	60	3	75
2	THF	37	*c*	56	19	12	3	10	25
			b	0	42	1	48	9	58
3	DEE	37	*c*	19	24	31	20	6	57
			b	0	37	1	58	4	63

[a] In percentages measured from the gas chromatogram of the mixtures. Standard deviation: ±5% of the given value. [b] After 20-25-hr reaction time. [c] About 10–15 min after the addition of the bromide, when most of the magnesium had disappeared.

Table II
Rates[a] of Ring-Cleavage Reaction and Hydrogen–Metal Exchange of I-Mg and II-Mg after They Have Been Generated in the Medium

Run	Solvent	Temp, °C	k_e for I-Mg ⟶ II-Mg	k_f for I-Mg ⟶ I-H	k_i for II-Mg ⟶ II-H
1	THF	66	1.7×10^{-4}	*b*	1.7×10^{-5}
2	THF	37	3.6×10^{-5}	1.2×10^{-5}	
3	DEE	37	4.1×10^{-5}	4.1×10^{-5}	6.4×10^{-6}

[a] Standard deviation: ±15% of the given value, k in reciprocal seconds. [b] The hydrogen–metal exchange of I-Mg is much slower than the ring-cleavage reaction (k_e) and the concentration of I-H remains constant (see Table I).

hydrocarbon (II-H). As for the 1-phenylbut-3-enyne (IV) formed during the reaction of cyclopropylidenephenylmethyl bromide (I-Br) with magnesium, its concentration remains constant at the beginning and then decreases slowly, probably because of further polymerization under the conditions of the reaction. Remarkable is the relatively high rate of formation of the hydrocarbons I-H and II-H at the beginning of the reaction, while the rates of hydrogen abstraction from the solvent by I-Mg and II-Mg decrease considerably after they have been generated in the medium (see Tables I and II).[7] Measurement and calculation of the rate constants for these different processes (see Table II) indicates that the rate of rearrangement of the cyclopropylidenephenylmethylmagnesium bromide (I-Mg) to the open-chain Grignard reagent II-Mg is little influenced by changing from THF to DEE (see runs 2 and 3, Table II). In refluxing THF (run 1) the ring cleavage (k_e) is much faster than the abstraction of hydrogen from the solvent (k_f), and the concentration of cyclopropylidenephenylmethane (I-H), which has been formed during the generation of the Grignard reagent I-Mg, remains constant.[8] Thus in boiling THF the only reaction of I-Mg to take place is the ring-cleavage reaction.

From our results it appears, therefore, that two different processes account for the rearrangement of the forming and the already formed Grignard reagent I-Mg.

Since evidence is accumulating that radicals are true intermediates in the formation and further reaction of Grignard compounds,[9] radical-induced reactions (and rearrangement when possible) are expected to occur, at least partially, during the formation of Grignard reagents. This is compatible with the same order of intramolecular cyclization ability which has been found during the formation of unsaturated Grignard reagents and when the corresponding radicals were generated from the halides with tin hydrides.[10] It was therefore of interest to study the behavior of both cyclopropylidenephenylmethyl radical (I°) and 4-phenyl-3-ynyl radical (II°). Crandall and Keyton[11] observed no intramolecular cyclization of the homopropargyl radical generated from 4-phenylbut-3-ynyl bromide (II-Br) with tributyltin hydride. We have reinvestigated their experiment and our results confirm their observation. Cyclopropylidenephenylmethyl radicals (I°) were generated from I-Br and tributyltin hydride in DEE at room temperature. After 15 min, glc analysis of the ethereal solution showed the presence of 1-phenylbutyne (II-H) and cyclopropylidenephenylmethane (I-H) in the ratio of 9:1, and a small amount (1–2%) of 1-phenylbut-3-enyne (IV). The high percentage of 1-phenylbutyne (II-H) is not surprising on account of the known instability of cyclopropylcarbinyl radicals[12] and the higher stability of alkyl radicals compared to that of the vinyl radicals[13] under the conditions of the reaction. The presence of cyclopropylidenephenylmethane (I-H, 9%) might be due to some stabilization of the radical I° by the adjacent phenyl group which enhances its lifetime and permits its reaction with a hydrogen radical before rearranging to the 4-phenylbut-3-ynyl-radical (II°). This was supported by increasing the hydrogen radical concentration in the reaction mixture through addition of thiophenol or by carrying out the reaction in neat tributyltin hydride. The corresponding II-H/I-H ratios were 4:1 for these two reactions (see Experimental Section, Table III). In all these experiments no 1-phenylcyclobutene (III-H) could be detected in the gas chromatograms of the reaction mixtures.

In another run, tributyltin deuteride was added dropwise to a solution of I-Br in refluxing THF. Glc–mass spectral analysis of the solution showed that no hydrogen incorporation in the 4-deuterio-1-phenylbutyne (II-D) was detectable under the conditions of measurement but that the cyclopropylidenedeuteriophenylmethane (I-D) contained 7–10% of the undeuterated hydrocarbon (I-H). Thus abstraction of hydrogen from the solvent (THF) by the cyclopropylidenephenylmethyl radicals probably does occur, at least partially. Small quantities of deuterated cyclopropylphenylmethane and deuterated 1-phenylbut-1-ene could be detected in the reaction mixture.[14]

The extensive ring cleavage to form the 4-phenylbut-3-ynylmagnesium bromide (II-Mg) and the simultaneous formation of the disproportionation product 1-phenylbut-3-enyne (IV) along with 1-phenylbutyne (II-H) found during the generation of cyclopropylidenephenylmethylmagnesium bromide (I-Mg) are comparable with the products obtained in the radical-induced reaction of cyclopropylidenephenylmethyl bromide (I-Br) with tributyltin hydride.

Three distinctly different types of mechanism may be reasonably conceived for the intramolecular cyclization and the related ring-cleavage reaction of organometallic compounds:[15] (a) the polarized covalent carbon–metal bond may ionize to a carbanion, which then rearranges; (b) the carbon–metal bond may dissociate to an univalent metal species and a free radical which undergoes rearrangement before recombination; (c) a concerted cyclic process may occur, induced by the formation of a metal π complex in which changes in carbon–carbon bonding occur simultaneously with transfer of the metal from one carbon to another.

According to our results (Scheme II) it seems reasonable to discuss the process of ring cleavage that we observed *during the formation of the Grignard I-Mg* in terms of a radical-induced mechanism. The occurrence or nonoccurrence of a radical-induced ring-closure reaction is one based on orbital overlap consideration. For ring closure to be favorable, the p orbital containing the odd electron and the orbital of the multiple bond must be close enough together and of proper orientation for good overlap to take place. For ring cleavage, a similar orbital overlap requirement is also necessary between the orbitals of the radical and the breaking carbon–carbon bond. This has been emphasized by the results of Friedrich and Holmstead[16] on the direction of ring opening in the benzobicyclo[4.1.0]hepten-2-yl radical. It is evident that this orbital overlap is maximal for ring opening in the cyclopropylidenephenylmethyl radical (I°). The ring-cleavage reaction must also be energetically favored owing to ring-strain release in the transition state and the greater stability of primary radicals compared to vinyl radicals.[13]

To explain our results we have envisaged the pathways shown in Scheme II, which are based on the mechanism proposed by Walborsky and Young.[17]

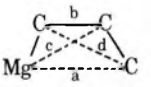
During the one-electron transfer from magnesium to halogen a reactive radical pair I-A is formed, which may react further according to three distinct pathways: (a) it can collapse to the more stable Grignard reagent I-Mg where the bonding electrons have reorganized themselves to form a carbon–metal bond; (b) it can undergo a ring-cleavage reaction to form the open-chain radical pair II-A [the latter can either disproportionate to form 1-phenylbut-3-enyne (IV) and 1-phenylbutyne (II-H), collapse to the Grignard reagent II-Mg, or abstract hydrogen to form II-H]; (c) I-A can also abstract a hydrogen radical to form I-H.

The Grignard reagent I-Mg *when formed* undergoes further ring cleavage to the more stable primary Grignard reagent II-Mg, but with a rate constant smaller than that observed for the similar rearrangement from the reactive species I-A. I-Mg can also abstract hydrogen from the solvent to yield I-H and it *is the relative rates of these two competitive reactions which determine the I-H:II-H ratio at the end of the reaction, i.e.,* when no more cyclopropylidenephenylmethylmagnesium bromide (I-Mg) is present in the mixture (see Table I, footnote *b*). At the end, 4-phenylbut-3-ynylmagnesium bromide (II-Mg) abstracts hydrogen to form II-H.

The formation of 4-phenylbut-3-ynylmagnesium bromide from cyclopropylidenephenylmethylmagnesium bromide could also be explained through an equilibrium between I-A and I-Mg. However, this would have increased simultaneously the concentration of I-H, II-H, and IV in the same proportion as that observed during the formation of the Grignard reagent I-Mg. We found that this was not the case and that the concentration of 1-phenylbut-3-enyne (IV) remained unchanged. Moreover, the rate of disappearance of cyclopropylidenephenylmethylmagnesium bromide (I-Mg) in refluxing THF equals that of appearance of 4-phenylbut-3-ynylmagnesium bromide (II-Mg).

Since an equilibrium between the species I-A and I-Mg must be excluded, another process must account for the further rearrangement of I-Mg to II-Mg. The small rate difference observed for the ring-cleavage reaction by replacing DEE with a solvent of higher dielectric constant, such as THF (see Table II, runs 2 and 3), is not compatible with an ionic mechanism in which a large variation in charge separation takes place when going from the ground state to the transition state. A concerted four membered ring process similar to the one proposed by Hill and Davidson[15] seems to be much more consistent with our results. In this process the energies which are necessary to form the common activated complex from the open-chain and cyclic products depend, among other factors, on the distance between the four interacting atoms. Measurements on Dreiding models of the average distances between these atoms in the homoallyl–cyclopropylcarbinyl and homopropargyl–cyclopropylidene systems gave the following results [Scheme III, L (average) = $(a + b + c + d)/4$].

Scheme III



	L		L	ΔL
Homoallyl	2.90 Å	Cyclopropylcarbinyl	2.82 Å	0.08
Homopropargyl	3.02 Å	Cyclopropylidene	2.50 Å	0.52

In the homoallyl–cyclopropylcarbinyl rearrangement the change in average distances is small relative to that in the homopropargyl–cyclopropylidene system (about six times greater for the latter). The geometry change between ground state and transition state must thus be much more important for the latter compared to the former and cyclization must require more drastic conditions. Moreover, in the cyclopropylidenemethyl Grignard reagent I-Mg the four centers are even closer together (2.5 Å) than in the cyclopropylcarbinyl system (2.82 Å) and the interaction between the orbitals, and thus the change in bondings, must be favored to form the open-chain product II-Mg.

The total rearrangement of cyclopropylidenephenylmethylmagnesium bromide (I-Mg) to the open-chain compound II-Mg and the irreversibility of this process does, however, not necessarily reflect the absence of stabilization of the adjacent vinyl carbon–metal bond by the cyclopropylidene substituent in I-Mg. For this a comparison with the properties of the homologous 1-phenyl-2-methylpropenylmagnesium bromide (V-Mg) should be worthwhile.

We may indeed assume that the more stable a Grignard reagent, the faster the radical pair (for instance I-A, Scheme II) will collapse to the Grignard (I-Mg), and consequently the concentration of the corresponding hydrocarbon (I-H) formed during that process (pathways c and d, Scheme II) will be smaller. In other words, the more stable the Grignard reagent, the smaller the ratio for the rate constants k_d/k_c. By deuterolysis of the Grignard mixtures from the cyclopropylidenephenylmethyl bromide (I-Br) and from the 1-phenyl-2-methylpropenyl bromide (V-Br) in refluxing THF just after most of the magnesium had disappeared in the solution, the ratios I-H:I-Mg and V-H:V-Mg were 0.74 and 0.18, respectively. This shows that the collapse reaction of the radical pairs I-A and V-A to the Grignards I-Mg and V-Mg is four times faster for compound V than for I. It could be objected that this difference reflects only the greater ability of the radicals I° to

abstract protons compared to that of radicals V°. However, in the hydrogen-abstraction reactions of cyclopropylidenephenylmethyl bromide (I-Br) and 1-phenyl-2-methylpropenyl bromide (V-Br) with tributyltin deuteride in refluxing THF, the ratios I-H:I-D and V-H:V-D were found to be 0.1–0.08 and 0.08–0.06, respectively, indicating that, at the worst, I° abstracts hydrogen 1.6–1.7 times faster than V°. By taking this into consideration, it still gives a rate constant 2.5 times larger for the collapse reaction of the radical pair V-A to the Grignard reagent V-Mg, compared to that of radical pair I-A to the Grignard I-Mg. This result would mean that, of the two Grignards I-Mg and V-Mg, the latter is more stable, and therefore that there is no stabilizing effect of the cyclopropylidene substituent on the adjacent carbon–metal bond in cyclopropylidenephenylmethylmagnesium bromide (I-Mg).

This surprisingly contradicts the weak stabilization observed elsewhere on metal–carbon bonds by conjugative interaction with a cyclopropane ring.[2,3] According to recent INDO calculations, Danen[18] concluded that, in general, C–C hyperconjugation is more favorable than C–H hyperconjugation in cationic and radical species, while the reverse is true for carbanions. If some correlations may exist in the causes of stabilization of metal–carbon bond and anionic charge, the irreversible isomerization of homoallenyl Grignard reagents to α-cyclopropyl vinyl Grignard reagents[3] might therefore be due to the partial stabilization of the metal–carbon bond through C–H rather than C–C hyperconjugation. Such an influence is indeed excluded in the cyclopropylidene system I.

It is a well-known fact that vinyl anions and carbon atoms in vinyl organometallic compounds are sp^2 hybridized and that vinyl metal compounds are geometrically stable.[19] Consequently, in the Grignard compound I-Mg the orbital of the carbon–magnesium bond interacts only with one of the two carbon–carbon bond orbitals of the adjacent cyclopropane ring. This must induce an *unsymmetrical* delocalization of the charges in the ring, which favors its opening, and this is in contrast with the symmetrical delocalization of the charges in the cyclopropylidene cation.

For the nonconjugative stabilization of the cyclopropyl ring on adjacent anion and carbon–metal bonds, it has been proposed that the relatively high s character of the bonds from a cyclopropyl substituent should raise its electronegativity.[2j] If this is true for the C_1–C_2 bond in I-X, which may have a hybridization between sp^2 and sp, there is no apparent reason for the hybridization of the carbon–metal bonding to have a higher s character. On the contrary, higher s character of the C_1–C_2 bonding should raise the p character in the C_1–metal orbital and therefore decrease its electronegativity and thus the stabilization of a negative charge (or negative polarization) on that carbon atom.[20]

2-Phenylcyclobutenylmagnesium Bromide, Radical, and Anion. Only 1-phenylcyclobutene (III-H) is formed by hydrolysis of the reaction mixture from 2-phenylcyclobutenyl bromide (III-Br) and magnesium in boiling THF or DEE. Deuterolysis of the Grignard solution in refluxing THF after most of the metal had disappeared yielded the corresponding hydrocarbon with 80–85% deuterium incorporation (III-D). By refluxing further in the same solvent we observed a slow decrease of the III-D:III-H ratio (k = $5.8 \times 10^{-5} \pm 0.5$),[7] showing that 2-phenylcyclobutenylmagnesium bromide (III-Mg) had exchanged its metal for hydrogen.

III-Br does not react at room temperature with either tributyltin or triphenyltin hydride in DEE or undiluted. Without solvent, a slow reaction takes place at higher temperature (80–100°) and yields 1-phenylcyclobutene (III-H) as the main product along with some phenylcyclobutane (5–10%).[14] No trace of isomeric compounds (such as I-H and/or II-H) was detectable in the gas chromatograms of the reaction mixtures. The slow reactions observed with tin hydride suggest a relatively high energy of activation in the transition state for the formation of the 2-phenylcyclobutenyl radical (III°) and are comparable with the small rate constants that we have reported for the solvolysis reaction of III-Br.[4]

Treatment of 2-phenylcyclobutenylmagnesium bromide (III-Mg) in THF with mercury(II) bromide gave the 2-phenylcyclobutenylmercuric bromide (III-HgBr), which has been isolated and characterized. III-HgBr was treated at 0° with a suspension of K/Na alloy[2g] in THF. Only 1-phenylcyclobutene (III-H, 80–90%) and phenylcyclobutane (20–10%) were formed by hydrolysis after 15 min.[21] The concentration of both compounds was decreased by stirring further the reaction mixture at 0°. Only polymeric materials were formed and at no time could we detect any other isomeric species which could have been derived from rearrangement of the 2-phenylcyclobutenyl anion (III⁻).

From the preceding results it appears that 2-phenylcyclobutenyl Grignard reagent (III-Mg), anion (III⁻), and radical (III°) are stable under the conditions of their generation or at least do not rearrange to other isomeric species. In those systems the substituents are not in an appropriate position for stabilization, nor are orbitals with high energy (such as the carbon–carbon bond orbitals of the four-membered ring) in a geometrically favorable position for good overlap which could initiate the rearrangement of the products.

Also the geometry required by the four-membered ring increases the s character of the orbital corresponding to the C–X bond in III-X. This must favor the stabilization (nonconjugative) of the negative charge in III⁻ and of the negative polarization in the corresponding metal compound III-Mg. It explains also the high activation energy for the formation of the 2-phenylcyclobutenyl radical (III°), the odd electron of which must be in a high energy level owing to the large s character of that orbital.

Conclusions

Of the two cyclic metal species (I-Mg and III-Mg) which could have reasonably resulted from the intramolecular rearrangement of the homopropargyl Grignard reagent II-Mg, 2-phenylcyclobutenylmagnesium bromide (III-Mg) was found to be the more stable. It was, however, found elsewhere[6] that II-Mg does not rearrange to III-Mg, probably because the linear geometry requirement of the triple bond in II-Mg prevents "effective" interaction between orbitals at the C_1 and C_4 atoms. It appears thus that in the intramolecular addition process of organometallic compounds to triple bonds a chain length of at least three atoms[10] is necessary between the unsaturated center and the metal–carbon bond.

Attempts to observe cyclization of the homopropargyl anion II⁻ generated from the 4-phenylbut-3-ynylmercuric bromide (II-HgBr) and K/Na alloy[2g] have been unsuccessful owing to the occurrence of competitive reactions.[22,23]

Experimental Section

Starting Materials. The preparation of cyclopropylidenephenylmethyl bromide (I-Br), 1-phenyl-2-methylpropenyl bromide (V-Br), and 2-phenylcyclobutenyl bromide (III-Br) has been reported elsewhere.[4] Grignard reactions were carried out with commercial magnesium turnings without further purification. Solvents (THF and ether) were distilled from lithium aluminum hydride immediately before use. Tributyltin hydride and deuteride were prepared according to Van Der Kerk.[24] The method of Kuivila[25] was used for obtaining the triphenyltin hydride and deuteride.

Table III

Compd	% in DEE	% in DEE in presence of thiophenol	% in pure *n*-Bu_3SnH
I-H	9	19	20
II-H	90	76	80
IV	1	5	

Analytical Methods. Glc–mass spectral analyses were performed with a Mat-311 Varian mass spectrometer combined with a gas chromatograph, using a 10 ft × 0.125 in. 10% Carbowax 20M column. Deuterium incorporation in hydrocarbons was evaluated from the mass spectra of the compounds by repeated cyclic scans between *m/e* 100 and 140. Calculations were performed on average values obtained for the peak intensities in the region of the molecular peaks and in the region corresponding to the fragmentation of the methyl and/or CH_2D group. Pure undeuterated compounds were obtained as described before[4] and pure deuterated substances were synthesized from the bromides and organotin deuteride (see below). Mass spectral analysis by the decelerating voltage method showed that the deuterium incorporation was equal to or higher than 99.5%. In two cases the hydrocarbons formed after deuterolysis of the Grignard mixtures were separated by preparative gas chromatography. Measurement and calculation of the deuterium incorporation in these hydrocarbons either by glc or direct injection through the inlet system of the mass spectrometer gave identical results, showing that there is sensibly no separation of deuterated and undeuterated species under the gas chromatographic conditions employed.

Reaction with Magnesium Metal. The reaction vessel, containing 10% excess of magnesium, was flame dried in a nitrogen stream. The solvent was added and the mixture was preheated at the desired temperature under a nitrogen atmosphere. A solution of the bromide in the corresponding solvent was added dropwise with a standard (xylene mixture) to the stirred magnesium suspension. Aliquots were pipetted out at time intervals, quenched with D_2O (99.9%), and analyzed by glc and glc–mass spectral methods as described above.

Reaction with Organotin Hydride (and Deuteride). In a general procedure a solution of the bromide was added dropwise to an equimolecular solution of the organotin compound in the same solvent (THF or DEE). The mixture was stirred at room temperature until no more starting material was present (about 15–30 min for I-Br and V-Br) and the mixture was analyzed by glc (10 ft × 0.125 in. 10% Carbowax column). The solvent and product(s) were distilled under vacuum and purified further by preparative glc when necessary. Whenever the reactions were carried out in neat materials a 20% excess of organotin material was used. This method was employed for the preparation of the deuterated hydrocarbons from the bromides I-Br, II-Br, and V-Br with tributyltin deuteride.

Cyclopropylidenephenylmethyl Bromide (I-Br). Glc analysis of the reaction mixture of I-Br with tributyltin hydride gave the following results (Table III).

In another run a solution of tributyltin deuteride was added dropwise to a solution of I-Br in refluxing THF. Glc–mass spectral analysis gave the following hydrogen ratios for the undeuterated and deuterated hydrocarbons formed during the reaction: I-H:I-D = 0.08–0.1; II-H:II-D = 0 (no hydrogen was detectable under the condition of the analysis).

1-Phenyl-2-methylpropenyl Bromide (V-Br). In an identical run with the one described above in refluxing THF but with V-Br as starting material the ratio V-H:V-D was found to be 0.06–0.08.

2-Phenylcyclobutenyl Bromide (III-Br). III-Br does not react at room temperature with tributyltin hydride and it takes about 20 hr for the reaction to be completed in *neat* materials at 80°. The 1-deuterio-2-phenylcyclobutene (III-D) was prepared from bromide III-Br and triphenyltin deuteride as follows. A 210-mg (1 mmol) portion of III-Br and 700 mg of triphenyltin deuteride were mixed in a distillation apparatus and heated at 100° under vacuum (3–4 Torr), the receiving flask being cooled at 0°. The reaction was stopped when no more substance distilled (about 15–20 hr). Analysis of the distillate showed that it corresponded to a mixture of deuterated cyclobutane (5–10%)[14] and 1-deuterio-2-phenylcyclobutene (III-D, 90%). III-D was purified by preparative gas chromatography and was found to contain more than 99.6% of deuterium.

2-Phenylcyclobutenylmercuric Bromide (III-HgBr). A mixture of 4 g of 2-phenylcyclobutenyl bromide (III-Br) and 0.5 g of magnesium in 40 ml of absolute THF was refluxed in a nitrogen atmosphere until no more starting material was present (glc, 6 ft × 0.125 in. 10% Silicone column). The solution was cooled to room temperature, decanted from the excess of magnesium, and added dropwise at room temperature under nitrogen to a stirred suspension of 7.5 g of $HgBr_2$ in absolute THF (15 ml). The mixture was then refluxed for 2 hr, stirred for 24 hr at room temperature, and treated with 5% aqueous acetic acid. After addition of ether the organic layer was decanted, washed with water, and dried over sodium sulfate. Solvents were distilled off under vacuum and the residue was purified by crystallization in petroleum ether (bp 30–60°)–ether mixture or ethanol (white cristals, mp 114–116°): nmr ($CDCl_3$) δ 2.62 (m, 2 H), 3.17 (m, 2 H) (these two multiplets are symmetrical), 7.42 (m, 5 H); mass spectrum *m/e* 410–412 (molecular peak), 129 (100% peak).

Reaction of 2-Phenylcyclobutenylmercuric Bromide with K/Na Alloy.[2g] A solution of 100 mg of 2-phenylcyclobutenylmercuric bromide in 15 ml of absolute THF was added at 0° in a nitrogen atmosphere to a stirred suspension of K/Na alloy (40 mg K/8 mg Na) in 15 ml of absolute THF containing a standard (diisoamyl ether). Samples were pipetted out at intervals and carefully quenched in a nitrogen atmosphere with an ethanol–water mixture. Glc analysis showed the presence only of phenylcyclobutene (III-H, 95%) and phenylcyclobutane (5%), but the concentrations of both compounds decreased with time to about one-third of the initial concentration after 3 hr. No traces of isomeric species (such as I-H or II-H) were detectable in the gas chromatogram of the reaction mixture at any time. A polymeric residue was obtained by working up the reaction mixture after 10–15 hr.

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Registry No.—I-Br, 41893-65-6; III-Br, 41893-67-8; III-HgBr, 51004-03-6; V-Br, 5912-93-6.

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Effects of Alkyl Substituents in the Chromic Acid Oxidation of Tetralins

John W. Burnham,[1a] William P. Duncan,[1b] and E. J. Eisenbraun*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

Gary W. Keen and Mynard C. Hamming

Research and Development Department, Continental Oil Company, Ponca City, Oklahoma 74601

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The chromic acid oxidation of a series of mono- and polyalkyl-1,2,3,4-tetrahydronaphthalenes was investigated. Preferential oxidation occurs at the benzylic methylene position para to an alkyl substituent in the aromatic ring. An alkyl group ortho to a benzylic methylene position may enhance or retard oxidation at that position, depending upon the degree of steric crowding by the alkyl group. 2-Alkyltetralins also undergo preferential oxidation in that 3-alkyl-1-tetralones predominate in the product mixture.

Chromic acid oxidation of hydrocarbons has been intensively studied. In general, for aliphatic hydrocarbons, the relative rates of oxidation in primary, secondary, and tertiary CH positions are 1:110:7000.[2] Although considerable data exist concerning the oxidation of aromatic–aliphatic systems,[3] very little information is available on oxidation of hydrocarbons containing nonequivalent benzylic positions capable of competing for the oxidizing agent. Linstead[4a] and Ghosal[4b] showed that a pronounced electronic effect is operative in the oxidation of 6-methoxytetralin to 6-methoxy-1-tetralone.

The mechanism of chromic acid oxidation of hydrocarbons has been extensively investigated.[2,3,4b,4c] A current rationalization utilizes an initial hydrogen abstraction to give a resonance hybrid of (a) an alkyl radical–Cr(V) complex and (b) a carbonium ion–Cr(IV) complex.[5,6] Since the rates of oxidation of hydrocarbons have been shown to parallel those for solvolysis of the corresponding tosylates, a carbonium ion intermediate is further implicated.[7a] It has been concluded that steric hindrance is not important in chromic acid oxidation of alkylcyclohexanes.[7b]

This study of the chromic acid oxidation of tetralins was prompted by an earlier observation that some alkyltetralins may be converted to 1-tetralones in high yield with considerable selectivity and thereby provide otherwise less accessible ketones.[8a] We previously utilized chromic acid in the conversion of indans to indanones in high yields.[8b]

The data presented in Table I provide ample evidence that an electronic effect is operative in the oxidation of tetralins substituted with alkyl groups in the aromatic ring. This is apparent from the ratio of product tetralones **3b:3c** (1.0:1.3) and **4b:4c** (2.7:1.0). Comparison of the latter ratio to those of **7b:7c** (2.9:1.0) and **10b:10c** (2.4:1.0) shows that the methyl, ethyl, and *tert*-butyl group have about the same electronic effect. The electronic effect responsible for the ratio of products obtained from **3a** and **4a** is manifest throughout the series in Table I. Steric effects result from alkyl groups at the peri position of the aromatic ring or from an alkyl group adjacent to a potential carbonyl site (C-2) in the saturated ring. The latter effect is illustrated by the products from **2a**, **5a**, and **8a** (methyl, ethyl, *tert*-butyl). The most obvious effect, steric and electronic, is shown by the products obtained in the oxidation of **6a** and **9a** compared to the products from **3a** (effects of peri alkyl groups) as well as by a comparison of the oxidation of **12a** and **13a** *vs.* **14a** and **15a** (methyl *vs.* *tert*-butyl groups). The ratio of products **16b:16c** (1.0:24) from **16a** suggests that the effects of 2-alkyl and peri alkyl groups are synergistic.

A diminution, owing to steric influence of methyl at C-2, appears in the ratio of products obtained from oxidation of **4a** and **12a**, the ratio decreasing from 2.7:1.0 to 2.0:1.0. Comparison of the ratios of 1-tetralones obtained from **10a**, **14a**, and **15a** indicate a very pronounced alkyl (*tert*-butyl) steric effect at the C-2 position. As expected, this effect decreases in changing from *tert*-butyl to methyl for **4a**, **12a**, and **13a**.

The alkyl groups in the aromatic ring may have a pronounced electronic influence on the ratio of 1-tetralones, as evidenced by comparison of the products from **3a**, **11a**, and **17a**, in which **3c**, **11c**, and **17c** predominate over **3b**, **11b**, and **17b** despite possible steric interference of the methyl group at the peri position. However, this effect is reversed for **6a** and **9a** (as expected) owing to the increased bulk of the ethyl and the *tert*-butyl group, and

the ratio becomes 1.2:1.0 (for **6b:6c**) and 2.9:1.0 (for **9b:9c**) as compared to 1.0:1.3 (for **3b:3c**).

The ratio of 1-tetralones formed from tetralins by chromic acid oxidation may become established at either the initial hydrogen abstraction or a subsequent stage during the conversion of alcohol or related species to ketone.[4c] We believe that the former is more likely, since in the oxidation of **15a**, no **15b** is formed. We argue that differences in rate of oxidation of alcohols can have no influence if one of the alcohols is not formed.

The ratios of 1-tetralones presented in Table I were obtained by glc studies.[9a,c] The identification of 1-tetralones responsible for individual peaks was made possible in the case of **5b:5c** (1.0:2.1) and **7b:7c** (2.9:1.0) through preparative glc separation,[9i] which yielded samples adequate for mass spectrometry but not for other analyses. The isomers **5b** and **5c** were distinguished by comparing relative peak intensity values at *m/e* 174 (M^+) and 146. The relative intensities of these peaks were 5.8 and 100 for **5b**, and 48 and 42 for **5c**, respectively. These peak positions and their relative intensities show that **5b** is capable of γ-hydrogen transfer whereas **5c** does not undergo this mode of fragmentation.[10b] Consequently, **5b** yields the smaller relative amount of M^+ and greater relative intensity at *m/e* 146. It should be noted that the relative intensity values for **8b** and **8c** were 2 and 24 at *m/e* 202 (M^+).

An authentic sample of **7c** was available with which to identify its glc peak. Mass spectrometry of samples of **7b** and **7c** isolated by preparative glc[9i] showed that these 1-tetralones are isomers.

The 1-tetralones from tetralins **12a**, **13a**, **14a**, and **17a** could not be separated. However, their identities and product ratios were readily established by ratios of pmr peaks observed for alkyl substituents at C-2 and C-3. It should be noted that the ratios obtained through glc studies agreed with those obtained from pmr spectra.

All of the remaining 1-tetralones in Table I were isolated in adequate quantities as pure compounds from reaction mixtures, and identification of compounds and determination of product ratios were precise and conclusive.

Experimental Section[9]

Preparation of Tetralins. The tetralins used in this study were obtained either from our API hydrocarbon synthesis project or as a gift.[10a] These tetralins were synthesized as outlined below and their purities were established by glc and spectral data.[9]

Tetralins 2a, 4a, 11a, and 16a were prepared *via* a previously described general Friedel–Crafts synthesis[11a] using benzene and methylsuccinic anhydride for **2b**, toluene and succinic anhydride for **4c**, *m*-xylene and succinic anhydride for **11b**, and *p*-xylene and methylsuccinic anhydride for **16b** and **16c**. Hydrogenolysis[11a] was used to convert **2b**, **4c**, **11b**, and **16b** or **16c** to **2a**,[11b] **4a**,[11b] **11a**,[11b] and **16a**,[11a] respectively.

Tetralin 5a was prepared by Pd/C-catalyzed hydrogenation of 2-ethylnaphthalene to a 1:1 mixture of **5a** and **7a**. This mixture was subjected to alkylation[12a] with *tert*-butyl chloride and $AlCl_3$. Distillation afforded a mixture of *tert*-butylated **5a** (52%) from which **5a**[12b] was obtained in 65% yield by de-*tert*-butylation[8a] with $AlCl_3$ in benzene, bp 62–63° (0.4 mm).

Tetralin 6a was prepared by Pd/C-catalyzed hydrogenation of 1-ethylnaphthalene to a mixture (1.0:1.3) of 1-ethyl-1,2,3,4-tetrahydronaphthalene and **6a**. These were separated by distillation[9g] to give pure **6a**,[12c] bp 94° (0.4 mm).

Tetralin 7a[12e] was prepared by hydrogenolysis[12d] of the semicarbazone of 5,6,7,8-tetrahydro-2-acetonaphthone, mp 236°.[12f]

Tetralin 8a was prepared by hydrogenation of 2-*tert*-butylnaphthalene and dealkylation of the resulting mixture of tetralins as previously described.[8a]

Tetralin 9a was prepared as previously described from ethyl 5,6,7,8-tetrahydro-1-naphthoate.[12g]

Tetralin 10a was prepared by *tert*-butylation of tetralin.[12a]

Tetralins 12a, 13a, 14a, and 15a were prepared by Pd/C-catalyzed hydrogenation of the corresponding naphthalenes in acetic acid. The purification of the gift[13a] dimethylnaphthalenes was accomplished *via* their picrates.[13b]

tert-Butylation[12a] of naphthalene provided a mixture of 2,6- and 2,7-di-*tert*-butylnaphthalene, which was separated by a combination of fractional crystallization of the arenes and selective formation of the thiourea clathrate of 2,6-di-*tert*-butylnaphthalene.[14]

Tetralin 17a. Hydrogenolysis[11a] of commercially available **17c** was used to prepare **17a**.

General Procedure for Chromic Acid Oxidations. To a magnetically stirred solution of 0.04 mol of hydrocarbon in 1 l. of acetic acid was added dropwise 170 ml of 10% aqueous CrO_3 acetic acid solution[15] over a period of 30 min. The reaction temperature was maintained between 17 and 21° with an ice bath. The reaction was allowed to proceed to completion (*ca.* 2 hr) as evidenced by glc.[9a] The reaction mixture was then diluted with 6 l. of distilled water and extracted with ether (2 × 1.5 l.). The combined ether extract was washed with water and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The resulting crude products were distilled and analyzed as outlined below.

Yield Maximization of 1-Tetralone (1b) from Tetralin (1a). A series of five experiments in which the molar ratio of CrO_3:**1a** ranged from 7.4:1 to 3.1:1 were carried out to determine optimum conditions. The maximum yield of **1f** (55%) was obtained with the ratio 5:1 as described above. In addition, three experiments varying the volume of acetic acid indicated that dilution over the amount specified in the procedure lowers the yield and allows survival of tetralin.

Tetralone 2b had bp 76–78° (0.3 mm) [lit.[16,17a] bp 127–131° (12 mm)]; ir[9f] (neat) 1681 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 160 (47), 131 (17), 118 (100), 90 (61), 89 (21), 28 (26); pmr[9e] ($CDCl_3$) δ 8.03–7.79 (m, 1, ArH peri to carbonyl), 7.94–6.94 (m, 3, ArH), 3.05–2.72 (m, 2, $ArCH_2$), 2.67–1.29 (m, 3, $ArCH_2CH_2CH$), 1.16 (d, 3, $ArCOCCH_3$).

Tetralone 2c had bp 78° (0.5 mm) [lit.[17d] bp 132° (14 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 160 (53), 145 (39), 118 (100), 115 (15), 91 (15), 90 (42); pmr[9e] ($CDCl_3$) δ 8.00–7.75 (m, 1, ArH peri to carbonyl), 7.52–6.92 (m, 3, ArH), 2.91–1.79 (envelope, 5, $ArCH_2CHCH_2$), 1.07 (d, 3, $ArCH_2CHCH_3$).

Tetralone 3b had mp 48–50°; mass spectrum (70 eV) *m/e* (rel intensity) 160 (63), 132 (100), 104 (56), 103 (22), 78 (23), 51 (22); pmr[9e] (CCl_4) δ 7.73 (d, 1, ArH peri to carbonyl), 7.33–6.90 (m, 2, ArH), 2.78 (t, 2, $ArCH_2$), 2.27 (s, 3, $ArCH_3$), 2.60–1.84 (m, 7, $ArCOCH_2CH_2$ and $ArCH_3$).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.58; H, 7.59.

Tetralone 3b had mp 48–50°; mass spectrum (70 eV) *m/e* (rel *m/e* (rel intensity) 160 (48), 132 (100), 104 (35), 103 (17), 78 (19), 51 (16); pmr[9e] (CCl_4) δ 7.30–6.76 (m, 3, ArH), 2.86 (t, 2, $ArCH_2$), 2.56 (s, 3, $ArCH_3$), 2.72–2.42 (m, 5, $ArCOCH_2$ and $ArCH_3$), 1.98 (m, 2, $ArCOCH_2CH_2$).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.39; H, 7.55.

Tetralone 4b had bp 75–77° (0.2 mm); mass spectrum (70 eV) *m/e* (rel intensity) 160 (51), 145 (18), 132 (100), 104 (40), 78 (19), 51 (18); pmr[9e] (CCl_4) δ 7.76 (d, 1, ArH peri to carbonyl), 7.06–6.84 (m, 2, ArH), 2.81 (t, 2, $ArCH_2$), 2.19 (s, 3, $ArCH_3$), 2.56–1.86 (m, 4, $ArCOCH_2CH_2$).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.60; H, 7.55.

Tetralone 4c[17a,b] had mp 32–34° (lit.[17a,b] mp 35–36°); ir (neat)[9f] 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 160 (73), 132 (100), 104 (75), 103 (23), 28 (21); pmr[9e] (CCl_4) δ 7.67 (s, 1, ArH peri to carbonyl) 7.08 (m, 2, ArH), 2.83 (t, 2, $ArCH_2$), 2.55–1.91 (m, 4, $ArCH_2CH_2CH_2$), 2.30 (s, 3, $ArCH_3$).

Tetralones 5b and 5c. These 1-tetralones were separated by glc,[9i] the minor component, **5b**, being eluted first, mass spectrum (70 eV) *m/e* (rel intensity) 174 (5.8), 146 (100), 145 (18), 118 (41), 115 (15), 90 (36). The major component, **5c**, had mass spectrum (70 eV) *m/e* (rel intensity) 174 (48), 146 (42), 145 (36), 118 (100), 115 (29), 90 (51). We were unable to obtain adequate samples for other analyses.

Tetralone 6b had bp 82° (0.1 mm); ir[9f] (neat) 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 174 (89), 159 (32), 146 (100), 118 (56), 117 (62), 115 (39); pmr[9e] (CCl_4) δ 7.98–7.79 (m, 1, ArH peri to carbonyl), 7.38–7.08 (m, 2, ArH), 2.08–2.45 (overlapping m, 4, $ArCH_2CH_2CH_2$), 2.60 (q, 2, $ArCH_2CH_3$, J = 8 Hz), 2.36–1.98 (m, 2, $ArCH_2CH_2$), 1.24 (t, 3, $ArCH_2CH_3$, J = 8 Hz).

Table I
Chromic Acid Oxidation Products of Tetralins

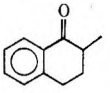
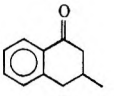
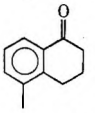
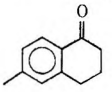
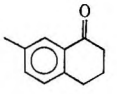
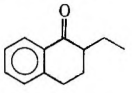
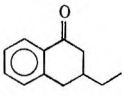
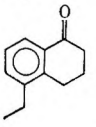
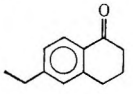
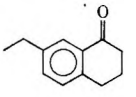
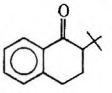
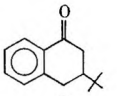
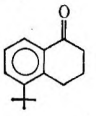
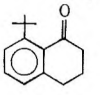
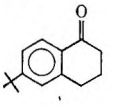
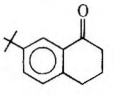
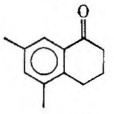
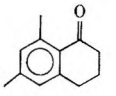
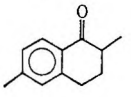
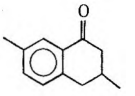
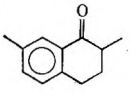
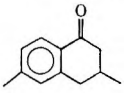
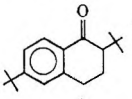
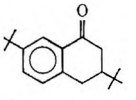
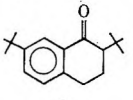
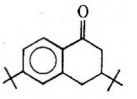
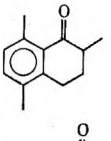
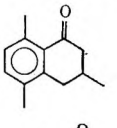
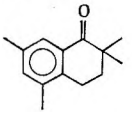
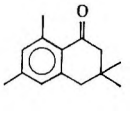
Tetralins[a]	1-Tetralones produced				Ratio b:c	Yield of combined 1-tetralones, %
1a	1b					55
2a	2b		2c		1.0:2.1[b,c]	72
3a	3b		3c		1.0:1.3[b]	60
4a	4b		4c		2.7:1.0[b,c]	72
5a	5b		5c		1.0:2.1[b]	83
6a	6b		6c		1.2:1.0[b,d,e]	71
7a	7b		7c		2.9:1.0[b,c,e]	63
8a	8b		8c		1.0:5.8[b,c]	70
9a	9b		9c		2.9:1.0[b]	62
10a	10b		10c		2.4:1.0[b]	58
11a	11b		11c		1.0:4.4[c,f]	62
12a	12b		12c		2.0:1.0[d,f]	65
13a	13b		13c		1.0:8.0[d,f]	66
14a	14b		14c		1.0:3.0[d,f]	75
15a	15b		15c		0.0:1.0[d,f]	71
16a	16b		16c		1.0:24[c,f]	74
17a	17b		17c		1.0:6.1[c,d,f]	57

Table I (*footnotes*)

[a] Corresponding to 1-tetralones of this table. [b] Ratio determined and separation achieved by glc.[9a,b,e,h,i] [c] Authentic samples of **2b, 2c, 4c, 7c, 8b, 8c, 11b, 11c, 16b, 16c,** and **17c** were available (*cf.* Experimental Section). [d] Ratio determined by pmr analysis based upon the differences in chemical shifts produced by alkyl substituents at C-2 and C-3. Pmr spectra of **8b** and **8c** show that the C-2 alkyl is deshielded relative to the C-3 alkyl group (*cf.* pmr spectra of **2b** and **2c** in Experimental Section).[8a] [e] Tetralins **6a** and **7a** were oxidized in part to the acetyl derivatives, which comprised 3 and 7% of the respective product mixtures. [f] Ratio verified by glc analysis.[9a,e]

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82,60; H, 8.09.

The red-orange 2,4-DNP melted at 188–190°.

Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12. Found: C, 60.93; H, 5.24.

Tetralone 6c had bp 85° (0.2 mm); ir[9f] (neat) 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 174 (50), 146 (100), 117 (33), 115 (21), 91 (14), 39 (13); pmr[9e] (CCl_4) δ 7.34–6.91 (m, 3, ArH), 3.16–2.79 (overlapping m, 2, $ArCH_2$), 3.01 (q, 2, $ArCH_2CH_3$, J = 7 Hz), 2.67–2.47 (m, 2, $ArCOCH_2$), 2.20–1.90 (m, 2, $ArCH_2CH_2$), 1.17 (t, 3, $ArCH_2CH_3$, J = 7 Hz).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.50; H, 8.05.

The dark red 2,4-DNP melted at 211–213°.

Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12. Found: C, 60.80; H, 5.24

Tetralones 7b and 7c. These 1-tetralones showed the glc[9c,i] ratio 2.9:1.0 for **7b:7c,** and they were separated[9i] in quantity adequate for mass spectrometry. The isomer **7c** preceded **7b** on the glc column.[9c,i] Isomer **7b** had mass spectrum (70 eV) *m/e* (rel intensity) 174 (46), 159 (19), 146 (100), 118 (19), 117 (19), 115 (17). Isomer **7c** had mass spectrum (70 eV) *m/e* (rel intensity) 174 (74), 159 (35), 146 (100), 118 (66), 117 (31), 115 (27). The glc[9c] of this mixture showed **7c:7b:**5,6,7,8-tetrahydro-2-acetonaphthone (18)[18] in the ratio 2.6:7.6:1.0 and that order of emergence from the column. Although **18** was present in the sample of **7b** used for mass spectral measurement and contributed to the spectrum, this contribution did not interfer with identification of **7b.** The mass spectrum of **7c** agreed with that of a commercial sample.[19]

Tetralones 8b and 8c. *Cf.* ref 8a.

Tetralone 9b had bp 96–98° (0.4 mm); ir[9f] (CCl_4) 1675 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 202, M^+ (28), 188 (15), 187 (100), 117 (13), 115 (19), 41 (11); pmr[9e] (CCl_4) δ 7.90, 7.82 (d of d, 1, ArH peri to carbonyl), 7.50, 7.42 (d of d, 1, ArH), 7.13 (t, 1, ArH), 3.14 (t, 2, $ArCH_2$), 2.54 (t, 2, $ArCH_2CH_2CH_2$), 2.06 (p, 2, $ArCH_2CH_2$), 1.42 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.07; H, 8.87.

Tetralone 9c had bp 93–95° (0.2 mm); ir[9f] (CCl_4) 1700 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 202, M^+ (85), 187 (94), 174 (100), 159 (96), 115 (49), 43 (35); pmr[9e] (CCl_4) δ 7.40–6.86 (m, 3, ArH), 2.84–2.54 (overlapping m, 4, $ArCH_2CH_2CH_2$), 2.17–1.90 (p, 2, $ArCH_2CH_2$), 1.38 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.03; H, 9.09.

Tetralone 10b had bp 102° (0.2 mm); ir[9f] (neat) 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 202 (24), 187 (100), 131 (18), 115 (13), 91 (9), 41 (11); pmr[9e] (CCl_4) δ 7.83 (d, 1, ArH peri to carbonyl), 7.30–7.10 (m, 2, ArH), 2.88 (t, 2, $ArCH_2$), 2.49 (t, 2, $ArCOCH_2$), 2.04 (p, 2, $ArCH_2CH_2$), 1.30 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.99; H, 8.94.

The red 2,4-DNP melted at 241–243°.

Anal. Calcd for $C_{20}H_{22}N_4O_4$: C, 62.81; H, 5.80. Found: C, 62.74; H, 5.85.

Tetralone 10c had mp 99–100° (lit.[17c] mp 101–102.5°); mass spectrum (70 eV) *m/e* (rel intensity) 202 (19), 188 (15), 187 (100), 156 (6), 131 (11), 115 (9); pmr[9e] (CCl_4) δ 7.94 (d, 1, ArH peri to carbonyl), 7.46–6.98 (m, 2, ArH), 2.88 (t, 2, $ArCH_2$), 2.53 (t, 2, $ArCOCH_2$), 2.08 (p, 2, $ArCH_2CH_2$), 1.33 (s, 9, *tert*-butyl).

Tetralones 11b and 11c. *Cf.* ref 11a.

Tetralones 12b and 12c had bp of 2.1:1.0 mixture 83–85° (0.2 mm). The ratio of isomers in this mixture was established by glc[9a] and by the ratio of two pmr[9e] (CCl_4) doublets centered at δ 1.14 and 1.04, respectively: mass spectrum of **9b:9c** (2.1:1.0) (70 eV) *m/e* (rel intensity) parent ion 174, M^+ (50).

Tetralones 13b and 13c had bp of 1.0:8.0 mixture 93–95° (0.3 mm). The ratio of isomers in this mixture was established by glc[9a] and by the ratio or two pmr[9e] (CCl_4) doublets centered at δ 1.13 and 1.00: mass spectrum of **10b:10c** (1.0:8.0) (70 eV) *m/e* (rel intensity) parent ion 174, M^+ (49).

Tetralones 14b and 14c had bp of 1.0:3.0 mixture 128–131° (0.2 mm). *Cf.* ref 8a.

Tetralones 15c. *Cf.* ref 8a.

Tetralones 16b and 16c. *Cf.* ref 11a.

Tetralones 17b and 17c had bp of 1.0:6.1 mixture 96–99° (0.3 mm). The ratio of isomers in this mixture was established by glc[9c] and by the ratio of two pmr[9e] (CCl_4) singlets at δ 1.09 and 0.98: mass spectrum of **14b:14c** (1.0:6.1) (70 eV) *m/e* (rel intensity) parent ion 202, M^+ (36). Tetralone **17c** was obtained from Aldrich Chemical Co.

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Registry No.—**1a,** 119-64-2; **2a,** 3877-19-8; **2b,** 1590-08-5; **2c,** 14944-23-1; **3a,** 2809-64-5; **3b,** 6939-35-1; **3c,** 51015-28-2; **4a,** 1680-51-9; **4b,** 51015-29-3; **4c,** 22009-37-6; **5a,** 32367-54-7; **5b,** 21568-62-7; **5c,** 51015-30-6; **6a,** 42775-75-7; **6b,** 51015-31-7; **6b** 2,4-DNP, 51015-32-8; **6c,** 51015-33-9; **6c** 2,4-DNP, 51015-34-0; **7a,** 22531-20-0; **7b,** 22577-91-9; **7c,** 22531-06-2; **8a,** 42044-22-4; **9a,** 42044-24-6; **9b,** 51015-35-1; **9c,** 51015-36-2; **10a,** 42044-26-8; **10b,** 51015-37-3; **10b** 2,4-DNP, 51015-38-4; **10c,** 22583-68-2; **11a,** 21693-54-9; **12a,** 7524-63-2; **12b,** 51015-39-5; **12c,** 51015-40-8; **13a,** 13065-07-1; **13b,** 51015-41-9; **13c,** 51015-42-0; **14a,** 42981-76-0; **15a,** 43012-91-5; **16a,** 30316-17-7; **17a,** 23342-25-8; **17b,** 51015-43-1; **17c,** 5409-55-2; CrO_3, 1333-82-0.

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(9) (a) 10 ft × 0.25 in. 25% Carbowax 20M on acid-washed Chromosorb W. (b) Preparative separations were made on a Carbowax 20M column, 10 ft × 0.375 in. (c) 11 ft × 0.25 in. 5% Silicone rubber UC W-98 on acid-washed, DMCS-treated Chromosorb W. (d) Petroleum ether, bp 60–68°. (e) Pmr spectra were determined on Varian HA-100 and A-60 spectrometers; mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer. (f) Ir spectra were obtained with a Beckman IR5A spectrometer; (g) Nester/Faust autoannular spinning band distillation system, Model NFA-200. (h) Ratios of 1-tetralone products were determined by triangulation of peaks in glc tracings. (i) 10 ft × 0.25 in. 15% FFAP on Anachrom ABS 70–80 mesh.

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Formation and Characterization of 1,2-Diiodoferrocene and Related Derivatives[1]

Paul V. Roling and Marvin D. Rausch*

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01002

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Iodoferrocene was mercurated and the 2-mercurated isomer, isolated as bis(2-iodoferrocenyl)mercury, was chemically characterized by conversion to the intramolecular anhydride, 1,2-ferrocenedicarboxylic anhydride. Iodination of bis(2-iodoferrocenyl)mercury gave 1,2-diiodoferrocene in essentially quantitative yield. Treatment of bis(2-iodoferrocenyl)mercury with deuterium chloride gave iodoferrocene-2-d_1. Mercuration of ferrocene was shown to produce 1,2-bischloromercuriferrocene in addition to the two major products, chloromercuriferrocene and 1,1′-bischloromercuriferrocene.

Although many 1,2-disubstituted ferrocenes are now known,[2] only 1,2-dichloroferrocene has been synthesized and reported in the 1,2-dihaloferrocene series.[3] This synthesis was accomplished by metalating chloroferrocene with *n*-butyllithium and then treating the intermediate with tri-*n*-butyl borate at −70°. After hydrolysis, the resulting boronic acid upon treatment with cupric chloride yielded 1,2-dichloroferrocene. Hedberg and Rosenberg[4] have very recently also reported that the lithiation of chloroferrocene, followed by reaction with hexachloroethane, affords 1,2-dichloroferrocene. Earlier, Huffman, Keith, and Ashbury[5] showed that lithiation of chloroferrocene followed by carbonation gave, by analogy with similar known substitutions of halobenzenes, 2-chloroferrocenecarboxylic acid. Unequivocal demonstration that the lithiation of chloroferrocene occurs in the 2 position has been recently provided by the studies of Slocum, *et al.*[6] On the other hand, bromoferrocene[7] and iodoferrocene[8] cannot be metalated as can chloroferrocene, since treatment with *n*-butyllithium gives the halogen–lithium interchange product, ferrocenyllithium.

Nefedov[9] has reported that the mercuration of haloferrocenes produces 1,3- and 1,1′-disubstituted ferrocenes. For example, mercuration of iodoferrocene (**1**) was indicated to produce 3-chloromercuriiodoferrocene (**2**) and 1-chloromercuri-1′-iodoferrocene (**3**). Iodination of the mercurials **2** and **3** then presumably produced 1,3-diiodoferrocene and 1,1′-diiodoferrocene, respectively.

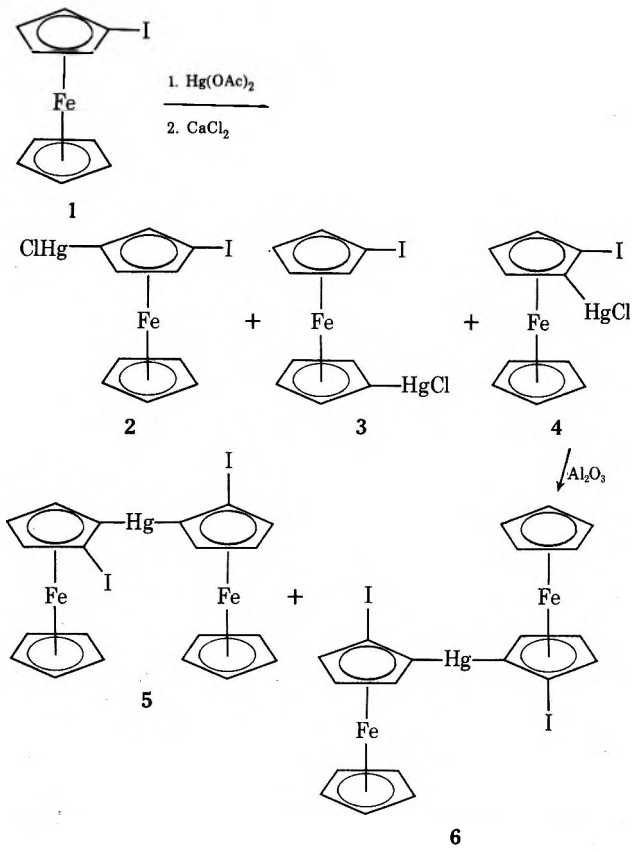
A number of investigators[10-12] have shown that the mercuration of ferrocene produces chloromercuriferrocene, 1,1′-bischloromercuriferrocene, and other unidentified mercurials. Nefedov[9,13] suggested that the mercuration of ferrocene with mercuric acetate followed by treatment with potassium bromide produced, besides bromomercuriferrocene and 1,1′-bisbromomercuriferrocene, 1,3-bisbromomercuriferrocene.

Results and Discussion

In an attempt to prepare 1,3-diiodoferrocene for some additional studies, Nefedov's work was repeated. However, his structural assignment has been found to be in error. Contrary to a previous report[14] that 2-chloromercuriiodobenzene symmetrized on alumina, Nefedov assigned the mercuration product that symmetrized on chromatography on alumina as 3-chloromercuriiodoferrocene (**2**).[9,15] Nefedov then iodinated the symmetrized product and obtained a material which he assigned as 1,3-diiodoferrocene. The structure of the product was supposedly proved by heating it with cuprous iodide and phenylmagnesium iodide to yield 1,3-diphenylferrocene having a melting point of 107° and exhibiting an infrared absorption at 905 cm^{-1}. The melting point of this derived diphenylferrocene without a mixture melting point determination with authentic 1,3-diphenylferrocene proves nothing, since 1,2-diphenylferrocene melts at 109–110°[18] and 1,3-diphenylferrocene melts at 107°.[18] Moreover, the fact that the infrared spectrum of the product shows a band at 905 cm^{-1} as does 1,1′,3,3′-tetraphenylferrocene[19] does not in itself prove a 1,3 disposition without a comparison of additional bands.[18]

In our work, iodoferrocene (**1**) was mercurated in the manner of Nefedov and worked up similarly, except that the alumina for chromatography was of activity 3.[20] As the *x*-chloromercuriiodoferrocenes (**2**–**4**) passed through the column, 2-chloromercuriiodoferrocene (**4**) selectively symmetrized and was eluted as a pale yellow solution of bis(2-iodoferrocenyl)mercury (**5**, **6**).

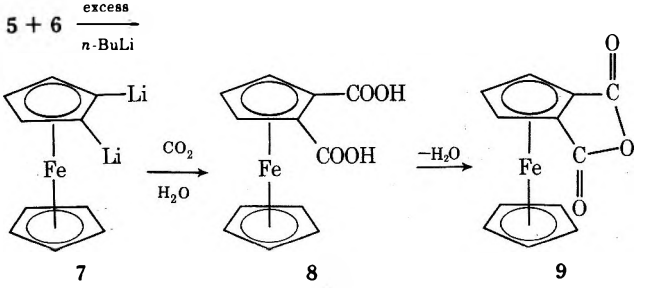
The melting point of the product obtained was the same as that reported by Nefedov.[9] The calculated nmr spectra (see Table I for chemical shift values of several monosubstituted ferrocenes) for bis(2-iodoferrocenyl)mercury and for bis(3-iodoferrocenyl)mercury indicate that these two possible homoannular positional isomers cannot be readily distinguished by nmr spectroscopy (see Table II). Further, the triplet resonance observed in the spectra of the product falls essentially under the two singlets, and hence no coupling constant values can be obtained which could be used in structural assignments. However, since bis(2-iodoferrocenyl)mercury isolated in this work has been shown to consist of a single positional isomer (*vide infra*), the two singlets observed therefore must represent the two possible stereoisomers—meso compound **6** and *dl* com-



1 2 3 4 5 6

pound **5**. A similar set of stereoisomers results from the symmetrization of 2-chloromercuriacetylferrocene.[17]

A reaction between bis(2-iodoferrocenyl)mercury (**5, 6**) and excess *n*-butyllithium gave 1,2-dilithioferrocene (**7**), and subsequent carbonation of this intermediate followed by hydrolysis gave a 52% yield of 1,2-ferrocenedicarboxylic acid (**8**). The infrared spectrum and the melting point of 1,2-ferrocenedicarboxylic acid (**8**) agree with literature data reported by Richards and Curphey.[21] Moreover, the nmr spectrum of the product in acetone shows a singlet (δ 4.40) for the five protons of the unsubstituted cyclopentadienyl ring, as well as a predicted[22] low-field doublet (δ 5.23) for the 3 and 5 protons and a higher field triplet (δ 4.88) for the 4 proton. The additivity of chemical shifts is shown for all compounds in Table II. The observed coupling constant of 2.8 Hz is also consistent with a 1,2 disposition of the carboxyl groups in the product.[23]



7 8 9

Subsequent dehydration of the diacid **8** produced 1,2-ferrocenedicarboxylic anhydride (**9**). Since the melting point of this compound and the reported melting point[21] of **9** differed by nearly 20°, the product was analyzed further to be certain that it was an intramolecular anhydride. A total elemental analysis indicated a formulation consistent with **9**. The mass spectrum gives a parent ion peak at *m/e* 256, and the nmr spectrum shows singlet, triplet, and doublet resonances of area intensities 5:1:2, respectively. The nmr spectrum shows the expected[22] deshielded 3,5 protons downfield as the doublet and the less deshielded 4 proton as a triplet just below the singlet.

Table I
Chemical Shift Values for Several Monosubstituted Ferrocenes[a]

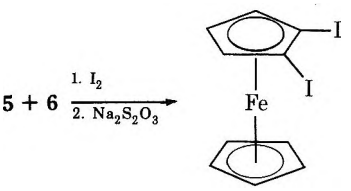
FcX	$\sigma_{1,5}$	$\sigma_{2,4}$
X = I[b]	0.23	−0.03
X = COOH[c]	0.62	0.27
X = −Hg−[b,d]	0.10	0.20
X = HgCl[e]	−0.10	0.10

[a] Values are determined by calculating the difference in chemical shift in parts per million between appropriate protons on the substituted ferrocene *vs.* the protons on ferrocene itself in the same solvent. A positive number indicates deshielded protons and a negative number indicates shielded protons relative to protons in ferrocene. [b] Taken in 5–10% solutions in $CDCl_3$. [c] Taken in saturated acetone solution. [d] Values calculated from the spectrum of *meso*-bis(2-acetylferrocenyl)mercury.[17] [e] Taken in dimethyl sulfoxide solution.

The infrared spectrum of this anhydride is identical with that of Richards and Curphey.[21] The structure of **9** is therefore confirmed, and the 1,2 disposition of bis(2-iodoferrocenyl)mercury (**5, 6**) is unequivocally established.

Other attempts to chemically characterize the 1,2 disposition of substituents in **5** and **6** included (1) heating 1,2-diiodoferrocene (**10**) derived from **5** and **6** with phenylmagnesium iodide and cuprous iodide, which led to a very small amount of a compound that was not 1,2-diphenylferrocene by a mixture melting point determination with authentic 1,2-diphenylferrocene, and not 1,3-diphenylferrocene by a mixture melting point determination with authentic 1,3-diphenylferrocene;[24] (2) heating 1,2-diiodoferrocene with excess cuprous cyanide at 160°, which resulted in no reaction after 2 hr; (3) heating 1,2-diiodoferrocene and excess cuprous cyanide in *N*-methyl-2-pyrrolidone at 155° for 3 hr, which gave only tar.

Iodination of bis(2-iodoferrocenyl)mercury (**5, 6**) by the method of Nefedov[9] gave 1,2-diiodoferrocene (**10**) in es-



10

sentially quantitative yield. The nmr spectrum of 1,2-diiodoferrocene (**10**) shows an AX_2 pattern for the substituted-ring protons with a doublet at δ 4.51 and a triplet at δ 4.22 in $CDCl_3$ solution. Table II lists the calculated values for 1,2-diiodoferrocene (**10**) and 1,3-diiodoferrocene (*vide infra*) and shows that the above-assigned 1,2-diiodoferrocene (**10**) does indeed fit the calculated spectrum. Nesmeyanov, Sazonova, and Sazonova[3] reported that 1,2-dichloroferrocene exhibited a triplet at δ 3.90, a singlet at δ 4.21, and a doublet at δ 4.29 with $J_{3,4}$ and $J_{3,5}$ = 2.3 Hz. The nmr data obtained on the diiodoferrocene obtained in our studies again substantiates a 1,2-disubstituted homoannular isomer, and the 1,3 assignment as originally proposed by Nefedov[9] must again be assumed to be incorrect.

The other monomercurated products **2** and **3** isolated from the mercuration of iodoferrocene were obtained as an inseparable mixture, and iodination of this mixture produced diiodoferrocenes. The nmr spectrum of the iodination product shows it to be a mixture of 1,3- and 1,1′-diiodoferrocenes. The spectrum exhibits the expected two triplets for 1,1′-diiodoferrocene (see Table II). In addition, a low field triplet, a higher field doublet, and a singlet are also present. This is the resonance pattern expected for

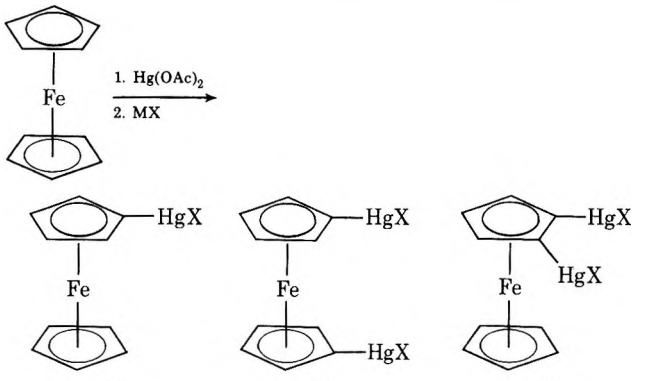
Table II
Calculated and Observed Nmr Spectra of Disubstituted Ferrocenes[a]

Compd	Triplet resonances		Doublet resonances		J, Hz	
	Calcd	Found	Calcd	Found	Exptl	Found
Bis(2-iodoferrocenyl)mercury	4.35[b]	4.23[c]	4.61[b]	4.60[c]	2–3	
			4.25[b]	3.97[c]		
Bis(3-iodoferrocenyl)mercury	4.51[b]		4.61[b]		1–1.5	
			4.25			
1,2-Ferrocenedicarboxylic acid[d]	4.70	4.89	5.05	5.23	2–3	2.8
1,3-Ferrocenedicarboxylic acid[d]	5.40		5.05		1–1.5	
1,1′-Diiodoferrocene[e]	4.41	4.38				
	4.15	4.16				
1,2-Diiodoferrocene[e]	4.12	4.22	4.38	4.51	2–3	2.5
1,3-Diiodoferrocene[e]	4.64	4.67	4.38	4.32	1–1.5	1.2
1,2-Bischloromercuriferrocene[f]	4.38	4.48	4.18	4.25	2–3	2.2
1,3-Bischloromercuriferrocene[f]	3.98		4.18		1–1.5	

[a] All values are given in δ parts per million; see Table I for chemical shift values used in the calculated nmr spectra. [b] Values were calculated for $CDCl_3$ solutions. [c] Values obtained in o-$C_6H_4Cl_2$ solutions. [d] Values are for acetone solutions. [e] Values are for $CDCl_3$ solutions. [f] Values are for dimethyl sulfoxide solutions.

1,3-diiodoferrocene, since the proton positioned between the two iodo substituents should produce a triplet, and that triplet should be doubly deshielded and therefore appear furthest downfield. The doublet represents the 4 and 5 protons, which are not as deshielded, since these protons are adjacent to only one iodo group. The observed coupling constant of *ca.* 1.2 Hz (representing $J_{2,4}$ and $J_{2,5}$) is also indicative of a 1,3-disubstituted ferrocene.[23]

The mercuration of ferrocene gives as major products the previously reported products, halomercuriferrocene (**11**) and 1,1′-bishalomercuriferrocene (**12**).[10-13] Nefedov



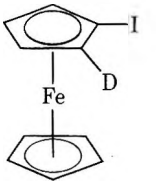
11 **12** **13**

and Nefedova[13] reported that in addition to the above two products there is also formed a small amount of 1,3-bishalomercuriferrocene. They identified this product on the basis of the derived haloferrocene, prepared by the mercuration of monohaloferrocenes. However, since Nefedov's 1,3-dihaloferrocenes have now been proved to be 1,2-dihaloferrocenes, it then follows that his previously assigned 1,3-bishalomercuriferrocenes are in fact 1,2-bishalomercuriferrocenes. Repetition of the work of Nefedov and Nefedova[13] gave a product (**13**, X = Cl) which on iodination yielded a diiodoferrocene that has an identical nmr spectrum in benzene solution with that of authentic 1,2-diiodoferrocene in the same solvent. The nmr spectrum of 1,2-diiodoferrocene prepared in this manner also exhibited a weak extra singlet at δ 3.96 which may have been due to iodoferrocene formed during the iodination, or may have resulted from chloromercuriferrocene (**11**, X = Cl) being present as an impurity. Likewise, lithiation of 1,2-bischloromercuriferrocene (**13**, X = Cl) followed by carbonation and acidification gave a mixture of acids, ferrocenecarboxylic acid and 1,2-ferrocenedicarboxylic acid (**8**), as shown by an nmr spectrum of the products.

The nmr spectrum of 1,2-bischloromercuriferrocene (**13**, X = Cl) in dimethyl sulfoxide solution shows a downfield triplet, an upfield doublet, and a singlet at still higher field at δ 4.53, 4.30, and 4.23, respectively. This is the expected order for the triplet and doublet resonances, since the nmr spectrum of 1-acetyl-2-chloromercuriferrocene shows that a chloromercuri group tends to shield protons α to this group to a greater extent than protons β to it.[25,26]

In benzene as the solvent, the nmr spectrum of iodoferrocene exhibits triplet resonances at δ 3.84 and 4.29, and a singlet at δ 4.02. The triplet at δ 4.29 can be assigned to the 2 and 5 protons due to the deshielding by the iodine atom. The 3 and 4 protons then appear at δ 3.84. Similarly, in carbon tetrachloride solution, the 2,5 protons appear at δ 4.33, the 3,4 protons at δ 4.05, and the singlet at δ 4.10.[27]

Since the 1,2 disposition of bis(2-iodoferrocenyl)mercury (**5**, **6**) has now been proved, the deuteration of this mercurial was carried out and yielded iodoferrocene-2-d_1 (**14**).



14

The nmr spectrum of **14** (benzene solution) is instructive as to proton assignments in iodoferrocene. The signal at δ 4.28 which is observed as a triplet integrates for 1.3 protons relative to the 5-proton singlet at δ 4.01, representing the unsubstituted cyclopentadienyl ring. The signal at δ 4.28 represents the 5 proton in **14** as well as 2,5 protons in iodoferrocene, a small amount of which is believed to be present. The 3,4 protons appear as a doublet at δ 3.83 and integrate for approximately two protons. These results therefore confirm the above proton assignments in the nmr spectrum of iodoferrocene.

Experimental Section

Nmr spectra were recorded on a Varian A-60 spectrometer in 5–10% solutions wherever possible. Ir spectra were taken on a Beckman IR-10 spectrometer and were calibrated using the 1601-cm^{-1} band of polystyrene. Mass spectra were recorded on an A. E. I. MS-9 spectrometer by Dr. Alan Siegel at Carnegie-Mellon University, Pittsburgh, Pa.

The alumina of activity grade 3 used throughout this work was made by shaking 1000 g of neutral, activated CAMAG alumina (Alfa Inorganics, Inc.) with 60 ml of water. All columns were packed dry. The dimensions of the column were not considered important as long as the stated amount of alumina was used and the column was packed evenly. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Dry ethyl ether was

distilled from lithium aluminum hydride. All microanalyses were carried out by the Microanalytical Laboratory, Office of Research Services, University of Massachusetts. Skellysolve B is the fraction of hydrocarbons boiling between 40 and 60°.

Mercuration of Iodoferrocene. The method given below is a modification of the procedure of Nefedov.[9] In a 2-l., three-necked flask under nitrogen were placed 49.2 g (0.16 mol) of iodoferrocene (1) and 120 ml of benzene. A solution of 51.2 g (0.16 mol) of mercuric acetate in 800 ml of methanol was added with stirring over 5 min. The reaction mixture was stirred at room temperature for 20 min, poured into a cold solution of 80 g (0.72 mol) of calcium chloride in 800 ml of methanol, and stirred for 1 min. This mixture was then poured into 2 l. of cold water and the precipitate was suction filtered, washed with 400 ml of cold water, and dried in air. The residue was stirred at room temperature with 500 ml of Skellysolve B for 6 hr and filtered, and the residue was again stirred with 500 ml of Skellysolve B for 6 hr and filtered. The Skellysolve B filtrates were combined and set aside. The residue was then stirred for 6 hr with a mixture of 250 ml of Skellysolve B and 250 ml of benzene, and filtered. The filtrate was saved and the residue was reextracted four more times as above with the 1:1 Skellysolve B–benzene mixture. The final residue, which amounted to 38.4 g, was not further investigated.

The Skellysolve B extracts were placed on a column of 450 g of alumina. Iodoferrocene (15.0 g, 30%) was eluted with Skellysolve B, leaving two bands on the column. Then 500 ml of the 1:1 Skellysolve B–benzene extract was placed on the same column. Elution with about 2 l. of a 1:1 Skellysolve B–benzene mixture removed a pale yellow solution from the column, although no formal band was visible. This solution contained bis(2-iodoferrocenyl)mercury (**5, 6**) resulting from symmetrization of 1-chloromercuri-2-iodoferrocene (4) on the column. When the solution became almost colorless, chloroform was used to remove the last band from the column.

The other 2 l. of Skellysolve B–benzene extracts was placed on another column of 1000 g of alumina. The bis(2-iodoferrocenyl-mercury (**5, 6**) was eluted with about 7 l. of 1:1 Skellysolve B–benzene and the last band was eluted with about 2 l. of chloroform.

The solvent was evaporated from the combined eluate containing bis(2-iodoferrocenyl)mercury and the residue was crystallized from a mixture of 50 ml of Skellysolve B and 50 ml of benzene to yield 4.10 g of yellow crystals, mp 175–177° (lit.[9] mp 175°). A second crop (1.38 g), mp 172–174°, was obtained to give a total of 5.48 g (8%) of bis(2-iodoferrocenyl)mercury (**5, 6**), nmr (o-dichlorobenzene) singlets at δ 4.26 and 4.30 and triplet at δ 4.23 (12 H, unsubstituted cyclopentadienyl ring protons of the *dl* and meso compounds and 4-protons), doublet of doublets at δ 3.97 (2 H, 3-protons) and doublet of doublets at δ 4.60 (2 H, 5-protons).

The solvent was removed from the last band to be eluted to produce 11.4 g (17%) of a powder. A 0.40-g sample of this product was iodinated in the manner of 1,2-diiodoferrocene, as described below, and the product was purified in a similar manner: nmr ($CDCl_3$) triplet at δ 4.16, singlet at δ 4.20, triplet at δ 4.38, doublet at δ 4.32, triplet at δ 4.67; nmr (C_6H_6) triplets at δ 3.82 (4 H, β protons on 1,1′-diiodoferrocene) and 4.18 (4 H, α protons on 1,1′-diiodoferrocene), singlet at δ 3.97 (5 H, unsubstituted ring protons of 1,3-diiodoferrocene), doublet at δ 4.10 (1.6 H, 4- and 5-protons of 1,3-diiodoferrocene), triplet at δ 4.45 (0.8 H, 2-proton of 1,3-diiodoferrocene). The integration of the nmr spectrum in benzene indicates that there is 55% of 1,1′-diiodoferrocene and 45% of 1,3-diiodoferrocene present.

All attempts to separate the yellow powder into pure samples of 1′-chloromercuri- (3) and 3-chloromercuri-1-iodoferrocene (2) *via* chromatography on an alumina column treated with sodium cyanide[17] failed to give any separation.

Three runs with 12.3 g of iodoferrocene, one run with 21.8 g of iodoferrocene, and two runs with 24.6 g of iodoferrocene produced essentially the same percentage yields of products as described above.

1,2-Ferrocenedicarboxylic Acid (8). Bis(2-iodoferrocenyl)mercury (**5, 6**, 0.52 g, 0.63 mmol), 20 ml of dry benzene, and 45 ml of dry ethyl ether were stirred under nitrogen for 10 min. Subsequently there was added 2.2 ml (5.0 mmol) of 2.25 *M* *n*-butyllithium in hexane. This mixture was stirred for 10 min, poured onto crushed Dry Ice, and allowed to warm to room temperature. Water (100 ml) was added and the ether layer was removed and discarded. The water layer was acidified with dilute hydrochloric acid and extracted four times with 50-ml portions of chloroform. The extracts were combined and dried over sodium sulfate and the solvent was evaporated. The residue was crystallized from chloroform to yield 0.18 g (52%) of 1,2-ferrocenedicarboxylic acid (**8**): mp (air) 205–207° dec; mp (sealed under nitrogen) 195–198° with foaming (lit.[21] mp 206–206.5° dec); nmr (acetone) singlet at δ 4.40 (5 H, unsubstituted cyclopentadienyl ring protons), triplet at δ 4.89 (1 H, 4-proton), doublet at δ 5.23 (2 H, 3,5-protons, J = 2.8 Hz); ir (KBr) 2900 (broad, -COOH), 1690 (-COOH), 1600 cm^{-1}.

Two other runs with 0.75 and 0.45 g of bis(2-iodoferrocenyl)-mercury gave 60 and 30% yields, respectively, of 1,2-ferrocenedicarboxylic acid. 1,2-Ferrocenedicarboxylic acid and its solutions should be protected from light, since photochemical decomposition takes place in a short time.

1,2-Ferrocenedicarboxylic Anhydride (9). 1,2-Ferrocenedicarboxylic acid (**8**, 0.09 g, 0.35 mmol) was dissolved in 10 ml of acetone. To this solution was added a solution of 0.07 g (0.34 mmol) of *N,N*-dicyclohexylcarbodiimide dissolved in 5 ml of acetone, and the mixture was stirred for 30 min, during which time it became cloudy. The reaction mixture was filtered, 5 ml of Skellysolve B was added, and the solution was again filtered. The volume was reduced and 1,2-ferrocenedicarboxylic anhydride (**9**) was crystallized to give 0.03 g (36%) of product, mp 143–150°. This material was recrystallized from Skellysolve B–benzene three times to yield 10 mg of 1,2-ferrocenedicarboxylic anhydride (**9**): mp (sealed under nitrogen) 157–160° (lit.[21] mp 176–176.5°); nmr ($CDCl_3$) singlet at δ 4.49 (5 H, unsubstituted cyclopentadienyl ring), triplet at δ 4.89 (1 H, 4-proton), doublet at δ 5.15 (2 H, 3- and 5-protons, J = 2.4 Hz); ir ($CDCl_3$) 1834 and 1775 cm^{-1} (anhydride); mass spectrum m/e 256 (calcd mol wt, 256).

Anal. Calcd for $C_{12}H_8FeO_3$: C, 56.29; H, 3.15; Fe, 21.81; O, 18.75. Found: C, 56.37; H, 3.19; Fe, 21.8; O, 18.59.

Another run with 0.30 g of 1,2-ferrocenedicarboxylic acid yielded 36% of 1,2-ferrocenedicarboxylic anhydride. This product is light sensitive and should be protected from light both in solution and in the solid state.

1,2-Diiodoferrocene (10). The method given below is a modification of the procedure of Nefedov.[9] To a boiling solution of 1.27 g (1.55 mmol) of bis(2-iodoferrocenyl)mercury (**5, 6**) in 60 ml of 1,2-dichloroethane was added 1.5 g (5.9 mmol) of iodine in 90 ml of 1,2-dichloroethane. The mixture was heated on the steam bath for 10 min and 10 g of finely ground sodium thiosulfate was added. The purple solution was stirred until it turned yellow. The solution was decanted, the solvent was evaporated, and the residual oil was dissolved in a small amount of Skellysolve B. This extract was placed on a column of alumina and the 1,2-diiodoferrocene (**10**) was eluted with Skellysolve B. The solvent was removed by a jet of air to yield 1.33 g (98%) of **10**: mp 42–44° (lit.[9] mp 47.5°); nmr ($CDCl_3$) singlet at δ 4.19 (5 H, unsubstituted cyclopentadienyl ring), triplet at δ 4.22 (1 H, β proton), doublet at δ 4.51 (2 H, α protons); nmr (C_6H_6) singlet at δ 3.96 (5 H, triplet), 3.73 (1 H), doublet at δ 4.21 (2 H); ir (KBr) 1100 and 995 cm^{-1} (unsubstituted cyclopentadienyl ring).

Iodoferrocene-2-d_1. Into a 250-ml round-bottom flask under nitrogen were placed 100 ml of dry dioxane (freshly distilled from lithium aluminum hydride), 0.55 g (0.67 mmol) of bis(2-iodoferrocenyl)mercury (**5, 6**), and 2.0 ml (111 mmol) of deuterium oxide. To this solution was added 10.0 g (75 mmol) of anhydrous aluminum chloride. An immediate green color developed with the evolution of heat. The mixture was stirred for 1.5 hr and poured into 500 ml of water containing 20 g of sodium bisulfite. The aqueous layer was extracted with ether and the extracts were washed three times with 50-ml portions of water and evaporated. The residue was dissolved in Skellysolve B and chromatographed on 50 g of alumina, eluting with Skellysolve B. Evaporation of the solvent gave an oil, which was crystallized from a methanol–mixture. The yield of iodoferrocene-2-d_1 was 0.27 g (67%): mp 42–45°; nmr (C_6H_6) doublet at δ 3.83 (2 H, 3,4-protons), singlet at δ 4.01 (5 H, unsubstituted cyclopentadienyl ring), triplet at δ 4.28 (1.3 H, 5-protons plus some 2-protons from iodoferrocene).

Mercuration of Ferrocene. Into a 5-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a heated dropping funnel were placed 148.8 g (0.80 mol) of ferrocene, 1500 ml of methanol, and 1000 ml of ethyl ether. The mixture was heated to reflux and a solution of 127.5 g (0.40 mol) of mercuric acetate in 800 ml of boiling methanol was added dropwise over 1 hr. After the addition was complete, the reaction mixture was stirred for an additional 5 hr, whereupon heating was discontinued and a solution of 17.8 g (0.42 mol) of lithium chloride in 200 ml of boiling methanol was added.

The entire contents of the reaction flask was transferred to a 4-l. beaker and evaporated overnight with a gentle jet of air. The residue was then placed in a Soxhlet cup in a 3-l. Soxhlet extrac-

tion apparatus and extracted for 2 days with Skellysolve B to give, upon evaporation of the solvent, 52 g (35%) of recovered ferrocene.

The material in the Soxhlet cup was next extracted for 2 days with methylene chloride to give, after evaporation of the solvent, 155 g of crude chloromercuriferrocene. Crystallization of this material from *n*-butyl alcohol gave 105 g of a material that melted at 160–185°, and a residue (residue 1) of 30 g. The 105 g of material was extracted twice with 500-ml portions of Skellysolve B to leave 76 g (45%) of chloromercuriferrocene, mp 194–196° dec (lit.[11] mp 193–194° dec). The Skellysolve B extracts yielded 29 g of ferrocene for a total of 81 g (55%) of recovered ferrocene.

The remaining material in the Soxhlet cup was extracted for 2 days with acetone. Upon evaporation of the solvent, there resulted 25 g of material which was combined with residue 1 and the total was dissolved in 750 ml of dimethylformamide. The residue that would not dissolve was filtered and combined with the residue left in the Soxhlet cup.

The dimethylformamide filtrate was chromatographed, one-third at a time, on three columns, each containing 450 g of alumina. Elution with a mixture of dimethylformamide–chloroform–methanol (5:3:2 volume ratio) produced a colored forerun that was discarded. The first and major band was then slowly eluted with the above solvent mixture, leaving two bands on the colunn, which were eluted with a 1:1 volume mixture of dimethylformamide–methanol.

The major band was worked up in the following manner. The volume of the solvent was tripled with water, and the organic layer was removed and evaporated to yield a total of 2.0 g (2%) of crude 1,2-bischloromercuriferrocene (**13**). The crude material was crystallized from acetone to give a yellow compound: mp 200–205° dec (sealed under nitrogen) with mercury given off at about 217°; ir (KBr) 3080, 1328, 1160, 1101, 998, 900, 806 cm^{-1}.

Anal. Calcd for $C_{10}H_8Cl_2FeHg_2$: C, 18.29; H, 1.23; Cl, 10.81; Fe, 8.51. Found: C, 18.39; H, 1.31; Cl, 10.91; Fe, 8.50.

The nmr spectrum (dimethyl sulfoxide) of 1,2-bischloromercuriferrocene (**13**) was not well defined, so the material was recrystallized from dimethyl sulfoxide to give orange crystals: mp (sealed under nitrogen) 170–172°;[28] nmr (dimethyl sulfoxide) singlet at δ 4.25 (5 H, unsubstituted cyclopentadienyl ring), doublet at δ 4.30 (2 H, α protons), triplet at δ 4.48 (1 H, β proton).

The remaining two bands were eluted together with dimethylformamide–methanol, and upon work-up as above yielded 1.5 g of material. Iodination of this material, as described for the iodination of 1,2-bischloromercuriferrocene, gave an oil which, from the nmr spectrum, proved to be 1,1′-diiodoferrocene with possibly a small impurity of 1,2- and/or 1,3-diiodoferrocene. The residue in the Soxhlet cup (*ca.* 50 g) was crystallized from dimethylformamide to yield 7 g (5%) of 1,1′-bischloromercuriferrocene (**12**), mp (sealed under nitrogen) 240° dec (lit.[11] decomposition at elevated temperatures).

Two other runs gave essentially the same results as described above.

Iodination of 1,2-Bischloromercuriferrocene (13). To 0.4 g (0.6 mmol) of crude 1,2-bischloromercuriferrocene (**13**) in 50 ml of 1,2-dichloroethane was added 0.4 g (1.6 mmol) of iodine. The reaction mixture was stirred for 10 min, after which time there was added 100 ml of a 10% solution of sodium thiosulfate. The mixture was stirred for 30 min, the layers were separated, and the organic layer was again treated with iodine and sodium thiosulfate as above. After separation of the organic layer for the second time, the solvent was evaporated and the residual oil was dissolved in a minimum of Skellysolve B and chromatographed on an alumina column. Elution with Skellysolve B and subsequent evaporation gave an oil: nmr (C_6H_6) triplet at δ 3.72 (1 H), singlet at δ 3.94 (5 H), doublet at δ 4.20 (2 H), singlet at δ 3.97 (0.3 H). This product can be assigned as 1,2-diiodoferrocene (**10**), since the nmr spectrum is in agreement with that of authentic 1,2-diiodoferrocene. The singlet at δ 3.97 is due to a small amount of iodoferrocene present.

Lithiation of 1,2-Bischloromercuriferrocene (13). Into a nitrogen-flushed flask were placed 0.05 g (0.08 mmol) of 1,2-bischloromercuriferrocene (**13**), 20 ml of anhydrous ethyl ether, and 1.0 ml (2.3 mmol) of 2.25 *M* *n*-butyllithium in hexane. The reaction mixture was stirred for 15 min at room temperature and then poured into Dry Ice. When the ether layer had warmed to room temperature, the lithium salts were extracted twice with 30-ml portions of water. The aqueous layer was separated, acidified with 3 ml of 6 *N* hydrochloric acid, and extracted twice with 50-ml portions of chloroform. The chloroform was evaporated on a rotary evaporator with aluminum foil placed around the flask to avoid photodecomposition. Attempts to recrystallize the material from chloroform only resulted in decomposition, so an nmr spectrum was taken: nmr (acetone) singlet at δ 4.18, singlet at δ 4.40, triplet at δ 4.38, triplets at δ 4.88, doublet at δ 5.23. This spectrum is in agreement with a mixture of ferrocenecarboxylic acid and 1,2-ferrocenedicarboxylic acid (8).

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Registry No.—**1,** 51021-52-4; **5,** 51021-54-6; **6,** 51021-55-7; **8,** 51021-53-5; **9,** 51004-02-5; **10,** 51021-51-3; **12** (X = Cl), 12145-90-3; **13** (X = Cl), 51021-49-9; **14,** 51021-50-2; ferrocene, 102-54-5; chloromercuriferrocene, 51108-07-7.

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(28) This is probably a solvated product, since redissolution in dimethyl sulfoxide followed by precipitation with water and drying gave a yellow powder, mp (sealed under nitrogen) 198–200° dec.

Notes

Reduction of Aryl Iodides with Sodium Hydride

Randall B. Nelson[1] and Gordon W. Gribble*[2]

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

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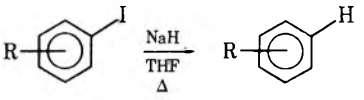
We wish to report the hydrogenolysis of aryl iodides by a refluxing suspension of sodium hydride in dry tetrahydrofuran. The reaction typically proceeds in 85–95% isolated yield in 24 hr or less with a 3–10 molar excess of NaH in a small volume of THF.



Reduction by NaH has been previously observed in benzylic halides,[3] nonenolizeable carbonyl compounds,[4] *gem*-dihalocyclopropanes,[5] and some disulfides.[6] Most examples of NaH reduction have required dipolar aprotic media. For example, quinoline and isoquinoline are reduced to a mixture of 1,2- and 1,4-dihydroquinolines and 1,2-dihydroisoquinoline, respectively, in a warmed slurry of NaH and hexamethylphosphoramide (HMPA).[7]

The reaction with substituted aryl iodides is insensitive to the position of electron-donating ring substituents in the cases studied. For example, *o*-, *m*-, and *p*-iodoanisole with NaH provide anisole[8] in 93, 95, and 91% yield, respectively (Table I). Similarly, the isomeric *o*-, *m*-, and *p*-iodotoluenes afford toluene in >90% yield as determined by gc analysis of the crude reaction mixture. The reaction of *p*-iodotoluene is complete in less than 2 hr as indicated by precipitated NaI and gc analysis. Similarly, iodobenzene gives benzene in 84% yield as determined by gc. Previous reductions of aryl iodides have required lithium aluminum hydride.[9]

Table I
Reaction of Aryl Iodides with NaH in Refluxing THF[a]

Substrate	Product	% yield[b]	Registry no.
Iodobenzene	Benzene	84[c]	591-50-4
o-Iodotoluene	Toluene	91[c]	615-37-2
m-Iodotoluene	Toluene	97[c]	625-95-6
p-Iodotoluene	Toluene	100[c,d]	624-31-7
o-Iodoanisole	Anisole	93[e]	529-28-2
m-Iodoanisole	Anisole	95	766-85-8
p-Iodoanisole	Anisole	91[e]	696-62-8
o-Iodobenzoic acid	Benzoic acid	μ5[f,i]	88-67-5
m-Iodobenzoic acid	Benzoic acid	75[g,i]	618-51-9
p-Iodobenzoic acid	Benzoic acid	20[h,i]	619-58-9
o-Bromobenzoic acid	Benzoic acid	75[g,i]	88-65-3
α-Iodonaphthalene	Naphthalene	88[e]	90-14-2

[a] Reaction time of 24 hr unless specified (registry no. for NaH, 7646-69-7). [b] Crude isolated yield unless specified. [c] Yield determined by gc with internal standard (toluene or benzene). [d] 2 hr reaction time. [e] 48 hr reaction time. [f] 72 hr reaction time. [g] 8 day reaction time. [h] 6 day reaction time. [i] Expressed as a per cent composition of a mixture of product and starting material.

Halobenzoic acids are only slowly reduced with NaH, perhaps due to heterogeneity of the reaction, and mixtures of starting material and benzoic acid[8] are obtained with o-bromobenzoic acid, o-iodobenzoic acid, *m*-iodobenzoic acid, and *p*-iodobenzoic acid.

The reaction yields unrecognizeable products when the aryl ring is substituted with electron-withdrawing groups such as carbomethoxy or nitro. With o-bromonitrobenzene a bright scarlet color initially appears, perhaps indicative of a σ-complex, followed by rapid darkening of the reaction mixture.

Whereas α-iodonaphthalene is smoothly reduced to naphthalene with NaH in THF, α-chloro- and α-bromonaphthalene are inert to NaH even in refluxing dioxane.

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 137 or 337 instruments. Nmr spectra were obtained with a Perkin-Elmer R-24 spectrometer. Woelm alumina was used for column chromatography. Organic solutions were dried with anhydrous granular K_2CO_3 and concentrated *in vacuo* with a Büchi rotary evaporator.

Representative Procedure. Naphthalene from α-Iodonaphthalene. An oven-dried, three-neck flask equipped with a reflux condenser and magnetic stir bar was allowed to cool to room temperature under a stream of dry nitrogen. The flask was then cooled to 0° and charged with 125 ml of dry THF. NaH was prepared by washing ~2 g of NaH oil dispersion (Ventron Chemical Corp.) with 25 ml of dry pentane and filtering the solid NaH on a fritted disk. The light gray NaH powder was rapidly weighed and 1.08 g (0.0450 mol) was transferred to the reaction flask at 0° under N_2. After being stirred 3 min, 2.85 g (0.0112 mol) of α-iodonaphthalene was added and the mixture was refluxed for 48 hr. The reaction was worked up by cooling to 0° and adding 95% EtOH dropwise under N_2. The mixture was diluted with 250 ml of H_2O and extracted with anhydrous ether. (One should ensure the ether does not contain peroxides as these oxidize the iodide and cause a darkening of the product.) The ethereal extract was washed with aqueous $NaHSO_3$, then H_2O, and dried over anhydrous K_2CO_3. Filtration and concentration *in vacuo* gave 1.43 g (100%) of light yellow orange material. Chromatography over 20 g of activity III basic alumina with ether–pentane (1:1) provided 1.26 g (88%) of pure naphthalene as a colorless solid, identical with authentic material (mixture melting point, nmr, ir).

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Formation of Carbon-Carbon Double Bonds by the Reaction of Vicinal Dihalides with Sodium in Ammonia[1]

Evan L. Allred,* Boyd R. Beck,[2] and Kent J. Voorhees

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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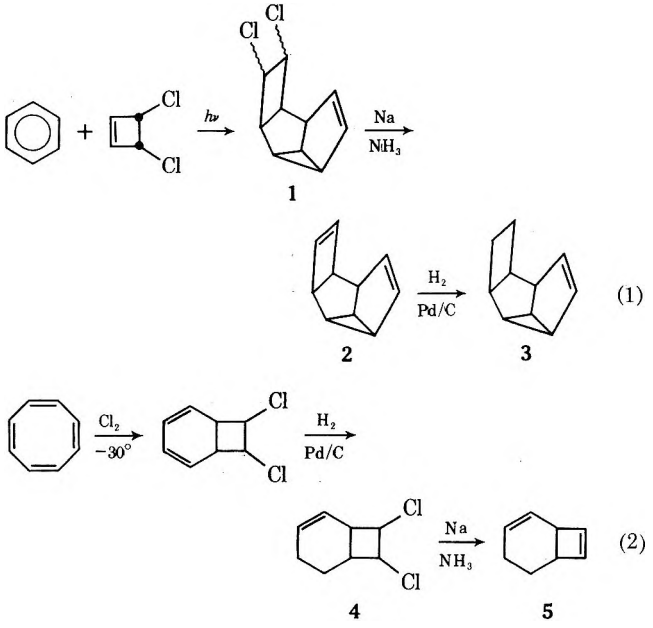
Recently we had need to transform vicinal dihalides to structures containing carbon–carbon double bonds.[3] One of the reagents we considered to be a prime candidate for effecting the dehalogenations was sodium in liquid ammonia. In surveying the literature, we found reports of such a reaction to be rare.[4-7] Much to our surprise, the treatises which deal with synthetic methods and reagents fail to illustrate,[8,9] or in most cases even reference, the reaction.[10-17] We have found the reaction of vicinal dihalides with sodium in ammonia to be very valuable in our work, and we believe that there should be more general awareness of the usefulness of this dehalogenation method.

Two synthetic sequences which illustrate our use of the method are shown by eq 1 and 2. When dichloride **1** was treated with excess sodium in ammonia for 1 hr, tetracyclo[5.3.0.0^{2,10}.0^{3,6}]deca-4,8-diene (**2**) was obtained in essentially quantitative yield. The structure **2** was established unequivocally by partial hydrogenation to known compound **3** of 3,6-endo configuration.[18] A similar dechlorination of **4** likewise gave a high conversion to bicyclo[4.2.0]octa-2,7-diene (**5**). The product structure was



confirmed by the nmr spectrum, which was comparable to those reported for **5**.[19,20]

The synthetic scope of the method was evaluated further with several simple vicinal dihalide systems. For example, treatment of 1,2-dichlorohexane, 1,2-dichlorocyclohexane, or 1,2-dichlorocyclooctane with sodium in ammonia for 1.5 hr gives >96% conversion to the corresponding alkene. Analogously, 1,2-dibromocyclohexane was transformed to cyclohexene (98%). When 1,2-dichlorocyclooctane was treated with sodium in ammonia for 10 min, a >95% conversion to cyclooctene was realized. We have not examined the question of the stereochemistry of the dehalogenations. However, an early mechanistic study indicates that the process is not stereospecific.[5,21]

It is often declared that dehalogenation of vicinal dihalides is of little synthetic value since the dihalides themselves are prepared from the alkenes.[12-14,16,23,24] Such statements are misleading in terms of synthetic usefulness. As illustrated by eq 1 and 2, dehalogenation can be an important part of a synthetic sequence which generates a structurally new double bond. Sodium in ammonia is an excellent reagent for this because the reaction is easily and rapidly completed, and the conversion to alkene is uniformly very high. For dehalogenation of **1** and **4** we found sodium in ammonia to be superior to the recently recommended arene–sodium reagents[22,25] in both convenience of procedure and in yield of isolated product.[3] It is clear that sodium in ammonia should be ranked among the best dehalogenating agents.[8-17,23-25]

Experimental Section[26]

4,5-Dichlorotetracyclo[5.3.0.0^{2,10}.0^{3,6}]dec-8-ene (1). The procedure used was a modification of the photochemical addition of benzene to cyclobutene.[18] A solution of 62.9 g (0.51 mol) of *cis*-3,4-dichlorocyclobutene[27] and 350 ml of benzene under a nitrogen atmosphere was irradiated (quartz) with a 450-W Hanovia medium-pressure mercury lamp for 20 hr. Progress of the reaction was followed by glpc (20% SE-30 on Chromosorb W, 15 ft × 0.125 in., programmed 70–130° at 6°/min). After this time the unreacted *cis*-3,4-dichlorocyclobutene and benzene were removed by vacuum distillation at 80° by gradually decreasing the pressure to 0.2 mm. This left a residue of 10.6 g of viscous brown oil. The distillate of reactants was again irradiated for 20 hr. A total of five of these cycles produced 46.8 g of crude photoadduct. Elution chromatography on 500 g of neutral alumina (pentane eluent) gave 19.1 g of **1** (31% based on the *cis*-3,4-dichlorocyclobutene consumed), mp 72.5–75°. An analytical sample was obtained by preparative glpc (15% FFAP on Chromosorb W, 10 ft × 0.375 in.): mp 77–78°; nmr (C_6D_6) δ 5.26 (d of d, 1 H), 5.02 (d of d, 1 H), 4.46 (apparent t, 1 H), 3.62 (br d, 1 H), 3.44 (apparent t, 1 H), 3.14 (m, 1 H), 2.68 (m, 1 H), 2.38 (apparent q, 1 H), 1.47 (apparent d of t, 1 H), 1.26 (apparent q, 1 H).

Anal. Calcd for $C_{10}H_{10}Cl_2$: C, 59.70; H, 5.01; Cl, 35.28. Found: C, 59.89; H, 4.88; Cl, 35.06.

Tetracyclo[5.3.0.0^{2,10}.0^{3,6}]deca-4,8-diene (2). A 4.0-g (0.174 g-atom) sample of freshly cut sodium (porcelain spatula) was added to 500 ml of dry ammonia which had been distilled from sodamide. To this stirred blue solution under a nitrogen atmosphere was added *via* a syringe 7.73 g (0.034 mol) of **1** in 75 ml of dry tetrahydrofuran. The reaction solution was stirred for 1 hr and then was quenched by cautiously adding ammonium chloride in small portions. Following this, 200 ml of ether and 800 ml of water were added. The aqueous mixture was extracted continuously with ether. The ether was removed from the dried extract ($MgSO_4$) by careful distillation, leaving 4.92 g (~98%) of **2**. A pure sample of **2** was obtained by preparative glpc (20% SE-30 on Chromosorb W, 10 ft × 0.375 in., 110°): ir (neat) 6.27 (C=C, cyclopentene),[28] 6.45 μ (C=C, cyclobutene);[28] nmr (C_6D_6) δ 6.18 (m, 1 H), 5.62 (d of d, 1 H), 5.50 (br d, 1 H), 5.00 (d of d, 1 H), 3.86 (m, 1 H), 3.70 (m, 1 H), 3.18 (apparent d of t, 1 H), 2.96 (apparent q, 1 H), 1.66 (apparent d of t, 1 H), 0.94 (apparent q, 1 H); high-resolution mass spectrum *m/e* 130.0790 (calcd for $C_{10}H_{10}$, *m/e* 130.0783).

Tetracyclo[5.3.0.0^{2,10}.0^{3,6}]dec-8-ene (3). A 40.1-mg (0.31 mmol) sample of **2** in 5 ml of ethyl acetate containing 30 mg of 5% palladium on carbon was partially reduced by the microhydrogenation procedure of Wiberg.[29] Stirring was stopped when

0.34 mmol of hydrogen (110%) had been absorbed (*ca.* 30 sec). Qualitative glpc analysis (15% FFAP on Chromosorb W, 8 ft × 0.125 in., 94°) showed one major and five minor products. The major product, which was collected by preparative glpc (20% SE-30 on Chromosorb W, 10 ft × 0.375 in., 110°), showed an nmr spectrum identical with that published for **3**:[18] nmr ($CDCl_3$) δ 5.80 (m, 2 H), 3.1 (br m, 3 H), 2.69 (br m, 1 H), 2.2-1.2 (series of m, 6 H).

7,8-Dichlorobicyclo[4.2.0]octa-2,4-diene. This dichloride was prepared in 54% yield from cyclooctatetraene and chlorine by the previously described method: bp 102-104° (2 mm);[30] nmr ($CDCl_3$) δ 5.2 (m, 4 H), 4.67 (t, 1 H), 4.45 (t, 1 H), 3.5 (br m, 1 H), 3.0 (br m, 1 H). On the basis of the nmr spectrum, our compound appears to be the *trans*-7,8-dichloro isomer.[31]

7,8-Dichlorobicyclo[4.2.0]oct-2-ene (4). A solution of 9.6 g (0.055 mol) of 7,8-dichlorobicyclo[4.2.0]octa-2,4-diene in 150 ml of a 50:50 methanol-ethyl acetate mixture and 50 mg of 5% palladium on carbon was partially reduced in a Parr shaker. The shaker was stopped when 0.055 mol of hydrogen had been absorbed (*ca.* 5 min). The solution was filtered, the solvent was removed, and the residue was distilled to give 6.8 g (73%) of **4**, bp 115-116° (30 mm). An analytical sample was obtained by preparative glpc (20% SE-30 on Chromosorb W, 20 ft × 0.25 in.): nmr ($CDCl_3$) δ 5.94 (m, 2 H), 4.7-3.9 (9-line m, 2 H), 3.4-1.3 (series of m, 6 H).

Anal. Calcd for $C_8H_{10}Cl_2$: C, 54.29; H, 5.65; Cl, 40.06. Found: C, 54.48; H, 5.85; Cl, 39.89.

Bicyclo[4.2.0]octa-2,7-diene (5). A 0.85-g (0.037 g-atom) sample of freshly cut sodium was added to 200 ml of ammonia. To this stirred solution under a nitrogen atmosphere was added 1.5 g (0.008 mol) of **4** in 100 ml of dry ether. The reaction solution was stirred for 1.5 hr and then was quenched with ammonium chloride. After this, 400 ml of water was added and the mixture was continuously extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent was removed by careful distillation, leaving 0.74 g (83%) of **5** which was >97% pure by glpc (20% SE-30 on Chromosorb W, 10 ft × 0.125 in., 70°): nmr (C_6D_6) δ 6.08 (d, 1 H), 5.9 (m, 3 H), 3.2 (br m, 2 H), 2.3-1.2 (series of m, 4 H).[19,20]

Reaction Scope Studies. The vicinal dihalides 1,2-dichlorohexane, 1,2-dichlorocyclohexane, 1,2-dichlorocyclooctane, and 1,2-dibromocyclooctane were prepared in the usual way by addition of halogen to the corresponding alkene at low temperature.[32] In all cases the dihalides were purified and had physical and spectral properties in agreement with the indicated structures. Dehalogenations were carried out by the procedure given above for the formation of **5**. The conversion of dihalide to alkene was quantitatively measured by glpc using appropriate *n*-alkane internal standards and detector response factors obtained from standardized solutions.

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Registry No.—**1**, 41326-65-2; **2**, 50987-22-9; **3**, 31750-01-3; **4**, 50987-23-0; **5**, 3786-98-9; benzene, 71-43-2; *cis*-3,4-dichlorocyclobutene, 2957-95-1; cyclooctatetraene, 629-20-9; *trans*-7,8-dichlorobicyclo[4.2.0]octa-2,4-diene, 34719-15-8.

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Cleavage of Protecting Groups with Boron Tribromide

Arthur M. Felix

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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Boron halides have been used for the cleavage of methyl ethers,[1,2] benzhydryl esters,[3] *tert*-butyloxycarbonyl amine protecting groups,[4,5] and hindered esters.[6] A recent report[7] that benzyloxycarbonyl amine protecting groups can be removed quantitatively with boron tribromide prompts us to report on our observations using this reagent in peptide chemistry. We observed that, in addition to the removal of *N*-*tert*-butyloxycarbonyl and *N*-benzyloxycarbonyl protecting groups, boron tribromide in methylene chloride gave rapid conversion of methyl, ethyl, *tert*-butyl, benzyl, and *p*-nitrobenzyl esters to their corresponding acids. The alkaline conditions usually employed to hydrolyze methyl and ethyl esters enhances the chances of racemization. The sensitivity of the *N*-benzyloxycarbonyl group[8] and the seryl peptide bond[9-11] to strongly basic conditions also render that method unattractive for general usage.

The products after boron tribromide treatment were isolated by ion-exchange chromatography, found to be analytically pure, and were obtained in yields of 60-90% after crystallization. Optical purity of the products was ascertained to be >99.9% using the procedure of Manning and Moore.[12] Table I summarizes the results obtained for the deprotection of a variety of substrates with boron tribromide. Many of the widely used amino acid side chain protecting groups[13] [Ser(Bzl), Tyr(Bzl), Tyr(Cl_2Bzl), Thr(Bu^t), Glu(OMe), Glu(OEt), Glu(OBzl), Asp(OBu^t), and Lys(Z)] were also removed by boron tribromide, whereas certain other groups [Arg(Tos), Cys(Bzl), and His(im-Bzl)] were unaffected. Although Arg(Tos) was not

Table I
Deprotection with 1.0 *M* BBr_2 (CH_2Cl_2)

Substrate	Registry no.	Product	Yield, %[a]	Yield, %[b]	Optical rotation, deg $[\alpha]^{25}D$ found / standard
					26.64 (*c* 1, 6 *M* HCl)
Z-Val-OH	1149-26-4	Val	86.5	71.5	27.50 (*c* 1, 6 *M* HCl)
					14.14 (*c* 2.1, 6 *M* HCl)
Boc-Leu-OH	13139-15-6	Leu		62.6	14.99 (*c* 2.2, 6 *M* HCl)
					13.70 (*c* 2.3, 6 *M* HCl)
Z-Leu-OMe	51021-87-5	Leu		61.0	14.99 (*c* 2.2, 6 *M* HCl)
Z-Glu(OMe)-OH	4652-65-7	Glu	99.7		
					29.13 (*c* 1.0, 6 *M* HCl)
Z-Glu(OBzl)-OH	5680-86-4	Glu	85.5	79.5	28.06 (*c* 1.0, 6 *M* HCl)
Z-Asp(OBu^t)-OH	5545-52-8	Asp	94.8		
					31.10 (*c* 1.0, 6 *M* HCl)
H-Glu(OEt)-OEt	16450-41-2	Glu		87.9	28.06 (*c* 1.0, 6 *M* HCl)
					28.20 (*c* 1.1, 6 *M* HCl)
H-Glu(OBzl)-OBzl[c]	2768-50-5	Glu	100	79.8	28.06 (*c* 1.0, 6 *M* HCl)
H-Val-OMe	4070-48-8	Val	82.7		
H-Val-OBu^t	13211-31-9	Val	94.2		
					6.97 (*c* 4.0, 6 *M* HCl)
Boc-Tyr(Bzl)-OH	2130-96-3	Tyr	81.4	76.2	7.62 (*c* 4.0, 6 *M* HCl)
Boc-Tyr(Cl_2Bzl)-OH	40298-71-3	Tyr	94.2		
					14.79 (*c* 4.4, 1 *M* HCl)
Boc-Ser(Bzl)-OH	23680-31-1	Ser	74.0	64.3	14.10 (*c* 9.0, 1 *M* HCl)
					−14.95 (*c* 1.0, 1 *M* HCl)
Z-Thr(Bu^t)OBzl(*p*-NO_2)	16879-87-1	Thr	78.5	74.3	−15.26 (*c* 1.0, 1 *M* HCl)
Z-Lys(Z)-OH	51021-86-4	Lys	99.8		
					−28.84 (*c* 0.5, H_2O)
Z-Trp-OH	7432-21-5	Trp	72.2	58.3	−30.88 (*c* 0.5, H_2O)
Z-His-OH	31008-76-1	His	89.1		
					24.71 (*c* 1.0, 1 *M* HCl)
Z-Met-OH	1152-62-1	Met	77.6	62.7	24.03 (*c* 1.0, 1 *M* HCl)
Boc-Cys(Bzl)-OH	5068-28-0	Cys(Bzl)	96.0		
					−20.37 (*c* 1.0, 1 *M* HCl)
Z-Ala-Leu-OEt	41041-70-7	Ala-Leu		73.5	−21.61 (*c* 1.0, 1 *M* HCl)
					−20.80 (*c* 1.0, 1 *M* HCl)
Z-Ala-Leu-OBzl	51021-85-3	Ala-Leu		92.1	−21.61 (*c* 1.0, 1 *M* HCl)

[a] By amino acid analysis of reaction mixture. [b] After recrystallization as analytically pure product. [c] Dissolved in a mixture of *N,N*-dimethylacetamide–CH_2Cl_2 (6:40).

cleaved by boron tribromide, Arg(NO_2) underwent partial deprotection and gave a mixture of Arg, Orn, and Arg(NO_2). Treatment of Z-Met, Z-Trp, and Boc-Tyr(Bzl) (without addition of scavenging reagents) gave the corresponding amino acids free of alkylated side products. Since methionine was reported to react slowly with boron tribromide,[14] quantitative amino acid analysis was performed on the crude product from the reaction of Z-Met with boron tribromide. No evidence for any ninhydrin-positive side products with the free methionine was observed. Therefore the mild conditions employed for the deprotection caused no secondary reaction of methionine.

Deprotection of derivatives of asparagine and glutamine with boron tribromide resulted in partial degradation to aspartic acid and glutamic acid. Treatment of Z-Asn-OH with boron tribromide gave a mixture of Asn (95.8%) and Asp (4.2%). Similar treatment of Z-Gln-OH afforded Gln (90.1%) and Glu (9.9%). The reaction of Z-Asn-OMe and Z-Gln-OMe with boron tribromide gave respective mixtures of asparagine–aspartic acid and glutamine–glutamic acid. There was no evidence for isoasparagine or isoglutamine and it was concluded that there was no intermediate formation of Z-L-aminosuccinimide or Z-L-α-aminoglutarimide by the new procedure as previously postulated[15] for the alkaline hydrolysis of Z-Asn-OMe and Z-Gln-OMe.

Treatment of Z-Ala-Leu-OBzl or Z-Ala-Leu-OEt with boron tribromide gave the free peptide, Ala-Leu, exclusively. In each case there was no evidence for the presence of Ala or Leu and it was concluded that the peptide bond is unaffected by the reagent. The boron tribromide deprotection reactions were generally carried out in methylene chloride. *N,N*-Dimethylacetamide was found to serve as a satisfactory cosolvent with methylene chloride for the deprotection of insoluble substrates.

Experimental Section

Boron tribromide was purchased from Ventron Corp., Beverly, Mass., and was used without further purification. Solutions of 1.0 *M* boron tribromide in methylene chloride were stored in a Teflon bottle, placed into a larger container containing Drierite, and kept at −20°. *N*-Benzyloxycarbonylamino acids and other amino acid derivatives were synthesized or purchased from Fox Chemical Co. and examined for purity by thin layer chromatography prior to usage. All amino acid derivatives used were of the L configuration. *N,N*-Diemthylacetamide (spectrophotometric grade) was purchased from Aldrich Chemical Co., Milwaukee, Wis., and dried over molecular sieve. All other reagents and solvents were of reagent grade and used without further purification. C, H, N microanalyses were determined to within ±0.4 of the theoretical values. Optical rotations were measured in a jacketed 1-dm cell on a Perkin-Elmer Model 141 polarimeter. Thin layer chromatography was performed on all amino acids and peptides using silica gel G in three separate systems and developed with fluorescamine.[16] [BuOH–AcOH–EtOAc–H_2O (1:1:1:1); BuOH–AcOH–H_2O (4:1:1); BuOH–AcOH–pyridine–H_2O (15:3:10:12)]. The crude amino acids and peptides following boron tribromide treatment were chromatographed on AG-50WX2 (Bio-Rad Laboratories, Richmond, Calif.). The resin was packed in a column (30 × 4.5 cm), regenerated with 2 *M* NaOH, H_2O, 2 *M* HCl, and H_2O, and equilibrated and eluted with 0.4 *M* pyridine acetate, pH 4.0. Amino acid analyses were performed on the Joel Model JLC-5AH amino acid analyzer.

Procedure for Protecting-Group Cleavage. The substrate (2.0 mmol) was dissolved in CH_2Cl_2 (50 ml) and cooled to −10° and 10 ml of 1 *M* BBr_3 in CH_2Cl_2 (10.0 mmol) added dropwise with stirring. Stirring continued at −10° for 1 hr and at 25° for 2 hr. The reaction was terminated by careful dropwise addition of

water (50 ml). The layers were separated, the organic phase was washed with H_2O (3 × 25 ml), and the combined aqueous layers were evaporated to dryness. The residue was taken up in H_2O and chromatographed on AG-50WX2 using 0.4 *M* pyridine acetate (pH 4.0) as eluent. In several cases the buffer was adjusted to higher pH in order to elute the product in a volume of 375-475 ml. The ninhydrin-positive fractions were pooled, lyophilized, and crystallized.

Acknowledgments. The author gratefully acknowledges the experimental assistance of Miss Maryann Pizzani and Miss Gene Terkelsen for performing the amino acid analyses. Helpful discussions with Professor R. B. Merrifield, Professor J. Rudinger, and Dr. J. Meienhofer are gratefully acknowledged.

Registry No.—Boron tribromide, 10294-33-4.

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Oxidation of Tyrosine and of NH_2-Terminal Tyrosine Peptides with the Cu^{2+}/H_2O_2 System

Clara L. Deasy*[1]

Tanners' Council Research Laboratory, University of Cincinnati, Cincinnati, Ohio 45221

Linda H. Walling and Sr. Alfreda Alexander

College of Mount St. Joseph on the Ohio, Mount St. Joseph, Ohio 45051

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The oxidations of tyrosine and of tyrosine-containing peptides to aminochromes have long been known as enzymatic reactions.[2] More recently, analogous chemical oxidations have been studied spectroscopically. Wilchek, *et al.*,[3] reported that, at room temperature, *N*-bromosuccinimide oxidation of tyrosine esters and of tyrosinamide (but not of free tyrosine) gave a product that was identified spectroscopically as an unstable red aminochrome, λ_{max} 480 and 320 nm. Dukler, *et al.*,[4] found that tyrosine methyl ester and di- and tripeptides with NH_2-terminal tyrosine were oxidized at room temperature by potassium nitrosodisulfonate (Fremy salt), forming a product with absorption maxima at 305 and 475 nm, characteristic for dopachrome (2, R = H). As in the case of the enzymatic reaction, oxidation by this reagent of peptides with COOH-terminal tyrosine resulted, not in an aminochrome, but in dopaquinone, indicated by the characteristic *o*-quinone absorption at 390 nm. Dukler, *et al.*, did not report on the oxidation of tyrosine itself, but found that carbobenzoxy-L-tyrosine gave, on short-term treatment with Fremy salt followed by treatment with $Na_2S_2O_4$ and cleavage of the carbobenzoxy moiety, 3,4-dihydroxy-L-phenylalanine; longer term treatment with Fremy salt gave polymeric oxidation products of tyrosine.

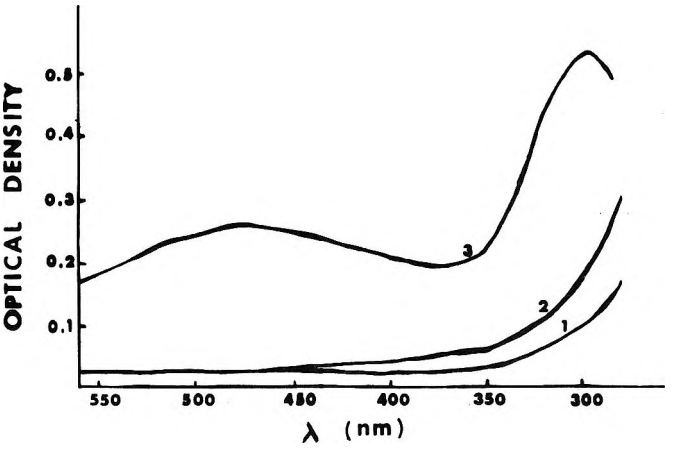
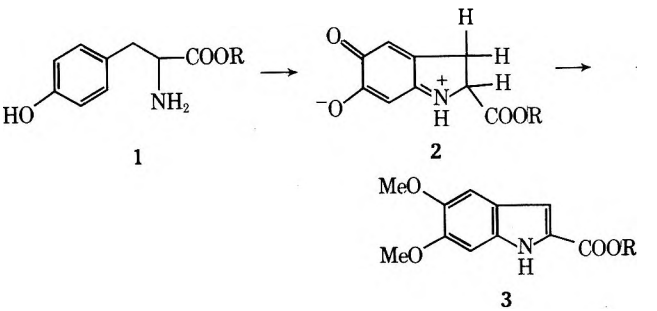


Figure 1. Oxidation of tyrosine by the Cu^{2+}/H_2O_2 system: curve 1, zero time; curve 2, after 16 hr at room temperature; curve 3, after 16 hr at room temperature, followed by addition of Pt black. No change in curve 3 was observed after 8 hr at room temperature.

We wish to report the effect of another oxidizing system, Cu^{2+}/H_2O_2 (3% unstabilized H_2O_2 containing trace amounts of Cu^{2+}), on tyrosine and on some NH_2-terminal and COOH-terminal tyrosine peptides, and the first direct nonenzymatic conversion of free tyrosine to an aminochrome. This metal-activated hydrogen peroxide system contains hydroxy and peroxy radicals, and oxidations by this system are considered to proceed by radical mechanisms.

Results and Discussion

Tyrosine. Tyrosine (1, R = H) was treated at room temperature with excess Cu^{2+}/H_2O_2 reagent, and the ultraviolet absorption spectrum was scanned at intervals against a Cu^{2+} blank of the same concentration. No evidence for dopachrome formation was obtained, even after 16 hr at room temperature. A predominant end absorption at shorter wavelengths was observed; the reagent and unreacted tyrosine are known to absorb in this region (Figure 1, curves 1 and 2).



Addition of Pt black at the end of the 16-hr period caused the immediate development of two absorption maxima at 305 and 475 nm, characteristic of dopachrome (2, R = H) (Figure 1, curve 3). These maxima did not change with time or with addition of more H_2O_2. In the absence of Cu^{2+} from the peroxide system, Pt black did not show this effect.

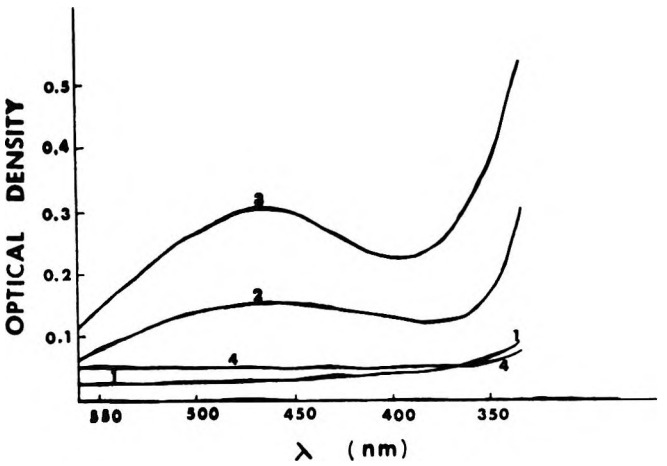


Figure 2. Oxidation of tyrosine peptides by the Cu^{2+}/H_2O_2 system: curve 1, L-tyrosyl-L-leucine at zero time; curve 2, L-tyrosyl-L-leucine after 45 min at room temperature; curve 3, L-tyrosyl-L-leucine after 3.75 hr at room temperature; curve 4, DL-leucyl-DL-tyrosine after 6 hr at room temperature.

Dukler, *et al.*,[4] reported that their dopachrome (**2**, R = CH_3), formed by the action of Fremy salt in a buffered solution (pH 8) on tyrosine methyl ester, on long standing in the presence of the reagents was converted into a dihydroxyindole. It is known that the rearrangement of dopachromes to dihydroxyindoles is catalyzed by acid and by alkali.[5,6] The rearrangement observed by Dukler, *et al.*, was therefore probably due to the alkalinity of the solution. A similar rearrangement was not observed in the present study when the reaction mixture containing the dopachrome was held at room temperature for 8 hr, since the pH of the solution was 5.0 and the dopachrome is known to be stable at this pH.[6]

The presence of dopachrome as a product of the reaction, indicated by the absorption maxima observed, was confirmed by its conversion to the known methyl 5,6-dimethoxyindole-2-carboxylate (**3**, R = Me) by the method of Dukler, *et al.*[4,7] The formation of dopachrome involves introduction of an oxygen ortho to the OH group, dehydrogenation, and intramolecular cyclization through a Michael-type addition reaction; this process evidently requires the hydrogen acceptor Pt black in the case of free tyrosine.

Spectroscopic Studies of the Oxidation of Tyrosine Peptides with the Cu^{2+}/H_2O_2 System. As is the case with other oxidizing agents, the effect of the Cu^{2+}/H_2O_2 system on tyrosine peptides depends on the position of the tyrosine moiety in the peptides.

With the NH_2-terminal tyrosine peptide, L-tyrosyl-L-leucine (**1**, R = leucine moiety), the Cu^{2+}/H_2O_2 system gave an absorption spectrum (Figure 2, curves 1, 2, and 3) similar to that found by Dukler, *et al.*,[4] when tyrosylglycylglycine was oxidized by potassium nitrosodisulfonate (maximum at 475 nm). Dukler, *et al.*, have attributed the spectrum to the fact that the N-terminal peptide was oxidized by a dopachrome mechanism, forming an aminochrome; analogously, the present product may be regarded as an aminochrome (**2**, R = leucine moiety). At room temperature and with excess Cu^{2+}/H_2O_2 the aminochrome absorption at 475 nm increased up to 4 hr, and then slowly began to decline. With neither potassium nitrosodisulfonate nor the present Cu^{2+}/H_2O_2 system was treatment with Pt black required for aminochrome formation from NH_2-terminal tyrosine peptides. Addition of Pt black produced no significant changes in the spectrum other than reduction of the end absorption at shorter wavelengths.

With the COOH-terminal tyrosine peptide DL-leucyl-DL-tyrosine, the absorption spectrum obtained on addition of excess Cu^{2+}/H_2O_2 gave no indication of formation of an aminochrome (maxima at 305 and 475 nm) or of an *o*-quinone (maximum at 390 nm) after 6 hr at room temperature (Figure 2, curve 4). Similar results were obtained with another COOH-terminal tyrosine peptide, glycyl-L-tyrosine. Even after 14 hr at room temperature, followed by treatment with Pt black, no spectral evidence that the COOH-terminal tyrosine peptides were oxidized by either an aminochrome mechanism or a dopaquinone pattern was obtained. The dopaquinone pattern of oxidation of COOH-terminal tyrosine peptides occurs on enzymatic oxidation[2] and on oxidation with potassium nitrosodisulfonate.[4]

Experimental Section

L-Tyrosyl-L-leucine, glycyl-L-tyrosine, and DL-leucyl-DL-tyrosine were obtained from Nutritional Biochemicals Corp., Cleveland, Ohio, and tyrosine from Matheson Coleman and Bell, Cincinnati, Ohio. The 3% H_2O_2 was prepared by dilution of 30% unstabilized H_2O_2 (Fisher Scientific Co.).

Tyrosine or the tyrosine peptide (0.3 mmol) was added to 50 ml of freshly prepared $CuSO_4$ (5×10^{-4} *M*)/H_2O_2 (3% unstabilized) (44.1 mmol of H_2O_2), and the mixture was allowed to stand at room temperature. At intervals aliquots were withdrawn from the solutions, and their absorption spectra were determined after dilution with distilled water (one part reaction mixture to 35 parts water for the spectra shown in Figure 1, and 1:3 for the spectra shown in Figure 2), using a Beckman DB spectrophotometer and reading against a $CuSO_4$ blank of the same concentration as the diluted solution. When Pt black was added to the diluted solution, the mixture was centrifuged to remove the metal after catalytic decomposition of the peroxide was complete, and the absorption spectrum of the supernatant was determined.

For confirmation of the identity of dopachrome produced in the oxidation of tyrosine, the reaction mixture on a preparative scale, after 4 hr at room temperature followed by treatment with Pt black, was allowed to stand overnight at room temperature with $Na_2S_2O_4$ and extracted with ethyl acetate, and the product obtained was converted by ethereal diazomethane to **3**, R = Me, mp 117–119°.

Anal. Calcd for $C_{12}H_{13}NO_4$: N, 5.96. Found: 5.99.

Registry No.—**1** (R = H), 60-18-4; **1** (R = leucine moiety), 17355-10-1; **3** (R = Me), 28059-24-7; $CuSO_4$, 10124-44-7.

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Hydrolysis and Alcoholysis of Orthothio Esters

Robert A. Ellison,* Warren D. Woessner, and Craig C. Williams

School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706

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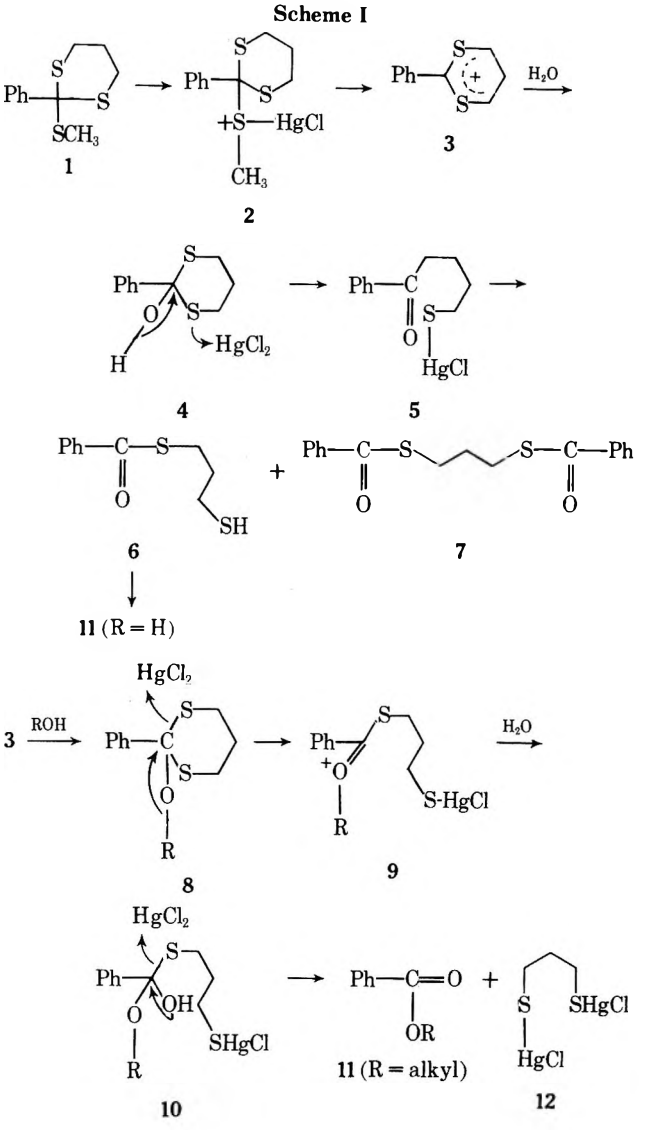
Recently we reported a convenient oxidation of aldehydes to esters and acids *via* 1,3-dithiane derivatives.[1] The hydrolysis to produce the carboxylic acids proceeded less efficiently and in poorer yield than alcoholysis and, unlike the latter, has now been found to give several neu-

Scheme I



tral intermediates which may be isolated as side products along with the acid. Further examination of this reaction using 2-methylthio-2-phenyl-1,3-dithiane (1) has permitted us to characterize, at least qualitatively, the mechanism of this reaction.

1 was prepared from 2-lithio-2-phenyl-1,3-dithiane[2] and methyl disulfide as previously described.[1] Reaction of 1 in refluxing acetone–water (2:1) in the presence of excess $HgCl_2$ for 24 hr resulted in a 63.2% yield of benzoic acid. When the reaction was conducted at 25° in acetone–water (12.5:1) for 66 hr, no acid was recovered but rather an oily mixture containing equal amounts of 6 and 7 (see Scheme I) which could be separated by preparative tlc. Both compounds displayed a carbonyl band in the ir spectrum at 6.02 μ and a broad band at 10.9 μ attributable to the methylene protons α to sulfur.

Confirmation of the assigned structures was obtained by spectroscopic and tlc comparison with authentic samples prepared synthetically. At reflux in acetone–water (12.5:1) but for only 4.5 hr, both 6 and 7 were recovered along with some benzoic acid (5.5:2:2.5, respectively). To further test that 6 and/or 7 were intermediates in the hydrolysis, the mercuric chloride salt of 6 (5) was prepared and exposed to $HgCl_2$ in refluxing acetone–water (2:1) for 24 hr. Benzoic acid was isolated in 52.4% yield. Similarly, at 25° for 71.5 hr, 5 gave a substantial amount of a 1:1 mixture of 6 and 7. Treatment of 7 under the same conditions at 25° for 20 hr gave only recovered starting material.

In contrast to hydrolysis, the ethanolysis of 1 proceeds smoothly. Complete reaction requires 1 equiv of $HgCl_2$ for each sulfur atom, as evidenced by the presence of starting material in reaction mixtures with $[HgCl_2]/[\text{orthothioformate}] < 3$. In the case of ratios ≥ 3, nmr analysis indicated complete reaction in a few minutes. However, when 1 was refluxed with $HgCl_2$ in *tert*-butyl alcohol–water (12:1) for 74 hr, the only isolable product was benzoic acid, which was isolated in 60% yield. *tert*-Butyl benzoate was prepared and found to be inert to these reaction conditions.[1] Thus benzoic acid may form directly from 1 and this suggests steric hindrance to the approach of the alcohol. In the case of the *n*-butyl or cinnamyl analogs of 1 the *tert*-butyl esters are formed in good yield, albeit after comparatively long reaction times.

When reactions were conducted using solvent mixtures consisting of two alcohols each having different steric bulk (1:1 v/v), the ester from the less bulky alcohol was formed either predominantly or exclusively. Thus, nmr analysis of products formed from mixtures of methanol with ethanol, isopropyl alcohol, *sec*-butyl alcohol, and *tert*-butyl alcohol gave ester ratios of 2.1:1, 2.9:1, 9:1, and infinity, respectively.

The mechanism we propose is outlined in Scheme I and is reminiscent of that described for ortho esters.[4] Comparison of reactions 4 → 5 and 8 → 9 (R = alkyl) shows why thio esters are obtained in the case of hydrolysis whereas only esters are derived from alcoholysis. Generation of thio esters like 6 and 7 has been encountered during the hydrolysis of ketene thioacetals.[5]

Experimental Section

General. Infrared spectra were recorded on a Beckman IR-5A spectrometer. Nmr spectra were recorded on a Varian A-60A spectrometer and chemical shifts were recorded in parts per million (δ) from internal tetramethylsilane. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The preparation of orthothioformates and of *tert*-butyl benzoate was described in the previous paper.[1]

Hydrolysis of Phenyl Orthothioformate (1). At Reflux. Phenyl orthothioformate 1 (238 mg, 1 mmol) was dissolved in 35% aqueous acetone (27 ml) with $HgCl_2$ (1.14 g) and HgO (353 mg) and refluxed for 24 hr. The reaction was cooled and worked up as previously described.[1] The only product was benzoic acid (80 mg), mp 122°. When the same quantities were refluxed for 4.5 hr there was isolated, in addition to benzoic acid (9 mg), an oily mixture (26 mg) of two neutral compounds (6 and 7) which are further characterized below.

At 22°. Phenyl orthothioformate (1, 475 mg) was dissolved in 8% aqueous acetone along with $HgCl_2$ (2.28 g) and stirred at room temperature for 66 hr. Upon work-up, no acidic material was detected. From the neutral fraction there was isolated a crude oil (172 mg) from which could be separated in low yield two compounds by preparative tlc on silica gel developed with benzene–ethyl acetate (10:1). The compound with higher R_f was shown to be chromatographically and spectroscopically identical with 6 which was prepared independently (see below). Similarly, the less polar compound was shown to be 7.

Preparation of Monothio Ester 6. Benzoyl chloride (1.26 g, 8 mmol) was added dropwise to a stirred solution of propanedithiol (2.01 ml, 20 mmol) in dry pyridine (10 ml). The resulting solution was refluxed for 30 min under nitrogen and then cooled to room temperature. Aqueous 5% $NaHCO_3$ (40 ml) was added and the solution was extracted with two 100-ml portions of CH_2Cl_2. The organic extracts were washed with aqueous NH_4Cl followed by aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield 6 as a clear oil (1.2 g, 72%) which was purified by distillation in a Kugelrohr apparatus: ir (neat) 6.01, 10.9 μ; nmr ($CDCl_3$) δ 1.33 (t, 1 H, J = 8.5 Hz), 1.98 (m, 2 H), 2.61 (m, 2 H), 3.13 (t, 2 H, J = 7.0 Hz). *Anal.* Calcd: C, 56.57; H, 5.70. Found: C, 56.63; H, 5.69.

Preparation of Bisthio Ester 7. Benzoyl chloride (7.56 g, 48 mmol) was added dropwise to a stirred solution of propanedithiol (1.75 ml, 17.4 mmol) in dry pyridine (10 ml). The reaction pro-

ceeded as described for the preparation of **6** to yield **7** as an oily solid which was purified by crystallization from hexane: mp 53–53.5°; ir (CCl_4) 6.00, 10.9 μ; nmr ($CDCl_3$) δ 2.10 (q, 2 H, J = 7.0 Hz), 3.15 (t, 4 H, J = 7.0 Hz). *Anal.* Calcd: C, 64.53; H, 5.10. Found: C, 64.64; H, 5.09.

Preparation of Salt 5. Monothio ester **6** (320 mg, 1.5 mmol) was dissolved in acetone–water (99:1, 35.5 ml). Addition of a solution of $HgCl_2$ (815 mg, 3 mmol) in acetone (5 ml) to the above solution immediately gave a white precipitate. After stirring for 15 min the reaction mixture was filtered and washed with cold acetone to yield a white power (510 mg). Evaporation of the filtrate followed by trituration with acetone–water gave additional, less pure powder (87 mg). The salt was insoluble in $CHCl_3$, acetone, and benzene but dissolved in warm THF, dioxane, or DMSO: ir (KBr) 6.01, 10.98 μ; nmr (DMSO-d_6) δ 1.92 (m, 2 H, J = 0 Hz), 3.21 (t, 2 H, J = 7 Hz).

Benzoic Acid from Salt 5. Salt **5** (223 mg) was refluxed under nitrogen with a solution of $HgCl_2$ (560 mg) and HgO (176 mg) in 35% aqueous acetone (27 mg) for 24 hr. The reaction mixture was filtered and the filtrate was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was separated into acid and neutral fractions. From the acid fraction, after evaporation of the CH_2Cl_2, benzoic acid was isolated (32 mg, 52%), mg 122°.

Reaction of Salt 5 at 22°. Salt **5** (223 mg) was dissolved in acetone–H_2O (92:8, 12.5 ml) with $HgCl_2$ (560 ml) and stirred for 72 hr at 22°. The reaction mixture was filtered and the filtrate was worked up as above to give an oily solid (19 mg) which was shown to be mostly **7** by tlc and nmr.

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Registry No.—**1**, 34858-82-7; **5**, 51025-51-5; **6**, 51021-88-6; **7**, 51021-89-7; benzoic acid, 65-85-0; benzoyl chloride, 98-88-4; propanedithiol, 109-80-8; $HgCl_2$, 7487-94-7.

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2,2-Bis(methylsulfonyl)vinylamines. A New Class of Vinylamines

Alan R. Friedman* and David R. Graber

Agricultural Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

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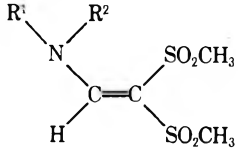
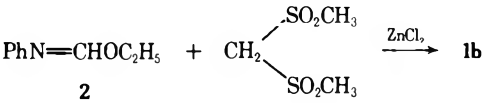
We were interested in preparing compounds of the general formula **1**. Surprisingly, compounds of this type appear not to be known, although many of the corresponding aminomethylene malononitrile and aminomethylene malonic ester derivatives have been reported.[1,2]

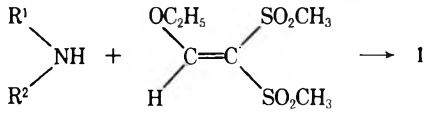


	R^1	R^2
1a	H	H
b	Ph	H
c	n-C_3H_7	H
d	C_2H_5	C_2H_5
e	PhNH	H
f	Ph	CH_3
g	H	O=CPh
h	H	O=CNHCH$_3$
i	H	Ts

N-[2,2-Bis(methylsulfonyl)vinyl]aniline (**1b**) was prepared in 20% yield by the zinc chloride catalyzed reaction of bis(methylsulfonyl)methane[3] (**3**) and ethyl N-phenylformimidate (**2**). A more efficient scheme for the preparation of bis(methylsulfonyl)vinylamines was the reaction of an amine with 2,2-bis(methylsulfonyl)vinyl ethyl ether (**4**), obtained by the reaction of **3** and triethyl orthoformate in the presence of acetic anhydride and zinc chloride. The reaction of **4** with amines proceeded under mild conditions to give the 2,2-bis(methylsulfonyl)vinylamines in 70–80% yield. The reaction of **4** with ammonia, propylamine, diethylamine, phenylhydrazine, or hydroxylamine proceeded without the addition of a catalyst. However, addition of acetic acid to the phenylhydrazine reaction gave a higher yield of **1e**. The reaction of **4** with aniline did not proceed smoothly without the addition of an acid catalyst.[5] N-Methylaniline would not condense with **4** directly; however, N-[2,2-bis(methylsulfonyl)vinyl]methylaniline (**1f**) could be prepared by the reaction of **1b** with dimethyl sulfate.

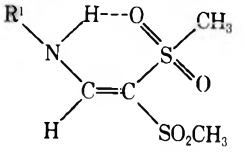


2 **3**

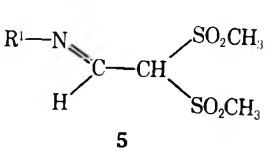


4

Infrared and pmr evidence indicate that the compounds **1a**, **1b**, **1c**, and **1e** exist mainly as the vinylamines and not as the tautomeric aldimines (**5**). This evidence includes a strong ir band at ~1600 cm^{-1} for the enamine sulfone system[4] of **1a**, **1b**, **1c**, and **1e**, as well as for **1d**, which cannot tautomerize, and an NH absorption for compounds **1b** and **1c**. The pmr evidence includes the large (J = 12–15 Hz) NHCH= coupling for compounds **1a**, **1b**, **1c**, and **1e**.

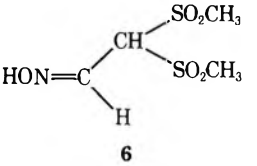


1a, b, c, e,



5

The reaction of hydroxylamine and **4** does not give N-[2,2-bis(methylsulfonyl)vinyl]hydroxylamine but rather, from ir (no 1600-cm^{-1} band) and pmr evidence, 2,2-bis(methylsulfonyl)acetaldehyde oxime (**6**). Although the melting point of **6** is sharp, its pmr in dimethyl sulfoxide-d_6 suggests a 2:1 mixture of the E and Z oximes.[7] 2,2-Bis(methylsulfonyl)vinylamine (**1a**) reacts as an amine with acylation-type reagents, benzoyl chloride, or methyl isocyanate, to yield the benzamide **1g** or methylurea **1h**. However, **1a** did not react with p-toluenesulfonyl chloride in the presence of triethylamine. Conversion to the anion (n-butyllithium) permitted preparation of the sulfonamide **1i**.



6

Experimental Section

2,2-Bis(methylsulfonyl)vinyl Ethyl Ether (4). Into a magnetically stirred 250-ml round-bottom flask equipped with a 10-in. Vigreux column were placed triethyl orthoformate (22.2 g, 0.15 mol), acetic anhydride (15.3 g, 0.15 mol), bis(methylsulfonyl)methane[3] (8.6 g, 0.05 mol), and anhydrous zinc chloride (1.5 g). The reaction mixture was heated to 140° in an oil bath, and, after 6 hr, more triethyl orthoformate (22.2 g) and acetic anhydride (15.3 g) were added. The oil bath temperature was raised to 160° and the remaining volatiles were distilled. The mixture was cooled to 25° and washed with hexane. The residue (12.6 g) was extracted with cold chloroform, the chloroform was evaporated under reduced pressure, and the residue (9.6 g) was recystallized from benzene (8.2 g, 72%): mp 124°; pmr ($CDCl_3$) δ 7.98 (s, 1), 4.47 (q, 2), 3.28 (s, 3), 3.17 (s, 3), 1.48 (t, 3).

Anal. Calcd for $C_6H_{12}O_5S_2$: C, 31.57; H, 5.30; S, 28.09. Found: C, 31.17; H, 5.62; S, 27.95.

2,2-Bis(methylsulfonyl)vinylamine (1a). 2,2-Bis(methylsulfonyl)vinyl ethyl ether (4, 41.7 g of 90% pure material, 0.167 mol) was dissolved in dry tetrahydrofuran (500 ml). The solution was cooled to −10° and anhydrous ammonia (3.9 g, 0.23 mol) was added. After 20 min the reaction was warmed to room temperature. After 20 hr the reaction mixture was filtered to obtain the first crop (17.6 g) of the amine. Additional crops of 1a were obtained from the filtrate for a total yield of 29.1 g (88%). An analytical sample recrystallized from ethyl acetate–benzene melted at 179–181°, pmr (DMSO-d_6) δ 8.62–7.33 (broad, 2), 7.83–7.50 (broad, 1), 3.08 (s, 3), 3.05 (s, 3).

Anal. Calcd for $C_4H_9NO_4S_2$: C, 24.14; H, 4.52; N, 7.04; S, 32.15. Found: C, 24.27; H, 4.41; N, 7.03; S, 32.28.

2,2-Bis(methylsulfonyl)vinylaniline (1b). A solution of 4 (8.15 g of 90% pure material, 0.032 mol), aniline (3.0 g, 0.032 mol), and toluenesulfonic acid (100 mg) was combined in chloroform (100 ml). After standing for 4.5 hr, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel. Elution with ethyl acetate–chloroform (1:6) gave the crude product (7.4 g, 83%). The analytical sample was recrystallized from benzene: mp 190–192°; pmr (DMSO-d_6) δ 9.82 (d, 1, J = 15 Hz, NH). 8.20 (d, 1, J = 15 Hz, HC=), 7.55–7.22 (m, 5), 3.28 (s, 1), 3.22 (s, 1).

Anal. Calcd for $C_{10}H_{13}NO_4S_2$: C, 43.67; H, 4.73; N, 5.09. Found: C, 43.90; H, 4.69; N, 5.10.

Compounds 1c, 1d, and 1e. Compounds **1c, 1d,** and **1e** were prepared similarly; yields, melting points, and analyses are as follows.

1c, 65%, 161–163°. *Anal.* Calcd for $C_7H_{15}NO_4S_2$: C, 34.85; H, 6.23; N, 5.82; S, 26.58. Found: C, 35.13; H, 6.41; N, 5.84; S, 26.34.

1d, 79%, 106–108°. *Anal.* Calcd for $C_8H_{17}NO_4S_2$: C, 37.63; H, 6.71; N, 5.48. Found: C, 37.39; H, 6.73; N, 5.54.

1e, 82%, 132–136°. *Anal.* Calcd for $C_{10}H_{14}N_2O_4S_2$: C, 41.41; H, 4.83; N, 9.66. Found: C, 41.38; H, 4.90; N, 9.53.

2,2-Bis(methylsulfonyl)acetaldehyde Oxime (6). A solution of 4 (22.8 g, 0.10 mol) in tetrahydrofuran (200 ml) was treated with hydroxylamine in methanol[6] (0.105 mol). After standing for 16 hr at 25° the solvent was removed under reduced pressure. The residue was taken up in hot ethyl acetate, filtered, and crystallized to yield 6 (12.4 g, 58%): mp 171–173°; pmr (DMSO-d_6) *E* (major) isomer δ 12.3 (s, 1, OH), 7.63 (d, 1, J = 8.5 Hz, HC=N), 6.33 (d, 1, J = 8.5 Hz, SO_2CHSO_2), 3.30 (s, 6, Me); *Z* (minor) isomer δ 12.6 (s, 1, OH), 7.18 (d, 1, J = 8.5 Hz, HC=N), 6.82 (d, 1, J = 8.5 Hz, SO_2CHSO_2), 3.30 (s, 6, Me).

Anal. Calcd for $C_4H_9NO_5S_2$: C, 22.35; H, 4.18; N, 6.52. Found: C, 22.55; H, 4.29; N, 6.70.

***N*-[2,2-Bis(methylsulfonyl)vinyl]-*N*-methylaniline (1f).** 2,2-Bis(methylsulfonyl)vinylaniline (**1b**, 2.75 g, 0.01 mol), dimethyl sulfate (1.26 g, 0.01 mol), and potassium carbonate (2.76 g, 0.02 mol) in acetone (70 ml) were heated at reflux for 20 hr. The reaction mixture was cooled, filtered, and concentrated. The residue, 3.0 g, was recrystallized from benzene–hexane, yield 2.15 g (75%). The analytical sample was recrystallized from benzene: mp 157–158°; pmr ($CDCl_3$) δ 7.93 (s, 1), 7.63–7.12 (m, 5), 3.70 (s, 3), 3.32 (s, 3), 3.27 (s, 3).

Anal. Calcd for $C_{11}H_{15}NO_4S_2$: C, 45.66; H, 5.23; N, 4.84. Found: C, 45.86; H, 5.32; N, 4.92.

***N*-[2,2-Bis(methylsulfonyl)vinyl]benzamide (1g).** 2,2-Bis(methylsulfonyl)vinylamine (3.98 g, 0.02 mol), benzoyl chloride (2.81 g, 0.02 mol), and triethylamine (2.02 g, 0.02 mol) were combined in tetrahydrofuran (100 ml) and heated at reflux for 20 hr. The mixture was cooled to room temperature, filtered to remove triethylamine hydrochloride, and concentrated under reduced pressure. The residue was washed with hexane (125 ml) and chromatographed over silica gel. The product was eluted with ethyl acetate–hexane (2:1) and recrystallized from isopropyl alcohol: yield 3.92 g (65%); mp 179–181°; pmr (DMSO-d_6) δ 10.95 (d, 1, J = 12.5 Hz), 8.61 (d, 1, J = 12.5 Hz), 8.17–7.50 (m, 5), 3.50 (s, 3), 3.37 (s, 3).

Anal. Calcd for $C_{11}H_{13}NO_5S_2$: C, 43.60; H, 4.28; N, 4.62; S, 21.12. Found: C, 43.66; H, 4.38; N, 4.59; S, 21.28.

1-[2,2-Bis(methylsulfonyl)vinyl]-3-methylurea (1h). 2,2-Bis(methylsulfonyl)vinylamine (3.98 g, 0.02 mol), methyl isocyanate (1.5 ml, 0.025 mol), and triethylamine (0.25 ml) were allowed to react at 25° in acetone (100 ml). After 1 hr the reaction mixture was heated at reflux for 30 min and cooled and the acetone was removed under reduced pressure. The residue was recrystallized from acetone–hexane to give the product (4.63 g, 90%): mp 229–231°; pmr (DMSO-d_6) δ 9.67 (broad d, 1, J = 13 Hz), 8.34, (d, 1, J = 13 Hz), 8.00 (broad, 1), 3.17 (s, 6), 2.66 (d, 3, J = 4 Hz).

Anal. Calcd for $C_6H_{12}N_2O_5S_2$: C, 28.15; H, 4.68; N, 10.93. Found: C, 28.55; H, 4.63; N, 11.03.

***N*-[2,2-Bis(methylsulfonyl)vinyl]-*p*-toluenesulfonamide (1i).** 2,2-Bis(methylsulfonyl)vinylamine (3.98 g, 0.02 mol) was dissolved in dry tetrahydrofuran (150 ml). A solution of *n*-butyllithium in hexane (13 ml, 0.02 mol) was slowly added, keeping the reaction temperature at 25°. *p*-Toluenesulfonyl chloride (3.81 g, 0.02 mol) in tetrahydrofuran (25 ml) was added dropwise. After 3 hr a second equivalent of *n*-butyllithium (0.02 mol) was added. After an additional 45 min the reaction mixture was poured into ice water (500 ml), acidified with hydrochloric acid, extracted with methylene chloride, dried ($MgSO_4$), and concentrated to give the crude product (6.95 g). Recrystallization from 95% ethanol gave the pure product (4.0 g, 57%): mp 219–222°; pmr (DMSO-d_6) δ 10.9 (s, 1), 8.25 (s, 1), 7.91 (d, 2), 7.50 (d, 2), 3.25 (s, 6), 2.43 (s, 3).

Anal. Calcd for $C_{11}H_{15}NO_6S_3$: C, 37.42; H, 4.25; N, 3.97. Found: C, 37.78; H, 4.41; N, 4.26.

Acknowledgment. The authors would like to thank the Physical Analytical Chemistry staff of The Upjohn Co. for the elemental analyses.

Registry No.—**1a,** 51022-16-3; **1b,** 51022-17-4; **1c,** 51022-18-5; **1d,** 51022-19-6; **1e,** 51022-20-9; **1f,** 51022-21-0; **1g,** 51022-22-1; **1h,** 51022-23-2; **1i,** 51022-24-3; **4,** 51022-25-4; (*E*)-**6,** 51021-67-1; (*Z*)-**6,** 51021-68-2; bis(methylsulfonyl)methane, 1750-62-5; ammonia, 7664-41-7; aniline, 62-53-3; hydroxylamine, 7803-49-8; dimethyl sulfate, 77-78-1; benzoyl chloride, 98-88-4; methyl isocyanate, 624-83-9; propylamine, 107-10-8; diethylamine, 109-89-7; phenylhydrazine, 100-63-0.

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(5) Boron trifluoride or *p*-toluenesulfonic acid worked equally well.
(6) Prepared from hydroxylamine hydrochloride and sodium methoxide in methanol. After stirring for 30 min the precipitated sodium chloride was filtered and the solution was used for the preparation of **5.**
(7) (a) The major isomer is assigned the *E* configuration from the chemical shift of the formyl proton, 0.45 ppm downfield from the formyl proton of the minor isomer. (b) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 226.

Cyclization of a 3,4-Dihydro-1-benzoxepin-5(2*H*)-ylidenemalononitrile

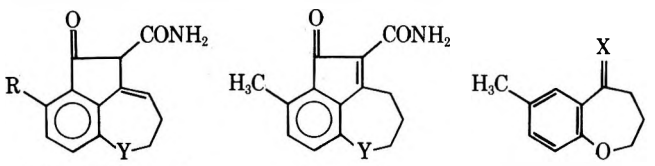
S. W. Schneller* and D. R. Moore

Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received October 24, 1973

Acidic cyclization of ylidenemalononitriles has proven to be a fruitful route to a variety of fused keto amides.[1,2]

Application of this procedure to the ylidenemalononitrile derivatives of benzosuberone and 2,3,4,5-tetrahydrobenzo[*b*]thiepin[1] has yielded compounds **1** and **2**. This reaction has now been successfully applied to the 3,4-dihydro-1-benzoxepin-5(2*H*)-ylidenemalononitrile (**3**).

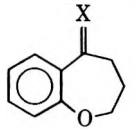


1, Y = CH_2; R = H
5, Y = O; R = CH_3

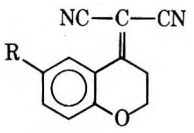
2, Y = S
6, Y = O

3, X = $C(CN)_2$
4, X = O

Compound **3**, which was readily available[1] from **4**,[3] immediately produced a wine-red solution, similar to the formation of **1**, when placed in polyphosphoric acid at 85°. Quenching the reaction yielded **5** as the only product with no indication of isomer **6**. In contrast to the sulfur series,[1] use of sulfuric acid as the cyclizing media produced only small amounts of **5**. On the other hand, no isolable material resulted when the 7-demethylated ylidenemalononitrile (**7**) was subjected to either polyphosphoric acid or sulfuric acid. This result parallels that in the sulfur series[1,4] in which the position para to the heteroatom is susceptible to electrophilic substitution.



7, X = $C(CN)_2$
8, X = O



9, R = H, CH_3

The structure of **5** was based on several lines of evidence: (a) white color analogous to that of **1**[5] and in contrast to the indenone **2**[1] which is red; (b) infrared bands at 5.82 (ketone carbonyl) and 6.08 μ (amide carbonyl) which are in exact agreement with those recorded in our laboratory for **1**; (c) ultraviolet absorptions at 245 and 268–278 nm similar to those of **1**;[5] and (d) an nmr spectrum analogous to that of **1**[6] possessing a vinylic proton absorption at τ 3.91.

The formation of **5** was unexpected in view of the formation of noncyclized ring-sulfonated products when **9**[7] was subjected to similar conditions. The fact that the reaction of **3** gives **5**, analogous to the carbocyclic system, rather than **6**, which would parallel the sulfur series, may be due simply to the similarity in size of O and CH_2. The larger sulfur atom in the sulfur analog may cause greater puckering in the thiepin ring, favoring the exo double bond.

Experimental Section[8]

3,4-Dihydro-1-benzoxepin-5(2*H*)-ylidenemalononitriles. A 400-ml xylene solution containing 190 mmol of either **4**[4] or **8**,[9] 33 g (500 mmol) of malononitrile, 12 g of ammonium acetate, and 36 ml of glacial acetic acid was refluxed with the aid of a Dean-Stark trap until the collection of water ceased. The xylene solution was cooled and decanted from a polymeric mass of malononitrile in the reaction vessel. After this mass was washed with xylene, the xylene fractions were combined and washed with water (3 × 100 ml). After drying over anhydrous $MgSO_4$, the xylene solution was concentrated *in vacuo* and the residue crystallized upon ice cooling.

3,4-Dihydro-1-benzoxepin-5(2*H*)-ylidenemalononitrile (7) was obtained in 65% yield as white needles from aqueous ethanol: mp 98–100°; ir (KBr) 4.50 μ (CN); nmr ($CDCl_3$) τ 2.36–3.10 (m, 4 H, aromatic), 5.89 (t, J = 6 Hz, 2 H, α to oxygen), 7.0 (t, J = 6 Hz, 2 H, γ to oxygen), 7.74 (pentet, J = 6 Hz, 2 H, β to oxygen).

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.28; H, 4.77. Found: C, 74.30; H, 4.90.

3,4-Dihydro-7-methyl-1-benzoxepin-5(2*H*)-ylidenemalononitrile (3) was obtained in 75% yield as yellow needles from cold aqueous ethanol: mp 60–62°; ir (KBr) 4.50 μ (CN); nmr ($CDCl_3$) τ 2.7 (m, 1 H, aromatic), 2.88–3.15 (m, 2 H, aromatic), 5.91 (t, J = 6 Hz, 2 H, α to oxygen), 7.0 (t, J = 6 Hz, 2 H, γ to oxygen), 7.72 (s, 3 H, methyl), 7.75 (br, 2 H, β to oxygen).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 75.00; H, 5.35. Found: C, 74.73; H, 5.50.

2,3,5,6-Tetrahydro-7-methyl-6-oxoindeno[7,1-*bc*]oxepin-5-carboxamide (5). Three grams (13.4 mmol) of **3** was slowly added to 40 g of mechanically stirred polyphosphoric acid at 85°. The resulting solution became wine red almost immediately and stirring was continued at 85° for 1 hr. The resultant solution was poured in 1.8 l. of ice water and the insoluble material which resulted was filtered, washed with water, and air dried. Several recrystallizations from 95% ethanol yielded 47% of **5** as white prisms: mp 186–188°; nmr (DMSO-d_6) τ 2.9–3.15 (br, 2 H, aromatic), 3.91 (br, 1 H, vinyl), 5.75 (t, J = 4 Hz, 2 H, α to oxygen), 5.95 (broad s, 1 H, methine), 7.57–7.88 (5 H, methyl singlet superimposed on multiplet of $-CH_2-$ β to oxygen); mass spectrum m/e (rel intensity) 243 (72), 226 (62), 200 (79), 198 (47), 185 (50), 141 (47), 128 (48), 115 (94), 44 (100), and 18 (68).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.35. Found: C, 68.97; H, 5.28.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and to Dr. T. R. Bosin of the Department of Pharmacology at Indiana University for his assistance in obtaining the mass spectrum for compound **5**.

Registry No.—**3**, 50790-48-2; **4**, 41177-66-6; **5**, 50790-49-3; **7**, 50790-50-6; **8**, 6786-30-7.

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(5) E. Campaigne, R. Subramanya, and D. R. Maulding, *J. Org. Chem.*, **28**, 623 (1963).
(6) The nmr spectrum of **1**, which has previously not been reported in the literature, was found to be (DMSO-d_6) τ 2.32–2.96 (m, 3 H, aromatic), 3.92 (t, J = 5 Hz, 1 H, vinyl), 5.90 (broad s, 1 H, methine), 6.91 (t, J = 5 Hz, 2 H, CH_2), 7.36 (br, 2 H, CH_2), and 8.02 (br, 2 H, CH_2).
(7) E. Campaigne and C. D. Blanton, Jr., *J. Heterocycl. Chem.*, **7**, 1179 (1970).
(8) Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. The nmr spectra were obtained on a Varian A-60 spectrometer using TMS as an internal standard. The ultraviolet absorption spectrum was determined with a Cary Model 14 recording spectrophotometer using 1-cm sample cells. Ir spectra were recorded on a Perkin-Elmer Model 225 spectrophotometer. The mass spectrum was determined on a Varian MAT CH-7 at Indiana University, Bloomington, Ind. The microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.
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Cyclization of δ- and γ-Alkenenitriles by Triethyloxonium Fluoroborate

Francis Johnson,* L. G. Duquette, W. L. Parker, and W. A. Nasutavicus

The Dow Chemical Company USA, Eastern Research Laboratory, Wayland, Massachusetts 01778

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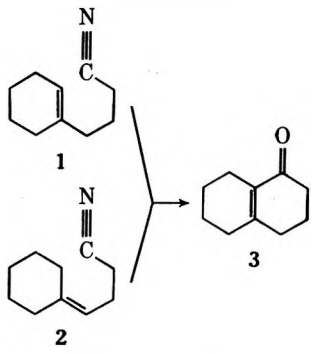
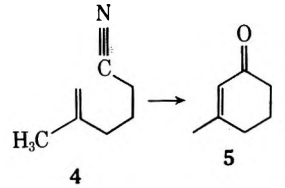
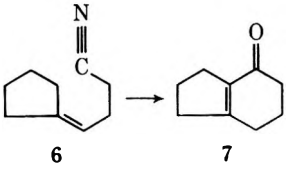
The acid-catalyzed cyclization of δ- and γ-unsaturated nitriles has received little study in the past. In the course of investigating the abnormal Beckmann rearrangement,

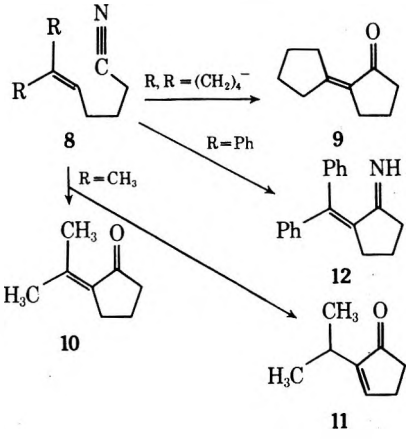
*Address correspondence to Department of Pharmacology, State University of New York at Stony Brook, Stony Brook, N.Y. 11790.

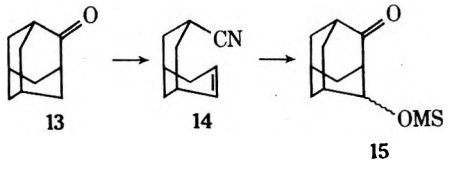
Hill and Conley[1] showed that the isomeric nitriles 1 and 2 both give rise to the octalone 3. Under the same conditions they found that 4 afforded 5 and in an extension of the work Conley and Nowak[2] were able to show that 6 afforded 7. Other reactions studied[2,3] involved the general system 8. In the methylenecyclopentane case 8 [R, R = $(CH_2)_4^-$] a single product 9 was obtained, whereas 8 (R = CH_3) afforded a mixture of 10 and 11. On the other hand, 8 (R = Ph) led to the imine 12 (isolated as the hydrochloride). More recently, Black and Gill[4] have suggested that the conversion[5] of adamantanone (13) to 15 by sodium azide in methanesulfonic acid proceeds *via* the intermediate 14, thus aligning it with the cyclications noted above.



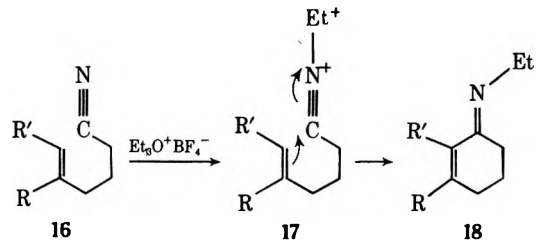


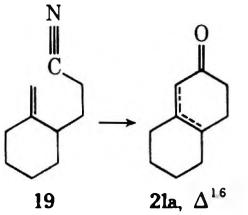


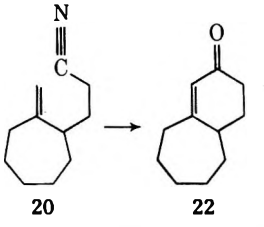




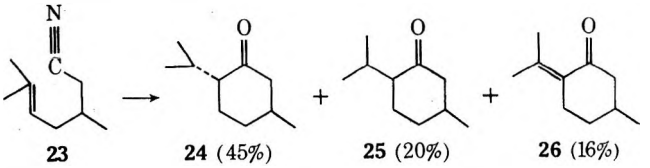
In our work we were interested in finding a method for accomplishing this reaction under conditions milder than hot polyphophoric acid. We decided therefore to examine the use of triethyloxonium fluoroborate as the cyclizing agent, since it seemed likely that the intermediate N-alkylated nitrile[6] (17) ought to undergo spontaneous cyclization with proton elimination to give the imine 18. Hydrolysis of the latter then could be expected to give the desired α,β-unsaturated ketone. In practice we found that little or no reaction could be induced by heating the unsaturated nitrile with triethyloxonium fluoroborate in methylene chloride or nitromethane. Under Meerwein's conditions[6] (heating the components together without solvent), however, reaction proceeded at a reasonable rate and at 80° almost all of the ether expected had been evolved after 30 min. In all cases the reaction product was hydrolyzed with aqueous acid and for the most part the desired products were isolated by steam distillation. The yields, however, were discouraging. In the case of 5-hexencarbonitrile (16, R = R′ = H) 2-cyclohexenone was obtained in only 10–12% yields, whereas the 2-cyanoethyl methylenecycloalkanes 19 and 20 afforded the corresponding bicycloalkenones 21 and 22 in 58 and 29% yields, respectively. The product from 19 was a mixture of 21a and 21b in the ratio 1:1.8, which is to be contrasted with the enamine synthesis[7] of 21, which affords these components in the ratio of 1:6.7 (72% yield). On the other hand, 20 gave 22 as the sole isomer, a result in accord with a recent Robinson–Mannich-style synthesis[8] of the latter compound.



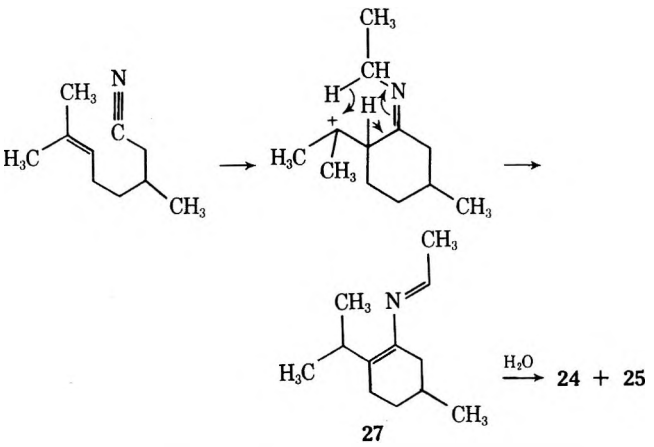




More interesting was the cyclization of citronellonitrile (23). This afforded a steam distillate consisting principally of three components, menthone (24), isomenthone (25), and pulegone (26), in the percentages noted. It appears that in this case the principal pathway followed involves an internal redox reaction, a possible mechanism for which is shown below. The final intermediate, 27, would give on hydrolysis 24, 25, and probably ammonia and acetaldehyde. No attempt was made to identify the latter compounds, however.



Attempts to extend this cyclization process to the synthesis of a five-membered ring did not succeed. The action of triethyloxonium fluoroborate on 28 did not afford



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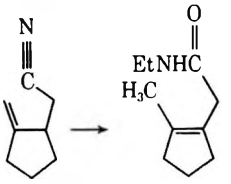
any steam-volatile product after hydrolysis of the reaction mixture. In fact, the only product that could be isolated was the *N*-ethylcarboxamide **29**, in which the double bond had migrated into the ring.



28 29

It should be mentioned also that attempts to effect some of these cyclizations with stannic chloride or boron trifluoride in benzene were unsuccessful. Finally, phenyldiazonium fluoroborate, which is known[6] to form *N*-phenyl salts with nitriles, was heated with **23**, but there was obtained only an 8% yield of a steam-volatile oil containing five components no one of which was pulegone. This was not investigated further.

In general, it may be concluded that triethyloxonium fluoroborate causes cyclization of δ-unsaturated nitriles to give, after hydrolysis of the intermediates, α,β-unsaturated ketones. However, the rather poor yields of product limit the usefulness of the reaction.

Experimental Section

The nmr spectra were obtained using a Varian A56-60 spectrometer while infrared spectra were taken on a Baird spectrophotometer, No. 4-55. Glc data were recorded by a Hewlett-Packard 5750 chromatograph with a helium flow rate of 100 ml/min unless stated otherwise.

2-(β-Cyanoethyl)-1-methylenecyclohexane (19). Sodium hydride dispersion (5.99 g, 56.1% NaH) was washed free of oil with dry petroleum ether (bp 30–60°) and then treated with dry dimethyl sulfoxide (50 ml). The mixture was held at 70° with stirring under nitrogen until homogeneous (1 hr) and then cooled in an ice bath. To this was added in one portion a solution of triphenylmethylphosphonium bromide (48 g) in dimethyl sulfoxide (125 ml). After stirring for 20 min, 2-(β-cyanoethyl)cyclohexanone (20 g) was added dropwise over 20 min. The mixture was heated to 65° for 30 min and then stirred at room temperature overnight. Water (150 ml) was then added and the total liquid was extracted with petroleum ether (4 × 100 ml). The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent afforded a thick oil (17.34 g), which was dissolved in methylene chloride and percolated through a column of silica gel (100 g) to remove triphenylphosphine oxide. The oil (16 g) obtained from the eluate was distilled to give the desired material (12.1 g): bp 95.5–96° (3.8 mm); glc R_f 5.0 (min), 205° (10 ft × 0.25 in. column, 5% QF-1 on Chromosorb), $n^{25}D$ 1.4770; ir (film) 2280 (CN), 1755 and 900 cm^{-1} (=CH_2).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.50; H, 10.11; N, 9.41.

2-(β-Cyanoethyl)-1-methylenecycloheptane (20). This compound was prepared in the same way as its lower homolog **19** using 10.5 g of sodium hydride dispersion (51% NaH), 72 g of triphenylmethylphosphonium bromide, and 32 g of 2-(β-cyanoethyl)-cycloheptanone. The crude product (30 g) was distilled to give the desired compound (17 g) as a colorless liquid: bp 96° (2.5 mm); ir (film) 2250 (CN), 1670 and 885 cm^{-1} (=CH_2).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.71; H, 10.64; N, 8.70.

2-Cyanomethyl-1-methylenecyclopentane (28). This compound was prepared according to the method described above using sodium hydride (56.1% NaH, 4.85 g) in dimethyl sulfoxide (40 ml), a solution of triphenylmethylphosphonium bromide (43 g) in dimethyl sulfoxide (100 ml), and 2-cyanomethylcyclopentanone (14.16 g). This afforded a pale yellow oil (6.74 g) which was distilled at 89–92° (13 mm) to give the pure desired product (4.7 g): $n^{25}D$ 1.4685; ir (film) 2275, 1660, 893 cm^{-1}; nmr (neat) 4.97 ppm (sextet, =CH_2, J = 4.5 Hz).

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.5; H, 9.4; N, 11.4.

Cyclization of 5-Hexene-1-carbonitrile (16, R = R′ = H). Triethyloxonium fluoroborate (8 g) was added to 5-hexene-1-carbonitrile[9] (2 g) under dry nitrogen. The mixture was warmed to 72° with stirring and rapidly became homogeneous and dark brown in color. After 65 min the resulting liquid was added to 6% aqueous acetic acid (50 ml) and the total mixture was steam distilled. The volatile oil (0.4 g) by glc showed two peaks in addition to that due to a small quantity of starting material (R_f 3.2, 80°, QF-1). Of these, by far the major peak could be identified as 2-cyclohexenone by comparison of the R_f (2.2 min, 80°, QF-1) with that of an authentic sample. Comparative glc also showed the yield to be 12%. A sample of the oil (96 mg) was treated with 2,4-dinitrophenylhydrazone reagent (0.4 ml). This gave an orange-red solid (29.7 mg) which was dissolved in benzene and percolated through a column of silica gel (10 g). Elution with benzene afforded the derivative as orange-red needles, mp 167–169°, which did not depress the melting point of an authentic specimen. Their infrared spectra were identical also.

The other component (~20%) of the product was separated by analytical glc (R_f 1.8, 80°, QF-1 on Chromosorb, column 12 ft × 0.25 in.). It showed a sharp band at 1635 cm^{-1} and a broad, very intense band at 1120 cm^{-1} in the infrared spectrum suggesting the presence of fluorine. It was not investigated further.

Attempted Cyclization of 2-Cyanomethyl-1-methylenecyclopentane. The olefinic nitrile **28** (1 g) was heated with triethyloxonium fluoroborate (3.14 g) at 80°. Initially the mixture rapidly liquified, became yellow, and evolved gas. After 3 hr, the red liquid was diluted with a mixture of water (10 ml) and acetic acid (1 ml). Extraction of the resulting solution with ether led to an orange oil (0.38 g). This was dissolved in benzene and chromatographed over silica gel (20 g). Elution with 10% ether in benzene (v/v) afforded a white solid (218 mg), which after repeated crystallization from ethyl acetate gave pure *N*-ethyl 2-[1′-(2′-methylcyclopent-1′-ene)]acetamide (**29**): mp 76–77°; nmr (CCl_4) 1.10 (t, $NHCH_2CH_3$, J = 7 Hz), 1.66 (s, CH_3 on double bond), 1.73 (m, CH_2), 2.30 (m, 2, CH_2), 2.91 (s, =CCH_2CO), 3.19 (p, -$NHCH_2CH_3$, J = 7 Hz), and 7.90 ppm (t, NH, J = 7 Hz); ir (Nujol) 330 (NH) and 1660 cm^{-1} (amide). The mass spectrum showed a fairly intense parent ion at m/e 167 and a base peak at m/e 81 corresponding to loss of the *N*-ethylacetamide group.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.80; H, 10.40; N, 8.40.

Bicyclo[4.4.0]-1-octen-3-one (21b) and Bicyclo[4.4.0]-1(6)-octen-3-one (21a). 2-[β-Cyanoethyl]methylenecyclohexane (**19**, 1.5 g) and triethyloxonium fluoroborate were heated together at 80° for 3.3 hr. Water (100 ml) containing acetic acid (3 ml) was then added and the mixture was steam distilled until no more oil came over. A little sodium bicarbonate was added to neutralize the distillate and the mixture was extracted with methylene chloride. This extract yielded a sweet-smelling oil (1.0 g) whose glc showed basically only two peaks (R_f 7.2 and 8.2, 205°, 5% QF-1 on Chromosorb on a 10 ft × 0.25 in. column) in the ratio of 1:1.8, in addition to a trace amount of starting material. The retention times were identical with those observed for an authentic specimen of these two substances prepared by the method of Stork, *et al.*,[7] except that the ratio of the components in the latter case was 1:6.7. Preparation of a 2,4-DNP according to Fieser[10] using the mixture of components from our procedure gave a brick-red crystalline compound, mp 172–174° (lit.[7] mp 168–170°).

Bicyclo[5.4.0]-7-undecen-9-one (22). 2-(β-Cyanoethyl)methylenecycloheptane (**20**, 4.5 g) and triethyloxonium fluoroborate (18 g) were heated together at 85° for 2 hr. Water (100 ml) containing concentrated hydrochloric acid (6 ml) was added and the mixture was boiled for 1 hr. The mixture was extracted with methylene chloride and the extract was washed with sodium bicarbonate so-

lution and then water and evaporated to give an oil (4.6 g). The latter was chromatographed over silica gel (100 g) and the desired product (1.3 g) was eluted with mixtures of 5–10% ethyl acetate in methylene chloride. The material showed a single peak on glc analysis [R_f 14.2, 205° (10 ft × 0.25 in., 5% QF-1 on Chromosorb)] and its infrared spectrum [1660 (carbonyl) and 1605 cm^{-1} (double bond)] was identical with that of a specimen prepared according to a known method.[8] Its mass spectrum showed a molecular ion at m/e 164 and the base peak at m/e 136 (M − 28). Other significant peaks appeared at m/e 122, 108, 93, 79, 41, and 39.

Cyclization of Citronellonitrile (23). Citronellonitrile (**23**, 24.4 g) and triethyloxonium fluoroborate (30.8 g) were heated together at 80° with stirring under dry nitrogen for 3 hr. Water (150 ml) containing acid (10 ml) was added and the mixture, after being stirred for a few minutes, was steam distilled. The distillate was neutralized using sodium bicarbonate and the product (6.32 g, 25%), a colorless oil with a peppermint odor, was isolated by extraction with methylene chloride. Glc analysis (5 ft × 0.25 in. column, McNair's phase, 30% on 60–80 mesh Chromosorb, 125°, He flow rate 75 ml/min) revealed the presence of six components: A (R_f 5.8, 8%), B (R_f 13.2, 44.6%), C (R_f 15.4, 19.7%), D (R_f 18.5, 4.2%), E (R_f 22.2, 6.3%), and F (R_f 26, 16.3%). Mass spectral data were obtained for each of these compounds. Component A showed parent ions (low-voltage study) at m/e 150 and 180 and was assumed to be a mixture. It and components D and E, both of which showed m/e 180 peaks for their parent ion, were not studied further. Components B and C, both with parent ions at m/e 154, were identified as methone and isomenthone, respectively, by comparison of their infrared spectra and R_f values, while component F by the same criteria, proved to be pulegone (parent at m/e 152, ir 1690 and 1625 cm^{-1}).

Registry No.—**16** (R = R′ = H), 5048-19-1; **19**, 2359-64-0; **20**, 51004-10-5; **22**, 19198-29-9; **23**, 51004-11-6; **28**, 51004-12-7; **29**, 51004-13-8; triphenylmethylphosphonium bromide, 1779-49-3; 2-(β-cyanoethyl)cyclohexanone, 4594-78-9; 2-(β-cyanoethyl)cycloheptanone, 33736-92-3; 2-cyanomethylcyclopentanone, 51004-14-9; triethyloxonium fluoroborate, 368-39-8.

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Organic Synthesis Using Borane–Methyl Sulfide. The Hydroboration–Oxidation of Alkenes

Clinton F. Lane

Aldrich-Boranes, Inc., a Subsidiary of the Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53233

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Borane–methyl sulfide (BMS) is a stable, liquid BH_3 complex, and its numerous advantages over borane–tetrahydrofuran solution as a storable reagent were discussed by Adams and coworkers.[1] The main advantages are that (1) BMS has a molar concentration of borane ten times that of borane–tetrahydrofuran solution, (2) BMS is soluble in and unreactive toward a wide variety of aprotic solvents, and (3) BMS is apparently stable indefinitely when refrigerated.

Table I
Hydroboration–Oxidation of 1-Hexene Using BMS. Solvent Study[a]

Solvent	1-Hexanol, %[b]	2-Hexanol, %[b]	Total yield, %[c]
Ethyl ether	94.4	5.6	100
Tetrahydrofuran	93.6	6.4	100
Hexane[d]	94.1	5.9	100
Toluene[d]	94.2	5.8	98.1
Methylene chloride[d]	93.6	6.4	99.4
Ethyl acetate[d]	94.2	5.8	100
Acetonitrile[d]	93.8	6.2	80.9

[a] All reactions involved the addition of BMS (11 mmol) to 1-hexene (30 mmol) dissolved in 10 ml of solvent at 0–5°. After 1 hr at 20–25°, the reaction mixture was oxidized with alkaline hydrogen peroxide. [b] Relative amount by gc analysis. [c] Total yield by gc analysis using an internal standard. [d] Ethanol (10 ml) added as cosolvent prior to oxidation.

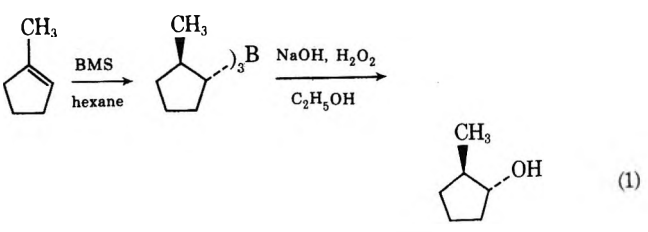
BMS is now commercially available and appears to be a useful borane reagent for organic synthesis.[2] However, a systematic investigation of the hydroboration of alkenes with BMS has not been reported. Such a study will now be described herein.

The miscibility of BMS with various solvents prompted an examination to determine if the solvent has any effect on the hydroboration of alkenes with BMS. 1-Hexene was chosen as a representative alkene. The standard procedure and the results of this solvent study are given in Table I.

As in the case of borane–tetrahydrofuran,[2] hydroboration of a monosubstituted alkene with BMS proceeds quantitatively, placing boron 94% in the terminal position and 6% in the secondary position. Surprisingly, the use of various solvents, most of which could not previously be used in hydroboration reactions, presented no problems for the hydroboration with BMS. Solvents such as ethyl ether, hexane, toluene, and methylene chloride, in which BH_3 has low or negligible solubility, readily dissolve BMS to give quantitative hydroborations. Even solvents which react with diborane can be used for hydroborations with BMS; *e.g.*, 1-hexene was hydroborated cleanly and quantitatively in ethyl acetate.

To define more fully the utility of BMS as a hydroborating agent, a series of representative alkenes were allowed to react with BMS in an appropriate solvent. Hexane was chosen as the solvent because an inexpensive grade is commercially available and is of sufficient purity to require no prior treatment.

The results of this study, as shown in Table II, indicate that the hydroboration–oxidation of alkenes with BMS in a hydrocarbon solvent is a general reaction and gives excellent yields of the corresponding alcohols. That the reaction is both regioselective and stereoselective was shown by the hydroboration–oxidation of 1-methylcyclopentene (eq 1).



(1)

100% yield, > 99% trans

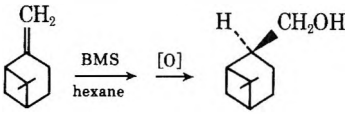
The synthetic utility of this new hydroboration–oxidation procedure was further demonstrated by treating α and β-pinene with BMS on a molar scale in hexane. From (−)-β-pinene an 85% isolated yield of (−)-*cis*-myrtanol

Table II
Hydroboration–Oxidation of Alkenes Using BMS[a]

Alkene	Time, hr[b]	Alcohol products	Relative amounts, %[c]	Total yield, %[d]
1-Hexene	1	1-Hexanol	93.6	100
		2-Hexanol	6.4	
2-Methyl-1-pentene	1	3-Methyl-1-pentanol		99.8
trans-3-Hexene	1	3-Hexanol		88.4
	3			100
Styrene	1	2-Phenylethanol	86.3	100
		1-Phenylethanol	13.7	
Cyclopentene	1	Cyclopentanol		96.5
Cyclohexene	1	Cyclohexanol		78.7
	1[e]			100
Norbornene	1	*exo*-Norborneol		87
	1[e]			94
1-Methyl-cyclopentene	1	*trans*-2-Methyl-cyclopentanol	>99[f]	86.4
	1[e]		>99[f]	100

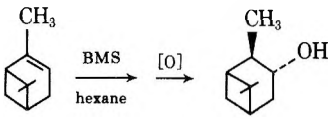
[a] All reactions involved the addition of BMS (11 mmol) to the alkene (30 mmol) dissolved in 10 ml of hexane at 0–5°. After an appropriate interval, ethanol (10 ml) was added and the reaction mixture was oxidized using 3 *N* aqueous NaOH (11 mmol) and 30% aqueous H_2O_2 (33 mmol). [b] Time for hydroboration at 20–25°. [c] By gc analysis. [d] By gc analysis using an internal standard. [e] Reaction mixture was heated to reflux for 1 hr to ensure complete hydroboration. [f] <1% cis isomer.

was obtained (eq 2), while *dl*-α-pinene gave *dl*-isopinocampheol in 92% isolated yield (eq 3).



(2)

85% isolated



(3)

92% isolated

It is now apparent that BMS is indeed a very useful reagent for the preparation of organoboranes *via* hydroboration of alkenes. The stability, commercial availability in pure form, and solubility in a wide variety of solvents should make BMS the reagent of choice for preparative hydroborations.

Experimental Section

All starting materials, including BMS, were used directly as obtained from the Aldrich Chemical Co. Since BMS is decomposed by atmospheric moisture, all manipulations of liquid BMS and the hydroboration reactions were carried out in dry glassware under a nitrogen atmosphere. A detailed description of the techniques necessary in handling air-sensitive solutions has been given elsewhere.[3]

(−)-*cis*-Myrtanol. A dry 2-l. flask equipped with a mechanical stirrer, pressure-equalizing dropping funnel, and reflux condenser was flushed with dry nitrogen and maintained under a positive nitrogen pressure. The flask was then charged with 238 ml (1.5 mol) of (−)-β-pinene and 500 ml of hexane and cooled to 0–5° with an ice–water bath. Hydroboration was achieved by the dropwise addition of 52.5 ml (0.55 mol) of BMS. Following the addition of the hydride (0.5 hr), the cooling bath was removed and the solution was stirred for 3 hr at 20–25°. Ethanol (500 ml) was then added followed by 165 ml of 3 *N* aqueous sodium hydroxide. After cooling to 0–5° in an ice–water bath, hydrogen peroxide (185 ml of a 30% aqueous solution) was added dropwise at such a rate that the reaction mixture warmed to 25–35°. Immediately following the addition of the peroxide (1 hr), the cooling bath was removed and the reaction mixture was heated at reflux for 1 hr. The reaction mixture was then poured into 6 l. of ice water. After adding 2 l. of ether and mixing thoroughly, the lower aqueous layer was removed and discarded. The upper organic layer was washed with water (2 × 1 l.), washed with saturated aqueous sodium chloride, dried over anhydrous potassium carbonate, filtered, and concentrated on a rotary evaporator to give 230 g of a light yellow oil. Short-path vacuum distillation of this oil gave 196 g (85%) of (−)-*cis*-myrtanol: purity >98% by gc analysis; bp 65–67° (0.2 mm); $n^{20}D$ 1.4911; $[\alpha]^{22}D$ −19.5° [lit.[4] bp 70–72° (1 mm); $n^{20}D$ 1.4910; $[\alpha]^{25}D$ −21°].

***dl*-Isopinocampheol.** Hydroboration–oxidation was carried out as described for *cis*-myrtanol using 500 ml of hexane, 160 ml (1.0 mol) of *dl*-α-pinene,[5] 52.5 ml (0.55 mol) of BMS, 500 ml of ethanol, 165 ml of 3 *N* aqueous sodium hydroxide, and 125 ml of 30% aqueous hydrogen peroxide. Isolation gave 154 g of a light yellow oil. Short-path vacuum distillation of this oil gave 141 g (92%) of *dl*-isopinocampheol, which crystallized upon cooling in the receiver, purity ~99% by gc analysis, bp 62–63° (0.25 mm), mp 39–41°. The sublimed alcohol exhibited mp 41–42° (lit.[4] for *l*-isopinocampheol, mp 54–56°).

Registry No.—Borane–methyl sulfide, 13292-87-0; 1-hexene, 592-41-6; (−)-*cis*-myrtanol, 51152-12-6; (−)-β-pinene, 18172-67-3; *dl*-isopinocampheol, 51152-11-5; *dl*-α-pinene, 2437-95-8.

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Relative Stabilities of α-Phenyl and α-Ferrocenyl Cations

Don Kaufman* and Robert Kupper

Department of Chemistry, Kearney State College, Kearney, Nebraska 68847

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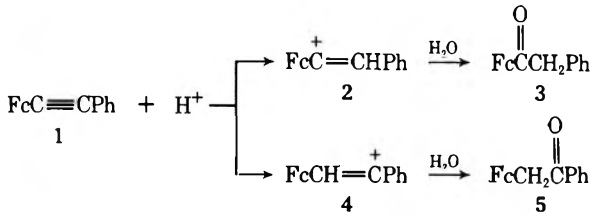
The existence of vinyl cations has now been demonstrated to the extent that these species are no longer hesitantly proposed as reaction intermediates. The first vinyl cations observed were generated in systems in which the positive charge could be delocalized as in substituted di- and triphenylethylenes. More recently, vinyl cations have been produced from a large number of compounds *via* a variety of reactions.[1-7]

In the course of our continued work with vinyl cations, the unusual stability of α-ferrocenyl alkyl cations was noted[8] and it appeared that the presence of an α-ferrocenyl moiety might also permit the ready generation of very stable vinyl cations. After exploratory work showed that various electrophilic additions to ethynylferrocene proceeded facilely, we sought to determine the relative abilities of ferrocenyl and phenyl groups to stabilize vinyl cations, *i.e.*, the relative stabilities of $FcC^+{=}CR_2$ and $PhC^+{=}CR_2$.

A qualitative answer to this question was ascertained by employing a type of intramolecular competition reaction in which either an α-phenyl or α-ferrocenyl vinyl cation could form as an intermediate as shown in Scheme I. When a dilute ethanolic solution of 1 was stirred at room temperature with a catalytic amount of 25% sulfuric acid, ferrocenylbenzyl ketone (3) was quantitatively produced. This result indicates that carbonium ion 2 was formed in preference to 4 and suggests that the α-ferrocenyl vinyl

cation is more stable than the analogous α-phenyl vinyl cation.

Scheme I



Consistent with the qualitative results just described are the kinetic data obtained for the acid-catalyzed hydrations of the compounds shown in Table I.

Table I
Relative Rates of Acid-Catalyzed Hydrations

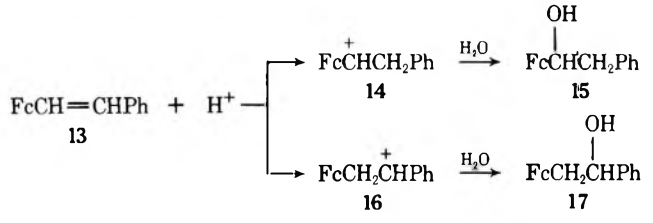
Compd	Reaction product	Relative rate[a,b]
FcC≡CH (**6**)	FcCCH$_3$ (**10**)	1.0
PhC≡CH (**7**)	PhCCH$_3$ (**11**)	10^{-5}
FcCH=CH$_2$ (**8**)	FcCHCH$_3$ (**12**)	0.11
PhCH=CH$_2$ (**9**)		No perceptible reaction

[a] Rates were determined by using uv spectroscopy to follow the disappearance of starting material. [b] First-order kinetics for longer than 5 half-lives were found for the three reactions which proceeded.

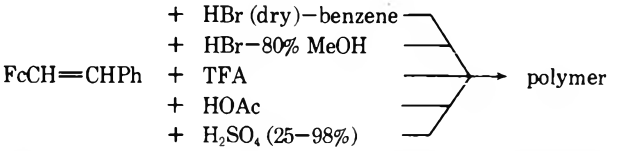
The first-order kinetics observed and the products yielded by compounds **6**, **7**, and **8** indicate an initial rate-determining protonation step for the hydration reactions. Thus, the relative reaction rates for **6** and **7** confirm the greater ease of formation for those vinyl cations stabilized by the α-ferrocenyl group.

To extend the present discussion to alkyl carbonium ions, a comparison of the relative rates of hydration of compounds **8** and **9** is used. On the basis of a faster reaction rate for **8**, it is seen that, just as was true for vinyl cations, alkyl cations are also generated more easily when α to the ferrocene ring. This result is in agreement with the work of Buell, *et al.*,[9] who noted the ready addition of weak electrophiles to vinylferrocene. Styrylferrocene (**13**) was synthesized and allowed to react as the model compound to see which of the two alkyl cations, **14** or **16** would intervene as shown in Scheme II.

Scheme II

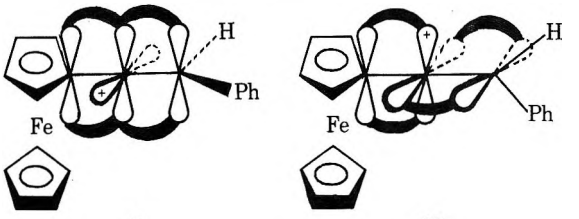


When allowed to react under the mild conditions used to effect the hydration of **1**, styrylferrocene did not react. In order to achieve any addition to styrylferrocene, it was necessary to employ much more drastic reaction conditions. However, under these severe conditions, only polymeric addition products were obtained and not the expected simple hydration products. For example



Based upon the ease of the acid-catalyzed hydration of vinylferrocene, the unreactivity of styrylferrocene in electrophilic additions was not expected. This lack of reactivity for **13**, however, can most likely be attributed to its unusual ground-state stability, which arises from the extended conjugation of the molecule. The reluctant addition to the conjugated system of **13** is not without parallel. For example, whereas bromine adds readily to styrene, it adds only slowly to stilbene. It is also of interest to note that Yates[10] found that electrophilic additions of Br_2, Cl_2, and ArSCl occurred significantly faster with alkyl-substituted olefins than with aryl-substituted olefins. This observation is not likely explained in terms of the relative energies of the carbonium ions. The greater ground-state stability of the conjugated aryl olefins could account for their lower reactivity in a fashion similar to that which is invoked above to explain the lack of reactivity of styrylferrocene.

The question still remains as to why compound **1** was hydrated more readily than **13**. If the unreactively of **13** is due to the loss of extended conjugation in going from the ground state to the intermediate carbonium ion, then it perhaps follows that, since FcC≡CPh (**1**) was seen to be quite reactive, its intermediate carbonium ion still retains the extended conjugation of the ground state. Such would require a structure similar to **18** rather than **19**.



18 **19**

If now the positive charge in **18** is to be delocalized, it would apparently have to be through direct participation of iron, since resonance with the ring would be impossible because of the orthogonality of the vacant p orbital on the vinyl carbon and the ring carbon to which it is attached. The origin of the stabilizing effect of the ferrocene ring in α-ferrocenyl alkyl cations has been the subject of much controversy, with some authors invoking direct participation of iron through its d orbitals while others promote direct conjugation with the ferrocene ring.[8]

The relative hydration rates of compounds **1** and **13** can be regarded as a specific example of the general question as to whether olefinic or acetylenic compounds will react more easily in electrophilic addition reactions. When the relative rates of reaction of compounds **6** *vs.* **8** and **7** *vs.* **9** are compared (Table I), it is seen that in each case the acetylenic compound has reacted appreciably faster than the analogous olefin. If an initial rate-determining protonation is assumed, these comparisons indicate that vinyl cations have formed more quickly than the corresponding alkyl carbonium ions. Finally, reference to the work of Yates[10] is again pertinent. He has shown that the relative reactivities of olefins and acetylenes in electrophilic addition reactions are very dependent upon solvent polarity. In solvent systems of relatively low polarity, olefins reacted significantly faster than the analogous acetylenes. However, acid-catalyzed hydrations, conducted in a polar medium of 48% aqueous sulfuric acid, proceeded at comparable rates for the olefins and acetylenes, with a slightly

faster rate being observed in several cases for the acetylene. An extension of this solvent polarity-olefin/acetylene relative reactivity relationship to the present work shows that our acetylenes were even more relatively reactive than would be expected, for the polarity of the solvent, ethanol, is substantially less than that of the aqueous sulfuric acid used by Yates. Thus, although solvent effects have been demonstrated to play an important role in determining olefin/acetylene relative reactivities, it would seem that other factors are also operative.

Experimental Section

General. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Kinetic data were obtained on a Beckman DB spectrophotometer. Ir spectra were run on a Beckman IR-10 while nmr spectra were run on a Varian A-60 instrument.

Ferrocenylphenylacetylene (1). This compound was synthesized in 85% yield according to the method of Rausch, *et al.*,[11] mp 128–129° (lit.[11] mp 127–128°).

Iodoferrocene. Iodoferrocene, utilized in the synthesis of **1**, was initially prepared according to the method of Nesmeyanov.[12] This method, which involves the preparation of the intermediate compound chloromercuriferrocene,[13] proved to be very time consuming and gave us at best a 35% yield based upon starting ferrocene. A new method, patterned after the synthesis of halobenzenes utilizing thallic trifluoracetate (TTFA),[14] was improvised. To a solution of 3.82 g of ferrocene in 500 ml of glyme at 40° was added 5 g of TTFA in small increments over the period of 1 hr. The resulting solution was stirred at 40° for 4 hr,[15] after which time it was shaken with 250 ml of a saturated solution of aqueous potassium iodide. The organic layer was separated, dried over calcium chloride, and evaporated to yield crude iodoferrocene as a viscous, red-orange oil which was purified *via* silica gel column chromatography. The purified iodoferrocene was obtained in 88% yield, mp 50–51° (lit.[16] mp 49–49.5°). It should be stressed that subsequent attempts to prepare iodoferrocene *via* this new method have not duplicated the high yield obtained on the first run. Efforts to ascertain what was done differently on the initial trial have not met with success. However, it is suggested that freshly prepared TTFA[17] be used.

Reaction of Ferrocenylphenylacetylene (1). A 100-ml portion of a 5×10^{-2} *M* ethanolic solution of **1** was stirred at room temperature with 0.2 ml of 25% sulfuric acid. The solution was neutralized and stripped of solvent on a rotary evaporator to yield a viscous red-brown oil, which when recrystallized from benzene–hexane (75:25) gave a quantitative yield of ferrocenyl benzyl ketone (**3**), mp 129–130° (lit.[18] mp 128°). **3** was identified by comparing its melting point, ir, and nmr spectra with those of an independently prepared sample.[18]

Ethynylferrocene (6). This compound was prepared from acetylferrocene using the method of Rosenblum, *et al.*[19] An 82% yield of **6** was obtained, mp 53–54° (lit.[19] mp 51–53°).

Vinylferrocene (8). This compound was prepared in 20% yield by dehydrating α-hydroxyethylferrocene according to the method of Arimoto and Haven,[20] mp 45–47° (lit.[20] mp 48–49°).

Phenylacetylene (7). This compound was purchased from Aldrich Chemical Co. (No. 11, 770-6) and was used without further purification.

Styrene (9). This compound was purchased from Aldrich Chemical Co. (No. S497-2) and fractionally distilled prior to use.

Kinetic Data. Rates for the acid-catalyzed hydration reactions were obtained by using uv spectroscopy[21] to follow the disappearance of starting material. In each run, 3 ml of a 5×10^{-3} *M* ethanolic solution of compound was placed in the cuvette in the spectrophotometer and allowed to reach an equilibrium temperature of 31°, after which 0.1 ml of 25% H_2SO_4 was added.

Identification of Hydration Products. The hydration products listed in Table I were identified by comparing melting points and ir and nmr spectra with those of an authentic sample of the compound in question. Acetylferrocene was prepared according to the method of Broadhead, *et al.*,[22] with a 45% yield being obtained, mp 83–84° (lit.[23] mp 83–85°). α-Hydroxyethylferrocene (**12**) was prepared by $LiAlH_4$ reduction of acetylferrocene according to the method of Arimoto and Haven[20] to obtain an 80% yield, mp 70–71° (lit.[20] mp 69–72°).

Styrylferrocene (13). This compound was prepared according to the general method of Arimoto and Haven by which vinylferrocene was prepared. Ferrocene carboxaldehyde was treated with the Grignard reagent of benzyl bromide to give α-ferrocenyl-β-phenylethanol (**15**) in 80% yield, mp 80–81° (lit.[18] mp 82.3°). A 1-g portion of **15** was dissolved in a minimum amount of dry benzene to which sufficient alumina (Baker, acid washed, activity 1) was added to form a thick slurry. After standing over the alumina for 24 hr in a nitrogen atmosphere, the solution was eluted and stripped of solvent to yield crude styrylferrocene in 75% yield. After recrystallization from hexane a melting point of 123–124° was found (lit.[18] mp 120–121.5°).

Registry No.—**1**, 51108-02-2; **6**, 12764-67-9; **7**, 536-74-3; **8**, 1271-51-8; **9**, 100-42-5.

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Syntheses of Potential Antimetabolites. XV. Syntheses of a Sulfonate Analog of Adenosine 5′-Phosphate and an Alternative Synthesis of 5′,8-*S*-Anhydroadenine Nucleosides and 5′-Deoxyspongoadenosine and Its Isomers[1]

Yoshihisa Mizuno,* Chisato Kaneko, and Yuji Oikawa

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan 060

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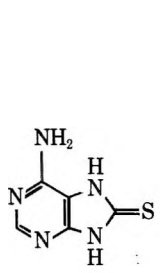
It has been well documented that *S*-anhydropurine nucleosides[2,4] as well as anhydropyrimidine nucleosides[3] are versatile intermediates for the interconversion of the nucleoside. In the preparation of 5′,8-*S*-anhydropurine nucleosides by a general procedure starting with preformed purine nucleosides, N^3,5′-cyclopurine nucleoside forma-

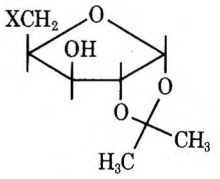
tion is quite often encountered.[5-8] In order to avert this side reaction, we developed an alternative synthetic procedure for the 5′,8-*S*-anhydroadenine nucleosides. Our new approach to the anhydro nucleoside consists in the initial synthesis of appropriate 8-alkylthioadenines, followed by the formation of an *N*-glycosyl bond. By this approach the unfavorable quaternization at N-3 could be avoided. Another and more important advantage inherent in this approach is that the anhydropurine nucleosides obtained must be the β nucleosides in the case of D-series sugars, irrespective of the kind of sugars as well as their protecting groups.[9]

In the present paper, we first deal with a novel synthetic procedure for 5′,8-*S*-anhydroadenine nucleosides (**9**, **10**, and **11**) and secondly with the conversion of these anhydro nucleosides to 9-(5-deoxy-β-D-xylofuranosyl)adenine-5′-sulfonic acid (**16**) and a number of 5′-deoxyadenine nucleosides.

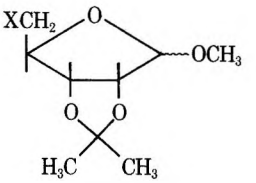
Treatment of the sodium (**1a**) or potassium salt (**1b**) of adenine-8-thione[10] with methyl 5-deoxy-5-iodo-2,3-di-*O*-acetyl-D-arabinofuranoside (**4a**) in refluxing methoxyethanol afforded a 40% yield of 8-(methyl-5-deoxy-2,3-di-*O*-acetyl-β-D-arabinofuranos-5-yl)thioadenine (**7**). The reaction of the sodium salt of adenine-8-thione (**1a**) with methyl 5-*O*-(*p*-toluenesulfonyl)-2,3-di-*O*-acetyl-D-arabinofuranoside (**4b**) gave the same result. A solution of **7** in acetic acid and acetic anhydride was treated with a small quantity of concentrated sulfuric acid at −5 to 0°. The reaction mixture was kept at room temperature for 2 days. After work-up (see Experimental Section), removal of the blocking group with methanolic ammonia gave rise to 5′,8-*S*-anhydro-β-D-arabinofuranosyladenine-8-thiol (**11**) in



1a, Na
b, K



2a, X = I
b, X = OTs



3a, X = I
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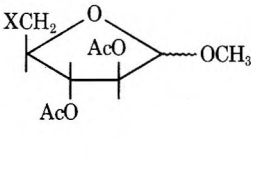
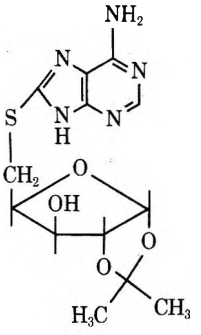


4a, X = I
b, X = OTs



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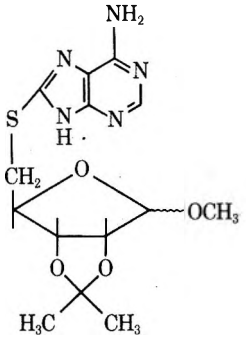

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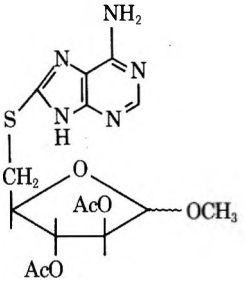

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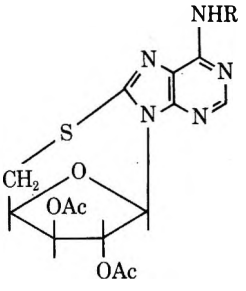
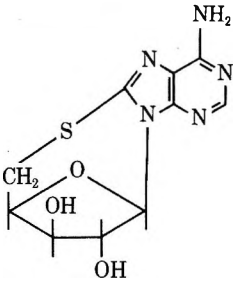


8a, X = H
b, X = CH_3CO



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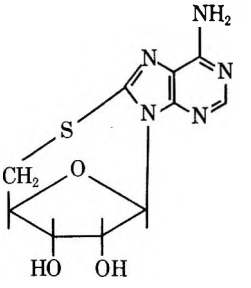

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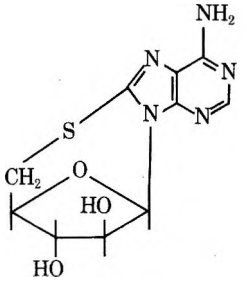

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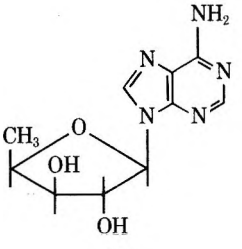

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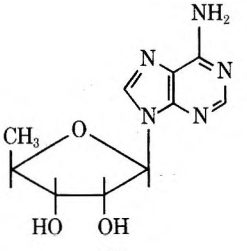

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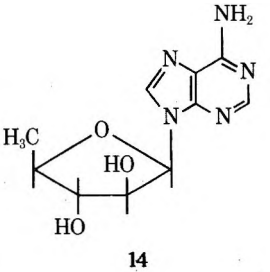

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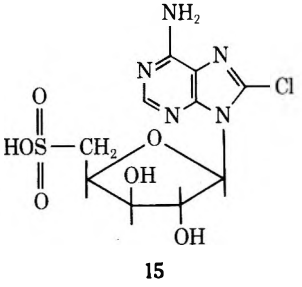

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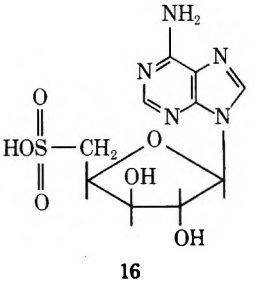

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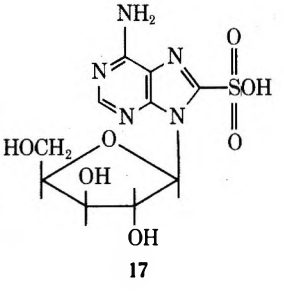

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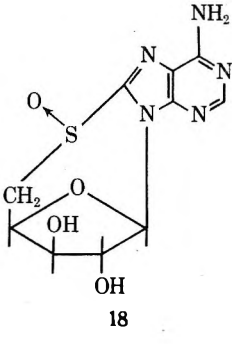

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Table I

Compd	Mp, °C	Yield, %	R_f A[a]	R_f C[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
12	228–229	65	0.51	0.69	47.77	5.21	27.88	47.65	5.31	27.61
13	204	61	0.54	0.62	47.77	5.21	27.88	47.55	5.35	27.58
14	174–175	58	0.49	0.61	47.77	5.21	27.88	47.80	5.00	27.81

[a] Solvent system.

40% yield. Structural confirmation rests upon elemental analysis, spectral data, and the fact that Raney nickel treatment led **11** to 5′-deoxy-β-D-arabinofuranosyladenine (5′-deoxyspongoadenosine, **14**).[12]

The "acetic acid–acetic anhydride–sulfuric acid treatment" (at higher temperature) has been previously employed for the acetolysis of the *N*-glycosyl bond of a guanosine derivative.[11] In the present case, the reaction proceeded in reverse direction, that is, an *N*-glycosyl bond was formed.

A series of parallel reactions starting from 5-iodo-5-deoxy-1,2-isopropylidene-β-D-xylofuranoside (**2a**)[13,14] or methyl 5-iodo-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranoside (**3a**)[15] gave rise to the corresponding anhydroadenine nucleosides (**9** or **10**) in overall yields of 44 and 20%, respectively. Again, 5-*O*-(*p*-toluenesulfonyl) derivatives **2b**[14] and **3b**[15] were able to replace **2a** and **3a** without reduced yields of **9** and **10**. Structural confirmation of **9** and **10** was performed on the basis of uv spectra and Raney nickel reduction. On the reduction, these two anhydro nucleosides afforded the corresponding 5′-deoxyadenine nucleosides **12**[12,17] and **13**.[18] Uv absorption maxima of these nucleosides **9**, **10**, and **11** did not shift in both acidic and basic pH regions, indicating that these compounds were 8,9 disubstituted.

The low yield with the ribose series was due to the formation of a significant amount of chloroform-insoluble and uv-absorbing by-product of unknown structure on acetic acid–acetic anhydride–sulfuric acid treatment. It is worthy of note that no indication of the presence of isomeric 7,8-disubstituted anhydro nucleosides was found in spectral and chromatographic data.

Treatment of a methanol solution of **9** with chlorine in the presence of hydrogen chloride gave rise to 5′-deoxy-β-D-xylofuranosyl-8-chloroadenine-5′-sulfonic acid (**15**) in 30% yield, which could be reduced to 9-(5-deoxyl-β-D-xylofuranosyl)adenine-5′-sulfonic acid (**16**) in quantitative yield. Oxidation of **9** with 30% hydrogen peroxide in acetic acid afforded an 81% yield of 9-β-D-xylofuranosyladenine-8-sulfonic acid (**17**). Nucleosides **16** and **17** moved as monoanions on paper electrophoresis at pH 8.5. Treatment of **9** with an aqueous solution of *N*-bromosuccinimide gave rise to the corresponding sulfoxide **18** in 71% yield, which in turn returned to the original anhydro nucleoside **9** on zinc powder reduction. Combustion values and nmr spectra of **18** were as expected for the assigned structure. The sulfoxide was a key intermediate for the conversion of a 5′,8-*S*-anhydro nucleoside to a normal nucleoside by Pummerer rearrangement.[4]

Experimental Section

Infrared (ir) spectra were determined with a Hitachi spectrometer. Ultraviolet (uv) spectra were determined using a Hitachi spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined with a high-resolution nmr spectrometer in deuteriochloroform. The chemical shifts were reported in parts per million downfield from tetramethylsilane as internal standard. Melting points were uncorrected. Before concentration the solution was dried over magnesium sulfate overnight. Solvents were removed in a rotating evaporator by a water aspirator (*ca.* 12 mm). Paper electrophoresis was performed on Toyo-Roshi paper No. 51A (10 × 40 cm) at pH 7.5 in 0.05 *M* triethylammonium bicarbonate (700 vol). Paper chromatography was performed on Toyo-Roshi paper 51A by the ascending technique. Solvent systems employed were (a) *n*-BuOH–H_2O (84:16); (b) EtOH–1 *M* AcOH (5:2); (c) *i*-PrOH–NH_4OH–H_2O (7:1:2). R_f (A) and R_f (B) in tlc (silica gel) refer to the systems $CHCl_3$–C_2H_5OH (35:5) and $CHCl_3$–C_2H_5OH (35:1), respectively. Spots were detected either by a sulfuric acid spray reagent or under the uv light.

Methyl 5-Iodo-5-deoxy-2,3-di-*O*-Acetyl-D-arabinofuranoside (4a). To a solution of methyl 5-*O*-(*p*-toluenesulfonyl)-D-arabinofuranoside (14 g, 44 mmol) in pyridine (63 ml) was added acetic anhydride (35 ml) at room temperature. The solution was allowed to stand overnight at this temperature. Water (2 ml) was then added to the solution at 0°. After 2 hr the solution was concentrated to dryness. The residue was dissolved in chloroform. The solution was washed with water, dried, and filtered. The filtrate was concentrated to dryness. Crystallization from ethanol afforded the analytical sample (**4b**, 16.5 g, 89%), mp 149–150°.

Anal. Calcd for $C_{17}H_{22}O_9S$: C, 50.75; H, 5.50; S, 7.96. Found: C, 50.55; H, 5.08; S, 7.80.

To a solution of methyl 5-*O*-(*p*-toluenesulfonyl)-2,3-di-*O*-acetyl-D-arabinofuranoside (7.65 g, 19 mmol) in acetone (50 ml) was added sodium iodide (7.6 g). The solution was heated for 6 hr at 100° (bath temperature) in a stoppered vessel. The solvent was removed to leave a gummy substance, which was dissolved in chloroform. Insoluble material was filtered off. The filtrate was washed with water, dried, and filtered. The filtrate was concentrated to dryness (5.74 g, 83%). This sample was used for the preparation of 8-alkylthioadenine (**7**).

8-(Methyl-2,3-di-*O*-acetyl-5-deoxy-D-arabinofuranos-5-yl)-thioadenine (7). Adenine-8-thione[10] was converted into the potassium salt by dissolving in methanol containing an equivalent amount of potassium hydroxide. The salt obtained by removal of solvent was used for the subsequent experiment without purification. The sodium salt **1a** was prepared similarly. The potassium salt of adenine-8-thione (2.8 g, 13.6 mmol) and **4a** (4.0 g, 10 mmol) were dissolved in methoxyethanol (40 ml). The solution was heated at reflux for 3.5 hr. The solution was concentrated to dryness. The residue was triturated with water (30 ml). Insoluble material was filtered off. The filtrate was concentrated to dryness. The residue was dissolved in methanol (10 ml). Insoluble material was again filtered off. The filtrate was concentrated to dryness. The residue was triturated with chloroform. The crude product was purified over silica gel column chromatography (silica gel, 200 g, $CHCl_3$–EtOH, 35:5). Eluate having R_f (A) 0.45 in tlc was pooled. The solvent was removed. The residue was crystallized from aqueous methanol: mp 233–235° dec; yield 12.87 g (70%); uv λ_{max} (pH 1) 287 nm, λ_{max} (pH 11) 285 nm, λ_{max} (H_2O) 285 nm.

Anal. Calcd for $C_{15}H_{19}N_5O_6S$: C, 47.59; H, 5.42; N, 19.82; S, 11.03. Found: C, 47.43; H, 5.41; N, 19.83; S, 11.12.

8-(1,2-*O*-Isopropylidene-5-deoxy-D-xylofuranos-5-yl)thioadenine (5). The sodium salt of adenine-8-thione (**1a**, 3.6 g, 19 mmol) and 1,2-O-isopropylidene-5-iodo-5-deoxy-D-xylofuranose (**2a**, 6.3 g, 21 mmol) was dissolved in methoxyethanol (120 ml). The solution was heated at reflux for 4 hr. The solvent was evaporated to give crude product, which was washed with water and then with acetone. Crystallization from acetone gave the analytical sample: 1.7 g (70%); mp 220–223°; uv λ_{max} (pH 1) 287 nm, λ_{max} (pH 11) 285 nm; ppc R_f (solvent system A) 0.89, R_f (solvent system B) 0.87.

Anal. Calcd for $C_{13}H_{17}N_5O_4S$: C, 46.10; H, 4.73; N, 20.69; S, 12.97. Found: C, 45.80; H, 4.54; N, 20.64; S, 12.78.

8-(Methyl-2,3-*O*-isopropylidene-5-deoxy-D-ribofuranos-5-yl)thioadenine (6). The sodium salt of adenine-8-thione (**1a**, 3.6 g, 19 mmol) and methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-D-ribofuranoside (**3a**, 5.66 g, 19 mmol) were dissolved in methoxyethanol (100 ml). The solution was refluxed for 5.5 hr. Work-up, as described above for **5**, gave the analytical sample, yield 4.96 g (74%), mp 274–275°.

Anal. Calcd for $C_{14}H_{19}N_5O_4S$: C, 47.59; H, 5.42; N, 19.82; S, 9.40. Found: C, 47.32; H, 5.64; N, 19.76; S, 9.38.

General Procedure for "Acetic Acid–Acetic Anhydride–Sulfuric Acid Treatment." Unless otherwise specified, "acetic acid–acetic anhydride–sulfuric acid treatment" was carried out as follows. To a solution of 8-alkylthioadenine (**5**, **6**, or **7**, 6 mmol) in a mixture of acetic acid (20 ml) and acetic anhydride (16 ml) was added in portions sulfuric acid (2.0 ml) at −5 to 0°. The solution was then allowed to return to ambient temperature and to stand at this temperature for 2 days. The solution was added to 650 ml of saturated sodium hydrogen carbonate solution and then completely neutralized with solid sodium hydrogen carbonate. The solution was concentrated to one-third of its volume. The solution was extracted with ethyl acetate or chloroform. The solution was washed with water, dried, and filtered. The filtrate was concentrated to dryness. The residue contained a mixture of 5′,8-*S*-anhydro-2′,3′-di-*O*-acetyl-β-D-pentofuranosyladenine and N^6,$O^{2'}$,$O^{3'}$-triacetyl-5′,8-*S*-anhydro-β-D-pentofuranosyladenine and weighed 1.0 (xylose series), 0.5 (ribose series), and 0.9 g (arabinose series), which were employed for subsequent deblocking without purification. However, isolation of two products could be achieved by silica gel chromatography (column size 3 × 30 cm, silica gel, 100 g, solvent system $CHCl_3$–EtOH 35:1).

5′,8-*S*-Anhydro-β-D-arabinofuranosyladenine-8-thiol (11). To a solution of **7** (0.8 g, 2 mmol) in acetic acid (6.6 ml) and acetic anhydride (6.0 ml) was added in drops 0.75 ml of concentrated sulfuric acid at −5 to 0°. After work-up as described above in the general procedure, crude products obtained were dissolved in methanol (24 ml) saturated with ammonia at 0°. The solution was kept at room temperature for 24 hr. The solvent was removed to leave **11**. Crystallization from aqueous methanol gave the analytical sample: yield 0.23 g (40%); uv λ_{max} (H_2O) 235 nm (ε 1.04 × 10^4), 278 (sh, 2.07 × 10^4), 285.5 (2.27 × 10^3), 295 (sh, 1.53 × 10^4); λ_{max} (0.1 *N* HCl) 277 nm (sh, 1.82 × 10^4), 285 (2.47 × 10^4), 295 (sh, 1.81 × 10^4); uv spectra in 0.1 *N* NaOH were the same as in water; R_f (solvent system A) 0.28.

5′,8-*S*-Anhydro-β-D-ribofuranosyladenine-8-thiol (10). Deblocking and recrystallization from water gave the product (0.33 g, 20%): mp 225–226°; R_f (solvent system C) 0.35; uv λ_{max} (H_2O) 237 nm (ε 8.6 × 10^3), 277 (sh, 1.78 × 10^4), 294 (sh, 1.32 × 10^4); λ_{max} (0.1 *N* HCl) 235 nm (sh, 5.2 × 10^3), 276 (sh, 1.90 × 10^4), 292 (sh, 1.58 × 10^4), 294 (sh, 1.38 × 10^4).

Anal. Calcd for $C_{10}H_{11}N_5O_3S \cdot \frac{1}{3}H_2O$: C, 41.81; H, 4.01; N, 24.39. Found: C, 41.95; H, 4.35; N, 24.18.

2′,3′-Di-*O*-Acetyl-5′,8-*S*-anhydro-β-D-xylofuranosyladenine-8-thiol (8a). Work-up and chromatography as described in the general procedure gave the product (**8a**, 1.15 g, 51%), mp 213–215° (after recrystallization from $CHCl_3$).

Anal. Calcd for $C_{14}H_{15}N_5O_5S$: C, 46.15; H, 4.15; N, 19.22; S, 8.80. Found: C, 45.98; H, 3.95; N, 19.20; S, 8.79.

5′,8-*S*-Anhydro-β-D-xylofuranosyladenine-8-thiol (9). Deblocking and recrystallization from water afforded the analytical sample: yield 0.76 g (45%); mp 267–269° dec; R_f (solvent system C) 0.38.

Anal. Calcd for $C_{10}H_{11}N_5O_3S$: C, 42.71; H, 3.94; N, 24.90; S, 11.40. Found: C, 42.61; H, 4.25; N, 24.70; S, 11.59.

Raney Nickel Reduction. A solution of 5′,8-*S*-anhydroadenine nucleosides (**9**, **10**, or **11**, 1 mmol) in 6 ml of water was refluxed with a spatulaful of Raney nickel until uv maxima did not shift. The crude solid obtained after work-up was completed was crystallized from absolute ethanol to afford a pure sample (see Table I).

9-(5′,8-*S*-Anhydro-β-D-xylofuranosyl)adenine-8-thiol *S*-Oxide (18). To a stirred suspension of **9** (281 mg, 1 mmol) in 6 ml of water was added *N*-bromosuccinimide (178 mg, 1 mmol) in 5 min. Stirring was continued until the complete solution resulted. The solution was neutralized with solid sodium hydrogen carbonate to deposit a solid substance, which was collected by filtration and washed with water: uv λ_{max} (H_2O) 262 nm; λ_{max} (pH 1) 262 nm; λ_{max} (pH 11) 265 nm; ir 1040 and 1080 cm^{-1} (^+S–O^-); yield 210 mg (71%).

Anal. Calcd for $C_{10}H_{11}N_5O_4S$: C, 40.41; H, 3.73; N, 23.56; S, 10.77. Found: C, 40.44; H, 3.77; N, 23.56; S, 10.77.

9-(5-Deoxy-β-D-xylofuranosyl)-8-chloroadenine-5′-sulfonic Acid (15). Chlorine gas was passed through a suspension of **9** (1 g, 3.57 mmol) in 50 ml of absolute methanol for 10 min at 13–18° and then hydrogen chloride gas was introduced into the suspension at this temperature for 2 hr, at which time the solution resulted. The solution was carefully concentrated to dryness below 30°. The residue was codistilled with benzene (3 × 5 ml), dissolved in 1 l. of water, and neutralized with triethylamine. The solution was applied to a DEAE-cellulose column (bicarbonate form, column size 2.5 × 35.5 cm). The column was washed with 2 l. of water (the eluate was discarded) and then washed with a linear gradient of 1 l. of water and 1 l. of 0.05 *M* triethylammonium bicarbonate, fraction size 15 ml. Fractions containing the desired product were pooled and concentrated to dryness (560 mg). An aqueous solution of the residue was treated with a IRC resin (H^+ form) and filtered. The filtrate was concentrated to dryness. The residue was crystallized from water: yield 430 mg (30%); mp 167–168° dec; uv λ_{max} (H_2O) 262.5 nm (ε 1.62 × 10^4); λ_{max} (0.1 *N* HCl) 260.5 nm (ε 1.75 × 10^4); λ_{max} (0.1 *N* NaOH) 252 nm (ε 1.64 × 10^4); ir ν_{max} (KBr) 1700 (C=NH^+), 1100, 1153, 1220 cm^{-1} (SO_3^-). Upon electrophoresis in 0.05 *M* triethylammonium bicarbonate (pH 8.5), the product had a mobility of 5.7 cm compared to 5.4 cm for adenosine 2′,3′-cyclic phosphate.

Anal. Calcd for $C_{10}H_{12}N_5O_6SCl \cdot HCl$: C, 29.85; H, 3.23; N, 17.41; S, 7.96; Cl, 17.66. Found: C, 30.06; H, 3.42; N, 17.20; S, 7.78; Cl, 17.66.

9-(5-Deoxy-β-D-xylofuranosyl)adenine-5′-sulfonic Acid (16). Hydrogen gas was passed through a solution of **15** (80 mg) in 20 ml of water in the presence of 10% palladium on charcoal. It required 4 hr before the hydrogen uptake ceased. The mixture was filtered. The filtrate was treated with a resin (IRC 120 OH^- form). The filtrate was concentrated to dryness. The residue was crystallized from water: yield 60 mg; mp 135° (sintering), 170–172° dec; uv λ_{max} (H_2O) 257 nm; λ_{max} (0.1 *N* NaOH) 260 nm. Upon electrophoresis in 0.05 *M* triethylammonium bicarbonate (pH 8.5), the product had a mobility of 6.4 cm compared to 6.4 cm for **15**, R_f (solvent system B) 0.04, R_f (solvent system C) 0.61.

Anal. Calcd for $C_{10}H_{13}N_5O_6S \cdot H_2O$: C, 34.38; H, 4.29; N, 20.05; S. 9.16. Found: C, 34.52; H, 4.28; N, 20.15; S, 9.20.

9-(β-D-Xylofuranosyl)adenine-8-sulfonic Acid (17). A solution of **9** (55 mg, 0.2 mmol) in 2.8 ml of acetic acid was treated with 0.4 ml of 30% hydrogen peroxide at 30° overnight, during which time crystals deposited. Recrystallization from water afforded an 81% (55 mg) yield of **17**: mp 250°; uv λ_{max} (H_2O) 262 nm (ε 1.73 × 10^4); λ_{max} (0.1 *N* NaOH) 265 nm (ε 1.70 × 10^4); λ_{max} (0.1 *N* HCl) 262 nm (ε 1.54 × 10^4); nmr 5.8 (s, 1 H, anomeric proton), 7.96 ppm (s, 1 H, H_2), absence of H_8. Upon electrophoresis at pH 8.5, the product had a mobility of 6.5 cm compared to 6.8 cm for adenosine 2′,3′-cyclic phosphate.

Anal. Calcd for $C_{10}H_{13}N_5O_7S$: C, 34.59; H, 3.77; N, 20.17. Found: C, 34.61; H, 3.88; N, 20.03.

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Registry No.—**1a**, 50600-33-4; **1b**, 50600-34-5; **2a**, 50600-39-0; **3a**, 50600-40-3; **4a**, 50600-41-4; **4b**, 50600-42-5; **5**, 50600-43-6; **6**, 50600-44-7; **7**, 50600-45-8; **8a**, 50600-46-9; **9**, 38099-23-9; **10**, 20789-80-4; **11**, 38099-25-1; **12**, 72-90-2; **13**, 4754-39-6; **14**, 4152-76-5; **15** hydrochloride, 50600-47-0; **16**, 50600-48-1; **17**, 50600-49-2; **18**, 51022-64-1; methyl 5-*O*-(*p*-toluenesulfonyl)-D-arabinofuranoside, 50600-50-5.

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Synthesis of 6-Hydroxypenicillanates and 7-Hydroxycephalosporanates

John C. Sheehan,* Young S. Lo, Jürg Löliger, and Clifford C. Podewell

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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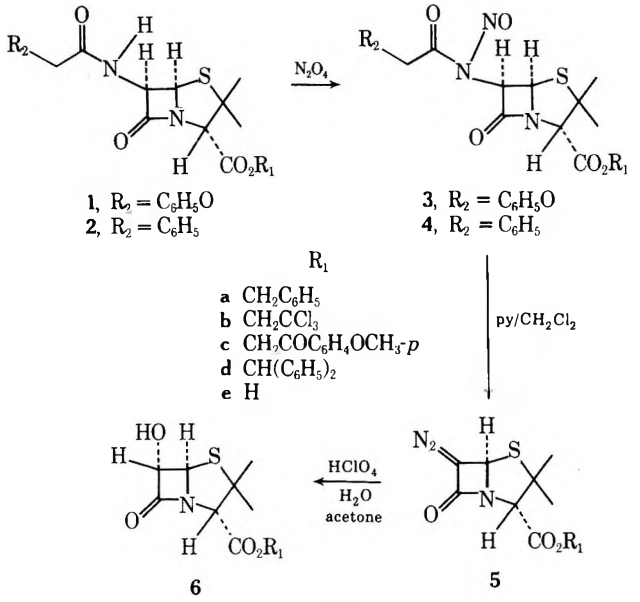
Benzyl 6-oxopenicillanate[1-3] has been shown to be a useful intermediate for the synthesis of novel β-lactam antibiotics. One precursor for this compound is benzyl 6α-hydroxypenicillanate (**6a**), derived from benzyl 6-diazopenicillanate (**5a**) (Chart I). Syntheses of **5a** have been

Chart I



reported by two methods: diazotization of 6-aminopenicillanic acid (Table I, a) or benzyl 6-aminopenicillanate (Table I, b) with nitrous acid and treatment of benzyl 6β-*N*-nitrosophenoxyacetamidopenicillanate with silica gel[4a] (Table I, c). The latter method especially suffers from a low yield. This method has been improved (Table I, c) and extended to make a greater variety of 6α-hydroxypenicillanates and 7α-hydroxycephalosporanates[4b] available.

In analogy to the diazomethane generating method with sodium hyroxide, the *N*-nitrosoamides (**3**, **4**, and **9**) should afford the diazo derivatives (**5** and **10**) on treatment with an appropriate base.

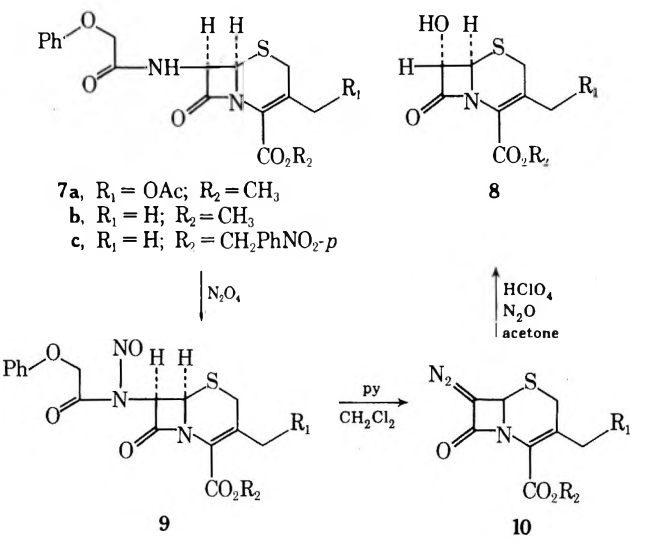
The nitrosoamides were prepared from penicillin (**1**, **2**) or cephalosporin (**7**, Chart II) derivatives according to the method of Hauser and Sigg[4a] using methylene chloride as solvent. The nitrosoamides were then treated with a base. Pyridine was found to be a better base than triethylamine for this reaction. Solvents such as ethyl acetate, methyl sulfoxide, tetrahydrofuran, and methylene chloride can be

Table I

Reaction	Yield, %
a 6-APA → **6a**	22[c]
b Benzyl 6-APA → **5a**	2.1[c]
c **1a** → **5a**	7.5[c]
d **1a** → **6a**	46
e **1b** → **6b**	30
f **1c** → **6c**	35
g **2b** → **5b**	72
h **5b** → **6b**	60
i **2b** → **6b**[a]	25
j **2e** → **6d**	7
k **7a** → **8a**	12
l **7b** → **8b**	15
m **7c** → **8c**[b]	24

[a] Without purification of **5b**. [b] Yield adjusted to account for recovered starting materials. [c] Reference 4a.

Chart II



used. Refluxing methylene chloride was found to be the best solvent, resulting in the shortest reaction time and easiest removal at the end of the reaction. Table I gives the transformations to which this method has been applied and the yields. In most cases compounds **5** and **10** were hydrolyzed with perchloric acid in aqueous acetone without previous isolation.

After refluxing **4b** in methylene chloride with pyridine, a brown oil was obtained which solidified and could be recrystallized from carbon tetrachloride–petroleum ether to give β,β,β-trichloroethyl 6-diazopenicillanate (**5b**) as yellow crystals. This is the first reported isolation of an ester of 6-diazopenicillanic acid in crystalline form.[5] Pure **5b** was hydrolyzed in aqueous acetone with perchloric acid to give a 60% yield of **6b**, which was isolated by crystallization (Table I, h). Crude **5b** was hydrolyzed to give, after chromatography, **6b** in only 40% yield. Thus, working with a pure diazo compound not only resulted in a higher yield but also facilitated isolation of the product.

The *N*-nitrosocephalosporanates were found to be surprisingly resistant to rearrangement. Under the rearrangement conditions used for penicillin derivatives, 53% of the *N*-nitrosocephalosporanate **9c** was recovered. Increased reaction time or temperature resulted in loss of the β-lactam. This difference in reactivity of the nitroso derivatives **3** or **4** and **9** may be due to the steric effect of the *gem*-dimethyl group of penicillin.[6]

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were

performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were recorded on a Perkin-Elmer 237 spectrophotometer; only significant maxima are listed. Nmr spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from TMS.

β,β,β-Trichloroethyl 6β-*N*-Nitrosophenylacetamidopenicillanate (4b). Dinitrogen tetroxide (24 g) was dissolved in 250 ml of methylene chloride. A solution of β,β,β-trichloroethyl phenylacetamidopenicillanate (**2b**, 10.5 g, 22.6 mmol) in methylene chloride (100 ml) was added in 20 min with stirring at −5° to a mixture of anhydrous sodium acetate (22 g), dinitrogen tetroxide (120 ml of above solution), and methylene chloride (100 ml). The mixture was stirred below 0° for 1 hr. Additional portions of dinitrogen tetroxide (30 ml, 100 ml) were added immediately after and 30 min after addition of the penicillin derivative. Excess dinitrogen tetroxide was consumed by adding saturated sodium bicarbonate. The aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to a yellow syrup, yield 11 g, ir (film) 1790, 1755, 1540, 1530 cm^{-1}; the NH vibration (3400 cm^{-1}) and the amide band (1690 cm^{-1}) of the parent compound were absent.

β,β,β-Trichloroethyl 6-Diazopenicillanate (5b). Pyridine (3 ml) was added to **4b** (11 g) in 300 ml of methylene chloride. After refluxing for 3 hr the brown solution was washed with water, saturated sodium bicarbonate, and water, dried (Na_2SO_4), and evaporated to give 8 g of a brown syrup which slowly solidified. Recrystallization from carbon tetrachloride–petroleum ether gave **5b**, 5.85 g (72%): mp 103.5–104° dec; ir (KBr) 2100, 1760, 1740, 1525 cm^{-1}; nmr ($DCCl_3$) δ 6.15 (s, 1 H), 4.75 (s, 2 H), 4.45 (s, 1 H), 1.70 (s, 3 H), 1.55 (s, 3 H).

Anal. Calcd for $C_{10}H_{10}Cl_3N_3O_3S$ (358.64): C, 33.45; H, 2.81; N, 11.71; S, 8.94; Cl, 29.67. Found: C, 33.55; H, 2.75; N, 11.67; S, 8.87; Cl, 29.82.

β,β,β-Trichloroethyl 6β-Hydroxypenicillanate (6b). Compound **5b** (1 g) was dissolved in 50 ml of acetone. A solution of 10 ml of 1 *N* perchloric acid in 40 ml of water was added with swirling. The solution was stored overnight at 5° and then extracted with methylene chloride. The extract was washed with saturated sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated to give a pale yellow solid. Crystallization from benzene–petroleum ether gave white crystals, 0.6 g (60%): mp 107.5–108°; ir (KBr) 3470, 1770, 1755, 1160 cm^{-1}; nmr ($DCCl_3$) δ 5.30 (d, J = 1 Hz, 1 H), 4.95–4.80 (d, br, 1 H), 4.82 (s, 2 H), 4.62 (s, 1 H), 4.50 (d, J = 8 Hz, 1 H), 1.60 (s, 3 H), 1.50 (s, 3 H).

Other 6α-hydroxypenicillanates (**6c**, **6d**) and 7α-hydroxycephalosporanates (**8a**, **8b**) were made analogously.

***p*-Methoxyphenacyl 6α-hydroxypenicillanate (6c)** had R_f 0.34 (1:4 Et_2O–CH_2Cl_2); ir (film) 3400, 1770, 1745, 1690, 1600 cm^{-1}; nmr ($DCCl_3$) δ 7.90 (d, J = 9 Hz, 2 H), 6.95 (d, J = 9 Hz, 2 H), 5.50–5.25 (s over d, 3 H), 4.85 (s, br, 1 H), 4.60 (s, 1 H), 3.90 (s, 3 H), 1.60 (s, 6 H).

Benzhydryl 6β-hydroxypenicillanate (6d) had mp 125–125.5°; ir (film) 3400, 1770, 1740 cm^{-1}; nmr ($DCCl_3$) δ 7.40 (s, 10 H), 6.90 (s, 1 H), 5.30 (d, J = 1.5 Hz, 1 H), 4.95 (br, 1 H), 4.82 (d, J = 1.5 Hz, 1 H), 4.55 (s, 1 H), 1.58 (s, 3 H), 1.25 (s, 3 H).

Methyl 7α-hydroxycephalosporanate (8a) had mp 138–139°; $[\alpha]^{25}D$ +127° (*c* 1.63, $CHCl_3$); ir (KBr) 3420, 1775, 1730, 1230 cm^{-1}; nmr ($DCCl_3$) δ 5.15–4.55 (m, 5 H), 3.90 (s, 3 H), 3.48 (q, 2 H), 2.10 (s, 3 H).

Anal. Calcd for $C_{11}H_{13}NSO_6$ (287.28): C, 46.10: H, 4.57; N, 4.88; S, 11.15. Found C, 45.94; H, 4.55; N, 4.87; S, 11.27.

Methyl 7α-hydroxydeacetoxycephalosporanate (8b) had R_f 0.45 (1:10 Et_2O–CH_2Cl_2); ir (film) 3380, 1775, 1730, 1235 cm^{-1}; nmr ($DCCl_3$) δ 4.75 (d, J = 1 Hz, 1 H), 4.65 (d, J = 1 Hz, 1 H), 3.85 (s, 3 H), 3.40 (q, 2 H), 2.20 (s, 3 H).

Benzyl 6α-hydroxypenicillanate (6a) had mp 162–163° (lit.[4a] mp 157–160°); ir and nmr were identical with those published.

***p*-Nitrobenzyl 7β-*N*-Nitrosophenoxyacetamidodeacetoxycephalosporanate (9c).** The procedure is the same as for **4b**. The product was crystallized from acetone–petroleum ether, 81%: mp 120–121° dec; $[\alpha]^{25}D$ −25.2° (*c* 0.76, $CHCl_3$); ir (CH_2Cl_2) 1790, 1745, 1725, 1535, 1350, 1225 cm^{-1}; nmr ($CDCl_3$) δ 8.28–7.50 (q, 4 H), 7.35–6.83 (m, 5 H), 5.87 (d, J = 4.5 Hz, 1 H), 5.57 (s, 2 H), 5.33 (d, J = 4 Hz, 2 H), 5.00 (d, J = 4.5 Hz, 1 H), 3.62–2.75 (q, J = 16, 2 H), 2.36 (s, 3 H).

Anal. Calcd for $C_{23}H_{20}N_4SO_8$ (512.49): C, 53.90; H, 3.93; N, 10.93; S, 6.26. Found: C, 53.82; H, 3.86; N, 10.76; S, 6.40.

***p*-Nitrobenzyl 7α-Hydroxydeacetoxycephalosporanate (8c).** Yellow crystals identified as **9c** deposited out of the hydrolysis solution (4.4 g, 41.5%). Chromatography on silicic acid of the oil left after evaporation of solvent gave an additional 1.2 g (11.3%) of **9c**, 0.6 g (6%) of **7c**, and 0.72 g (10%) of **8c**.

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Registry No.—**1a**, 1256-06-0; **1b**, 19474-19-2; **1c**, 51056-22-5; **2b**, 26774-86-7; **2e**, 61-33-6; **4b**, 51056-23-6; **5a**, 20097-92-1; **5b**, 51056-24-7; **6a**, 51056-25-8; **6b**, 51056-26-9; **6c**, 51056-27-0; **6d**, 51056-28-1; **7a**, 22266-10-0; **7b**, 10209-06-0; **7c**, 28974-31-4; **8a**, 51157-41-6; **8b**, 51056-29-2; **8c**, 51056-20-3; **9c**, 51056-21-4; dinitrogen tetroxide, 10544-72-6; 6-aminopenicillanic acid, 551-16-6; benzyl 6-aminopenicillanate, 3956-31-8.

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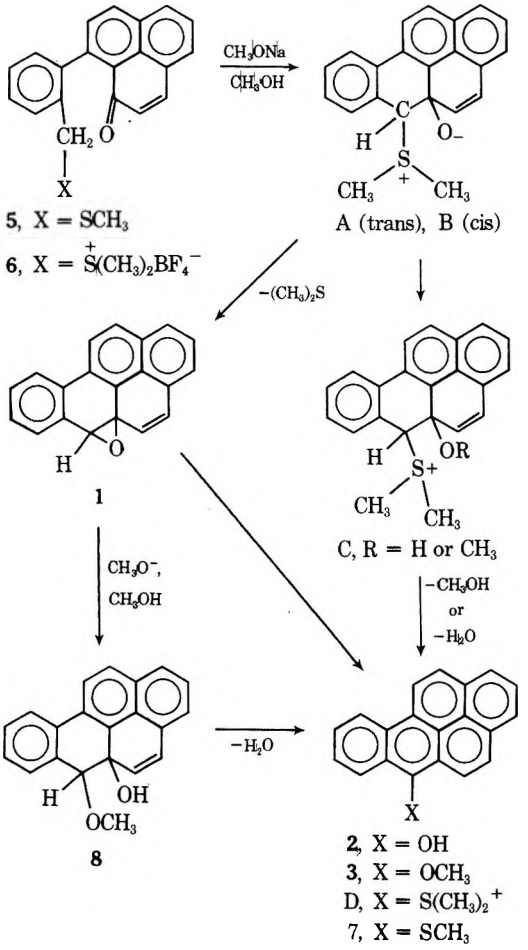
A New Synthesis of 6-Substituted Benzo[*a*]pyrenes Involving 5a,6-Epoxy-5a,6-dihydrobenzo[*a*]pyrene[1]

Summary. A new synthesis of 6-substituted benzo[*a*]pyrene derivatives, which involves as a key step the base-induced cyclization of dimethyl[*o*-(9-phenalenonyl)benzyl]-sulfonium tetrafluoroborate, **6**, is described.

Two general methods for the synthesis of arene epoxides have been developed. One stems from chemical reactions[2-4] applied to adjacent dihydrodiols which are obtained by hydroxylation of a phenanthrene-type bond with osmium tetroxide[5,6] or by reduction of a quinone to a mixture of cis and trans diols,[3,7] and the other by the dehydrobromination of polybromoepoxide precursors.[8-10] In this paper we describe efforts to prepare a new type of arene epoxide, 5a,6-epoxy-5a,6-dihydrobenzo[*a*]pyrene, **1**. Although we have not isolated **1**, our method of synthesis of 6-hydroxybenzo[*a*]pyrene, **2**, and 6-methoxybenzo[*a*]pyrene, **3**, described below undoubtedly involves the formation of **1** followed immediately by isomerization to **2** or reaction with methoxide ion to form **3**.

Treatment of phenalenone,[11] **4**, with o-(methylthiomethyl)phenyllithium, followed by an oxidative work-up,[12] produced 9-[o-(methylthiomethyl)phenyl]phenalenone,[13] **5**. Treatment with methyl iodide followed by silver tetrafluoroborate afforded dimethyl[o-(9-phenalenonyl)benzyl]sulfonium tetrafluoroborate,[13] **6**. Reaction of **6** with sodium methoxide in methanol resulted in the formation of **2** (67%) (best isolated as the corresponding acetate[14]), **3**[15] (11%), and 6-methylthiobenzo[*a*]pyrene,[13] **7** (10%).



We interpret these results in the following way. The sulfur ylide formed by treatment of **6** with sodium methoxide attacks the carbonyl group in two ways to yield the trans intermediate, A, and the cis intermediate, B. The predominant isomer, A, rapidly cyclizes to the epoxide, **1**. Most of the epoxide rearranges to **2** but a small amount reacts with sodium methoxide to yield **3**. The cis isomer, **B**, is either protonated or methylated (see below) to form an unstable intermediate C which loses water (or methanol) to yield a dimethyl-6-benzo[*a*]pyrenylsulfonium salt, D. As D is an alkylating agent, it can alkylate B (see above) or methoxide ion and be thereby converted to **7**. An alternate intramolecular alkylation of B to form 5a,6-dihydro-5a-methoxy-6-methylthiobenzo[*a*]pyrene (not shown) is unlikely.[16]

The chemistry involving conversion of **6** to **1** was modeled after the comparable acyclic reaction of Corey and Chaykovsky.[17] In the present case, bases, sodium methoxide (or sodium hydroxide in methanol–acetonitrile), weaker than the bases, butyllithium, and sodium hydride used previously,[17] can be used because the ylide need not be prepared before reaction with the carbonyl component.[18]

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Department of Chemistry
The Ohio State University
Columbus, Ohio 43210

Melvin S. Newman*
Len-Fang Lee

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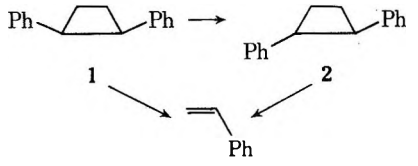
Geometric Isomerization and Cycloreversion in 1,2-Diphenylcyclobutane. Photochemical *vs.* Thermal Activation[1]

Summary: The ratio of cracking to geometric isomerization is 2.0 ± 0.3, 7.1 ± 0.7, and 2.6 ± 0.2 for *cis*-1,2-diphenylcyclobutane activated thermally, by direct irradiation, and by acetone sensitization, respectively, indicating that there may be a significant concerted component to cycloreversion in the singlet excited state.

Sir: A number of studies compared losses in stereochemistry attending cyclobutane cycloreversion, the Norrish type II photoelimination, and nitrogen extrusion from cyclic azo compounds.[2] In an extension of this discussion which attempted to establish structure–spin–reactivity relationships for thermal and photochemical reactions in principle involving diradicals, we would like to furnish data concerning the decomposition of 1,2-diphenylcyclobutane in which the reactivity "fingerprint" of cracking *vs.* geometrical isomerization for several modes of activation may be readily compared.

Solutions of *cis*-1,2-diphenylcyclobutane[3] in tetrachloroethylene were heated at 190–210°. Decomposition and the appearance of styrene and trans isomer **2** were followed by nmr. The reactions were quantitative, smoothly first order, and unaffected in rate by use of a more polar solvent (nitrobenzene) or by increasing the surface to volume ratio by the introduction of glass wool. Rate constants over one half-life for cracking and isomerization of **1** (200°) were 5.2 ± 0.4 × 10^{-5} and 2.4 ± 0.1 × 10^{-5} sec^{-1}, respectively. From data at three temperatures, Arrhenius parameters were calculated: for cracking, E_a = 35.8 kcal/mol, log A = 12.8; for isomerization, E_a = 35.6 kcal/mol, log A = 12.9. The decomposition of **1** was uncomplicated kinetically since **2** was stable under the conditions. Clean, first-order disappearance of **2** did occur at 230° (k = 3.7 ± 0.3 × 10^{-4} sec^{-1}), giving styrene only with even traces of **1** unobserved.



Irradiations of 0.02 M solutions of **1** or **2** at 254 nm gave styrene and cyclobutane isomer as major products by glc along with an unidentified peak which is presumed to be 1-phenyltetralin or 1-phenyltetrahydroazulene, reported previously[4] as low yield photochemical products at high conversion. Parallel irradiations (10–15% conversion) using a merry-go-round apparatus and a toluene/2-heptene actinometer[5] produced quantum yields which are summarized in Table I.

Quantum efficiencies for decomposition of **1** in the presence of triplet sensitizers such as benzophenone, acetophenone, and *m*-methoxyacetophenone were exceedingly low.[6] On the other hand, acetone (as solvent) provided sensitization with reaction efficiency comparable to direction irradiation (see Table I), suggesting that the quantum yield data in acetone reflect reaction of triplet excited cyclobutane since quenching of acetone singlets should be inefficient. In agreement is the effective sensitization of a phenylcyclopropane chromophore by acetone[10] and the rapid quenching of the type II photoelimination of 4-methyl-2-pentanone by 1,1,2,2-tetraphenylcyclopropane.[9]

The data concerning retention of configuration in **1** as measured by the product ratio of styrene/**2**[2d] for the different modes of activation are compiled in Table II. We

Table I
Quantum Yields in the Photolysis of *cis*- and *trans*-1,2-Diphenylcyclobutane

Cyclobutane	Solvent	$\phi_{styrene}$	ϕ_{isomer}
1	MeCN	0.019	0.003
1	MeOH	0.018	0.002
1	MeCN (1.0 M *trans*-2-heptene)[a]	0.018	0.002
1	MeCN (0.1 M dimethyl maleate)[a]	0.021	0.006
1	Acetone[b]	0.018	0.007
2	MeCN	0.018	0.007

[a] Light absorbed by cyclobutane. [b] Light absorbed by acetone.

Table II
Stereoretention in the Decomposition of 1 and 3

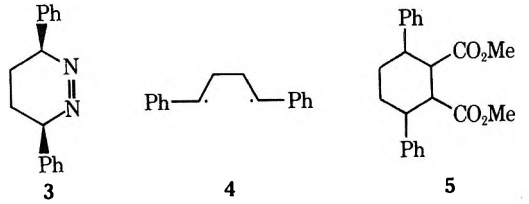
Starting material	Mode of activation	Styrene/**2**[a]
1	Thermal (190–210°)	2.0 ± 0.3
1	Direct irradiation	7.1 ± 0.7
1	Sensitized irradiation	2.6 ± 0.2
3	Thermal (63–280°)	4.6 ± 0.4

[a] Errors are average deviations of product ratios or the square root of the sum of squares of rate constant uncertainties.

assign the lowest singlet state of **1** as the excited species giving rise to products in direct irradiation since the reactions are not quenched by 2-heptene[11] or dimethyl maleate (E_T (estd) = 72 kcal/mol[12]) (see Table I), although a short-lived triplet (apparently not formed *via* acetone sensitization; compare product ratios) cannot be ruled out. Also assumed is that a single excited state partitions to products upon direct and sensitized irradiation, so that quantum yield ratios are rate constant ratios. For additional comparison the results of decomposition of azo compound **3** as reported by Kopecky[13] are included.

Clearly stereoretention values are not dramatically a function of mode of activation.[15] A common diradical **4**[16] could be involved in all cases if subtle dynamic effects produce the difference in partition to styrene and **2** (at most 67/33 *vs.* 88/12 for thermolysis and direct photolysis, respectively). In fact increased stereoretention in the series, thermal decomposition *vs.* azo compound fragmentation *vs.* direct photochemical activation, is in general agreement with the suggestion of Stephenson and Brauman[2a] that vibrationally excited diradicals may be involved in the latter two cases. However, in view of the recognition[2b,c] of mechanical forces which largely relieves the need for the "hot diradical" proposal for solution studies of several systems, the rapid internal relaxation from upper vibrational levels expected[19] for a species with as many atoms as **4**, and the observed dramatic independence of the decomposition of **3** on pressure,[14] we favor an alternative for an explanation of the small stereoretention differences. An economical suggestion is that concerted, perhaps orbital symmetry sanctioned, cycloreversion to styrene is an important contributor to the direct photolysis of **1** and the thermolysis of **3**. In agreement are reports[20] of high stereospecificity in the direct photochemical decomposition of a bicyclic cyclobutane related to **1** and **2**[20a] and in the thermal fragmentation of azo compounds related to **3**.[20b] Concerted fragmentation for **1** (photochemically) to give styrene and for **3** to the extent of 50 and 30%, respectively, combined with a common diradical component would rationalize the stereoretention results.

Using thermodynamic data[21] and the experimental activation energy for cracking of **1**, a ground-state potential



3 4 5

surface with a secondary minimum (~10 kcal/mol deep) may be estimated. Despite the reasonably long lifetime (10^{-8} sec at 200°) indicated for a diradical on this surface, trapping by good "diylophiles" such as dimethyl maleate[22] and dodecanethiol[23] in pyrolysis (trapping agent used as solvent) and photolysis experiments is not observed. Expected products **5** and 1,4-diphenylbutane were obtained independently and shown to survive the decomposition conditions. The diradical dichotomy which persists involves a species which on the one hand may have a lifetime of a bond rotational period (for stereochemical loss *via* an intermediate) but which eludes direct detection ($\tau < 10^{-11}$ sec?). The latter elusiveness is predicted by theoretical calculation of the surfaces for small ring reorganizations.[24]

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Department of Chemistry **Guilford Jones, II***
Boston University **Virginia L. Chow**
Boston, Massachusetts 02215

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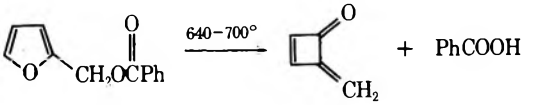
On the Mechanism of the Formation of Methylenecyclobutenone from the Pyrolysis of Furfuryl Benzoate

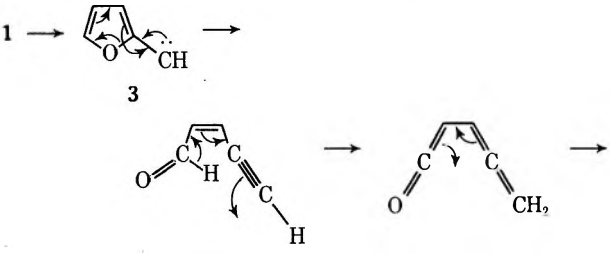
Summary: Aspects of the mechanism of the formation of methylenecyclobutenone by the pyrolysis of furfuryl benzoate are defined by the findings that pyrolysis of furfuryl-α,α-d_2 benzoate gives methylenecyclobutenone-5,5-d_2 and pyrolysis of 5-methylfurfuryl benzoate gives a good yield of 2,5-dimethylene-2,5-dihydrofuran.

Sir: Recently we reported that the low pressure (~10^{-4} Torr) gas phase pyrolysis of furfuryl benzoate (**1**) gives methylenecyclobutenone (**2**) in fair yield.[1]



1 2 (40%)

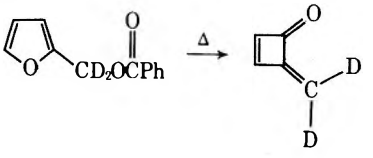
A likely mechanism for this interesting reaction involves the initial formation of furfurylidene (**3**) by α elimination followed by rearrangement of this carbene to *cis*-pent-2-en-4-ynal (*cis*-**4**), rearrangement of *cis*-**4** to allenylketene (**5**), and rearrangement of **5** to **2**. This mechanism



3 *cis*-4 5

is supported by the fact that **3** is known to rearrange to **4**[2] and by the detection by ir and nmr spectroscopy of small amounts of *trans*-**4** in the pyrolysis product mixture from **1**.

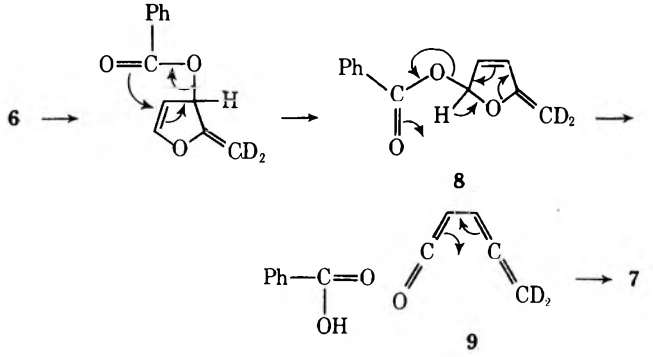
This mechanism predicts that pyrolysis of the α,α-dideuterio ester (**6**) would give **2** that contains only one deuterium atom. We wish to report that the pyrolysis of **6**[3] gives a 40% yield of **2** which has both methylene protons



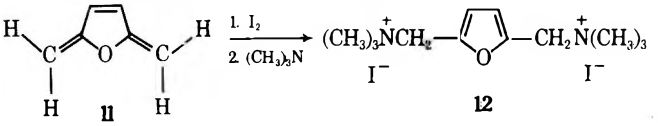
6 7

replaced with deuterium atoms (7). The nmr ($CDCl_3$) spectrum of the product shows only two strong peaks, a doublet (J = 2.75 Hz) at δ 8.65 and a doublet (J = 2.75 Hz) at 6.98. These peaks have been assigned to the ring protons of 2[1] and their different splitting pattern (compared to 2) is accounted for by the replacement of the two methylene protons with deuterium atoms. Integration of the *four* signals of 2 showed that each methylene position contained >96% deuterium.

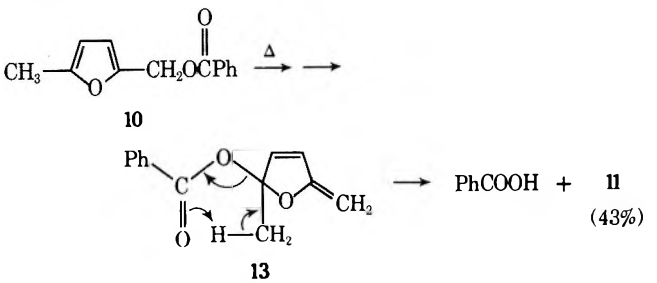
These results clearly rule out the mechanism presented above which involves α elimination and indicate that both α substituents of the ester end up on the methylene carbon of the product, an observation that could be useful in attempting to prepare substituted methylenecyclobutenones. A mechanism which accounts for these results is the following one which involves initial migration of the benzoate group into the furan ring.[4]



Support for this mechanism was gained by the study of the pyrolysis of 5-methylfurfuryl benzoate (10). Pyrolysis of 10[5,6] at 640° gave a 43% yield of 2,5-dimethylene-2,5-dihydrofuran (11). Compound 11 was identified by its nmr spectrum [δ 6.41 (s, 2), 4.50 (d, J = 1.5 Hz, 2), 4.21 (d, J = 1.5 Hz, 2)] and conversion to the known[7] bis(quaternary ammonium iodide) 12: nmr δ 7.06 (m, 2), 4.77 (m, 4), 3.27



(s, 18); dec pt 227–229° (lit.[7] dec pt 227–229°). Production of 11 is consistent with the above mechanism since the expected intermediate 13 should undergo β elimination to give 11.



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(3) Ester **6** was prepared by reducing methyl 2-furoate with lithium aluminum deuteride (Ventron Co., Alfa Products, 97.5% D) and esterifying the alcohol with benzoyl chloride in the presence of triethylamine. The nmr spectrum of **6** showed no α protons and mass spectral analysis indicated that the ester was 94% d_2, 5% d_1, and 1% d_0.
(4) The conversion of **8** to **9** could be a one-step process or a two-step process involving α elimination of benzoic acid to form a carbene which then rearranges to **9**.
(5) Ester **10** was prepared by reducing 5-methyl-2-furfural (Aldrich) with sodium borohydride in water and esterifying the alcohol with benzoyl chloride in the presence of pyridine: nmr ($CDCl_3$) δ 8.00–7.12 (m, 5), 6.35 (d, J = 3.2 Hz, 1, H_3), 5.91 (m, 1, H_4), 5.22 (s, 2, CH_2), 2.28 (s, 3, CH_3); ir ($CDCl_3$) 1715 (vs), 1265 (vs), 1100 (m), 1089 (m) cm^{-1}; mass spectrum calcd for $C_{13}H_{12}O_3$ 216.07865, found 216.07846.
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Department of Chemistry
Iowa State University of Science and Technology
Ames, Iowa 50010

Walter S. Trahanovsky*
Myong-Gi Park

Received January 29, 1974

Alkylation of α-Bromosulfonyl Compounds with Trialkylboranes

Summary: α-Alkylated sulfonyl derivatives have been prepared in good yields by treatment of the corresponding α-bromosulfonyl compounds with trialkylboranes in the presence of potassium *tert*-butoxide.

Sir: One general method for the preparation of sulfonyl derivatives[1] involves alkylation of α-sulfonyl carbanions. This method is likely to suffer in those systems where alkyl halides other than primary are employed, or for unsymmetrical sulfones when there is little if any difference in the relative acidities of the hydrogens α to the sulfonyl grouping. Trialkylboranes have been shown to serve as excellent alkylating agents for α-haloalkanoic esters, α-halo ketones, and α-halonitriles.[2] We wish to report the facile reaction of α-bromomethanesulfonyl compounds[3] with trialkylboranes under the influence of potassium *tert*-butoxide to produce the alkylated derivatives in good to excellent yields (eq 1).

$$R_3B + BrCH_2SO_2Y \xrightarrow[tert\text{-}BuOH]{tert\text{-}BuOK} RCH_2SO_2Y \qquad (1)$$

$$Y = C_6H_5,\ C_2H_5,\ OCH_2C(CH_3)_3,\ N(C_2H_5)_2$$

The reaction is easily performed and appears to be complete within a relatively short period of time under mild conditions. The trialkylborane is prepared by treating the appropriate olefin with a calculated amount of diborane in tetrahydrofuran according to the standard procedure.[4] The bromosulfonyl derivative is then added, followed by dropwise addition of potassium *tert*-butoxide in *tert*-butyl alcohol at either 0 or −40°. The results of this study are summarized in Table I. The reaction appears to be general, although somewhat lower isolated yields are realized employing cyclic secondary boranes.

Presumably the reaction involves the steps indicated in Scheme I.[2]

Scheme I

$$BrCH_2SO_2Y + t\text{-}BuO^- K^+ \longrightarrow K^+ {}^-CHBrSO_2Y + t\text{-}BuOH$$

$$R_3B + K^+ {}^-CHBrSO_2Y \longrightarrow K^+ [R_3BCHBrSO_2Y]^-$$

$$K^+ [R_3BCHBrSO_2Y]^- \longrightarrow R_2BCHSO_2Y + KBr \quad (R = \text{migrating group})$$

$$R_2BCHSO_2Y + t\text{-}BuOH \longrightarrow RCH_2SO_2Y + t\text{-}BuOBR_2$$

The following procedure for the preparation of cyclopentylmethyl phenyl sulfone is representative.

A dry 50-ml round-bottomed flask equipped with a septum inlet, a magnetic stirring bar, and a nitrogen inlet was flushed with nitrogen and maintained under a constant pressure of nitro-

Table I

$$R_3B + BrCH_2SO_2Y \xrightarrow[tert\text{-}BuOH]{tert\text{-}BuOK} RCH_2SO_2Y$$

1a–6d

1, R = *n*-C_4H_9 **a**, Y = C_6H_5
2, R = *i*-C_4H_9 **b**, Y = C_2H_5
3, R = *n*-C_6H_{13} **c**, Y = $OCH_2C(CH_3)_3$
4, R = *n*-C_8H_{17} **d**, Y = $N(C_2H_5)_2$
5, R = c-C_5H_9
6, R = c-C_6H_{11}

Borane	a[a] % yield[b]	a[a] Mp, °C	b[a] % yield[b]	b[a] Mp [bp (mm)], °C	c[a] % yield[b]	c[a] Bp, °C (mm)	d[a] % yield[b]	d[a] Bp, °C (mm)
1	99	31.5–32.5[c]	78	57.5–60[d]	76	77 (0.1)	84	87 (0.1)
2	92	35–36.5[e]	81	[74 (0.1)][f]	59	87 (0.3)	82	74 (0.1)
3	96	37–38	91	67–69	76	97 (0.05)	85	110 (0.6)
4	79	42–43	81	75–77	75	123 (0.15)	77	120 (0.35)
5	82	37–38	78	[101 (0.1)]	73	106 (0.15)	68	102 (0.35)
6	87	52–53[g]	65	[110 (0.1)]	60	111 (0.5)	72	111 (0.5)

[a] The nmr and ir spectral data of the products were consistent with the assigned structures. [b] Isolated yields. [c] Lit. mp 28.7–31.6°,[5] 31–32°.[6] [d] Lit.[5] mp 56–57°. [e] Lit.[6] mp 35.5–36.5°. [f] Lit.[7] mp 15°. [g] Lit.[8] mp 53–54°.

gen. The flask was charged with 4.25 ml of a 2.35 *M* solution of borane (30 mmol of hydride) in tetrahydrofuran and diluted with an additional 8 ml of tetrahydrofuran. The solution was cooled to 0° with stirring and cyclopentene (2.65 ml, 30 mmol) was added dropwise *via* a syringe over a 3-min period; then the clear solution was stirred at room temperature for 1 hr. The mixture was cooled to 0° and a solution of bromomethyl phenyl sulfone (2.35 g, 10 mmol, in 10 ml of tetrahydrofuran) was added *via* Cannula. Potassium *tert*-butoxide (9.1 ml of a 1.10 *M* solution in *tert*-butyl alcohol, 10 mmol) was added dropwise *via* a syringe over a 20-min period while the reaction stirred at 0°.[9] The addition of the first few drops of base to the clear solution immediately produced a white precipitate and the reaction remained heterogeneous until work-up.

After the reaction mixture had been stirred an additional 30 min at 0°,[10] sodium hydroxide (5.0 ml, 3 *N* aqueous solution, 15 mmol) was added followed by *slow*, dropwise addition of hydrogen peroxide (5.0 ml, 30% aqueous solution, 48 mmol); both solutions were added *via* a syringe. The mixture was stirred at 55° for 2 hr and cooled to room temperature, diethyl ether added, and the aqueous layer removed. The organic layer was washed with two 10-ml portions of water and one 10-ml portion of brine, dried over $MgSO_4$, and filtered. Concentration *in vacuo* yielded a residue, which was recrystallized from an ether–pentane mixture to yield 1.85 g of cyclopentylmethyl phenyl sulfone, mp 37–38°, 82%.

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(2) For reviews see H. C. Brown and M. M. Rogić, *Organometal. Chem. Syn.*, **1**, 305 (1972); H. C. Brown, "Boranes in Organic Synthesis," Cornell University Press, Ithaca, N. Y., 1972.
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(9) The addition of base in the bromomethyl ethyl sulfone series was done at −40°, maintained at −40° for 30 min, then slowly warmed to 0°.
(10) For the sulfonamides, initial addition of base was done at 0°; then the reaction was allowed to proceed overnight at ambient temperature before work-up. Dichlormethane was used rather than ether for extractions in this series.

(11) Financial support to L. A. M. by the Colgate-Palmolive Co. during the course of this work is hereby gratefully acknowledged.

Department of Chemistry
Purdue University
West Lafayette, Indiana 47907

William E. Truce*
Lawrence A. Mura[11]
Peter J. Smith
Fred Young

Received January 16, 1974

rof.
rof.

ollege

oc. Prof.
. Prof.
sst. Prof.
. Prof.
Asst. Prof.

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PhD, *Professor*
nD, *Professor*
Professor
1D, *Assoc. Prof.*
, *Assoc. Prof.*
, *Assoc. Prof.*
PhD, *Assoc. Prof.*
, *Assoc. Prof.*
D, *Assoc. Prof.*
e H., MS, *Assoc. Prof.*
., PhD, *Assoc. Prof.*
hD, *Asst. Prof.*
PhD, *Asst. Prof.*
D, *Asst. Prof.*
PhD, *Asst. Prof.*
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., PhD, *Asst. Prof.*
PhD, *Asst. Prof.*

orgia

stry,

istry
C., PhD, *Professor*
C., PhD, *Professor*
PhD, *Professor*
ert A., PhD, *Professor*
., PhD, *Professor*
ton J., PhD, *Res. Prof.*
illiam L., PhD, *Res. Prof.*
M., PhD, *Assoc. Prof.*
W. Scott, PhD, *Assoc. Prof.*
an, Daniel V., PhD, *Assoc. Prof.*
d V., BS, *Assoc. Professor*
V., PhD, *Assoc. Prof.*
n, PhD, *Assoc. Prof.*
, Lars G., PhD, *Assoc. Prof.*
bert E., PhD, *Assoc. Prof.*
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nald S., PhD, *Asst. Prof.*
ichard J., PhD, *Asst. Prof.*
, Norman G., PhD, *Asst. Prof.*
va, Prakash N., PhD, *Asst. Prof.*
ler, John E., PhD, *Asst. Prof.*

ty of Georgia

30602
ry Dept., (404) 542-2626
Chemistry

on, Charles E. (H), PhD, *Professor*
, Richard K., PhD, *Professor*
etier, S. William, PhD, *Professor*
lbrook, George E., PhD, *Professor*
inger, Norman L., PhD, *Res. Prof.*
ng, R. Bruce, PhD, *Res. Prof.*
aldwin, Winfield M., PhD, *Assoc. Prof.*
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A Wynne, Kenneth J., PhD, *Asst. Prof.*
A Bobbio, Stephen M., PhD, *Instructor*
A Carreira, Nionel A., PhD, *Instructor*
Kutal, Charles R., PhD, *Instructor*
Leyden, Donald E., PhD, *Instructor*
Seitz, William R., PhD, *Instructor*

University of Georgia

Athens 30602
Dept. of Medicinal Chemistry,
(404) 542-3077
B, M, D, Medicinal Chemistry

X LaRocca, Joseph P. (H), PhD, *Professor*
OX Blanton, DeWitt C., Jr., PhD, *Assoc. Prof.*
OX Honigberg, Irwin L., PhD, *Assoc. Prof.*
AX Stewart, James T., PhD, *Assoc. Prof.*
BX Thompson, Bobby B., PhD, *Assoc. Prof.*
BX Martinelli, Louis C., PhD, *Asst. Prof.*
AX Sternson, Larry A., PhD, *Asst. Prof.*

Gordon Junior College (2)

Barnesville 30204
Dept. of Math-Science, (205) 358-1700,
Ext. 72

AGO Smith, Maurice R., MS, *Instructor*

LaGrange College

LaGrange 30240
Dept. of Chemistry, (404) 882-2911,
Ext. 71
B, Chemistry

ABGO Hicks, Arthur M. (H), PhD, *Professor*
AIPX Hicks, Patrick M., MS, *Assoc. Prof.*
ABOP Cooper, Kenneth, PhD, *Asst. Prof.*

Macon Junior College (2)

Macon 31206
Div. of Natural Sciences and Mathematics,
(912) 745-8551, Ext. 262, 263

G Dever, David F., PhD, *Assoc. Prof.*

Mercer University

Macon 31207
Dept. of Chemistry, (912) 743-1511,
Ext. 287
B, Chemistry

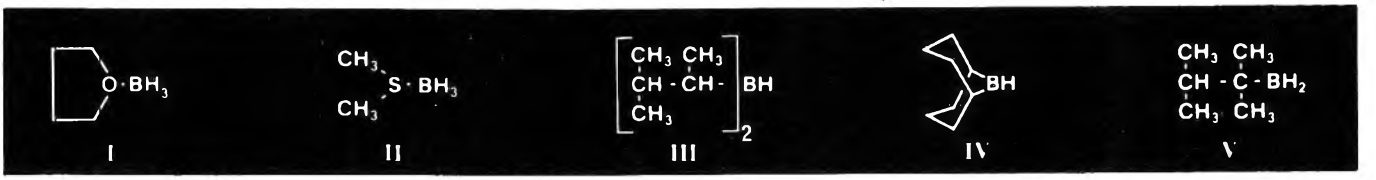
AG James, Franklin W. (C), PhD, *Professor*
AIG Furse, Clare T., PhD, *Professor*
GP Marquart, John R., PhD, *Assoc. Prof.*
OX Wiesler, Donald P., PhD, *Asst. Prof.*
GO Taylor, Robert E., MEd, *Instructor*

Mercer University in Atlanta

Atlanta 30341
Dept. of Science and Mathematics,
(404) 451-0331, Ext. 46
B, Chemistry

AIGO Edwards, Henry L. (C), PhD, *Professor*

Hydroboration Reagents: How, When, and Which to use.



BH_3•THF (**I**) is the most reactive and extensively studied[1] reagent for the hydroboration of olefins. The *cis* addition of the B-H moiety to 1-methylcyclohexene under mild conditions gives, upon oxidation, the isomerically pure *trans*-alcohol[2] (eq 1). A highly concentrated and inexpensive alternate to **I** is BH_3•$(CH_3)_2S$ (**II**) which hydroborates olefins in a variety of aprotic solvents[3] (eq 2).

Disiamylborane (**III**) is more selective than I or II for the mono-hydroboration of dienes and acetylenes, giving, with a terminal acetylene, a vinylborane with boron attached to the terminal position in >98% purity[4] (eq 3). **III** is the reagent of choice for the conversion of a terminal olefin to a primary iodide[5] (eq 4).

9-BBN (**IV**) readily reacts with monosubstituted olefins to place boron in the terminal position at >99% selectivity. However, unlike **III** , 9-BBN reacts with terminal acetylenes to produce 1,1-diborylalkanes.[7] In many synthetic processes, the alkyl group of a *B*-alkyl-9-BBN derivative undergoes preferential reaction, an important consideration in reactions of R_3B where only one R group is converted to the product[8] (eq 5). Thexylborane (**V**) is a useful reagent for the cyclic hydroboration of dienes[9] to produce cyclic ketones upon carbonylation[10] (eq 6).

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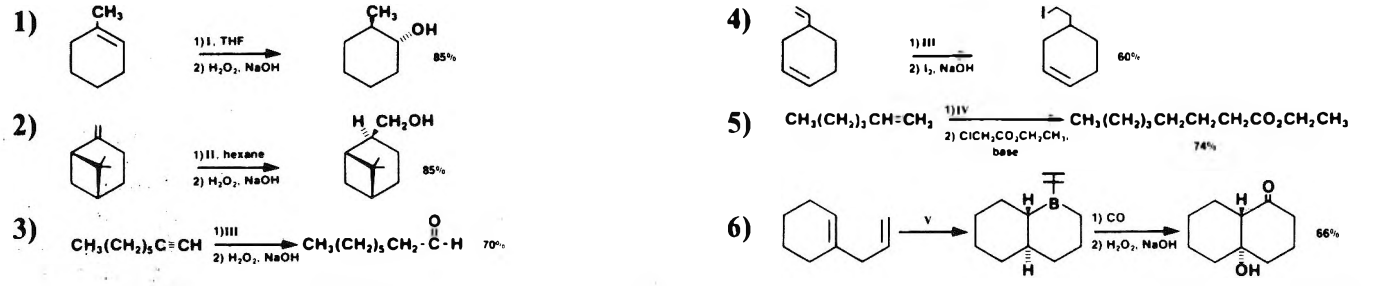
For a recent review covering additional applications of these reagents, see H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1973 (Aldrich catalog no. Z10,080-3, $28.50).



I	**17,619-2**	**Borane•tetrahydrofuran complex, 1*M* in THF**	**900g (*ca* 1l) $37.50**
II	**17,982-5**	**Borane•methyl sulfide complex**	**80g (*ca* 1 mole) $19.50; 500g $60.00**
III	**18,525-6**	**Disiamylborane Preparation Kit (Reagents plus instructions for preparing 1 mole in THF)**	**1 each $47.50**
IV	**15,107-6**	**9-BBN, 0.5*M* in THF**	**900g (*ca* 1l) $33.75**
	17,871-3	**9-BBN, crystalline solid**	**25g $25.00; 100g $80.00**
V	**18,485-3**	**Thexylborane Preparation Kit (Reagents plus instructions for preparing 1 mole in THF)**	**1 each $82.00**

Aldrich Chemical Company, Inc.

Home Office:
Aldrich Chemical Co., Inc.
940 W. St. Paul Ave.
Milwaukee, Wisconsin 53233

In Great Britain:
Ralph N. Emanuel Ltd.
264 Water Rd., Wembley, Middx.
HAO 1PY, England

In Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium

In Germany:
EGA-Chemie KG
7924 Steinheim am Albuch
Germany