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AUTHOR INDEX

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the paper should be addressed is marked with an asterisk in the by-line.

Mass Spectrometry in Structural and Stereochemical Problems. CCXIII.[1]
The Effect of Ring Size upon the Electron Impact Induced
Behavior of Steroidal Ketones[2]

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Received June 28, 1971

Comparison of the mass spectra of D-norpregnan-20-one, pregnan-20-one, and D-homopregnan-20-one demonstrates that the relief of ring strain plays a minor role in the determination of the site of charge localization in 20-ketones. The differences observed among the spectra are instead best rationalized on the basis of the stabilities of the ions and neutral species produced by fragmentation. The electron impact induced behavior of D-homoandrostan-17a-one and -17-one is qualitatively similar to that of androstan-1-one and -2-one, respectively. The similarity of the mass spectra of D-norandrostan-16-one and D-norandrostane-16β-carboxylic acid (and several other D-nor steroids) below m/e 218, in conjunction with metastable ion evidence, suggests that these low mass ions may arise from a common precursor, the m/e 218 ion. The mass spectra of D-bishomoandrostan-17b-one and -17a-one are also discussed.

It has long been realized that fragmentations about ring D are of particular diagnostic importance in the interpretation of the electron impact induced behavior of steroids.[5] In order to understand the mechanistic details of these much studied fragmentations, a program was launched in these laboratories to determine the mass spectra of steroids structurally modified in the D ring. Specifically, D-nor-, D-homo-, and D-bishomoandrostanones and -pregnan-20-ones were prepared and their mass spectra were observed.

Results and Discussion

Pregnan-20-ones.—The electron impact induced behavior of steroidal ketones has been the subject of numerous investigations.[6] An interesting generalization apparent from these studies is that ions structurally analogous to a usually do not participate directly in the most prevalent fragmentation processes of the molecule. When the carbonyl moiety is contained within a ring, this observation is not surprising. A simple α-cleavage reaction (eq 1), well-known in the mass spectra of aliphatic ketones, generates a species b from which most of the molecule's fragmentations can be rationalized.

$$ (1) $$

On the other hand, if a molecule such as pregnan-20-one (I) undergoes α cleavage, a fragment ion must be produced (eq 2). Nevertheless, the major frag-

$$ M^+-15, m/e\ 287 \qquad (2) $$

$$ M^+-43, m/e\ 259 $$
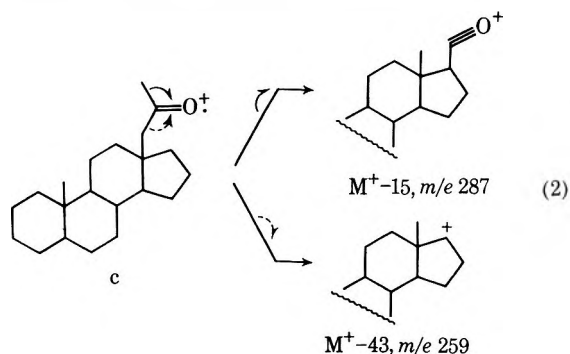
mentations in the mass spectrum of pregnan-20-one (Figure 2) can best be rationalized on the basis of a molecular ion of structure d.[7] Generation of ion d is clearly a favorable process; cleavage of the C-13–C-17 bond generates a tertiary carbonium ion and a resonance-stabilized radical. In addition, it relieves the strain inherent in the trans-fused hydrindan system

(1) For paper CCXII, see M. Katoh, D. N. Jaeger, and C. Djerassi, J. Amer. Chem. Soc., submitted for publication.

(2) Financial assistance from the National Institutes of Health (Grant AM 12758) is gratefully acknowledged.

(3) Recipient of an IREX fellowship while on leave (1970–1971) from the Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia.

(4) National Institutes of Health Predoctoral Fellow, 1968–1971.

(5) P. de Mayo and R. I. Reed, Chem. Ind. (London), 1481 (1956).

(6) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, Chapter 20.

(7) L. Tökes, R. T. LaLonde, and C. Djerassi, J. Org. Chem., 32, 1020 (1967).

D-Homopregnan-20-one (II)	Isotopic purity	M+	M+ − CH₃	M+ − H₂O	M+ − CH₃ − H₂O	M+ − C₃H₆O	M+ − C₄H₁₁O
d₀		316	301	298	283	258	217
17a,21,21,21-d₄	92% d₄	320	305	302	287	258	217

[a] Reported shifts are corrected for isotopic impurities as well as ¹³C contributions and are greater than 90% unless otherwise indicated.

d
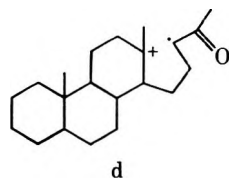
of ring D. It is of considerable interest to evaluate the importance of the latter effect, since it has been invoked as a partial explanation for the preferential fragmentation of pregnane itself about ring D.[8] Thus, *D*-homopregnan-20-one (II), containing a strain-free

I

II

III
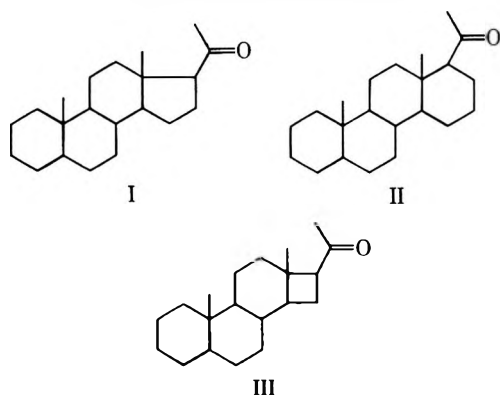
trans-decalin system, was prepared. Its mass spectrum (Figure 3) exhibits no evidence for more extensive participation of ions of structure c in the fragmentation processes. The intensity of the M − 43 peak (*m/e* 273) is not enhanced relative to its intensity in the mass spectrum of pregnan-20-one itself. Similarly, deuterium-labeling experiments (Table I) demonstrate that the C-21 methyl group is not implicated in the genesis of the M − 15 peak, exactly as in pregnan-20-one itself.[7] Since the major peaks in both spectra are best rationalized on the basis of molecular ions analogous to d, and not c, it must be concluded that the ring strain inherent in the trans-fused hydrindan system is not an important factor in inducing charge localization in the 13–17 bond.

It is interesting to note that the mass spectrum of *D*-norpregnan-20-one (III, Figure 1) exhibits no peaks which can be attributed to charge localization on the carbonyl group (e). The complete absence of an M − 43 peak (*m/e* 245) in Figure 1 suggests that the highly strained cyclobutane ring of III causes virtually complete charge localization in the 13–16 bond (f) prior to decomposition.

e

f

(8) L. Tökes, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968).
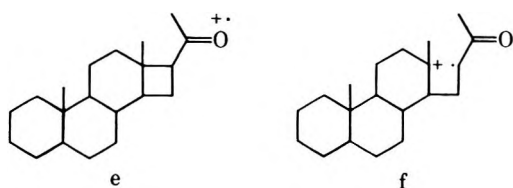
A peak appears at *m/e* 43 in the spectra of all three pregnan-20-ones (Figures 1, 2, and 3). Although the *m/e* 43 peak might *a priori* be envisaged as arising directly from a molecular ion of structure c (eq 3), the

c   *m/e* 43   (3)
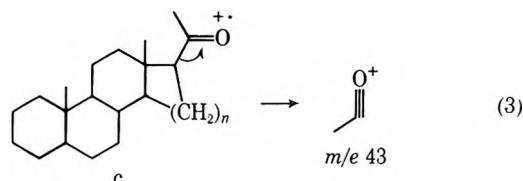
absence of the peak in the low-voltage spectra of these compounds suggests that it arises from one or more fragment ions. Consequently, variations in the intensity of the *m/e* 43 peak are not readily explicable on the basis of preferential charge localization in the molecular ion.

Although all three 20-ketones appear to fragment predominantly from ions of similar structure, a cursory inspection of Figures 1, 2, and 3 indicates that the fragmentation pattern of *D*-norandrostan-20-one (III) differs dramatically from that of the five- and six-membered ring D compounds. Consideration of these differences sheds considerable light on the mechanisms of fragmentation of pregnan-20-one itself.

M − 58 Peak.—The M − 58 peak appears at *m/e* 244 in the mass spectrum (Figure 2) of pregnan-20-one. It has been proposed[7] that this peak arises largely (60%) by the pathway depicted in eq 4. Abstraction of the C-14 hydrogen atom generates an ion of structure g which can then undergo a McLafferty-type rearrangement to yield the peak at *m/e* 244. It is important to note that the ion g is formed in eq 4 by

d

g

d

h, *m/e* 244   (4)
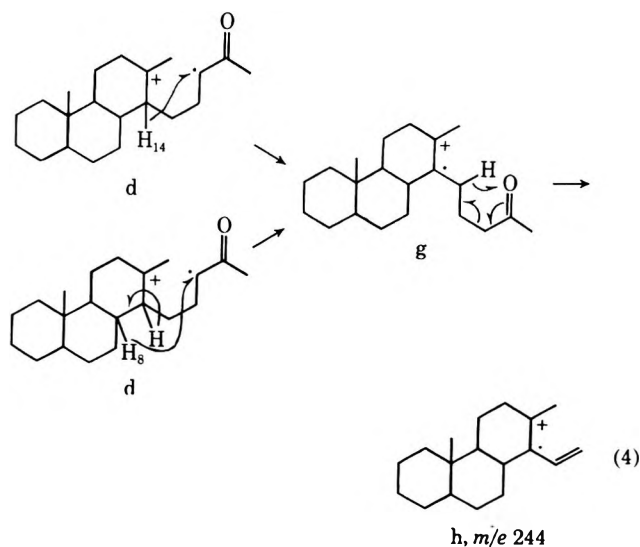
hydrogen abstraction through a transition state involving a five-membered ring. A significant portion (40%) of the mass 244 ion is formed by the abstraction of the unactivated hydrogen atom at C-8 (eq 4).

D-Norpregnan-20-one (III)	Isotopic purity	M[+]	M[+] − CH₃	M[+] − H₂O	M[+] − CH₃ − H₂O	M[+] − C₃H₆O	M[+] − C₄H₆O	M[+] − C₄H₇O	M[+] − C₄H₉O	M[+] − C₅H₉O
d_0		288	273	270	255	230	218	217	215	203
16,21,21,21-d_4	95% d_4	292	277	274	259	230	218	217	215	203

[a] Reported shifts are corrected for isotopic impurities as well as ¹³C contributions and are greater than 95% unless otherwise indicated.

The prevalence of the latter process must be attributed to the well-known preference for hydrogen abstraction through a six-membered ring.

The very abundant ion of mass 230 in the spectrum of *D*-norpregnan-20-one (Figure 1) presumably arises through a similar mechanism, although this has not been fully substantiated by deuterium labeling experiments (Table II). Abstraction of a C-12 hydrogen through a six-membered transition state would generate the ionized keto olefin i, which can undergo a McLafferty rearrangement to an ion of mass 230 (eq 5).

Figure 1.—Mass spectrum of *D*-nor-5α-pregnan-20-one.

Figure 2.—Mass spectrum of 5α-pregnan-20-one.

Figure 3.—Mass spectrum of *D*-homo-5α-pregnan-20-one.

(5)

j, m/e 230
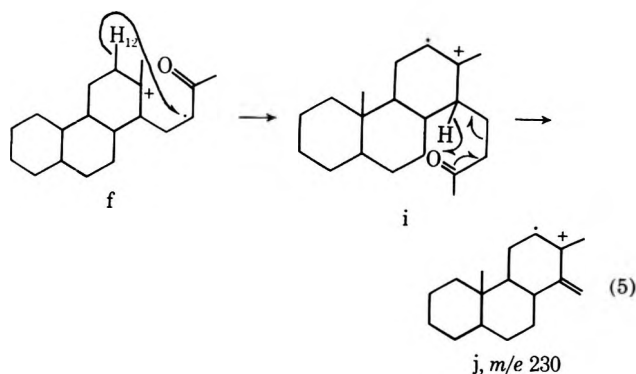
The dramatic increase in the abundance of the M − 58 ion in the spectrum of *D*-norpregnan-20-one (III) must be attributed to the presence of activated hydrogens at C-12 which can be extracted through the very favorable six-membered transition state.

Abstraction of an activated hydrogen atom from C-14 in the molecular ion k of *D*-homopregnan-20-one (II) also involves a six-membered ring transition state. The small size of the M − 58 peak (m/e 254) in Figure 3 must therefore be attributed to the unactivated nature of the C-16 hydrogen which needs to participate in the McLafferty rearrangement (eq 6).

at m/e 232 in the mass spectrum of pregnan-20-one (1) (Figure 2); the corresponding peak is not observed in the mass spectrum of *D*-homopregnan-20-one (II) (Figure 3).

Deuterium-labeling experiments on pregnan-20-one demonstrated[7] that this process involves the expulsion of C-16, C-17, C-20, and C-21, as depicted in eq 7. The increased intensity of the corresponding peak in the spectrum of *D*-norpregnan-20-one (Figure 1) must be attributed to the greater stability of an ionized double bond (o) as compared to an ionized cylopropane (n). Similarly, the complete absence of the M − 70 peak in the spectrum of *D*-homopregnan-20-one must be attributed to the even less favored character of the ionized cyclobutyl species p.

The variation in the abundance of the M − 70 peak can thus be rationalized on the basis of the stability of the resulting ionic species. Conversely, the variation in the abundance of the m/e 218 peak in the spectra of the three ketones is attributable to the stability of the neutral species produced. The expulsion of an olefin

k   l

(6)

m

M − 70 Peak.—This fragmentation gives rise to the intense peak at m/e 218 in the mass spectrum of *D*-norpregnan-20-one (III) (Figure 1) and the weak peak

d → n, *m/e* 232 (7)

f → o, *m/e* 218 (8)

k → p, *m/e* 246 (9)
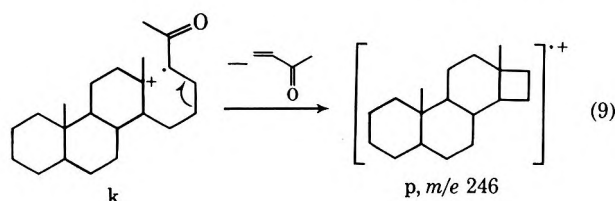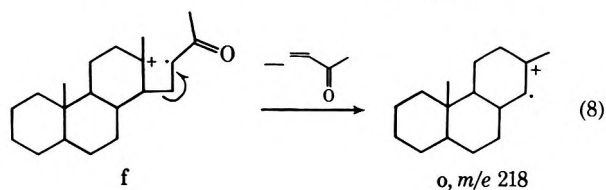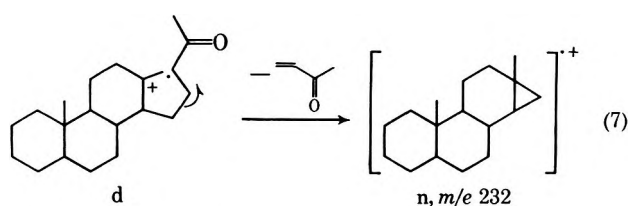
(eq 8) is energetically preferable to the expulsion of a cyclopropane (eq 10) or cyclobutane (eq 11).

d → o, *m/e* 218 (10)

→ o, *m/e* 218 (11)
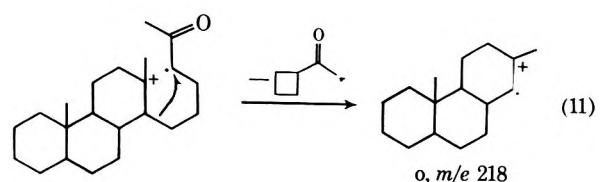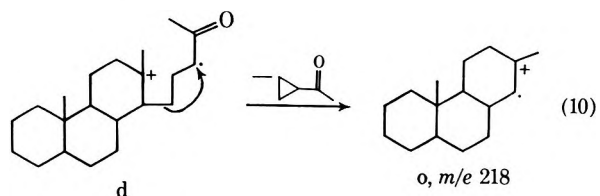
m/e **217 Peak.**—All three ketones exhibit an intense peak at *m/e* 217, corresponding to the elimination of ring D with an additional hydrogen atom. Deuterium-labeling experiments have implicated C-8 and C-14

d → p, *m/e* 217 (12)

f → p, *m/e* 217 (13)

k → p, *m/e* 217 (14)
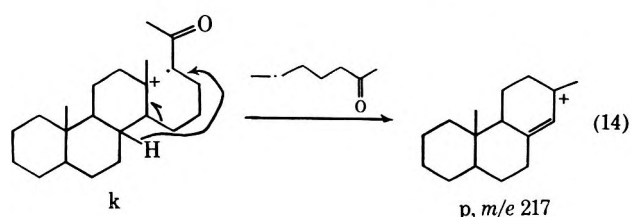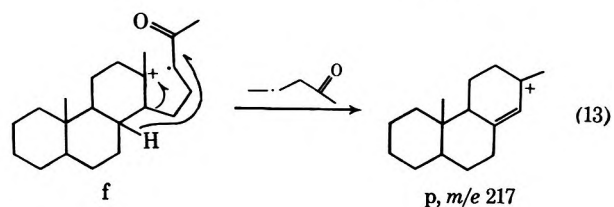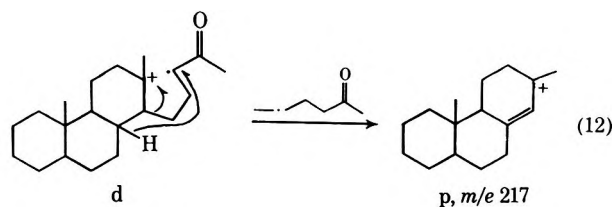
as the sources of the extra hydrogen atom in the fragmentation of pregnan-20-one itself (eq 12).[7] Deuterium-labeling experiments have not been performed on *D*-nor- or *D*-homopregnan-20-one to establish the origin of the extra hydrogen atom; it appears plausible, however that the *m/e* 217 peak in Figures 1 and 3 arises in an analogous manner (eq 13 and 14).

m/e **215 Peak.**—Metastable ion evidence suggests that the *m/e* 215 peak in the mass spectrum of *D*-norpregnan-20-one (Figure 1) is formed by the elimination of a methyl group from the *m/e* 230 peak (eq 15).

j → q, *m/e* 215 (15)
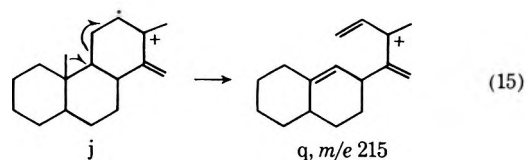
The ion of mass 215 in the spectrum of pregnan-20-one (Figure 2) probably arises in an identical manner.

Other Fragmentations.—The mass spectrum of *D*-norpregnan-20-one (Figure 1) exhibits a series of peaks at *m/e* 203, 175, 162, 161, 148, and 109 which are characteristic of all the D-nor steroids prepared in this study. Discussion of the genesis of these ions will be deferred to the subsequent section dealing with *D*-norandrostan-16-one and *D*-norandrostane-16β-carboxylic acid, since more extensive deuterium-labeling data are available for the latter compound.

Androstan-16-, -17-, -17a-, and -17b-ones.—The electron impact induced behavior of androstan-16-one (IV)[9] and androstan-17-one (V)[10] has been the object of careful study, and a number of unusual mechanistic proposals have been advanced to account for the fragmentations of these compounds.

V   IV
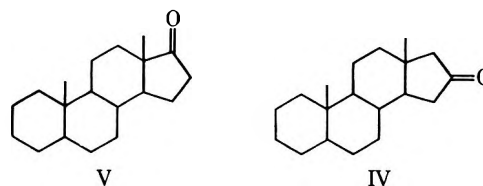
It was of interest, therefore, to compare the mass spectra of analogous *D*-nor, *D*-homo, and *D*-bishomo ketones; the effect of adding or removing a methylene group adjacent to the carbonyl moiety should shed considerable light on the mechanisms of a number of very favorable process in the mass spectra of steroidal ketones.

M − 15 Peak.—The M − 15 peak appears in the spectra of all the keto steroids investigated in this study. Deuterium-labeling experiments performed on androstan-17-one (V) indicated that the C-19 methyl group was eliminated three times as readily as the C-18 methyl group.[10] This observation was attributed to preferential charge localization in the C-13–C-17 bond, rather than the required C-13–C-18 bond (eq 16).

It was relevant, therefore, to determine the origin of the M − 15 peak in the *D*-homo steroids. In *D*-homo-androstan-17a-one (VI), the ratio of C-19 loss to C-18 loss decreases to 1:1 (*cf.* Table III). This observation

(9) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 269 (1964).

(10) L. Tökes, R. T. LaLonde, and C. Djerassi, *J. Org. Chem.*, **32**, 1012 (1967); G. Jones and C. Djerassi, *Steroids*, **10**, 653 (1967).

(16)

(17)

m/e 274
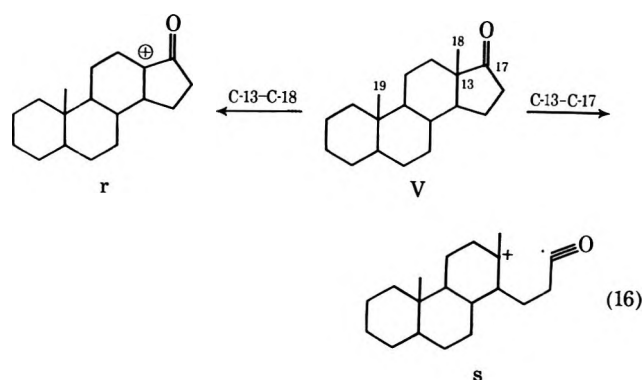
Table III

EFFECT OF STRUCTURE ON THE RATIO OF C-19 METHYL LOSS
TO C-18 METHYL LOSS IN STEROIDAL KETONES

Compd	C-19/C-18
Androstan-17-one (V)	3:1
Androstan-2-one (IX)	1:1
D-Homoandrostan-17a-one (VI)	1:1
D-Homo-13α-androstan-17a-one (VII)	3:1

is, in itself, consistent with the earlier explanation, because the *trans*-decalone system of the D-homo steroid should be less strained than the *trans*-hydrindanone system of the normal steroid; cleavage of the 13–17a bond should, therefore, be less favorable. However, the *cis*-decalone system of D-homo-13α-androstan-17a-one (VII) is more strained than the *trans*-decalone system. Nevertheless, the ratio of C-19 loss to C-18 loss increases to 3:1, despite the apparent driving force favoring cleavage of the 13–17a bond.

VI   VII
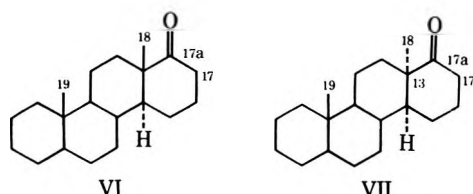
These results suggest that the original explanation[10] for the ratio observed in the spectra of androstan-17-one is oversimplified. Until more extensive comparisons are available, the factors determining the ratio of methyl elimination must remain poorly understood.

M — H₂O Peak.—Extensive deuterium-labeling experiments (Table V) on D-homoandrostan-17a-one (VI) demonstrate that the elimination of water is a random process, with no labeled position accounting for more than a small fraction of the hydrogen atoms eliminated. A similar conclusion must be drawn from the D-homo 17 ketones (Table VI) and D-bishomo (Tables VII and VIII) steroids, although on the basis of much less extensive labeling data. This is in complete accord with the results already described for the elimination of water from androstan-17-one.[10]

M — C₂H₄ Peak.—The second most intense peak in the mass spectrum of D-bishomoandrostan-17a-one (VIII, Figure 8) appears at *m/e* 274, corresponding to the elimination of 28 mass units from the molecular ion. Deuterium-labeling experiments suggest that the process occurs as depicted in eq 17. It is interesting to note that the elimination of ethylene is not observed in the spectra of any of the other ketones investigated
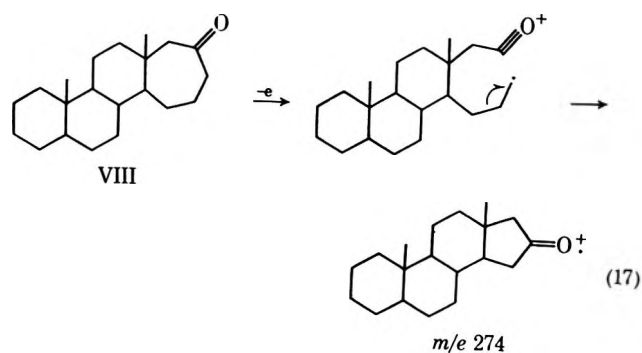
in this study. This observation can be rationalized, however. In those ketones in which the carbonyl group is adjacent to the angular methyl [D-norandrostan-16-one (XI), D-homoandrostan-17a-one (VI), and D-bishomoandrostan-17b-one (XV)], charge localization occurs predominantly between the carbonyl group and the tertiary carbon (eq 18), not the carbonyl group and the primary carbon (eq 19), as required by the mechanism depicted in eq 17.

(18)

(19)
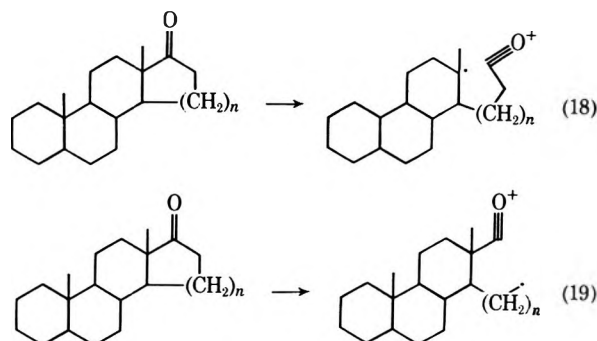
The absence of an M — 28 peak in the spectrum of D-homoandrostan-17-one (IX, Figure 6) cannot be attributed to this effect. The explanation must lie in the greater strain inherent in the cyclobutane system t, which would form after the elimination of ethylene (eq 20).

(20)

t
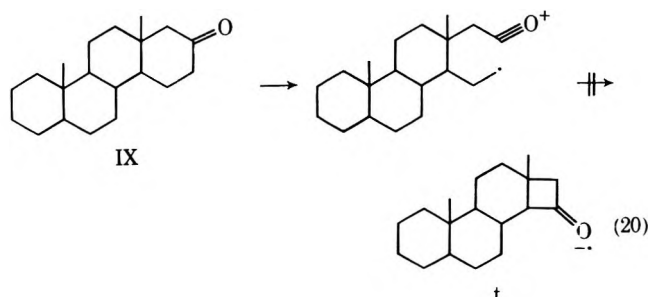
m/e **230 and 231.**—The most intense peaks in the mass spectrum of D-homoandrostan-17-one (IX, Figure 7) appear at *m/e* 230 and 231. Although the absence of extensive deuterium labeling data makes detailed discussion of the origin of these peaks difficult, the observation of analogous peaks in the mass spectrum of androstan-2-one (X)[11] permits a qualitative discussion of their genesis.

The *m/e* 231 peak in the mass spectrum[11] of androstan-2-one (X) arises by the elimination of a C₃H₇ frag-

(11) J. E. Gurst and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 5542 (1964).

TABLE IV
SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-NORANDROSTANE-16β-CARBOXYLIC ACID (XVI)

D-Norandrostan-16β-carboxylic acid (XVI)	Isotopic purity	M⁺	M⁺ − CH_3	M⁺ − $C_2H_4O_2$	M⁺ − $C_3H_4O_2$	M⁺ − $C_3H_5O_2$	M⁺ − $C_4H_7O_2$	M⁺ − $C_6H_{11}O_2$	M⁺ − $C_8H_{13}O_2$	M⁺ − $C_8H_{14}O_2$	M⁺ − $C_{11}H_{17}O_2$
d_0	...	290	275	230	218	217	203	175	149	148	109
3-d_1	85% d_1	291	276	231	219	218	204	176	150 (90%) 149 (10%)	149 (80%) 148 (20%)	110 (70%) 109 (30%)
14α-d_1	80% d_1	291	276	231 (60%) 230 (40%)	219 (80%) 218 (20%)	218 (80%) 217 (20%)	204 (80%) 203 (20%)	176 (60%) 175 (40%)	150 (5%) 149 (95%)	149 (20%) 148 (80%)	110 (<20%) 109 (>80%)
15α-d_1	58% d_1	291	276	231 (85%) 230 (15%)	218	217	203	176 (40%) 175 (60%)	149	149 (10%) 148 (90%)	110 (20%) 109 (80%)
16α-d_1	98% d_1	291	276	230	218	217	203	175	149	148	110 (20%) 109 (80%)

[a] Reported shifts are corrected for isotopic impurities as well as ^{13}C contributions and are greater than 95% unless otherwise indicated.

TABLE V
SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-HOMOANDROSTAN-17a-ONE (VI)

D-Homoandrostan-17a-one (VI)	Isotopic purity	M⁺	M⁺ − CH_3	M⁺ − H_2O	M⁺ − CO	M⁺ − H_2O − CH_3	M⁺ − CO − CH_3	M⁺ − C_4H_9	M⁺ − C_4H_{10}	M⁺ − C_4H_7O	M⁺ − C_4H_9O	M⁺ − $C_5H_{18}O$	M⁺ − $C_9H_{17}O$
d_0		288	273	270	260	255	245	231	230	217	215	189	149
3-d_1	98% d_1	289	274	271	261	256	246	232	231	218	216	190	150
14α-d_1	90% d_1	289	274	271 (80%) 270 (20%)	261	256	246	232	231	218 (50%) 217 (50%)	215	189	149
16,16-d_2	98% d_2	290	275	272	262	257	247	233	231 (50%) 323 (50%)	217	215	189	149
17,17-d_7	93% d_2	290	275	272	262	257	247	233	232	217	215	189	149
18,18,18-d_3	98% d_2	291	276 (50%) 273 (50%)	273	263	258	248	234	230	220	218	192 (50%) 189 (50%)	149

[a] Reported shifts are corrected for isotopic impurities as well as ^{13}C contributions and are greater than 90% unless otherwise indicated.

TABLE VI
SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-HOMOANDROSTAN-17-ONE (VIII)

D-Homoandrostan-17-one (VIII)	Isotopic purity	M⁺	M⁺ − CH_3	M⁺ − H_2O	M⁺ − CH_3 − H_2O	M⁺ − C_4H_9	M⁺ − C_3H_6O
d_0		288	273	270	255	231	230
d_4	75% d_4	292	277	274	259	235	230

[a] Reported shifts are corrected for isotopic impurities as well as ^{13}C contributions and are greater than 95% unless otherwise indicated.
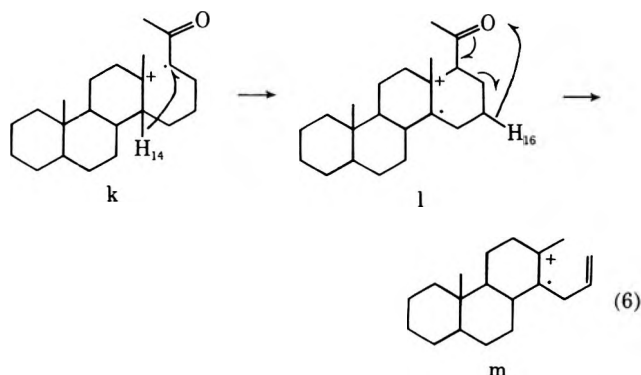
TABLE VII
SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-BISHOMOANDROSTAN-17a-ONE (VIII)

D-Bishomoandrostan-17-one (VIII)	Isotopic purity	M⁺	M⁺ − CH_3	M⁺ − H_2O	M⁺ − C_2H_4	M⁺ − CH_3 − H_2O	M⁺ − C_3H_6O	M⁺ − C_5H_9O
d_0		302	287	284	274	269	244	217
17,17,17b,17b-d_4	80% d_4	306	291	288	276	273	244	217

[a] Reported shifts are corrected for isotopic impurities as well as ^{13}C contributions and are greater than 95% unless otherwise indicated.

TABLE VIII
SHIFTS[a] OF MASS SPECTRAL PEAKS OF *D*-BISHOMOANDROSTAN-17b-ONE (XV)

D-Bishomoandrostan-17b-one (XV)	Isotopic purity	M⁺	M⁺ − CH_3	M⁺ − H_2O	M⁺ − C_3H_7	M⁺ − C_5H_9O
d_0		302	287	284	259	217
17a,17a-d_2	98% d_2	304	289	286	261	217

[a] Reported shifts are corrected for isotopic impurities as well as ^{13}C contributions, and are greater than 95% unless otherwise indicated.

demonstrate that ring D hydrogens are retained. It appears plausible that fragmentation is occurring about ring A as depicted in eq 22.

$$\text{(21)} \qquad m/e\ 231$$

$$\text{(22)} \qquad m/e\ 231$$

ment from ring D (eq 21). High-resolution mass spectrometry on the m/e 231 peak of *D*-homoandrostan-17-one (IX) indicates that it arises by the elimination of C_4H_9, and deuterium labeling experiments (Table VI)

Figure 4.—Mass spectrum of *D*-nor-5α-androstan-16-one.

Figure 5.—Mass spectrum of 5α-androstan-17-one.
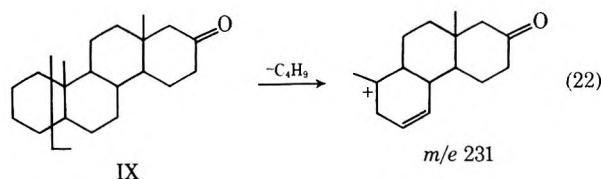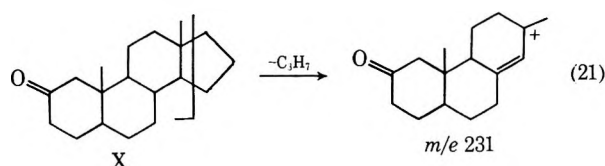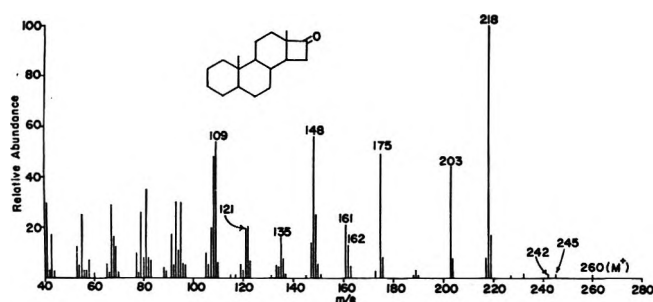
Figure 6.—Mass spectrum of *D*-homo-5α-androstan-17a-one.

The genesis of the *m/e* 216 peak in the mass spectrum of androstan-2-one has been fully elucidated[11] by deuterium labeling; the proposed mechanism is depicted in eq 23. Transfer of a hydrogen atom to C-1 generates the ionized keto olefin u, which undergoes fragmentation by abstracting a C-6 hydrogen atom (u → v).

$$(23)$$
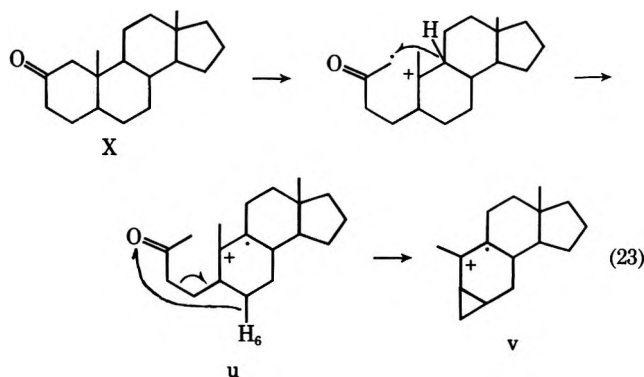
High-resolution mass spectrometry on the *m/e* 230 peak in the spectrum of *D*-homoandrostan-17-one (IX) is in complete accord with the occurrence of an analogous process in the formation of this ion (eq 24). Moreover, deuterium-labeling experiments demonstrate that C-16 and C-17a are eliminated in this fragmentation.
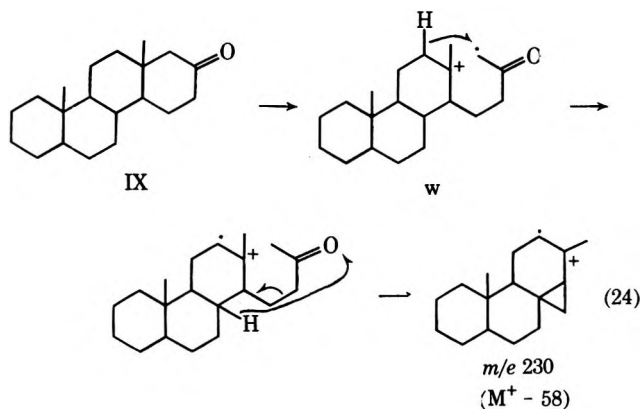
$$(24)$$

over, deuterium-labeling experiments demonstrate that C-16 and C-17a are eliminated in this fragmentation.

The *m/e* 230 peak in the mass spectrum of androstan-17-one (Figure 5) arises in a mechanistically distinct manner; its genesis has been discussed in an earlier publication.[10]

Deuterium-labeling experiments (Table V) indicate that the small peaks at *m/e* 230 and 231 in the spectrum of *D*-homoandrostan-17a-one (Figure 6) are formed by several distinct mechanistic pathways, and that the plausible cleavage depicted in eq 25 is not the
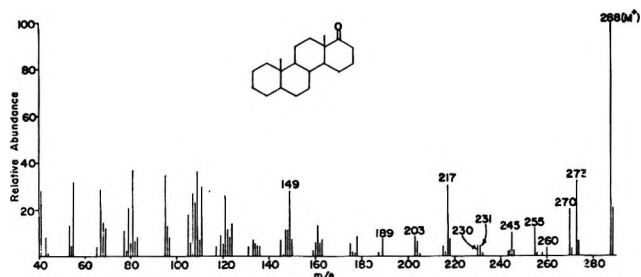
predominant source of the *m/e* 231 ion. It is interesting to note then, that cleavage about ring A is observed in the spectrum of *D*-homoandrostan-17-one (IX) but not in the spectrum (Figure 6) of *D*-homoandrostan-17a-one (VI). This difference can be attributed to the greater stability of ions of structure x vs. those of structure w. Apparently, charge localization in the 1–10 bond (y) can compete with the formation of the species w.
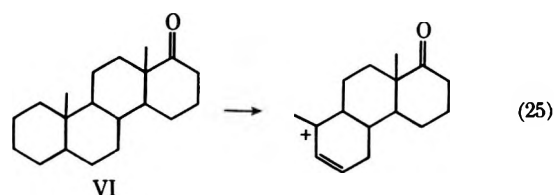
$$(25)$$
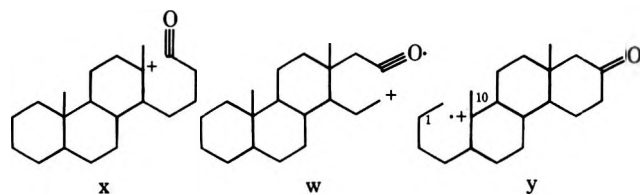
***m/e* 218 Peak.**—The most abundant peak in the spectrum (Figure 4) of *D*-norandrostan-16-one (XI) appears at *m/e* 218. This process corresponds to the elimination of ring D as ketene, without hydrogen transfer (eq 26). Charge localization in the 13–16

$$(26)$$
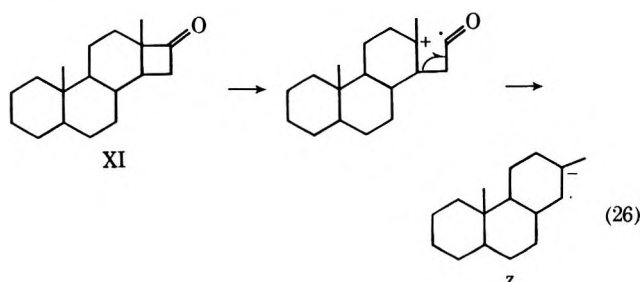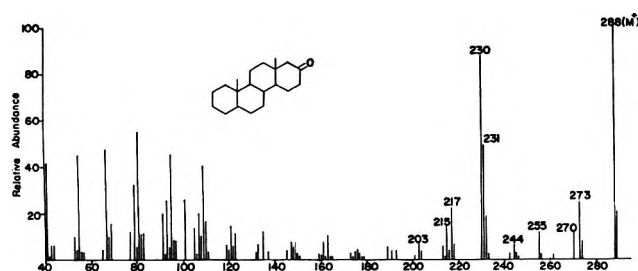
Figure 7.—Mass spectrum of *D*-homo-5α-androstan-17-one.
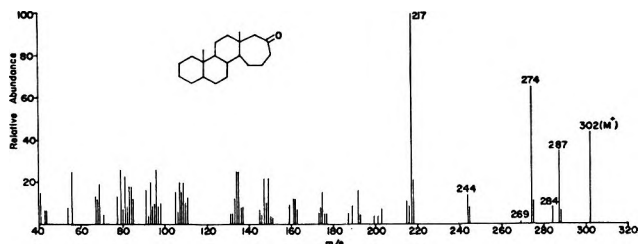
Figure 8.—Mass spectrum of *D*-bishomo-5α-androstan-17a-one.

bond generates a tertiary carbonium ion and a stabilized radical, in addition to relieving the strain inherent in the trans-fused cyclobutanone system. The elimination of ketene generates the ionized olefin z.

Although deuterium-labeling experiments on *D*-nor-pregnane (XII)[12] and *D*-norpregnan-20-one (III) demonstrate that a reciprocal hydrogen transfer is not involved in the genesis of the mass 218 ion, different results are obtained for *D*-norandrostane-16β-carboxylic acid-*14α-d₁* (XIII); approximately 20% of the 14-deuterium is eliminated, and labels at C-15 and C-16 are completely lost (Table IV). It appears likely, then, that the back transfer of hydrogen involves the acidic hydrogen on the carboxyl oxygen. The observation that the elimination of the 14-deuterium decreases to less than 5% in the genesis of the ion of mass 218 of the corresponding methyl ester XIV is consistent with this conclusion. Further experimentation would be necessary to clarify the complete mechanism of this unusual process.

XII   XIII

XIV   XV
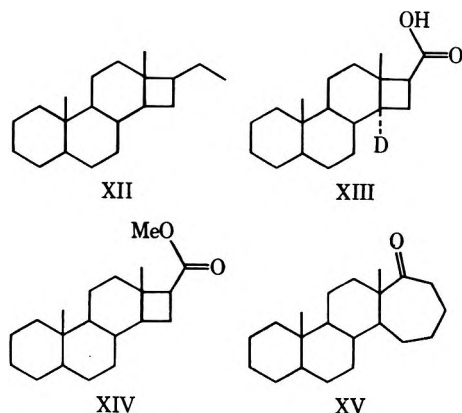
The mass spectrum of androstan-17-one (Figure 5) also exhibits a peak at *m/e* 218. Deuterium-labeling experiments[10] were consistent with the mechanism depicted in eq 27. The virtual absence of a peak at *m/e*

(12) G. Eadon, S. Popov, and C. Djerassi, submitted for publication.
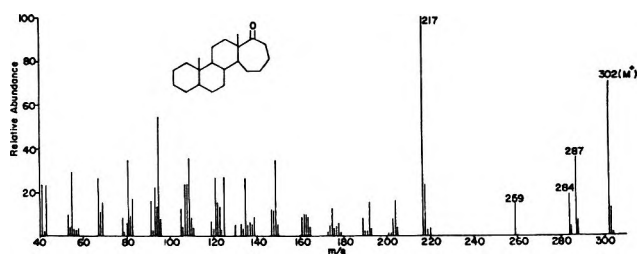
Figure 9.—Mass spectrum of *D*-bishomo-5α-androstan-17b-one.

218 in the spectra (Figures 6 and 9) of *D*-homoandro-stan-17a-one (VIII) and *D*-bishomoandrostan-17b-one

$$\text{s} \xrightarrow[-\text{C}_2\text{H}_4]{-\text{CO}} \text{o, } m/e \text{ 218} \tag{27}$$
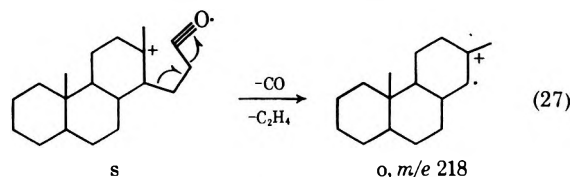
(XV) is in complete harmony with this mechanism. Formation of a mass 218 ion by these compounds would require the elimination of cyclopropane and cyclobutane, respectively.

m/e **217 Peak.**—The *m/e* 217 peak in the mass spectrum (Figure 5) of androstan-17-one arises by the elimination of ring D and an additional hydrogen atom. Deuterium labeling demonstrated that the extra hydrogen was partially (50%) extracted from C-14; abstraction of the remaining 50% was a random process.[10]

A similar mechanism pertains to *D*-homoandrostan-17a-one (eq 28). The ring D labels were completely eliminated, along with 50% of the C-14 hydrogen.[13]

$$\text{x} \rightarrow \text{aa} \rightarrow \tag{28}$$

p
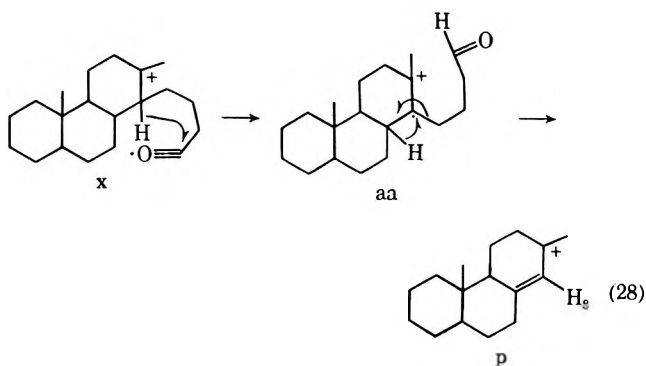
Very abundant peaks appear at *m/e* 217 in the mass spectra of *D*-bishomoandrostan-17a-one (VIII, Figure 8) and *D*-bishomoandrostan-17b-one (XV, Figure 9). Deuterium labeling experiments (Tables VII and VIII) demonstrate that these processes involve the expulsion of ring D, so it appears likely that a similar mechanism prevails.

(13) The 1,2 shift of the C-8 hydrogen (aa → p) is postulated solely to avoid the formation of the presumably high energy ionized carbene p′. Work is currently underway in these laboratories to differentiate between the pathways leading to p and p′.

aa   p′
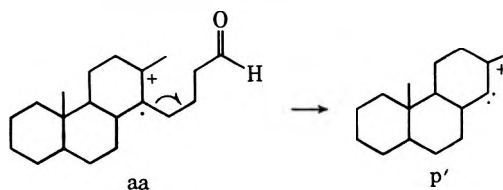
In the mass spectrum (Figure 4) of *D*-norandrostan-16-one (XI) the *m/e* 217 peak is small. The process becomes more favorable in the electron impact induced behavior of the 16β-carboxylic acid (XVI). Deuterium-labeling experiments (Table IV) demonstrate that only 25% of the abstracted hydrogen originates from C-14. The lowered specificity of this process in the *D*-nor steroids probably can be explained on the basis of the ring sizes involved in the transition states for hydrogen abstraction. Removal of the C-14 hydrogen requires a four-membered ring in the transition state (eq 29), while a competing process, the abstraction of a C-12 hydrogen, proceeds through a more favorable six-membered transition state.
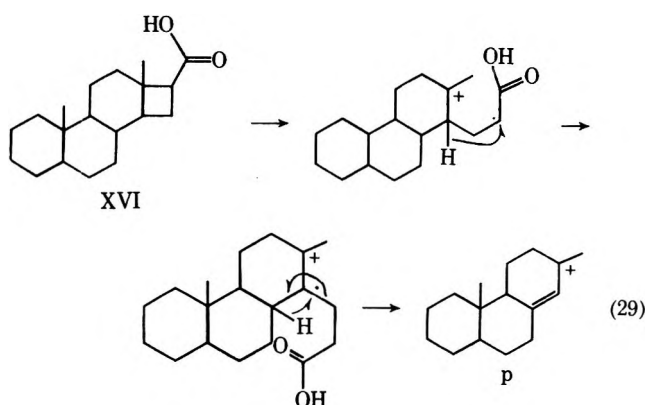
(29)

Other Fragmentations.—The mass spectra of *D*-norpregnane (XII),[12] *D*-norandrostane,[12] *D*-norandrostan-16-one (XI, Figure 4), and *D*-norandrostan-16β-carboxylic acid (XV, Figure 10) are virtually identical below *m/e* 218. This similarity, coupled with the uniformly high intensity of the *m/e* 218 peak and the observation that the ring D labels are largely eliminated (Table IV), suggests that the *m/e* 218 peak is the precursor for most of these low mass ions. Metastable evidence is completely consistent with this hypothesis.

The peak at *m/e* 203 in Figures 4 and 10 arises by the elimination of methyl from the *m/e* 218 ion, according to metastable ion evidence. An exactly similar process has been observed[12] in the spectra of the *D*-nor steroid hydrocarbons, which also generate a mass 218 ion.

Metastable ion evidence suggests that the ion of mass 175 also arises from the *m/e* 218 ion. In agreement with this observation, the peak remains largely at *m/e* 175 when the acid XV is labeled in ring D, and shifts

(30)
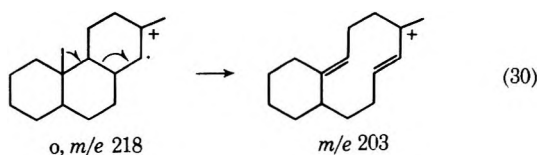
completely when the acid is labeled in ring A (Table IV). A plausible representation of this process appears in eq 31.

(31)
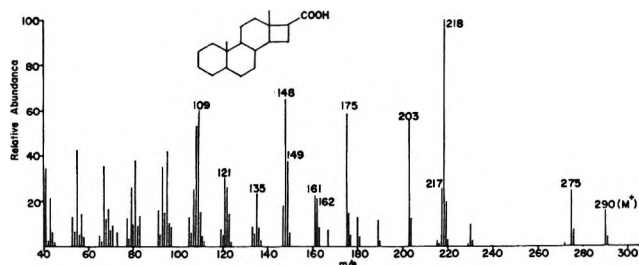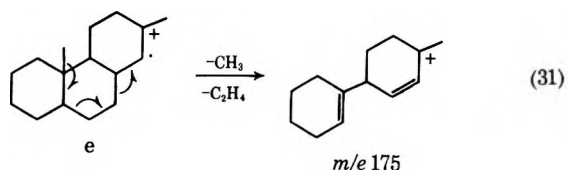
Figure 10.—Mass spectrum of *D*-nor-5α-androstane-16β-carboxylic acid.

The shifts of a number of additional peaks in the spectrum of *D*-norandrostane-16β-carboxylic acid are listed in Table IV. In the absence of more complete deuterium-labeling data, it does not appear worthwhile to speculate on the genesis of these ions.

Synthesis.—The D-nor ketones utilized in this investigation were prepared essentially according to the procedure of Meinwald, *et al.*[14] Androstan-17-one (V) was converted to 16-oximinoandrostan-17-one (XVI) by treatment with isoamyl nitrite in *tert*-butyl alcohol containing potassium *tert*-butoxide. The oxime was converted to the corresponding diazo ketone (XVII) by reaction with chloramine. Irradiation of the diazo ketone yielded *D*-norandrostane-16β-carboxylic acid (XV). Reaction of the acid with methyllithium yielded *D*-norpregnan-20-one (III). Baeyer–Villager oxidation of III gave, after hydrolysis of the intermediate acetate, *D*-norandrostan-16β-ol (XVIII). Jones oxidation gave *D*-norandrostan-16-one (XI).

V, R₁ = R₂ = H
XVI, R = NOH
XVI, R₁ = H; R₂ = N₂

XV, R₁ = CO₂H; R₂ = H
III, R₁ = O=C—CH₃; R₂ = H
XVIII, R₁ = OH; R₂ = H
XI, R₁ = R₂ = O
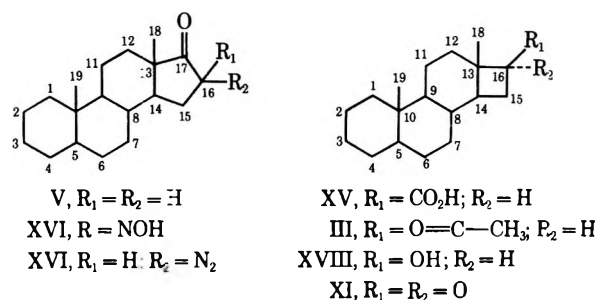
The preparation of several deuterated derivatives of *D*-norpregnan-20-one and *D*-norandrostane-16β-carboxylic acid was straightforward. Base-catalyzed exchange of the ketone III in deuteriomethanol gave *D*-norpregnan-20-one-*16,21,21,21-d₄*. *D*-norandrostane-16β-carboxylic acid-*3-d₁* was prepared by ring contraction of androstan-17-one-*3-d₁*[10] in the usual manner.

The synthesis of *D*-norandrostane-16β-carboxylic acid-*14α-d₁* and -*15α-d₁* required Δ¹⁴-androstan-17-one (XIX), whose preparation has already been described.[12] Deuterioboration of the unsaturated ketone XIX, followed by hydrolytic cleavage of the alkylborane intermediate and Jones oxidation gave androstan-17-one-*14α-d₁*; conversion to *D*-norandrostane-16β-carboxylic acid-*14α-d₁* was accomplished routinely. Alternatively, hydroboration of Δ¹⁴-androsten-17-one (XIV), followed by hydrolytic cleavage with propionic acid-*O-d* and Jones oxidation gave an-

(14) J. Meinwald, L. Labana, and T. Wheeler, *J. Amer. Chem. Soc.*, **92**, 1006 (1970); see also M. P. Cava and E. Moroz, *ibid.*, **84**, 115 (1962); J. L. Mateos and C. Chao, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **13**, 3 (1961); G. Muller, C. Huynh, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 296 (1962).

drostan-17-one-*15α-d₁* which was converted into *D*-norandrostane-16β-carboxylic acid-*15α-d₁*.

The preparation of *D*-homoandrostan-17a-one (VI) and *D*-homoandrostan-17-one (VIII) was accomplished using well-known reactions (Scheme I).[15]

SCHEME I

XX, R₁ = H; R₂ = CN
XXI, R₁ = H; R₂ = CH₂NH₂

VI + VIII
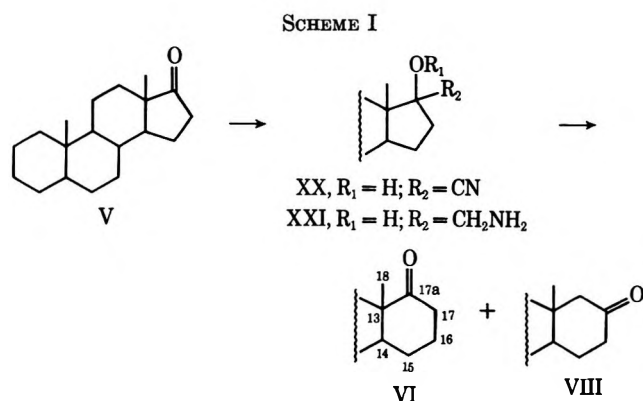
Condensation of androstan-17-one (V) with hydrogen cyanide gave the cyanohydrin XX. Catalytic reduction yielded the hydroxy amine XXI, which after treatment with dilute aqueous nitrous acid gave *D*-homoandrostan-17- and -17a-one.

The preparation of several labeled derivatives of these ketones was straightforward. Exchange of the parent ketones in deuteriomethanol containing catalytic amount of sodium deuteroxide gave *D*-homoandrostan-17a-one-*17,17-d₂* and *D*-homoandrostan-17-one-*16,16,17a,17a-d₄*. Homologation of androstan-17-one-*3-d₁*[10] and androstan-17-one-*14a-d₁*[12] gave *D*-homoandrostan-17a-one-*3-d₁* and -*14a-d₁*. Androstan-*17*-one-*16,16-d₂* was prepared by base-catalyzed exchange of androstan-17-one. Homologation gave *D*-homoandrostan-17a-one-*16,16-d₂*.

The preparation of *D*-homandrostan-17a-one-*18,18,18-d₃* (XXVIII) was accomplished by total synthesis as depicted in Scheme II.[16,17]

Reaction of *D*-homopregn-Δ^{17,20}-ene (XXIX)[12] with diborane yielded an organoborane which was converted directly[18] into *D*-homopregnan-20-one (II).

XXIX   II
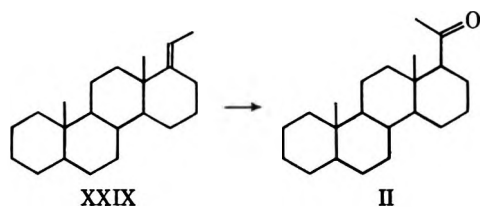
D-Bishomoandrostan-17a-one (VIII) was prepared by the homologation of *D*-homoandrostan-17a-one (VI). Condensation of the ketone VI with hydrogen cyanide gave the cyanohydrin XXX; catalytic hydrogenation gave the hydroxy amine XXXI, which

SCHEME II

XXII   XXIII

XXIV   XXV

XXVI, R₁ = R₂ = H
XXVII, R₁ = H; R₂ = CHS-*n*-Bu

XXVIII

yielded the desired ketone VIII upon Tiffeneau rearrangement.

D-Bishomoandrostan-17b-one (XV) was prepared by bishomologation of androstan-17-one using diazomethane.

The corresponding α-deuterated *D*-bishomoandrostan-17a- and -17b-ones were prepared by base-catalyzed exchange of the unlabeled ketones.

VI   XXX, R = CN
      XXXI, R = CH₂NH₂

VIII

V   XV

(15) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 583.

(16) W. S. Johnson, J. Szmuskovicz, E. R. Rogier, H. I. Hadler, and H. Wynberg, *J. Amer. Chem. Soc.*, **78**, 6285 (1956); W. S. Johnson, B. Bannister, and R. Pappo, *ibid.*, **78**, 6331 (1956).

(17) We gratefully acknowledge a gift of the tetracyclic ketone XXII from Professor W. S. Johnson of this department.

(18) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

Experimental Section[19]

D-Norpregnan-20-one (III) and *D*-Norpregnan-20-one-*16,21,-21,21-d₄*.—The preparation of these compounds has already been described.[12]

D-Norandrostan-16-one (XI).—*D*-Norandrostan-16β-ol[12] (90 mg) was oxidized by treatment with Jones reagent at room temperature. After 15 min, the solution was taken up into methylene chloride, washed thoroughly with water, dried over MgSO₄, and concentrated under vacuum. Preparative tlc [hexane–ether (1:1) eluent] gave *D*-norandrostan-16-one (XI) (52 mg) as an oil.
Anal. Calcd for $C_{18}H_{28}O$: mol wt, 250. Found: M⁺, 250.

D-Norandrostane-16β-carboxylic Acid (XV).—The preparation of this compound has already been described.[12]

D-Norandrostane-16β-carboxylic Acid-*3-d₁*, -*14α-d₁*, and -*15-d₁*.—These compounds were prepared from androstan-17-one-*3-d₁*,[7] androstan-17-one-*14α-d₁*, and androstan-17-one-*15-d₁*,[12] respectively, by ring contraction according to a procedure which has already been reported.[12]

D-Norandrostane-16β-carboxylic Acid-*16α-d₁*.—The diazo ketone XVII (30 mg)[12] was irradiated in a solution of dry tetrahydrofuran (100 ml) and deuterium oxide (40 ml) containing 120 mg of sodium bicarbonate. The irradiation and isolation were carried out in the usual manner.[12] Pure *D*-norandrostane-16β-carboxylic acid-*16α-d₁* (13 mg, mp 204–205°) was isolated after recrystallization from methanol.

D-Homopregnan-20-one (II).—An ethereal solution of *D*-homopregn-Δ¹⁷ᵃ,²⁰-ene (30 mg)[12] was treated with 3 equiv of borane in tetrahydrofuran[20] at 0°. After 1 hr at 0° and 3 hr at room temperature, the organoborane was oxidized directly with chromic oxide and sulfuric acid.[18] The complex mixture obtained after work-up was purified by preparative tlc (eluent CH₂Cl₂) to yield *D*-homopregnan-20-one (5 mg), mp 165–168°.
Anal. Calcd for $C_{22}H_{36}O$: mol wt, 316; C, 83.48; H, 11.47. Found: C, 83.36; H, 11.27; M⁺, 316.

D-Homopregnan-20-one-*17a,21,21,21-d₄*.—The unlabeled ketone II (5 mg) was dissolved in 4 ml of deuteriomethanol con-

taining 1 ml of 20% sodium deuterioxide in deuterium oxide; the solution was heated overnight at reflux. The solvent was evaporated at reduced pressure and the residue redissolved in 5 ml of deuteriomethanol. After the exchange process had been repeated three times, the residue was purified by preparative tlc. The *D*-homopregnan-20-one-*17a,21,21,21-d₄* isolated (3 mg, 92% *d₄*) exhibited melting point, tlc mobility, and vpc retention time identical with those of the unlabeled starting material II.

D-Homoandrostan-17a-one (VI), -*18,18,18-d₃* (XXVIII), -*17a,-17a-d₂*, -*17,17-d₂*, *16,16-d₂*, *14α-d₁*, and -*3,3-d₂*.—The preparation of these compounds has already been described.[12]

D-Homoandrostan-17-one (VIII).—The 17-ketone was isolated as a minor product in the preparation of *D*-homoandrostan-17a-one by the nitrous acid ring expansion of androstane-17-methyl-amino-17-ol (XXI).[12] The ketone exhibited mp 171.5–172.5°, in excellent agreement with the value already reported.[21]
Anal. Calcd for $C_{20}H_{32}O$: mol wt, 288; C, 83.27; H, 11.18. Found: C, 83.48; H, 11.08; M⁺, 288.

D-Homoandrostan-17-one-*16,16,17a,17a-d₄*.—The unlabeled 17-ketone VIII was exchanged in deuteriomethanol–sodium deuterioxide–deuterium oxide in a manner described above. The product, *D*-homoandrostan-17-one-*16,16,17a,17a-d₄*, was isolated in high isotopic purity (80% *d₄*).

D-Bishomoandrostan-17a-one (XIII) and -17b-one (XV).—The preparation of these compounds has already been reported.[12]

D-Bishomoandrostan-17a-one-*17,17,17b,17b-d₄* and *D*-Bishomoandrostan-17b-one-*17a,17a-d₂*.—The parent ketones were subjected to base-catalyzed exchange with deuteriomethanol–deuterim oxide in a manner analogous to that described above. The labeled ketones were isolated in high isotopic purity (80% *d₄* and 98% *d₂*, respectively.)

(19) Melting points are uncorrected, and were determined in unsealed capillaries. Infrared spectra were measured in chloroform solution on a Perkin-Elmer Model 700 spectrophotometer. Nmr spectra were determined in deuteriochloroform solution with tetramethylsilane as an internal reference on a Varian T-60 spectrometer, unless otherwise indicated. Mass spectra were determined on an Atlas CH-4 spectrometer with a TO-4 ion source using the direct inlet procedure. The authors are grateful to Mr. Richard Conover for performing these measurements. All mass spectral samples were purified by preparative vpc on a Hewlett–Packard 402 gas chromatograph immediately prior to submission. Thin layer chromatography was performed on silica gel H₂₅₄. The elemental analyses are due to Messrs. E. Meier and J. Consul.

(20) Purchased from Ventron Corp., Beverly, Mass.

(21) D. N. Kirk. C. M. Peach, and M. P. Wilson, *J. Chem. Soc. C*, 1454 (1970).

Mass Spectrometry of Cyclonucleosides

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Mass spectra of pyrimidine cyclonucleosides containing 2,2', 2,3', 2',6, and 5',6 linkages were studied in order to determine the effects of differing positions of sugar and base linkage, and of anomeric configuration of the base, upon fragmentation reactions. In analogy to previously reported data for purine cyclonucleosides, the 2'- and 3'-linked compounds could be readily distinguished from the 5' isomer but not from each other. The spectra of free cyclonucleosides were found to show numerous complex fragmentation paths and rearrangements, some of which are related to thermal changes during sample vaporization. Base + H and + 2H ions common to conventional nucleosides were observed, but the intact sugar fragment was not. Alternatively, trimethylsilylation provided derivatives which were sufficiently volatile for sample introduction by gas chromatograph, thereby avoiding thermal problems, and which exhibited fragmentation more clearly representative of structural details. Several major ions from trimethylsilyl derivatives showed evidence of an unusual exchange in which a single trimethylsilyl hydrogen had been replaced by hydrogen from the remainder of the molecule during the fragmentation sequence.

In recent years, a variety of cyclonucleosides have been synthesized[1] and used as models for studies of nucleoside conformation[2] and as key intermediates in the synthesis of nucleoside analogs.[1,3] Mass spectrometry would be expected to be a highly useful means of characterizing these compounds in view of its considerable utility in dealing with structural problems of conventional nucleosides.[4] A previous report on cyclonucleoside mass spectra was made by Ikehara and coworkers, who studied the mass spectra of a number of adenosine 8-cyclonucleosides.[5,5a] Their data indicated that the 8,5' compound **1** could be differentiated from its 8,2' or 8,3' isomers (**2, 3**), but the latter two could not be distinguished from each other. In addition, the mechanistic

1

2

3

origins and structures of several prominent ions were not determined, although much information was obtained by high-resolution techniques and by examination of the analogous 8-S-cyclonucleosides. Based on the known fragmentation behavior of adenosine analogs,[6] we found the general similarity of spectra of **1–3**, as well as their apparent complexity, to be somewhat surprising. We have therefore undertaken a detailed study of the mass spectra of a number of pyrimidine cyclonucleosides in order to determine what structural information can be deduced from their spectra, and whether the same difficulties exist as for the purine cyclonucleosides. In addition, the mass spectra and gas chromatographic properties of the analogous trimethylsilylated compounds were examined as alternatives to the less volatile free cyclonucleosides.
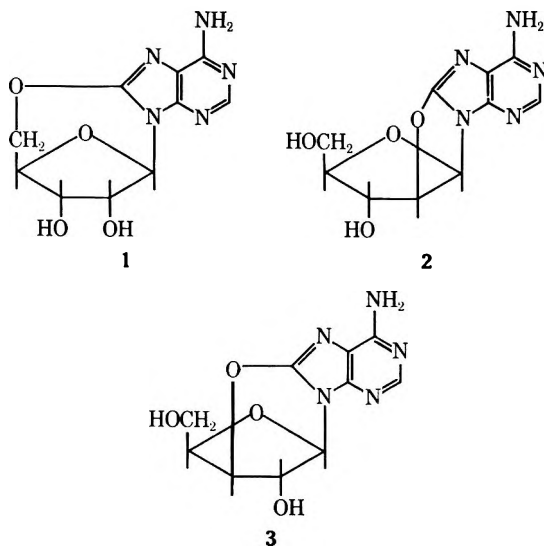
Mass Spectra of Free Cyclonucleosides.—Model compounds were chosen which would represent the effects of α,β anomerism [2,2'-anhydro-1-(β-D-arabinofuranosyl)uracil, **4**; its α anomer, **5**]; and differing points of attachment to the sugar [2,3'-anhydro-1-(β-D-xylofuranosyl)uracil, **6**; 5',6-anhydro-1-(β-D-ribofuranosyl)-6-hydroxyuracil, **7**], and to the base [2',6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuracil, **8**]. Mass spectra were acquired at the minimum possible vaporization temperatures which would produce an ion beam of moderate intensity (*ca.* 200–240°), since changes in ion abundance were observed to occur with either increased temperature, or over a period of time at lower temperatures. The spectrum of **4** shown in Figure 1 exhibits most of the basic ion types which were common to the series. In contrast to the mass spectrum of uridine,[7] all molecular ions show substantial abundance due to the increased cyclic nature of the molecules. The principal fragmentation pathway in the upper mass range proceeds by loss of a hydroxyl radical (*m/e* 209) followed by expulsion of CH_2O from the 5' moiety to produce *m/e* 179. Plausible mechanisms can be written for both **4** (or **5**) and **6** which do not require opening of the ribose ring. Space-filling CPK nucleic acid models[8] indicate that O-4' is sterically a suitable acceptor site for the hydrogen which is retained. This process is blocked in the 5'-linked compound **7**, which instead expels the elements of CHO

(1) See, for example, (a) M. Ikehara, *Accounts Chem. Res.*, **2**, 47 (1969); (b) J. J. Fox, *Pure Appl. Chem.*, **18**, 223 (1969).

(2) See, for instance, (a) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967); (b) M. Ikehara, M. Kaneko, K. Muneyama, and H. Tanaka, *Tetrahedron Lett.*, 3977 (1967); W. Voelter, G. Barth, R. Necords, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6165 (1969).

(3) For example, (a) R. E. Holmes and R. K. Robins, *J. Org. Chem.*, **28**, 3483 (1963); (b) E. A. Falco, B. A. Otter, and J. J. Fox, *ibid.*, **35**, 2326 (1970).

(4) J. A. McCloskey in "Basic Principles in Nucleic Acid Chemistry," P. O. P. Ts'o, Ed., Academic Press, New York, N. Y., in press.

(5) M. Ikeda, Y. Tamura, and M. Ikehara, *J. Heterocycl. Chem.*, **7**, 1377 (1970).

(5a) NOTE ADDED IN PROOF.—D. Lipkin and J. A. Rabi [*J. Amer. Chem. Soc.*, **93**, 3309 (1971)] have recently commented on the principal features of 5'-link pyrimidine cyclonucleosides. Their conclusions agree with ours with exception of the even-electron b + 2H peak from **7** (*m/e*) which they report as being small or absent.

(6) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **92**, 2510 (1970).

(7) K. Biemann and J. A. McCloskey, *ibid.*, **84**, 2005 (1962).

(8) W. L. Koltun, *Biopolymers*, **3**, 665 (1965).
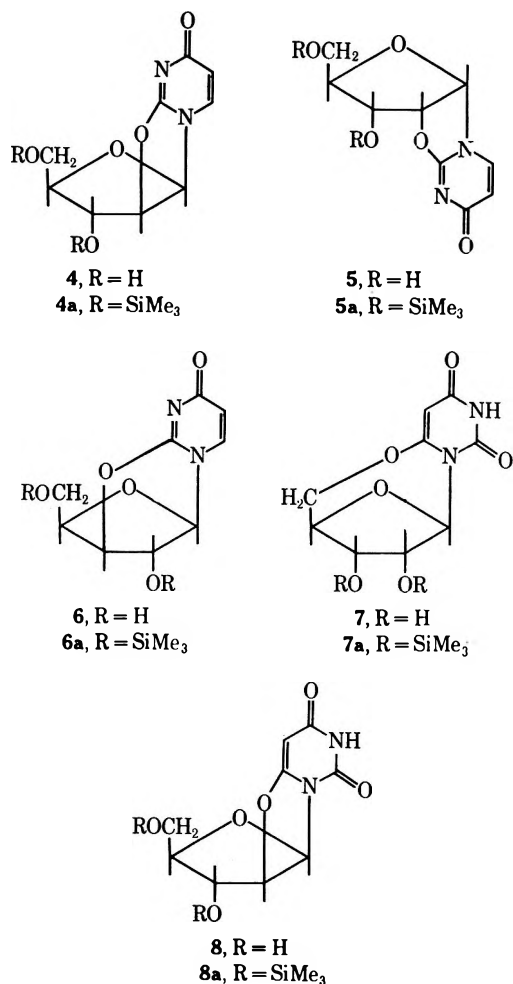
Figure 1.—Mass spectrum of 2,2′-anhydro-1-(β-D-arabino-furanosyl)uracil (4). Values in parenthesis refer to relative intensity values for the isomers 5 and 6, respectively.

arises by simple loss of 5′-CH$_2$OH,[5] and is suitably absent in the spectrum of 7. Further elimination of H$_2$O to form m/e 177 is marked by a metastable peak.

A more complex process is represented by the loss of 59 mass units (m/e 167, Figure 1), earlier determined by Ikehara[5] to involve elimination of C-4′,5′, the ribose ether oxygen, and one rearranged hydrogen. This assignment was confirmed by measurement of exact mass in the spectrum of 5. The complex origin of this peak

m/e 167 (4)

is indicated by its presence in the spectrum of the 5′-linked model 7 (m/e 183, rel intensity 17%), which requires the unfavorable rupture of the C-6,O-5′ bond. This ion is reportedly absent in the spectrum of 1,[5] but our results cannot completely exclude the possibility that the skeletal atoms of C-3′ and -4′ are being lost in the case of compound 7.

One of the most abundant ions in the spectra of 4–6 is the even-electron ion m/e 137, C$_6$H$_5$N$_2$O$_2$. The analogous ion was reported by Ikehara and coworkers,[5] who concluded only that it must contain the base and its heteroatom link to the sugar. Since the composition of m/e 137 requires inclusion of the base, the most reasonable structure consists of the base plus C-1′ and -2′. The spectrum of O-3′,O-5′-4-d$_2$ shows that m/e 137 contains one labile hydrogen rearranged from the sugar fragment which is lost. Unlike 4 and 6, the α anomer 5 is

from 5′ (confirmed by measurement of exact mass), presumably with retention of hydrogen at the unsat-

m/e 209 (4, 5)   m/e 179

m/e 209 (6)   m/e 179

urated C-6 in the base. Although the absence of a peak at M − 47 (OH + CH$_2$O) would appear to be diagnostic of a 5′-linked molecule, it is also absent in the spectrum of 8. More useful is m/e 195 (Figure 1) which

molecular ion 7 — $\xrightarrow[*]{-\cdot CHO}$ —

m/e 213, 33% rel intensity

m/e 226 (5)   m/e 137

conformationally capable of providing m/e 137 without ring opening, by transfer of hydrogen from O-3′. The analogous ion is also formed from **7**, indicating the occurrence of extensive bond breaking and making in its formation. Since the production of m/e 137 from the 3′-linked isomer **6** seemed particularly unlikely, metastable focussing was employed in order to determine the identities of its precursors. The results showed that the molecular ion (m/e 226), M − 31, and M − 59 all produced m/e 137, further testament to its relatively indiscriminate and multiple modes of formation.
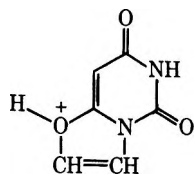
m/e 153 (**7**), 8.0% rel intensity
(**8**), 58% rel intensity

The principal fragmentation reaction in common with conventional nucleosides was found to be the ubiquitous[4] formation of the free base and its protonated forms, m/e 112 (b + H), 113 (b + 2H). As in the case of the cycloadenosines, their formation requires double and triple hydrogen rearrangements, respectively, in contrast to single and double transfers for nucleosides. In the formation of b + H and b + 2H from the 6-linked isomers **7** and **8**, the 5′- or 2′-O bond is broken in preference to the energetically less favorable 6-O bond, after which the oxygen at C-6 is free to abstract hydrogen from the ribose moiety. The b + H and b + 2H ions from 6-linked cyclonucleosides therefore retain the bridge oxygen and characteristically occur at m/e 128 and 129, 16 mass units higher than in the 2-linked isomers.[5a]

m/e 112 m/e 113

m/e 128 m/e 129
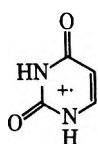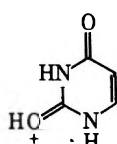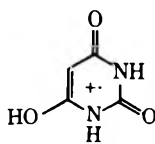
7, 42% rel intensity   86% rel intensity
8, 7.2% rel intensity   4.4% rel intensity
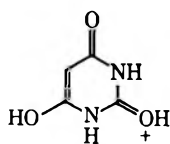
Other peaks in the spectrum of **8** cannot be represented as arising by any obvious mechanism, and may in part have thermal origins. Principal among these are m/e 168 ($C_7H_6NO_4$, 97% rel intensity) and m/e 150 ($C_7H_4NO_3$, 68% rel intensity), which differ by the elements of H_2O, and contain a portion of the base.

In spectra of conventional pyrimidine nucleosides, rupture of the glycosidic bond leads to a usually abundant ion (m/e 133 from ribonucleosides) consisting of the intact sugar fragment.[7] This ion is predictably absent from cyclonucleoside spectra, since its formation would require not only the breakage of a bond α to an unsaturated carbon (C-2 or -6), but also, in the case of

4–6, transfer of hydrogen to the sugar from unsaturated carbons in the base (C-5 or -6). However, an important sugar-containing ion which is prominent in the spectra of the β-2,2′ and β-2,3′ isomers (**4,6**) is m/e 115, shown by measurement of exact mass to have the composition $C_5H_7O_3$. Examination of the spectrum of O-3′,O-5′-4-d_2 indicates a maximum of one labile hydrogen to be present, although the exact distribution could not be determined, due to the shift of m/e 113 and partial reexchange of the label during sample vaporization. However, these data indicate a structure isomeric with that shown below, although structural details as to the identity of oxygens or hydrogens are not available with the present evidence. Other numerous ions in the
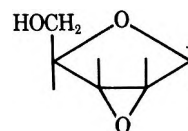
m/e 115

low mass region of the spectrum in Figure 1 were shown at high resolving power to be multiplets, which mostly involve fragments of the base moiety. Compositions shown in Figure 1 for m/e 69, 85, and 96 represent the most abundant species in each case, as determined from the high-resolution spectrum of **5**.

The foregoing data reveal that mass spectra of isomeric free cyclonucleosides represent a number of complex processes which give rise to spectra which exhibit fewer differences than would be expected *a priori*. In particular, the presence of m/e 137 from other than 2′-linked models, and of the M − 59 ion from the 5′-linked model **7**, limits the usefulness of the spectra in a predictive sense, although other useful characteristic features are present. Two factors which are believed to play a role in this anomalous behavior are the high temperatures necessary for vaporization and the considerable ring strain inherent in the rigid tricyclic system. For example, on our LKB instrument, the vaporization of **4** commences at 150° (sample holder temperature), some 40° higher than uridine. It seems likely that many fragmentation processes are initiated by ring opening before fragmentation, thus reducing structural differences and increasing the opportunity for skeletal rearrangements.

Mass Spectra of Trimethylsilyl Derivatives. —Trimethylsilylation has been previously demonstrated to be an effective means of reducing the polarity of nucleosides[9] and nucleotides,[10] thereby enhancing their volatility.[11] The derivatization reaction is rapid, and easily applied on a microgram scale. The derivatives formed (*e.g.*, **4a–8a**) are sufficiently volatile for gas chromatography (see Experimental Section), permitting introduction of the sample into the mass spectrometer directly by gas chromatograph. The method is therefore potentially useful for the direct analysis of reaction mixtures, and provides an independent means of characterization of cyclonucleosides by their relative retention times. Of primary importance in the present study, the mass spectra of trimethylsilyl derivatives were found

(9) J. A. McCloskey, A. M. Lawson, K. Tsuboyama, P. M. Krueger, and R. N. Stillwell, *J. Amer. Chem. Soc.*, **90**, 4182 (1968).

(10) A. M. Lawson, R. N. Stillwell, M. M. Tacker, K. Tsuboyama, and J. A. McCloskey, *ibid.*, **93**, 1014 (1971).

(11) For leading references to the trimethylsilylation of nucleosides and nucleotides for gas chromatography, see ref 10 and C. W. Gehrke and C. D. Ruyle, *J. Chromatogr.*, **38**, 473 (1968).
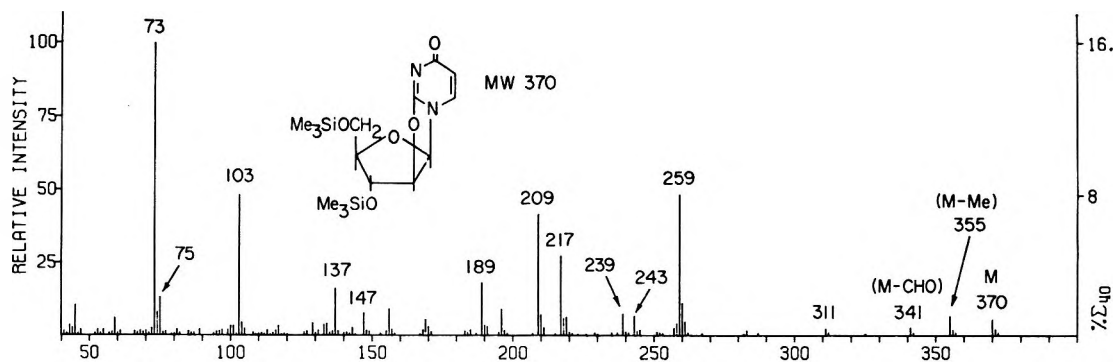
Figure 2.—Mass spectrum of the trimethylsilyl ether of 2,2'-anhydro-1-(β-D-arabinofuranosyl)uracil (4a).
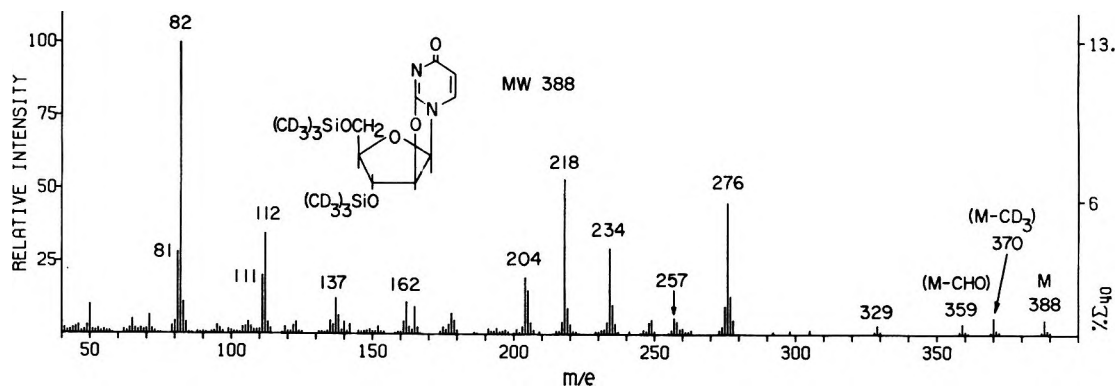
Figure 3.—Mass spectrum of the trimethylsilyl-d_9 ether of 2,2'-anhydro-1-(3-D-arabinofuranosyl)uracil (4b).

to be more truly representative of the parent cyclonucleoside structure than in the case of the free compounds.

Mass spectra of the uridine derivatives 4a–8a are shown in Figures 2 and 4–6. Further correlations were made through the spectra of the trimethylsilyl derivatives of the anomeric cyloorotidine derivatives 9 and 10, which were not sufficiently volatile for vaporization as free compounds. The corresponding trimethylsilyl-d_9 derivatives of each compound were also prepared and their mass spectra examined (e.g., 4b, Figure 3) as a highly useful means[12] of corroborating structural assignments and computer-derived elemental compositions obtained from exact mass data.

Many of the major ions represented in Figures 2–5 were found to be structurally, but not mechanistically, analogous to ions produced by the free compounds. Of principal importance is m/e 209 (Figures 2, 4), shown by deuterium labeling (m/e 218, Figure 3) and measurement of exact mass to consist of the base + C_2H_2 + $SiMe_3$. The ion is therefore analogous to m/e 137 in Figure 1, but bears a trimethylsilyl group, rather than hydrogen, transferred from O-3' or O-5'.[13] The spectra of 9 and 10 show the same ion species, shifted 58 units higher to m/e 267. The corresponding ion from 8a (Figure 6) is shifted 16 mass units (m/e 225), a characteristic of base-containing ions derived from the

m/e 209 R = H (4a, 5a)
m/e 267 R = CO₂Me (9, 10)

m/e 225 (8a)
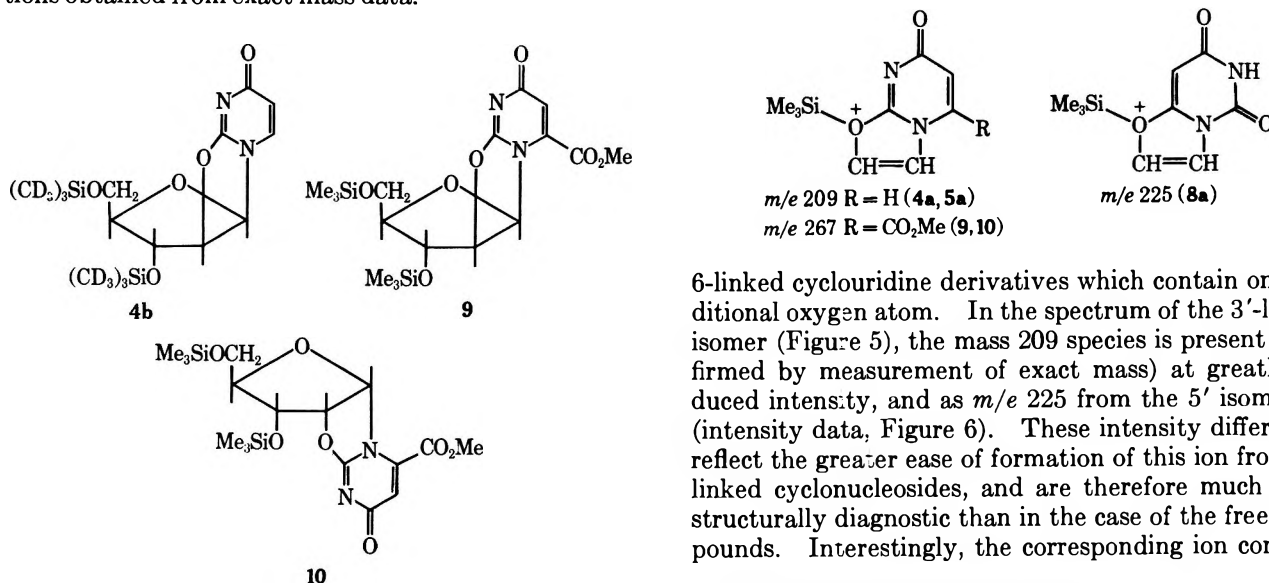
6-linked cyclouridine derivatives which contain one additional oxygen atom. In the spectrum of the 3'-linked isomer (Figure 5), the mass 209 species is present (confirmed by measurement of exact mass) at greatly reduced intensity, and as m/e 225 from the 5' isomer 7a (intensity data, Figure 6). These intensity differences reflect the greater ease of formation of this ion from 2'-linked cyclonucleosides, and are therefore much more structurally diagnostic than in the case of the free compounds. Interestingly, the corresponding ion contain-

4b

9

10

(12) J. A. McCloskey, R. N. Stillwell, and A. M. Lawson, Anal. Chem., 40, 233 (1968).

(13) The parallel tendency of H and SiMe₃ to rearrange in forming structurally similar ions is also found in the mass spectra of conventional trimethylsilyl nucleoside derivatives.³
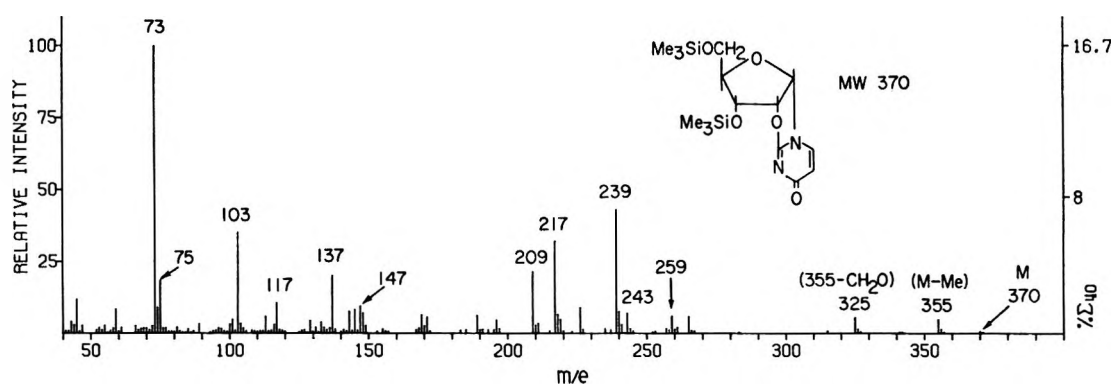
Figure 4.—Mass spectrum of the trimethylsilyl ether of 2,2'-anhydro-1-(α-D-ribofuranosyl)uracil (**5a**).
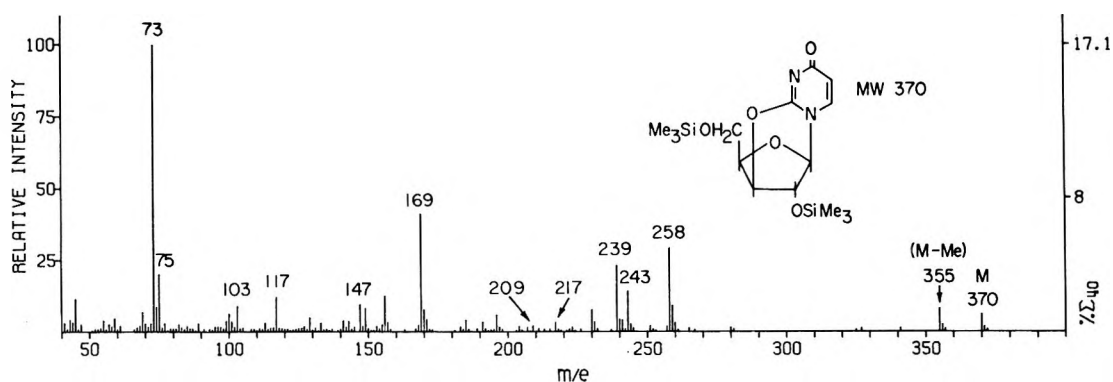
Figure 5.—Mass spectrum of the trimethylsilyl ether of 2,3'-anhydro-1-(β-D-xylofuranosyl)uracil (**6a**).

ing rearranged hydrogen rather than trimethylsilyl is also present, shifting 72 mass units lower (m/e 137, Figures 2–4), but is absent in the case of **6a** and **7a**. Deuterium labeling in the trimethylsilyl moiety (*i.e.*, **4b**) shows the ribose skeleton to be the source of rearranged hydrogen in m/e 137.

Fragmentation of the ribose ring with loss of C-4', C-5' and O-4' is responsible for the ion of mass 239, which predominates in the α anomers **5a** and **10** (m/e 297, 44% rel intensity), and is structurally analogous to the M − 59 peak from free cyclonucleosides[5] (m/e 167, Figure 1). The composition $C_{10}H_{15}N_2O_3Si$, derived from exact mass data (**6a**) and deuterium labeling, requires that one hydrogen from C-4' or -5' be retained in m/e 239. Migration of the silyl function from O-5' prior to rupture of the C-1',O-4' and C-3',C-4' bonds is also feasible, as evidenced by the occurrence of a peak at M − 59 in spectra of the 2'-linked models **4a** (m/e 311) and **8a** (m/e 327, Figure 6). Deuterium labeling in both instances reveals retention of two intact silyl groups. The absence of both ions in the spectrum of the 5'-linked model **7a** provides a further means of characterizing the 5' linkage.

Further similarity to ions occurring in spectra of free cyclonucleosides is represented by m/e 259 (Figures 2, 4) shown by measurement of mass to be $C_{11}H_{23}O_3Si_2$. This ion, which is most abundant in spectra of 2,2'-linked cyclonucleosides, contains the entire ribose carbon skeleton, in analogy to m/e 115 in Figure 1. Unlike m/e 115, which bears only one labile hydrogen, m/e 259 retains both silyl ether moieties. As a plausible process we envision ring opening with abstraction of hydrogen from C-3' to form the intermediate unsaturated species a, which further decomposes by cleavage of the glycosidic bond. The lower abundance of m/e

259 in the α anomers **5a** (Figure 4) and **10** may reflect the decreased availability of skeletal hydrogen after ring opening compared with **4a** or **9**. This well-sta-

9, 15% rel intensity
10, 7.6% rel intensity
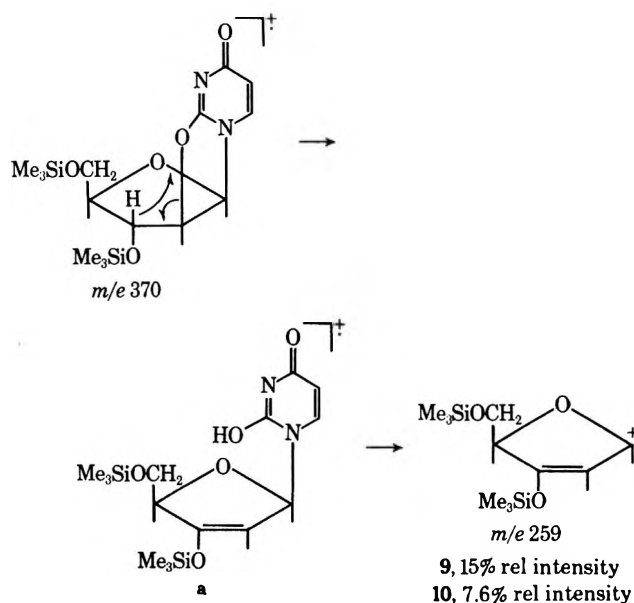
bilized ion is also prominent in the mass spectra of conventional nucleoside trimethylsilyl derivatives, where it is formed by elimination of Me_3SiOH and a methyl radical from the sugar moiety.[9] When the cyclic linkage is made at other positions, a related ion species (m/e 258) containing one less hydrogen is formed in preference to m/e 259 [Figures 5, 6 (**7a**)]. Further loss of CH_3 from m/e 258 to produce m/e 243 is a common feature, and is marked by metastable peaks in the spectra of **6a** and **7a**.
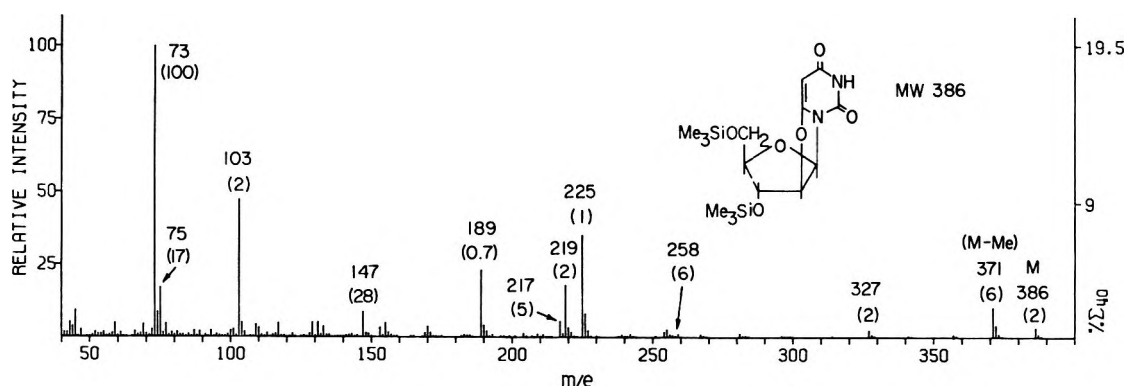
Figure 6.—Mass spectrum of the trimethylsilyl ether of 2',6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuracil (**8a**). Numbers in parentheses refer to relative intensity values from the spectrum of **7a**.

When the mass spectra of trimethylsilyl-d_9 derivatives were examined to confirm the number of silicon atoms in m/e 258 or 259, mass shifts of primarily (>90%) 17 units rather than the expected 18 were found, as shown in Figure 3 (m/e 276), in those cases for which the shifts could be measured without interference from adjacent ions. The sole exception was compound **7a**, which showed more than 50% of the ion as the fully labeled d_{18} species. Although these unexpected results could be explained simply by loss of a trimethylsilyl hydrogen during formation of m/e 258 or 259, evidence from other ions (discussed below) indicates that *exchange* of one trimethylsilyl hydrogen has occurred at some point previous to formation of m/e 259 or 258. The daughter ion m/e 243 also shows replacement of one deuterium by hydrogen (again with the exception of **7a**) although to slightly less extent in each case than the corresponding m/e 258 ion.

As previously discussed, expulsion of CHO from the molecular ion was significant only in the case of the 5'-linked model **7**. This process still operates after ionization of trimethylsilyl derivatives, but, as is evident in Figures 2 and 5, occurs in other isomers as well, probably by migration of trimethylsilyl and hydrogen from the 5' position, prior to loss of CHO. Elimination of the entire 5' group as the elements of formaldehyde also occurs, primarily in the α anomers **5a** and **10**, following migration of trimethylsilyl and ubiquitous loss of a trimethylsilyl methyl radical (m/e 355 → 325, Figure 4).

The clearest indicator of the 5' group is m/e 103, shown by previous studies of trimethylsilylated nucleosides[9] and mononucleotides[10] to be the intact 5' moiety. This ion was found to be abundant in every case except **6a** (Figure 5), and was predictably absent in the case of the 5' model **7a**. Deuterium labeling in most instances showed that substantial amounts of hydrogen from the trimethylsilyl moiety were exchanged prior to cleavage of the 4'-5' bond, as shown by m/e 111 and 112 in Figure 3. The ratio m/e 111:m/e 112 from **4b** was examined as a function of ionizing electron en-

$$\overset{+}{\text{CH}_2}=\text{OSi(CR}_3)_3 \qquad \overset{+}{\text{CH}_2}=\text{OSi(CD}_3)_2$$
$$m/e\ 103,\ R\ =\ H \qquad\qquad |$$
$$m/e\ 112,\ R\ =\ D \qquad\qquad \text{CD}_2\text{H}$$
$$m/e\ 111$$

ergy, and was found to smoothly increase from 14 (ratio 0.75) to 70 eV (1.7). Although the exchange of a single hydrogen from C-5' does not indicate that randomization in the usual sense has occurred, the tendency toward increased exchange at lower energies is charac-

teristic of hydrogen randomization reactions, and has been attributed to increased ion lifetimes in the low-energy region.[14]

Exchange of a single trimethylsilyl hydrogen was also noted in m/e 217, an ion which occurs widely in the mass spectra of trimethylsilylated polyols such as carbohydrates and related compounds.[9,10,15] In the spectra

$$\overset{+}{\text{CH}}-\text{CH}=\text{CH} \qquad\qquad \overset{+}{\text{CH}}-\text{CH}=\text{CH}$$
$$|\qquad\qquad\quad | \qquad\qquad |\qquad\qquad\quad |$$
$$(\text{CR}_3)_3\text{SiO}\qquad \text{OSi(CR}_3)_3 \quad (\text{CD}_3)_3\text{SiO}\qquad \text{OSi(CD}_3)_2$$
$$R\ =\ H,\ m/e\ 217 \qquad\qquad\qquad\qquad\qquad |$$
$$R\ =\ D,\ m/e\ 235 \qquad\qquad\qquad\qquad\qquad \text{CD}_2\text{H}$$
$$m/e\ 234$$
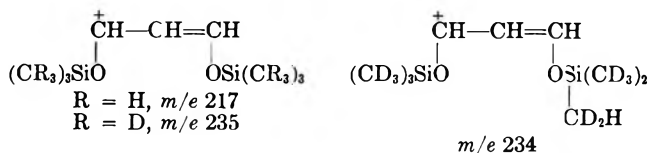
of deuterium-labeled models (m/e 234, Figure 3), the extent of hydrogen exchange could be measured without interference in every case but **6a** and **8a**. Shifts of 17 mass units accounted for over 80% of the ion species in each of the remaining cases except **7a**, which showed approximately 40% d_{17} and 60% d_{18} upon labeling. The substantially reduced exchange observed in **7a** for both m/e 217 and m/e 258, discussed previously, seems to implicate the 5' position in the exchange mechanism. It is noteworthy that the exchange is apparently not extensive at the molecular ion stage, since none was indicated in any of the $M - CH_3$ ions from the seven labeled trimethylsilyl derivatives which were examined. The spectrum of **4a** shows a metastable peak in support of the transition m/e 259 → 217, which may in part account for the generally similar labeling pattern in the two ions.

In the absence of skeletal rearrangements, m/e 217 should be a useful indicator of the proximity of hydroxyl groups in the parent cyclonucleoside. The very low abundance of m/e 217 in the spectrum of **6a** (Figure 5), which does not contain silyl ether functions within the requisite three skeletal carbons, seems to validate this hypothesis. However, the well-known tendency for trimethylsilyl group migration[16] imposes a note of caution in this interpretation. For example, the structurally similar two-carbon fragment m/e 189 (Figures 2, 6), whose structure as shown was supported by measurement of exact mass and deuterium labeling

(14) A. N. H. Yeo, R. G. Cooks, and D. H. Williams, *Chem. Commun.,* 1269 (1968).

(15) For example (a) O. S. Chizhov, N. V. Molodtsov, and N. K. Kochetkov, *Carbohyd. Res.,* **4,** 273 (1967); (b) G. Petersson and O. Samuelson, *Acta Chem. Scand.,* **21,** 1251 (1967); (c) W. R. Sherman, N. C. Eilers, and S. L. Goodwin, *Org. Mass Spectrom.,* **3,** 829 (1970).

(16) See E. White, V. and J. A. McCloskey, *J. Org. Chem.,* **35,** 4241 (1970), and references cited therein.

obviously arises by trimethylsilyl migration (O-3' to O-4' or O-5' to O-2').

$$CH{=}CH$$
Me$_2$SiO   OSiMe$_3$
m/e 189
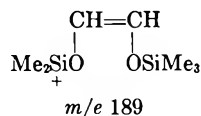
Other degradation processes in the sugar moiety include m/e 169,[10] which is abundant only in the spectrum of **6a**, and can be represented by either of the stable isomeric structures shown. Other ions characteristic of trimethylsilyl ethers[17] include the abundant trimethylsilyl ion m/e 73 (SiMe$_3^+$), m/e 75 (Me$_2$SiOH$^+$), m/e 117 (C$_2$H$_3$O$_2$SiMe$_2^+$),[18] and the rearranged species

Me$_3$SiO

m/e 169   OSiMe$_3$ Me$_3$SiOSiMe$_2$
                               m/e 147
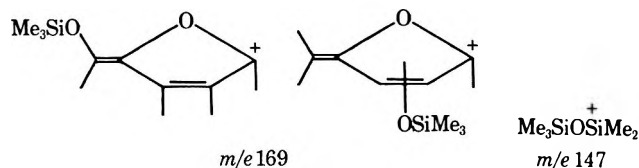
m/e 147. All are certain to have multiple paths of formation, and were found to generally show only small amounts of hydrogen exchange in silyl methyl groups.

Experimental Section

Melting points (uncorrected) were measured on a Kofler hot-stage melting point apparatus. Uv spectra were determined using a Cary Model 15 instrument.

Low-resolution mass spectra were recorded on an LKB 9000 instrument, with sample introduction by direct probe (**4–8**) or through the gas chromatographic inlet (**4a–8a, 9, 10**); 6 ft, 1 ft or 6 in. × 0.25 in. (glass) 1% OV-17, temperature programmed at 5–10°/min from 150–200°; carrier gas separator temperature 250°, ion source 270°, probe temperatures 150–250°; accelerating voltage 3.5 kV, ionizing energy 70 eV. High resolution spectra of **5, 7, 8, 4a, 6a,** and **8a** were photographically recorded on a CEC 21-110B instrument, with sample introduction by direct probe after removal of solvents and reagents (for trimethylsilyl derivatives) in the direct inlet vacuum lock.

All trimethylsilyl derivatives showed sharp peaks with slight tailing on gas chromatography, and **7a** showed markedly decreased peak height at long retention times. Elution temperatures after programming at 10°/min from 200° (3 ft, 1% OV-17, 50 cc/min of N$_2$, Barber-Colman 5000 instrument): **7a** and **8a**, 235°; **4a**, 251°; **6a**, 256°; **5a** and **9**, 259°; **10**, 265°.

(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 471.

(18) D. C. DeJongh, T. Radford, J. D. Hribar, S. Hanessian, M. Bieber, G. Dawson, and C. C. Sweeley, *J. Amer. Chem. Soc.*, **91**, 1728 (1969).

2,2'-Anhydro-1-(β-D-arabinofuranosyl)uracil (**4**), 2,2'-anhydro-1-(α-D-ribofuranosyl)uracil (**5**), 2,2'-anhydro-1-(β-D-arabinofuranosyl)-6-carbomethoxyuracil, and 2,2'-anhydro-1-(α-D-ribofuranosyl)-6-carbomethoxyuracil were purchased from Terra-Marine Bioresearch, La Jolla, Calif.

2,3'-Anhydro-1-(β-D-xylofuranosyl)uracil (**6**) and 2',6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuracil (**8**) were supplied by Dr. J. J. Fox, Sloan-Kettering Institute for Cancer Research, Rye, N. Y.

O-3',O-5'-4-d_2 was prepared by solution of **4** (5–10 μg) in D$_2$O in the direct probe glass sample holder. The sample was dried overnight, and introduced by direct probe simultaneously with CH$_3$OD from a reservoir inlet. The labeling pattern measured from the molecular ion was 11% d_0, 37% d_1, 39% d_2, 13% d_3, sufficient to determine the shifts of major fragment ions.

5',6-Anhydro-1-(β-D-ribofuranosyl)-6-hydroxyuracil (**7**) was prepared following the outline of Lipkin, *et al.*[19] A solution of 5-iodouridine (68 mg) in 10 ml of dry DMSO was added rapidly to a solution of potassium tert-butoxide (20 mg) in 10 ml of dry tert-butyl alcohol under dry nitrogen. The solution was maintained at 60° with stirring for 24 hr. Excess potassium tert-butoxide was destroyed by water, the solution was applied to a water-washed Dowex 50 (H$^+$) (3 ml), and the eluate was concentrated to a syrup *in vacuo*. Recrystallization from aqueous ethanol afforded 21 mg (48%) of **7** in two crops: mp 283–285° dec (darkens above 275°) (lit.[19] mp 283–285° dec); $\lambda_{max}^{pH\ 7}$ 262 mμ (ε 12,200) (lit.[19] $\lambda_{max}^{pH\ 7}$ 262 mμ (ε 12,080)).

Compounds from all sources were checked for purity by gas chromatography–mass spectrometry of their trimethylsilyl derivatives, and by tlc (Eastman chromagram) using either 2-propanol–water (3:2) or water–saturated 1-butanol solvent systems.

Preparation of Trimethylsilyl Derivatives.—To a solution of cyclonucleoside (10–30 μg) in 30 μl of pyridine was added 30 μl of bis(trimethylsilyl)acetamide and 1 μl of trimethylchlorosilane (Pierce Chemical Co., Rockford, Ill.). The reaction mixture was allowed to stand for a short period (10–30 min) and then heated at 100° for 5–10 min. These conditions proved satisfactory and no further study of optimal conditions was made. Deuterium-labeled trimethylsilyl derivatives were prepared in a similar manner using bis(trimethylsilyl)acetamide-d_{18} and trimethylchlorosilane-d_9 (Merck Sharp and Dohme of Canada, Ltd., Montreal).

(19) D. Lipkin, C. Cori, and M. Sano, *Tetrahedron Lett.*, 5993 (1968).

Epoxyamines. II. Synthesis, Reactions, and Rearrangement[1]

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Treatment of the lithium salt of ethylenimine on α-bromocyclohexyl phenyl ketone yields 2-(1-aziridinyl)-2-phenyl-1-oxaspiro[2.5]octane (3), the first epoxyamine ever to be isolated and characterized. Reactions of this compound with dilute hydrochloric acid, sodium borohydride, methanol, benzoic acid, and organolithium compounds are discussed in detail. When heated to reflux temperature in o-dichlorobenzene for 15 hr under a nitrogen atmosphere, the epoxyamine rearranges with ring expansion to give 2-(1-aziridinyl)-2-phenylcycloheptanone (17) and not to the expected α-(1-arizidinyl)cyclohexyl phenyl ketone (19). The structure of the rearrangement product is established both by synthetic and by degradative studies.

Ethylenimine is known to differ from other cyclic and acyclic secondary amines in its reaction with carbonyl compounds.[3,4] Thus aliphatic aldehydes and ketones react with ethylenimine in equimolar quantities, yielding stable aminohydrines which are generally unknown with other amines. This unusual reactivity of ethylenimine prompted a study of the reactions of its lithium salt on α-bromo ketones as part of a general investigation of the reaction of α-halo ketones with various nucleophiles.

Treatment of α-bromocyclohexyl phenyl ketone (1) with the lithium salt of ethylenimine in ether at room temperature gave 65–78% of a material which was subsequently shown to be an epoxyamine, 2-(1-aziridinyl)-2-phenyl-1-oxaspiro[2.5]octane (3) on the basis of its elemental analysis, spectral data, and chemical reactions. The infrared spectrum of 3 did not show any hydroxyl or carbonyl absorptions, but had strong peaks at 1025 and 1045 cm^{-1} indicative of an ether linkage. The nmr spectrum was consistent with the structure, showing aromatic protons from τ 2.45 to 2.85 and the saturated ring protons from τ 7.8 to 9.0 in the ratio 5:14. The reaction of α-bromocyclopentyl phenyl ketone (2) with the lithium salt of ethylenimine proceeded in the same manner, yielding the epoxyamine, 2-(1-aziridinyl)-2-phenyl-1-oxaspiro-[2.5]heptane (4).[5]

direction of the opening of the epoxide ring with hydride ion is the same as in the reduction of epoxy ethers with lithium aluminum hydride.[8]

Catalytic hydrogenation of the aziridinyl alcohol 5 in ethanol at atmospheric pressure in the presence of 10% palladium on carbon opened the aziridine ring[9] to give 85% of 1-(α-N-ethylaminobenzyl)cyclohexanol (10) characterized as its hydrochloride. Amino alcohol 10 was also formed in 80% yield by the direct hydrogenation of 3 in methanol using the same catalyst. The first step in this reduction is probably hydrogenolysis of the aziridine ring to the intermediate epoxyamine 8, compounds of which type are known to rearrange rapidly to the α-hydroxyimines.[10] α-Hydroxycyclohexyl phenyl ketone N-ethylimine (9) thus formed would be reduced under the hydrogenation conditions to give the amino alcohol 10. Hydroxyimine 9 was synthesized by heating a mixture of hydroxy ketone 6 and ethylamine in a sealed tube in the presence of potassium carbonate as a dehydrating agent. This imine 9 was reduced with sodium borohydride in methanol to give 85% of 10 identical in all respects with the hydrogenation products of 3 and 5.

Epoxyamine 3 reacted with methanol in the presence

1, $n = 5$
2, $n = 4$

3, $n = 5$
4, $n = 4$

Reactions.—Epoxyamines are very susceptible to acid hydrolysis. Thus on treatment with dilute hydrochloric acid, 3 was rapidly hydrolyzed to the known α-hydroxycyclohexyl phenyl ketone[6] (6) in 90% yield. Reduction of 3 with sodium borohydride in methanol at room temperature gave 75% of 1-(α-1-aziridinylbenzyl)cyclohexanol (5). The fact that the aziridine ring was not cleaved with sodium borohydride is in agreement with previous findings.[7] Also the

3   5

6   7

8   9   10

(1) Paper I in this series: C. L. Stevens and P. M. Pillai, *J. Amer. Chem. Soc.*, **89**, 3084 (1967).

(2) Abstracted in part from the Ph.D. dissertation of P. M. Pillai, Wayne State University, 1968; Frank Knoller Predoctoral Fellow, 1966–1967.

(3) A. Dornow and W. Schacht, *Chem. Ber.*, **82**, 464 (1949).

(4) W. J. Rabourn and W. L. Howard, *J. Org. Chem.*, **27**, 1039 (1962).

(5) C. L. Stevens, T. R. Potts, and P. M. Pillai, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967, P-25.

(6) C. L. Stevens and E. Farkas, *J. Amer. Chem. Soc.*, **74**, 618 (1952).

(7) C. L. Stevens, M. E. Munk, C. H. Chang, K. G. Taylor, and A. L. Schy, *J. Org. Chem.*, **29**, 314 (1964).

(8) C. L. Stevens and T. H. Coffield, *J. Amer. Chem. Soc.*, **80**, 1919 (1958).

(9) Hydrogenation of ethylenimines to ethylamines is well established. See ref 7 and also M. Kharasch and H. Priestly, *J. Amer. Chem. Soc.*, **61**, 3425 (1939).

(10) C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963).

of a trace of hydrogen chloride to give 1-(α-1-aziridinyl-α-methoxybenzyl)cyclohexanol (7) in 78% yield. In this reaction, epoxyamines closely resemble epoxy ethers which form α-hydroxy ketals under the same conditions.[6] The infrared spectrum of 7 indicated the presence of a hydroxyl group and the nmr spectrum showed that an aziridine ring was present in the molecule. The structure of 7 was further confirmed by its hydrolysis with dilute hydrochloric acid to the α-hydroxy ketone 6 and also by the formation of amino alcohol 10 when 7 was hydrogenated in the presence of 10% palladium on carbon as catalyst.

Treatment of epoxyamine 3 with an equivalent amount of benzoic acid in refluxing hexane opened the epoxide and aziridine rings to give 70% of α-hydroxy-cyclohexyl phenyl ketone N-(2-benzoyloxyethyl)imine (11). Acid hydrolysis of 11 to the α-hydroxy ketone 6 showed the position of the C=N bond in the molecule. Formation of 11 in 60% yield by the reaction of benzoic acid with 7 in refluxing benzene provides further evidence for the structure of 11. Treatment of the imino ester 11 with sodium borohydride not only reduced the imine function in the molecule but also cleaved the ester group to give 1-(α-2-hydroxyethyl-aminobenzyl)cyclohexanol (12) in 63% yield. Compound 12 was also prepared by heating the aziridinyl

their hydrochlorides. The aziridine ring was also opened by heating 15 with 1 N perchloric acid to yield the amino diols 16.
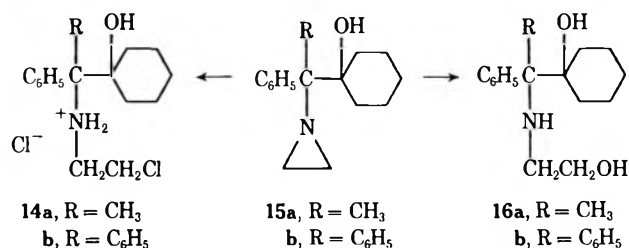
| 14a, R = CH₃ | 15a, R = CH₃ | 16a, R = CH₃ |
| b, R = C₆H₅ | b, R = C₆H₅ | b, R = C₆H₅ |

Rearrangement.—When heated to the reflux temperature in o-dichlorobenzene for 15 hr under a nitrogen atmosphere, epoxyamine 3 rearranged with ring expansion to give 2-(1-aziridinyl)-2-phenylcyclohepta-none (17) in 30-40% yield, the remainder of the material being an intractable resin.[12] Although the direction of the epoxide ring opening in this rearrangement is in agreement with the acid-catalyzed rearrangement of epoxy ethers,[13] it does not conform to a previous postulate by Kirmann[14] which would predict the formation of α-(1-aziridinyl) cyclohexyl phenyl ketone (19) as the rearrangement product. Studies on an-

alcohol 5 with 1 N perchloric acid according to a procedure previously reported.[7] Reduction of the imine without cleavage of the ester group was accomplished by catalytic hydrogenation in the presence of 10% palladium on carbon to yield 1-(α-2-benzoyloxy-ethylaminobenzyl)cyclohexanol (13). Compound 13 was also prepared by refluxing equimolar quantities of aziridinyl alcohol 5 and benzoic acid in benzene. The ester group in 13 was hydrolyzed with aqueous alcoholic sodium hydroxide to give 88% of 12.

Treatment of the epoxyamine with both methyl-lithium and phenyllithium opened the epoxide ring in a way analogous to the reaction of Grignard reagents with epoxy ethers.[11] The aziridinyl alcohols (15) thus formed were treated with hydrogen chloride in ethyl acetate to give the 2-chloroethylamino derivatives as

(11) C. L. Stevens and W. Holland, *J. Org. Chem.*, **23**, 781 (1958).

(12) Epoxyamine **3** polymerizes slowly at room temperature and rapidly if heated without a solvent.
(13) C. L. Stevens and S. J. Dykstra, *J. Amer. Chem. Soc.*, **76**, 4402 (1954).
(14) A. Kirmann, R. Muths, and J.-J. Richl, *Bull. Soc. Chim. Fr.*, 1469 (1958).

other epoxyamine indicate[5] that the direction of this rearrangement is general in the case of epoxyamines with an aziridinyl group. The direction of the rearrangement and the stability of the epoxyamine are probably controlled by the steric requirements of the lone pair of electrons on the nitrogen.[15]

In order to show that the conjugated amino ketone 19 was not an intermediate in this transformation of 3 to 17, 19 was prepared by the general method[7,16] involving the action of ethylenimine on the epoxy ether, 2-methoxy-2-phenyl-1-oxaspiro[2.5]octane.[6] After 19 was subjected to the same rearrangement conditions, most of the starting material was recovered unchanged and an examination of the infrared spectrum of the crude reaction mixture provided evidence that no detectable amount of 17 was formed.

The rearranged amino ketone 17 was also formed in 40% yield when 7 was heated at 180° in *o*-dichlorobenzene under a nitrogen atmosphere for 24 hr. The formation of 17 from 7 can be envisaged as proceeding through the intermediate epoxyamine or through a six-membered ring cyclic transition state 27. However,

27
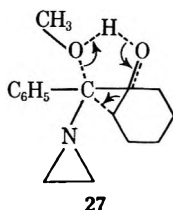
the experimental data available are not sufficient to differentiate between the two mechanistic pathways.

Amino ketone 17 was further characterized by its reduction with sodium borohydride in methanol to 2-(1-aziridinyl)-2-phenylcycloheptanol (18) and by its reaction with an excess of hydrogen chloride in ethyl acetate to give 2-(2-chloroethyl)amino-2-phenylcycloheptanone hydrochloride (21). Upon catalytic hydrogenation in ethyl acetate at atmospheric pressure in the presence of 10% palladium on carbon, 17 was selectively reduced to 2-*N*-ethylamino-2-phenylcycloheptanone (20) characterized as its hydrochloride. Amino ketone 20 was converted to the corresponding oxime, 23, by treating it with hydroxylamine hydrochloride in alcohol in the presence of pyridine. Synthesis of 23 was also achieved by the action of ethylamine on the known 2-chloro-2-phenylcycloheptanone oxime.[17] The structure of the amino ketone oxime 23 was further confirmed by the formation of 6-benzoylhexanamide (26) when the oxime was subjected to Beckmann degradation conditions using polyphosphoric acid.[18] The conversion of 23 to 26 by this second-order Beckmann reaction can be explained as taking place through the intermediate formation of iminonitrile 24, which would then be hydrolyzed to the ketoamide under the

experimental conditions.[19] On treatment with aqueous alcoholic sodium hydroxide, 26 was hydrolyzed to the known 6-benzoylhexanoic acid[20] (25), the identity of which was established by direct comparison with an authentic sample.

The *α*-aziridinyl ketone 19 was further characterized by treating it with an excess of hydrogen chloride in ethyl acetate to give *α*-*N*-(2-chloroethylamino)cyclohexyl phenyl ketone hydrochloride (28). Also reduction of 19 with sodium borohydride in methanol gave the amino alcohol 29.

28   ← 19 →   29

30
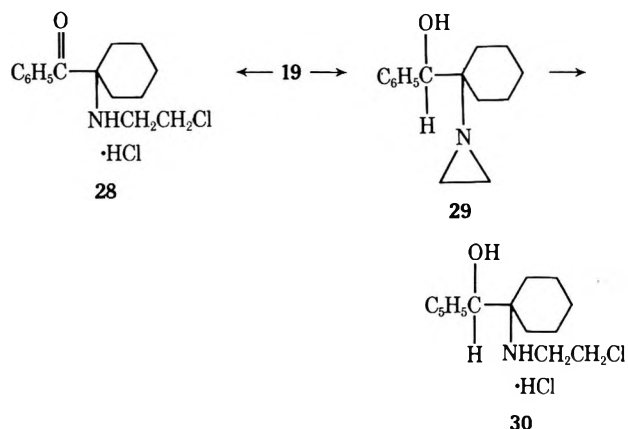
Treatment of 29 with hydrogen chloride in ethyl acetate afforded 1-(2-chloroethyl)amino-1-*α*-hydroxylbenzylcyclohexane hydrochloride (30).

Experimental Section[21]

2-(1-Aziridinyl)-2-phenyl-1-oxaspiro[2.5]octane (3).—A 500-ml three-necked round-bottomed flask was fitted with a mechanical stirrer, an efficient water condenser, and a dropping funnel. The entire system was flushed with dry nitrogen and a steady nitrogen atmosphere was maintained. Freshly distilled ethylenimine[22] (3.9 g, 90 mmol) dissolved in 100 ml of dry ether was transferred into the flask. A solution of 1.6 *M* *n*-butyllithium[23] in hexane (28 ml, 45 mmol) was added drop by drop while the mixture was being stirred. As the reaction was exothermic, the ether refluxed. After stirring for 30 min 8.01 g (30 mmol) of *α*-bromocyclohexyl phenyl ketone[6] (1) dissolved in 50 ml of dry ether was added dropwise with continued stirring. This reaction was also exothermic and the ether again was refluxed. Five minutes after the addition of the bromo ketone, a thin layer chromatography (silica gel H on 5 × 15 cm plate, 50:50 hexane-benzene system) showed that the bromo ketone had disappeared completely. The mixture was poured into a separatory funnel containing a mixture of 200 g of ice, 200 ml of water, and 200 ml of pentane. After shaking the mixture thoroughly, the pentane layer was quickly separated and dried over K₂CO₃ for 10 min. The solution was filtered and the solvent was evaporated off under reduced pressure at room temperature. The residue was evaporatively distilled (bath temperature 90–100°, 0.01 mm) to give 5.2 g (75%) of 3 as a colorless liquid. An analytical sample was made by redistilling the compound evaporatively, n^{25}D 1.5870.

(15) The stability of the natural product cyclopenin [H. Smith, P. Wegfahrt, and H. Rapoport, *J. Amer. Chem. Soc.*, **90**, 1668 (1968)] and that of a recently reported epoxyamine with a quinuclidinone system [D. L. Coffen and D. G. Korzan, *J. Org. Chem.*, **36**, 390 (1971)] lends further support for this view.

(16) C. L. Stevens and C. H. Chang, *J. Org. Chem.*, **27**, 4392 (1962).

(17) D. Ginsberg and R. Pappo, *J. Amer. Chem. Soc.*, **75**, 1098 (1953).

(18) For Beckmann rearrangements using polyphosphoric acid as catalyst, see E. C. Horning and V. L. Stromberg, *ibid.*, **74**, 2680 (1952).

(19) M. Ohno, N. Narause, S. Torimitsu, and I. Teresara [*ibid.*, **88**, 3168 (1966)] report the synthesis of *ω*-cyanoaldehydes by second-order Beckmann rearrangement of 2-alkoxy-, 2-ethylthio-, and 2-alkylaminocycloalkanone oximes with phosphorus pentachloride.

(20) C. Hauser, F. Swamer and B. Ringler, *ibid.*, **70**, 4023 (1948).

(21) All melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer (Model 237B) grating spectrophotometer. Nuclear magnetic resonance spectra were run in CDCl₃ using a Varian Associates A-60 spectrometer with tetramethylsilane as internal standard. The pKₐ's were determined in 50% aqueous methanol. Elemental analyses were provided by Midwest Microlab, Inc., Indianapolis, Ind.

(22) Dow Chemical Co., Midland, Mich., is gratefully acknowledged for a generous gift of ethylenimine.

(23) Available from Foote Mineral Co., Exton, Pa.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.65; H, 8.51; N, 6.12.

In subsequent preparations of **3**, the yield ranged from 65 to 78%. An attempted fractionation of the liquid at 0.001 mm resulted in excessive polymerization, only part of it distilling over at 90–95°. The compound was crystallized by cooling a pentane solution in a Dry Ice–acetone bath, mp 20–22°.

Compound **3** (545 mg) was treated with 10 ml of 0.5 N HCl at room temperature. Hydrolysis took place almost instantaneously. The product was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 440 mg (90%) of **6**, mp 49–50°, undepressed on mixing with an authentic sample of **6**.

1-(α-1-Aziridinylbenzyl)cyclohexanol (5).—A solution of 500 mg of $NaBH_4$ in 20 ml of CH_3OH at 0° was added to 2.29 g (10 mmol) of **3** and the mixture was stirred magnetically. An additional 1.0 g of $NaBH_4$ was added in small portions to this solution. Stirring was continued at room temperature for 12 hr. Most of the CH_3OH was evaporated under reduced pressure. The product crystallized out on adding water to the mixture. It was filtered, washed with water, and dried to give 1.75 g (75%) of **5**, mp 110–112°. A small sample was recrystallized from hexane for analysis: mp 113–114°; nmr τ 2.7 (s, 5, aromatic), 7.12 (s, 1, benzilic), 7.68 (s, 1, OH), and 7.8–9.2 (complex m, 14).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.70; H, 9.25; N, 6.11.

α-Hydroxycyclohexyl Phenyl Ketone N-Ethylimine (9).—A mixture of 4.08 g (20 mmol) of **6**, 20 ml of ethylamine, and 5.0 g of K_2CO_3 (anhydrous) was heated in a sealed tube at 100° for 6 days. The mixture was extracted with ether and the solvent was evaporated to dryness. The residue was distilled evaporatively [bath temperature 100–105° (0.01 mm)] to give 3.9 g (85%) of **9** which crystallized on storage in the refrigerator, mp 36–38°. It was recrystallized from hexane for analysis, mp 38–39°, ir (neat) 1650 cm⁻¹ (C=N).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.61; H, 9.29; N, 6.18.

1-(α-N-Ethylaminobenzyl)cyclohexanol (10). A. By the Hydrogenation of 3.—A solution of 1.7 g (7.4 mmol) of **3** in 50 ml of CH_3OH was hydrogenated at atmospheric pressure in the presence of 250 mg of 10% Pd/C. Over a period of 3 hr, 310 ml (94%) of H_2 was absorbed. The catalyst was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ether and converted to the HCl salt by adding a solution of HCl in isopropyl alcohol. The crystalline material was filtered and recrystallized twice from ethanol–ether to give 1.6 g (80%) of **10** as the HCl salt, mp 223–224° dec.

Anal. Calcd for $C_{15}H_{24}ClNO$: C, 66.75; H, 8.96; N, 5.19. Found: C, 66.63; H, 8.91; N, 5.05.

B. By the Hydrogenation of 5.—A solution of 231 mg (1 mmol) of **5** in 10 ml of ethanol was hydrogenated and worked up as in the previous experiment to give 233 mg (85%) of **10** as HCl salt, mp 222–224° dec.

C. By the Reduction of 9.—A solution of 462 mg (2 mmol) of **9** in CH_3OH was reduced with 250 mg of $NaBH_4$ under the standard conditions. After 6 hr, CH_3OH was evaporated and water was added to the residue. The mixture was extracted with ether and dried (K_2CO_3) and HCl in isopropyl alcohol was added to the filtrate. The crystalline material was filtered and recrystallized from ethanol–ether to give 455 mg (85%) of **10** as the HCl salt, mp 222–224° dec. Samples of **10** prepared by methods A, B, and C were shown to be identical by mixture melting point determinations.

1-(α-1-Aziridinyl-α-methoxybenzyl)cyclohexanol (7).—Epoxyamine **3** (532 mg, 2.41 mmol) was dissolved in 10 ml of absolute CH_3OH and a drop of a saturated solution of HCl in isopropyl alcohol was added. The mixture was kept at room temperature for 3 hr and the solvent was removed *in vacuo*. The residue was recrystallized from hexane to give 470 mg (70%) of **7**: mp 124–125°; ir (CHCl₃) 3560 cm⁻¹ (OH) and no C=O; nmr (CDCl₃) τ 6.8 (s, 3, OCH₃), 7.5 (s, 1, OH), 7.95 and 8.25 (q's, 2 each, aziridinyl group).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.53; H, 8.99; N, 5.52.

Compound **7** (100 mg) was hydrolyzed with 2 N HCl at room temperature for 2 hr. The product was extracted with ether and dried (K_2CO_3) and the solvent was removed. The residue on recrystallization from hexane gave 45 mg (58%) of α-hydroxycyclohexyl phenyl ketone (**6**), mp 49–50°.

A solution of 500 mg (1.91 mmol) of **7** in ethyl acetate was hydrogenated at atmospheric pressure in the presence of 150 mg of 10% Pd/C. The product, isolated as the HCl salt, gave 428 mg (83%) of **10**, mp 222–223° dec.

α-Hydroxycyclohexyl Phenyl Ketone N-(2-Benzoyloxyethyl)-imine (11). A. From Epoxyamine 3.—A solution of a mixture of 1.43 g (6.24 mmol) of **3** and 761 mg (6.24 mmol) of benzoic acid in 50 ml of dry hexane was refluxed on a steam bath for 3 hr. The solvent was evaporated and the residue was crystallized from hexane to give 1.55 g (71%) of **11**, mp 80–83°. Recrystallization from hexane gave raised mp 86–87°; ir (CHCl₃) 3300 cm⁻¹ (OH), 1720 (ester C=O), 1650 (C=N); nmr (CDCl₃) τ 5.5 (t, 2, –OCH₂), 6.6 (t, 2, =NCH₂).

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.40; H, 7.06; N, 4.08.

B. From Compound 7.—A mixture of 261 mg (1.0 mmol) of **7** and 122 mg (1.0 mmol) of benzoic acid was dissolved in 10 ml of dry benzene and refluxed on a steam bath for 4 hr. The solvent was removed and the residue was recrystallized from hexane to give 210 mg (60%) of **11**, mp 84–85°.

Imino ester **11** (100 mg) was hydrolyzed with 10 ml of 2 N HCl at room temperature for 2 days to give 28 mg (48%) of **6**, mp 49–50°.

1-(α-2-Hydroxyethylaminobenzyl)cyclohexanol (12). A. By the Hydrolysis of 5.—Compound **5** (200 mg) was heated with 10 ml of 1 N perchloric acid on a steam bath for 12 hr. The mixture was extracted with ether to remove any neutral by-products. The aqueous layer was basified with NaOH and extracted repeatedly with ether. The ether extracts were dried (K_2CO_3) and evaporated to dryness. The residue was recrystallized from hexane to give 81 mg (39%) of **12**, mp 77–78°.

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.47; H, 9.48; N, 5.73.

B. From the NaBH₄ Reduction of 11.—Sodium borohydride (600 mg) was added in small portions to a solution of 300 mg of **11** in CH_3OH while the mixture was stirred magnetically. The stirring was continued for 7 hr at room temperature. Most of the methanol was evaporated under reduced pressure and water was added to the residue. The mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 135 mg (64%) of **12**, mp 77–78°.

1-(α-2-Benzoyloxyethylaminobenzyl)cyclohexanol (13). A. By the Hydrogenation of 11.—A solution of 351 mg (1.0 mmol) of **11** in 20 ml of ethyl acetate was hydrogenated at atmospheric pressure in the presence of 100 mg of 10% Pd/C for 6 hr. The catalyst was filtered and the filtrate was evaporated to dryness. The residue was crystallized from hexane to give 248 mg (70%) of **13**: mp 103–104°; ir (CHCl₃) 1705 cm⁻¹ (ester C=O); nmr (CDCl₃) τ 5.65 (t, 2, OCH₂) and 7.2 (t, 2, –NCH₂).

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.65; H, 7.69; N, 3.89.

B. From 5.—A mixture of 231 mg (1.0 mmol) of **5** and 122 mg (1.0 mmol) of benzoic acid was dissolved in 20 ml of dry benzene and refluxed on a steam bath for 1 hr. The solvent was evaporated and the residue was recrystallized from hexane to give 245 mg (83.5%) of **13**, mp 103–104°.

A solution of 100 mg of **13** in 5 ml of CH_3OH was hydrolyzed by treating with 100 mg of NaOH in 3 ml of water at room temperature for 1 hr. The mixture was diluted with water and most of the methanol was evaporated under reduced pressure. The mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 62 mg (88%) of **12**, mp 76–77°.

1-(α-1-Aziridinyl-α-methylbenzyl)cyclohexanol (15a).—A 1.7 M methyllithium[23] solution in ether (10 ml, 17 mmol) was added dropwise with stirring to a solution of 1.42 g (6.1 mmol) of **3** in 20 ml of ether under a nitrogen atmosphere. After stirring at room temperature for 5 hr, the mixture was poured into water and extracted with ether. The ether solution was dried (K_2CO_3) and evaporated to dryness. The residue was crystallized from hexane to give 750 mg of **15a**, mp 108–109°.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.30; H, 9.44; N, 5.71. Found: C, 78.60; H, 9.54; N, 6.01.

A part of **15a** was converted to the perchlorate salt by treating it with an ether solution of anhydrous perchloric acid. The salt was recrystallized from acetone–ether, mp 163–164°.

Anal. Calcd for $C_{16}H_{24}ClNO_5$: C, 55.58; H, 7.00; N, 4.05. Found: C, 55.60; H, 6.95; N, 3.96.

1-(α-Methyl-α-2-hydroxyethylaminobenzyl)cyclohexanol (16a).—A mixture of 500 mg (2.2 mmol) of 15a and 25 ml of 1 N perchloric acid was heated on a steam bath for 12 hr. The neutral by-products from the reaction mixture were removed by extraction with ether and the aqueous solution was basified with NaOH. The mixture was repeatedly extracted with ether, and the ether extracts were dried (K_2CO_3) and evaporated to dryness. The residue was crystallized from hexane to give 375 mg (70%) of 16a, mp 131–132°.

Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.95; H, 9.56; N, 5.32. Found: C, 72.72; H, 9.44; N, 5.27.

1-(α-1-Aziridinyl-α-phenylbenzyl)cyclohexanol (15b).—A 2 M solution of phenyllithium[24] in ether–benzene (40 ml, 80 mmol) was added dropwise with stirring to a solution of 5.8 g (25.3 mmol) of 3 in 50 ml of ether under a nitrogen atmosphere. After stirring at room temperature for 12 hr, the mixture was poured into water and extracted repeatedly with ether. The ether extracts were dried (K_2CO_3) and evaporated to dryness. The residue was recrystallized from acetone to give 6 2 g (81%) of 15b, mp 154–155°.

Anal. Calcd for $C_{21}H_{25}NO$: C, 82.03; H, 8.20; N, 4.56. Found: C, 81.73; H, 8.07; N, 4.50.

A part of 15b was converted to the perchlorate salt, mp 174–177°.

Anal. Calcd for $C_{21}H_{26}ClNO_5$: C, 61.81; H, 6.42; N, 3.43. Found: C, 61.82; H, 6.46; N, 3.27.

Another portion of 15b was dissolved in ethyl acetate and treated with an excess of HCl in ethyl acetate to give 1-(α-phenyl-α-chloroethylaminobenzyl)cyclohexanol hydrochloride (14b), mp 211–212° after recrystallization from ethanol–ether.

Anal. Calcd for $C_{21}H_{27}Cl_2NO$: C, 66.28; H, 7.15; N, 3.68. Found: C, 65.89; H, 7.25; N, 3.67.

1-(α-Phenyl-α-2-hydroxyethylaminobenzyl)cyclohexanol (16b).—Compound 15b (500 mg) was converted to 85 mg of 16b, mp 132–133°, under the same conditions for the preparation of 14b.

Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.47; H, 8.33; N, 4.30. Found: C, 77.18; H, 8.39; N, 4.63.

2-(1-Aziridinyl)-2-phenylcycloheptanone (17). A. By the Rearrangement of 3.—A solution of 5.53 g (23.3 mmol) of 3 in 30 ml of o-dichlorobenzene was refluxed under a nitrogen atmosphere on a metal bath at 190–195° for 15 hr. The reaction mixture was cooled and the solvent was removed under vacuum (0.01 mm) at 40–50°. The residue was evaporatively distilled (bath temperature 90–100°, 0.01 mm) to give 2.06 g (38.65%) of 17, ir (neat) 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.75; H, 8.32; N, 5.95.

In subsequent experiments the yield of 17 ranged from 30–40%.

B. By the Rearrangement of 7.—A solution of 1.0 g of 7 in 10 ml of o-dichlorobenzene was refluxed under a nitrogen atmosphere on a metal bath at 190–195° for 24 hr. The reaction mixture was cooled and worked up as in A above to give 456 mg (40%) of 17, ir superimposable with that of the product from A.

A portion of 35 was dissolved in ether and was treated with an excess of HCl in ethyl acetate. The crystalline material was filtered and recrystallized from ethanol–ether to give 2-(2-chloroethyl)amino-2-phenylcycloheptanone hydrochloride (21), mp 205–207° dec, ir (KBr) 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{21}Cl_2NO$: C, 59.63; H, 7.00; Cl, 23.46; N, 4.63. Found: C, 59.69; H, 6.88; Cl, 23.59; N, 4.89.

2-(1-Aziridinyl)-2-phenylcycloheptanol (18).—A solution of 458 mg (2 mmol) of 17 in 20 ml of ethanol was cooled in an ice bath and stirred magnetically. $NaBH_4$ (300 mg) was added in small portions. The mixture was stirred at room temperature for 12 hr. Most of the ethanol was removed and water was added to the residue. The mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was crystallized from hexane to give 328 mg (71%) of 18, mp 124°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.82; H, 9.15; N, 6.22.

The crystalline material, as indicated by the sharp melting point, consisted of only one, presumably the trans isomer.[25]

2-N-Ethylamino-2-phenylcycloheptanone (20).—A solution of 635 mg (2.73 mmol) of 17 in 20 ml of dry ethyl acetate was hydrogenated at atmospheric pressure in the presence of 100 mg of 10% Pd/C. One mole of H_2 was absorbed over a 2-hr period. The catalyst was filtered and the filtrate was evaporated to dryness. The residue was redissolved in ether and a solution of HCl in ethyl acetate was added until precipitation was complete. It was filtered and recrystallized from ethanol–ether to give 650 mg (88%) of 20 as the HCl salt, mp 226–228° dec. One more crystallization from the same solvent gave raised mp 233–235° dec, ir (KBr) 1705 cm^{-1} (C=O), pK_a' = 7.70.

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.30; H, 8.28; N, 5.23. Found: C, 67.59; H, 8.34; N, 5.41.

2-N-Ethylamino-2-phenylcycloheptanone Oxime (23). A. From Amino Ketone 20.—A mixture of 200 mg of amino ketone (20) hydrochloride, 400 mg of hydroxylamine hydrochloride, 5 ml of pyridine, and 5 ml of ethanol was refluxed on a steam bath for 6 hr. All the volatile materials were removed under reduced pressure and water was added to the residue. The solution was neutralized with NaOH and the mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 135 mg (64%) of 23, mp 105–106°, pK_a' = 8.75.

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.94; H, 8.91; N, 11.27.

B. From 2-Chloro-2-phenylcycloheptanone Oxime[17] (22).—A mixture of 4.3 g of 22, 6 ml of ethylamine, and 200 ml of benzene was stirred in a stoppered flask at room temperature for 110 hr. The benzene solution was concentrated to 50 ml and extracted with 2 N HCl. The acid solution was basified with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 125 mg (3%) of oxime 23, identical in all respects with the product from A above.

6-Benzoylhexanamide (26).—A mixture of 200 mg of 23 and 12.0 g of polyphosphoric acid[26] was heated on a steam bath with occasional shaking for 3 hr, by which time the oxime had completely disappeared. The mixture was cooled and poured onto ice. It was diluted with 100 ml of water and neutralized with NaOH. The white precipitate formed was extracted with ether and dried (K_2CO_3), and the solvent was removed. The residue was recrystallized from $CHCl_3$–ether to give 125 mg (60%) of 26, mp 107–108°, ir ($CHCl_3$) 1675 (C=O), 3530, and 3410 cm^{-1} (-NH$_2$).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.14; H, 7.92; N, 6.41.

Amide 26 (51 mg) was hydrolyzed with NaOH in aqueous alcohol to give 46 mg (90%) of 6-benzoylhexanoic acid (25), mp 82–83°. The melting point of a mixture of this acid with an authentic sample of 25 was undepressed.

α-(1-Aziridinyl)cyclohexyl Phenyl Ketone (19).—A mixture of 5.3 g of 2-methoxy-2-phenyl-1-oxaspiro[2.5]octane[6] and 10.1 g of ethylenimine was heated in a sealed tube at 125–130° for 36 hr. The volatile materials were removed and the residue (6.57 g) was fractionated at 0.01 mm. The fraction boiling at 102–105° was collected and redistilled evaporatively to give 4.13 g (66.4%) of 19, n^{25}D 1.5502, ir (neat) 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.52; H, 8.49.

A solution of HCl in ethyl acetate was added with shaking to a portion of 19 dissolved in ether. The product was recrystallized from ethanol–ether to give α-(2-chloroethyl)aminocyclohexyl phenyl ketone hydrochloride (28), mp 183–185° dec.

Anal. Calcd for $C_{15}H_{21}Cl_2NO$: C, 59.63; H, 7.00; Cl, 23.46; N, 4.63. Found: C, 59.71; H, 6.89; Cl, 23.26; N, 4.82.

Attempted Rearrangement of 19.—A solution of 830 mg of 19 in 16 ml of o-dichlorobenzene was refluxed on a metal bath at 190–195° for 18 hr under a nitrogen atmosphere. An ir spectrum of the cooled mixture showed only one C=O band, at 1675 cm^{-1}. The solvent was removed at 50–60° under 0.01 mm and the residue was evaporatively distilled (bath temperature 90°, 0.01 mm) to give 450 mg (55%) of 19. The ir spectrum of this product was superimposable with that of the starting material.

1-(1-Aziridinyl)-1-α-hydroxybenzylcyclohexane (29).—A solution of 1.1 g (4.8 mmol) of 29 in methanol was reduced with 1.0 g of NaBH$_4$ at room temperature for 12 hr. The product,

(24) Purchased from Alpha Inorganics, Inc., Beverly, Mass.

(25) Sodium borohydride reduction of α-amino ketones in six-membered ring system has been shown to give predominantly the trans isomer. *Cf.* C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. D. Pillai, and J. W. Stoddard, *J. Org. Chem.*, **31**, 2593 (1966).

(26) Purchased from Matheson Coleman and Bell, Norwood (Cincinnati), Ohio, and the sample contained 82.84% of phosphorus pentoxide.

after the usual work-up, was recrystallized from hexane to give
1.0 g (90%) of **29**, mp 90–91°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found:
C, 77.80; H, 9.18.

A part of **29** was converted to the perchlorate salt, mp 159–
160° after recrystallization from acetone–ether.

Anal. Calcd for $C_{15}H_{22}ClNO_5$: C, 54.33; H, 6.68; N,
4.22. Found: C, 54.12; H, 6.66; N, 4.18.

Another part of **29** was dissolved in ether and treated with an
excess of HCl in ethyl acetate to give 1-(2-chloroethyl)amino-1-
α-hydroxybenzylcyclohexane hydrochloride (**30**), mp 216° dec,
after recrystallization from ethanol–ether.

Anal. Calcd for $C_{15}H_{23}Cl_2NO$: C, 59.23; H, 7.62; N, 4.60.
Found: C, 59.02; H, 7.59; N, 4.54.

Registry No.—**3**, 15817-11-5; **5**, 15817-31-9; **7**,
32515-75-6; **9**, 32515-76-7; **10** HCl, 15946-21-1; **11**,
32515-78-9; **12**, 32515-79-0; **13**, 32515-80-3; **14b**,
32515-81-4; **15a**, 32515-82-5; **15a** perchlorate, 32515-
83-6; **15b**, 32515-84-7; **15b** perchlorate, 32515-85-8;
16a, 32515-86-9; **16b**, 32515-87-0; **17**, 15817-32-0; **18**,
32515-89-2; **19**, 32515-90-5; **20** HCl, 15817-12-6; **21**,
32515-98-3; **23**, 15885-97-9; **26**, 15817-09-1; **28**,
32515-94-9; **29**, 32515-95-0; **29** perchlorate, 32515-96-1;
30, 32515-97-2.

A New Type of Basic Amide Hydrolysis, Characterized by Alkyl–Nitrogen Fission

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Amides of the type $RNHCH(R')C_6H_4N=NR^2$ [R = alkyl C=O, aryl C=O, alkyl SO_2, aryl SO_2, $H_2NC=O$,
$C_6H_5NHC=O$, $(C_6H_5)_2NC=O$; R^1 = H, CH_3, C_6H_5; R^2 = phenyl, substituted phenyl, naphthyl] undergo basic
hydrolysis under mild conditions to give RNH_2 and $R^1C(=O)C_6H_4NHNHR^2$. A similar reaction occurs when
the substituents are ortho to one another. No reaction takes place when the groups are in the meta position.
The effects of structural modifications on the course of the reaction were studied, and a mechanism for the
reaction has been proposed.

In 1832, Liebig and Wöhler[2] described the first hy-
drolysis of an acyl amide in their classical paper on the
benzoyl radical; the base-catalyzed reaction proceeded
via the now familiar acyl–nitrogen cleavage (eq 1). It

$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}\text{---}NH_2 + HOH \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}OH + NH_3 \quad (1)$$
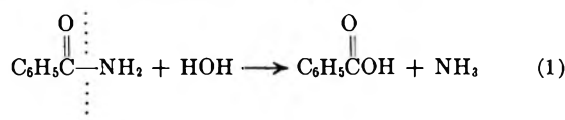
was not until 1960 that a second type of amide hydrol-
ysis became known. In that year, Lacey[3] reported
that under acid conditions some highly branched am-
ides hydrolyze with alkyl–nitrogen fission (eq 2).

$$R\overset{\overset{\displaystyle O}{\|}}{C}NH\text{---}R' + HOH \longrightarrow R\overset{\overset{\displaystyle O}{\|}}{C}NH_2 + R'OH \quad (2)$$
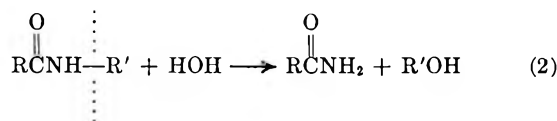
Work here has now shown that this second type of
cleavage also occurs in basic solution with certain am-
ides containing an azo group.

The "amidazo" reaction was encountered during an
attempt to prepare *p*-phenylazobenzylamine by sapon-
ification of its acetyl derivative **1**; instead of the antic-
ipated behavior, a more complicated reaction was ob-
served (eq 3). Reaction conditions consisted of 3-hr
refluxing under nitrogen in 0.36 *N* KOH in alcohol, 1.2
mol of alkali being used per mol of amide; the yields of
acetamide and 4-formylhydrazobenzene (**2**) were 37 and
62%, respectively.

This novel reaction appeared to be of sufficient the-

oretical interest to warrant further scrutiny; so a study
of its general nature was undertaken. First, some lim-
itations of the reaction were established by demon-
strating that the following compounds do not undergo
alkyl–nitrogen cleavage when refluxed with alcoholic
KOH.
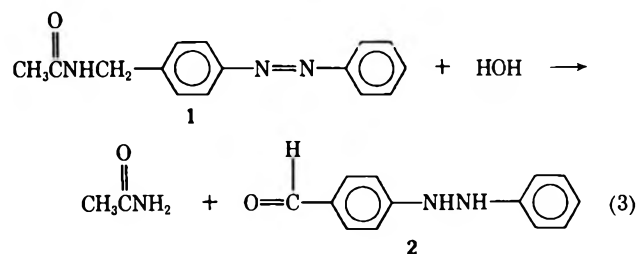
$$\text{CH}_3\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{NHCH}_2\text{---}\bigcirc\text{---N}=\text{N---}\bigcirc + \text{HOH} \longrightarrow$$

1

$$\text{CH}_3\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{NH}_2 + \text{O}=\overset{\overset{\displaystyle H}{|}}{\text{C}}\text{---}\bigcirc\text{---NHNH---}\bigcirc \quad (3)$$

2

$$\text{CH}_3\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{NHCH}_2\text{CH}_2\text{---}\bigcirc\text{---N}=\text{NC}_6\text{H}_5$$

3

$$\text{C}_6\text{H}_5\overset{\overset{\displaystyle O}{\|}}{\text{C}}\overset{\overset{\displaystyle CH_3}{|}}{\text{N}}\text{CH---}\bigcirc\text{---N}=\text{NC}_6\text{H}_5$$

4

5

$$\text{C}_6\text{H}_5\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{NHCH}_2\text{---}\bigcirc\text{---N}=\text{CHC}_6\text{H}_5$$

6
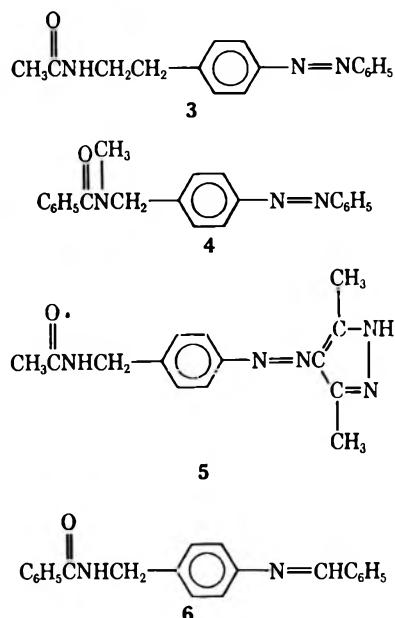
(1) This is a laboratory of the Northern Marketing and Nutrition Re-
search Division, Agricultural Research Service, U. S. Department of Agricul-
ture.

(2) J. von Liebig and F. Wöhler, *Justus Liebigs Ann. Chem.*, **3**, 268
(1832).

(3) R. N. Lacey, *J. Chem. Soc.*, 1633 (1960).

These preliminary experiments indicated that the amidazo reaction might be restricted to compounds of the general type **7**. However, another possibility became apparent when a mechanism for the reaction was postulated that included the intermediate **8**.

7
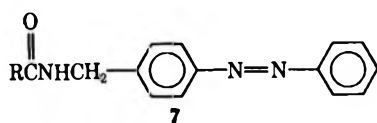
sibility became apparent when a mechanism for the reaction was postulated that included the intermediate **8**.

8
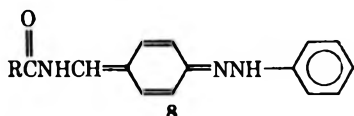
Involvement of this quinoid structure suggested that the reaction might also occur with ortho compounds of type **9** since they, too, are capable of assuming a quinoid form, as shown in **10**.

9   **10**
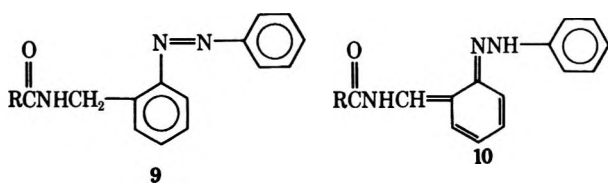
It was found that the ortho compounds do, indeed, undergo the amidazo reaction, the only difference being that they yield 2-phenylindazole (**11**), a dehydration product of the expected aldehyde **12**.

11   **12**
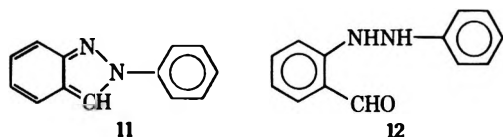
On the same basis, meta compounds would not be expected to undergo the amidazo reaction because of their inability to form quinoid structures; this reasoning was shown to be correct when **13** proved to be unaltered by alcoholic KOH under amidazo reaction conditions.

13
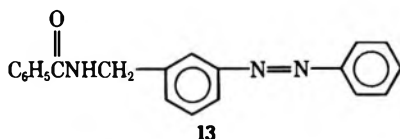
Next, a study of the effect of structural modifications was initiated to provide further insight into the nature of the amidazo reaction. The experiments directed toward this end were all conducted under reflux in a stream of nitrogen with 1 mmol of amide in 20 ml of 0.39 N KOH in 95% alcohol (7.8 mol of KOH per mol of amide). The yield of ammonia formed by hydrolysis of the primary amide product was obtained by passage of the nitrogen through standard acid; yields of aldehydes and ketones are based on isolated azo compounds (or a suitable derivative) after oxidation of the hydrazo compounds with periodic acid; yields of amides were calculated from isolated products, and of 2-phenylindazole, from the salt formed with 2,4-dinitrobenzenesulfonic acid. Reaction times ranged from 1 to 8 hr.

Results for the para and ortho series, showing the effects of varying R and R^1, and of modifying rings A and B, are the following.

A. Variations in R.—Studies on compounds having R^1 = H (rings A and B unsubstituted) demonstrated that the amidazo reaction takes place with compounds having the R groups shown in Table I. All of the compounds (except **1**) listed in this table were prepared from *p*-phenylazobenzylamine carbamate (**14**). The yields of amides from compounds **19**, **20**, and **23-26** were 45, 51, 67, 62, 27, and 6%, respectively.
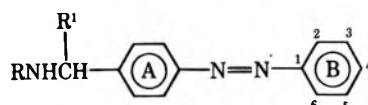
From Table I it is apparent that the amidazo reaction is quite general so far as the R group is concerned, although the nature of this group can have a marked effect on the rate of the reaction. The high yield of ammonia observed with the formyl compound **15** can, to a great extent, be accounted for by the complete hydrolysis of formamide. However, it appears likely that a part of the ammonia comes from the *p*-phenylazobenzylamine formed by ordinary acyl–nitrogen cleavage, since hydrolysis of this amine under amidazo reaction conditions gave a 20% yield of ammonia in 3 hr.

B. Variations in R^1.—Table II gives the results of modifying R^1 (rings A and B unsubstituted) in the amidazo compounds, the carbonyl products in this series being ketones instead of aldehydes. The compounds listed in Table II were prepared from α-methyl-*p*-(phenylazo)benzylamine hydrochloride (**31**) and α-phenyl-*p*-(phenylazo)benzylamine (**32**).

The low yields of azo ketones reported in Table II appear to be due merely to the slowness of the reaction; when an 8-hr hydrolysis was carried out on **34**, the yield of azo ketone was 49% (12% NH₃, 46% recovered starting material), compared to 9% for 1 hr. No attempt was made to determine the reaction time required for maximum yield. The lethargic reactions observed in this series are to be expected since it is well known that tertiary carbanions are less stable than secondary ones (see mechanism).

C. Modification of Ring A.—Compounds **41** and **42** gave no evidence of undergoing the amidazo reaction, although they were considerably altered by the alkaline treatment. It cannot be claimed, however,

41

42
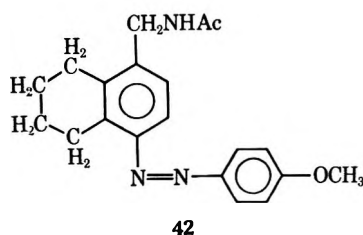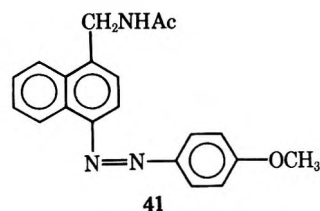
TABLE I

SYNTHESIS, PROPERTIES, AND EFFECTS OF SUBSTITUENTS ON HYDROLYSIS OF PARA SERIES COMPOUNDS[a]

(R^1 = H; RINGS A AND B UNSUBSTITUTED)

Compd	R	Time, hr	NH$_3$, %	p-C$_6$H$_5$N=NC$_6$H$_4$CHO, %	Method of preparation[b]	Crystallization solvent[c]	Mp, °C[d]
15	HC(=O)-	1	61	52	A	A	154–155
15	HC(=O)-	3	64	51			
1	CH$_3$C(=O)-	1	22	70			
1	CH$_3$C(=O)-	2	41	82			
1	CH$_3$C(=O)-	8	78	85			
16	HOOCCH$_2$CH$_2$C(=O)-	5	66	78	B	A	196–197
17	CH$_3$(CH$_2$)$_6$C(=O)-	3	25	83	C	A	140–141
18	C$_6$H$_5$CH$_2$C(=O)-	2	39	86	C	B	174–175
19	C$_6$H$_5$CH=CHC(=O)-	5	26	81	C	A	182–183
20	C$_6$H$_5$(CH=CH)$_2$C(=O)-	6	16	79	C	C	219–220
21	C$_6$H$_5$C(=O)-	1	3	85	B	A	161–162
22	(C$_6$H$_5$)$_2$CHC(=O)-	3	10	86	C	D	172–173
23	CH$_3$-(2,4,6-(CH$_3$)$_3$C$_6$H$_2$)C(=O)-	3	0	83	C	E	161–163
24	(1-naphthyl)C(=O)-	2	3	84	C	F	204–205
25	CH$_3$SO$_2$-	3	0	28	C	G	157–158
26	C$_6$H$_5$SO$_2$-	3	0	10	C	A	169–170
27	(2,4,6-(CH$_3$)$_3$C$_6$H$_2$)SO$_2$-	3	0	25	C	G	137–138[e]
28	H$_2$NC(=O)-	3	3	70	D	H	248–250
29	C$_6$H$_5$NHC(=O)-	3	0	83	E	H	229–230
30	(C$_6$H$_5$)$_2$NC(=O)-	3	0	89	C	B	150–151

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all compounds listed in the table. [b] Reagent for reaction with compound 14: (A) formic acetic anhydride; (B) anhydride and pyridine; (C) acid chloride, 2.5 N NaOH and tetrahydrofuran (see compound 24 in Experimental Section for typical procedure); (D) urea nitrate; (E) phenyl isocyanate and dimethylformamide (DMF). [c] (A) 95% EtOH, (B) acetone–hexane, (C) absolute EtOH, (D) EtOH–hexane, (E) acetone, (F) EtOH–EtOAc, (G) DMF–H$_2$O, (H) DMF. [d] Hot stage, uncorrected. [e] Solidifies and remelts at 147–148°.

that the failure of these compounds to show alkyl–nitrogen cleavage is due entirely to the modification of ring A; the inhibiting effect of the p-methoxy group located on ring B (see section D) could allow other re-actions to occur, leading to the extensive decomposition observed. Unfortunately, compounds of this type with ring B unsubstituted are not readily accessible.

Table II

Synthesis, Properties, and Effects of Substituents on Hydrolysis of Para Series
Compounds[a] (Ring A and B Unsubstituted)

Compd	R	R¹	Time, hr	NH₃, %	p-C₆H₅N= NC₆H₄COR', %	Recovered starting material, %	Method of preparation[b]	Crystallization solvent[c]	Mp, °C[d]
33	CH₃C(O)-	CH₃	3	6	15	66	A	A	155–156
34	C₆H₅C(O)-	CH₃	1	1	9	87	B	B	194–195
35	(α-naphthoyl) C(O)-	CH₃	2	0	5	91	C	C	214–215
36	CH₃SO₂-	CH₃	3	0	1	95	D	D	106–107
37	C₆H₅NHC(O)-	CH₃	3	4	27	46	E	E	207–208
38	CH₃C(O)-	C₆H₅	3	4	13	75	F	F	186–187
39	C₆H₅C(O)-	C₆H₅	1	0	5	92	G	B	205–206
40	C₆H₅NHC(O)-	C₆H₅	3	8	53	37	H	B	258–260

[a] Satisfactory analytical data ($\pm 0.4\%$ for C, H, and N) were reported for all compounds listed in the table. [b] (A) Ac₂O and compound 31; (B) (C₆H₅CO)₂O, pyridine, and compound 31; (C) α-naphthoyl chloride, aqueous KOH, tetrahydrofuran, and compound 31; (D) methylsulfonyl chloride, aqueous KOH, tetrahydrofuran, and compound 31; (E) C₆H₅NCO, DMF, and compound 31; (F) Ac₂O and compound 32; (G) (C₆H₅CO)₂O, pyridine, and compound 32; (H) C₆H₅NCO, DMF, and compound 32. [c] (A) 80% EtOH; (B) DMF; (C) acetone–N-methylpyrrolidone; (D) EtOAc–hexane; (E) DMF–80% EtOH; (F) acetone–H₂O. [d] Hot stage, uncorrected.

D. Substitution on Ring B.—The effects of substitution on ring B on the amidazo reaction are shown in Table III (R¹ = H; ring A unsubstituted).

In general, it can be stated that the effects of ring B substituents on rates (hence, yields) of the amidazo reaction are readily explainable in terms of effects of substituents on the relative stabilities of the anionic intermediates shown in the proposed mechanism.

E. Replacement of Ring B by a Naphthalene Ring. The naphthalene compound **57** undergoes the amidazo reaction in much the same way that the corresponding benzene compound does.
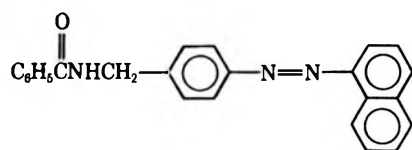
57

4% NH₃, 79% azo, 71% benzamide; time, 1 hr.

Ortho Series.—Behavior of the ortho series of compounds in the amidazo reaction is summarized in Table IV.
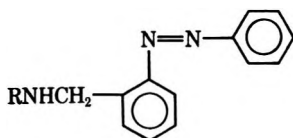
The depicted mechanism, which involves addition of water to an imide type of compound, appears to rationalize the products of the amidazo reaction (Scheme I).

The behavior of compound **62** suggests that a mechanism different from the above may be in operation with ortho-substituted sulfonamides.

Experimental Section

Unless otherwise noted, melting points were determined on a Fisher[4] hot-stage apparatus and were not corrected. The capillary melting points were corrected.

N-p-Phenylazobenzylacetamide (**1**).—*N-p*-Aminobenzylacetamide[5] (37.74 g, 0.230 mol) was dissolved in 100 ml of HOAc at 40° and nitrosobenzene (24.88 g, 0.232 mol) was added gradually to the solution. After 4 days at room temperature water was added and the solid separated (43.2 g, 74%). Crystallization from alcohol gave orange needles of 1 melting at 173–174°.

Anal. Calcd for C₁₅H₁₅N₃O: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.1; H, 6.05; N, 16.6.

Hydrolysis of 1 to 4-Formylhydrazobenzene (2) and Acetamide. —Compound 1 (5.0€6 g, 0.020 mol) was dissolved in 32 ml of 95% EtOH in a 200-ml flask attached to a distilling head equipped with a gas inlet tube and a dropping funnel. Nitrogen was passed over the solution for 15 min and bubbled through 50 ml of standard acid. A solution of KOH (1.68 g, 0.030 mol) in 1.70 ml of water and 35 ml of 95% EtOH was then added to the solution of 1. The reaction mixture was refluxed gently for 3 hr under a current of nitrogen. Back titration gave a 41% yield of a base, which was identified as ammonia by conversion to benzamide (mp 126–127° cap).

The reaction mixture was added to 300 ml of water and extracted with 500 ml of ether. The ether extract was washed with three 25-ml portions of water, the pH of the combined water fractions adjusted to 7, and the neutral solution lyophilized. Sublimation of the resulting powder at 80° and 1 mm yielded 193 mg of acetamide (mp 82–83°, cap), which was characterized as the chloral derivative (mp 162–163°, cap). Additional acetamide isolated from the lyophilization condensate raised the yield to 434 mg (37%).

The washed ether extract was concentrated to about 25 ml and 50 ml of benzene was added. Further concentration to 15 ml gave 2.03 g of crude 2 in the form of light tan bars. A second crop brought the yield of crude product to 3.16 g (75%). Recrystallization from alcohol yielded almost pure material of mp 141–143°

(4) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

(5) H. H. Fox, *J. Org Chem.*, **13**, 438 (1948); J. N. Ashley and M. Davis, *J. Chem. Soc.*, 812 (1957).

TABLE III

SYNTHESIS, PROPERTIES, AND EFFECTS OF SUBSTITUENTS ON HYDROLYSIS OF PARA SERIES COMPOUNDS[a]

(R^1 = H; RING A UNSUBSTITUTED, RING B SUBSTITUTED)

Compd	Ring B substitution	R	Time, hr	NH_3, %	Substituted aldehyde, %	Recovered starting material, %	Method of preparation[b]	Crystallization solvent[c]	Mp °C[d]
43	4-CH_3	$CH_3C(=O)-$	3	42	72		A	A	200–201
44	4-C_6H_5	$CH_3C(=O)-$	3	40	77		B	B	241–242
45	4-Cl	$CH_3C(=O)-$	3	56	85		A	C	214–215
46	4-OCH_3	$CH_3C(=O)-$	3	20	28		B	D	178–179
47	4-$OCH_2C_6H_5$	$CH_3C(=O)-$	3	13	18	56	B	E	202–204
48	4-SCH_3	$CH_3C(=O)-$	3	54	73		B	C	198–199
49	4-OH	$C_6H_5C(=O)-$	1	0	0	98	C		
50	4-OCH_3	$C_6H_5C(=O)-$	1	1	37	48	C		
51	4-NH_2	$CH_3C(=O)-$	3	4		91	C		
52	4-NMe_2	$C_6H_5C(=O)-$	1	0	0	82	C		
53	3-CF_3	$CH_3C(=O)-$	3	58	83		B	A	172–173
54	2-CH_3	$CH_3C(=O)-$	3	50	75		B	D	145–146
55	2-OCH_3	$CH_3C(=O)-$	3	58	60		B	F	143–144
56	2-C_6H_5	$CH_3C(=O)-$	3	55	59		B	G	170–171

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all compounds listed in the table. [b] (A) p-Aminobenzylacetamide and substituted nitrosobenzene (1 mmol of each; 1 ml of CH_3OH and 0.5 ml of HOAc; 60–70°); (B) p-nitrosobenzylacetamide (for preparation, see compound 5 in Experimental Section) and substituted aniline (same conditions as in A); (C) see Experimental Section. [c] (A) 95% EtOH; (B) EtOH; (C) DMF–H_2O; (D) 80% EtOH; (E) DMF; (F) EtOAc–hexane; (G) EtOAc. [d] Hot stage; uncorrected.

TABLE IV

EFFECTS OF SUBSTITUENTS ON HYDROLYSIS OF ORTHO SERIES COMPOUNDS[a]

Compd	R	NH_3, %	2-Phenylindazole, %
58	$CH_3C(=O)-$	31	67
59	$C_6H_5C(=O)-$	15	66
60	$H_2NC(=O)-$	2	72
61	$C_6H_5NHC(=O)-$	1	46
62	$C_6H_5SO_2-$[b]	0	97

[a] Time, 3 hr. [b] A 98% yield of benzenesulfonamide was obtained. The high yield in this reaction contrasts sharply with the 10% value obtained with compound 26 (Table I).

(2.65 g, 63%). Two crystallizations from benzene afforded pure 2 (mp 143–144°, cap) as off-white bars.

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.02. Found: C, 73.5; H, 5.72; N, 13.3.

4-Formylhydrazobenzene oxime was prepared by heating 2 with hydroxylamine acetate in alcohol for 10 min (mp 164–165°, cap).

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.72; H, 5.77; N, 18.50. Found: C, 68.9; H, 5.77; N, 18.7.

4-Formylhydrazobenzene semicarbazone (mp 216–218°, cap) was prepared in the same way as the oxime.

Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.43; H, 5.61; N, 26.01. Found: C, 62.4; H, 5.40, N, 26.2.

Compound 2 was readily oxidized at room temperature by HIO_4 in alcohol to red crystals (mp 121–122°, cap), which were shown to be 4-phenylazobenzaldehyde by comparison with an authentic sample.[6] The phenylhydrazones[6] were also identical (mp 167–168°, cap).

1-p-Phenylazophenyl-2-acetaminoethane (3).—1-p-Aminophenyl-2-acetaminoethane[7] (4.43 g, 0.0249 mol) and nitrosobenzene (2.66 g, 0.0249 mol) were heated at 60° for 6 hr in 25 ml of HOAc. On crystallization from alcohol the crude product (5.23 g, 78%) gave orange needles of 3 (mp 148–149°).

Anal. Calcd for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 72.2; H, 6.47; N, 15.9.

N-p-Phenylazobenzyl-N-methylbenzamide (4).—N-Methyl-p-nitrobenzylamine[8] was prepared from 21.6 g of p-nitrobenzyl bromide and 100 ml of 40% CH_3NH_2–H_2O in 200 ml of absolute EtOH (1 week at room temperature). The alcohol was removed under reduced pressure and the crystals were separated. The

(6) P. Freundler, *C. R. Acad. Sci.*, **134**, 1559 (1902).

(7) M. Borovička, Z. Šedivý, J. O. Jílek, and M. Protiva, *Chem. Listy*, **49**, 231 (1955); J. Comin and W. Keller-Schierlein, *Helv. Chim. Acta*, **42**, 1730 (1959).

(8) C. Paal and H. Sprenger, *Chem. Ber.*, **30**, 61 (1897); J. C. Craig, N. Y. Mary, and L. Wolf, *J. Org. Chem.*, **29**, 2868 (1964).

Scheme I
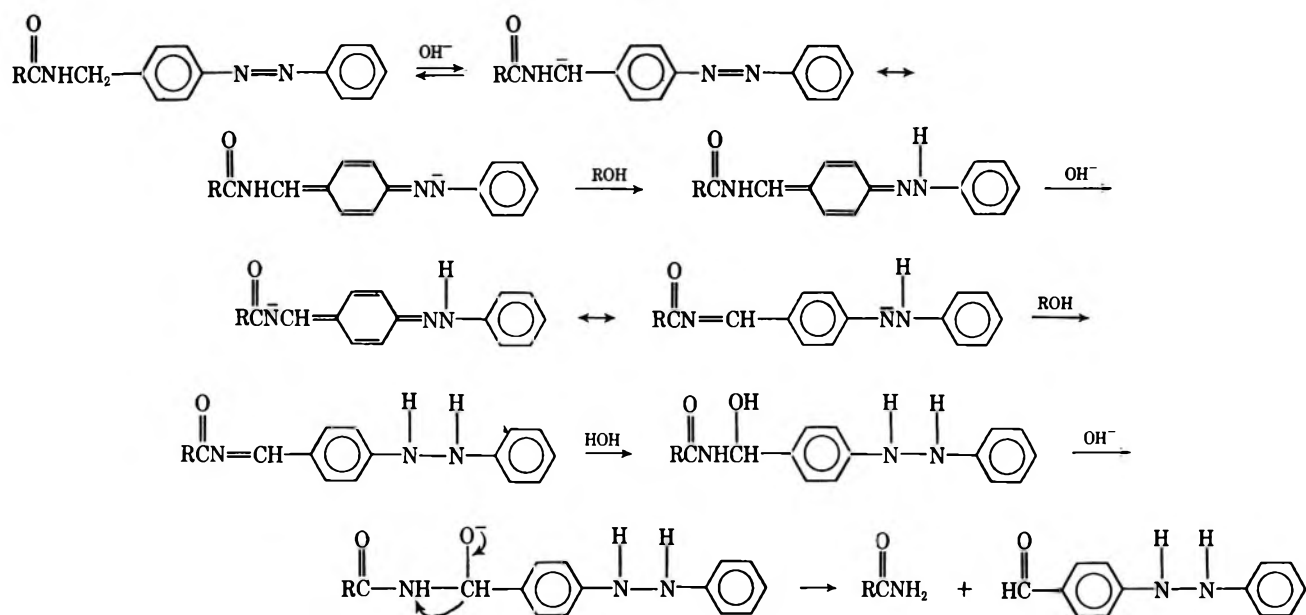
filtrate was extracted with ether and the aqueous phase was made alkaline with NaOH. Extraction of the alkaline solution with ether and removal of the ether gave 14.1 g (85%) of N-methyl-p-nitrobenzylamine. Benzoylation with benzoic anhydride in pyridine gave a 95% yield of N-p-**nitrobenzyl**-N-**methylbenzamide**, which was purified by crystallization from acetone–hexane. The light tan needles melted at 95–96°.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.37. Found: C, 66.6; H, 5.21; N, 10.3.

The benzoyl derivative was reduced to the amine (PtO$_2$, 95% EtOH), which was converted to the azo compound by reaction with nitrosobenzene (HOAc–CH$_3$OH, 70°, 6 hr). Crystallization from benzene–hexane gave orange-brown crystals of **4** (mp 90–91°).

Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.8; H, 6.05; N, 12.5.

3,5-Dimethylpyrazole-4-azo-4′-acetaminomethylbenzene-1 (5).—N-p-Nitrosobenzylacetamide was prepared as follows. To 11.0 g of N-p-nitrobenzylacetamide[6] in 25 ml of 95% EtOH was added a solution of 2.27 g of NH$_4$Cl in 25 ml of 50% EtOH. Zinc dust (14.2 g) was added with stirring at a rate that maintained the temperature at 65–70° (about 25 min). The reaction mixture was filtered and the filtrate was added dropwise to a stirred solution of 38.3 g of FeCl$_3$·6H$_2$O in 300 ml of water. The solid was separated and the filtrate was extracted three times with CHCl$_3$. Removal of the solvent gave 7.66 g (76%) of tan crystals. Crystallization from CHCl$_3$–hexane yielded colorless plates (mp 122–124°, green melt) of N-p-**nitrosobenzylacetamide**.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66. Found: C, 60.8; H, 5.87.

The nitroso compound (890 mg, 0.005 mol) was condensed with 4-amino-3,5-dimethylpyrazole[9] (555 mg, 0.005 mol) in 5 ml of HOAc (1 hr, 70°). The crude azo compound (99%) was crystallized from ethanol–acetone to give orange needles of **5** (mp 231–232°).

Anal. Calcd for $C_{14}H_{17}N_5O$: C, 61.97; H, 6.32; N, 25.81. Found: C, 61.5; H, 6.29; N, 26.3.

N-Benzylidene-p-benzoylaminomethylaniline (6).—N-p-Nitrobenzylbenzamide[10] (mp 158–159°) was reduced (Pd/C; absolute EtOH) to the amine, which crystallized from dilute alcohol in the form of bars. The pure N-p-**aminobenzylbenzamide** melted at 142–143°.

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 73.9; H, 6.23; N, 12.4.

A solution of the amine (1.13 g, 0.005 mol) and benzaldehyde (0.584 g, 0.0055 mol) in alcohol was heated 5 min at 95°. The product was crystallized from acetone–DMF to yield white crystals of **6** (mp 154–155°).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.25; H, 5.77; N, 8.91. Found: C, 80.0; H, 5.75; N, 9.00.

m-Phenylazobenzylbenzamide (13).—m-Nitrobenzylamine hydrochloride[11] was converted to the benzoyl derivative with benzoyl chloride and aqueous KOH. Crystallization from 80% EtOH gave colorless needles of m-nitrobenzylbenzamide (mp 139–140°).

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.61; H, 4.72; N, 10.93. Found: C, 65.9; H, 4.88; N, 10.9.

The nitro compound was reduced (PtO$_2$, EtOH) to the amine, which was converted to the azo compound by reaction with nitrosobenzene in HOAc (2 hr, 60°). Crystallization from 80% EtOH and from acetone–hexane gave yellow-orange crystals of **13** (mp 160–161°).

Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.2; H, 5.50; N, 13.6.

p-Phenylazobenzylamine Carbamate (14).—N-p-Aminobenzylacetamide[5] (3.28 g) was heated for 4 hr on a steam bath with 15 ml of 6 N HCl; evaporation to dryness gave the dihydrochloride of p-aminobenzylamine.[12] The dihydrochloride (8.13 g) was dissolved in 20 ml of water containing 5.2 g of KOH. Three CHCl$_3$ extractions gave an oil, which was converted to the solid carbamate with CO$_2$ (5.37 g).

The carbamate (28.83 g, 0.100 mol) was dissolved in a mixture of 135 ml of HOAc and 270 ml of 95% EtOH. Nitrosobenzene (23.70 g, 0.22 mol) was dissolved in the carbamate solution with stirring. After 27 hr at room temperature, 1.6 l. of ether was added and the orange precipitate of acetate was separated (42.0 g, 77%). The acetate was decomposed with 12 g of KOH in 100 ml of water, and the amine was extracted with ether. Passage of CO$_2$ through the ether solution gave p-phenylazobenzylamine carbamate (14) (34.98 g, 75%) as an orange powder, which melted at 87–92° with evolution of gas.

Anal. Calcd for $C_{27}H_{26}N_6O_2$: C, 69.51; H, 5.62; N, 18.02. Found: C, 69.6; H, 5.74; N, 18.4.

N-p-Phenylazobenzyl-α-naphthamide (24).—p-Phenylazobenzylamine carbamate (14) (488 mg, 0.00096 mol) was heated for a few minutes in a silicone bath (140°) to give a clear red melt of the free amine. After cooling, the amine was dissolved in 5 ml of tetrahydrofuran, and to this solution was added 5 ml (0.0125 mol) of 2.5 N NaOH. A solution of α-naphthoyl chloride (366 mg, 0.00192 mol) in 5 ml of tetrahydrofuran was added and the mixture was shaken for 10 min. Addition of water gave a 91% yield of crude amide of mp 190–196°. Recrystallization from DMF–95% EtOH yielded **24** in the form of orange plates (75%, mp 204–205°).

Anal. Calcd for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.9; H, 5.17; N, 11.8.

(9) R. Hüttell, F. Büchele, and P. Jochum, *Chem. Ber.*, **88**, 1577 (1955).
(10) A. Hafner, *ibid.*, **23**, 337 (1890).
(11) K. G. Lewis, *J. Chem. Soc.*, 2249 (1950).
(12) H. Amsel and A. W. Hofmann, *Chem. Ber.*, **19**, 1284 (1886).

1-*p*-Phenylazophenylethylamine Hydrochloride (31).—*p*-Aminoacetophenone oxime[13] was reduced to the diamine by the Raney alloy method of Staskun and van Es.[14] An ether solution of the crude liquid diamine treated with 3 *N* HCl–CH₃OH gave 1-*p*-aminophenylethylamine dihydrochloride (mp 225–230°) in the form of a white powder.

Anal. Calcd for C₈H₁₄Cl₂N₂: C, 45.95; H, 6.75; N, 13.40. Found: C, 46.0; H, 6.91; N, 13.3.

The free amine (6.13 g, 0.045 mol) (prepared from the dihydrochloride) and nitrosobenzene (5.08 g, 0.047 mol) were dissolved in 70 ml of 95% EtOH and 35 ml of HOAc. After 3 days at room temperature the reaction mixture was poured into water and excess alkali added. Ether extraction gave an oil, which was converted to **31** with 3 *N* HCl–CH₃OH. The hydrochloride melted at 230–232°.

Anal. Calcd for C₁₄H₁₆ClN₃: C, 64.24; H, 6.16; N, 16.05. Found: C, 64.4; H, 6.55; N, 15.6.

Phenyl-*p*-phenylazophenylmethylamine (32).—*p*-Aminobenzophenone was converted to a mixture of oximes,[15] which was reduced to the diamine with Raney nickel alloy and alkali.[14] The crude product was dissolved in ether and additior. of 3 *N* HCl–CH₃OH gave colorless needles of **phenyl-*p*-aminophenylmethylamine dihydrochloride** (mp 235–240°).

Anal. Calcd for C₁₃H₁₆Cl₂N₂: C, 57.58; H, 5.95; N, 10.33; Cl, 26.15. Found: C, 57.7; H, 6.12; N, 10.1; Cl, 26.0.

The diamine (10.26 g, 0.0517 mol) and nitrosobenzene (5.81 g, 0.0543 mol) were dissolved in 75 ml of 95% EtOH and 37 ml of HOAc. After 3 days at room temperature the reaction mixture was diluted with water and excess alkali added. Ether extraction yielded 12.58 g of crude azo compound (85%). Crystallization from ether and from 95% EtOH gave **32** (mp 94–95°).

Anal. Calcd for C₁₉H₁₇N₃: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.3; H, 6.38; N, 14.4.

1-Acetaminomethyl-4-*p*-methoxyphenylazonaphthalene (41).—1-Methyl-4-nitronaphthalene (4.00 g, 0.0214 mol) was converted to 1-bromomethyl-4-nitronaphthalene by the method of Benigni and Minnis.[16] The crude product left after removal of CCl₄ was refluxed for 20 min with urotropine (3.00 g, 0.0214 mol) in 30 ml of CHCl₃. Filtration gave 6.12 g of addition compound (mp 175–180°). This product was triturated with 12 ml of 6 *N* HCl, allowed to stand at room temperature for 3.5 hr, and then steam distilled for 1 hr with 100 ml of 3 *N* HCl to remove formaldehyde. Cooling in ice and filtration yielded 2.80 g of 1-nitro-4-naphthalene methylamine hydrochloride. Acetylation gave 1-acetaminomethyl-4-nitronaphthalene (mp 159–160°).

Anal. Calcd for C₁₃H₁₂N₂O₃: C, 63.92; H, 4.95. Found: C, 64.3; H, 4.98.

Reduction of the nitro compound (Pd/C, 95% EtOH), diazotization of the amine, coupling of the diazonium salt with phenol, and methylation of the azo phenol gave 41 (mp 200–201°).

Anal. Calcd for C₂₀H₁₉N₃O₂: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.5; H, 5.94; N, 12.8.

1-Acetaminomethyl-4-*p*-methoxyphenylazo-5,6,7,8-tetrahydronaphthalene (42).—1-Acetaminomethyl-4-nitronaphthalene described above was reduced[17] (Raney nickel, 1 hr, 100°, 800 lb/in.², absolute EtOH) to **1-acetaminomethyl-4-amino-5,6,7,8-tetrahydronaphthalene**, which melted at 164–165° after crystallization from absolute EtOH.

Anal. Calcd for C₁₃H₁₈N₂O: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.3; H, 8.45; N, 12.6.

Acetylation of the amine gave **1-acetaminomethyl-4-acetamino-5,6,7,8-tetrahydronaphthalene** (mp 227–228°).

Anal. Calcd for C₁₅H₂₀N₂O₂: C, 69.37; H, 7.76. Found: C, 69.4; H, 7.76.

1 - Acetaminomethyl - 4 - amino - 5,6,7,8 - tetrahydronaphthalene (3.01 g, 0.0138 mol) was diazotized in 15 ml of 2 *N* HCl with 1.03 g of NaNO₂ (0.015 mol) in 5 ml of water and coupled with phenol. The resulting azo phenol was methylated with CH₂N₂–CH₃OH–ether to give compound 42, which melts at 176–177°, solidifies, and remelts at 186–187°.

Anal. Calcd for C₂₀H₂₃N₃O₂: C, 71.19; H, 6.87; N, 12.45. Found: C, 70.9; H, 6.95; N, 12.2.

N-*p*-Hydroxyphenylazobenzylbenzamide (49).—N-*p*-Aminobenzylbenzamide (2.26 g, 0.010 mol; for preparation see compound 6) was converted to the diazonium chloride (2.2 ml of concentrated HCl, 18 ml of H₂O, and 0.75 g of NaNO₂ in 5 ml of H₂O) and coupled with phenol (941 mg, 0.010 mol, 20 ml of 1 *N* NaOH). Crystallization from ethanol gave the red azo phenol 49 (mp 230–231°).

Anal. Calcd for C₂₀H₁₇N₃O₂: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.6; H, 5.26; N, 12.5.

N-*p*-Methoxyphenylazobenzylbenzamide (50).—Compound 49 was methylated with CH₂N₂–CH₃OH–ether and the unreacted phenol removed by extraction of an ether solution with 2 *N* NaOH. Crystallization from 95% EtOH gave 50 (mp 170–171°).

Anal. Calcd for C₂₁H₁₉N₃O₂: C, 73.02; H, 5.54; N, 12.17. Found: C, 72.8; H, 5.60; N, 12.0.

N-*p*-Aminophenylazobenzylacetamide (51).—N-*p*-Nitrosobenzylacetamide (3.14 g, 0.0177 mol, for preparation see compound 5), *p*-aminotrifluoroacetanilide (3.60 g, 0.0177 mol) [prepared by reduction (Pd/C, EtOH) of *p*-nitrotrifluoroacetanilide[18]] in 18 ml of CH₃OH and 9 ml of HOAc were heated for 1 hr at 65° to give an 85% yield of crude azo compound. Crystallization from alcohol yielded pure **1-acetaminomethylbenzene-4-azo-4′-trifluoroacetaminobenzene-1** (mp 275–276°).

Anal. Calcd for C₁₇H₁₅F₃N₄O₂: C, 56.04; H, 4.15; N, 15.38. Found: C, 55.6; H, 4.14; N, 15.1.

The trifluoro compound (3.64 g, 0.010 mol) was dissolved in 55 mol of 0.55 *N* NaOH and kept at room temperature for 4 days. The solution was then brought to the boiling point and cooled and the pH adjusted to 7. Addition of water gave crude amine (2.62 g, 98%) of mp 165–166°, which on crystallization from alcohol yielded 51 (mp 167–168°).

Anal. Calcd for C₁₅H₁₆N₄O: C, 67.14; H, 6.01; N, 20.88. Found: C, 67.42; H, 6.06; N, 20.6.

N-*p*-Dimethylaminophenylazobenzylbenzamide (52).—N-*p*-Aminobenzylbenzamide (2.26 g, 0.010 mol; see compound 6 for preparation) was converted to the diazonium chloride (4.2 ml of 6 *N* HCl in 15 ml of H₂O and 745 mg of NaNO₂ in 5 ml of H₂O). To an ice-cold solution of the salt was added dropwise with stirring a solution of dimethylaniline (1.49 g, 0.0123 mol) in 5 ml of alcohol. After 30 min of stirring a solution of 2.72 g of NaOAc·3H₂O was added dropwise. After 2 hr of stirring the azo compound was separated and purified on a Bio-Sil A column (EtOAc eluate). Crystallization from alcohol gave pure 52 of mp 209–210°.

Anal. Calcd for C₂₂H₂₂N₄O: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.3; H, 6.34; N, 16.0.

N-*p*-α-Naphthylazobenzylbenzamide (57).—N-*p*-Aminobenzylbenzamide (9.04 g, 0.040 mol; see compound 6 for preparation) was suspended in 100 ml of absolute EtOH, and 10 ml of concentrated H₂SO₄ in 50 ml of absolute EtOH was added gradually. *n*-Butyl nitrite (12 ml) was then added dropwise with stirring. After 30 min standing at room temperature the white crystals of diazonium sulfate (11.64 g) were separated and dissolved in 14 ml of water. This solution was added dropwise to a stirred solution of α-naphthylamine (5.72 g, 0.040 mol) in 150 ml of 95% EtOH. After 30 min of stirring, 12 g of NaOAc·3H₂O in water was added and the stirring continued for 15 min. The azo compound was separated (12.7 g, 84%, mp 170–190°) and crystallized from DMF–EtOH to give pure **1-benzoylaminomethylbenzene-4-azo-4′-aminonaphthalene-1**, mp 198–200°.

Anal. Calcd for C₂₄H₂₀N₄O: C, 75.77; H, 5.30; N, 14.73. Found: C, 76.1; H, 5.69; N, 14.8.

The amine (3.80 g, 0.10 mol) was dissolved at 95° in 50 ml of HOAc containing 1 ml of water. The solution was cooled to room temperature and 10 ml of concentrated H₂SO₄ in 20 ml of HOAc was added. The solution was cooled in ice and 800 mg of NaNO₂ in 1 ml of water was added, followed by 10.6 g of Na₃PO₄·H₂O (0.10 mol) in 3 ml of concentrated H₂SO₄ in 20 ml of water. After 2.5 hr in ice, the reaction mixture was allowed to warm to room temperature. When the evolution of nitrogen ceased, the solution was shaken with CHCl₃ and water. The CHCl₃ solution was washed well with water and concentrated to a red-brown oil. Purification on an Al₂O₃ (grade I) column and crystallization from CHCl₃–hexane gave 57 (mp 175–176°) in small yield.

Anal. Calcd for C₂₄H₁₉N₃O: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.7; H, 5.22; N, 11.3.

N-*o*-Phenylazobenzylacetamide (58).—*o*-Nitrobenzyl bromide[19]

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(18) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952).

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was converted to the urotropine addition compound in CHCl₃. This product (78 g) was refluxed for 1.5 hr with 60 ml of concentrated NH₄OH in 360 ml of water. Formaldehyde in 40% solution (20 ml) was added to the hot reaction mixture, from which an oil had separated. On cooling, the oil solidified and the solid was separated (34.12 g). On concentration on a steam bath with 20 ml of concentrated HCl, this solid gave crystals and liquid. Trituration with absolute EtOH and filtration yielded 26.5 g (66%) of o-nitrobenzylamine hydrochloride,[20] mp 245–250°.

Acetylation of the hydrochloride gave N-o-nitrobenzylacetamide,[20] which was reduced (Pd/C, 95% EtOH) to N-o-aminobenzylacetamide.[21] A solution of this amine (1.71 g, 0.0104 mol) and nitrosobenzene (1.11 g, 0.0104 mol) in 10 ml of CH₃OH and 5 ml of HOAc was heated at 65° for 2 hr to yield 1.28 g of crude azo compound (mp 105–112°). Purification on a silicic acid column (Bio-Sil A, ether eluate) and crystallization from ethanol–hexane gave 58, mp 126–127°.

Anal. Calcd for C₁₅H₁₅N₃O: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.2; H, 5.96; N, 16.4.

N-o-Phenylazobenzylbenzamide (59).—N-o-Aminobenzylbenzamide[21] (2.16 g, 0.0084 mol) was condensed with nitrosobenzene (907 mg, 0.0084 mol) in 10 ml of HOAc (60°, 2 hr). The crude azo compound (1.79 g, 67%) was crystallized from dilute alcohol to give compound 59, mp, 134–135°.

Anal. Calcd for C₂₀H₁₇N₃O: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.2; H, 5.67; N, 13.2.

o-Phenylazobenzylurea (60).—o-Nitrobenzylurea[22] was reduced (Pd/C, 80% EtOH) to o-aminobenzylurea, which was crystallized from 95% EtOH. It melted at 190–191°.

Anal. Calcd for C₈H₁₁N₃O: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.3; H, 7.00; N, 25.1.

A solution of the amine (1.85 g, 0.0112 mol) and nitrosobenzene (1.32 g, 0.0123 mol) in 12 ml of CH₃OH and 6 ml of HOAc was heated at 70° for 7 hr. The crude azo compound (2.46 g, 86%, mp 155–165°) was crystallized from 50% EtOH to give 60, mp 177–178°.

Anal. Calcd for C₁₄H₁₄N₄O: C, 66.12; H, 5.55; N, 22.03. Found: C, 66.4; H, 5.69; N, 21.5.

1-Phenyl-3-o-phenylazobenzylurea (61).—To a solution of freshly prepared o-nitrobenzylamine (2.60 g, 0.0171 mol) in dimethylformamide was added 1.83 g (0.0154 mol) of phenyl isocyanate. The solution was heated at 95° for 30 min, cooled, and added to water. The crude product (4.12 g, 99%) was crystallized from 95% EtOH to give 1-phenyl-3-o-nitrobenzylurea, mp 183–184°.

Anal. Calcd for C₁₄H₁₃N₃O₃: C, 61.98; H, 4.83; N, 15.49. Found: C, 61.8; H, 5.03; N, 15.3.

The nitro compound was reduced (Pd/C, absolute EtOH) to the amine, which was purified by crystallization from 95% EtOH. Pure 1-phenyl-3-o-aminobenzylurea melted at 208–209°.

Anal. Calcd for C₁₄H₁₅N₃O: C, 69.69; H, 6.27; N, 17.50. Found: C, 69.7; H, 6.15; N, 17.3.

A solution of the amine (4.64 g, 0.0192 mol) and nitrosobenzene (2.26 g, 0.0211 mol) in 20 ml of CH₃OH, 10 ml of HOAc, and 40 ml of 95% EtOH was heated at 60° for 12 hr. The crude azo compound (5.57 g, 88%) on crystallization from HOAc and from DMF–H₂O gave pure 61, mp 201–202°.

Anal. Calcd for C₂₀H₁₈N₄O: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.7; H, 5.59; N, 16.9.

N-o-Phenylazobenzylbenzenesulfonamide (62).—N-o-Aminobenzylbenzenesulfonamide[23] (3.43 g, 0.0131 mol) and nitrosobenzene (1.54 g, 0.0144 mol) were heated for 8 hr at 65° in 13 ml of CH₃OH and 6.5 ml of HOAc. The crude azo compound was a sticky black solid (4.25 g, 93%), which was purified on a silicic acid column (Bio-Sil A, ether–EtOAc eluate) and by crystallization from EtOAc–hexane and from alcohol. Pure 62 melted at 130–131°.

Anal. Calcd for C₁₉H₁₇N₃O₂S: C, 64.93; H, 4.88; N, 11.96. Found: C, 64.7; H, 5.01; N, 11.9.

Millimol Hydrolyses of Amidazo Compounds.—The apparatus used for the hydrolyses was in two parts: (1) A 50-ml round-bottomed flask with a 24/40 female joint. (2) A distilling bulb (5-cm diameter) situated 4 cm above a male joint. A dropping funnel and a gas inlet tube were connected to the 4-cm portion of the tube above the joint. To the top of the distillation bulb was attached 9-mm tubing, which extended horizontally 10 cm and downward 25 cm.

For the hydrolyses 1 mmol of the amidazo compound, 10 ml of 95% EtOH, and a bubbling tube were put in the 50-ml flask. The two parts were connected (Lubriseal) and the exit tube placed in 50 ml of 0.1 N HCl in a 150-ml beaker. After nitrogen was passed through the system for 15 min, 1 ml of 7.8 N aqueous KOH and 9 ml of 95% EtOH were added through the dropping funnel. The reaction mixture was refluxed gently by heating in a silicone bath (100°), while nitrogen was slowly passed through the apparatus.

At the end of the reaction, the alcohol solution was shaken with 100 ml of water and 300 ml of ether. After three washings with water, the ether solution was concentrated to a solid.[24] This product was dissolved in a minimum of 95% EtOH at about 50° and a saturated solution of 456 mg of H₅IO₆ in 95% EtOH was added to oxidize hydrazo compounds to the azo state. After 5 min at room temperature, the solution was added to water and extracted with ether. The ether solution was washed with water, NaHCO₃ solution, and water. Removal of ether gave a solid, which was extracted with 20-ml portions of boiling hexane. The azo carbonyl compounds and 2-phenylindazole were readily soluble, leaving a solid residue of primary amide and unchanged starting material.

Removal of hexane yielded a solid "A Fraction," which was analyzed as described below under Analyses for Table I.

The hydrolysis products from compounds 3, 4, 5, and 6 were not investigated; it was assumed that the amidazo reaction did not take place with these compounds since no ammonia was evolved. For this series, the reaction times were 3, 1, 7, and 3 hr, respectively.

Analyses for Table I.—Analytical conditions were established with pure reagents as follows. A solution of 4-phenylazobenzaldehyde of mp 120–121° (200 mg) and 4-biphenylamine (177 mg, 10% excess) in 4 ml of HOAc was heated on a steam bath for 30 min. After cooling the reaction mixture to room temperature, the crystalline precipitate of benzylidene derivative was filtered on a tared funnel. The yield was 97.4% (335 mg). Recrystallization from acetic acid raised the melting point of the N-p-phenylazobenzylidene-4-biphenylamine only 1° to 218–219°.

Anal. Calcd for C₂₅H₁₉N₃: C, 83.08; H, 5.30; N, 11.73. Found: C, 82.9; H, 5.53; N, 11.4.

The above conditions were used in the analysis of the A fractions obtained from the compounds in Table I, 50 mg of material being used if available. All of the benzylidene derivatives showed satisfactory melting points (215–218°) without recrystallization. The yields were not corrected for losses inherent in the method of analysis.

Analyses for Table II.—For compounds 33–37, an analytical method based on the following was used. A solution of pure p-phenylazoacetophenone (50 mg, mp 115–116°) and 2,4-dinitrophenylhydrazine (49 mg, 10% excess) in 0.5 ml of HOAc containing 2 drops of concentrated HCl was heated on a steam bath for 10 min and then cooled to room temperature. The product was filtered and weighed (84.3 mg, 93.5%). The p-phenylazoacetophenone-2,4-dinitrophenylhydrazone melted at 244–245°.

Anal. Calcd for C₂₀H₁₆N₆O₄: C, 59.39; H, 3.99; N, 20.78. Found: C, 59.0; H, 4.15; N, 21.0.

The analyses were uncorrected for the inaccuracy of the analytical method.

For compounds 38–40, p-phenylazobenzophenone was isolated from the A fractions and compared with an authentic sample of mp 104–105°.

Results for Compound 41.—A 65% yield of ammonia was obtained in this 8-hr reaction. Fraction A was a black tar with an odor of naphthalene. With 4-biphenylamine it gave a small yield of a black product (mp 150–160°), which was not investigated further.

Results for Compound 42.—This 8-hr reaction gave a 17% yield of ammonia; no definite products were isolated from fraction A.

Analyses for Table III.—Except for compounds 49, 51, and 52, the A fractions were condensed with 4-biphenylamine as described under Analyses for Table I.

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(21) S. Gabriel and R. Jansen, *ibid.*, **23**, 2807 (1890).

(22) S. Gabriel and R. Jansen, *ibid.*, **24**, 3091 (1891).

(23) G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, 1158 (1906).

(24) For compounds **49, 51,** and **52,** this solid was used directly, without further treatment for determination of the amount of unchanged starting material.

Compound 43.—*p*-Tolylazobenzylidene-4-biphenylamine had mp 201–203°.

Anal. Calcd for C$_{26}$H$_{21}$N$_3$: C, 83.17; H, 5.64; N, 11.19. Found: C, 83.5; H, 5.93; N, 11.2.

Compound 44.—*N*-4-Biphenylazobenzylidene-4-biphenylamine melted at 292–295°.

Anal. Calcd for C$_{31}$H$_{23}$N$_3$: C, 85.10; H, 5.30; N, 9.60. Found: C, 84.7; H, 5.74; N, 9.34.

Compound 45.—*N*-*p*-Chlorophenylazobenzylidene-4-biphenylamine melted at 235–237°.

Anal. Calcd for C$_{25}$H$_{18}$ClN$_3$: C, 75.85; H, 4.58; N, 10.61. Found: C, 76.2; H, 4.78; N, 10.5.

Compound 46.—*N*-*p*-Methoxyphenylazobenzylidene-4-biphenylamine of mp 211–213° was obtained. See compound 50 for analytical data.

Compound 47.—*N*-*p*-Benzyloxyphenylazobenzylidene-4-biphenylamine melted at 232–234°.

Anal. Calcd for C$_{32}$H$_{25}$N$_3$O: C, 82.20; H, 5.39; N, 8.99. Found: C, 81.9; H, 5.29; N, 8.84.

Compound 48.—*N*-*p*-Mercaptomethylphenylazobenzylidene-4-biphenylamine melted at 231–233°.

Anal. Calcd for C$_{26}$H$_{21}$N$_3$S: C, 76.63; H, 5.19; N, 10.31. Found: C, 76.3; H, 5.32; N, 10.4.

Compound 49.—A 98% recovery of unchanged starting material (mp 230–232°) was obtained.

Compound 50.—*N*-*p*-Methoxyphenylazobenzylidene-4-biphenylamine melted at 212–213°.

Anal. Calcd for C$_{26}$H$_{21}$N$_3$O: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.3; H, 5.54; N, 10.3.

Compound 51.—Acetylation of the product of this reaction gave a 91% yield of a compound of mp 227–230°, which was shown to be 1-acetaminomethylbenzene-4-azo-4'-acetaminobenzene-1 by comparison with an authentic sample of mp 230–231°.

Anal. Calcd for C$_{17}$H$_{18}$N$_4$O$_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.6; H, 5.96; N, 17.7.

Compound 52.—An 82% yield of unchanged starting material (mp 205–207°) was obtained.

Compound 53.—*N*-*m*-Trifluoromethylphenylazobenzylidene-4-biphenylamine melted at 177–178°.

Anal. Calcd for C$_{26}$H$_{18}$F$_3$N$_3$: C, 72.72; H, 4.23; N, 9.79. Found: C, 72.8; H, 4.48; N, 9.84.

Compound 54.—*N*-*o*-Tolylazobenzylidene-4-biphenylamine melted at 169–170°.

Anal. Calcd for C$_{26}$H$_{21}$N$_3$: C, 83.17; H, 5.64; N, 11.19. Found: C, 83.2; H, 6.09; N, 11.4.

Compound 55.—*N*-*o*-Methoxyphenylazobenzylidene-4-biphenylamine melted at 154–156°.

Anal. Calcd for C$_{26}$H$_{21}$N$_3$O: C, 79.77; H, 5.41; N, 10.73. Found: C, 80.0; H, 5.52; N, 10.7.

Compound 56.—*N*-*o*-Biphenylazobenzylidene-4-biphenylamine melted at 178–179°.

Anal. Calcd for C$_{31}$H$_{23}$N$_3$: C, 85.10; H, 5.30; N, 9.60. Found: C, 85.2; H, 5.65; N, 9.43.

Compound 57.—*N*-*p*-α-Naphthylazobenzylidene-4-biphenylamine melted at 177–178°.

Anal. Calcd for C$_{29}$H$_{21}$N$_3$: C, 84.85; H, 4.91; N, 10.24. Found: C, 84.7; H, 5.28; N, 10.1.

Analyses for Table IV.—For compounds 58–62, an analytical method based on the following was used. 2,4-Dinitrobenzenesulfonic acid (153 mg, 0.000617 mol) was dissolved in 30 ml of dry ether. This solution was added dropwise to a solution of 2-phenylindazole (100 mg, 0.000515 mol) in 5 ml of dry ether. The precipitate of fine needles was separated (221 mg, 97.2% yield, mp 177–179°). Crystallization from absolute EtOH gave pure **2-phenylindazole 2,4-dinitrobenzenesulfonate** (mp 180–181°).

Anal. Calcd for C$_{19}$H$_{14}$N$_4$O$_7$S: C, 51.58; H, 3.19; N, 12.67. Found: C, 51.2; H, 3.34; N, 12.4.

Action of Alcoholic KOH on *p*-Phenzylazobenzylamine.—A mmol of *p*-phenylazobenzylamine (as carbamate) was hydrolyzed for 3 hr under amidazo reaction conditions. A 20% yield of NH$_3$ was obtained.

Synthesis of Isonitriles[1]

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A convenient synthesis of isonitriles has been devised using a N,N-dimethylformamide (DMF) solution of chlorodimethylformiminium chloride, prepared *in situ* from thionyl chloride and DMF, to dehydrate a variety of formamides. This general procedure enables one to prepare aliphatic, alicyclic, vinylic, and aromatic isonitriles in excellent yields. The reduction of isocyanates with lithium tri-*tert*-butoxylaluminum hydride to yield formamides is described.

Of the many methods available for the preparation of isonitriles,[2] those that appear to have the most general application involve the reaction of alkyl halides with heavy metal cyanide salts,[3] the addition of dichlorocarbene to amines, the reduction of isocyanates and isothiocyanates,[4] the copper-catalyzed addition of hydrogen cyanide to tertiary olefins,[5] and the dehydration of formamides.[6] This final method has provided the most convenient approach using reagents such as tosyl chloride,[6,7] phosphorus oxychloride,[8] cyanuryl chloride,[9] and triphenylphosphine–carbon tetrachloride[10] to effect the dehydration. By far the most preferred dehydrating procedure is that of Ugi,[2,11] who used phosgene in the presence of a tertiary amine.

To circumvent the use of phosgene, chlorodimethylformiminium chloride[12] (1) (Vilsmeier reagent[13]) was selected as a possible dehydrating agent for the preparation of isonitriles from formamides. This reagent 1 can readily be prepared, *in situ*, from thionyl chloride and N,N-dimethylformamide (DMF). Although isonitriles have been shown[14] to react with this reagent,
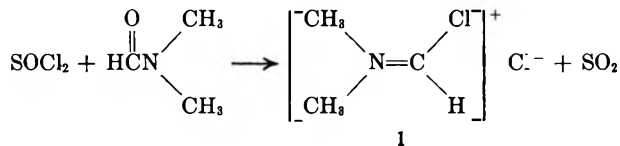
it was hoped that in the presence of a suitable base its dehydrative properties could be utilized.

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(2) For an excellent review of the various methods to prepare isonitriles, see I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offerman, *Angew. Chem., Int. Ed. Engl.*, **4**, 472 (1965); I. Ugi, "Organic Chemistry," Vol. 20, Academic Press, New York, N. Y., 1971.

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(8) I. Ugi, R. Meyr, and M. Lipinski, *Org. Syn.*, **41**, 41 (1961).

(9) R. Wittman, *Angew. Chem.*, **73**, 219 (1961).

(10) R. Appel, R. Kleinstuck, and K.-D. Ziehn, *Angew. Chem., Int. Ed. Engl.*, **10**, 132 (1971).

(11) I. Ugi, W. Betz, U. Fetzer, and K. Offerman, *Chem. Ber.*, **94**, 2814 (1961); I. Ugi and F. Bodesheim, *ibid.*, **94**, 1157 (1961).

(12) O. Wallach and M. Hoffmann, *Justus Liebigs Ann. Chem.*, **184**, 75 (1877).

(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 286, and references cited therein.

(14) Y. Ito, M. Okano, and R. Oda, *Tetrahedron*, **22**, 447 (1966).

Cyclohexylformamide was used as the model compound. When an equivalent of 1 in DMF was added to a DMF solution of cyclohexylformamide in the presence of triethylamine at 0°, the solution darkened. Although the characteristic isonitrile odor was evident, only a trace of isonitrile and starting formamide was isolated upon work-up of the reaction mixture. Higher temperatures did not improve the yield.

The low yield obtained was assumed to be due to the following factors. First, the isonitrile, once formed, could react with 1 as previously reported[14] (eq 2b). Second, although triethylamine reacts with hydrochloric acid, DMF likewise complexes with the acid so that, in an equilibrium situation, hydrochloric acid is kept in solution (eq 2b). Proton-catalyzed polymerization can result (eq 2e), or hydrochloric acid can add to the isonitrile which, after addition of water, gives back the starting formamide (eq 2c).

$$RNHCHO + [(Me)_2N{=}CHCl]^+ Cl^- \longrightarrow$$
$$RN{=}C + (CH_3)_2NCHO{\cdot}HCl \quad (2a)$$

$$2RN{=}C + [(Me)_2N{=}CHCl]^+ Cl^- \longrightarrow$$
$$(RN{=}CCl)_2CHN(CH_3)_2 \quad (2b)$$

$$RN{=}C + HCl \rightleftharpoons RN{=}C\overset{H}{\underset{Cl}{\diagup}} \overset{H_2O}{\longrightarrow} RNHCHO \quad (2c)$$

$$(CH_3)_2NCHO + R'_3N \rightleftharpoons (CH_3)_2NHCO + R'_3N{\cdot}HCl \quad (2d)$$

$$nRN{=}C + H^+ \longrightarrow [RN{=}C{<}]_n \quad (2e)$$
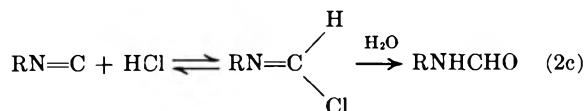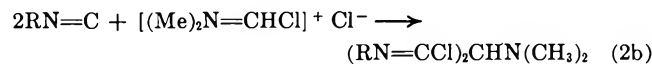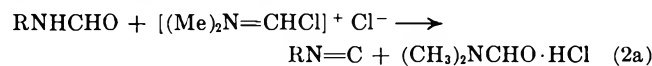
In order to circumvent reaction 2b, low temperatures (*ca.* −50°) were used. This was to allow the intermediate adduct 2 (eq 3) to form without decomposing

$$RNHCHO + 1 \xrightarrow{-50°} RN{=}C\overset{H}{\underset{H}{\diagdown}}\overset{OCN(CH_3)_2}{\underset{Cl}{\diagup}} + HCl \quad (3a)$$

$$\mathbf{2}$$

$$HCl + (CH_3)_2NCHO \rightleftharpoons (CH_3)_2NCHO{\cdot}HCl \quad (3b)$$

$$RN{=}C + (CH_3)_2NCHO{\cdot}HCl \quad (3c)$$

$$2Na_2CO_3 + (CH_3)_2NCHO{\cdot}HCl \longrightarrow$$
$$(CH_3)_2NCHO + 2NaCl + 2NaHCO_3 \quad (3d)$$
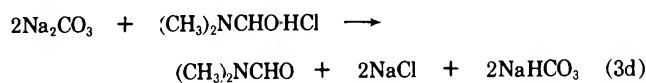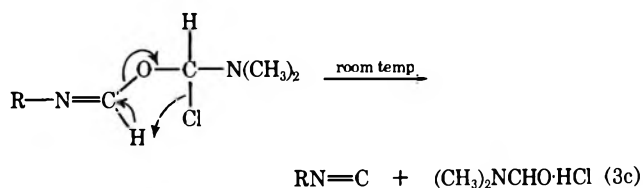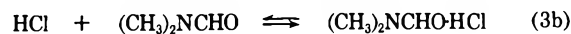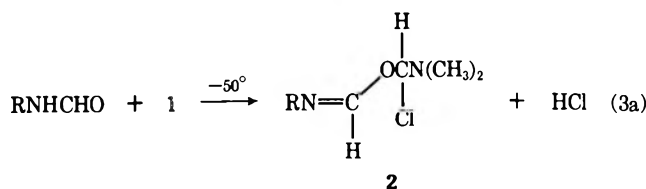
immediately to the products (isonitrile and DMF) before the addition was completed. In this manner it was hoped that, after addition, the intermediate **2** could be decomposed at higher temperatures to give the desired isonitrile. To circumvent reactions 2c and 2d, solid sodium carbonate was added, after the addition of **1** to the formamide was completed, in order to irreversibly consume the hydrochloric acid and completely eliminate it from the reaction mixture. The result was that, as the reaction mixture warmed, it turned a pale yellow (*ca.* −15°) and then colorless (*ca.* 10°). Cyclohexylisonitrile was isolated in 87% yield after distillation.

Isonitrile formation with the Vilsmeier reagent appears to proceed as outlined in eq 3. In reaction 3a, the Vilsmeier reagent reacts at −50° with the formamide to produce intermediate **2** and hydrochloric acid, which immediately complexes with DMF (3b). After addition of sodium carbonate, the hydrochloric acid is irreversibly disposed of (3d) so that the elimination 2c can proceed, at ambient temperatures, in a slightly basic medium.

As can be seen from Table I, this procedure provides a general, convenient method for the preparation of iso-

RNC	Registry no.	Yield, %	Reaction scale, mol
Aliphatic			
n-Hexyl[a]		82	0.13
Cyclohexyl[b]		87	0.10
tert-Butyl[b]		55	0.20
1,1,3,3-Tetramethylbutyl[c]	14542-93-9	93	0.53
Benzylic			
Benzyl[b]		63	0.12
(*R*)-(+)-2-Phenyl-2-butyl	32528-86-2	92	0.04
1,1-Diphenylethyl	32528-87-3	90	0.08
Trityl[d]		95	0.27
		94	0.06
Cyclopropyl			
(*R*)-(−)-2,2-Diphenyl-1-methylcyclopropyl	32528-88-4	88	0.019
	32528-89-5[f]	70	0.003
Vinyl			
(*E*)-1,2-diphenylvinyl	32528-90-8	84	0.06
Aromatic			
Phenyl[b]		60	0.18
2,6-Dimethylphenyl[b]		74	0.11
p-Methoxyphenyl[e]		82	0.18
1-Naphthyl[b]		72	0.04

[a] M. Lipp, F. Dallacker, and I. M. Kocker, *Monatsh. Chem.*, 90, 41 (1959). [b] See ref 3. [c] See ref 5. [d] N. E. Alexander, *J. Org. Chem.*, 30, 1335 (1965). [e] I. Ugi and R. Meyr, *Chem. Ber.*, 93, 239 (1960). [f] ± isomer.

nitriles. Cyclic, acyclic, benzylic, cyclopropyl, vinylic, and aromatic isonitriles have been prepared in very good yields. Optically active isonitriles have also been prepared.

The amides used in this work were usually obtained by the conventional formylation of the amine precursor using formic acid or *S*-ethyl thioformate. However, when the amine was not stable, *i.e.*, 1-amino-2,2-di-

phenyl-1-methylcyclopropane, or when the amine was not available as in the case of vinyl amines, then the amides were prepared by the reduction of isocyanates with lithium tri-*tert*-butoxylaluminum hydride. The reduction of isocyanates to formamides by lithium tri-*tert*-butoxylaluminum hydride was alluded to when it was reported[15] that 1 equiv of the hydride was consumed by phenyl isocyanate at 0°. However, isocyanates are known to dimerize and trimerize under mild basic conditions.[16] We have found that phenyl isocyanate with sodium borohydride in DMF results not in reduction but rather trimerization. Moreover, we have observed that the reduction of 1-methyl-2,2-diphenylcyclopropyl isocyanate with lithium tri-*tert*-butoxylaluminum hydride at ambient temperature did not produce the desired formamide but instead a compound (83% yield) whose physical data (see Experimental Section) were consistent with the structure **3**.
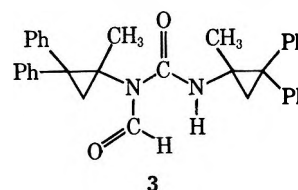
3

When reduction was carried out at a low temperature (−15°), the desired formamide was obtained in 85% yield.

Experimental Section

Materials.—Industrial grade dimethylformamide (DMF) was purified by distilling a forecut at atmospheric pressure and then collecting the rest at 30–40 mm from barium oxide. Reagent grade tetrahydrofuran (THF) was distilled from lithium aluminum hydride. Bulk solvents were distilled before use. All other reagent grade materials were used as received from the commercial supplier unless further purification was judged necessary.

1,1,3,3-Tetramethylbutylisonitrile (TMBI).—The following procedure was used to prepare all the isonitriles reported in Table I.

To a stirred solution of 83 g (0.528 mol) of *N*-(1,1,3,3-tetramethylbutyl)formamide[17] in 1 l. of DMF was added, under a nitrogen atmosphere, a solution of 40.3 ml (0.55 mol) of thionyl chloride dissolved in 150 ml of DMF at a rate so that the temperature never exceeded −50°. After addition, the bath was removed momentarily to allow the temperature to rise to −35°;[18] then it was replaced, and 118 g (1.11 mol) of anhydrous sodium carbonate was added. The bath was removed, and the reaction was stirred from 6 to 16 hr, during which time the temperature rose to 25°.[19] The mixture was diluted with ice-cold water in a separatory funnel and extracted into pentane. The extract was dried over sodium sulfate, evaporated, and distilled to yield 68.4 g (0.49 mol, 93%) of the isonitrile: bp 55.5–56.6° (11 mm) [lit.[5] bp 96–97° (69 mm)]; n^{30}D 1.4178 (lit.[5] n^{20}D 1.4214); d^{25} 0.7944; ir (neat) 2110 cm⁻¹ (s); nmr (neat) δ 1.08 [s, 9, C(CH₃)₃], 1.43 [t, 6, J = 2 Hz, C(CH₃)₂], 1.58 (t, 2, J = 2.3 Hz, CH₂).

(*R*)-(+)-2-Amino-2-phenylbutane.[20]—To a solution of 6.8 g (0.0382 mol) of (*R*)-(−)-2-methyl-2-phenylbutanoic acid[21] [[α]^{24}₅₄₆₁ −33.6 ± 0.4° (*c* 2, benzene); mp 84–86°] in 90 ml of acetone and 6.1 ml (0.043 mol) of triethylamine was added 4.2

(15) H. C. Brown and P. M. Weisman, *Isr. J. Chem.*, 1, 430 (1963).

(16) P. A. S. Smith, "The Organic Chemistry of Open-Chain Nitrogen Compounds," W. A. Benjamin, New York, N. Y., 1965.

(17) H. B. Henbest and M. J. W. Strattford, *J. Chem. Soc. C*, 995 (1966).

(18) For primary and secondary aliphatic and aromatic formamides, −45° is recommended.

(19) Alternatively, the reaction mixture was heated to 35° with rapid stirring and then stirring was continued at ambient temperature for 1 hr.

(20) D. J. Cram and J. S. Bradshaw, *J. Amer. Chem. Soc.*, 85, 1108 (1963).

(21) The acid was prepared and resolved according to the procedure of D. J. Cram and J. D. Knight, *ibid.*, 74, 5835 (1952).

ml (0.043 mol) of ethyl chloroformate dissolved in 10 ml of acetone at −10°.[22] After stirring for 2 hr, 4.2 g (0.065 mol) of NaN₃ in 45 ml of water was added dropwise. The mixture was stirred for an additional 4 hr, taken up in pentane, and extracted first with dilute hydrochloric acid and then with a sodium carbonate solution. After drying (sodium sulfate), the pentane was evaporated and the residue was placed in a vacuum desiccator for 4 hr. The crude azide was decomposed in refluxing benzene (5 hr) under a nitrogen atmosphere, the mixture was cooled to 0°, and 40 ml of concentrated hydrochloric acid was added dropwise. Stirring was continued at 10° for 48 hr, and the reaction mixture was then transferred to a separatory funnel, diluted with water, and extracted with ether. The aqueous layer was neutralized, and the amine was extracted into ether which was dried (sodium carbonate) and evaporated to give 4.8 g of material. Distillation yielded 4.1 g (0.0275 mol, 72%) of the optically pure amine: bp 58° (2.2 mm), 69° (3.7 mm) [lit.[20] bp 50–52° (2 mm)]; [α]²⁴₅₄₆₁ +18.1 ± 0.3° (*c* 3, benzene).

N-(1,1-Diphenylethyl)formamide.—A solution of 30 g (0.152 mol) of 1-amino-1,1-diphenylethane[23] (prepared in 62% yield from 1,1-diphenylpropanoic acid[24] using the above procedure), 20 ml (0.35 mol) of 88% formic acid, and 150 ml of toluene was refluxed and the water removed with the aid of a Dean–Stark apparatus. Evaporation to dryness and recrystallization of the residue from ethanol–water yielded 17.1 g (0.076 mol, 50%) of the formamide: mp 109.5–112°; ir (CCl₄) 3420 (w), 3382 (w), 3200 (broad), 1690 (s), 1596 (w), 1494 (w), 1447 (m), 693 cm⁻¹ (s); nmr (CDCl₃) δ 1.97 and 2.13 (s, 3, CH₃, ratio 1.5:1.0), 6.7 and 7.4 (broad s, 1, NH, ratio 1:1.4), 7.12 and 7.16 (s, 10, aromatic, ratio 7.12 < 7.16), 7.75 and 7.94 (s, 1, CHO, ratio 1:1.4).

Anal. Calcd for C₁₅H₁₅NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.95; H, 6.70; N, 6.33.

(R)-(+)-N-(1-Methyl-1-phenylpropyl)formamide.—To a refluxing solution of 7.10 g (0.0476 mol) of optically pure (R)-(+)-2-amino-2-phenylbutane in 50 ml of THF, in a flask equipped with a distilling column having an adjustable reflux control, was added a solution of 4.29 g (0.0476 mol) of S-ethyl thioformate in 25 ml of THF. Ethanethiol was removed as formed by regulating the reflux ratio. After the reflux temperature reached a constant level (65° for 4 hr), the excess THF was evaporated. The residual oil was taken up in methylene chloride, washed with diluted hydrochloric acid and sodium bicarbonate solution, and dried over magnesium sulfate. Removal of the solvent afforded 7.85 g (0.0443 mol, 93%) of analytically pure formamide: [α]²⁴₅₄₆₁ +9.37 ± 0.09° (*c* 4, dioxane); bp 82.5° (0.015 mm); ir (CCl₄) 3420 (w), 3390 (w), 3200 (m, broad), 2750 (w), 1688 (s), 692 cm⁻¹ (s); nmr (CCl₄) δ 0.66 and 0.78 (t, 3, J = 7 Hz, CH₃, ratio 0 78 > 0.66), 1.55 and 1.57 (s, 3, CH₃, ratio 1.57 > 1.55), 1.8 (m, 2, CH₂), 7.03 and 7.17 (s, 5, aromatic, ratio 7.03 > 7.17), 7.33 and 8.12 (s, broad, 1, NH, ratio 2:1), 7.6–7.7 (m, 0.66, CHO), 7.87 (s, 0.33, CHO).

Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.78; H, 8.61; N, 7.95.

(±)-1-Carbazido-2,2-diphenyl-1-methylcyclopropane.—Following the above procedure, 19.8 g (0.0785 mol) of racemic 2,2-diphenyl-1-methylcyclopropanecarboxylic acid[25] together with 13.5 ml (0.097 mol) of triethylamine in 200 ml of acetone was treated with 8.7 ml (0.091 mol) of ethyl chloroformate in 30 ml of acetone and then with 9.8 g (0.15 mol) of sodium azide in 98 ml of water to yield 20.8 g of the crude azide. The azide was dissolved in 150 ml of pentane (25°), then cooled slowly to −78°. After decanting the pentane, the crystals were dried in a vacuum desiccator: yield 19.5 g (0.074 mol, 90%); mp 62–63° dec; ir (CCl₄) 2133, 1710, 1697, 1180, 1025 cm⁻¹; nmr (CCl₄) δ 1.15 (s, 3, CH₃), 1.45 (d, 1, J = 5 Hz, HCH), 2.30 (d, 1, J = 5 Hz, HCH), 7.1–7.6 (m, 10 aromatic).

Anal. Calcd for C₁₇H₁₅N₃O: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.42; H, 5.41; N, 14.98.

(R)-(−)-1-Carbazido-2,2-diphenyl-1-methylcyclopropanecarboxylic Acid.—Similarly, 7.61 g (0.03 mol) of (R)-(+)-2,2-diphenyl-1-methylcyclopropanecarboxylic acid, [α]²⁴₅₄₆₁ +43.1° (*c* 2.3, CHCl₃), gave 7.83 (0.03 mol) of the crude azide, which was recrystallized from pentane to yield 7.36 g (0.0266 mol, 88%): mp 57–59° dec; [α]²⁴₅₄₆₁ −47.4 ± 0.2° (*c* 2, CHCl₃).

Anal. Calcd for C₁₇H₁₅N₃O: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.81; H, 5.52; N, 15.11.

(E)-2,3-Diphenylpropenoyl Azide.—In a like manner, 24.1 g (0.107 mol) of (E)-2,3-diphenylpropenoic acid[26] gave a solution of the vinyl azide in acetone at −15°. The cold mixture was taken up in ether, diluted with water (0°), washed with ice-cold acid and base solutions, then dried over sodium sulfate at −10°. Evaporation (0°) of the solvent followed by low-temperature vacuum drying gave 24.8 g of the crude azide, mp 62–65° dec. Recrystallization was accomplished from a 50:50 methylene chloride–pentane mixture by dissolving the azide at 10–15° in a minimum amount of solvent followed by cooling in a Dry Ice–acetone bath to yield 23.2 g (0.093 mol, 87%) of the pure azide:[27] mp 68–70° dec; ir (CCl₄) 3060, 2130 (s), 1692 and 1683 (s), 1616 (m), 1372 (m), 685 cm⁻¹ (s); nmr (CDCl₃) δ 6.8–7.6 (m, 10, aromatic), 7.87 (s, 1, vinyl).

(±)-N-(2,2-Diphenyl-1-methylcyclopropyl)formamide.—A solution of 18.5 g (0.067 mol) of racemic 1-carbazido-2,2-diphenyl-1-methylcyclopropane in benzene was refluxed for 6 hr to yield 16.6 g (0.066 mol) of the isocyanate (a thick oil), ir (CCl₄) 6124, 4500, 2265 cm⁻¹. The isocyanate was transferred to an addition funnel with 100 ml of anhydrous THF and added slowly (3 hr) to a solution of 25 g (0.1 mol) of lithium tri-tert-butoxyaluminum hydride in 150 ml of THF at −15°. After 2 hr of additional stirring, 50 ml of 50% formic acid was added dropwise with fast mechanical stirring (−15°). The mixture was taken up in ether, washed with dilute hydrochloric acid and saturated sodium carbonate solution, and dried over magnesium sulfate. Evaporation of the solvent gave 17 g of the crude formamide, which was crystallized from chloroform–hexane to yield 14.2 g (0.57 mol, 85%), mp 114–114.5°. Recrystallization gave the pure formamide: mp 115.5–116.5°; ir (CCl₄) 3415 (w, doublet), 2750 (w), 1704 (s), 1215 cm⁻¹ (s); nmr δ 1.41 (s, 3, CH₃), 1.3–1.9 (m, 2, CH₂), 5.95 (s, broad, 1, NH), 7.1–7.7 (m, 10, aromatic), 7.82 (1, CHO).

Anal. Calcd for C₁₇H₁₇NO: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.31; H, 6.97; N, 5.55.

(R)-(−)-N-(2,2-Diphenyl-1-methylcyclopropyl)formamide.—Similarly, 4.14 g (0.015 mol) of optically pure (R)-(−)-1-carbazido-2,2-diphenyl-1-methylcyclopropane yielded 3.1 g (0.012 mol) of the formamide, mp 138–140°, [α]²⁴₅₄₆₁ −99.1 ± 0.5° (*c* 1, CHCl₃).

Anal. Calcd for C₁₇H₁₇NO: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.31; H, 6.86; N, 5.56.

(E)-N-(1,2-Diphenylvinyl)formamide.—In like manner, 19.2 g (0.077 mol) of (E)-2,3-diphenylpropenoyl azide was refluxed in 150 ml of hexane for 4 hr to give the isocyanate: ir (neat) 3055, 2255 (s), 1635 (m), 1359 (m), 989, 691 cm⁻¹ (s). Reduction with lithium tri-tert-butoxyaluminum hydride yielded 16.9 g (0.0757 mol, 98%), mp 106–108°. Recrystallization from chloroform–petroleum ether (bp 30–60°) gave 16.2 g (0.0727 mol, 94%): mp 109–110°; ir (CCl₄) 3420 and 3390 (w), 3195 (w, broad), 2965 (w), 2870 (w, broad), 1704 and 1693 (s), 1635 (m), 1371 (m), 688 cm⁻¹ (m); nmr (CDCl₃) δ 6.32 (s, 1, vinyl), 6.7–7.5 (m, 10, aromatic), 8.1–8.6 (m, 2, -NHCHO).

Anal. Calcd for C₁₅H₁₃NO: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.64; H, 5.95; N, 6.30.

Reduction of (R)-2,2-Diphenyl-1-methylcyclopropyl Isocyanate at 25°.—In a similar manner, the (R)-cyclopropyl isocyanate [prepared from 7.11 g (0.0256 mol) of the (R)-(−)-cyclopropyl azide] was added to a THF solution of 9.8 g (0.038 mol) of lithium tri-tert-butoxyaluminum hydride at 25°. Crystallization of the product afforded 5.29 g (0.021 mol, 83%) of a compound whose physical data were consistent with 3: mp 177.5–179.5°; [α]²⁴₅₄₆₁ −267 ± 2° (*c* 1, CHCl₃); ir (CCl₄) 3278 (m), 1716 (s), 1681 (m), 1515 cm⁻¹ (m); nmr (CDCl₃) δ 1.2–2.2 (m, 10), 6.3–8.6 (m, 22); mass spectrum (70 eV) m/e 500 (P), 472 (P − CO).

Anal. Calcd for C₃₄H₃₂N₂O₂: C, 81.57; H, 6.44; N, 5.48. Found: C, 81.67; H, 6.43; N, 5.57.

1,1-Diphenyl-1-ethylisonitrile.—Following the general procedure, 18.1 g (0.080 mol) of N-(1,1-diphenylethyl)formamide in 300 ml of DMF was treated with 5.2 ml (0.084 mol) of thionyl chloride in 15 ml of DMF and 18 g (0.17 mol) of sodium carbonate to give after distillation 15.0 g (0.73 mol, 90%) of the isonitrile: bp 74–75° (0.025 mm); ir (neat) 2120 (s), 1598 (m), 1493 (s),

(22) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

(23) I. Heilbron, "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1965.

(24) P. L. Pickard and E. F. Engles, *J. Amer. Chem. Soc.*, **73**, 864 (1951).

(25) H. M. Walborsky, L. Barash, A. E. Young, and F. J. Impastato, *ibid.*, **83**, 2517 (1961).

(26) R. E. Buckles and K. Bremer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 777.

(27) The azide decomposes slowly at room temperature to the isocyanate.

1447 (s), 690 cm^{-1} (s); nmr (CCl$_4$) δ 1.97 (s, 3, CH$_3$), 6.9–7.35 (m, 10, aromatic).

Anal. Calcd for C$_{15}$H$_{13}$N: C, 86.92; H, 6.32; N, 6.76. Found: C, 87.02; H, 6.44; N, 6.56.

(*R*)-(+)-2-Phenyl-2-butylisonitrile.—Following the general procedure, 7.85 g (0.044 mol) of (*R*)-(+)-*N*-(1-methyl-1-phenyl-propyl)formamide in 150 ml of DMF yielded, after distillation, 6.51 g (0.041 mol, 92%) of the optically pure isonitrile: bp 96.97° (9 mm); [α]$^{24}_{5461}$ +2.87 ± 0.07° (*c* 3, dioxane); ir (neat) 2125 (s), 1498 (m), 755 (s), 692 cm^{-1} (s); nmr (CCl$_4$) δ 0.84 (t, 3, *J* = 7 Hz, CH$_3$), 1.67 (t, 3, *J* = 2 Hz, CH$_3$), 1.90 (m, 2, J_{AB} = 7 Hz, J_{AC} = 2 Hz, CH$_2$), 7.40 (m, 5, aromatic).

Anal. Calcd for C$_{11}$H$_{13}$N: C, 82.97; H, 8.23. Found: C, 83.08; H, 8.45.

(*E*)-1,2-Diphenylvinylisonitrile.—Similarly, 14.2 g (0.0637 mol) of (*E*)-*N*-(1,2-diphenylvinyl)formamide in 400 ml of DMF was treated with the DMF–SOCl$_2$ reagent, however, at −60°. The mixture was allowed to stir at −50° for 10 min prior to the addition of sodium carbonate. The mixture was taken up in 50:50 ether–pentane for the washings, and the organic layer was dried over sodium sulfate. Evaporation of the solvent gave 10.9 g (0.0532 mol, 84%) of the isonitrile, bp 109° dec (0.03 mm), which contained only a trace of the formamide. Prior to use small quantities were purified by molecular distillation at high vacuum to prevent decomposition (the isonitrile darkens on standing): ir (neat) 2105 (s), 1620 (w), 1372 (m), 689 cm^{-1}; nmr (CDCl$_3$) δ 6.94 (s, vinyl), 6.9–7.5 (m, aromatic). Mass spectral data are shown in Table II.

Anal. Calcd for C$_{15}$H$_{11}$N: C, 87.77; H, 5.40; N, 6.83. Found: C, 87.46; H, 5.44; N, 6.68.

(±)-2,2-Diphenyl-1-methylcyclopropylisonitrile.—In a like manner, 4.68 g (0.0187 mol) of racemic *N*-(2,2-diphenyl-1-methylcyclopropyl)formamide in 93 ml of DMF was treated with the thionyl chloride–DMF reagent. After the mixture had stirred for 16 hr, the contents of the flask were rinsed into a beaker with THF; 400 ml of cold water was added slowly at 0°. The precipitate was collected, washed with water, and dried to yield 4.35 g of material, mp 109–115°. Crystallization from chloroform–petroleum ether gave 3.84 g (0.017 mol, 88%) of the isonitrile: mp 118–129°; ir (CCl$_4$) 2120 (s), 1494 (s), 684 cm^{-1} (s); nmr

TABLE II

Peak	Obsd mass	Calcd mass	Anal.	Rel intensity
P + 1	206.0913	206.0924	C^{13}C$_{14}$H$_{11}$N	19.7
P	205.0884	205.0890	C$_{15}$H$_{11}$N	100.0
P − H	204.0788	204.0812	C$_{15}$H$_{10}$N	92.4
P − HCN	178.0745	178.0782	C$_{14}$H$_{10}$	32.4
P − C$_7$H$_5$N	102.0430	102.0469	C$_8$H$_6$	24.5
P − C$_8$H$_6$N	89.0378	89.0391	C$_7$H$_5$	23.6

(CDCl$_3$) δ 1.38 (s, 3, CH$_3$), 1.56 (d, 1, J_{AB} = 6 Hz, HCH), 1.93 (d, 1, J_{AB} = 6 Hz, HCH), 7.1–7.9 (m, 10, aromatic).

Anal. Calcd for C$_{17}$H$_{15}$N: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.47; H, 6.58; N, 5.94.

(*R*)-(−)-2,2-Diphenyl-1-methylcyclopropylisonitrile.—Similarly, 0.8354 g (0.00329 mol) of optically pure (*R*)-(−)-*N*-(2,2-diphenyl-1-methylcyclopropyl)formamide in 25 ml of DMF was treated with 0.28 ml (0.038 mol) of thionyl chloride in 1.5 ml of DMF followed by 0.81 g (0.0076 mol) of sodium carbonate. The precipitate, 0.726 g, mp 140–149°, was crystallized from benzene–petroleum ether: yield 0.537 g (0.00231 mol, 70%); mp 150.5–152°; [α]$^{25}_{5461}$ −166 ±1° (*c* 1, CHCl$_3$).

Anal. Calcd for C$_{17}$H$_{15}$N: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.47; H, 6.58; N, 5.94.

The Base-Catalyzed Dehydrohalogenation of Two Isomeric 3,4-Dibromo-2-ethoxytetrahydropyrans[1]

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The reactions of the two isomers, 3α,4β-dibromo-2α-ethoxytetrahydropyran (1a) and 3α,4β-dibromo-2β-ethoxytetrahydropyran (1b), with refluxing ethanolic sodium ethoxide have been examined. Total yields of isolable products were 19–38%. Compound 1a afforded *trans*-5,6-diethoxy-5,6-dihydro-2*H*-pyran (6), *cis*-2,5-diethoxy-5,6-dihydro-2*H*-pyran (7c), and *trans*-2,5-diethoxy-5,6-dihydro-2*H*-pyran (7t) in the relative proportion 5.6:4.8:1.6, along with a trace of 3-bromo-2-ethoxy-5,6-dihydro-2*H*-pyran (2). Compound 1b furnished the same products 6, 7c, 7t, and 2 in the relative proportion 1:1:16:6. The diethoxydihydropyrans were stable under the reaction conditions, but compound 2 reacted further to produce 6, 7c, and 7t in the proportion 1.4:3.5:22.9.

It has been reported[4] that the reaction of hot ethanolic potassium hydroxide or sodium ethoxide with a mixture of the two isomers of 3,4-dibromo-2-ethoxytetrahydropyran 1a and 1b produces in poor yield a mixture containing 3-bromo-2-ethoxy-5,6-dihydro-2*H*-pyran (2) and a compound suggested to be 2,4-diethoxy-5,6-dihydro-2*H*-pyran (3) (Scheme I). Prolonged treatment of the mixture of dibromides 1a and 1b under these conditions led to a bromine-free product from

which was isolated by distillation a diethoxydihydropyran 3. Compound 2 was isolated in 50% yield by dropping a solution of 1a and 1b in toluene onto molten potassium hydroxide. Neither of the structures 2 or 3 was definitely established. Compound 2 was assigned its structure on the basis of the analogy to the behavior of α,β-dibromocarbonyl compounds in dehydrobromination reactions. A tentative assignment of the structure of 3 was based on the finding that catalytic hydrogenation of 3 gave a diethoxytetrahydropyran 5 (evidence for one double bond in 3) and that acid hydrolysis of 3, followed by phenylhydrazone formation from the hydrolysis product, gave a substance which contained one ethoxy group.

SCHEME I

1a + 1b

KOH, C₂H₅OH Δ

2

3

H₂-Pd/C

4

5
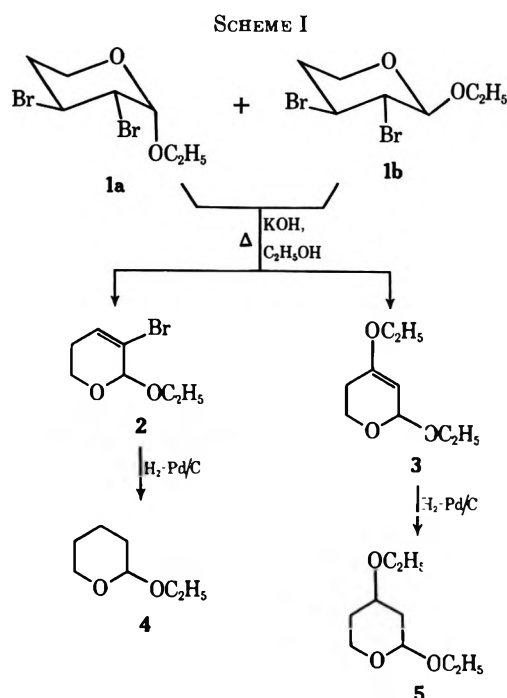
In view of the ease with which enol ethers are hydrolyzed under acidic conditions,[5,6] it is expected that **3** would cleave not only at the acetal function but also at the enol ether linkage, with loss of both ethoxy groups. Hence structure **3** is not consistent with the hydrolysis data.[4]

It is also known that 1,2-dibromocyclohexane, treated with ethanolic base, is converted in reasonably good yield to 3-ethoxycyclohexene.[7] Accordingly under similar conditions, dehydrohalogenation of **1a** and **1b** might be expected to give one or more of the α,β-unsaturated ethers **6–9** as well as the monobromo

6

7

8

9
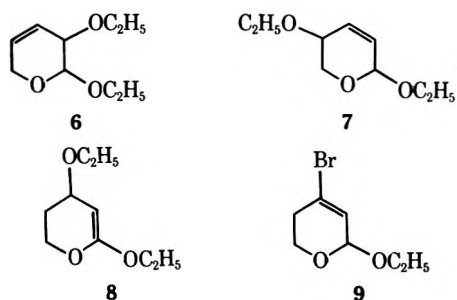
compound **2**. In view of our experience and that of McElvain, *et al.*,[8] that the anomeric proton of acetals is difficult to remove by ordinary bases, the likelihood that **8** is formed seems remote but cannot be ruled out.

Our interest in dihydro- and tetrahydropyrans, as well as the above anomalies, prompted a reexamination of the reactions of the dibromides **1a** and **1b** with alcoholic base. This paper reports the results obtained.

Results and Discussion

The mixture of the two isomeric 3,4-dibromo-2-ethoxytetrahydropyrans **1a** and **1b** was prepared ac-

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(6) A. Ledwith and H. J. Woods, *J. Chem. Soc.*, 753 (1960).

(7) C. J. Gogek, R. Y. Moir, J. A. McRae, and C. B. Purves, *Can. J. Chem.*, **29**, 938 (1951).

(8) S. M. McElvain, R. L. Clarke, and G. D. Jones, *J. Amer. Chem. Soc.*, **64**, 1966 (1942).

cording to published directions.[4,9] Although the minor isomer **1b**, a solid, could be separated readily in pure form by crystallization from a mixture of **1a** and **1b**, the major isomer **1a**, a liquid, was freed from contaminating **1b** only with much difficulty.

When **1a**, contaminated with **1b** to the extent of 10%, was heated for 24 hr in a refluxing solution of sodium ethoxide in dry ethanol, a 30% yield of colorless liquid was obtained by fractional distillation. This was found by gas–liquid chromatography (glc) to consist of four substances in the molar ratio of 2.7:2.3:1:1. These were separated first by preparative glc into three fractions, the first of which was a mixture of the two major products, while the second and third were the two individual minor products. Subsequent glc with a 5-ft column separated the two major products. These four products are shown in Scheme II as compounds **6**, **7c**, **7t**, and **2**, respectively. The proportions obtained are shown in Table I.

TABLE I

MOLAR PROPORTIONS OF PRODUCTS OBTAINED FROM
THE BASE-CATALYZED DEHYDROBROMINATION
OF 1a, 1b, AND 2

Starting material	Reaction conditions[a]	Overall yield, %	Molar proportion of			
			6	7c	7t	2
90% 1a 10% 1b	Δ for 24 hr	30	2.7	2.3	1	1
1a	Δ for 24 hr	19	5.6	4.8	1.6	Trace
1b	Δ for 24 hr	38	1	1	16	6
2	Δ for 24 hr	35	1.4	3.5	22.9	5.7

[a] All reactions were done in ethanol solvent containing sodium ethoxide.

The larger of the two major products was identified as *trans*-5,6-diethoxy-5,6-dihydro-2*H*-pyran (**6**) on the basis of (a) the infrared spectrum which shows no absorption in the region characteristic of vinyl ethers,[10,11] (b) the elemental analysis, (c) agreement of the 100-MHz proton magnetic resonance (pmr) spectrum and its analysis by double irradiation spin decoupling, with structure **6**, and (d) its conversion by catalytic hydrogenation to a compound identical with authentic *trans*-2,3-diethoxytetrahydropyran. The conformation of **6** is considered to be that shown in Scheme II, on the basis of (a) the long-range coupling between H-6 and H-4 requiring the geometric arrangement[12]

H∼∼∼H

which suggests that H-6 must be equatorial, (b) the *anomeric effect*[13] which gives preference to the conformation in which the anomeric alkoxy group is axial or quasiaxial.[13,14]

The smaller of the two major products is considered to be *cis*-2,5-diethoxy-5,6-dihydro-2*H*-pyran (**7c**) on the basis of the following information. (a) The infrared spectrum shows no absorption in the region char-

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(11) M. Sharma and R. K. Brown, *Can. J. Chem.*, **44**, 2825 (1966).

(12) (a) E. W. Garbisch, Jr., *Chem. Ind. (London)*, 1715 (1964); (b) A. Rassat, C. W. Jefford, J. M. Lehn and B. Waegell, *Tetrahedron Lett.*, No. 5, 233 (1964).

(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 375–377.

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SCHEME II

6   7c   7t   2
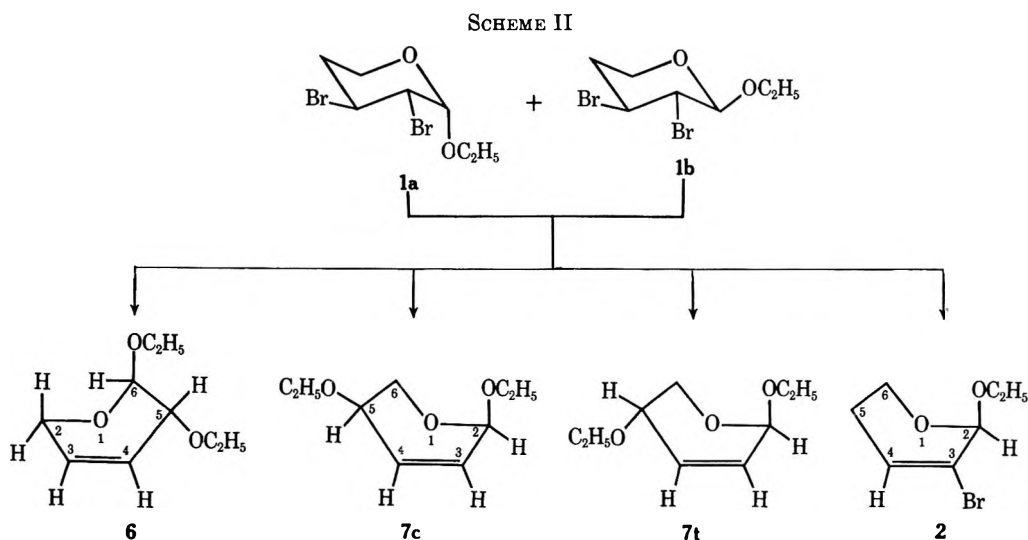
acteristic of vinyl ethers.[10,11]   (b) The elemental analysis agrees with such a structure.   (c) Analysis of the 100-MHz pmr spectrum using double irradiation to locate the signal positions of the various protons agrees with such a structure and shows that the anomeric proton, H-2, is situated on a carbon atom attached to a –HC=CH– group.   As well, the unusually large allylic coupling (~1.8 Hz) between H-3 and H-5 indicates that H-5 is quasiaxial because it is only in such an orientation that the σ–π overlap is maximum, generating such a large allylic coupling.[15a]   (d) The preference for the conformation which has the quasiaxial orientation of the anomeric alkoxy group.[13,14] It is the *cis*- but not the *trans*-2,5-diethoxy-5,6-dihydro-2*H*-pyran which accommodates observations c and d.

The third product obtained in the proportion 1:7 is considered to be *trans*-2,5-diethoxy-5,6-dihydro-2*H*-pyran (7t) on the basis of the following evidence.   (a) Elemental analysis agrees with such a structure.   (b) The infrared spectrum shows no absorption in the region characteristic of vinyl ethers.[10,11]   (c) The mass spectrum showed m/e 171, one unit less than the expected molecular weight.   However, the exceptional ease with which the anomeric hydrogen (H-2) can be removed to provide a resonance-stabilized carbonium ion[15b] would account for this one unit difference.   (d) The preference for the conformation possessing the quasiaxial orientation of the anomeric alkoxy group.[13,14]   (e) The 100-MHz pmr spectrum and spin-decoupling experiments support structure 7t, showing that the anomeric proton H-2 is located on a carbon atom attached to a –CH=CH– group.   A small long-range coupling (~1 Hz) between H-4 and the anomeric proton H-2 indicates that these two protons are in the required

arrangement[12] and hence H-2 is equatorial.   Also, the small couplings of the two C-6 protons, with H-5 ($J_{5,6}$ ax or eq ~ 3 Hz and $J_{5,6}$ eq or ax ~ 2.2 Hz) require H-5 to be gauche to both C-6 protons.   In the conformation in which the anomeric alkoxy group is quasi-

axial, H-5 can be gauche to both C-6 protons only if the C-5 alkoxy group is quasiaxial and hence H-5 is quasiequatorial.   Only structure 7t satisfies the above observations and since compounds 7t and 7c have different retention times on the glc, as well as different pmr spectra, yet their elemental analyses are identical, it is clear that they must be cis and trans isomers.

The last compound was identified as 3-bromo-2-ethoxy-5,6-dihydro-2*H*-pyran (2) on the basis of the following evidence.   (a) The elemental analysis agreed with structure 2.   (b) The mass spectrum gave a signal at m/e 206 with a ^{81}Br satellite signal at m/e 208 of about the same intensity.   (c) The infrared spectrum (neat) shows a band of medium strength of 1650 cm^{-1} for C=CBr.   This agrees with the observation of absorption at 1650 cm^{-1} for the double bond in 1-bromocyclohexene.[16]   (d) The 100-MHz pmr spectrum and its analysis with the aid of double irradiation spin decoupling clearly agrees with structure 2.   The quartet for the lone olefinic proton signal, with couplings of 6.0 and 2.8 Hz with the two high-field protons on C-5, shows that the bromine atom is attached to C-3 and not to C-4.   If the proton were attached to C-3, its signal would be a doublet which might be split again to a small extent (<1.5 Hz) due to long-range or to allylic coupling.   (e) The anomeric effect[13,14] would cause the structure to assume the conformation in which the C-2 alkoxy group is quasiaxial as shown by 2.   (f) Hydrogenation of 2 produces 2-ethoxytetrahydropyran.   The evidence above confirms the structural assignment previously suggested[4] for this monobromo compound.

Following the structural determination of the products obtained from the dehydrohalogenation of 1a containing 10% of 1b, pure 1a was heated for 24 hr in refluxing ethanol containing sodium ethoxide.   A liquid was obtained in 19% yield, analyzing for a mixture of 6, 7c, 7t, and 2 in the proportion 5.6:4.8:1.6: trace.   When the period of reflux was reduced to 8 hr, the crude liquid obtained showed 2 was present in greater than trace amount.

Pure 1b treated similarly for 24 hr gave a liquid (38% yield) which was found to be a mixture of 6, 7c, 7t, and 2 in the proportion 1:1:16:6, respectively.

(15) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Fransisco, Calif., 1964, p 108; (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretations of Mass Spectra of Organic Compounds," Holden-Day, San Fransisco, Calif., 1964, p 52.

(16) G. Chiurdoglu, R. Ottinger, J. Reisse, and A. Toussaint, *Spectrochim. Acta*, 18, 215 (1962).

Finally, although compounds **6**, **7c**, and **7t** were found to be stable to this alkaline treatment, compound **2** was unstable. Pure **2**, heated for 20 hr under the usual alkaline conditions, provided a liquid mixture which contained **6**, **7c**, **7t**, and **2** in the proportion 1.4:3.5:22.9:5.7, along with a small amount (proportion ~1.0) of an unknown material. The above information is assembled in Table I for comparison.

How the dibromides **1a** and **1b** are converted by base to the four products shown in Scheme II is not at all clear. Since **1b** produces a high proportion of **7t** along with a fair quantity of **2** plus a minor amount of **6** and **7c**, and because **2** itself is converted under similar conditions primarily to **7t** along with a small amount of **6** and **7c**, it is reasonable to assume that **1b** first is converted into **2** which subsequently reacts further. This does not appear to be the procedure followed by **1a**, since here the bulk of the product is a nearly equal quantity of **6** and **7c**. However, the low yields (19-38%) obtained make such speculation unsatisfactory.

It is well established that base-catalyzed dehydrohalogenations occur more readily if the relevant hydrogen and halogen atoms can assume a mutual trans diaxial relationship. Only in the alternate chair form can either **1a** or **1b** provide such a favorable spatial arrangement, and this would lead to an allylic bromide 5-bromo-6-ethoxy-5,6-dihydro-2*H*-pyran (**10**), which then must form the four products of Scheme II. However it is known that base-catalyzed cis elimination of halogen acid can also occur[17] and hence **1a** and **1b** could produce **2** directly by this route. The isomeric vinyl bromide, 4-bromo-2-ethoxy-5,6-dihydro-2*H*-pyran (**9**), has not been found, although it may have been produced and been less stable than the 3-bromo isomer **2**.

How **2** is induced to form the diethoxydihydropyrans **7t**, **6**, and **7c** is not clear. Since the interconversion of allylic and vinyl chlorides has been shown to occur in the presence of a strong base[18] it is possible that here also a base-catalyzed isomerization to an allyl bromide (*e.g.*, **10**) takes place (Scheme III). Such a

SCHEME III

10a   **2**   **10b**

rearrangement of a vinyl bromide to an allyl bromide has been suggested to explain the formation of an enamine from 2-bromo-3-methylbenzo[*b*]thiophene 1,1-dioxide.[19] The allyl bromide then could provide **6**

by an S$_N$2 reaction and **7c** and **7t** by an S$_N$2' reaction with ethoxide ion. The proportion of these products would depend upon the detailed structure of the allyl bromide. The S$_N$2' reactions of allylic systems and their relation to the S$_N$2 reactions have been examined and reported.[19-22]

Our attempts to isolate an intermediate allyl bromide have been unsuccessful. Reaction of **1a** (containing 10% of **1b**) with sodium ethoxide in ethanol at room temperature for 25 hr gave a product consisting of starting material containing a small amount of olefinic product. When the room temperature reaction was extended for 7 days, the product contained essentially **6** and **7c**.

Experimental Section

Boiling points are uncorrected. For liquids isolated in very small amounts by glc, the boiling points were determined by both micro boiling point technique and by heating them very slowly in a two-bulb micro distillation apparatus under vacuum, with the lower bulb immersed in a heating bath. When the liquid began to distill from the lower bulb, the bath temperature was recorded. The latter method was preferred to the usual micro boiling point method since in trial comparative runs on compounds of known boiling point it gave results more in accord with the correct values.

Analysis of products by glc was carried out with an F & M Model 700 apparatus or with an Aerograph Autoprep, Model A-700. The following columns were employed. (a) Butanediol succinate (BDS, 20%) on Gas-Chrom P (60-80 mesh) in a column $^1/_8$ in. × 12 ft. For preparative work a 0.25 in. × 6 ft (or 12 ft) column was used (BDS-P). (b) Carbowax 6000 (25%) on Gas-Chrom W (60-80 mesh) in a $^1/_8$ in. × 12 ft column (CW). For preparative work a column 0.25 in. × 6 ft (or 12 ft) was employed (CW-P). Helium was the carrier gas.

Elemental analyses were made by Mrs. Darlene Mahlow of this department. The 60-MHz pmr spectra were made by Mr. Robert Swindlehurst, and the 100-MHz pmr spectra and spin-decoupling experiments were done by Mr. Glen Bigam, both of this department. The instruments employed were the Varian A-60 MHz and Varian HR-100 MHz spectrometers. Tetramethylsilane was the reference compound. The solvent was CDCl$_3$ unless otherwise stated. All the *J* values reported in this paper are the approximate coupling constants determined by observation of the signal spacings on the spectrum. The infrared spectra were obtained by Mr. Robert Swindlehurst, using a Perkin-Elmer Model 421 grating spectrometer. Solvents were removed by rotary evaporator under vacuum unless otherwise stated.

trans-2,3-Diethoxytetrahydropyran.—Following the general alkylation procedure previously described[23] but reversing the sequence of addition of reagents, 10 g (0.068 mol) of *trans*-2-ethoxy-3-hydroxytetrahydropyran[24] in 75 ml of dry 1,2-dimethoxyethane (DME) was added slowly (1 hr) to a stirred mixture of 11.7 g (0.075 mol) of ethyl iodide and 1.86 g (0.078 mol) of sodium hydride in 375 ml of DME kept at ~30°. The mixture was stirred overnight and then worked up as described.[23] Ordinary fractional distillation followed by a second fractional distillation with a spinning-band column gave a colorless liquid boiling at 79-80° (10 mm), yield 7.7 g (65%). Analysis by glc on the BDS column showed a slight contamination (<5%) by starting material. Use of the 12 ft preparative column (BDS-P) at 160° with a helium gas flow rate of 150 ml/min gave pure material of the same boiling point: n^{22}D 1.4318; 100-MHz pmr τ 5.56 (d, 1, anomeric, $J_{2,3}$ ~ 4 Hz), 6.00-6.70 (m, 6, HCO),
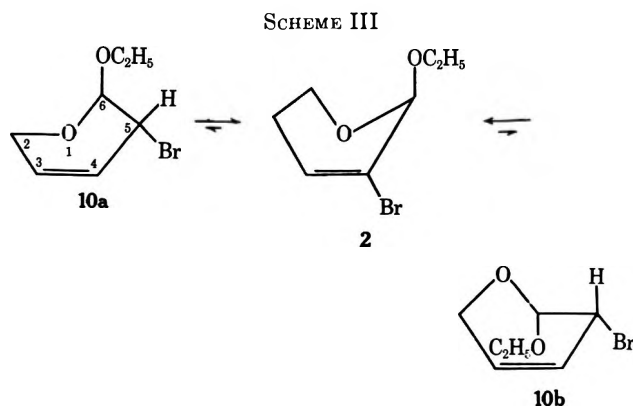
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(23) U. E. Diner, F. Sweet, and R. K. Brown, *Can. J. Chem.*, **44**, 1591 (1966).

(24) F. Sweet and R. K. Brown, *ibid.*, **44**, 1571 (1966).

6.82 (m, 1, HCO for H-3, $J_{3,4 eq or ax} \sim 3.0$ Hz, $J_{3,4 ax or eq} \sim 6.0$ Hz), 7.80–8.80 (m, 4, HC aliphatic), 8.78 (t, 3, HC aliphatic, $J \sim 7$ Hz), and 8.81 (t, 3, HC aliphatic, $J \sim 7$ Hz).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.79; H, 10.64.

Isomerization of *trans*-**2,3-Diethoxytetrahydropyran to the Cis Isomer.**—A solution of 1.5 g (0.0086 mol) of *trans*-2,3-diethoxy-tetrahydropyran in 25 ml of absolute ethanol containing 100 mg of *p*-toluenesulfonic acid monohydrate was heated under reflux for 4 hr. To the cooled solution was added sufficient 10% ethanolic potassium hydroxide to neutralize the acid. Removal of the solvent by fractional distillation left a liquid which contained some colorless solid. An ether solution (100 ml) of this total residue was washed with water (four 5-ml portions) and dried (Na_2SO_4). The filtered solution was freed from ether by fractional distillation to provide a light yellow liquid (1.1 g, 73%). Analysis by glc on a BDS column at 125° (helium flow rate, 50 ml/min) showed two overlapping peaks in the approximate area ratio 2:1. The two peaks in order of appearance were due to *trans*- and *cis*-2,3-diethoxytetrahydropyran, respectively. This isomeric mixture boiled at 77–78° (10 mm), $n^{24}D$ 1.4318.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.12; H, 10.46.

The 60-MHz pmr spectrum showed two anomeric proton signals, one at τ 5.21 (d, $J \sim 3.5$ Hz) for the cis isomer, the other at τ 5.55 (d, $J \sim 4.0$ Hz) for the trans isomer. The signal area ratio was 2:1.

3-Bromo-2-ethoxy-5,6-dihydro-2H-pyran (2).—This was prepared essentially by the method of Woods and Temin.[4] From 16.5 g (0.057 mol) of a 3:1 isomeric mixture of 1a and 1b there was obtained 7.7 g of a yellowish liquid. Glc on a BDS column showed two peaks in the area ratio 3:1. Fractional distillation by a Vigreux column gave two fractions.

The first fraction (4.48 g, 38%) was an oil: bp 84–85° (8 mm): $n^{25}D$ 1.4880 [lit.[4] bp 88° (10 mm), $n^{21}D$ 1.4900; lit.[25] bp 100–101° (20 mm), $\eta^{21.5}D$ 1.4903].

Anal. Calcd for $C_7H_{11}O_2Br$: C, 40.60; H, 5.36; Br, 38.60. Found: C, 40.65; H, 5.37; Br, 38.47.

The infrared spectrum (neat) showed a band at 1650 cm^{-1} (C=C—Br); 100-MHz pmr τ 3.77 (q, 1, HC=C< for H-4, $J_{2,4} < -0.5$ Hz, $J_{4,5 eq} \sim 6.0$ Hz, $J_{4,5 ax} \sim 2.8$ Hz), 5.18 (apparent singlet, 1, anomeric for H-2, $J_{2,5ax} \sim 1.5$ Hz, $J_{2,6 eq} \sim 1$ Hz), 5.90–6.30 (m, 1, HCO for H-6 ax, $J_{6 ax, 6 eq} \sim -12$ Hz), 6.10–6.40 (m, 1, HCO for H-6 eq), 6.30–6.64 (m, 2, HCO), 7.40–7.80 (m, 1, HC aliphatic for H-5 ax, $J_{5 ax, 5 eq} \sim -18$ Hz, $J_{5 ax, 6 ax} \sim 11$ Hz, $J_{5 ax, 6 eq} \sim 6$ Hz), 7.90–8.20 (m, 1, HC aliphatic for H-5 eq, $J_{5 eq, 6 ax} \sim 4$ Hz, $J_{5 eq, 6 eq} \sim 1.5$ Hz), 8.77 (t, 3, HC aliphatic, $J \sim 7$ Hz). The computer simulation, using the observed chemical shifts and coupling constants, gave a spectrum closely similar to that obtained experimentally.

The second fraction (2.05 g, 12.4%) was a light yellow liquid, bp 108–110° (6.5 mm). The 60-MHz pmr spectrum indicated it to be essentially 1a containing a small amount of impurity (unknown).

Dehydrobromination of 3,4-Dibromo-2-ethoxytetrahydropyran (1a and 1b).—Sodium metal (8 g, 0.35 g-atom) was dissolved in 150 ml of dry ethanol. To this, cooled to room temperature, was added a solution of 25 g (0.09 mol) of 1a containing 10% of the isomer 1b,[9] in 25 ml of dry ethanol. The mixture was heated under reflux for 24 hr, during which time it developed a deep amber color, and sodium bromide precipitated. Part of the solvent (100 ml) was removed by fractional distillation at atmospheric pressure, and the residue when diluted with 200 ml of ether deposited more of the salt. The solid was separated and the filtrate diluted with 200 ml more of ether, was washed with water (eight 25-ml portions) and dried ($MgSO_4$). This was then separated from the solid and freed from solvent. Fractional distillation of the residue gave fraction a, 2.8 g, bp 94° (12 mm), and fraction b, 1.8 g, bp 90° (9 mm), combined yield $\sim$30% assuming both fractions to be a diethoxydihydropyran. Analysis by glc (CW column at 150°, helium flow rate, 55–60 ml/min) showed both fractions to be the same, giving three main peaks (A, B, C) in the area ratio 5:1:1 in order of appearance, plus two very minor peaks of shorter retention time (1.5 and 8.5 min) comprising <3% of the combined areas. Preparative glc (CW-P column, 12 ft), under the same conditions as for the glc analysis above,

(25) R. Paul and S. Tchelitcheff, *Bull. Soc., Chim. Fr.*, 869 (1956).

separated the three major peaks having retention times of 13, 16.5, and 18.5 min, respectively. Only 10-μl injections could be made at a time for effective separation.

The **major component A** on reinjection gave the same characteristic broad peak when the above mixture was analyzed by glc, bp 83–85° (10 mm) by the two-bulb method.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 63.04; H, 9.44.

The infrared spectrum showed no absorption between 1610 and 1690 cm^{-1} (no vinyl ether) and no absorption above 3100 cm^{-1} (no OH).

The 60-MHz pmr spectrum showed two anomeric proton signals, one at τ 5.08 (m, $W_{1/2} \sim 5$ Hz), the other at τ 5.22 (d, $J \sim 2.7$ Hz) in the area ratio 0.85:1.0, respectively, indicative of two substances.

Glc with a 0.25 in. × 50 ft column containing 10% neopentyl glycol sebacate on Gas-Chrom W (acid washed) at 150° and with helium gas flow rate of 60 ml/min separated the two components but only if no greater than 20 μl amounts were used for each injection. Four peaks of retention times 51, 55, 61, and 64 min were observed. The first two were the major peaks and were separated and isolated in small amount, while the latter two very minor peaks could not be isolated. Quantities of the major components obtained were insufficient for a boiling point determination.

The first of the two major components of A.—The infrared spectrum (neat) showed very weak bands at 1732, 1700, and 1592 cm^{-1}. The Raman spectrum (neat) showed a medium intensity band at 1664 cm^{-1} (>C=C< stretching); 100-HMz pmr τ 3.95–4.30 (m, 2, HC=C for H-3 and H-4), 5.24 (d, 1, anomeric for H-6, $J_{5,6} \sim 2.5$ Hz), 5.87 (m, 2, HCO, $W_{1/2} \sim 7$ Hz), 5.98–6.60 (m, 6, HCO), 8.75 (t, 3, HC aliphatic, $J \sim 7$ Hz), and 8.78 (t, 3, HC aliphatic, $J \sim 7$ Hz).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.94; H, 9.68.

The second of the two major components of A.—No elemental analysis due to the minute amount isolated. The infrared spectrum (neat) showed the same three weak bands at 1730, 1700, and 1592 cm^{-1} as did the first major component of A; 100-MHz pmr τ 3.98 (d, 1, HC=C for H-4, $J_{3,4} \sim 10$ Hz, $J_{2,4} \sim 1$ Hz), 4.28 (d of t, 1, HC=C for H-3, $J_{2,3} \sim 2$ Hz, $J_{3,5} \sim 1.8$ Hz), 5.11 (m, 1, anomeric for H-2, $W_{1/2} \sim 6$ Hz), 5.80–6.70 (m, 7, HCO), 8.88 (t, 3, HC aliphatic, $J \sim 7$ Hz), and 8.91 (t, 3, HC aliphatic $J \sim 7$ Hz).

Component B.—Colorless liquid; reinjection gave one symmetrical peak in the glc. The amount of B was insufficient for a boiling point determination.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.40, 62.29; H, 9.77, 9.47.

The infrared spectrum (neat) showed very weak absorption at 1740 cm^{-1}; the mass spectrum m/e 171 for M − 1; 100-MHz pmr τ 3.89 (q, 1, HC=C for H-4, $J_{3,4} \sim 10$ Hz, $J_{4,6} \sim 1$ Hz, $J_{2,4} \sim 1$ Hz), 4.07 (q, 1, HC=C for H-3, $J_{2,3} \sim 2.5$ Hz), 5.02 (d, 1, HC, anomeric for H-2), 5.92 (q, 1, HCO for H-6 ax, $J_{6 ax, 6 eq} \sim 12$ Hz, $J_{5,6 ax} \sim 3$ Hz), 6.13 (q, 1, HCO for H-6 eq, $J_{5,6 eq} \sim 2.2$ Hz), 6.15–6.62 (m, 5, HCO), 8.88 (t, 3, HC, aliphatic, $J \sim 7$ Hz), and 8.90 (t, 3, HC aliphatic, $J \sim 7$ Hz).

Component C.—Colorless liquid, bp 85–86° (8 mm).

Anal. Calcd for $C_7H_{11}O_2Br$: C, 40.60; H, 5.36; Br, 38.60. Found: C, 40.44; H, 5.44; Br, 38.87.

The mass spectrum had m/e 206, m/e 208 (^{81}Br satelite). Infrared and 100-MHz pmr spectra were identical with those obtained for compound 2 prepared above.

Hydrogenation of Component A.—A quantity of A (1.53 g, 0.0089 mol), isolated by glc, was dissolved in 50 ml of 95% ethanol. To this was added 500 mg of 5% palladium on charcoal. The mixture was shaken with hydrogen at 40 psi for 2 hr at room temperature. The catalyst was removed and the solvent separated by fractional distillation. The weight of the residual oil indicated nearly quantitative yield of hydrogenated product. Glc analysis (BDS column at 120°, helium flow rate, 60 ml/min) showed only two peaks in the area ratio 1.0:0.85 with retention times of 7.5 and 9 min, respectively. Separation was achieved with a BDS-P column (0.25 in × 12 ft) at 140° with a helium gas flow rate of 72–75 ml/min, and 25-μl quantities for each injection. The material appearing first was *trans*-2,3-diethoxy-tetrahydropyran, a colorless liquid, bp 76° (10 mm), $n^{21}D$ 1.4317.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.15; H, 10.52.

The material of longer retention time, cis-2,5-diethoxytetra-hydropyran, by glc analysis was found to contain ~5% of trans-2,3-diethoxytetrahydropyran, bp 75° (10 mm), n^{22}D 1.4313.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.91; H, 10.55.

The 5% impurity could be removed by injection of 10-μl quantities into a BDS-P column (0.25 in. × 6 ft) at 120°; helium gas flow rate, 50 ml/min: bp (pure cis-2,5-diethoxytetra-hydropyran) 75–76° (10 mm); n^{22}D 1.4314; 100-MHz pmr τ 5.37 (t, 1, anomeric for H-2, $J_{2,3}$ ax or eq ~ 2.7 Hz, $J_{2,3}$ eq or ax ~ 2.3 Hz), 6.10–6.90 (m, 7, HCO), 8.0–8.7 (m, 4, HC aliphatic), 8.86 (t, 3, HC aliphatic, J ~ 7 Hz), and 8.90 (t, 3, HC aliphatic, J ~ 7 Hz).

Dehydrobromination of Pure 1b.—Pure 1b (25 g, 0.09 mol) was dehydrobrominated as described for the 9:1 mixture of 1a and 1b above, except that 80 ml of ethanol was used to dissolve 1b. The reaction afforded 8 g of brown liquid. Fractional distillation gave 6 g of colorless liquid, bp 88–89° (10 mm). Glc analysis showed this to be a mixture of A, B, and C in the ratio 1:18:3, yield ~38%.

Hydrogenation of a Mixture of Components B and C Obtained from the Dehydrobromination of Pure 1b.—A mixture of B and C (1.35 g), separated from A by glc, was hydrogenated for a period of 4 hr at 40 psi in ethanol containing 0.75 g of potassium hydroxide (to prevent acid-catalyzed isomerization) and 500 mg of 5% palladium on charcoal. The reaction mixture was worked up as in the hydrogenation of A above, affording 0.7 g of crude liquid. Analysis by glc (BDS column at 145°, helium gas flow, 100 ml/min) showed only two peaks in the area ratio of 1.0:7.5. The first peak (minor component) showed a retention time identical with that of 2-ethoxytetrahydropyran.[26] The major component, trans-2,5-diethoxytetrahydropyran, was isolated by glc with a BDS-P column (0.25 in. × 12 ft): bp 85–86° (10 mm); n^{25}D 1.4318; mass spectrum m/e 174; 100-MHz pmr τ 5.38 (q, 1, anomeric for H-2, $J_{2,3}$ eq ~ 2.5 Hz, $J_{2,3}$ ax ~ 3.5 Hz), 6.00–6.80 (m, 7, HCO), 7.85–8.25 (m, 2, HC aliphatic for H-3 eq and H-4 eq[27,28]), 8.25–8.65 (m, 2, HC aliphatic for H-3 ax and H-4 ax[27,28]), and 8.80 (t, 6, HC aliphatic, J ~ 7 Hz).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.96; H, 10.62.

Dehydrobromination of Pure 1a.—Pure 1a (45 g, 0.16 mol) was dehydrobrominated as described for the 9:1 mixture of 1a and 1b above. The brown liquid (12 g) was distilled to give three fractions: (a) 4.2 g, bp 86–87° (9.5 mm); (b) 0.75 g, bp 85° (7.5 mm); and (c) 0.15 g, bp 68–70° (2.5 mm). The combined yield was 19%. Glc of each fration with a CW column at 150°

showed each to be composed of components A and B plus a trace of C. Overall proportion of A:B ~ 0:0.8.

Isomerization of trans-2,5-Diethoxytetrahydropyran.—A solution of 400 mg of trans-2,5-diethoxytetrahydropyran (obtained from the hydrogenation of components B and C above) in 7 ml of absolute ethanol containing 50 mg of *p*-toluenesulfonic acid monohydrate was heated under reflux for 4 hr. The cooled solution was basified with 10% alcoholic potassium hydroxide. The ether (100 ml) extract was washed with water (five 3-ml portions) and dried (Na_2SO_4). Removal of the drying agent, and then the solvent by fractional distillation at atmospheric pressure, gave a light yellow oil. Analysis by glc, using a BDS column, showed two overlapping peaks in the area ratio ~1.0:0.75. This mixture was isolated by glc with the BDS-P column.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.00; H, 10.40.

Glc with a BDS-P column (0.25 in. × 6 ft) at 105°, gas flow rate 55 ml/min and with 5–6-μl injection quantities, gave a small amount of the larger component. The 100-MHz pmr was identical with that of cis-2,5-diethoxytetrahydropyran obtained from the hydrogenation of component A above.

Reaction of 3-Bromo-2-ethoxy-5,6-dihydro-2*H*-pyran (2) with Sodium Ethoxide in Ethanol.—To a cooled solution of sodium (0.81 g, 0.035 g-atom) in 15 ml of dry ethanol was added an absolute ethanol (5 ml) solution of 2 g (0.01 mol) of 2. This was heated under reflux for 20 hr, and then most of the solvent was removed by fractional distillation. The cooled residue, when diluted with ether (25 ml), deposited sodium bromide. The ether filtrate was washed with water (six 5-ml portions) until free of base and then dried (Na_2SO_4). Removal of the solvent by fractional distillation gave a colorless liquid. This was distilled under vacuum in a two-bulb micro boiling point apparatus, affording 0.6 g of colorless liquid, bp 80–85° (8 mm). The glc analysis showed four peaks in the area ratio 1.0:4.9:22.9:5.7 with retention times 6.8, 13, 15.5, and 17.5 min, respectively. The last three were coincident with those of components A, B, and C above. These were separated by glc and the liquids were identified as A, B, and C by their pmr spectra. The first peak of retention time 6.8 min was not isolated or identified.

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The Reaction of Acetylenes with Chlorosulfonyl Isocyanate[1]

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The addition of chlorosulfonyl isocyanate (CSI) to 2-butyne (1a), 3-hexyne (1b), 4-octyne (1c), methyl-*tert*-butylacetylene (1e), phenylmethylacetylene (1f), and phenylacetylene (1g) led to 1:1 rearranged 6-chloro-1,2,3-oxathiazine 2,2-dioxide cycloadducts, respectively, 4,5-dimethyl- (2a), 4,5-diethyl- (2b), 4,5-di-*n*-propyl- (2c), 4-*tert*-butyl-5-methyl- (2e), 5-methyl-4-phenyl- (2f), and 4-phenyl- (2g).   Treatment of 2-hexyne (1d) with CSI gave a 73:27 mixture of 6-chloro-5-methyl-4-*n*-propyl- (2d) and 6-chloro-4-methyl-5-*n*-propyl-1,2,3-oxathiazine 2,2-dioxide (2d').   Orientation of 4,5 substituents on the oxathiazine ring system seems to be due both to steric (2d, 2e) and electronic effects (2f, 2g).   The oxathiazine ring structure in 2 has been established by spectroscopic means (uv, ir, nmr, mass spectrometry, and X-ray) and chemically: (1) nucleophilic substitution of the 6-chloro group with thiophenol–pyridine afforded thiophenyl ethers 6a–c,e–g; (2) reduction with 0.5 mol equiv of LiAlH₄ gave 3,4-dihydro derivatives 3a–c,e,f,1; (3) reaction with nucleophiles H₂O, ⁻OCH₃, and CH₃OH led to ring-cleavage products, respectively, ketones 7a–h,l, bis esters of unsaturated β-amino(*N*-sulfonic acid) carboxylic acid (8a–c,e–h), and β-keto ester 9; catalytic hydrogenation of 8b and 8g afforded the corresponding saturated bis esters 10b and 10g, which were independently prepared by treatment of 1-chlorosulfonyl-3,4-diethyl- (11b) and 1-chlorosulfonyl-4-phenyl-2-azetidinone (11g) with NaOCH₃–CH₃OH;   (4) oxidation (O₃ and KMnO₄) gave ring-cleavage products, 3,4-hexanedione (14), 3-hexanone (7b), and propionic acid (15), while reductions with excess LiAlH₄ led successively to 2-ethyl-2-pentenal (12) and 2-ethyl-2-penten-1-ol (13).   Methylation of 3a–c,e,f with CH₃I–K₂CO₃ afforded *N*-methyl derivatives 4a–c,e,f some of which were dechlorinated with Li in *tert*-BuOH to 5a–c,f.   Diphenylacetylene (1h) and CSI gave two unstable products, the appropriate oxathiazine (2h) and the 1:2 cyclo-adduct bis(chlorosulfonyl)-5,6-diphenyluracil (19); hydrolysis and methanolysis of the former gave 7h and 8h, while 19 was converted to 5,6-diphenyluracil (20).   1-Hexyne (1i) and CSI led only to 2-heptynamide derivatives 21–23.   With CSI, 3-diethylamino-1-propyne (1j) gave the tertiary amine CSI salt while ynamine 1-diethylamino-1-propyne (1k) led to an unstable 1:1 adduct believed to have oxete structure 26.   CSI reacted only with the acetylene function in 1-octen-4-yne (1l) to form 6-chloro-4-*n*-propyl-5-(2-propenyl)-1,2,3-oxathiazine 2,2-dioxide (2l).   In competitive rate studies with equimolar mixtures of 1d–*trans*-2-hexene and 1d–cyclohexene, CSI reacted solely with acetylene 1d.   With equimolar mixtures of 1f–*trans*-β-methylstyrene and 1g–styrene, CSI gave, respectively, 1:1 and 2:1 mixtures of azetidinone–oxathiazine adducts.   The initial cyclo-addition of CSI is proposed to occur in near-concerted fashion to 1a–e,l and in a stepwise process to 1f–h.   CSI addition to benzyne precursor benzenediazonium carboxylate (28) afforded only 3-chlorosulfonyl-1,2,3-benzo-triazin-4-one (29).

The ease with which chlorosulfonyl isocyanate (CSI) stereospecifically adds to carbon–carbon multiple bonds (alkenes, conjugated dienes, cumulenes, polyenes) affording 2-azetidinones (I)[3,4] raised the possibility of
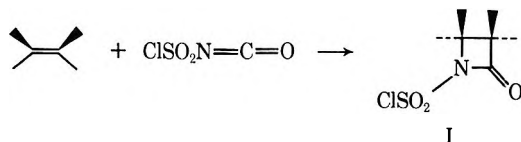
similar reactivity toward carbon–carbon triple bonds. Thus cycloaddition of CSI to acetylenes proceeding by such limiting mechanisms as (1) a concerted $\pi^2 a + \pi^2 s$ process *via* a polar, unsymmetrical transition state (II)[5] and/or (2) a stepwise, electrophilic addition *via* an initially formed dipolar vinyl cation III[6] could lead to azetinones IV[7] and/or oxetes (V).[8,9]

We recently reported that addition of freshly distilled CSI in methylene chloride solution to an equimolar quantity of 3-hexyne (1b) at ambient temperature led to the 1:1 rearranged adduct 6-chloro-4,5-diethyl-1,2,3-

(7) Only a few of which are known (i–iii).

(i) K. R. Henery-Logan and J. V. Rodricks, *J. Amer. Chem. Soc.*, **85**, 3524 (1963); (ii) E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1960); (iii) G. Ege and E. Beisiegal, *Angew. Chem., Int. Ed. Engl.*, **7**, 393 (1965).
(8) Examples of which include iv and v.
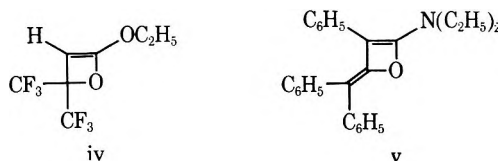
(iv) W. J. Middleton, *J. Org. Chem.*, **30**, 1307 (1965); (v) M. E. Kuehne and P. J. Sheeran, *ibid.*, **33**, 4406 (1968).
(9) However, the N– *vs.* O-cyclization rates would seem to be competitive.   The factors which determine the preferred mode (to β lactams) have not been elucidated.   To date, O-cyclized products have been obtained directly only on addition of CSI to cycloheptatriene[10] and a vinyldihydro-naphthalene[11] and indirectly by rearrangement of the initial *N*-chlorosulfonyl-β-lactam cycloadducts obtained from CSI addition to olefin[12] and conjugated dienes.[6,12a,14]
(10) E. J. Moriconi, C. F. Hummel, and J. F. Kelly, *Tetrahedron Lett.*, 5325 (1969).
(11) R. J. P. Barends, W. N. Speckamp, and H. O. Huisman, *ibid.*, 5301 (1970).
(12) T. W. Doyle and T. T. Conway, *ibid.*, 1889 (1969).
(13) (a) E. J. Moriconi and W. C. Meyer, *ibid.*, 3823 (1968); (b) E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968).
(14) Th. Haug, F. Lohse, K. Metzger, and H. Batzer, *Helv. Chim. Acta*, **51**, 2069 (1968); P. Goebel and K. Clauss, *Justus Liebigs Ann. Chem.*, **722**, 122 (1969).

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(2) Graduate Research Assistant (1967–1970) on a grant[1] supported by NIH; taken entirely from the Ph.D. Thesis of Y. Shimakawa, Fordham University, New York, 1971.
(3) R. Graf, *Angew. Chem., Int. Ed. Engl.*, **7**, 172 (1968).
(4) E. J. Moriconi, "Mechanisms of Reaction of Sulfur Compounds," Vol. 3, Intra-Science Research Foundation, Santa Monica, Calif., 1968, p 131.
(5) We have recently suggested that CSI may play an antarafacial role as a $\pi^2 a$ component in concerted reactions with $\pi^2 s$ systems [E. J. Moriconi and W. C. Meyer, *J. Org. Chem.*, **36**, 2841 (1971)].   In this process the rate of formation of the second bond may lag behind the formation of the first.   The formation of such as II in the rate-determining step permits the orientation, polar effect, and stereospecificity observed.
(6) M. Hanack, *Accounts Chem. Res.*, **3**, 209 (1970), and references contained therein.   There is the inevitable question of timing.   If the reaction is stepwise, the vinyl cationic intermediate III should be of sufficient stability to be trapped by external reagents.   This has occurred only with diphenylacetylene (1h).

oxathiazine 2,2-dioxide (**2b**, 96%).[15] The major chemical evidence provided in support of structure **2b** included (1) nucleophilic substitution of the 6-chloro group in **2b** to 4,5-diethyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide (**6b**) using thiophenol–pyridine–acetone (this reagent normally reduces NSO_2Cl functions to NH while producing SO_2, pyridine hydrochloride, and diphenyl disulfide);[3] (2) reduction of **2b** with 0.5 mol equiv of $LiAlH_4$ to 6-chloro-4,5-diethyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**3b**, 81%) whose nmr revealed a new methine proton (δ 3.93, X portion of an ABX pattern) coupled to both NH and the CH_2 of an ethyl group.

The structure of **2b** was confirmed by X-ray crystallographic analysis,[15,16] while its formation was rationalized by a sequence of cycloaddition (VI), electrocyclic ring opening to the ketene–imine–*N*-sulfonyl chloride (VII), 1,5-sigmatropic halogen shift (VIII), and elec-

trocyclic ring closure to oxathiazine **2b**. Rotation about the acyl carbon single bond of VIII must precede the final cyclization step.
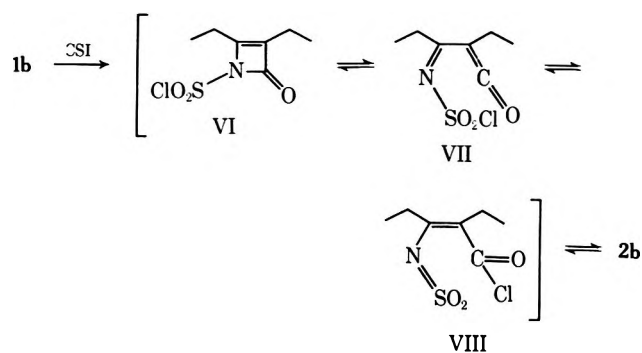
The reversibility of steps VI ⇌ VII ⇌ VIII ⇌ **2b** would account for the appearance in the mass spectrum of **2b** of a fragment m/e 124 corresponding to the loss of SO_2Cl from the molecular ion. Under electron impact or thermal conditions in the mass spectrometer, **2b** reverted to VI. The mass spectrum of **3b** had no M − SO_2Cl fragment but did show two fragments (IX, X)
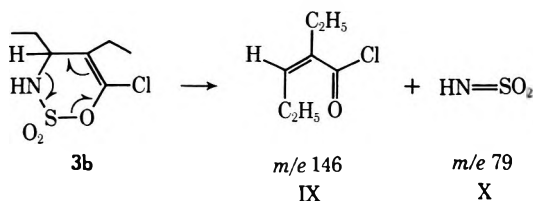
resulting from a retro-Diels–Alder rearrangement of **3b**.[17]

Shortly after the publication of our initial report, there appeared two communications[18] in which the structures of the CSI adducts with 2-butyne (**1a**), phenylacetylene (**1g**), and phenylmethylacetylene (**1f**) were variously considered to be XI–XV. All are incorrect.
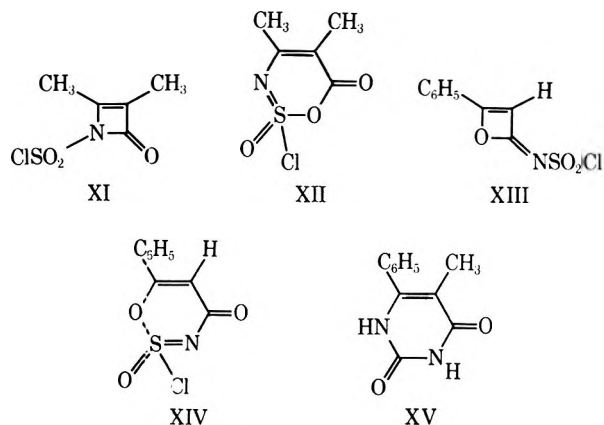
In this concluding paper, we report (1) on the reaction of CSI with **1a**, **1b**, 4-octyne (**1c**), 2-hexyne (**1d**), methyl-*tert*-butylacetylene (**1e**), **1f**, and **1g**; (2) chemical degradation studies on oxathiazine adducts **2** and dihydro derivatives **3**; (3) the unique behavior of CSI on reaction with diphenylacetylene (**1h**), 1-hexyne (**1i**), 3-diethylamino-1-propyne (**1j**), 1-diethylamino-1-propyne (**1k**), 1-octen-4-yne (**1l**), and benzenediazonium carboxylate (**28**); and (4) competitive rate studies of CSI with acetylene–olefin mixtures which clarify to some extent the nature of the initial mode of addition (near concerted or stepwise).

CSI Addition to Acetylenes (Scheme I)—Addition to CSI to equimolar amounts of **1a**, **1c**, **1e**, and **1f** in anhydrous methylene chloride at ambient temperatures afforded the following 6-chloro-1,2,3-oxathiazine 2,2-dioxides, respectively: 4,5-dimethyl- (**2a**, 42%), 4,5-di-*n*-propyl- (**2c**, 86%), 4-*tert*-butyl-5-methyl- (**2e**, 51%), and 5-methyl-4-phenyl- (**2f**, 86%). Similar treatment of **1d** with CSI led to a 73:27 mixture (92%) of 6-chloro-5-methyl-4-*n*-propyl- (**2d**) and 6-chloro-4-methyl-5-*n*-propyl-1,2,3-oxathiazine 2,2-dioxide (**2d'**). The reaction of **1g** with CSI at room temperature led mostly to polymers and no distinguishable products were isolated from the reaction mixture. Lowering the reaction temperature to −20–0° led, however, to the crude, unstable 6-chloro-4-phenyl-1,2,3-oxathiazine 2,2-dioxide (**2g**, ~50%) which could be separated by cooling to −78°, followed by rapid filtration. Since all attempts to purify this solid material were unsuccessful, the crude adduct was immediately converted to 4-phenyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide (**6g**) with benzenethiol–pyridine in acetone. In all cases, no other products were isolated other than polymeric material.

The low yield of **2a** may be attributed to the volatility of **1a**. The orientation of 4,5 substituents on the

(17) The high-resolution mass spectra were run by Dr. R. A. Salomone while a NIH Postdoctoral Trainee, 1967–1969 (GM 015230), in the Department of Chemistry, Massachusetts Institute of Technology.

(18) (a) K. Clauss and H. Jensen, *Tetrahedron Lett.*, 119 (1970); (b) K-D. Kampe, *ibid.*, 123 (1970).

(15) E. J. Moriconi, J. G. White, R. W. Franck, J. Jansing, J. F. Kelly, R. A. Salomone, and Y. Shimakawa, *Tetrahedron Lett.*, 27 (1970).

(16) J. Jansing and J. G. White, unpublished results.

SCHEME I

PREPARATION OF 1,2,3-OXATHIAZINE 2,2-DIOXIDES AND THEIR DERIVATIVES

	R_1	R_2
1a	CH_3	CH_3
1b	C_2H_5	C_2H_5
1c	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$
1d	$n\text{-}C_3H_7$	CH_3
1e	$(CH_3)_3C$	CH_3
1f	C_6H_5	CH_3
1g	C_6H_5	H
1h	C_6H_5	C_6H_5
1i	$n\text{-}C_4H_9$	H
1j	$CH_2N(C_2H_5)_2$	H
1k	$N(C_2H_5)_2$	CH_3
1l	$n\text{-}C_3H_7$	$CH_2CH{=}CH_2$
1m	CH_3	$CH{=}C(CH_3)_2$

	R_1	R_2
2a	CH_3	CH_3
2b	C_2H_5	C_2H_5
2c	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$
2d	$n\text{-}C_3H_7$	CH_3
2d'	CH_3	$n\text{-}C_3H_7$
2e	$(CH_3)_3C$	CH_3
2f	C_6H_5	CH_3
2g	C_6H_5	H
2h	C_6H_5	C_6H_5
2l	$n\text{-}C_3H_7$	$CH_2CH{=}CH_2$

	R_1	R_2
3a	CH_3	CH_3
3b	C_2H_5	C_2H_5
3c	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$
3e	$(CH_3)_3C$	CH_3
3f	C_6H_5	CH_3
3l	$n\text{-}C_3H_7$	$CH_2CH{=}CH_2$

	R_1	R_2
6a	CH_3	CH_3
6b	C_2H_5	C_2H_5
6c	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$
6e	$(CH_3)_3C$	CH_3
6f	C_6H_5	CH_3
6g	C_6H_5	H

	R_1	R_2
5a	CH_3	CH_3
5b	C_2H_5	C_2H_5
5c	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$
5f	C_6H_5	CH_3

	R_1	R_2
4a	CH_3	CH_3
4b	C_2H_5	C_2H_5
4c	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$
4e	$(CH_3)_3C$	CH_3
4f	C_6H_5	CH_3

oxathiazine ring in 2e and 2d seems to be primarily due to the greater steric effects[19] of *tert*-butyl and n-propyl groups, respectively, in the cycloaddition step, while that in 2f[20] and 2g undoubtedly reflects the greater electronic stabilization of the incipient vinyl carbonium by the adjacent phenyl group either in transition state II or intermediate III.[6,21] In general, the rate of CSI addition to acetylenes was accelerated in more polar solvents, and the thermal stability of the oxathiazine products increased with increasing size of substituents at C-5.

In the infrared, adducts 2a–g exhibited *no* carbonyl absorptions; the bands at 1626–1600 (6.15–6.25 μ) and 1500–1471 cm^{-1} (6.67–6.80 μ) in these oxathiazines are assigned to C=C and C=N absorptions. Adducts 2a–g all showed the strong, sharp, split band patterns for SO_2 stretching modes in the 1399–1379- (7.15–7.25 μ) and 1212–1190-cm^{-1} (8.25–8.40 μ) regions.[22] In

(19) On the basis of Taft's substituent constants, the difference between the inductive effects of a methyl and *tert*-butyl group is relatively small ($\Delta\sigma^* = 0.30$): J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 97.

(20) The rate for the CSI-1e cycloaddition was less than one-third as fast as the CSI-1b reaction whose rate was comparable to that for CSI-1f.

(21) A. Hassner, R. J. Isbister, and A. Friederang, *Tetrahedron Lett.*, 2939 (1969).

(22) Sulfones absorb in the 1350–1300 (7.41–7.69 μ) and 1160–1120-cm^{-1} (8.62–8.93 μ) regions. Attachment of two electronegative atoms (O, N) to S in cycloadducts 2 would be expected to result in frequency shifts of both characteristic bands toward higher frequencies: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, pp 360–363.

the ultraviolet, adducts 2a–e displayed a chromophore with λ_{max} 292–295 nm (ϵ 3600–3800); phenyl group extension of the conjugated system in 2f and 2g shifted the λ_{max} to 297–302 nm (ϵ 12,000–12,700). The combined effect of spectral data alone (ir, uv, nmr, and X-ray) decisively preclude structures XI–XV or the acetylene–CSI cycloadducts.

Reaction of Oxathiazines (2) with Nucleophiles (Scheme II).—Methanolysis of 2b led to the β-keto ester, methyl 2-ethyl-3-oxopentanoate (9, 60%); hydrolysis of 2b afforded 3-hexanone (7b, 70%), the decarboxylation product of its β-keto acid precursor 2-ethyl-3-oxopentanoic acid. Similar hydrolysis of 2a, 2c–g with water or aqueous bicarbonate solution gave ketones 7a, 7c–g (31–81%), respectively. Treatment of 2a–c, 2e–g with 3 mol equiv of sodium methoxide in absolute methanol at 0° resulted in the formation of bis esters of β-amino(N-sulfonic acid)carboxylic acids 8a–c, 8e–g (30–98%), respectively. Catalytic hydrogenation of 8b and 8g afforded the corresponding saturated diesters 10b and 10g, which were independently prepared by treatment of 1-chlorosulfonyl-*cis*-3,4-diethyl- (11b)[13b] and 1-chlorosulfonyl-4-phenyl-2-azetidinone (11g)[13b] with sodium methoxide–methanol.[3] These results show that no rearrangement of the carbon skeleton had occurred during cycloaddition and rearrangement, and the carbon of CSI had become affixed to the acetylene function. As already noted with 2b and 2g, treatment of 2a, 2c, 2e, and 2f with thiophenol–

SCHEME II
RING DEGRADATION REACTIONS OF 1,2,3-OXATHIAZINE 2,2-DIOXIDES

(23) An alternative hydrolysis mechanism might involve enolization of XIX followed by nucleophilic attack at the carbonyl carbon and ring opening to 16.
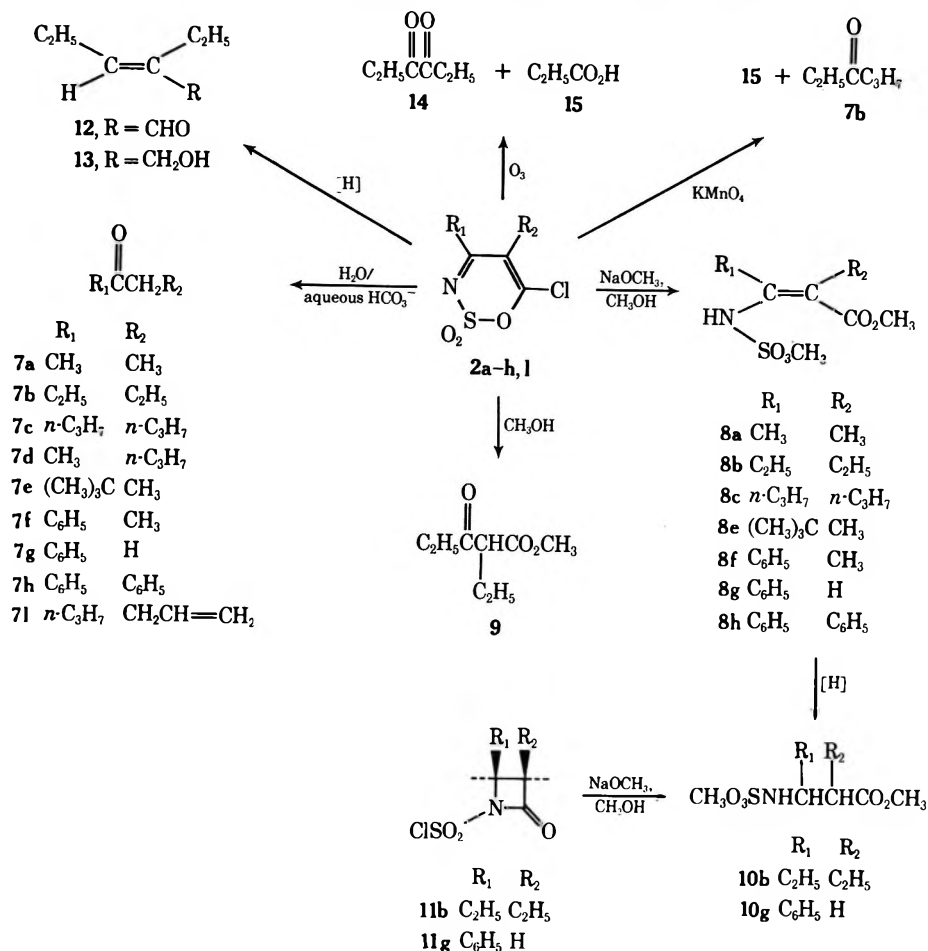
pyridine in acetone afforded thioethers **6a, 6c, 6e,** and **6f** (27–44%), respectively. Nucleophilic substitution of the vinyl chloride in **2** finds its analogy in the pyridine ring system where the polarity of electrons toward nitrogen invites attack by nucleophiles at the γ position. In **2** the entering negative charge may reside not only on the C and N atoms but can be further delocalized into the adjacent SO₂ group *via* d–p$_\pi$ bonding XVI ↔ XVII ↔ XVIII.

A general mechanism for the response of the 1,2,3-oxathiazine system to nucleophiles (H₂O, CH₃OH, ⁻OCH₃, C₆H₅SH) is proposed in Scheme III. Expulsion of chloride under the influence of the strong nucleophile thiophenol readily converts intermediate XVI ↔ XVII ↔ XVIII to the more stable conjugated thioethers **6**. Further attack by the appropriate nucleophile at the S site of the less stable substitution products XIX[23] and XX leads ultimately to cleavage

products **7** and **9**. The bis esters **8**, structurally correspondent to proposed ring-cleaved intermediates XXI and XXII, have been isolated.

Reduction and Oxidation.—Reduction of **2b** with 2 and 4 mol equiv of LiAlH₄ afforded 2-ethyl-2-pentenal (**12**, 30%) and 2-ethyl-2-penten-1-ol (**13**, 36%), respectively. The use of 0.5 mol equiv converted **2a–c, 2e,f** and **2l** to the corresponding dihydro derivatives **3a–c, 3e,f,** and **3l**, respectively. In all the latter, decreased conjugation was evidenced by the absence of any C=N stretching bands in the ir and a large hypsochromic shift in the uv [*e.g.*, *cf.* **2b**, λ_{max} 292 nm (ϵ 3600), and **3b**, λ_{max} 233 nm (ϵ 1500)]. A similar reduction of **2g** led only to polymeric material.

Methylation of **3a–c** and **3f** with CH₃I–K₂CO₃ in acetone afforded the *N*-methyl derivatives **4a–c** and **4f** (48–73%). With this reagent combination, **3e** reacted slowly and gave mostly ring-cleaved products. When the reaction was carried out in DMSO with a large excess of CH₃I and an equimolar amount of K₂CO₃, the desired 6-chloro-4-*tert*-butyl-3,5-dimethyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**4e**, 48%) was obtained. Although a large steric effect is expected between the neighboring *tert*-butyl and *N*-methyl groups in **4e**, nitrogen inversion was not observed in the nmr at room temperature.[24]

Dechlorination of **4a–c** and **4f**, unsuccessful with **3,**

(24) F. A. L. Anet and J. M. Osyany, *J. Amer. Chem. Soc.*, **89**, 352, 357 (1968).

was achieved using Li in *tert*-BuOH[25] to give **5a–c** and **5f** (69–93%), respectively. The nmr of 4,5-diethyl-3-methyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**5b**), for example, displayed a new vinyl proton (δ 6.30) coupled both to the methine C-4 proton and the methylene proton of the C-5 ethyl group.

Finally, catalytic hydrogenation of **2b** followed by hydrolytic work-up gave ketone **7b** (77%); similar reduction and hydrolysis of **6b** afforded phenyl 2-ethyl-3-oxothiopentanoate **17** (39%).

$$\mathbf{6b} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. [H]}} \underset{\substack{|\\ \text{C}_2\text{H}_5\\ \mathbf{17}}}{\text{C}_2\text{H}_5\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CHC}\overset{\text{O}}{\overset{\|}{}}\text{SC}_6\text{H}_5}$$
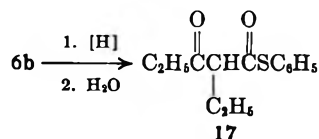
Ozonation of **2b** followed by oxidative work-up gave 3,4-hexanedione (**14**, 20%) and propionic acid (**15**, 14%). Potassium permanganate oxidation of **2b** afforded **15** (47%) and **7b** (20%). Alkaline hydrogen peroxide treatment of **3b** gave 2-ethyl-3-(aminosulfonic acid)pentanoic acid (**18**, 23%), identical with that formed directly (50%) *via* aqueous hydrolysis of **3b**.

$$\mathbf{3b} \xrightarrow{\text{aqueous KOH}} \underset{\substack{|\\ \text{C}_2\text{H}_5\\ \mathbf{18}}}{\text{HOSO}_2\text{NH}\overset{\overset{\text{C}_2\text{H}_5}{|}}{\text{CH}}\text{CHCO}_2\text{H}}$$
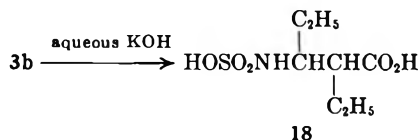
Miscellaneous Acetylenes.—Diphenylacetylene (**1h**) reacted slowly[26] with CSI (at least $^1/_{30}$ the rate of **1b**) to form two unstable products. The first, 1,3-bis(chlorosulfonyl)-5,6-diphenyluracil (**19**, 57%), was identified as its hydrolysis product 5,6-diphenyluracil (**20**).[27a] For the second, recrystallization from methanol gave methyl 2,3-diphenyl-3-(methoxysulfonylamino)propenoate (**8h**, 17%) while hydrolysis afforded deoxybenzoin (**7h**, 13%). Both **7h** and **8h** can be rationalized as methanolysis and hydrolysis products, respectively, of 6-chloro-4,5-diphenyl-1,2,3-oxathiazine 2,2-dioxide (**2h**). Mechanistically, the results suggest a slow,[6,26] stepwise addition of CSI to **1h**. The 1,4-dipolar intermediate XXIII can both cyclize to oxathiazine **2h**

$$\mathbf{1h} \xrightarrow{\text{CSI}} \left[\begin{array}{c} \text{C}_6\text{H}_5\overset{+}{\text{C}}=\text{CC}_6\text{H}_5 \\ | \\ \text{ClSO}_2\overset{-}{\text{N}}-\text{C}\overset{\nwarrow}{}\text{O} \end{array}\right] \xrightarrow{} \mathbf{2h} \xrightarrow{\text{CH}_3\text{OH}} \mathbf{8h}$$

XXIII

$$\downarrow \text{H}_2\text{O}$$

7h

$$\downarrow \text{CSI}$$

19, R = SO$_2$Cl
20, R = H

and be intercepted by a second molecule of CSI to form **19**.[27b,28]

1-Hexyne (**1i**) also reacted slowly with CSI. The initial adduct contained neither the oxathiazine nor uracil structures since the crude product displayed carbonyl (5.91 μ) and NH (3.1 μ) absorption bands in the ir and no vinyl proton in the nmr. Aqueous hydrolysis of this crude oil led to 2-heptynamide (**22**, 20%), while treatment with aniline afforded the *N*-sulfonylanilide of 2-heptynamide (**23**, 30%). These

$$\text{C}_4\text{H}_9\text{C}\!\equiv\!\text{C}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{NH}_2$$

22

$$\uparrow \text{H}_2\text{O}$$

$$\mathbf{1i} \xrightarrow{\text{CSI}} \left[\begin{array}{c} \text{C}_4\text{H}_9\overset{+}{\text{C}}\overset{\frown}{=}\overset{}{\text{C}}\!-\!\text{H} \\ \underset{\text{O}}{\overset{|}{\text{C}}}\text{N}\!-\!\text{SO}_2\text{Cl} \end{array}\right] \xrightarrow{} \text{C}_4\text{H}_9\text{C}\!\equiv\!\text{C}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{NHSO}_2\text{Cl}$$

XXVI   **21**

$$\downarrow \text{C}_6\text{H}_5\text{NH}_2$$

$$\text{C}_4\text{H}_9\text{C}\!\equiv\!\text{C}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{NHSO}_2\text{NHC}_6\text{H}_5$$

23
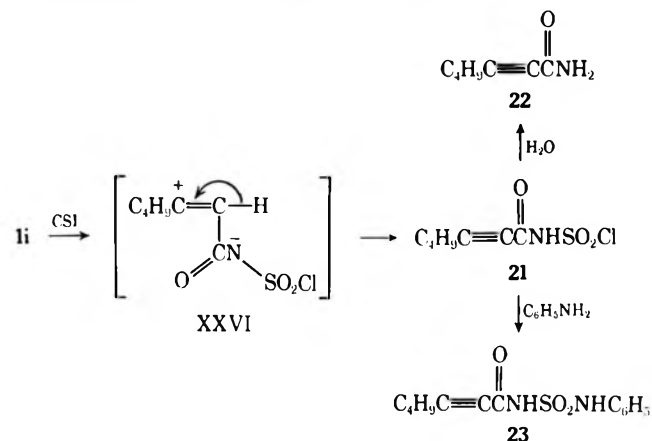
results suggest the original unstable adduct to be the *N*-sulfonyl chloride of 2-heptynamide (**21**) whose formation must involve initial, stepwise attack by CSI at the terminal C atom of **1i** to intermediate XXVI followed by proton transfer to N.

Both 3-diethylamino-1-propyne (**1j**) and ynamine 1-diethylamino-1-propyne (**1k**) reacted with CSI rapidly and quantitatively in pentane ($-78°$) to yield unstable 1:1 adducts which decomposed under work-up conditions at room temperature. At low temperature, the unstable **1j**–CSI adduct could be isolated as a hygroscopic, white solid whose ir displayed isocyanate (2222 cm^{-1}, 4.50 μ) and acetylenic (2105 cm^{-1}, 4.75 μ) absorptions. Since careful hydrolysis of this material gave **1j** (70%), and its hydrochloride **25**, a reasonable structure for the initial adduct would be merely the *tert*-amine–CSI salt (**24**).[29]

$$\mathbf{1j} \underset{\substack{\text{aqueous NaOH,}\\\text{acetone}}}{\overset{\text{CSI}}{\rightleftarrows}} \text{HC}\!\equiv\!\text{CCH}_2\text{N(C}_2\text{H}_5)_2\cdot\text{ClSO}_2\text{NCO} \xrightarrow[\text{acetone}]{\text{aqueous NaOH,}}$$

$$\underset{\substack{+\\ \text{Cl}^-\\ \mathbf{25}}}{\text{HC}\!\equiv\!\text{CCH}_2\overset{\overset{\text{H}}{|}}{\text{N}}(\text{C}_2\text{H}_5)_2}$$

(25) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).

(26) The low electron-withdrawing power of phenyl substituents in acetylenes is well documented; *e.g.*, in an approximate order of reactivity for tanycyclophiles, **1h** failed to react [P. G. Gassman, *Accounts Chem. Res.*, **4**, 128 (1971)]. The steric effects of diphenyl substituents should also lower the reaction rate. See also ref 32.

(27) (a) Uracil structures have also been proposed for the reaction products between fluorosulfonyl isocyanate (FSI) and both **1a** and **1f**.[18] (b) A bis(*N*-chlorosulfonyl)uracil intermediate was also proposed as one of the cycloaddition products of CSI and 3-methyl-1,2-butadiene: E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **32**, 3036 (1968). A more recent precedent is the formation of 5-isopropenylhydantoin from the addition of CSI to 1-methylcyclopropene: T. J. Barton, R. Rogido, and J. C. Clardy, *Tetrahedron Lett.*, 2081 (1970).

(28) Oxathiazine **2h** and uracil **19** could also be formed *via* common intermediates XXIV ⇌ XXV.

$$\left[\begin{array}{c}\text{C}_6\text{H}_5\text{C}_6\text{H}_5 \\ \overset{|}{\underset{\text{ClSO}_2}{}}\text{N}\text{O} \end{array}\right] \rightleftharpoons \left[\begin{array}{c}\text{C}_6\text{H}_5\text{C}_6\text{H}_5 \\ \text{N}\text{C} \\ \overset{|}{\text{SO}_2\text{Cl}}\text{O}\end{array}\right] \overset{\nearrow \mathbf{2h}}{\underset{\searrow \mathbf{19}}{}}$$

XXIV   XXV
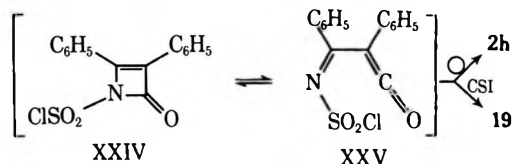
(29) R. Graf, German Patent 1,000,807 (1957); *Chem. Abstr.*, **54**, 1555h (1960).

SCHEME III
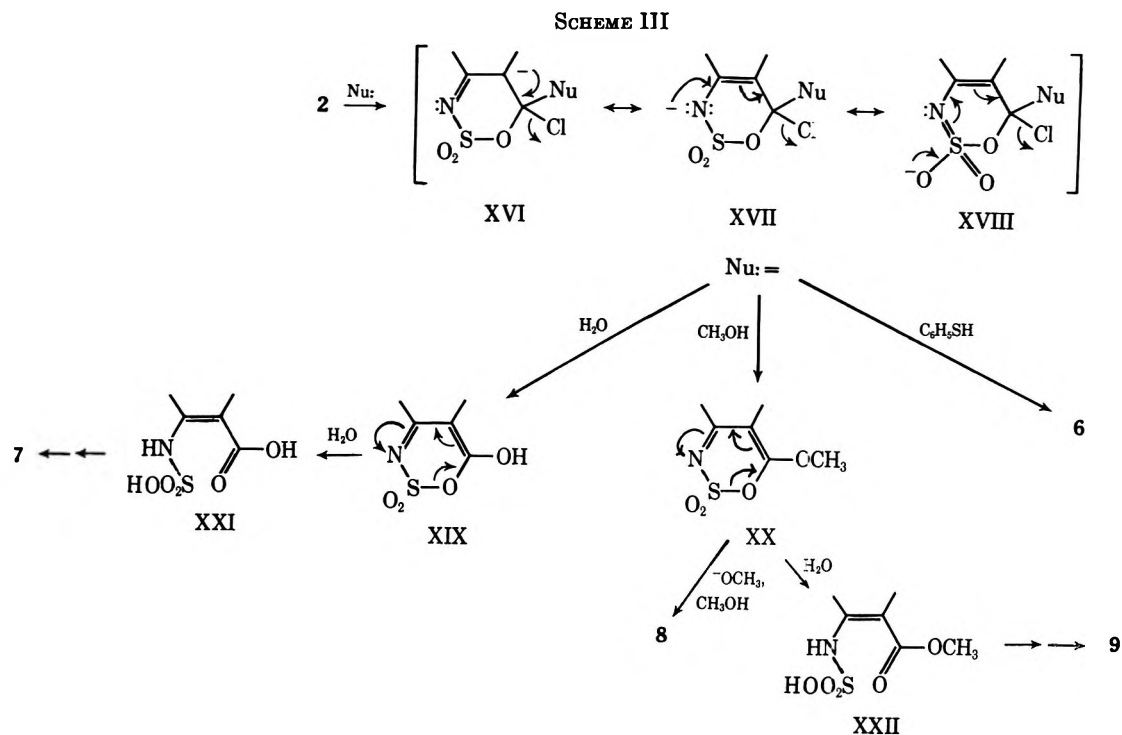
Similar isolation of the **1k**-CSI adduct afforded an unstable, yellow material whose ir showed C=C/C=N and SO_2 absorptions but no C=O band. Its nmr was also suggestive of an oxete-type structure **26**; hydrolysis, methanolysis, reduction, and oxidation of this material, however, led to no isolable products.

26
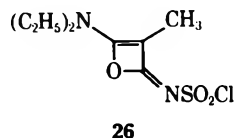
1-Octen-4-yne (1l). Competitive Reaction Rates of Acetylenes and Olefins with CSI. Reaction Mechanisms.—1-Octen-4-yne (**1l**) and CSI reacted at about $^1/_3$ the rate of the reaction of **1c** and CSI. On the basis of spectral data [ir 1640 cm^{-1} (6.10 μ) (C=C/ C=N), no C=O absorption; nmr three vinyl protons], the adduct obtained in 75% yield was assigned the structure 6-chloro-4-n-propyl-5-(2-propenyl)-1,2,3-oxathiazine 2,2-dioxide (**2l**). Reductions of **2l** with 0.5 mol equiv of LiAlH$_4$ afforded the expected dihydro derivative (**3l**, 70%) while reductive hydrolysis with aqueous sodium sulfite solution[30] gave 1-octen-5-one (**7l**, 80%). It was unexpected that the electrophilic CSI preferred to react with the acetylenic function in **1l** rather than the terminal double bond.

The addition of CSI to the conjugated enyne, 2-methyl-2-hexen-4-yne (**1m**), at low temperature always resulted in the formation of intractable polymers.

There is now considerable evidence which indicates that addition of electrophiles such as 2,4-dinitrobenzenesulfenyl chloride[31] and bromine,[32] *inter alia*, to olefins proceeds *via* a two-step process with the formation of a discrete ionic intermediate in the rate-determining step. While the intrinsic mechanism of

addition of such electrophiles to acetylenes has not been firmly established,[33] it has long been suggested that the π electrons of acetylenes are more tightly held than are those of corresponding alkenes. Consequently, if the mechanism of electrophilic addition to corresponding acetylenes and alkenes is similar, then the rate for the former would be predictably slower. Comparison of the results for the addition of 2,4-dinitrobenzenesulfenyl chloride[31] and bromine[32] to acetylenes with those for the appropriate olefins show significantly lower reaction velocities for the acetylenes.

To determine relative reaction rates for the addition of CSI to acetylenes and olefins, equimolar mixtures of 2-hexyne (**1d**)-*trans*-2-hexene and **1d**-cyclohexene were treated with an insufficient amount of CSI. In each case, only acetylene **1d** reacted. Thus, on the basis of these relative rate studies, we suggest that, in the absence of any overwhelming electronic substituent effect (as in acetylenes **1a-e** and **1l**), addition of CSI to acetylenes proceeds *via* the near-concerted transition state II. The orientation in cycloadduct **21** may be rationalized by the greater stability of XXVII over XXVIII.[34] Homoallylic stabilization of XXVIII (*via* XXIX) was therefore not significant.

When a mixture of **1f**-*trans*-β-methylstyrene in methylene chloride was treated with 0.5 molar equiv of CSI, nmr analysis of the product indicated a nearly 1:1 mixture derived from cycloaddition of CSI to both acetylene and olefin. In the more polar solvent, the acetylene-CSI reaction rate increased the product mixture ratio to 1.4:1. Finally, an equimolar mixture of **1g**-styrene with CSI afforded a 2:1 mixture of the

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(30) T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).

(31) N. Kharasch and C. N. Yiannios, *ibid.*, **29**, 1190 (1964).

(32) P. W. Robertson, W. E. Dasant, R. M. Milburn, and W. H. Oliver, *J. Chem. Soc.*, 1628 (1950).

(33) In electrophilic addition reactions (hydrolysis, hydrochlorination, reaction with trifluoroacetic acid) to acetylenes, vinyl cations have been proposed: P. E. Peterson and J. E. Duddy, *J. Amer. Chem. Soc.*, **88**, 4990 (1966), and references cited therein; R. C. Fahey and D. J. Lee, *ibid.*, **89**, 2780 (1967); D. S. Noyce, M. A. Matesich, and P. E. Peterson, *ibid.*, **89**, 6225 (1967); D. S. Noyce and M. D. Schiavelli, *ibid.*, **90**, 1020, 1023 (1968).

(34) The difference in inductive effect of the n-propyl and propenyl groups is small; *cf.* Taft's σ^* value for n-butyl (-0.13) and 2-butenyl ($+0.13$) groups.[19]

XXVII

XXVIII

XXIX

azetidinone–oxathiazine adducts. Thus in the reaction of CSI with acetylenes **1f** and **1g**, the mechanism of addition begins to change with increasing involvement of more stable vinyl cation intermediates, since the phenyl group can localize positive charge on the adjacent carbon. In the two-step addition of CSI to acetylene **1h**, the fully developed vinyl cation intermediate XXIII is trapped as the uracil **19**, while **1i** leads to unsaturated amide **21** *via* intermediate XXVI.

Benzenediazonium Carboxylate (28).—The propensity of benzyne to undergo cycloaddition reactions with olefins,[35] conjugated dienes,[36] and trienes[37] suggested the possibility that benzoazetinone **27** might be prepared by the cycloaddition of benzyne with CSI.[38]

27
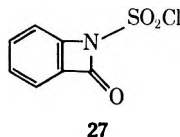
Thus benzyne precursor, benzenediazonium carboxylate (**28**), was prepared and treated with CSI at 70–80°. The sole product obtained was 3-chlorosulfonyl-1,2,3-benzotriazin-4-one (**29**, 80%) which was converted to 1,2,3-benzotriazin-4-one (**30**, 78%) on

29, R = SO₂Cl
30, R = H
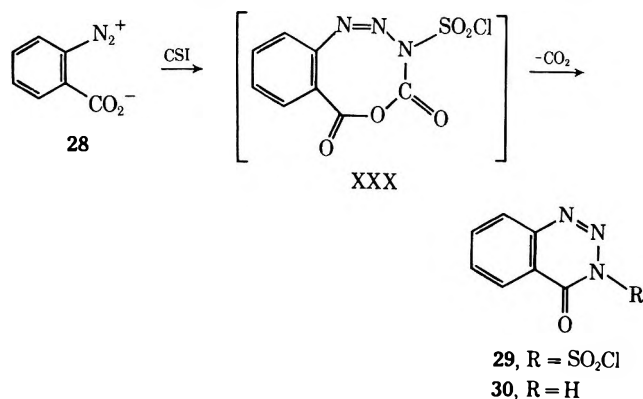
recrystallization from methanol. Benzotriazinone formation can be rationalized by initial attack of CSI on **28** to intermediate XXX, decarboxylation of which

(35) H. E. Simmons and R. W. Hoffmann in "Dehydrobenzene and Cycloalkynes," R. W. Hoffmann, Ed., Academic Press, New York, N. Y., 1967.

(36) M. Jones, Jr., and R. H. Levin, *J. Amer. Chem. Soc.*, **91**, 6411 (1969); R. W. Atkin and C. W. Rees, *Chem. Commun.*, 152 (1969).

(37) I. Tabushi, H. Yamada, Z. Yoshida, and H. Kuroda, *Tetrahedron Lett.*, 1093 (1971).

(38) The reaction of benzyne with phenyl isocyanate afforded only 9-phenoxyphenanthridine: J. C. Sheehan and G. D. Daves, Jr., *J. Org. Chem.*, **30**, 3247 (1965).

afforded **29**. Benzotriazinone **30** was also obtained in 20% yield by the reaction of **28** with CSI–pyridine salt[29] and *N,N'*-bischlorosulfonylurea.[3] No reaction was observed on irradiation of **30** in THF under an Hanovia 450-W lamp for 10 hr at room temperature; **30** was quantitatively recovered.

Experimental Section[39]

Reaction of CSI with Acetylenes (1a–g).—The general procedure used was as follows. To a stirred solution (0°) of the acetylene in dry CH₂Cl₂ (0.3 mol, 50 ml) was added dropwise an equimolar amount of freshly distilled CSI in the same solvent (0.3 mol, 30 ml). Upon completion of the addition, the reaction mixture was allowed to warm to room temperature and the reaction was continued until the ir spectrum showed the absence of the isocyanate peak at 4.4 μ (3–15 hr). The solvent was then evaporated *in vacuo* leaving a yellow oil which was extracted with seven 50-ml portions of boiling pentane. The solution was cooled to −20° to give the crude 1:1 adduct **2** which was purified *via* repeated recrystallizations from 1:3 ether–pentane. Concentration of the filtrate occasionally gave additional amounts of product. Variations in isolation procedure for **2** are noted under each acetylene.

2-Butyne (**1a**, 2.16 g, 0.040 mol, 9 hr) gave 3.25 g (42%) of 6-chloro-4,5-dimethyl-1,2,3-oxathiazine 2,2-dioxide (**2a**): mp 47.0–48.5°; uv (isooctane) 295 nm (ε 3700); ir (KBr) 1625 and 1500 (C=C and C=N), 1389 and 1212 cm⁻¹ (SO₂); nmr (CDCl₃) δ 2.43 (s, 3, CH₃C=N) and 2.12 (s, 3, CH₃C=C).

Anal. Calcd for C₅H₆NO₃SCl: C, 30.79; H, 3.08; N, 7.18. Found: C, 30.73; H, 3.45; N, 7.38.

3-Hexyne (**1b**, 24.6 g, 0.30 mol, 6 hr) gave 63.8 g (95%) of 6-chloro-4,5-diethyl-1,2,3-oxathiazine 2,2-dioxide (**2b**) as colorless needles: mp 54–55°; uv max (isooctane) 292 nm (ε 3600); ir (KBr) 1615 and 1490 (C=C and C=N), 1385 and 1209 cm⁻¹ (SO₂); nmr (CDCl₃) δ 3.05–2.40 (two quartets, 4, six equally spaced peaks, J = 7 Hz, CH₂CH₃), and 1.45–1.00 (two triplets, 6, CH₂CH₃).

Anal. Calcd for C₇H₁₀NO₃SCl: C, 37.59; H, 4.51; N, 6.26; mol wt, 224. Found: C, 37.78; H, 4.63; N, 6.02; mol wt, 229 (cryoscopic).

4-Octyne (**1c**, 8.8 g, 0.080 mol, 6 hr) gave 17.3 g (86%) of 6-chloro-4,5-di-*n*-propyl-1,2,3-oxathiazine 2,2-dioxide (**2c**) as colorless needles: mp 26.0–27.0° (from hexane); uv (isooctane) 293 nm (ε 3700); ir (KBr) 1610 and 1490 (C=C and C=N), 1399 and 1212 cm⁻¹ (SO₂); nmr (CDCl₃) δ 2.80–2.35 (m, 4, CH₂CH₂CH₃), 1.91–1.28 (m, 4, CH₂CH₂CH₃), and 1.20–0.85 (two triplets, 6, CH₂CH₂CH₃).

Anal. Calcd for C₉H₁₄NO₃SCl: C, 43.10; H, 5.57; N, 5.57. Found: C, 42.84; H, 5.41; N, 5.52.

2-Hexyne (**1d**, 12.3 g, 0.15 mol, 6 hr) gave 30.5 g (92%) of a mixture of 6-chloro-5-methyl-4-*n*-propyl-1,2,3-oxathiazine 2,2-dioxide (**2d**) and 6-chloro-4-methyl-5-*n*-propyl-1,2,3-oxathiazine

2,2-dioxide (2d'). The mixture solidified upon cooling to $-30°$ but all attempts to separate 2d from 2d' by fractional crystallization were unsuccessful. The nmr of this mixture indicated that the ratio of 2d to 2d' was 73:27:[41] ir (neat) 1625 and 1500 (C=C and C=N), 1390 and 1210 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 2.85–2.40 (m, 4, CH$_2$CH$_2$CH$_3$), 2.49 and 2.16 (two singlets, total 3, CH$_3$C=N, and CH$_3$C=C), 1.92–1.42 (m, 4, CH$_2$CH$_2$-CH$_3$), and 1.15–0.91 (t, 6, CH$_2$CH$_2$CH$_3$).

4,4-Dimethyl-2-pentyne (1e, 3.84 g, 0.040 mol) was treated with an equimolar amount of CSI in 10 ml of CH$_2$Cl$_2$ for 15 hr at room temperature to give 4.85 g (51%) of **4-tert-butyl-6-chloro-5-methyl-1,2,3-oxathiazine 2,2-dioxide** (2e): mp 65.0–66.0°; uv max (isooctane) 293 nm (ε 3800); ir (KBr) 1600 and 1470 (C=C and C=N), 1379 and 1200 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 2.30 (s, 3, CH$_3$C=C) and 1.40 (s, 9, tert-C$_4$H$_9$).

Anal. Calcd for C$_8$H$_{12}$NO$_3$SCl: C, 40.50; H, 5.07; N, 5.92. Found: C, 40.39; H, 5.02; N, 5.82.

Phenylmethylacetylene (1f, 4.64 g, 0.040 mol, 6 hr) gave 8.85 g (86%) of **6-chloro-5-methyl-4-phenyl-1,2,3-oxathiazine 2,2-dioxide** (2f) after extraction with three 20-ml portions of boiling hexane: mp 58.0–59.0°; uv max (CHCl$_3$) 297 nm (ε 12,700); ir (KBr) 1600 and 1475 (C=C and C=N), 1389 and 1190 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.58 (s, 5, C$_6$H$_5$) and 2.08 (s, 3, CH$_3$C=C)

Anal. Calcd for C$_{10}$H$_8$NO$_3$SCl: C, 46.70; H, 3.11; N, 5.45. Found: C, 36.53; H, 3.09; N, 5.52.

Phenylacetylene (1g, 10 g, 0.10 mol) gave 11.5 g (48%) of **6-chloro-4-phenyl-1,2,3-oxathiazine 2,2-dioxide** (2g). After addition of 1g to CSI, the mixture was stirred for 3 hr at 0° (the solution darkened), after which an equal volume of pentane was added and cooled to $-60°$. The dark solid which precipitated was filtered quickly and washed with three 5-ml portions of cold ether to give crude 2g which was unstable at room temperature. All attempts to further purify this adduct led to decomposition: mp 106–108° dec; uv max (CH$_2$Cl$_2$) 302 nm (ε 12,000); ir (KBr) seven bonds in 1720–1440-cm^{-1} region (C=C and C=N), 1379 and 1198 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 8.10–7.75 (m, 5, C$_6$H$_5$) and 6.97 (s, 1, HC=C).

Crude 2g (1.22 g, 5.0 mmol) was treated with benzenethiol-pyridine in acetone to give 0.6 g (38%) of **4-phenyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide** (6g) after the same work-up as 6f: mp 91.0–93.5° (from pentane–CH$_2$Cl$_2$); ir (KBr) five bands in 1585–1425-cm^{-1} region (C=C and C=N), 1379 and 1198 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.92–7.47 (m, 10, C$_6$H$_5$) and 6.37 (s, 1, C=CH).

Anal. Calcd for C$_{15}$H$_{11}$NO$_3$S$_2$: C, 56.78; H, 3.47; N, 4.42. Found: C, 56.82; H, 3.78; N, 4.64.

Reaction of Oxathiazines (2) with Nucleophiles. Thiophenol–Pyridine.—The general procedure used was as follows. A solution of pyridine in acetone (0.1 mol, 15 ml) was added dropwise (30 min) to a stirred solution ($-30°$) of 0.1 mol of oxathiazine (2) and 2 mol equiv of C$_6$H$_5$SH in 25 ml of acetone. After the mixture was stirred for an additional 30 min, an amount of water equal to the volume of solvent acetone was added slowly with stirring. The oil which separated was extracted with six 20-ml portions of ether. The combined ether extracts were dried (MgSO$_4$) and evaporated to dryness, and the residue was recrystallized to give the phenyl thioether 6. Any variations in isolation procedures for 6 are noted under each oxathiazine.

Compound 2a (0.59 g, 3.0 mmol) gave 0.35 g (44%) of **4,5-dimethyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide** (6a): mp 120–122° (from ether–pentane); ir (KBr) 1600 and 1481 (C=C and C=N), 1370 and 1205 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.52 (s, 5, C$_6$H$_5$), 2.35 (s, 3, N=CCH$_3$), and 2.11 (s, 3, C=CCH$_3$).

Anal. Calcd for C$_{11}$H$_{11}$NO$_3$S$_2$: C, 49.10; H, 4.09; N, 5.20. Found: C, 48.92; H, 3.87; N, 5.33.

Compound 2b (11.2 g, 0.050 mol) gave 5.2 g (35%) of **4,5-diethyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide** (6b): mp 92.0–93.0° (from ether–pentane); uv max (C$_2$H$_5$OH) 321 nm (ε 6200); ir (KBr) 1575 and 1471 (C=C and C=N), 1370 and 1190 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.43 (s, 5, C$_6$H$_5$), 2.80–2.30 (two quartets, 4, CH$_2$CH$_3$), and 1.35–0.95 (two triplets, 6, CH$_2$CH$_3$).

Anal. Calcd for C$_{13}$H$_{15}$NO$_3$S$_2$: C, 52.50; H, 5.09; N, 4.71. Found: C, 52.48; H, 5.09; N, 4.83.

Compound 2c (3.75 g, 0.015 mol) gave 1.30 g (27%) of **4,5-dipropyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide** (6c): mp

73.0–74.5° (from ether–pentane); ir (KBr) 1575 and 1450 (C=C and C=N), 1379 and 1205 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.42 (s, 5, C$_6$H$_5$), 2.73–2.25 (m, 4, CH$_2$CH$_2$CH$_3$), 1.92–1.30 (m, 4, CH$_2$CH$_2$CH$_3$), and 1.15–0.78 (two triplets, 6, CH$_2$CH$_2$CH$_3$).

Anal. Calcd for C$_{15}$H$_{19}$NO$_3$S$_2$: C, 55.40; H, 5.84; N, 4.31. Found: C, 55.47; H, 6.07; N, 4.36.

Compound 2e (0.50 g, 2.1 mmol) gave 0.2 g (31%) of **4-tert-butyl-5-methyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide** (6e): mp 87.0–89.0° (from ether–pentane); ir (KBr) 1563 and 1460 (C=C and C=N), 1379, and 1198 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.50 (s, 5, C$_6$H$_5$), 2.30 (s, 3, C=CCH$_3$), and 1.40 (s, 9, tert-C$_4$H$_9$).

Anal. Calcd for C$_{14}$H$_{17}$NO$_3$S$_2$: C, 54.01; H, 5.47; N, 4.52. Found: C, 53.81; H, 5.62; N, 4.72.

Compound 2f gave **5-methyl-4-phenyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide** (6f). To a stirred solution of 2.57 g (0.010 mol) of 2f and 2 mol equiv of C$_6$H$_5$SH in 25 ml of acetone cooled to $-60°$ was added dropwise a solution of 0.79 g (0.01 mol) of pyridine in 5 ml of acetone and the solution was stirred for 30 min. Pentane (50 ml) was then added with stirring at $-60°$. The precipitate was filtered while it was still cold, and the filtrate was evaporated in vacuo to dryness. The residual oil was deposited on a 1.0 × 20 cm column packed with silica gel and successively eluted with 50 ml of pentane, 50 ml of ether, and 50 ml of CH$_2$Cl$_2$. Evaporation of the CH$_2$Cl$_2$ fraction gave a yellow solid which was recrystallized from 1:3 CH$_2$Cl$_2$–pentane to afford 1.60 g (48%) of **5-methyl-4-phenyl-6-thiophenyl-1,2,3-oxathiazine 2,2-dioxide** (6f): mp 166.0–167.5°; ir (KBr) 1585, 1550, and 1455 (C=C and C=N), 1379 and 1190 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.59–7.53 (two doublets, 10, C$_6$H$_5$) and 2.12 (s, 3, C=CCH$_3$).

Anal. Calcd for C$_{16}$H$_{13}$NO$_3$S$_2$: C, 58.10; H, 3.93; N, 4.23. Found: C, 57.97; H, 3.87; N, 4.53.

Methanol.—To 75 ml of CH$_3$OH cooled in an ice bath was added 22.4 g (0.10 mol) of oxathiazine (2b) and the solution was stirred for 30 min at room temperature. After the CH$_3$OH was evaporated in vacuo, the residual oil was distilled to give 9.5 g (50%) of **methyl 2-ethyl-3-oxopentanoate** (9): bp 51–52° (0.6 mm) [lit.[42] bp 81–85° (11 mm)]; ir (neat) 1739 and 1709 cm^{-1} (C=O); nmr (neat) δ 3.72 (s, 3, CO$_2$CH$_3$), 3.48 (t, J = 7.5 Hz, 1, CH next to ethyl group), 2.58 (1, J = 7.5 Hz, 2, COCH$_2$CH$_3$), 2.12–1.60 (m, 2, CH$_2$CH$_3$), and 1.17–0.90 (t, 6, CH$_2$CH$_3$).

A second product, bp 110° (0.3 mm), was obtained in 2.5-g yield but could not be identified.

Water.—The general procedure used was as follows. To 50 ml of water was added 10 g (0.040 mol) of 2 and the mixture was heated to 50–60° at which reflux temperature 2 began to decompose rapidly. The solution was refluxed gently for 2 hr after which it was cooled slowly and extracted with three 30-ml portions of n-pentane. The combined pentane extracts were dried (MgSO$_4$), filtered, and distilled to give the ketone 7 identified where possible by comparison with an authentic sample.

Compound 2a (1.0 g, 5.0 mmol) gave 0.3 g (81%) of **2-butanone** (7a), bp 79.0°.

Compound 2b (10 g, 0.045 mol) gave 3.1 g (70%) of **3-hexanone** (7b), bp 124–125°.

Compound 2c (2.5 g, 0.010 mol) gave 1.0 g (80%) of **4-octanone** (7c), bp 52–53° (7 mm).

A mixture of 2d and 2d' (prepared from a 1:1 mixture of 2-hexyne and CSI) afforded a mixture of **3-hexanone** (7b) and **2-hexanone** (7d). To 10 g (0.045 mol) of mixture 2d and 2d' was added 50 ml of water and the solution was refluxed for 1 hr after which it was allowed to cool to room temperature and extracted with three 20-ml portions of CH$_2$Cl$_2$. The aqueous layer was saturated with NaCl and then extracted with three 20-ml portions of CH$_2$Cl$_2$. The combined CH$_2$Cl$_2$ extracts were dried (MgSO$_4$), filtered, and evaporated in vacuo. The residue was distilled to give 2.55 g (58%) of a mixture of 7b and 7d, bp 122–125°.

A vpc of this mixture demonstrated that the 7b:7d ratio was 75:25, while the nmr showed a 77:23 ratio: ir (CCl$_4$) 1725 cm^{-1} (C=O); nmr (neat) δ 2.70–2.27 (m, COCH$_2$), 2.13 (s, COCH$_3$), 1.85–1.28 (m, CH$_2$CH$_3$), and 1.20–0.85 (two triplets, CH$_2$CH$_3$). The integral ratio of these peaks were 4.3:1.0: 3.3:6.8.

Compound 2e (0.75 g, 3.2 mmol) gave 0.15 g (41%) of **2,2-dimethyl-3-pentanone** (7e). To a solution of 2e in 5 ml of

(41) The integral ratio of the methyl protons linked to C=C and C=N bonds were compared. The methyl protons linked to a C=N bond were always found to be more deshielded than those linked to a C=C bond.

(42) J. Buchi, P. Schneeberger, and R. Lieberherr, *Helv. Chem. Acta*, **36**, 1402 (1953).

acetone was added 20 ml of H_2O and the solution was refluxed gently for 4 hr, after which it was extracted with three 10-ml portions of CH_2Cl_2. The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was distilled to give pure 7e: bp 123–124° (lit.[43] bp 125–126°); ir (CCl_4) 1709 cm^{-1} ($C=O$); nmr ($CDCl_3$) δ 2.50 (q, 2, CH_2CH_3), 1.15 (s, 9, *tert*-C_4H_9), and 1.00 (t, 3, CH_2CH_3).

Compound 2f (2.0 g, 8.0 mmol) gave 0.80 g (77%) of propiophenone (7f), bp 217°.

Compound 2g (3.0 g, 0.012 mol) gave 0.5 g (52%) of acetophenone (7g) after the reaction (30 min at 65°) was followed by extraction with three 10-ml portions of ether.

Hydrolysis of 2g (2.0 g, 8.2 mmol) with 10 ml of saturated aqueous $NaHCO_3$ solution at 0° for 1 hr also afforded 0.3 g (31%) of 7g.

Sodium Methoxide–Methanol.—The general procedure used was as follows. To a cooled (0°) solution of oxathiazine 2 in absolute CH_3OH (1 mmol/2 ml) was added slowly a solution of $NaOCH_3$ (3 mol equiv) prepared by the inverse Tishler procedure[44] in 10 ml of CH_3OH, and the solution was stirred for 30 min at 0°.

The reaction mixture was neutralized with 4 N HCl solution and after the solvent was evaporated *in vacuo* the residual oil was extracted with three 40-ml portions of 1:1 CH_2Cl_2–H_2O. The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and evaporated. In the case of 2b, the residual oil was distilled to give 9. The combined water extracts were acidified with 4 N HCl and then extracted with three 20-ml portions of CH_2Cl_2. These combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and evaporated to give crude 8.

Compound 2a (0.4 g, 2.0 mmol) gave 0.15 g (33%) of methyl 2-methyl-3-methoxysulfonylamino-*trans*-2-butenoate (8a): ir (neat) 3280 (NH), 1730 cm^{-1} ($C=O$); nmr ($CDCl_3$) δ 5.80–5.37 (broad singlet, 1, NH), 3.88 (s, 3, SO_2CH_3), 3.74 (s, 3, CO_2CH_3), 2.22 (s, 3, $C=CCH_3$), and 1.36 (s, 3, $C=CCH_3$).

Compound 2b (2.24 g, 0.010 mol) gave 0.31 g (20%) of 9 and 1.26 g (50%) of methyl 2-ethyl-3-methoxysulfonylamino-*trans*-2-pentenoate (8b). Compound 8b was purified by chromatography (a 1.0 × 20 cm column packed with silica gel) using ether as eluent: ir (neat) 3200 (NH), 1670 cm^{-1} ($C=O$); nmr ($CDCl_3$) δ 6.80–7.00 (broad, 1, NH), 3.89 and 3.70 (two singlets, 6, CO_2CH_3 and SO_3CH_3), 2.90–2.20 (m, 4, CH_2CH_3), and 1.30–0.90 (two triplets, 6, CH_2CH_3).

Compound 2c (2.0 g, 8.0 mmol) gave 0.90 g (40%) of methyl 2-*n*-propyl-3-methoxysulfonylamino-*trans*-2-hexenoate (8c): bp 128–130° (0.3 mm); ir (neat) 3430 (NH), 1740 cm^{-1} ($C=O$) nmr ($CDCl_3$) δ 5.66–5.32 (broad singlet, 1, NH) 3.85 (s, 3; SO_3CH_3), 3.72 (s, 3, CO_2CH_3), 2.62–2.05 (m, 4, $CH_2CH_2CH_3$), 1.86 (m, 4, $CH_2CH_2CH_3$), and 1.12–0.78 (two triplets, 6, $CH_2CH_2CH_3$).

Compound 2e (0.50 g, 2.1 mmol) gave 0.6 g (98%) of methyl 2,4,4-trimethyl-3-methoxysulfonylamino-*trans*-2-pentenoate (8e) which could not be distilled without decomposition. The crude 8e was purified by chromatography (0.5 × 20 cm column packed with silica gel using 1:1 pentane–ether mixture as an eluent): ir (neat) 3280 (NH), 1724 cm^{-1} ($C=O$); nmr ($CDCl_3$) δ 6.31 (s, 1, NH), 3.97 (s, 3, SO_3CH_3), 3.78 (s, 3, CO_2CH_3), 2.02 (s, 3, $C=CCH_3$), and 1.20 (s, 9, *tert*-C_4H_9).

Compound 2f (2.0 g, 7.8 mmol) gave 1.65 g (79%) of methyl 2-methyl-3-methoxysulfonylamino-*trans*-cinnamate (8f) which could not be distilled without decomposition. The crude 8f was purified by chromatography (0.5 × 20 cm column packed with silica gel using ether as an eluent): ir (neat) 3226 (NH) 1739 cm^{-1} ($C=O$); nmr ($CDCl_3$) δ 8.10–7.90 (broad singlet, 1, NH), 7.40 (s, 5, C_6H_5), 3.80 (s, 3, SO_3CH_3), 3.68 (s, 3, CO_2CH_3), and 1.65 (s, 3, $C=CCH_3$).

Compound 2g (1.5 g, 6.2 mmol) gave 0.5 g (30%) of methyl 3-methoxysulfonylamino-*trans*-cinnamate (8g) as colorless needles: mp 80.5–81.0° (from CH_3OH–pentane); uv max (CH_3OH) 273.5 nm (ε 5400); ir (KBr) 3150 (NH), 1681 cm^{-1} ($C=O$); nmr ($CDCl_3$) δ 7.52 (m, 6, NH and C_6H_5), 5.42 (s, 2, $C=CH$), 3.88 and 3.83 (two singlets, 6, SO_3CH_3 and CO_2CH_3).

Anal. Calcd for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.80; N, 5.27. Found: C, 48.54; H, 4.80; N, 5.23.

Catalytic Hydrogenation of 8b and 8g.—A mixture of 1.0 g (4.0 mmol) of 8b in 100 ml of C_2H_5OH and 0.2 g of 5% Pd/C

was hydrogenated in Paar apparatus under 50 psi for 20 hr. The catalyst was filtered and the solvent evaporated to dryness. The residual oil was purified by chromatography (0.5 × 15 cm column packed with silica gel; ether as eluent) to give 0.80 g (80%) of methyl 2-ethyl-3-methoxysulfonylaminovalerate (10b). Compound 10b is a viscous oil which could not be distilled without decomposition: ir (neat) 3250 (NH), 1730 cm^{-1} ($C=O$); nmr ($CDCl_3$) δ 6.90 (broad singlet, 1, NH), 3.89 and 3.70 (two singlets, 6, OCH_3), 3.60–3.40 (m, 1, CH next to CH_2 and NH), 2.95–2.60 (m, 1, CHCO), 2.05–1.60 (m, 4, CH_2CH_3), and 1.30–1.00 (t, 6, CH_2CH_3).

Hydrogenation (5% Pd/C) of 8g (1.0 g, 3.7 mmol) gave 0.75 g (75%) of methyl 3-methoxysulfonylamino-3-phenylpropanoate (10g). Compound 10g was stable at room temperature but unstable to distillation. Vpc indicated the presence of only a single component: ir (neat) 3226 (NH), 1709 ($C=O$), 1342 and 1163 cm^{-1} (SO_2); uv max (C_2H_5OH) 206.5 nm (ε 8450), 263.5 (790); nmr ($CDCl_3$) δ 7.40 (s, 5, C_6H_5), 6.25 (d, J = 8.5 Hz, 1, NH), 5.10–4.70 (m, 1, CH next to NH and CH_2, J = 6.5 Hz), 3.60 and 3.55 (two singlets, 6, OCH_3), and 2.90 (d, J = 6.5 Hz, 2, CH_2CO).

Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.35; H, 5.49; N, 5.13. Found: C, 48.18; H, 5.58; N, 5.06.

Reaction of 1-Chlorosulfonyl-*cis*-3,4-dimethyl- (11b) and 1-Chlorosulfonyl-4-phenyl-2-azetidinone (11g) with Sodium Methoxide–Methanol.—To a solution of 2.2 g (0.010 mol) of 11b[13b] in 10 ml of CH_3OH cooled to 0° was added slowly a solution of $NaOCH_3$ (0.03 mol equiv) in CH_3OH, and the solution was stirred for 24 hr at room temperature. The solution was neutralized with 4 N HCl and the solvent then was removed *in vacuo*. The residue was extracted with three 10-ml portions of CH_2Cl_2. The solution was dried ($MgSO_4$) and purified by chromatography (10 × 20 cm column packed with silica gel; ether as eluent) to give 2.3 g (80%) of 10b.[13b] Similar treatment of 11g[13b] afforded 10g in 50% yield.

Reduction of 2b with LiAlH$_4$ (2 Mol Equiv).—A slurry of 3.8 g (0.10 mol) of LiAlH$_4$ in 250 ml of anhydrous ether was added slowly to a stirred solution of 11.2 g (0.50 mol) of 2b in 50 ml of anhydrous ether. The mixture was stirred at room temperature for 30 min and then decomposed with 30% NH$_4$Cl solution. The solid was filtered and washed with five 10-ml portions of ether. The combined filtrates were dried ($MgSO_4$), filtered, and evaporated. The residue was added to 50 ml of a saturated solution of 2,4-DNPH in CH_3OH and the solution was allowed to stand for 2 hr. Concentration of this solution gave an orange solid which was recrystallized twice from C_2H_5OH to give 0.5 g (30%) of the DNPH derivative of 2-ethyl-2-pentenal (12): mp 170.5–171.5° (lit.[45] mp 173°); ir (KBr) 1613 cm^{-1} ($C=C$); nmr ($CDCl_3$) δ 11.06 (s, 1, NH), 9.10 (d, 1, CH=N), 8.40–7.26 (m, 3, aromatic), 5.90 (t, J = 4 Hz, 1, C=CH), 2.66–2.10 (m, 4, CH_2CH_3), and 1.30–0.90 (two triplets, 6, CH_2CH_3).

Reaction of 2b with LiAlH$_4$ (4 Mol Equiv).—To a slurry of 16.2 g (0.43 mol) of LiAlH$_4$ in 300 ml of anhydrous ether cooled to 0° was added a solution of 22.4 g (0.10 mol) of 2b in 100 ml of anhydrous ether. The mixture was stirred overnight at room temperature and then decomposed in the cold with 30% NH$_4$Cl. The solid was filtered and washed with 50 ml of ether. The combined filtrates were dried ($MgSO_4$), filtered, and evaporated. The residual yellow oil was distilled to give 4.1 g (36%) of 2-ethyl-2-penten-1-ol (13): bp 76–77° (30 mm) [lit.[46] bp 66–67° (25 mm)]; ir (neat) 3226 cm^{-1} (OH); nmr (neat) δ 5.40 (t, J = 5 Hz, 1, C=CH), 4.47 (broad singlet, 1, OH), 4.05 (d, J = 7.5 Hz, 2, CH_2OH), 2.32–1.82 (m, 4, CH_2CH_3), and 1.2–0.85 (two triplets, 6, CH_2CH_3).

Reduction of Oxathiazines (2) with LiAlH$_4$ (0.5 Mol Equiv).— The general procedure used was as follows. To a solution of 2 in anhydrous ether (0.050 mol/75 ml) was added slowly (20 min) a slurry of LiAlH$_4$ (0.5 mol equiv) in anhydrous ether (0.025 mol/ 100 ml) with vigorous stirring. The mixture was stirred for 30 min at room temperature and then a saturated solution (30%) of NH$_4$Cl was added until any reaction ceased. The mixture was filtered through filter cell and the solid was washed with 50 ml of ether. The combined filtrates were dried ($MgSO_4$), filtered, and evaporated. The residual yellow oil was chromatographed on silica gel (1 × 20 cm column) with ether as eluent to give the pure dihydro derivative of oxathiazine (3). Variations in isolation procedure of 3 are noted under each oxathiazine.

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Compound **2a** (0.97 g, 5.0 mmol) gave 0.60 g (62%) of 6-chloro-4,5-dimethyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**3a**). After the reaction, crude **3a** was deposited on a 0.5 × 10 cm silica gel column and eluted successively with 20 ml of pentane and 20 ml of ether. Evaporation of both fractions afforded **3a** as a viscous oil. Neither crystallization nor distillation of **3a** was successful but tlc indicated the presence of only a single component: ir (neat) 3226 (NH), 1653 (C=C), 1370 and 1198 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 5.24–4.98 (broad doublet, 1, NH), 4.33–3.88 (m, 1, CHCH$_3$), 1.82 (s, 3, C=CCH$_3$), and 1.52–1.40 (d, 3, CHCH$_3$).

Anal. Calcd for C$_5$H$_8$NO$_3$SCl: C, 30.45; H, 4.05; N, 7.12. Found: C, 30.68; H, 4.06; N, 7.11.

Compound **2b** (11.2 g, 0.050 mol) gave 9.0 g (81%) of 6-chloro-4,5-diethyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**3b**): mp 58.0–59.0° (from pentane): uv max (*n*-hexane) 233 nm (ε 1500); ir (KBr) 3195 (NH), 1642 (C=C), 1364 and 1202 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 5.00 (d, *J* = 7 Hz, 1, NH), 3.93 (X portion of an ABX pattern, J_{BX} = 5.5, J_{AX} = 7.5 Hz, further split by NH, *J* = 7 Hz, 1, CH next to ethyl group), 2.50–1.60 (m, 4 CH$_2$CH$_3$), and 1.30–0.85 (m, 6, CH$_2$CH$_3$).

Anal. Calcd for C$_7$H$_{12}$NO$_3$SCl: C, 37.25; H, 5.36; N, 6.26; mol wt, 226. Found: C, 37.11; H, 5.26; N, 6.06; mol wt, 225 (from mass spec).

Compound **3b** can be recrystallized from hot water without decomposition.

Compound **2c** (5.10 g, 0.020 mol) gave 3.35 g (66%) of 6-chloro-4,5-di-*n*-propyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**3c**): mp 34.5–35.0° (from 1:1 pentane–ether); ir (KBr) 3226 (NH), 1639 (C=C), 1370 and 1198 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 5.20–5.00 (broad doublet, 1, NH), 4.27–3.88 (m, 1, CH next to *n*-propyl group), 2.38–2.07 (m, 2, C=CCH$_2$CH$_2$CH$_3$), 1.86–1.30 (m, 6, CH$_2$ of *n*-propyl groups), and 1.17–0.85 (two triplets, 6, CH$_2$CH$_3$).

Anal. Calcd for C$_9$H$_{16}$NO$_3$SCl: C, 42.71; H, 6.33; N, 5.54. Found: C, 42.63; H, 6.48; N, 5.41.

Compound **2e** (0.80 g, 3.3 mmol) gave 0.4 g (50%) of 4-*tert*-butyl-6-chloro-5-methyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**3e**): mp 74.0–75.0° (from 1:1 ether–pentane); ir (KBr) 3226 (NH), 1626 (C=C), 1399 and 1205 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 5.67 (d, *J* = 5.5 Hz, 1, NH), 3.79 (d, *J* = 5.5 Hz, 1, CH next to NH), 1.95 (s, 3, C=CCH$_3$), and 1.10 (s, 9, *tert*-C$_4$H$_9$).

Anal. Calcd for C$_8$H$_{14}$NO$_3$SCl: C, 40.17; H, 5.35; N, 5.85. Found: C, 40.20; H, 5.77; N, 5.98.

Compound **2f** (2.10 g, 8.2 mmol) gave 1.10 g (52%) of 6-chloro-5-methyl-4-phenyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**3f**): colorless needles; mp 83.0–84.5° (from 1:3 ether–pentane); ir (KBr) 3226 (NH), 1653 (C=C), 1408 and 1205 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.40 (s, 5, C$_6$H$_5$), 5.10 (broad singlet, 1, CH), 4.90–4.70 (broad singlet, 1, NH), and 1.57 (s, 3, C=CCH$_3$).

Anal. Calcd for C$_{10}$H$_{10}$NO$_3$SCl: C, 46.33; H, 3.86; N, 5.40. Found: C, 46.19; H, 4.10; N, 4.99.

Methylation of 3.—The general procedure used was as follows. To a stirred solution of **3** and an excess of CH$_3$I (3–5 mol equiv) in acetone (15 ml/0.01 mol) was added slowly an equimolar amount of K$_2$CO$_3$ and the mixture was stirred for 20 hr at room temperature. The mixture was then filtered and the filtrate evaporated *in vacuo* leaving a yellow oil which was dissolved in ether. Addition of pentane and cooling to −30° precipitated the *N*-methyl derivative **4**. Any variation in reaction and isolation procedures for **4** are noted under each dihydro derivative.

Compound **3a** (0.5 g, 3.0 mmol) gave 0.35 g (65%) of 6-chloro-3,4,5-trimethyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**4a**): mp 29.0–30.0° (from hexane); ir (KBr) 1653 (C=C), 1399 and 1212 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 4.10 (q, *J* = 7.5 Hz, 1, CHCH$_3$), 2.92 (s, 3, NCH$_3$), 1.81 (s, 3, C=CCH$_3$), and 1.52 (d, *J* = 7.5 Hz, 3, CHCH$_3$).

Anal. Calcd for C$_6$H$_{10}$NO$_3$SCl: C, 34.12; H, 4.74; N, 6.65. Found: C, 34.38; H, 5.01; N, 6.81.

Compound **3b** (5.0 g, 0.022 mol) gave 3.2 g (64%) of 6-chloro-4,5-diethyl-3-methyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**4b**): mp 31.5–32.0° (from hexane); ir (KBr) 1653 (C=C), 1399 and 1176 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 3.80–3.47 (two doublets, J_{AX} = 10.0, J_{BX} = 5.5 Hz, 1, CH next to ethyl group), 2.92 (s, 3, NCH$_3$), 2.50–1.70 (m, 4, CH$_2$CH$_3$), and 1.3–0.9 (two triplets, 6, CH$_2$CH$_3$).

Anal. Calcd for C$_8$H$_{14}$NO$_3$SCl: C, 40.10; H, 5.85; N, 5.85. Found: C, 39.98; H, 5.98; N, 5.73.

Compound **3c** (1.5 g, 6.0 mmol) gave 1.15 g (73%) of 6-chloro-3-methyl-4,5-di-*n*-propyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**4c**). The crude **4c** was chromatographed on silica gel (0.5 × 15 cm column) with 2:1 ether–pentane as eluent to afford pure **4c** as a viscous oil, which could not be distilled without decomposition: ir (neat) 1653 (C=C), 1399 and 1212 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 3.90–3.60 (two doublets, J_{AX} = 10.0, J_{BX} = 4.0 Hz, 1, CH next to *n*-propyl group), 2.90 (s, 3, NCH$_3$), 2.37–1.93 (m, 2, =CCH$_2$CH$_2$CH$_3$), 1.83–1.22 (m, 6, =CCH$_2$CH$_2$CH$_3$ and CHCH$_2$CH$_2$CH$_3$), and 1.10–0.80 (two triplets, 6, CH$_2$CH$_2$CH$_3$).

Anal. Calcd for C$_{10}$H$_{18}$NO$_3$SCl: C, 45.00; H, 6.74; N, 5.24. Found: C, 45.30; H, 6.78; N, 5.25.

Compound **3e** (0.20 g, 0.80 mmol) gave 0.10 g (48%) of 6-chloro-3,5-dimethyl-4-*tert*-butyl-3,4-dihydro-1,2,3-oxathiazine 2,-2-dioxide (**4e**). To a solution of **3e** in 5 ml of DMSO was added large excess of CH$_3$I (5 g, 0.04 mol) and K$_2$CO$_3$ (0.1 g, 1 mmol). The mixture was stirred for 10 hr at room temperature after which 10 ml of CH$_2$Cl$_2$ was added. The mixture was then filtered, and the filtrate was extracted with ten 10-ml portions of water to remove DMSO. The solution was dried (MgSO$_4$), filtered, and evaporated *in vacuo* to leave a viscous oil which was crystallized from pentane to give **4e**: mp 50.0–51.0°; ir (KBr) 1667 (C=C), 1351 and 1176 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 3.28 (s, 1, CH next to *tert*-butyl group), 3.00 (s, 3, NCH$_3$), 1.98 (s, 3, C=CCH$_3$), and 1.07 (s, 9, *tert*-C$_4$H$_9$).

Anal. Calcd for C$_9$H$_{16}$NO$_3$SCl: C, 42.70; H, 6.32; N, 5.53. Found: C, 42.71; H, 6.25; N, 5.45.

Compound **3e** (2.55 g, 0.010 mol) gave 1.95 g (73%) of 6-chloro-3,5-dimethyl-4-phenyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**4f**). The crude **4f** was deposited on a 0.5 × 20 cm column packed with silica gel and eluted successively with 40 ml each of pentane, ether, and CH$_2$Cl$_2$. Evaporation of the first two fractions gave **4b** as a viscous oil, which could not be distilled without decomposition. Tlc indicated the presence of only a single component: ir (neat) 1667 (C=C), 1370 and 1207 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.40 (s, 5, C$_6$H$_5$), 4.70 (s, 1, CH next to phenyl group), 2.70 (s, 3, NCH$_3$), and 1.58 (s, 3, C=CCH$_3$).

Anal. Calcd for C$_{11}$H$_{12}$NO$_3$SCl: C, 48.40; H, 4.39; N, 5.13. Found: C, 48.26; H, 4.46; N, 5.33.

Dechlorination of 4 with Li-*tert*-BuOH.—To a stirred solution of 0.50 g (2.0 mmol) of **4b** and 1.0 g (0.014 mol) of *tert*-BuOH in 20 ml of dry THF cooled in an ice bath was slowly added 0.20 g (0.029 mol) of finely chopped Li wire under nitrogen. After 20 min, a vigorous exothermic reaction began which was maintained at steady reflux for 2 hr. As the exothermic reaction subsided the reaction mixture was heated externally to continue refluxing for an additional 2 hr and then stirred finally at room temperature for 1 hr. The mixture was poured onto 20 ml of ice and extracted with six 10-ml portions of ether. The combined ether extracts were washed with three 20-ml portions of water and two 10-ml portions of saturated NaCl solution. The ethereal solution was dried (MgSO$_4$), filtered, and evaporated *in vacuo* leaving a white solid which was recrystallized three times from ether–pentane to give 0.4 g (93%) of 4,5-diethyl-3-methyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**5b**) as colorless needles: mp 35.5–36.0°; ir (CHCl$_3$) 1660 (C=C), 1389 and 1176 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 6.30 (m, 1, C=CH), 3.92–3.57 (two doublets, J_{AX} = 10, J_{BX} = 5 Hz, 1, CH next to ethyl group), 2.90 (s, 3, NCH$_3$), 2.32–1.72 (m, 4, CH$_2$CH$_3$), and 1.17–0.92 (two triplets, 6, CH$_2$CH$_3$).

Anal. Calcd for C$_8$H$_{15}$NO$_3$S: C, 46.82; H, 7.32; N, 6.82. Found: C, 46.64; H, 7.42; N, 6.58.

Compound **4a** (0.50 g, 2.3 mmol) gave 0.35 g (86%) of 3,4,5-trimethyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**5a**) after similar work-up as **5b**: mp 32.0–33.0°; ir (CHCl$_3$) 1653 (C=C), 1379 and 1190 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 6.34–6.20 (broad singlet, 1, C=CH), 3.98 (q, *J* = 7 Hz, 1, CHCH$_3$), 2.90 (s, 3, NCH$_3$), 1.72 (s, 3, C=CCH$_3$), and 1.51 (d, 3, CHCH$_3$, *J* = 7 Hz).

Compound **4c** (0.50 g, 1.9 mmol) gave 0.3 g (69%) of 3-methyl-4,5-di-*n*-propyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (**5c**) as a viscous oil after a similar work-up as **5b** followed by chromatography on a 0.5 × 20 cm silica gel column using ether as eluent. Compound **5b** could not be distilled without decomposition: ir (neat) 1653 (C=C), 1380 and 1189 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 6.27 (d, *J* = 1.5 Hz, 1, C=CH), 3.90–3.65 (two broad peaks, 1, CH next to propyl group), 2.90 (s, 3, NCH$_3$), 2.25–1.80 (m, 2, C=CCH$_2$CH$_2$CH$_3$), 1.80–1.15 (m, 6, CHCH$_2$-

CH_2CH_3 and $C = CCH_2CH_2CH_3$), and 1.10–0.78 (two triplets, 6, $CH_2CH_2CH_3$).

Compound **4f** (1.0 g, 3.6 mmol) gave 0.6 g (69%) of **3,5-dimethyl-4-phenyl-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide (5f)** after a similar work-up as **5b**. The product was a pale yellow viscous oil which could not be distilled without decomposition, but tlc indicated the presence of only a single component: ir (neat) 1613 (C=C), 1408 and 1335 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 7.42–7.15 (m, 5, C$_6$H$_5$), 6.02–5.90 (m, 1, C=CH), 4.72–4.55 (broad singlet, 1, CHC$_6$H$_5$), 2.98 (s, 3, NCH$_3$), and 2.05 (s, 3, C=CCH$_3$).

Catalytic Hydrogenation of 2b and 6b.—A mixture of 3.5 g (1.56 × 10^{-2} mol) of **2b** in 30 ml of ethyl acetate and 0.2 g of 5% Pd–BaSO$_4$ was hydrogenated in a Paar apparatus under 50 psi of hydrogen for 20 hr. The catalyst was filtered and the solvent evaporated to dryness. Chromatographic purification of the residue led to decomposition. This residual oil was dissolved in 10 ml of CH$_2$Cl$_2$ and 4 N KOH solution was added with stirring until it was neutral to litmus paper. The CH$_2$Cl$_2$ layer was separated, dried (MgSO$_4$), and distilled to give 1.56 g (77%) of **3-hexanone (7b)**.

Catalytic hydrogenation (30% Pd/C) of **6b** followed by similar hydrolytic work-up gave 0.78 g (39%) of **phenyl 2-ethyl-3-oxothiopentanoate (17)** as a yellow oil which could not be distilled without decomposition: ir (neat) 1720 and 1690 cm^{-1} (C=O); nmr (CCl$_4$) δ 7.35–7.00 (m, 5, C$_6$H$_5$), 3.50 (t, J = 6.0 Hz, 1, CH next to CH$_2$), 2.70–2.40 (q, 2, CH$_2$CO), 1.90–1.60 (m, 1, CH$_2$CH$_3$), and 1.02 (t, 6, CH$_2$CH$_3$, J = 8 Hz).

Ozonation of 2b.—Excess ozone (3.4 × 10^{-2} mol) was bubbled through a solution of 3.0 g (1.3 × 10^{-2} mol) of **2b** in 150 ml of CH$_2$Cl$_2$ at 0°. The solution was then flushed with nitrogen and warmed to room temperature. Upon addition of 100 ml of 1:1 10% NaOH–30% H$_2$O$_2$ solution, the mixture was agitated with nitrogen bubbling for 1 hr and then refluxed for 18 hr. The CH$_2$Cl$_2$ layer was separated from water, washed with two 50-ml portions of 5% NaOH solution, and dried (MgSO$_4$). Removal of the solvent in vacuo afforded 0.3 g (20%) of **3,4-hexanedione (14)**, bp 127–129° (lit.[47] bp 130°). The aqueous layer was concentrated to 1/3 of the initial volume, acidified with concentrated HCl, saturated with NaCl, and then extracted with three 30-ml portions of ether. The solvent was evaporated to dryness leaving the residue from which was obtained 0.2 g (14%) of **propionic acid (15)**.

Permanganate Oxidation of 2b.—To a solution of 2.29 g (0.010 mol) of **2b** in 20 ml of acetone was added an oxidation mixture composed of 1.26 g of KMnO$_4$ and 0.96 g of MgSO$_4$ in 30 ml of water. The mixture was stirred for 2 hr at room temperature after which 10 g of NaHSO$_3$ was added to destroy excess oxidant. The mixture was filtered, the acetone was evaporated, and the remaining aqueous layer was extracted with six 20-ml portions of ether. The combined ether extracts were dried (MgSO$_4$) and the solvent was evaporated to leave an oil which was distilled to give 0.7 g (47%) of **propionic acid (15)** and 0.2 g (20%) of **3-hexanone (7b)**.

Alkaline Peroxide Oxidation of 3b.—To a solution of 1.0 g (0.040 mol) of **3b** and 5 ml of 30% H$_2$O$_2$ in 20 ml of CH$_3$OH was added slowly 5 ml of 10% NaOH solution. The solution was warmed on a steam bath for 30 min and 20 ml of water added. The resulting aqueous solution was acidified with 0.1 N HCl and extracted with four 10-ml portions of ether. The combined ether extracts were dried (MgSO$_4$), filtered, and evaporated in vacuo. The residual oil was purified by chromatography using a 0.5 × 15 cm column packed with silica gel and ether as eluent to give **2-ethyl-3-(aminosulfonic acid)pentanoic acid (18)** as a single component on tlc. Compound **18** was unstable to distillation and could not be induced to crystallize: ir (neat) 3250 (NH), 1710 cm^{-1} (C=O); nmr (D$_2$O) δ 3.72–3.40 (m, 1, CH next to CH$_2$, CH and NH), 3.00–2.65 (m, 1, CH next to CH$_2$ and CO$_2$H), 2.05–1.60 (m, 4, CH$_2$CH$_3$), and 1.30–0.98 (t, 6, CH$_2$CH$_3$).

Compound **3b** (2.4 g, 0.010 mol) was treated with 25 ml of 10% KOH solution for 18 hr at room temperature, followed by acidification with concentrated HCl and evaporation to dryness. The residue was extracted with three 20-ml portions of CH$_2$Cl$_2$ and the combined extracts were dried (MgSO$_4$). Evaporation of the solvent in vacuo afforded an oil which was chromatographed

using 1 × 20 cm silica gel column and ether as eluent to give 1.2 g (50%) of **18** as a single component on tlc.

Reaction of Diphenylacetylene (1h) with CSI.—A solution of 3.6 g (0.020 mol) of **1h** and 3.50 g (0.025 mol) of CSI in 30 ml of CH$_2$Cl$_2$ was stirred for 10 days at room temperature. The solvent was evaporated in vacuo and the residue was extracted with four 10-ml portions of n-pentane to remove unreacted **1h**. The residual oil was then extracted with five 20-ml portions of ether. The combined ether extracts were evaporated in vacuo leaving a dark solid which was recrystallized several times from CH$_3$OH to give 1.20 g (17%) of **methyl 2,3-diphenyl-3-(methoxysulfonylamino)propenoate (8h)**: mp 131.0–133.5°; ir (KBr) 3279 (NH), 1653 (C=O), 1389 and 1176 (SO$_2$), 1266 cm^{-1} (OCH$_3$); uv max (CH$_3$OH) 290 nm (ε 15,000); nmr (CDCl$_3$) δ 11.80 (s, 1, NH), 7.20–7.00 (two peaks, 10, C$_6$H$_5$), and 3.75 and 3.70 (two singlets, 6, OCH$_3$).

Anal. Calcd for C$_{17}$H$_{17}$NO$_5$S: C, 58.80; H, 4.90; N, 4.03. Found: C, 59.20; H, 5.06; N, 4.03.

To a solution of the ether extract in 20 ml of CH$_2$Cl$_2$ was added 20 ml of H$_2$O and the whole mixture was refluxed for 1 hr. The CH$_2$Cl$_2$ layer was separated, dried (MgSO$_4$), and evaporated in vacuo. The residue was recrystallized several times from ethanol to give 0.5 g (13%) of **deoxybenzoin (7h)**: mp 55–57° (lit.[48] mp 55–56°).

The ether insoluble part was crystallized from the 1:1 MEK-pentane mixture to give 5.2 g (57%) of **1,3-bis(chlorosulfonyl)-5,6-diphenyluracil (19)** as a pale yellow solid: mp 186–188° dec; ir (KBr) 1745 and 1700 (C=O), 1375 and 1200 cm^{-1} (SO$_2$); nmr (DMSO-d_6) δ 7.40–7.00 (aromatic).

Compound **19** is unstable at room temperature and all attempts to recrystallize it from hot CH$_3$OH quantitatively converted it to **5,6-diphenyluracil (20)**: mp 302–303°; ir (KBr) 3333 (NH), 1725 and 1650 cm^{-1} (C=O); uv max (CH$_3$OH) 292 nm (ε 10,500); nmr (DMSO-d_6) 8.10–7.80 (two peaks, 2, CONH) and 7.35–7.00 (two peaks, 10, C$_6$H$_5$).

Anal. Calcd for C$_{16}$H$_{12}$N$_2$O$_2$: C, 72.72; H, 4.56; N, 10.60. Found: C, 72.48; H, 4.86; N, 10.40.

Reaction of 1-Hexyne (1i) with CSI.—A solution of 4.92 g (0.060 mol) of **1i** in 10 ml of dry CH$_3$NO$_2$ was added to a solution of 8.52 g (0.060 mol) of CSI in 10 ml of dry CH$_3$NO$_2$ and the whole mixture was stirred for 24 hr at ambient temperature. The solvent was evaporated in vacuo to dryness; the residual oil was extracted with three 10-ml portions of n-pentane to give **N-chlorosulfonyl-2-heptynamide (21)** which could not be further purified by distillation or chromatography without decomposition.

To a stirred solution of 2.4 g (0.010 mol) of crude **21** in 10 ml of CH$_2$Cl$_2$ was added dropwise excess aniline (0.03 mol) at 0° and stirring was continued for 2 hr. Addition of 10 ml of pentane to the reaction mixture precipitated a yellow solid which was filtered and the filtrate was extracted with ten 10-ml portions of H$_2$O to remove unreacted aniline. The CH$_2$Cl$_2$ layer was dried (MgSO$_4$), filtered, and evaporated in vacuo leaving an oil which was purified by chromatography (1.0 × 20 cm column packed with silica gel; a 1:1 pentane–ether mixture as eluent) to give the **N-sulfonylanilide of 2-heptynamide (23, 30%)** as a single component on tlc: mp 142–144°; ir (CHCl$_3$) 3200 (NH), 1650 cm^{-1} (C=O); nmr (CDCl$_3$) δ 11.80 (s, 2, CONH), 8.65–7.90 (m, 5, C$_6$H$_5$), 5.90 (s, 1, NH), 2.90–2.30 (m, 2, CCH$_2$), 1.85–1.20 (m, 4, CH$_2$CH$_3$), and 1.00 (t, 3, CH$_2$CH$_3$, J = 6 Hz).

Hydrolysis of the crude **21** with 4 N NaOH in acetone led to **2-heptynamide (22, 20%)**: bp 130–132° (15 mm); ir (CHCl$_3$) 3550 (NH$_2$), 1670 cm^{-1} (C=O); nmr (CDCl$_3$) δ 7.70–7.50 (s, 2, CONH$_2$), 2.65–2.40 (m, 2, ≡CCH$_2$), 1.75–1.50 (m, 4, CH$_2$CH$_2$CH$_3$), and 0.95 (t, J = 6 Hz, 3, CH$_2$CH$_3$).

Reaction of 3-Diethylamino-1-propyne (1j) and 1-Diethylamino-1-propyne (1k) with CSI.—To a cooled solution (−78°) of 1.68 g (0.015 mol) of **1j** in 15 ml of n-pentane was added dropwise a solution of 2.13 g (0.015 mol) of CSI in 10 ml of the same solvent and the whole mixture was stirred for 1 hr. The white precipitate obtained was filtered and rinsed with five 20-ml portions of cold (−78°) pentane and dried in vacuo to give 3.6 g (95%) of **3-diethylamino-1-propyne–CSI salt (24)**: mp 112° dec; ir (KBr) 3226 (≡C—H), 2222 (N=C=O), 2105 cm^{-1} (C≡C); nmr (D$_2$O) δ 4.10 (d, J = 2.5 Hz, 2, CH$_2$C), 3.38 (q, J = 7.5 Hz, 4, CH$_2$CH$_3$), 3.11 (d, 1, C≡CH), and 1.23 (t, 6, CH$_2$CH$_3$, J = 7.5 Hz).

(47) J. Wegmann and H. Dahn, *Helv. Chim. Acta*, **29**, 101 (1946); I. Heilbron, "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, London, 1965, p 1607.

(48) C. F. H. Allen and W. E. Barker, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1957, p 156.

Salt **24** was too unstable to analyze. Hydrolysis of **24** (1.0 g, 1.4 mmol) with 4 N NaOH aqueous solution in acetone at ambient temperature afforded 0.3 g (70%) of **1j** and 0.2 g (20%) of **3-diethylamino-1-propyne hydrochloride** (**25**): mp 197–199° dec; ir (KBr) 3175 ($\equiv$CH), 2564 (N^+H), 2105 cm^{-1} (C$\equiv$C); nmr (D$_2$O) δ 4.10 (d, J = 2.5 Hz, 2, CH$_2$C), 3.38 (q, 4, CH$_2$CH$_3$), 3.11 (c, 1, CH, J = 2.5 Hz), and 1.32 (t, 6, CH$_2$CH$_3$, J = 7.5 Hz).

Addition of CSI to a pentane solution of an equimolar amount of **1k** at −78° resulted in the immediate precipitation of a yellow solid. The solution was decanted, and the yellow solid was rinsed several times with cold (−78°) pentane and dried *in vacuo* to give quantitatively a 1:1 adduct structured as **26**: mp 47° dec; ir (KBr) 1630 (C$\equiv$C), 1420 and 1160 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 4.0–3.2 (broad, 4, NCH$_2$), 2.2–2.0 (m, *ca.* 1.5, CCH$_3$), and 1.5–1.2 (m, *ca.* 7.5, CH$_2$CH$_3$).

Hydrolysis, methanolysis, reduction, and oxidation of **26** resulted in the formation of polymers in all cases.

Reaction of 1-Octen-4-yne (11) with CSI.—To a stirred solution of 7.10 g (0.050 mol) of CSI in 15 ml of CH$_2$Cl$_2$ was added slowly 5.40 g (0.050 mol) of **11** in 10 ml of CH$_2$Cl$_2$ and the solution was stirred for 24 hr at ambient temperature. The solvent was then evaporated *in vacuo* leaving an oil which was extracted with three 5-ml portions of pentane to remove unreacted **11**. The residue was purified by chromatography (1.0 × 20 cm column packed with silica gel; CCl$_4$ as eluent) to give 11.00 g (90%) of **6-chloro-4-n-propyl-5-(2-propenyl)-1,2,3-oxathiazine 2,2-dioxide** (**21**): ir (CCl$_4$) 1640 (C$\equiv$C), 1410 and 1200 cm^{-1} (SO$_2$); nmr (CDCl$_3$) δ 6.25–5.00 (m, ABC pattern, 3, CH$\equiv$CH$_2$), 3.30 (d, J = 5.0 Hz, 2, CH$_2$ next to vinyl group), 2.85–2.60 (t, 2, CH$_2$–C$\equiv$C), 2.00–1.35 (m, 2, CH$_2$CH$_3$), and 1.03 (t, 3, CH$_2$CH$_3$, J = 6.5 Hz).

Reduction of **21** (6.00 g, 0.024 mol) with 0.5 mol equiv of LiAlH$_4$ in anhydrous ether gave 4.2 g (70%) of **6-chloro-4-n-propyl-5-(2-propenyl)-3,4-dihydro-1,2,3-oxathiazine 2,2-dioxide** (**31**): ir (CCl$_4$) 3350 (NH) and 1625 cm^{-1} (C$\equiv$C); nmr (CDCl$_3$) δ 6.10–5.15 (m, 3, ABC pattern, HC$\equiv$CH$_2$), 5.00 (s, 1, NH), 4.20–3.80 (m, 1, CHCH$_2$), 2.89 (d, J = 5.5 Hz, 2, CH$_2$C$\equiv$C), 1.85–1.20 (m, 4, CH$_2$CH$_2$CH$_3$), and 1.10–0.80 (t, 3, CH$_2$CH$_2$CH$_3$).

Reduction of **21** (3.0 g, 0.012 mol) in 20 ml of ether with 25% aqueous Na$_2$SO$_3$ at 0° gave 1.2 g (80%) of **1-octen-5-one** (**71**): bp 94–95° (68–70 mm); ir (CCl$_4$) 1725 (C$\equiv$O), 1635 cm^{-1} (C$\equiv$C); nmr (CDCl$_3$) δ 6.25–4.85 (m, ABC pattern, 3, CH$\equiv$CH$_2$), 2.60–2.30 (m, 6, CH$_2$CH$_2$COCH$_2$), 1.90–1.35 (m, 2, CH$_2$CH$_3$), and 0.92 (t, 3, CH$_2$CH$_3$, J = 7.0 Hz).

Competitive Reactions of 1:1 Acetylene–Olefin Mixtures with CSI.—The general procedure used was as follows. To a 1:1 molar equiv mixture of acetylene and olefin in CH$_2$Cl$_2$ (10 ml, 0.01 mol) was added dropwise 0.5 molar equiv of CSI in the same solvent at ambient temperature and the solution was stirred for 4–6 hr. Aliquot quantities of the reaction mixtures were taken after 2 and 4 hr, whereupon the solvent and unreacted starting materials were evaporated *in vacuo*. The residual oil was extracted with five 20-ml portions of cold pentane (−20°) to remove unreacted acetylenes, and the residual components were analyzed by nmr. Mixtures of **2-hexyne** (**1d**)–*trans*-2-**hexene** and **1d**–**cyclohexene** so treated with CSI gave, in each case, only the **1d**–CSI oxathiazine adduct.

A 1:1 mixture of **1f**–*trans*-β-**methylstyrene** in methylene chloride gave a nearly 1:1 mixture of **2f** and **1-chlorosulfonyl-3-methyl-4-phenyl-2-azetidinone** adducts based on nmr integration of the methyl groups in each adduct: nmr (CDCl$_3$) δ 7.55 (s, 5, C$_6$H$_5$), 7.40 (s, 5, C$_6$H$_5$), 4.88–4.80 (d, 1, H at C-4), 3.50–3.20 (m, 1, H at C-3), 2.02 (s, 3, CH$_3$C$\equiv$C), and 1.40 (d, J = 7.5 Hz, 3, CHCH$_3$).

The same mixture in anhydrous ether gave a 1.4:1 oxathiazine:azetidinone product ratio.

Finally a 1:1 mixture of **1g**–styrene in CH$_2$Cl$_2$ gave a 2:1 mixture of azetidinone–oxathiazine adducts based on nmr integration of vinyl and β-lactam protons: nmr (CDCl$_3$) δ 7.45 (s, 15, C$_6$H$_5$), 6.88 (s, 1, C$\equiv$CH), 5.50–5.20 (m, 2, H at C-4), and 3.90–3.28 (m, 4, H at C-3).

Reaction of Benzenediazonium Carboxylate (28) with CSI.—To a slurry of **28**[49] prepared from 3.0 g (0.022 mol) of anthranilic acid in 30 ml of ethylene chloride was added a solution of 5.35 g (0.022 mol) of CSI in 10 ml of the same solvent at 0° with stirring. The mixture was stirred for an additional 30 min at 0° after which it was gradually warmed to 70–80°, whereupon the stirring was continued until gas evolution stopped (*ca.* 2.5 hr). The resulting precipitate was filtered and washed with three 10-ml portions of ethylene chloride to give crude **3-chlorosulfonyl-1,2,3-benzotriazin-4-one** (**29**, 80%): mp 113–116° dec; ir (KBr) 1695 (C$\equiv$O), 1325 and 1149 cm^{-1} (SO$_2$).

Compound **29** was too unstable to analyze. Recrystallization of **29** from CH$_3$OH resulted in the formation of 1.5 g (78%) of **1,2,3-benzotriazin-4-one** (**30**): mp 210–211° dec; ir (KBr) 1681 cm^{-1} (C$\equiv$O); uv max (C$_2$H$_5$OH) 278 nm (ϵ 6500); nmr (DMSO-d_6) 11.00 (s, 1, CONH) and 8.10–7.60 (m, 4, aromatic).

Anal. Calcd for C$_7$H$_5$N$_3$O: C, 57.00; H, 3.40; N, 28.70. Found: C, 56.81; H, 3.35; N, 29.02.

Reaction of **28** with CSI–pyridine salt[29] and *N,N*-bischlorosulfonylurea[3] at 40–50° also ultimately gave **30** in 20% yield in each case.

A solution of 0.35 g (2.4 mmol) of **30** in 120 ml of dry THF was irradiated under an Hanovia 450-V lamp for 10 hr at room temperature. No reaction was observed and **30** was quantitatively recovered.

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π-Equivalent Heterocyclic Congeners of Tropone.   Azatropones[1]

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Seven azatropones, π-equivalent heterocyclic congeners of tropone, have been prepared and characterized. Thus treatment of 4,7-dimethyl- (10), 4,6,7-trimethyl- (12), and 3,4,6,7-tetramethyl-1H-azepine-2,5-dione (14) with triethyloxonium fluoborate afforded respectively, 7-ethoxy-2,5-dimethyl-4H-azepin-4-one (19), 5-ethoxy-4,6,7-trimethyl-2H-azepin-2-one (22), and 5-ethoxy-3,4,6,7-tetramethyl-2H-azepin-2-one (28). With the same reagent, 1H-benz[f]azepine-2,5-dione (16) and 5H-morphanthridine-6,11-dione (18) gave 2-ethoxy-5H-benz[f]azepin-5-one (34) and 11-ethoxybenz[c]cyclohexadienyl[5,6-f]-2H-azepin-2-one (42), respectively. Trimethyloxonium fluoborate also converted 12 and 14 to their respective azatropones, 5-methoxy-4,6,7-trimethyl- (26) and 5-methoxy-3,4,6,7-tetramethyl-2H-azepin-2-one (31). Proof of structure of 4-azatropones, 19 and 34, and 2-azatropones, 22, 26, 28, 31, and 42, is provided and mechanisms for their formation are suggested. Nmr data show no evidence of a ring current in any of these azatropones, and the ease with which they are both hydrogenated and/or hydrolyzed indicates no special aromatic stabilization.

General syntheses of π-equivalent[3] azacyclic congeners of azulene (10π) and cyclooctatetraene (8π) have been realized with the preparation of azaazulene (1)[4] and 2-alkoxyazocines (2).[5]

Synthetic pathways devised to prepare azatropones (3–5), the monocyclic 6π-equivalent heterocyclic congeners of tropone, and their annelated derivatives has been strewn with failure,[6–10] error,[11–15] and limited success (6–8).[13,14]

An avowed purpose for all these preparations of (4n + 2)π-equivalent heterocyclic conjugated systems is their characterization by nmr spectroscopy to determine the degree of π-electron delocalization. Extensive charge delocalization (aromaticity) would be reflected in an appreciable induced ring current which in turn would be revealed by substantial deshielding of vinyl protons and methyl substituents on the azatropone ring system.

Azatropones 6 and 8 have neither of these substituents, while the vinyl proton singlet (δ 8.81) in 7 is adjacent to both nitrogen and the fused aromatic ring and its downfield position could alternatively be explained by conventional deshielding effects and not a ring current.

This paper describes a convenient, two-step synthesis of substituted and annelated azatropones and reports on a study of their chemical and physical properties which provides sufficient evidence for a conclusion regarding their aromaticity.

Thus, the observed ring expansion of alkyl-1,4-benzo-, 1,4-naphtho-, and 9,10-anthraquinones to 2,5-azepinediones under Schmidt reaction conditions[16–19] coupled with the extraordinary propensity of Meerwein's reagent, trialkyloxonium fluoborate, to selectivity O-alkylate amides,[20] afforded a direct route to the synthesis of 4H-azepin-4-ones (type 3) and 2H-azepin-2-ones (type 5).

Treatment of 2,5-dimethyl- (9), 2,3,5-trimethyl- (11), and 2,3,5,6-tetramethyl-1,4-benzoquinone (13) with sodium azide in concentrated sulfuric acid gave 4,7-dimethyl- (10, 66%), 4,6,7-trimethyl- (12, 70%), and 3,4,6,7-tetramethyl-1H-azepine-2,5-dione (14, 79%), respectively.[16–18] Similarly 1,4-naphthoquinone (15) and anthraquinone (17) afforded the corresponding 1H-benz[f]azepine-2,5-dione (16, 65%)[20] and 5H-morphanthridine-6,11-dione (18, 86%)[19] (Scheme I).

Azatropones (Schemes II and III).—The reaction of 10 with triethyloxonium fluoborate[20] in methylene chloride afforded the azatropone 7-ethoxy-2,5-dimethyl-

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TABLE I
NMR, IR, AND UV SPECTRAL DATA FOR AZATROPONES

Aza-tropone	Nmr (δ) =CCH₃ Chemical shift	Multiplicity	Coupling constant, Hz	=CH Chemical shift	Multiplicity	Coupling constant, Hz	Ir λ_max^{KBr-film}, cm⁻¹ (μ) C=O	=COC	Uv λ_max^{EtOH}, nm (ε)
19	2.20	s		6 70	q	$J = 1$	1620 (6.17)	1230 (8.13)	225 (26,500)
	2.08	q	$J = 1$	6 13	s				300 (7,100)
22	2.30	q	$J = 0.5$	6 68	q	$J = 1$	1640 (6.10)	1275 (7.85)	225 (25,000)
	2.20	d	$J = 1$						310 (7,700)
	2.08	q	$J = 0.5$						
26	2.30	q	$J = 0.5$	6.68	q	$J = 1$	1640 (6.10)	1270 (7.88)	225 (21,000)
	2.20	d	$J = 1$						310 (6,000)
	2.10	q	$J = 0.5$						
28	2.13	q	$J = 0.5$				1625 (6.15)	1285 (7.78)	230 (22,000)
	2.10 (6 H)	s							320 (7,300)
	1.97	q	$J = 0.5$						
31	2.13	q	$J = 0.5$				1620 (6.17)	1295 (7.72)	230 (20,000)
	2.10 (6 H)	s							320 (5,100)
	1.97	q	$J = 0.5$						
34				6.81	q (AB)	$J = 12$	1610 (6.21)	1220 (8.20)	218 (38,000)
				6.65	q (AB)	$J = 12$			265 (10,600)
42							1660 (6.02)	1275 (7.85)	233 (32,500)

SCHEME I

	R₁	R₂	R₃	R₄
9	CH₃	H	CH₃	H
11	CH₃	H	CH₃	CH₃
13	CH₃	CH₃	CH₃	CH₃

	R₁	R₂	R₃	R₄
10	CH₃	H	CH₃	H
12	CH₃	H	CH₃	CH₃
14	CH₃	CH₃	CH₃	CH₃

15   16

17   18

SCHEME II

10   19

21   20

methoxy-3,4,6,7-tetramethyl-2*H*-azepin-2-one (**31**, 63%), respectively. Although the purpose of making the OCH₃ derivatives was to simplify the nmr spectrum of these azatropones, the nmr spectra of **22** and **28** were analogous to **26** and **31**, respectively (apart from the OR group), and the corresponding uv spectra were virtually superimposable.

Differences in preparative procedure (*vide infra*), the dramatic difference in yields, and subtle differences in pertinent spectral data (tabulated in Table I) initially delineated but did not distinguish the 4-azatropone **19** from 2-azatropones **22** (**26**) and **28** (**31**).

Structure Proof of 19, 22, and 28.—Hydrogenation of **19** over 5% Pd/C at atmospheric pressure resulted in an uptake of 2 mol equiv of hydrogen and afforded a distillable oil. The vinyl protons were absent from the nmr spectrum of this reduction product and the methyl groups were aliphatic doublets. The ir spectrum displayed a new carbonyl band at 1775 cm⁻¹ (5.63 μ) and gave no evidence of NH absorption. Only end absorption was observed in the uv, and vpc indicated a two-component mixture. The spectral and analytical evidence was consistent with a stereoisomeric mixture of 7-ethoxy-2,5-dimethyl-2,3,5,6-tetrahydro-4*H*-azepin-4-one (**20**, obtainable only from **19**). Hydrogenation of **10** over 30% Pd/C afforded a white

4*H*-azepin-4-one (**19**, 4%) (Scheme II). Alkylation of **12** and **14** with the same reagent, however, gave 5-ethoxy-4,6,7-trimethyl-2*H*-azepin-2-one (**22**, 63%) and 5-ethoxy-3,4,6,7-tetramethyl-2*H*-azepin-2-one (**28**, 70%), respectively (Scheme III). The 4-azatropone **19** can be envisioned as arising from O-alkylation of the enol of **10**, while vinylogous lactam–lactim tautomerism of **12** and **14** followed by O-alkylation[21] may account for **22** and **28**.

Trimethyloxonium fluoborate[20] converted **12** and **14** to 5-methoxy-4,6,7-trimethyl- (**26**, 51%) and 5-

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(21) N-Methylation of **14** was achieved by treatment of a solution of **14** in DMF with sodium hydride and methyl iodide. The distinguishing feature of the nmr spectrum of product 1,3,4,6,7-pentamethyl-1*H*-azepine-2,5-dione (**33**, 86%) was a new methyl proton singlet at δ 3.17. This is consistent with a methyl group on N and not O: *cf.* **33** with **26** and **31**. Refluxing **14** with dimethyl sulfate in benzene for 24 hr led only to the recovery of starting material.

product (21) whose spectral data indicated a keto compound with substantial enol tautomerism. Alkylation of 21 with triethyloxonium fluoborate gave the identical mixture of stereoisomeric O-alkylated imino ethers (20) obtained from hydrogenation of 19. As with tropone,[22] 19 failed to give a 2,4-DNPH derivative.

Hydrogenation of 22 at ambient temperature and atmospheric pressure ceased after 1 mol equiv of hydrogen had been absorbed.[23] The product nmr spectrum indicated that hydrogenation of the sterically less hindered double bond had occurred and suggested structure 23, 5-ethoxy-4,6,7-trimethyl-3,4-dihydro-1*H*-azepin-2-one. Thus we attribute the 3 H multiplet (δ 2.68–2.22) to the CH_2 protons (sharp multiplet centered at δ 2.47) adjacent to the C=O, superimposed upon a broad allyl CH resonance which extends the multiplet upfield to δ 2.22.[24]

Column chromatography of 23 led *via* hydrolysis of the labile vinyl ether function to the keto–amide tautomer 4,6,7-trimethyl-2,3,4,5-tetrahydro-1*H*-azepine-2,5-dione (24, 72%). The structure of 24 was confirmed by successive hydrogenation (1 mol equiv) of 12 followed by column chromatography to 24 (71%). Alkylation of 24 prepared in this manner with triethyloxonium fluoborate afforded 23 (23%). Compounds 23 and 24 prepared by these alternative methods were identical by all the usual criteria.

Careful reduction (30% Pd/C) of 26 with 3 mol equiv of hydrogen led to a mixture of 5-methoxy-4,6,7-trimethylhexahydro-1*H*-azepin-2-ones (27, 65%); four isomers of 27 could be distinguished by vpc and nmr spectroscopy.

Since acid-catalyzed hydrolysis of 22 and 26 quantitatively converted them to 12, it is not surprising that treatment of 22 and 26 with 2,4-DNPH under

(22) H. J. Dauben, Jr., and H. J. Ringold, *J. Amer. Chem. Soc.*, **73**, 876 (1951).

(23) Reduction under more vigorous conditions led to hydrogenolysis of the labile ethoxy group.

(24) The alternative azatropone structure I on similar reduction with 1 mol equiv of hydrogen would give II whose CH proton adjacent to C=O would normally appear at distinctly lower field from the allyl CH_2 resonance. Precedent[25,26] and the position of the CH proton resonance in **20** and **24** support this view.

I → II

(25) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, p 137.

(26) O. L. Chapman, D. J. Pasto, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1216 (1962), have prepared the dihydro tropone III. The CH proton adjacent to C=O in this carbocyclic analog of II indeed appears as

III

a multiplet skewed distinctly downfield (δ 2.91–2.25) from the (sharp) allyl CH_2 resonance (δ 2.44). The large difference in λ_{max} for **23** [300 nm (ϵ 10,000)] and III [331 nm (ϵ 7160)] also supports the presence of different chromophores in these two systems. We are grateful to Professor Chapman for a Xerox copy of this portion of the nmr spectrum which was absent in the cited paper.

acidic conditions gave a hydrazone 25 identical in all respects with that obtained directly from 12.

Hydrogenation (30% Pd/C) of 28 afforded an unstable, white, crystalline powder (22%) which could be recrystallized and purified only with substantial loss of product. In the nmr, the recrystallized material displayed three methyl singlets (δ 2.10, 1.90, and 1.65), a relatively shielded methyl doublet (δ 1.16), an NH proton (δ 6.50), and an alicyclic ring proton (δ 2.67). Since this latter proton does not seem to appear sufficiently downfield to be adjacent to nitrogen, the hydrogenation product was structured as 32 which would result from conventional hydrogenation of the double bond at $\Delta^{3,4}$ (28 → 29) followed by a 1,5-sigmatropic hydrogen shift to 32. The π–π^* transition of 32 [λ_{max} 223 nm (ϵ 8800)] is intermediate between and less probable than in the nonconjugated acetamide [λ_{max} 179 nm (ϵ 9500)] and the highly conjugated acetanilide [λ_{max} 238 nm (ϵ 10,500)].[27,28]

Acid-catalyzed hydrolysis of 28 and 31 resulted in quantitative conversion to 14. Thus, treatment of 14, 28, and 31 with 2,4-DNPH under acidic conditions led to the same hydrazone 30.

Benz-Fused Azatropones (Schemes IV and V).—The spectral and chemical properties of Schmidt rearrangement product 16 were similar to 7,8-dimethyl-1*H*-benz[*f*]azepine-2,5-dione (38) prepared by bromination–dehydrobromination of 7,8-dimethyl-3,4-dihydro-1*H*-benz[*f*]azepine-2,5-dione (39).[30] Treatment of 16 with triethyloxonium fluoborate transformed it to 2-ethoxy-5*H*-benz[*f*]azepin-5-one (34, 6.5%) with no recovery of starting material. In the nmr, the presence of an aromatic peri proton doublet at δ 8.08 coupled to both ortho- and meta-ring protons was sufficient to assign azatropone structure 34 to this O-alkylation product.

In an attempted synthesis of an azatropolone, Rees[30] had converted 39 to 7,8-dimethyl-2,3,4,5-tetrahydro-1*H*-benz[*f*]azepine-2,4,5-trione (41) *via* anil 40. The insolubility of 41 precluded spectral studies in solution but the very limited chemical evidence available excluded heterotropolone behavior in 41. The availability of 16 permitted a preparation of the unsubstituted trione 37. Thus, hydrogenation of 16 (Pd/C) afforded 3,4-dihydro-1*H*-benz[*f*]azepine-2,5-dione (35, 86%). Base-catalyzed condensation of 35 with *N,N*-dimethyl-*p*-nitrosoaniline led to the bright red anil 36 (50%); acid hydrolysis of 36 gave yellow-green 2,3,4,5-tetrahydro-1*H*-benz[*f*]azepine-2,4,5-trione (37, 11%) which was insoluble in all the usual organic solvents. The carbonyl region in the infrared spectra of 37 (KBr) and

(27) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, pp 9, 18.

(28) The completely unsubstituted analog IV of **32** has been prepared in

IV

which the π–π^* transition occurs below 210 nm and whose n–π^* absorption appears at 258 nm (log ϵ 3.7).[29] Dihydroazepin-2-one **32** displayed a λ_{max} 285 nm (log ϵ 3.72) in which normal alkyl substitution effects would contribute to the observed bathochromic shift.

(29) E. Vogel, R. Erb, G. Lenz, and A. Bothner-by, *Justus Liebigs Ann. Chem.*, **682**, 1 (1965).

(30) Prepared in a six-step synthesis from o-xylene: A. H. Rees, *J. Chem. Soc.*, 3111 (1959).

SCHEME III

12, 22-26, $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$
14, 28-31, $R_1 = R_2 = R_3 = R_4 = CH_3$
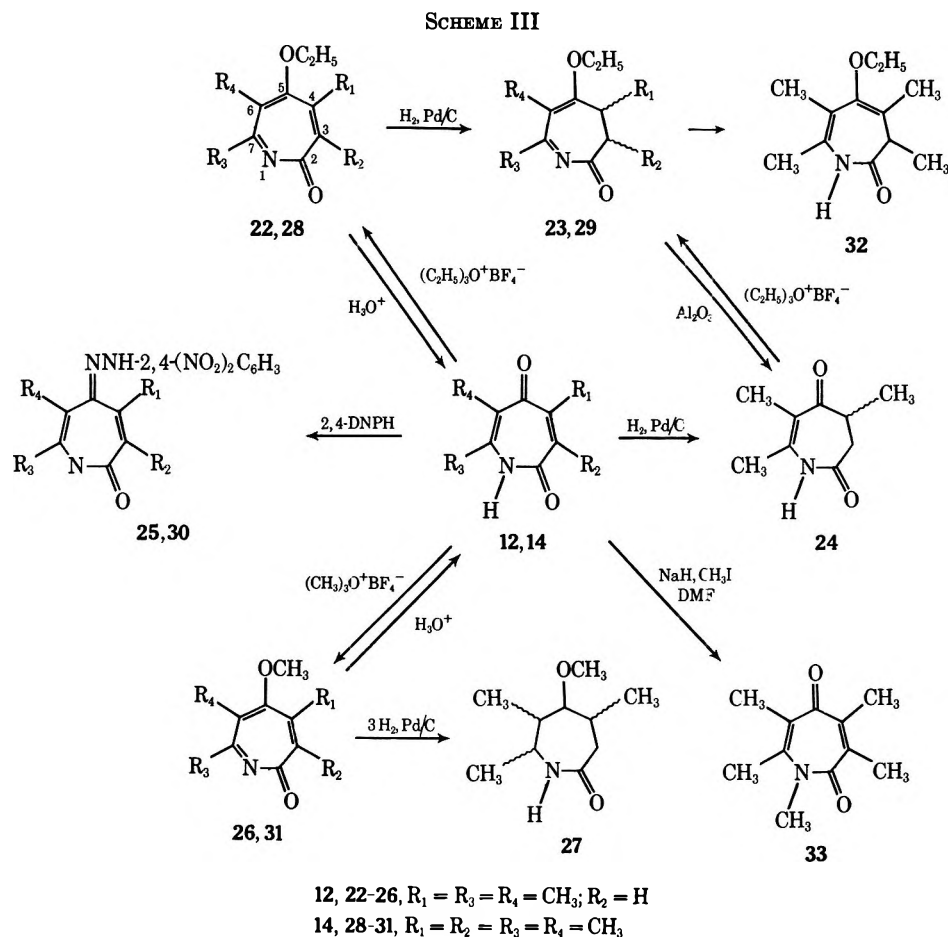
41 (Nujol) were almost identical, suggesting the absence also of any enol tautomer of **37**.

Alkylation of **18** with triethyloxonium fluoborate proceeded experimentally in a manner analogous to **12** and **14** and afforded a single O-alkylation product (71%). The choice between the assigned structure **42** (11-ethoxybenz[c]cyclohexadienyl[5,6-f]-2H-azepin-2-one) and the alternative **42a** was based on the following evidence: (1) the absence of any deshielded

42a
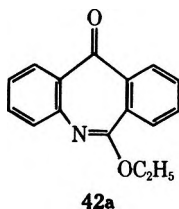
aromatic peri protons in the nmr spectrum of **42**; (2) reduction of **42** with excess NaBH₄ did not give the tetrahydro amine anticipated from **42a**,[31] but led instead to the dihydro product 11-ethoxy-6-hydroxybenz-[c]cyclohexadienyl[5,6-f]-2H-azepine (**43**), (3) acid hydrolysis of **43** afforded the unknown 6-hydroxy-5,6-dihydro-11-morphanthridinone (**44**) whose physical properties [mp 247–249°; ir 1660 cm⁻¹ (6.20 μ) (C=O); nmr δ 6.01 (OH) and 5.60 (CH)] clearly distinguish it from the known, isomeric 11-hydroxy-6(5H)-morphanthridone (**45**)[32] [mp 138–139°; ir 1740 cm⁻¹ (5.75 μ)

(31) R. F. Borsch, *Tetrahedron Lett.*, 61 (1968).
(32) *Chem. Abstr.*, **62**, 10422 (1965); J. O. Jilek, J. Pomykacek, E. Luatek, V. Seidlova, M. Rajsner, K. Pelz, B. Hoch, and M. Protivia *Collect. Czech. Chem. Commun.*, **30** (2), 445 (1965) [*Chem. Abstr.*, **63**, 4257 (1965)].

(C=O); nmr δ 3.82 (OH) and 6.50 (CH)], prepared *via* the Meerwein–Ponndorf–Verley reduction of **18**. Isomer **45** would have been the expected product had the reduction and hydrolysis sequence (**42** → **43** → **44**) commenced with **42a**. Acid hydrolysis of **42** afforded **18**, and, not unexpectedly, treatment of **18** and **42** with 2,4-DNPH under acidic conditions gave the same hydrazone **47**.

Of spectral interest was the dialkylated product obtained from the reaction of **45** with either equimolar or excess triethyloxonium fluoborate. Distillation of the viscous reaction product afforded a small amount of 11-ethoxy-5-ethyl-6-morphanthridinone (**46**, 11%) characterized by microanalytical and spectral data. The CH₂ group directly attached to the nitrogen appears as a mound in the nmr (30°) centered at δ 3.41. Progressive resolution of the mound occurred as the temperature was raised until, at 75°, it became a fairly sharp quartet. This temperature dependency is attributed to slow nitrogen inversion at low temperature with the nmr spectrum at 30° recording the coalescence point.

Aromaticity.—The position of ring protons (δ 6.13–6.81) and methyl groups (δ 1.97–2.30) in the nmr of 4-azatropones **19** and **34** and 2-azatropones **22**, **26**, **28**, and **31** remain well within the vinyl region and were not significantly shifted to lower fields relative to their respective precursor azepinediones. Thus there is no nmr evidence to support the postulation of a ring current. Finally, the ease with which all these azatropones could be both hydrogenated and/or hydrolyzed leads us to the inescapable conclusion that these azatropones have no special "aromatic" stabilization.

SCHEME IV

16, 35-37, $R_1 = R_2 = H$
38-41, $R_1 = R_2 = CH_3$
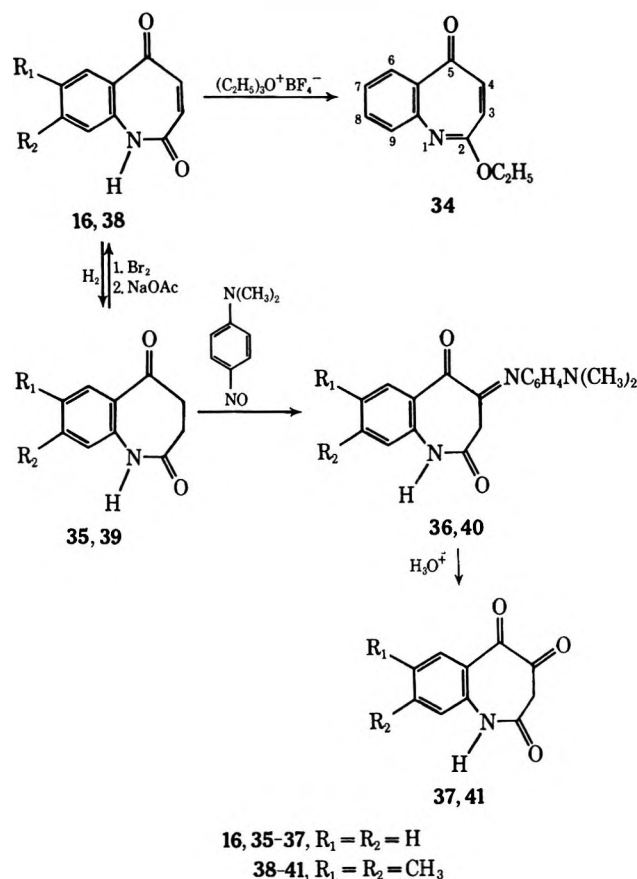
SCHEME V
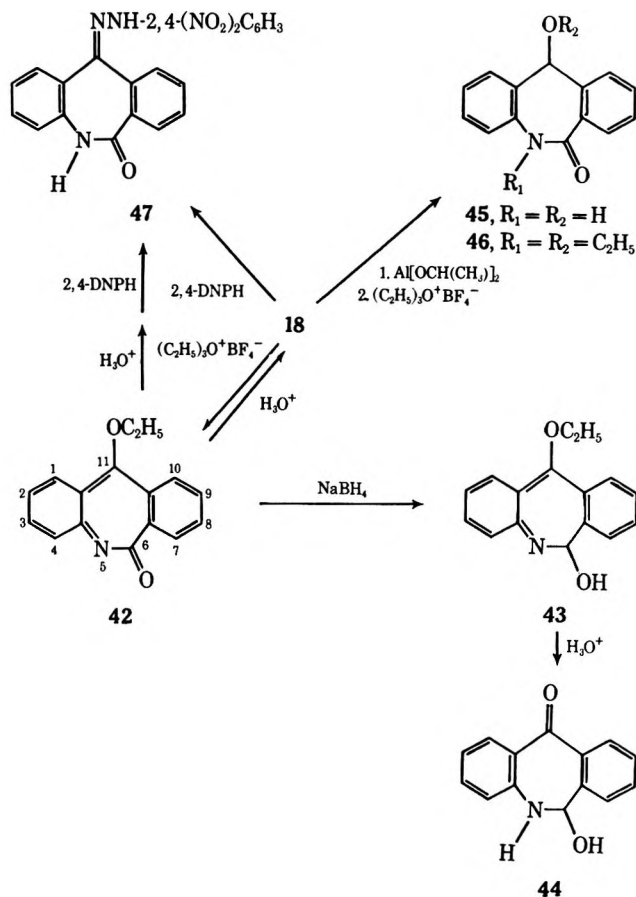
Experimental Section[33]

Schmidt Reaction.—4,7-Dimethyl- (**10**), 4,6,7-trimethyl- (**12**), and 3,4,6,7-tetramethyl-1*H*-azepine-2,5-dione (**14**) were prepared by the procedure of Misiti, Moore, and Folkers;[16] 1*H*-benz[*f*]-azepine-2,5-dione (**16**)[17] and 5*H*-morphanthridine-6,11-dione (**18**)[19] were also prepared by literature methods. Physical constants and spectral properties of these diones were in agreement with those reported therein.

7-Ethoxy-2,5-dimethyl-4*H*-azepin-4-one (19).—A suspension of **10** (5.0 g, 0.033 mol) in dry CH₂Cl₂ was stirred with 6.3 g (0.033 mol) of (C₂H₅)₃O⁺BF₄⁻.[20] After 3 hr the starting material completely dissolved and the solution began to darken. At this point, the reaction was terminated by quenching with 50 ml of 10% aqueous K₂CO₃ solution. The organic layer was separated, dried (Na₂SO₄), and evaporated *in vacuo*. The residual tacky material was extracted with three 100-ml portions of pentane. Filtration and evaporation of the pentane left 255 mg of **19** (4.3%) which was purified by sublimation at ambient temperature at 0.1 mm. An analytical sample was prepared by dissolving 100 mg in 0.5 ml of CH₂Cl₂, depositing this solution on top of a 70 × 5 mm Woelm neutral, activity grade I, alumina column, and eluting with pentane. Evaporation of the pentane afforded pure **19**: mp 57-58°; nmr (CCl₄) δ 6.70 (q, 1, vinyl H, $J = 1$ Hz), 6.13 (s, 1, vinyl H), 4.20 (q, 2, OCH₂CH₃, $J = 7$ Hz), 2.20 (s, 3, CH₃), 2.08 (q, 3, CH₃, $J = 1$ Hz), and 1.32 (t, 3, OCH₂CH₃, $J = 7$ Hz).

Anal. Calcd for C₁₀H₁₃NO₂: C, 66.99; H, 7.25; N, 7.81. Found: C, 67.03; H, 7.11; N, 7.88.

Hydrogenation of 23.—Hydrogenation of 150 mg 0.0010 mol) of **19** in 5 ml of 95% C₂H₅OH with 5% Pd/C at atmospheric pressure (2 hr) consumed 47 ml of hydrogen (0.002 mol). The solution was filtered and evaporated in a stream of dry nitrogen. Distillation of the residual oil at 42° (0.2 mm) gave 95 mg of **7-ethoxy-2,5-dimethyl-2,3,5,6-tetrahydro-4*H*-azepin-4-one** (**20**, 62%). The vpc and nmr data indicated the presence of two isomers: ir 1775 (C=O), 1590 (C=N), 1210, and 1040 cm⁻¹ (=COC); nmr (CCl₄) δ 4.08 (doublet of q, 2, OCH₂CH₃, $J = 7$ Hz), 3.83-3.33 (m, 1, NCH), 3.08-1.91 (m, 5, ring protons), 1.32 (d, 3, CH₃, $J = 6$ Hz), 1.28 (d, 3, CH₃, $J = 6$ Hz), and 1.13 (t, 3, OCH₂CH₃, $J = 7$ Hz); vpc retention times 60 and 70 sec (6 ft × ⅛ in., 10% SE 30 column at 150°), 110 and 120 sec (6 ft × ⅛ in., 3% Apiezon L column at 125°). Carrier gas flow rate was 20 ml/min in both cases.

Anal. Calcd for C₁₀H₁₇NO₂: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.21; H, 8.45; N, 7.44.

Imino ether mixture **20** was also prepared by hydrogenation of **10** to the completely saturated isomer **21** followed by treatment with triethyloxonium fluoroborate. Thus, hydrogenation (Parr shaker, 40 psi, 12 hr) of **10** (5.0 g, 0.033 mol) in 30 ml of 95% C₂H₅OH over 30% Pd/C (100 g) afforded, after catalyst removal and solvent evaporation, a viscous oil which solidified upon standing. Recrystallization from CH₂Cl₂–pentane followed by an ether wash gave 3.8 g (73%) of **4,7-dimethylhexahydro-1*H*-azepine-2,5-dione** (**21**): mp 166-168° (from CH₃CN); ir 3400, 3280 (NH), 1675 (C=O), 1680 and 1670 cm⁻¹ (NCO); nmr (DMSO-*d₆*) δ 7.08 (mound, 1, NH), 4.62 (d, 2, =COH, $J = 5$ Hz), 4.00-1.42 (m, 5, ring protons plus enolic OH), 1.08 (d, 3, CH₃, $J = 7$ Hz), and 0.78 (d, 3, CH₃, $J = 7$ Hz); nmr (DMSO-*d₆*-D₂O) absorptions at δ 7.08, 4.62, and 4.00-1.42 (for one proton) disappear.

Anal. Calcd for C₈H₁₁NO₂: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.69; H, 7.55; N, 9.39.

A mixture of **21** (2.0 g, 0.013 mol) and 2.5 g of (C₂H₅)₃O⁺BF₄⁻ in 10 ml of CH₂Cl₂ was stirred overnight and quenched with 50 ml of 10% aqueous K₂CO₃ solution. The CH₂Cl₂ layer was separated, dried (Na₂SO₄), and evaporated *in vacuo* to give a

(33) Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 337 grating spectrophotometer utilizing potassium bromide wafers for solids and salt plates for liquids. The ultraviolet spectra were recorded on a Cary 15 dual-beam recording spectrophotometer using 95% ethanol as a solvent. The nmr spectra were obtained on a Varian Associates A-60A spectrometer with the solvent noted; chemical shifts are reported in parts per million (δ) downfield from TMS as the internal standard. Vpc analyses were performed on a Perkin-Elmer 880 gas chromatograph or a Perkin-Elmer F 21 preparative gas chromatograph. Microanalyses were determined by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The mass spectra were obtained using the facilities of the Battelle Memorial Institute, High Resolution Mass Spectrometry Center, sponsored by the National Institutes of Health, Division of Research Resources, Contract No. NIH-69-2226.

light oil which was distilled [42° (0.2 mm)] to give the isomeric mixture 20 identical by all the usual criteria with 20 prepared from 19.

5-Ethoxy-4,6,7-trimethyl-2H-azepin-2-one (22).—To a suspension of 5.0 g (0.03 mol) of 12 in anhydrous CH_2Cl_2 was added 6.0 g (0.032 mol) of $(C_2H_5)_3O^+BF_4^-$. The mixture was refluxed overnight, quenched by the addition of 10% aqueous K_2CO_3 solution (60 ml), and worked up in the manner described for isolation of crude 28. The crystalline material isolated was dissolved in pentane, charcoaled (Darco), and filtered. The clear filtrate was concentrated, cooled, and filtered to give 3.4 g (63%) of 22 as colorless needles. An analytical sample was prepared by sublimation at 40° (0.1 mm): mp 71–72°; nmr (CCl_4) δ 6.68 (q, 1, vinyl H, $J = 1$ Hz), 4.25 (q, 2, OCH_2CH_3, $J = 7$ Hz), 2.30 (q, 3, CH_3, $J = 0.5$ Hz), 2.20 (d, 3, CH_3, $J = 1$ Hz), 2.08 (q, 3, CH_3, $J = 0.5$ Hz), and 1.37 (t, 3, OCH_2-CH_3, $J = 7$ Hz).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.30; H, 7.76; N, 7.24; mol wt, 193.1103. Found: C, 68.53; H, 8.06; N, 7.24; mol wt, 193.1104 (mass spectrum).

5-Methoxy-4,6,7-trimethyl-2H-azepin-2-one (26, 51%) was prepared in a similar manner from 12 and $(CH_3)_3O^+BF_4^-$:[20] colorless; mp 52°; nmr (CCl_4) δ 6.68 (q, 1, vinyl H, $J = 1$ Hz), 3.77 (s, 3, OCH_3), 2.30 (q, 3, CH_3, $J = 0.5$ Hz), 2.20 (d, 2, CH_3, $J = 1$ Hz), and 2.10 (q, 3, CH_3, $J = 0.5$ Hz).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.22; H, 7.37; N, 8.08.

5-Ethoxy-3,4,6,7-tetramethyl-2H-azepin-2-one (28).—A suspension of 1.79 g (0.010 mol) of 14 in 15 ml of anhydrous CH_2Cl_2 and 1.90 g (0.010 mol) of $(C_2H_5)_3O^+BF_4^-$ was stirred overnight in a stoppered flask. Work-up was as follows. Aqueous K_2CO_3 solution (10%) was added slowly to the reaction mixture. The mixture was filtered to remove any inorganic material and the filter cake washed with CH_2Cl_2. The washings and filtrate were combined and the water layer was separated. Drying the organic layer (Na_2SO_4) and removal of the solvent in vacuo (no heat) led to a solid product. This material was extracted with pentane, the combined extracts were filtered, and the solvent was removed in vacuo to give 28 (1.44 g, 70%). Purification of 28 was achieved by dissolution in a small amount of CH_2Cl_2, deposition upon a 20 × 1 cm Woelm neutral alumina (activity grade I) column, and elution with pentane, giving 1.2 g of 28 as white needles. An analytical sample was sublimed at 40° (1.0 mm): mp 68.5–70°; nmr (CCl_4) δ 4.17 (q, 2, OCH_2CH_3, $J = 7$ Hz), 2.13 (q, 3, CH_3, $J = 0.5$ Hz), 2.10 (s, 6, CH_3), 1.97 (q, 3, CH_3, $J = 0.5$ Hz), and 1.10 (t, 3, OCH_2CH_3, $J = 7$ Hz).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.67; mol wt, 207.1259. Found: C, 69.39; H, 8.31; N, 6.60; mol wt, 207.1245 (mass spectrum).

5-Methoxy-3,4,6,7-Tetramethyl-2H-azepin-2-one (31, 63%) was prepared in a similar manner from 14 and $(CH_3)_3O^+BF_4^-$:[20] mp 84–85° (sublimation at 30°, 0.1 mm); nmr (CCl_4) δ 3.73 (s, 3, OCH_3), 2.13 (q, 3, CH_3, $J = 0.5$ Hz), 2.10 (s, 6, CH_3), and 1.97 (q, 3, CH_3, $J = 0.5$ Hz).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found C, 68.64; H, 8.08; N, 7.53.

1,3,4,6,7-Pentamethyl-1H-azepine-2,5-dione (33).—To 50 ml of dry DMF was added 0.14 g (0.0058 mol) of pentane-washed sodium hydride. 14 (1 g, 0.0056 mol) and an excess of methyl iodide (1.15 g, 0.0080 mol) was then added and the solution was stirred at ambient temperature for 4 hr. The reaction mixture was poured into 200 ml of H_2O and the whole mixture was continuously extracted with hexane for 18 hr. The hexane was filtered to recover unreacted starting material. The filtrate was dried (Na_2SO_4), filtered, and evaporated in vacuo to give 0.946 g (86%) of 33 as a yellow oil: bp 103° (1 mm); ir 1640 and 1635 cm⁻¹ (C=O); uv max 241 nm (ε 13,000) and 330 (2300); nmr (CCl_4) δ 3.17 (s, 3, N=CH₃), and 2.07, 2.02, 1.95, 1.85 (all q, each 3, CH_3, $J = 0.5$ Hz).

Anal. Calcd for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.13.

Hydrogenation of 22.—An ethanolic solution of 1.93 g (0.010 mol) of 22 was hydrogenated (50 mg of 30% Pd/C) at atmospheric pressure and ambient temperature. The reaction stopped when 300 ml of hydrogen had been consumed (1.2 equiv); vpc analysis indicated all starting material had reacted. Filtration over Filter-Cel left a yellow solution containing a light oil. A vpc analysis indicated two minor products (ca. 10%) and one major product (ca. 90%). Initial distillation partially separated the mixture but prolonged heating decomposed the major compound. An analytical sample was obtained by preparative gc and re-

distilled to give **5-ethoxy-4,6,7-trimethyl-3,4-dihydro-1H-azepin-2-one (23)** as an oil which could not be induced to crystallize: bp 64° (0.1 mm); ir 1660 (C=O) and 1275 cm⁻¹ (=COC); uv max 300 nm (ε 10,000); nmr (CCl_4) δ 4.20 (q, 2, OCH_2CH_3, $J = 7$ Hz), 1.68–2.22 (m, 3, CH and CH_2), 1.97 (q, 3, CH_3, $J = 0.5$ Hz), 1.82 (q, 3, CH_3, $J = 0.5$ Hz), 1.27 (t, 3, OCH_2CH_3, $J = 7$ Hz), and 1.10 (d, 3, CH_3, $J = 7$ Hz).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.76; N, 7.13. Found: C, 67.89; H, 8.61; N, 7.42.

4,6,7-Trimethyl-2,3,4,5-tetrahydro-1H-azepine-2,5-dione (24).—Partially purified 23 (1.0 g, 0.0050 mol) was dissolved in 5 ml of CH_2Cl_2 and deposited on a 20 × 1 cm alumina column (Woelm activity grade I, neutral). Successive elutions with pentane, carbon tetrachloride, methylene chloride, and chloroform afforded 250 mg (25%) of starting material. The column was stripped with methanol, and the solvent evaporated to give 640 mg (72%) of 24 as fine white needles, mp 94–96°. Two recrystallizations from hexane raised the mp to 101–102°: ir 1700, 1670, and 1665 cm⁻¹ (C=O); uv max 295 nm (ε 10,900); nmr (CCl_4) δ 8.83 (mound 1, NH), 3.12–2.50 (m, 3, CH and CH_2), 2.12 (q, 3, CH_3, $J = 0.5$ Hz), 1.88 (q, 3, CH_3, $J = 0.5$ Hz), and 1.22 (d, 3, CH_3, $J = 7$ Hz).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.68; H, 7.79; N, 8.38. Found: C, 64.43; H, 7.64; N, 8.15.

Tautomer 24 could be prepared directly from 12 in the following manner. A suspension of 12 (1.0 g, 0.0050 mol) in 95% C_2H_5OH was hydrogenated (5% Pd/C) at ambient temperature and atmospheric pressure. The reaction was terminated after slightly less than 1 equiv of hydrogen (150 ml) was taken up; after filtration of the catalyst, the solution was reduced in volume to 5 ml. A small amount of starting material precipitated from the chilled solution. Filtration and evaporation of the mother liquor left a residual oil. This oil was dissolved in a minimum amount of CH_2Cl_2 and deposited on a 20 × 1 cm Woelm, activity grade I, neutral alumina column and eluted with a 50:50 mixture of CH_2Cl_2–ether. Evaporation of the eluent afforded 720 mg (71%) of 24 as fine white needles, mp 100–101°, identical by all the usual criteria with 24 obtained from 23.

Conversion of 24 to 23 was effected by treatment of the former (1.0 g, 0.0060 mol) in 50 ml of CH_2Cl_2 with $(C_2H_5)_3O^+BF_4^-$ for 18 hr. The solution was then washed with cold 10% aqueous K_2CO_3. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated. The residual colorless liquid was distilled at 69° (0.1 mm) to give 260 mg (23%) of 23 identical by all the usual criteria with 23 obtained by hydrogenation of 22.

Hydrogenation of 26.—A solution of 26 (100 mg) in 10 ml of 95% C_2H_5OH was hydrogenated (10 mg 30% Pd/C) at room temperature and atmospheric pressure for 24 hr. Slightly more than 3 molar equiv of hydrogen (49 ml) was consumed. The catalyst was filtered and the filtrate evaporated in vacuo to give a clear oil, 68 mg (65%). Vpc analysis and nmr data confirmed the presence of four isomers: ir 3500, 3200, 1705, 1670, 1165, and 1095 cm⁻¹; nmr $(CDCl_3)$ δ 3.98, 3.82 3.70, 3.63 (all s, 3, OCH_3), 3.33–1.67 (m, 6, ring protons + NH), 1.15 (d, 3, CH_3, $J = 7$ Hz), and 1.12 (d, 6, CH_3, $J = 7$ Hz); nmr $(CDCl_3$–$D_2O)$ δ 3.33–1.67 (m, 5, ring protons) with no other alterations in the spectrum.

Hydrogenation of 28.—A solution of 250 mg (0.012 mol) of 28 in C_2H_5OH was hydrogenated (30% Pd/C) at atmospheric pressure. The reaction swiftly consumed 2 molar equiv of hydrogen (140 ml) and then ceased. The solution was filtered through Filter-Cel and the filtrate was evaporated in a stream of nitrogen with gentle warming. A white powder and a yellow oil were obtained. Washing with CCl_4 removed the oil and left 60 mg (22%) of crude **5-ethoxy-3,4,6,7-tetramethyl-1,3-dihydro-2H-azepin-2-one (32)**. This crude material was recrystallized from CH_2Cl_2–pentane only with substantial decomposition: mp 143–145°; ir 3400 (NH) and 1675 cm⁻¹ (C=O); uv max 223 nm (ε 8800), 285 (5200), and 325 (4400); nmr $(CDCl_3)$ δ 6.50 (mound, 1, NH), 3.27 (doublet of q, 2, OCH_2CH_3, $J = 7$ Hz), 2.67 (q, 1, CH, $J = 7$ Hz), 2.17, 1.90, 1.65 (all s, 3, =CCH₃), 1.23 (t, OCH_2CH_3, $J = 7$ Hz), and 1.16 (d, 3, CH_3, $J = 7$ Hz).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69; mol wt, 209. Found: 68.52; H, 9.45; N, 6.37; mol wt, 209 (mass spectrum).

2,4-Dinitrophenylhydrazones.—The general procedure used was as follows.[34] To 100 mg (5.0 mmol) of 2,4-DNPH was

(34) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, p 219.

added 0.5 ml of concentrated H_2SO_4 and 1 ml of H_2O. The mixture was then poured into 2.5 ml of 95% C_2H_5OH. An equimolar amount of the carbonyl compound in 5 ml of C_2H_5OH was added to the 2,4-DNPH solution. On standing overnight, the hydrazone precipitated; it was filtered, washed with cold C_2H_5OH, and recrystallized from ethyl acetate or C_2H_5OH.

Compounds **12, 22,** and **26** gave the identical hydrazone **25,** mp 277–279°.

Anal. Calcd for $C_{15}H_{15}N_5O_5$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.00; H, 4.50; N, 20.42.

Similarly **14, 28,** and **31** afforded the same hydrazone **30,** mp 215–217°.

Anal. Calcd for $C_{16}H_{17}N_5O_5$: C, 53.48; H, 4.77; N, 19.49. Found: C, 53.50; H, 4.80; N, 19.30.

2-Ethoxy-5H-benz[f]azepin-5-one (34).—To a solution of **16** (1.0 g, 0.0053 mol) in 50 ml of dry CH_2Cl_2 was added 1.1 g (0.0053 mol) of $(C_2H_5)_3O^+BF_4^-$ and the whole mixture was refluxed 3 hr. The green-black reaction mixture was quenched with 10 ml of 20% aqueous K_2CO_3 solution. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to dryness. The green residue was sublimed [30° (0.1 mm)] to give **34** (70 mg, 6.5%). An analytical sample was obtained by chromatography on a 50 × 5 mm Woelm, neutral, alumina column (activity grade I). Elution with pentane gave **34** as white crystals: mp 46°; nmr (CCl_4) δ 8.08 (distorted d, 1, peri H, J = 8 Hz, 1.5 Hz), 7.58–7.10 (m, 3, aromatic), 6.81 (v_B of AB quartet, 1, J = 12 Hz), 6.65 (v_A of AB quartet, 1, J = 12 Hz), 4.31 (q, 2, OCH_2CH_3, J = 7 Hz), and 1.35 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.92; H, 5.52. Found: C, 72.12; H, 5.82.

3,4-Dihydro-1H-benz[f]azepine-2,5-dione (35).—A suspension of 1.0 g (0.057 mol) of **16** in 25 ml of ethanol was hydrogenated overnight on a Parr shaker with 30% Pd/C at 40 psi. An additional 50 ml of C_2H_5OH was added and the whole mixture was filtered. The filtrate was concentrated *in vacuo* to give 0.87 g (86%) of **35.** Recrystallization from benzene led to a colorless product: mp 187–188°; ir 3250 cm⁻¹ (NH); uv max 223 nm (ε 33,200), 254 (8800), and 317 (3300); nmr (DMSO-d_6) δ 8.00–6.70 (m, 5, aromatic + NH), and 3.08–2.50 (A_2B_2, 4, CH_2CH_2).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.50; H, 5.18; N, 8.01. Found: C, 68.64; H, 5.17; N, 8.31.

4-(p-Dimethylaminophenylimino)-3,4-dihydro-1H-benz[f]-azepine-2,5-dione (36).—*N,N*-Dimethyl-*p*-nitrosoaniline (1.5 g, 0.010 mol) and **35** (1.0 g, 0.0060 mol) were dissolved in hot CH_3-OH. A 2 N NaOH solution (2 ml) was added and on standing **36** precipitated as tiny red plates. The solid was filtered and repeatedly washed with acetone. Recrystallization from DMF gave 800 mg (50%) of **36** as red plates, mp 310–312°.

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.20; H, 5.30; N, 13.82.

Concentrated HCl (10 ml) was added to 500 mg (0.0060 mol) of **36.** The mixture was heated (steam bath) for 30 min and the dark suspension was filtered on a sintered glass funnel. The residue was successively washed with H_2O, hot EtOH, and acetone to give 60 mg (11%) of **37.** This insoluble, yellow-green trione, mp 250° dec, defied all attempts at further purification: ir 3385 (NH), 1660, 1615, 1590, 1570 cm⁻¹.[35]

Anal. Calcd for $C_{10}H_7NO_3$: mol wt, 187. Found: mol wt, 187 (mass spectrum).

11-Ethoxybenz[c]cyclohexadienyl[5,6-f]-2H-azepin-2-one (42).—A suspension of **18** (10 g, 0.045 mol) in 200 ml of dry CH_2Cl_2 was treated overnight with 10 g (0.053 mol) of $C_2H_5)_3O^+BF_4^-$. The previously described aqueous K_2CO_3 work-up afforded a white solid which was continuously extracted with pentane for 24 hr (Soxhlet). Evaporation of the pentane left a yellow solid which was dissolved in CH_2Cl_2, deposited on a 2 × 2 cm neutral, alumina column, and eluted with 30–60° petroleum ether to give **42** as white crystals (7.4 g, 71%). An analytical sample was prepared by recrystallization from pentane: mp 101–102°; nmr (CCl_4) δ 8.08–7.00 (m, 8 aromatic), 4.28 (q, 2, OCH_2CH_3, J = 7 Hz), and 1.44 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.45; H, 5.21; N, 5.61. Found: C, 76.29; H, 5.51; N, 5.65.

Compounds **18** and **42** gave the identical hydrazone **47,** mp 280° (from ethyl acetate).

Anal. Calcd for $C_{20}H_{13}N_5O_5$: C, 59.55; H, 3.25; N, 17.37. Found: C, 59.44; H, 3.29; N, 17.11.

11-Hydroxy-6(5H)-morphanthridinone (45).—A suspension of 10 g (0.045 mol) of **18** and 10 g (0.049 mol) of aluminum isopropoxide in 200 ml of dry isopropyl alcohol was slowly distilled through a 20-cm Vigreux column so that 1 drop of solvent was collected per minute. The distillate was tested for the presence of acetone by means of a 10% 2,4-DNPH solution. After two successive negative tests the reaction was assumed complete. Most of the isopropyl alcohol was removed *in vacuo* and the residue acidified with 100 ml of 10% HCl. The resulting solid was filtered, washed acid-free with water, and recrystallized from DMF–water to give 9.3 g (92%) of **45:** mp 247–248° (lit.[32] 250°); nmr (DMSO-d_6) δ 7.75–6.83 (m, 9, aromatic + NH), 6.12 (d, 1, OH, J = 5 Hz), and 5.62 (d, 1, CH, J = 5 Hz); nmr (DMSO-d_6-D_2O) δ 7.75–6.83 (m, 8, aromatic) and 5.62 (s, 1, CH).

11-Ethoxy-6-hydroxybenz[c]cyclohexadienyl[5,6-f]-2H-azepine (43).—A solution of 2.5 g (0.0010 mol) of **42** in 20 ml of wet THF was treated with a large excess of $NaBH_4$ (1.0 g, 0.030 mol). The mixture was stirred for 4 hr, poured into 100 ml of H_2O, and extracted with two 50-ml portions of ethyl ether. The ether layer was separated, dried (Na_2SO_4), and evaporated to give a viscous oil. Crystallization was induced by vigorous scratching. To effect recrystallization the solid was dissolved in CH_2Cl_2 and 30–60° petroleum ether was added to the cloud point. Upon standing at −10° crystals formed. This procedure was repeated to give a white solid: mp 105–106°; ir 3350 cm⁻¹ (OH); uv max 210 nm (ε 36,800) and 285 (5700); nmr (CCl_4) δ 7.72–6.83 (m, 8, aromatic), 5.08 (s, 1, CH), 4.50 (m, 2, OCH_2CH_3) 3.29 (mound, 1, OH), and 1.47 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.04; H, 5.90; N, 5.79.

6-Hydroxy-5,6-dihydro-11-morphanthridinone (44).—A two-phase mixture of **43** (1.0 g, 0.0040 mol) and 20 ml of 1 N HCl was thoroughly stirred for 1 hr. The aqueous layer was separated and carefully adjusted to pH 6.9 by the addition of 1 N NaOH solution. The white precipitate that separated was filtered, washed with water, and recrystallized from C_2H_5OH to give dense white crystals: mp 138–139°; ir 3460 (OH), 3375 (NH), and 1740 cm⁻¹ (C=O); uv max 215 nm (ε 42,500) and 295 (7500); nmr (CCl_4) δ 8.10–6.50 (m, 9, aromatic plus CH) and 3.82 (mound, 2, OH, NH, exchangeable with D_2O).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.40; H, 4.86; N, 6.44.

11-Ethoxy-5-ethyl-6-morphanthridinone (46).—A suspension of **45** (2.25 g, 0.010 mol) in 15 ml of dry CH_2Cl_2 was treated with 1.90 g (0.010 mol) of $(C_2H_5)_3O^+BF_4^-$. After solution was effected, the reaction was quenched by the addition of 50 ml of 10% aqueous K_2CO_3. Methylene chloride (50 ml) was added to the mixture and the organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo* to leave a viscous oil. This oil was distilled at 120° (0.1 mm) to give 300 mg (11%) of **46** and a non-distillable glassy residue which could not be identified. The distillate solidified on cooling to −10° overnight. Recrystallization from CH_3OH gave white cubes: mp 67–68°; ir 1650 (C=O), 1145 and 1220 cm⁻¹ (COC); uv max 230 nm (ε 21,600) and 280 (5000); nmr (CCl_4) δ 7.67–6.83 (m, 8, aromatic), 4.82 (s, 1, CH), 4.40 (doublet of q, 2, OCH_2CH_3, J = 7 Hz), 3.41 (mound, 2, NCH_2CH_3) (at 60°, q, 2, NCH_2CH_3, J = 6 Hz), 1.33 (t, 3, OCH_2CH_3, J = 7 Hz), and 1.15 (t, 3, NCH_2CH_3, J = 6 Hz).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.82; N, 4.98. Found: C, 76.54; H, 6.65; N, 5.24.

Acid Hydrolysis of Azatropones.—The general procedure involved treatment of an alcoholic solution of the azatropone with a catalytic amount of H_2SO_4. After standing for several hours, a precipitate appeared. The mixture was cooled to −10°, filtered, washed with cold H_2O, dried, and recrystallized to quantitatively yield the corresponding azepinediones. Thus, **22** and **26** gave **12, 28** and **31** led to **14,** and **42** afforded **18.**

(35) To be compared with the carbonyl absorptions in **41**: 1660, 1620, 1590, and 1570 cm⁻¹.[30]

Lithiation of Substituted Pyrazoles. Synthesis of Isomerically Pure 1,3-, 1,3,5-, and 1,5-Substituted Pyrazoles

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Four syntheses of isomerically pure substituted pyrazoles are described (A–D). Using a lithiation procedure, 1,3,5- and 1,5-substituted pyrazoles can be obtained directly, e.g., (A) 1,3-dimethyl-α-phenylpyrazole-5-methanol (5) and 3-methyl-α-phenyl-1-propylpyrazole-5-methanol (11), (B) 5-methyl-α-phenylpyrazole-1-ethanol (8), and (C) α-phenyl-1-propylpyrazole-5-methanol (16). (A) Treatment of a 2:1 mixture of 1,3-dimethylpyrazole (2) and 1,5-dimethylpyrazole (7) with n-butyllithium equivalent to less than the amount of 2 followed by the addition of benzaldehyde yields 5. (B) Lithiation of pure 7 and reaction with benzaldehyde yields 8. (C) Reaction of 1-propylpyrazole (15) with an equivalent of n-butyllithium followed by the addition of benzaldehyde yields 16. Pure 1,3-disubstituted pyrazoles were synthesized in high yield in two steps. 5-Chloro-1-methyl-3-substituted pyrazoles lithiate on the 1-methyl group. Thus (D) 5-chloro-1,3-dimethylpyrazole (3) was allowed to react with n-butyllithium followed by benzaldehyde yielding 5-chloro-3-methyl-α-phenylpyrazole-1-ethanol (17). Catalytic hydrogenation of 17 yielded 3-methyl-α-phenylpyrazole-1-ethanol (6). Two generalizations have been drawn concerning the position of metalation: (1) a 1-methyl substituent on a pyrazole will undergo metalation with n-butyllithium to some extent; (2) a pyrazole with an unactivated 1 substituent and a 5-H undergoes metalation exclusively on the 5 position. Changes in the nmr spectra in CDCl₃ and DMSO-d₆ have been useful in differentiating isomeric 1,3- and 1,5-disubstituted pyrazoles. A pyrazolyl ketone, 1,3-dimethyl-pyrazol-5-yl phenyl ketone (25), was synthesized by addition of an excess of benzaldehyde to the corresponding pyrazolyl lithium reagent.

Most syntheses of 1-alkylpyrazoles result in mixtures of 1,3- and 1,5-disubstituted pyrazoles. From these mixtures, pure products are obtained with difficulty if at all.[1-6] One of us had earlier found the synthetic utility of 5-chloro-1,3-disubstituted 4-lithiopyrazoles (available by halogen–metal exchange).[7,8] Thus we decided to investigate the lithiation of some readily available unsymmetrical pyrazoles, pyrazole isomeric mixtures, and the conversion of the resulting lithio reagents to isomerically pure substituted pyrazoles. A recent publication on the "Lithiation of Five-membered Heteroaromatic Compounds" including the lateral metalation of 1,3,5-trimethylpyrazole (1)[9] has led us to report some of our results with unsymmetrical pyrazoles.

Habraken and Moore[6] have prepared pure 1,3-dimethylpyrazole (2) in 20% yield by Raney nickel catalyzed hydrogenation of 5-chloro-1,3-dimethylpyrazole (3). These workers also reported the positions of the nmr signals for the methyl substituents. A number of reports on the lithiation of 1-methylpyrazoles have appeared.[5,10] These workers isolated products corresponding to lithiation at the 5 position. Our reinvestigation of the lithiation of 1-methylpyrazoles has shown that lithiation also occurs on the 1-(lateral) methyl group. The earlier workers had relied upon

the melting points of the acids resulting from the carbonation of the lithio intermediates, since most of the expected acids were known. Stock, Donahue, and Amstutz have reported that the combination of sodium ethoxide, diethyl oxalate, and 1-methylpyrazole (4) reacts on the 1-methyl group.[11]

We chose to react the lithio intermediates with benzaldehyde because of the higher yields, greater stability, lower water solubility, experimental ease, and non-amphoteric nature of the expected products. These products would most likely be unknown; however, it was felt that the nmr studies of Habraken and Moore,[6] Finar and Mooney,[12] as well as those of Tensmeyer and Ainsworth[13] and others,[14a-e] would allow differentiation between 1,3-, 1,5-, and laterally substituted pyrazoles. Vapor phase chromatography was performed on samples of the crude hydrolyzed reaction mixtures as well as on the final products to avoid missing noncrystalline products.

The reaction of pure 1,3-dimethylpyrazole (2) with an equivalent of n-butyllithium followed by benzaldehyde resulted in a 90% yield of a 2:1 mixture of 1,3-dimethyl-α-phenylpyrazole-5-methanol (5) and 3-methyl-α-phenylpyrazole-1-ethanol (6).

Because of the yield reported by Habraken and Moore[6] in their preparation of 2, we also reinvestigated the reaction of 4,4-dimethoxy-2-butanone with methyl-

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hydrazine reported by Burness.[15] We have found that by changing the reaction time and work-up conditions a 93% yield of a 2:1 mixture of 2 and 1,5-dimethyl-pyrazole (7) can be obtained. More importantly, the reaction of this mixture with *n*-butyllithium and benzaldehyde equivalent to slightly less than the amount of 2 present results in the conversion of that isomer into 5 with little contamination by other products (93–99% of the total crude alcohol by vpc). The trace products are 6 and 5-methyl-α-phenylpyrazole-1-ethanol (8). We believe that this result can be best explained by the intermediacy of laterally metalated 7 metalating 2 in the 5 position.

Since 7 apparently does not undergo nuclear metalation[16] and 1-alkyl groups larger than methyl are not readily metalated (see synthesis D), we concluded that a 1-(higher alkyl)-3(5)-substituted pyrazole mixture would show preferential nuclear metalation at the 5 position of the 1,3 isomer. To test this hypothesis, a mixture of 3-methyl-1-propylpyrazole (9) and 5-methyl-1-propylpyrazole (10) (63–37% by vpc) was prepared by alkylation of 3-methylpyrazole.[15] Metalation of this mixture with *n*-butyllithium equivalent to both isomers followed by an equivalent of benzaldehyde resulted in a 95% yield of 3-methyl-α-phenyl-1-propyl-pyrazole-5-methanol (11). This series of reactions constitutes a versatile synthesis of isomerically pure 1,3,5-trisubstituted pyrazoles from the readily prepared but difficultly separable 1,3(5)-disubstituted pyrazole mixtures (A).

Metalation of the 2:1 mixture of 2 and 7 with *n*-butyllithium equivalent to the total amount of pyrazole present followed by reaction with benzaldehyde gave a 40:35:25 mixture of 5, 6, and 8 in 90% combined yield. The presence of 8 (easily identified in the nmr) led us to synthesize pure 7 by decarboxylation of 1,5-dimethylpyrazole-3-carboxylic acid.[3] Pure 7 when treated with *n*-butyllithium followed by benzaldehyde gave an 80% yield of 5-methyl-α-phenylpyrazole-1-ethanol (8). Addition of cyclohexanone to the lithio reagent gave 1-[(5-methylpyrazol-1-yl)methyl]cyclohexanol (12). Thus this sequence affords pure 1,5-disubstituted pyrazoles (B); it is limited by the relative difficulty of obtaining pure 1-methyl-5-substituted pyrazoles.

The metalation of 1-methylpyrazole[17] (4) was investigated in the same manner resulting in a 88% yield of a 66:34 mixture of 1-methyl-α-phenylpyrazole-5-methanol (13) and α-phenylpyrazole-1-ethanol (14). The variance of our results from some of those reported earlier on the metalation of 1-methylpyrazoles can be explained by the inverse of our reasons for choosing the reaction with benzaldehyde for derivatization of the metalated intermediates. The relative insolubility and crystallinity of the α-phenyl-substituted pyrazole-1-ethanols was fortuitous.

As in the case of 9 and 10, we concluded that a 1-(higher alkyl)-pyrazole would show preferential metalation on the 5 position. To test this hypothesis, 1-propylpyrazole (15) was prepared by alkylation of pyrazole. Reaction and derivatization of 15 in the

same manner resulted in an 81% yield of α-phenyl-1-propylpyrazole-5-methanol (16). Hence, this sequence also affords pure 1,5-disubstituted pyrazoles (C).

We also investigated the reaction of 5-chloro-1-methyl-3-substituted pyrazoles and found exclusive lateral metalation. Thus the reaction of 3 with an equivalent of *n*-butyllithium followed by reaction of the lithio intermediate with benzaldehyde gives a high yield of 5-chloro-3-methyl-α-phenylpyrazole-1-ethanol (17). The nmr spectrum of 17 clearly shows the presence of the 3-methyl group and a complex abc pattern for the 1-CH₂CH–, demonstrating the position of lithiation. Removal of the 5-chloro substituent in this product or in other derivatives by Pd-catalyzed hydrogenation gives in high yield isomerically pure 1,3-disubstituted pyrazoles (D). This sequence allows the synthesis of a wide variety of 1,3-disubstituted pyrazoles unavailable by other methods (see Experimental Section for examples 6, 18, 19, 23, 24). This sequence is limited by the fact that 1-alkyl groups other than methyl react only under forcing conditions to give complex mixtures. Our results are summarized in Scheme I.

Two generalizations can be drawn from this work: (1) a 1-methyl substituent on a pyrazole will undergo metalation with *n*-butyllithium to some extent; (2) a pyrazole with an unactivated 1-substituent and a 5-H undergoes metalation with *n*-butyllithium exclusively on the 5 position.

We believe that the results of lithiation on 1-alkyl-pyrazoles can best be explained by the following as stated by Kost and Grandberg.[18] The 1-nitrogen atom of the *n*-substituted pyrazoles contributes its electron pair to the formation of an aromatic sextet, and thus assumes some cationic character which is balanced by the slight anionic character assumed by the remaining ring atoms. The second nitrogen atom in the ring (like that in pyridine and in contrast to pyrrole) contributes two electrons in the formation of σ bonds and one electron toward the aromatic sextet and retains an electron pair which gives it basic properties. Thus the inductive effect of the "cationic character" of the 1-nitrogen activates the 1-methyl to lithiation as well as the 5-hydrogen and the inductive effect is not transmitted to the 3-hydrogen. It is also possible that the free pair of electrons on the second nitrogen atom has an anionic inductive effect on the 3-hydrogen which reinforces the preference for lithiation at the five position. Finar and coworkers[19,20] have published molecular orbital calculations of 1-alkylpyrazoles using both the LCAO–MO and CNDO/2 methods. Their data correctly predict electrophilic substitution by bromine at the 4 position. As we interpret their results, the differences between the 3 and 5 positions of 1-methyl-pyrazole are too small to account for the difference in reactivity toward *n*-butyllithium. It is possible that the latter reaction is nucleophilic and these molecular orbital calculations are only accurate for electrophilic substitution.

The lithio reagents resulting from lateral or nuclear metalation undergo the typical reactions of alkyl-

(15) D. M. Burness, *J. Org. Chem.*, **21**, 97 (1956).

(16) This also explains the isolation of 1,3-dimethylpyrazole-5-carboxylic acid from presumably impure **7** (contaminated by **2**) by lithiation followed by carboxylation in the work of Hüttel and Schön.[5]

(17) I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 3314 (1957).

(18) L. N. Kost and I. I. Grandberg, *Advan. Heterocycl. Chem.*, **6**, 389 (1966).

(19) I. L. Finar, *J. Chem. Soc. B*, 725 (1968).

(20) R. E. Burton and I. L. Finar, *ibid.*, 1692 (1970).

SCHEME I

(A)

2

+

7

9

+

10

(B)

7　　　　8

(C)

15

(D)

3, R = CH₃　　　　17, R = CH₃

6, R = CH₃

2

5

4

13　　　　14
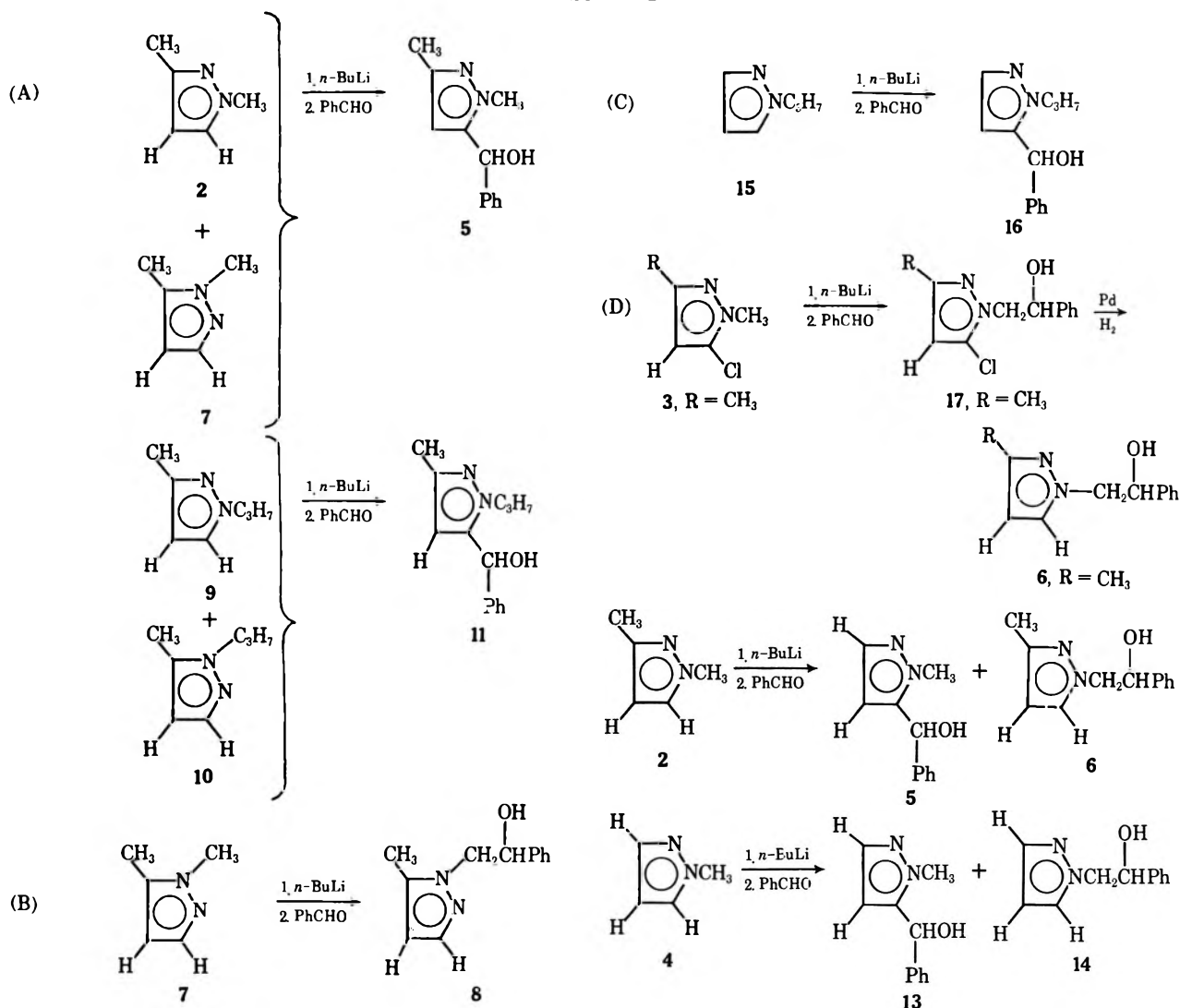
and aryllithium compounds.[21] A number of examples have been included in the Experimental Section (12, 18, 19, 20). Some of the products have been transformed into other substituted pyrazoles to demonstrate the versatility of these synthetic sequences (22, 23, 24, 25).

The nmr spectra were used to establish the identity of the isomeric products from the metalation of all the pyrazoles investigated. Our results on the nmr spectra of 2 and 7 and mixtures are essentially identical with those of Habraken and Moore.[6] A potentially useful method of distinguishing the 1,3 and 1,5 isomers was found when the spectra in CDCl₃ were compared to those in DMSO-d_6. The doublet due to the C-5 pyrazole proton peak was shifted to a markedly lower field while the C-3 pyrazole proton peak is found at essentially the same position. Several examples of this spectral difference are recorded in the Experimental Section. The substituted α-phenylpyrazole-1-ethanols exhibit a complex abc pattern for the –CH₂CH– protons, allowing easy identification.

An interesting experimental sidelight was the preparation of a pyrazolyl ketone, 1,3-dimethylpyrazol-5-yl phenyl ketone (25), by the slow addition of an excess of benzaldehyde to the corresponding lithio reagent.

(21) U. Schöllkopf in "Methoden Der Organischen Chemie," Vol 13/1, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1970. p 170–224.

Experimental Section[22]

as described by Burness.[15] 1,5-Dimethylpyrazole-3-carboxylic acid, mp 173–176° (recrystallized from acetonitrile) (lit. mp 176°), was prepared as described by von Auwers and Hollmann.[3] This acid, mp 165–170°, contained 10% of the other isomer, shown by the presence of **2** after pyrolysis. 1-Methylpyrazole (**4**), bp 124–126° (lit. bp 124–125°),[17] was prepared by alkylation of pyrazole.

1,3-Dimethylpyrazole (2).[25]—A solution of 5-chloro-1,3-dimethylpyrazole (**3**) (120 g, 0.9 mol) in methanol (500 ml) was treated with 20% Pd/C (1 g) and hydrogen at 50 psi. Hydrochloric acid (100 ml, 1.17 mol) was added and the reaction mixture was concentrated at reduced pressure. The residue was treated with 50% NaOH (160 g, 2.0 mol) and extracted with ether. The extracts were dried (MgSO$_4$) and the solvent and product were distilled through a Vigreux column to yield **2**: 80 g (92.5%); vpc shows a trace (less than 2%) of the starting material; bp 135–137° (lit. bp 136–139°);[3] nmr (CDCl$_3$) δ (TMS) 7.20 (1 H, doublet, 5-H), 5.93 (1 H, doublet, 4-H), 3.75 (3 H, singlet, 1-CH$_3$), 2.22 (3 H, singlet, 3-CH$_3$); nmr (DMSO-d_6) δ (TMS) 7.51 (1 H, doublet, 5-H), 6.00 (1 H, doublet, 4-H), 3.73 (3 H, singlet, 1-CH$_3$), 2.12 (3 H, singlet, 3-CH$_3$).

Anal. Calcd for C$_5$H$_8$N$_2$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.20; H, 8.62; N, 29.09. Picrate mp 135–136° (lit. mp 136°).[3]

1,3-Dimethylpyrazole (2) and 1,5-Dimethylpyrazole (7).[26]— Methylhydrazine (184 g, 4.0 mol) was added to stirred and cooled 4,4-dimethoxy-2-butanone (20–25°) (528 g, 4.0 mol). The mixture was stirred for 16 hr at room temperature. The mixture of cis- and trans-methylhydrazone was poured into hydrochloric acid (780 ml, 6 N) with stirring. All of the methanol was removed by distillation and the solution was treated with charcoal, filtered through a filter aid, and cooled. The mixture was made basic (50% NaOH) and extracted with ether. The extracts were dried (MgSO$_4$) and distilled through a Vigreux column to yield **2** and **7**, 351 g (91.5%), bp 130–155°. A vpc showed the mixture to contain 63.5% **2** and 36.5% **7**: nmr (CDCl$_3$) δ (TMS) 7.32 (1 H, doublet, 3-H), 7.20 (1 H, doublet, 5-H), 5.95 (2 H, doublet, 2 4-H), 3.77 (3 H, singlet, 1-CH$_3$ of the 1,3 isomer), 3.72 (3 H, singlet, 1-CH$_3$ of the 1,5 isomer), 2.23 (6 H, singlet, 2 3-CH$_3$); nmr (DMSO-d_6) δ (TMS) 7.51 (1 H, doublet, 5-H), 7.29 (1 H, doublet, 3-H), 6.00 (2 H, doublet, 2 4-H), 3.73 (3 H, singlet, 1-CH$_3$ of the 1,3 isomer), 3.69 (3 H, singlet, 1-CH$_3$ of the 1,5 isomer), 2.22 (3 H, singlet, 3-CH$_3$ of the 1,5 isomer), 2.12 (3 H, singlet, 3-CH$_3$ of the 1,3 isomer).

1,3-Dimethyl-α-phenylpyrazole-5-methanol (5).—A solution of **2** and **7** (99 g, 1.03 mol of a 64:36 mixture) in ether (1 l.) was stirred and treated dropwise with a n-butyllithium (0.5 mol) solution in heptane (350 ml). The mixture was stirred and refluxed for 30 min, a solution of benzaldehyde (63.6 g, 0.6 mol) in ether (250 ml) was added in a steady stream, and refluxing was continued for 15 min. Water (200 ml) was added, the layers were separated, and the aqueous layer was extracted with ether. The organic layer was dried (MgSO$_4$) and distilled to yield **5**: 92.5 g (91.5%); bp 133–135° (0.3 mm); nmr (CDCl$_3$) δ (TMS) 7.33 (5 H, singlet aromatic CH), 5.80 (2 H, singlet, -CH-, 4-H), 5.6–5.1 (1 H, broad singlet, OH), 3.60 (3 H, singlet, NCH$_3$), 2.04 (3 H, singlet, 3-CH$_3$); nmr (DMSO-d_6) δ (TMS) 7.34 (5 H, broad singlet, aromatic CH), 6.06 (1 H, broad doublet, OH), 5.8 (1 H, broad doublet, -CH-), 3.63 (3 H, singlet, NCH$_3$), 2.05 (3 H, singlet, 3-CH$_3$).

Anal. Calcd for C$_{12}$H$_{14}$N$_2$O: C, 71.26; H, 6.98; N, 13.86. Found: C, 71.35; H, 7.06; N, 13.63.

3-Methyl-1-propylpyrazole (9) and 5-Methyl-1-propylpyrazole (10).—A mixture of 3-methylpyrazole[15] (104 g, 1.27 mol), propyl bromide (187 g, 1.5 mol), and anhydrous potassium carbonate (527 g, 3.8 mol) in 2-butanone (700 ml) was refluxed with vigorous stirring for 72 hr. Tlc showed the absence of starting material. The mixture was filtered and treated with hydrochloric acid (150 ml, 1.75 mol) and concentrated *in vacuo*. The residue was dissolved in a minimum amount of water and washed with ether. The water layer was made strongly basic with 50% NaOH (160

g, 2.0 mol) and extracted with ether (four 1-l. portions). The combined extracts were dried (MgSO$_4$) and distilled through a Vigreux column to yield **9** and **10**: 125 g (78%); bp 51–58° (6 mm), 63–37% by vpc and nmr; nmr (CDCl$_3$) δ (TMS) 7.40 (1 H, doublet, 3-H), 7.25 (1 H, doublet, 5-H), 5.99 (2 H, doublet, 2 4-H), 3.99 (4 H, triplet, 2 NCH$_2$-), 2.26 (6 H, singlet, 2 3-CH$_3$), 2.25–1.55 (4 H, multiplet, 2 -CH$_2$-), 0.9 (6 H, triplet, 2 -CH$_3$); nmr (DMSO-d_6) δ (TMS) 7.52 (1 H, doublet, 5-H), 7.28 (1 H, doublet, 3-H), 5.97 (2 H, doublet, 2 4-H), 3.94 (4 H, triplet, 2 NCH$_2$-), 2.23 (3 H, singlet, 3-CH$_3$ of the 1,5 isomer), 2.12 (3 H, singlet of the 1,3 isomer), 2.11–1.4 (4 H, multiplet, 2 -CH$_2$-), 0.79 (6 H, triplet, 2 -CH$_3$).

Anal. ⁰Calcd for C$_7$H$_{12}$N$_2$: C, 67.69; H, 9.74; N, 22.57. Found: C, 67.95; H, 9.81; N, 23.85.[27]

3-Methyl-α-phenyl-1-propylpyrazole-5-methanol (11).—A solution of **9** and **10** (12.4 g, 0.1 mol) in ether (300 ml) was stirred and treated with a solution of n-butyllithium in heptane (0.1 mol). The mixture was stirred for 30 min and benzaldehyde (11.6 g, 0.11 mol) was added rapidly. The reaction was stirred for 2 min after the exothermic phase had subsided and water (100 ml) was added. The organic layer was dried (MgSO$_4$) and distilled to yield **11**: 14 g (95% based on the amount of **9** present); bp 115–117° (0.09 mm) (99.7% by vpc); nmr (CDCl$_3$) δ (TMS) 7.32 (5 H, singlet, aromatic CH), 5.88 (1 H, singlet, -CH-), 5.83 (1 H, singlet, 4-H), 4.9–4.3 (1 H, broad singlet, OH), 3.86 (2 H, triplet, NCH$_2$-), 2.10 (3 H, singlet, 3-CH$_3$), 2.09–1.15 (2 H, multiplet, -CH$_2$-), 0.77 (3 H, triplet, -CH$_3$).

Anal. Calcd for C$_{14}$H$_{18}$N$_2$O: C, 73.00; H, 7.88; N, 12.16. Found: C, 73.04; H, 8.02; N, 12.36.

1,5-Dimethylpyrazole (7).—1,5-Dimethylpyrazole-3-carboxylic acid[3] (28 g, 0.2 mol) was pyrolyzed at 240–255° to yield **7**: 17.5 g (91%); bp 157–158° (lit. bp 158°);[6] nmr (CDCl$_3$) δ (TMS) 7.33 (1 H, doublet, 3-H), 5.96 (1 H, multiplet,[28] 4-H), 3.74 (3 H, singlet, NCH$_3$), 2.23 (3 H, singlet, 5-CH$_3$); nmr (DMSO-d_6) δ (TMS) 7.26 (1 H, doublet, 3-H), 5.98 (1 H, multiplet, 4-H), 3.68 (3 H, singlet, NCH$_3$), 2.21 (3 H, singlet, 5-CH$_3$); **7** picrate mp 170–173° (lit. 172°)[3] (softens 160°).

5-Methyl-α-phenylpyrazole-1-ethanol (8).—A solution of **7** (10 g, 0.104 mol) in ether (350 ml) was treated with a solution of n-butyllithium (0.1 mol) in heptane (65 ml) with stirring and cooling (20–25°). The mixture was stirred for 30 min and benzaldehyde (12 g, 0.11 mol) was added. The mixture was stirred for 5 min and water (100 ml) was added. The mixture was cooled (0°) and the product was filtered and dried to yield **8**: 16 g (80%); mp 130–132°; nmr (CDCl$_3$) δ (TMS) 7.42 (1 H, doublet, 3-H), 7.28 (5 H, singlet, aromatic CH), 5.97 (1 H, multiplet, 4-H), 5.30–5.0 (1 H, multiplet, -CH-), 4.90–4.65 (1 H, broad singlet, OH), 4.28–4.06 (2 H, multiplet, -CH$_2$-), 2.04 (3 H, singlet, 5-CH$_3$); nmr (DMSO-d_6) δ (TMS) 7.31 (1 H, doublet, 3-H), 7.25 (5 H, singlet, aromatic CH), 5.92 (1 H, condensed multiplet, 4-H), 5.70–5.50 (1 H, broad singlet, OH), 5.15–4.75 (1 H, multiplet, -CH-), 4.25–4.00 (2 H, multiplet, NCH$_2$-), 2.02 (3 H, singlet, 5-CH$_3$).

Anal. Calcd for C$_{12}$H$_{14}$N$_2$O: C, 71.26; H, 6.98; N, 13.86. Found: C, 71.23; H, 7.04; N, 13.91.

1-Propylpyrazole (15).[29,30]—A mixture of sodium ethoxide (from 29 g, 1.2 g-atoms sodium metal), pyrazole (68 g, 1 mol), and ethanol (500 ml) was stirred and refluxed while propyl iodide (220 g, 1.29 mol) was added dropwise. The mixture was refluxed for 18 hr and cooled, hydrochloric acid (100 ml, 1.17 mol) was added, and the mixture was concentrated at reduced pressure. The residue was dissolved in a minimum of water, made strongly basic (NaOH), and extracted with ether (four 1-l. portions). The extracts were dried (MgSO$_4$) and distilled to yield **15**: 80 g (72%); bp 152–155° (760 mm) (lit. bp 166–167°);[30] nmr (CDCl$_3$) δ (TMS) 7.50 (1 H, doublet, 3-H), 7.37 (1 H, doublet, 5-H), 6.40–6.13 (1 H, multiplet, 4-H), 4.04 (2 H, triplet, NCH$_2$-), 2.15–1.58 (2 H, multiplet, -CH$_2$-), 0.97 (3 H, triplet, -CH$_3$); nmr (DMSO-d_6) δ (TMS) 7.66 (1 H, doublet, 5-H), 7.42 (1 H, doublet, 3-H), 6.33–6.16 (1 H, multiplet, 4-H), 4.04 (2 H, triplet, NCH$_2$-), 2.13–1.43 (2 H, multiplet, -CH$_2$-), 0.80 (3 H, triplet, -CH$_3$).

Anal. Calcd for C$_6$H$_{10}$N$_2$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.03; H, 9.13; N, 26.33.[27]

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(25) This is merely a variation on the method of Habraken and Moore[6] resulting in a better yield. Most of the lower molecular weight alkylpyrazoles seem to codistill with many solvents, *i.e.*, benzene, heptane, methanol, and each other. Ether is the solvent of choice to minimize this problem; however, even this was always separated by distillation through a Vigreux column.

(26) Using conditions approximating those of Burness,[15] *i.e.*, 1 hr at 100°, only a 65% conversion (vpc) to the mixture of cis- and trans-methylhydrazone took place.

(27) This N analysis is anomalous.

(28) Others have reported this as a doublet.[6]

(29) R. G. Jones, *J. Amer. Chem. Soc.*, **71**, 3994 (1949).

(30) C. Alberti and G. Zerbi, *Farmaco, Ed. Sci.*, **16**, 527 (1961); *Chem. Abstr.*, **58**, 5660c (1963).

15 picrate had mp 96–98°.

Anal. Calcd for $C_{12}H_{13}N_5O_7$: C, 42.47; H, 3.87; N, 20.65. Found: C, 42.20; H, 3.83; N, 20.35.

α-Phenyl-1-propylpyrazole-5-methanol (16).—A solution of 15 (22 g, 0.2 mol) in ether (500 ml) was treated with a solution of *n*-butyllithium (0.2 mol) in heptane (140 ml) with stirring and cooling (20–25°). The mixture was stirred for 1 hr and benzaldehyde (21.2 g, 0.2 mol) was added rapidly. The mixture was stirred for 20 min and water (100 ml) was added. The organic layer was dried (MgSO₄) and distilled to yield 16: 35 g (81%); bp 118–120° (0.15 mm); nmr (CDCl₃) δ (TMS) 7.29 (5 H, singlet, aromatic CH), 7.16 (1 H, doublet, 3-H), 5.93 (1 H, doublet, 4-H), 5.80 (1 H, singlet, –CH–), 5.16–4.66 (1 H, broad singlet, OH), 4.10–3.70 (2 H, multiplet, NCH₂–), 2.00–1.14 (2 H, multiplet, –CH₂–), 0.75 (3 H, triplet, –CH₃); nmr (DMSO-d_6) δ (TMS) 7.35 (5 H, singlet, aromatic CH), 7.31 (1 H, doublet partially superimposed on the aromatic singlet, 3-H), 6.23–5.74 (3 H, complex, 4-H, –CH–, OH), 4.16–3.84 (2 H, multiplet, NCH₂–), 2.00–1.24 (2 H, multiplet, –CH₂–), 0.74 (3 H, triplet, –CH₃).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.20; H, 7.46; N, 12.95. Found C, 72.43; H, 7.51; N, 13.05.

5-Chloro-3-methyl-α-phenylpyrazole-1-ethanol (17).—A solution of *n*-butyllithium in heptane (0.5 mol) was added to a stirred, cooled (15–20°) solution of 5-chloro-1,3-dimethylpyrazole[23] (3) (60 g, 0.46 mol) in anhydrous ether (1 l.). The mixture was stirred at 15° for 30 min and a solution of benzaldehyde (53 g, 0.5 mol) in ether (100 ml) was added. The mixture was stirred at reflux for 5 min and cooled, and water (200 ml) was added. The organic layer was dried (MgSO₄) and concentrated, and the solid was triturated with petroleum ether (bp 30–60°) to yield 17: 90 g (86%); mp 85–87°; nmr (CDCl₃) δ (TMS) 7.31 (5 H, singlet, aromatic CH), 5.98 (1 H, singlet, 4-H), 4.97–5.25 (1 H, quartet, –CH–), 4.07–4.45 (3 H, multiplet, –CH₂– and OH), 2.20 (3 H, singlet, 3-CH₃).

Anal. Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 60.69; H, 5.51; N, 11.83.

3-Methyl-α-phenylpyrazole-1-ethanol (6).—A solution of 17 (11.9 g, 0.05 mol) in methanol (120 ml) containing sodium acetate (4.3 g, 0.05 mol) was hydrogenated at 50 psi using 20% Pd/C (1 g) at 25°. The mixture was concentrated, dissolved in chloroform, and washed with dilute NaOH and water. The organic layer was dried (MgSO₄) and evaporated. The product was recrystallized (*n*-hexane) to yield 6: 9.5 g (93%); mp 123–124°; nmr (CDCl₃) δ (TMS) 7.28 (5 H, singlet, aromatic CH), 7.17 (1 H, doublet, 5-H), 5.96 (1 H, doublet, 4-H), 5.2–4.9 (1 H, quartet, –CH–), 4.7–4.3 (1 H, broad singlet, OH), 4.3–4.04 (2 H, multiplet, –CH₂–); nmr (DMSO-d_6) δ (TMS) 7.45 (1 H, doublet, 5-H), 7.32 (5 H, singlet, aromatic CH), 5.96 (1 H, doublet, 4-H), 5.60 (1 H, doublet, OH), 5.15–4.88 (1 H, multiplet, –CH–), 4.12 (2 H, doublet, 1-CH₂–), 2.14 (3 H, singlet, 3-CH₃).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.86. Found: C, 71.30; H, 7.07; N, 13.78.

5-Chloro-α,α,3-triphenylpyrazole-1-ethanol (18).—A solution of 5-chloro-1-methyl-3-phenylpyrazole[24] (19.3 g, 0.10 mol) in ether (400 ml) was stirred, cooled (15–20°), and treated with *n*-butyllithium in heptane (0.10 mol). The mixture was stirred for 30 min and benzophenone (18.2 g, 0.10 mol) was added. After stirring for 5 min, water (100 ml) was added, and the organic layer was separated, dried (MgSO₄), and concentrated. The solid was recrystallized (methanol) to yield 18: 34 g (90%); mp 107–109°; nmr (CDCl₃) δ (TMS) 7.9–7.2 (15 H, complex pattern, 15 aromatic CH), 6.7–6.55 (1 H, broad singlet, OH), 6.40 (1 H, singlet, 4-H), 4.85 (2 H, singlet, –CH₂–).

Anal. Calcd for $C_{23}H_{19}ClN_2O$: C, 73.71; H, 5.11; N, 7.47. Found: C, 73.49; H, 5.21; N, 7.37.

α,α,3-Triphenylpyrazole-1-ethanol (19).—18 (12 g, 0.032 mol) was hydrogenated in the same manner as 17 to yield 19, 9.5 g (87%) (after recrystallization from benzene–petroleum ether): mp 124–126°; nmr (CDCl₃) δ (TMS) 7.95–7.15 (16 H, complex, 15 aromatic CH and 5-H), 6.45–6.25 (2 H, doublet with broad singlet, 4-H and OH), 4.81 (2 H, singlet, –CH₂–).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.96; H, 6.00; N, 8.46.

1-[(5-Methylpyrazol-1-yl)methyl]cyclohexanol (12).—A solution of 7 (9.6 g, 0.1 mol) in ether (300 ml) was treated with a solution of *n*-butyllithium (0.1 mol) in heptane (65 ml). After refluxing for 15 min, the mixture was cooled to −78° and a solution of cyclohexanone (11 g, 0.11 mol) in ether (25 ml) was added dropwise. The mixture was allowed to warm to room tempera-

ture and water (50 ml) was added. The organic layer was dried (MgSO₄), concentrated, and distilled to yield 12: 14 g (72%); bp 68–70° (0.15 mm); nmr (CDCl₃) δ (TMS) 7.40 (1 H, doublet, 3-H), 6.03 (1 H, multiplet, 4-H), 4.83–4.35 (1 H, broad singlet, OH), 3.93 (2 H, singlet, NCH₂–), 2.26 (3 H, singlet, 5-CH₃), 2.0–0.95 (10 H, broad complex, five –CH₂–); nmr (DMSO-d_6) δ (TMS) 7.28 (1 H, doublet, 3-H), 5.98 (1 H, multiplet, 4-H), 4.47 (1 H, singlet, OH), 3.92 (2 H, singlet, NCH₂), 2.26 (3 H, singlet, 5-CH₃), 2.0–0.83 (10 H, broad singlet, five –CH₂–).

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.43. Found: C, 68.30; H, 9.56; N, 14.20.

1,3-Dimethyl-α-phenylpyrazole-5-ethanol (20).—A solution of 2 and 7 (192 g, 2 mol, 64–36%) in ether (2.5 l.) was stirred and cooled (−6 to 0°) and a solution of *n*-butyllithium (1 mol) in heptane (630 ml) was added dropwise over 2.5 hr. The pale yellow suspension was treated with a solution of styrene oxide (120 g, 1 mol) in ether (250 ml) (not exothermic). The mixture was refluxed for 2 hr after the addition of THF (1 l.). After cooling, water (250 ml) was added, and the organic layer was dried (MgSO₄) and distilled to yield 20: 134 g (62%); bp 123–125° (0.1 mm); vpc shows 4% of a product assumed to be 1,3-dimethyl-β-phenylpyrazole-5-ethanol (21); nmr (CDCl₃) δ (TMS) 7.22 (5 H, singlet, aromatic CH), 5.77 (1 H, singlet, 4-H), 5.05–4.78 (2 H, multiplet superimposed upon a broad singlet, –CH– and OH), 3.26 (3 H, singlet, NCH₃), 3.1–2.75 (2 H, doublet, –CH₂–), 2.05 (3 H, singlet, 3-CH₃).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.20; H, 7.46; N, 12.95. Found: C, 72.30; H, 7.56; N, 12.68.

5-Benzyl-1,3-dimethylpyrazole (22). Method A.—To a stirred solution of lithium aluminum hydride (20 g, 0.52 mol) in ether (600 ml) was added a solution of aluminum chloride (69 g, 0.52 mol) in ether-toluene (300–100 ml). The mixture was refluxed for 5 min and 5 (104 g, 0.52 mol) was added dropwise. The mixture was refluxed for 1 hr and with caution treated with water (20 ml), 25% NaOH (94 g), and water (52 ml). The slurry was filtered, concentrated, and distilled to yield 22: 73 g (76%); bp 77–80° (0.1 mm); nmr (CDCl₃) δ (TMS) 7.50–6.90 (5 H, multiplet, aromatic CH), 5.80 (1 H, singlet, 4-H), 3.90 (2 H, singlet, –CH₂–), 3.60 (3 H, singlet, NCH₃), 2.21 (3 H, singlet, 3-CH₃).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.37; H, 7.58; N, 15.04. Found: C, 77.07; H, 7.73; N, 15.02.

Method B.—A solution of 5 (66 g, 0.33 mol) in glacial acetic acid (500 ml) was hydrogenated at 50 psi using 20% Pd/C (10 g) as catalyst. The mixture was concentrated and distilled to yield 22, 52 g (84%), bp 70–74° (90 μ); ir and nmr spectra identical with those from method A.

2-(5-Chloro-3-methylpyrazol-1-yl)acetophenone (23).[31]—A mixture of 17 (23.6 g, 0.1 mol), acetic anhydride (20.5 g, 0.2 mol), and dimethyl sulfoxide (300 ml) was heated on the steam bath for 18 hr and distilled at reduced pressure to yield 23, 20 g (85%), bp 150–155° (0.25 mm), crystallized. Recrystallization from ether gave 15 g: mp 109–111°; nmr (CDCl₃) δ (TMS) 8.2–7.25 (5 H, complex pattern, aromatic CH), 6.11 (1 H, singlet, 4-H), 5.53 (2 H, singlet, NCH₂–), 2.25 (3 H, singlet, 3-CH₃).

Anal. Calcd for $C_{12}H_{11}ClN_2O$: C, 61.41; H, 4.75; N, 11.93. Found: C, 61.38; H, 4.98; N, 12.08.

3-Methyl-1-phenethylpyrazole (24).—A mixture of 17 (71 g, 0.3 mol), sodium acetate (25 g, 0.3 mol), and 20% Pd/C (3 g) in glacial acetic acid (500 ml) was hydrogenated at 50 psi and 46°. The catalyst was filtered and the filtrate was concentrated *in vacuo* and dissolved in ether (1 l.). This solution was washed with dilute NaOH and water and dried (MgSO₄). Distillation yielded 24: 51 g (91%); bp 118–120° (10 mm); nmr (CDCl₃) δ (TMS) 7.5–6.95 (5 H, multiplet, aromatic CH), 7.02 (1 H, doublet superimposed on the aromatic multiplet, 5-H), 5.92 (1 H, doublet, 4-H), 4.44–4.08 (2 H, multiplet, NCH₂–), 3.33–2.95 (2 H, multiplet, –CH₂–), 2.27 (3 H, singlet, 3-CH₃); nmr (DMSO-d_6) δ (TMS) 7.42 (1 H, doublet, 5-H), 7.20 (5 H, singlet, aromatic CH), 5.94 (1 H, doublet, 4-H), 4.45–4.10 (2 H, multiplet, NCH₂–), 3.28–2.92 (2 H, multiplet, –CH₂–), 2.16 (3 H, singlet, 3-CH₃).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.37; H, 7.58; N, 15.05. Found: C, 76.98; H, 7.79; N, 15.10.

(31) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).

1,3-Dimethylpyrazol-5-yl Phenyl Ketone (25).[32]—A mixture of 2 and 7 (20 g, 0.208 mol, 63–37%) in ether (300 ml) was treated with a solution of n-butyllithium (0.1 mol) in heptane (65 ml). The mixture was stirred and refluxed for 30 min and benzaldehyde (32 g, 0.3 mol) was added dropwise. The amount of benzaldehyde used for the oxidation was added over a 2-hr period. Water (100 ml) was added and the layers were separated. The organic layer was evaporated and the residue was mixed with 48% HBr (25 ml) and heated on the steam bath overnight to hydrolyze any benzyl benzoate. The mixture was poured into excess dilute NaOH and extracted with ether (three 250-ml portions). The extracts were dried (MgSO$_4$) and distilled to yield 25: 17 g (85%); bp 86–88° (0.1 mm); ir 1652 cm^{-1} (C=O); nmr (CDCl$_3$) δ (TMS) 8.00–7.30 (5 H, multiplet, aromatic CH), 6.44 (1 H, singlet, 4-H), 4.12 (3 H, singlet, NCH$_3$), 2.28 (3 H, singlet, 3-CH$_3$).

Anal. Calcd for C$_{12}$H$_{12}$N$_2$O: C, 71.93; H, 6.04; N, 14.00. Found: C, 72.14; H, 6.04; N, 13.75.

Results of Lithiation of Pure 2 with an Equivalent of n-Butyllithium Followed by Benzaldehyde.—A solution of 2 (9.6 g, 0.1 mol) in ether (250 ml) was stirred and treated with a solution of n-butyllithium in heptane (65 ml, 0.1 mol). The mixture was refluxed for 30 min, a solution of benzaldehyde (11.7 g, 0.11 mol) was added, and refluxing was continued for 30 min. Water (100 ml) was added and a vpc showed a 66:34 mixture of 5 and 6. The organic layer was dried (MgSO$_4$) and distilled to yield 5 and 6, 17 g (84%), bp 120–124° (0.2 mm). Fractional crystallization from methanol yielded 6, 3 g, mp 120–122°, ir and nmr identical with those of 6 prepared by hydrogenation of 17. In one experiment, phenyllithium gave the same mixture of products.

Results of Lithiation of the Mixture of 2 and 7 with a Full Equivalent of n-Butyllithium Followed by Benzaldehyde.—A solution of 2 and 7 (96 g, 1 mol), 66:34 mixture in ether (1.5 l.), was stirred, cooled (−20 to −30°), and treated with a solution of n-butyllithium (1 mol) in heptane (630 ml). The mixture was stirred for 30 min and treated with a solution of benzaldehyde (106 g, 1 mol) in ether (250 ml). After stirring for 30 min, water (200 ml) was added and the organic layer was dried (MgSO$_4$). A vpc on this solution showed a three-alcohol mixture (40:35:25) of 5, 6, and 8. The organic layer was concentrated and allowed to stand overnight. A crop of crystals was separated. This was a mixture of 5 and 8, 50 g, mp 109–120° (34:66) by nmr. The

second crop, 21 g, mp 103–105°, was a 66:34 mixture of 5 and 8. Distillation of the mother liquors yielded 5 and 6, 110 g, bp 120–145° (0.2 mm), partially crystalline. The total weight of 181 g corresponds to a 90% conversion of the starting pyrazoles.

Results of the Lithiation of 1-Methylpyrazole (4).[17]—A solution of 4 (16 g, 0.2 mol) in ether (300 ml) was treated with a solution of n-butyllithium in heptane (0.2 mol). The mixture was stirred for 90 min and benzaldehyde (21.2 g, 0.2 mol) was added at 10°. Water (100 ml) was added and the organic layer was separated and dried (MgSO$_4$). The product was crystallized from benzene–petroleum ether to yield 20 g (62.5%), mp 88.5–92°. A vpc indicated a 69:31 mixture. An nmr indicated a mixture of 1-methyl-α-phenylpyrazole-5-methanol (13) and α-phenylpyrazole-1-ethanol (14). Fractional crystallization from ether yielded 13: 1.6 g; mp 106.5–110°; vpc 100%; nmr (CDCl$_3$) δ (TMS) 7.30 (5 H, singlet, aromatic CH), 7.18 (1 H, doublet, 3-H), 5.96 (1 H, doublet, 4-H), 5.88 [1 H, doublet (singlet after a D$_2$O wash), –CH–], 4.86 [1 H, doublet (removed by D$_2$O wash), OH], 3.59 (3 H, singlet, NCH$_3$); nmr (DMSO-d_6) 7.35 (5 H, singlet, aromatic CH), 7.28 (1 H, doublet, 3-H), 6.2–5.8 (3 H, a multiplet superimposed on a doublet at 5.92, 4-H, –CH–, OH), 3.72 (3 H, singlet, NCH$_3$). An nmr on the crude product (mp 88.5–92°) clearly showed the typical abc pattern for the α-phenylpyrazole-1-ethanol (14) as well as the multiplet at 6.20–6.00 for the 4-H in a 1-substituted pyrazole.

Anal. Calcd for C$_{11}$H$_{12}$N$_2$O: C, 70.18; H, 6.42; N, 14.88. Found: C, 70.15; H, 6.57; N, 15.07.

The mixture was sublimed and the sublimated compound was recrystallized twice from chloroform to yield 14: 0.95 g; mp 123–127°; vpc 100%; nmr (CDCl$_3$) δ (TMS) 7.47 (1 H, doublet, 3-H), 7.29 (5 H, singlet, aromatic CH), 7.24 (1 H, doublet, 5-H), 6.19 (1 H, triplet, 4-H), 5.18–4.92 (1 H, multiplet, –CH–), 4.43–3.93 (3 H, multiplet superimposed on singlet at 4.27, OH, –CH$_2$–); nmr (DMSO-d_6) δ (TMS) 7.56 (1 H, doublet, 5-H), 7.41 (1 H, doublet, 3-H), 7.29 (5 H, singlet, aromatic CH), 6.17 (1 H, triplet, 4-H), 5.63 (1 H, doublet, OH), 5.14–4.80 (1 H, multiplet, –CH–), 4.23 (2 H, doublet, –CH$_2$–).

Anal. Calcd for C$_{11}$H$_{12}$N$_2$O: C, 70.18; H, 6.42; N, 14.88. Found: C, 70.00; H, 6.40; N, 14.77.

Registry No.—2, 694-48-4; **5**, 32492-99-2; **6**, 32493-00-8; **7**, 694-31-5; **8**, 32493-01-9; **9**, 32493-02-0; **10**, 32493-03-1; **11**, 32493-04-2; **12**, 32493-05-3; **13**, 32500-65-5; **14**, 32500-66-6; **15**, 32500-67-7; **15** picrate, 32544-40-4; **16**, 32500-68-8; **17**, 32500-69-9; **18**, 32500-70-2; **19**, 32500-71-3; **20**, 32500-72-4; **22**, 32500-73-5; **23**, 32500-74-6; **24**, 32500-75-7; **25**, 32500-76-8.

(32) This constitutes a synthesis of ketones from lithium reagents simply by adding an excess of aldehyde. This resembles a variation of the Oppenauer oxidation and Meerwein–Pondorff–Verley reduction using lithium as the metal. Marshall[33] reported using phenyl Grignard reagent and benzaldehyde to prepare benzophenone.

(33) J. Marshall, *J. Chem. Soc.*, **105**, 527 (1914).

Studies on Pyrazines. I. The Syntheses of 2,3-Dihydroxypyrazines and Their Derivatives

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This report describes a new method for the preparations of 2,3-dihydroxypyrazines **3** containing (a) H, H, (b) H, CH_3, (c) CH_3, CH_3, (d) H, C_6H_5, (e) CH_3, C_6H_5 and (f) C_6H_5, C_6H_5 at 5,6 positions. As starting materials, five amino ketals **1b–f** were prepared by two steps from phthalimido ketones **4b–f**. Amino ketals **1a**, **1b**, and **1d** (R_1 = H) were readily condensed with ethyl oxamate to provide oxamoyl amino ketals **2** in good yields, although condensations of amino ketals **1c**, **1e**, and **1f**, which were sterically crowded with methyl or phenyl groups, with ethyl oxamate required drastic conditions. The subsequent cyclizations of oxamoyl amino ketals **2a**, **2b**, and **2c** in acetic acid proceeded in excellent yields to 2,3-dihydroxypyrazines **3a**, **3b**, and **3c**, respectively. While a steric hindrance due to the substituents was recognized, cyclizations of **2d**, **2e**, and **2f** ($R_2 = C_6H_5$) in acetic acid in the presence of *p*-toluenesulfonic acid provided the corresponding 2,3-dihydroxypyrazines in 50–60% yields. The structures of these 2,3-dihydroxypyrazines were established by conversion to 2,3-dichloropyrazines **9a–f** and subsequently 2,3-diaminopyrazines **10b**, **10d**, and **10e**.

In 1947, McDonald and Ellingson[1] reported first that 2,3-di(N^4-acetylsulfamido)pyrazine was hydrolyzed with hydrochloric acid to provide 2,3-dihydroxypyrazine. Subsequently, various methods for the preparation of 2,3-dihydroxypyrazine and its 5,6-dimethyl and 5,6-diphenyl derivatives were reported, most of which were derived *via* hydrolysis of the corresponding amino-,[2,3] halo-,[4,5] or nitropyrazine[6,7] derivatives. In 1962, the authors reported briefly a new method for the synthesis of 2,3-dihydroxypyrazine,[8,9] which involves cyclization of oxamoyl amino acetal, obtained from ethyl oxamate and amino acetal, in acetic acid as a condensing agent (Scheme I).
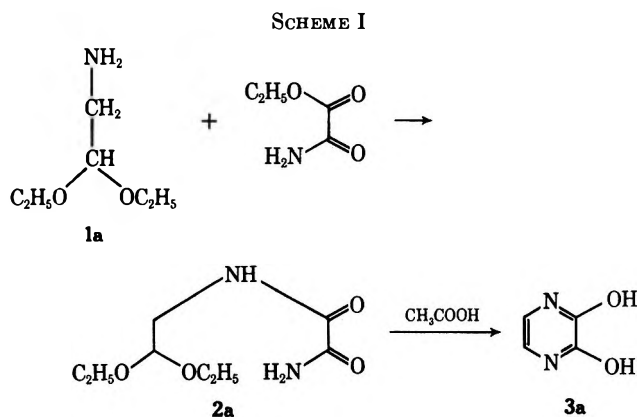
Scheme I

The present paper reports this method and its successful application to syntheses of 2,3-dihydroxypyrazine with methyl or/and phenyl groups at 5 and 6 positions. This sequence is outlined in Scheme II. This method would be applicable to the preparations of 2,3-dihydroxypyrazines substituted by other alkyl or aryl groups.

Scheme II

	R_1	R_2
a	H	H
b	H	CH_3
c	CH_3	CH_3
d	H	C_6H_5
e	CH_3	C_6H_5
f	C_6H_5	C_6H_5

Preparation of Amino Ketals 1b–f.—The key step of this synthetic method is the preparation of amino ketals **1b–f** because α-amino ketones are readily self-condensed.[10] Our starting materials, amino ketals, were prepared by the method shown in Scheme III.

Scheme III
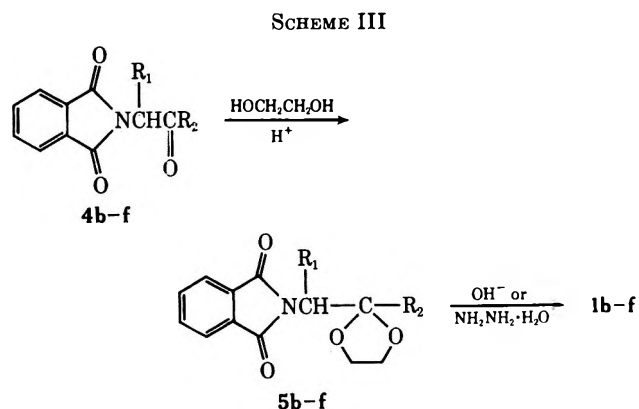
Phthalimido ketones **4b–d**[11] and **4e**[12] were transformed into their ketals **5** by treatment with ethylene

(1) F. G. McDonald and R. C. Ellingson, *J. Amer. Chem. Soc.*, **69**, 1034 (1947).

(2) M. S. Habib and C. W. Rees, *J. Chem. Soc.*, 3371 (1960).

(3) L. Bernardi, G. Palamidessi, A. Leone, and G. Lariri, *Gazz. Chim. Ital.*, **91**, 1431 (1961).

(4) G. Karmas and P. E. Spoerri, *J. Amer. Chem. Soc.*, **78**, 4071 (1956).

(5) G. Karmas and P. E. Spoerri, *ibid.*, **79**, 680 (1957).

(6) G. Karmas and P. E. Spoerri, *ibid.*, **75**, 5517 (1953).

(7) J. D. Ratajczyk and J. A. Carbon, *J. Org. Chem.*, **27**, 2644 (1962).

(8) J. Adachi and K. Kishimoto, reported to the 15th Annual Meeting of Chemical Society of Japan, Tokyo, April 1962.

(9) The analogous method for the preparation of 2,3-dihydroxypyrazine was also reported: G. Palamidessi and M. Bonanomi, *Farmaco, Ed. Sci.*, **21**, 799 (1966); *Chem. Abstr.*, **66**, 37884 (1967).

(10) I. J. Krems and P. E. Spoerri, *Chem. Rev.*, **40**, 290 (1947).

(11) J. C. Sheehan and W. A. Bolhofer, *J. Amer. Chem. Soc.*, **72**, 2786 (1950).

(12) Shu-Sing Cheng, S. Jonsson, and F. T. Semeniuk, *J. Pharm. Sci.*, **51**, 108 (1962).

glycol in the presence of *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of the water formed (see Table III). Ketalization of **4f** in refluxing benzene was not successful, because of the steric hindrance due to its two bulky phenyl groups. However, in refluxing toluene the conversion proceeded successfully to give **5f** in about 60% yield.

On hydrolysis of phthalimido ketals to amino ketals **1**, a steric effect due to the substituents of **5** on the ease of the hydrolysis emerged (see Table IV). Thus, **5b–d** (R_1 = H or CH_3) could be easily hydrolyzed by treatment with 30% aqueous sodium hydroxide. Whereas hydrolysis of **5e** (R_1 = CH_3; R_2 = C_6H_5) required drastic conditions (45% aqueous sodium hydroxide), **5e** and **5f** were readily converted to **1** in excellent yields by use of hydrazine hydrate in the place of an aqueous sodium hydroxide.

Preparation of 2,3-Dihydroxypyrazines 3 from Amino Ketals 1.—For the first step, amino ketals **1a**, **1b**, and **1d** (R_1 = H), excepting **1c** and **1e** (R_1 = CH_3), were easily condensed with ethyl oxamate in refluxing ethanol to give the corresponding oxamoyl amino ketals **2** (see Table I). In the condensation of **1e**

TABLE I
CONDENSATION OF AMINO KETALS 1
WITH ETHYL OXAMATE

Amino ketal	Condensing solvent	Reaction time, hr	Yield of **2**, %	Other products (%)
1a	C_2H_5OH	6	91.5	
1b	C_2H_5OH	6	73.7	
1c	C_2H_5OH	4.5	20.6	
1c	C_2H_5OH	24	54.3	Salt[a]
1c	i-C_4H_9OH	29	61.5	7c (1.0)
1c	i-$C_5H_{11}OH$	120	40.3	7c (49.7)
1d	C_2H_5OH	7	67.0	
1e	C_2H_5OH	7	28.4	6 (20.3)
1e	i-$C_5H_{11}OH$	148	61.1	6 (2.4), 7e (3.7)
1f	i-$C_5H_{11}OH$	120	39.4[b]	
1f		1.5	54.1	

[a] The structure has not been determined. [b] Melting point is in the range of 175–195° because of contamination with minor components.

with ethyl oxamate, a large amount of insoluble salt **6** was produced in the refluxing reaction mixture. When isobutyl alcohol was used as a condensing solvent, a slight amount of oxamide was formed but **2c** was obtained in good yield, which was contaminated with **7c**. The structures of **6** and **7** were confirmed by elemental

6

7
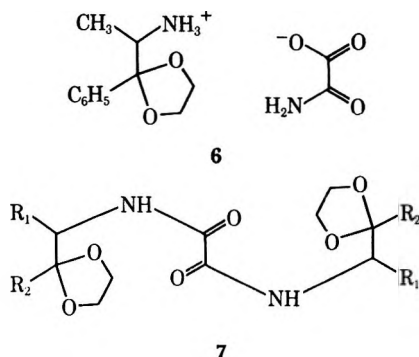
and spectral analyses. In refluxing isoamyl alcohol as a condensing agent, the yield of **7c** was increased. Under the same conditions, **2e** was prepared in 61%

yield and formation of the insoluble by-products (**6**, **7e**, and oxamide) was reduced. These experimental results suggest that the steric hindrance to this series of condensations is influenced by both R_1 and R_2 substituents of the amino ketals, and therefore it is especially difficult to condense **1f** with ethyl oxamate. Actually, the condensation product obtained in refluxing isoamyl alcohol was a mixture of **2f**, **7f**, and the salt or/and oxamide. An improvement in the yield of **2f** was was achieved by fusing **1f** with ethyl oxamate for shorter time to reduce formation of **7f**. The results in a series of these condensations are satisfactorily interpretable by considering their steric hindrances.

Cyclization of oxamoyl amino ketals **2a–c**⁻(R_2 = H or CH_3) in refluxing glacial acetic acid provided 2,3-dihydroxypyrazines **3a–c** in excellent yields (see Table II). In contrast, **2d–f** (R_2 = C_6H_5) were unreactive

TABLE II
CYCLIZATION OF OXAMOYL AMINO KETALS 2

Oxamoyl amino ketal	Solvent	Reaction time, hr	Product	Yield, %
2a	CH_3COOH	6	3a	98.5
2b	CH_3COOH	93	3b	84.8
2c	CH_3COOH	116	3c	93.7
2d	0.01N HCl	3	8d[a]	100
2d	CF_3COOH[c]	24	8d[a]	83.2
2d	TsOH[b]–CH_3COOH	93	3d	50.5
2d	TsOH[b]–C_2H_5COOH	120	3d	61.3
2e	0.1 *N* HCl	17	3e	50.4
2e	CF_3COOH[c]	28	3e	43.2
2e	TsOH[b]–CH_3COOH	107	3e	53.6
2f	CF_3COOH[d]	21	8f	100
2f	TsOH[b]–CH_3COOH	120	3f	52.7

[a] This compound was converted to **3d** in 21% yield by treatment with CH_3COOH in the presence of TsOH. [b] TsOH–CH_3COOH or C_2H_5COOH (1 g/50 ml). [c] At room temperature. [d] At reflux.

under the same conditions. Some experiments under various acidities afforded following results. The reaction of **2d** with refluxing 0.01 *N* hydrochloric acid proceeded quantitatively to ketone **8d**, and that of **2e** with refluxing 0.1 *N* hydrochloric acid provided 2,3-dihydroxypyrazine **3e**. With trifluoroacetic acid, **2d**

8
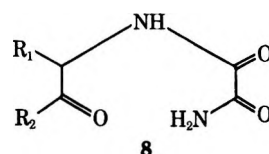
and **2f** afforded ketones **8d** and **8f**, respectively, but **2e** gave only **3e**. Consequently, cyclization to 2,3-dihydroxypyrazines **3d–f** was successful only by treating the oxamoyl amino ketals in refluxing glacial acetic acid or propionic acid in the presence of *p*-toluenesulfonic acid. In those cyclizations, a steric influence of substituent R_1 was unrecognized, and the yields were in a range of 50–60%.

Chlorination and Amination of 2,3-Dihydroxypyrazines.—The 2,3-dihydroxypyrazines were treated with excess phosphoryl chloride to provide the corresponding 2,3-dichloropyrazines **9** in 70–90% yields.

Some procedures for amination of 2,3-dichloro- and 2-halo-3-aminopyrazines have been reported,[13-17] which consist of heating in a sealed vessel with ammonium hydroxide in the presence of activated copper powder for about 24 hr or longer at 120–140° to give 2,3-diaminopyrazines. By this procedure, 2,3-dichloropyrazines **9a** and **9b** were converted not to diaminopyrazines **10** but to chloroaminopyrazines **11** in
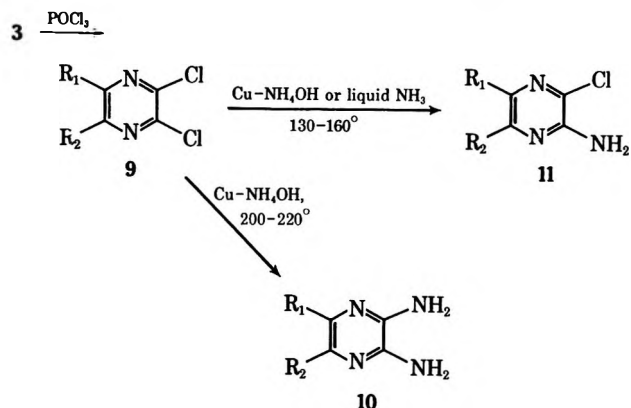
60–70% yields.[18] Diaminopyrazines **10b**, **10d**, and **10e** were prepared only at elevated temperature, 200–220°, in 28–66% yields.

Experimental Section

Melting points were determined in capillary and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on Hitachi Model EPI-G₃ grating spectrometer. Ultraviolet spectra (95% C₂H₅OH) were recorded on JASCO Model ORD/UV-5 spectrometer. Nmr spectra were recorded on JEOL Model JNM-C-60HL or JNM-PS-100 instruments with tetramethylsilane as an internal standard.

A. Reaction of α-Halo Ketone and Potassium Phthalimide. 2-(N-Phthalimido)-1,2-diphenylacetaldehyde (4f).—Potassium phthalimide (63.0 g, 0.34 mol) was added in small portions to a stirred solution of 2-chloro-1,2-diphenylacetaldehyde (75.7 g, 0.33 mol) in 500 ml of dimethylformamide, and the suspension was refluxed for 41 hr. The reaction mixture was allowed to stand at room temperature, poured into 1000 ml of water, and extracted with 200 ml of chloroform. After further extraction with a 100-ml portion of chloroform, the combined chloroform extracts were washed with 3% aqueous sodium hydroxide and a large amount of water, dried over magnesium sulfate, and evaporated. The crystalline residue was washed with ether to afford 45.7 g (43.9%), mp 155–158°, of **4f**. Recrystallization from ethanol gave colorless crystals, mp 158–159°.

Anal. Calcd for C₂₂H₁₅NO₃: C, 77.40; H, 4.43; N, 4.10. Found: C, 77.47; H, 4.59; N, 4.23.

B. General Procedure for Ketalization of Phthalimido Ketones 4.—An apparatus for this procedure consists of a 300–500-ml three-necked round-bottomed flask (A) fitted on a mantle heater and a magnetic stirrer, a condenser (B), and a water removable separator (C) with a U-tube (D) packed anhydrous calcium chloride. An azeotropic mixture was condensed in B to drop into C and returned into A through D.

A solution of phthalimido ketone 4 (0.20 mol) and ethylene glycol (50 ml) in 100–200 ml of benzene or toluene in the presence of p-toluenesulfonic acid (2.0 g) was refluxed with stirring for about 50 hr, and additional ethylene glycol (50 ml) was added to it and then refluxed again for the total time indicated in Table III. The reaction mixture was cooled to room temperature, the

(13) R. C. Ellingson and R. L. Henry, *J. Amer. Chem. Soc.*, **70**, 1257 (1948).

(14) E. Schipper and A. R. Day, *ibid.*, **74**, 350 (1952).

(15) F. L. Muehlmann and A. R. Day, *ibid.*, **78**, 242 (1956).

(16) R. H. Martin and Z. Tarasiejska, *Bull. Soc. Chim. Belg.*, **66**, 136 (1957); *Chem. Abstr.*, **51**, 10533 (1957).

(17) F. Armarego, *J. Chem. Soc.*, 4304 (1963).

(18) In the absence of activated copper powder, **11b** was obtained in 77% yield (see Experimental Section).

TABLE III
Ketalization of Phthalimido Ketones 4[a]

Phthalimido ketone	Reaction time, hr[b]	Yield of 5, %	Mp, °C
4b	100	80.2	93–95[c]
4c	136	89.0	60–62[d]
4d	95	94.7	145[c]
4e	137	93.8	131[c]
4f	100	59.1	172–173[c]

[a] Satisfactory analytical data (±0.37% for C, H, and N) were reported for all compounds: Ed. [b] Reactions of **4b–e** were carried out in benzene; toluene was used for **4f**. [c] Recrystallized from ethanol. [d] Distilled [bath temperature 250° (3 mm)].

benzene layer was separated, and the ethylene glycol layer was extracted with two or three 100-ml portions of benzene or ether. The combined benzene and/or ether extracts were washed with 5% aqueous sodium hydroxide and then with water, dried over magnesium sulfate, and evaporated to afford phthalimido ketal 5, which was purified by recrystallization from ethanol or by distillation.

C. General Procedure for Hydrolysis of Phthalimido Ketals 5.—A solution of 5 (0.60 mol) in 500 ml of 15% aqueous sodium hydroxide was refluxed with stirring and sodium hydroxide (75 g) was added in one or several portions to it. Sodium phthalate precipitated on standing at room temperature and was redissolved by addition of water and the resulting solution was extracted with ether mechanically or on a continuous liquid extractor. The ether extracts were dried over sodium or potassium hydroxide pellets, filtered, and evaporated. The residue was distilled affording 1 as a colorless oil.

The method of using hydrazine hydrate was as follows. A solution of 5 (0.20 mol) in 100 ml (2.0 mol) of 80% hydrazine hydrate was refluxed. The reaction mixture was allowed to stand

TABLE IV
Hydrolysis of Phthalimido Ketal 5[a]

Phthalimido ketal	Hydrolytic reagent	Reaction time, hr	Yield of 1, %
5b	30% NaOH	65	88.3
5c	30% NaOH	90	77.2
5c	80% NH₂NH₂·H₂O	46	86.6
5d	30% NaOH	90	87.0
5e	30% NaOH	120	30.4
5e	45% NaOH[a]	149	81.3
5e	80% NH₂NH₂·H₂O	24	86.5
5f	80% NH₂NH₂·H₂O	48	97.4

[a] Ethylene glycol–water–sodium hydroxide (50:15:12) at 150°.

TABLE V
Physical Properties of Amino Ketals 1[a]

Amino ketal	Bp, °C (mm)	n^{26}D	Nmr,[b] τ
1b	73 (31)	1.4420	8.81 (s, 3 H), 8.55 (s, 2 H, NH₂), 7.49 (s, 2 H), 6.19 (s, 4 H)
1c	86 (50)	1.4420	8.92 (d, 3 H, 7.1 Hz), 8.75 (s, 3 H), 8.64 (s, 2 H), 7.11 (q, 1 H, 7.0 Hz), 6.04 (s, 4 H)
1d	156 (30)	1.5311	8.60 (s, 2 H, CH₂), 7.08 (s, 2 H), 6.6–5.7 (br, 4 H), 2.8–2.3 (m, 5 H)
1e	110–111 (4)	1.5240	9.06 (d, 3 H, 7.5 Hz), 8.49 (s, 2 H), 6.87 (q, 1 H, 7.3 Hz), 5.95–5.8 (m, 4 H), 2.8–2.3 (m, 5 H)
1f	250[c] (2)	1.5720	8.22 (s, 2 H), 6,4–6.0 (m, 4 H), 5.80 (s, 1 H), 2.81 (s, 5 H), 2.75 (s, 5 H)

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Nmr spectra, excepting of **1b**, were determined in CDCl₃; that of **1b** was measured in DMSO-d₆. [c] Bath temperature. Mp 20–22°.

TABLE VI
PHYSICAL PROPERTIES OF CONDENSATION PRODUCTS 2 AND 7[a]

Material	Mp,[b] °C	Ir (KBr), cm^{-1} νNH		Amide I
2a	140–141[c]	3400, 3310, 3270		1655
2b	121	3400, 3350, 3200		1678
2c[d]	113	3370, 3310, 3200		1658
7c[e]	151–152	3310		1653
2d	124–125	3375, 3320, 3200		1655
2e[f]	164–165	3380, 3350, 3250		1675
7e[g]	211–213	3350		1678
2f	203–204	3400, 3340, 3210		1668
7f	227–229	3370		1668

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Recrystallized from ethanol. [c] Lit.[9] mp 146°. [d] Nmr (CDCl₃) τ 8.78 (d, 3, J = 7.4 Hz, CH₃CH), 8.68 (s, 3, CH₃), 6.01 (s, 4, OCH₂CH₂O), 5.83 (d of q, 1, J = 10.0 and 7.4 Hz, CH₃CHNH), 3.29 and 2.40 (each s, 1 + 1, H₂NC=O), 2.43 (br d, 1, J = 10.0 Hz, CHNH-C=O). [e] Nmr (CDCl₃) τ 8.78 (d, 6, J = 7.4 Hz, 2CH₃CH), 8.68 (s, 6, 2CH₃), 6.00 (s, 8, 2OCH₂CH₂O), 5.84 (d of q, 2, J = 10.0 and 7.4 Hz, 2CH₃CHNH), 2.48 (br d, 2, J = 10.0 Hz, 2CHNHC=O). [f] Nmr (CDCl₃) τ 8.91 (d, 3, J = 7.5 Hz, CH₃CH), 6.4–5,8 (m, 4, OCH₂CH₂O), 5.60 (d of q, J = 10.0 and 7.5 Hz, CH₃CHNH), 3.83 (s, 1, one proton of NH₂C=O), 2.9–2.3 (m, 1 + 1 + 5, CHNHC=O, one proton of H₂NC=O, and C₆H₅). [g] Nmr (CDCl₃) τ 8.93 (d, 6, J = 7.5 Hz, 2CH₃), 6.4–5.8 (m, 8, 2OCH₂CH₂O), 5.62 (d, of q, 2, J = 10.0, and 7.5 Hz, 2CH₃CHNH), 2.9–2.3 (m, 2 + 10, 2CHNHC=O and 2C₆H₅).

pressure giving the second crop. The combined products were recrystallized from ethanol to afford 2.

Compound 7c was obtained by recrystallization of the second crop from ethanol. Compound 7e was isolated by extraction of the insoluble material in refluxing isoamyl alcohol with hot chloroform. The undissolved material in hot chloroform was recrystallized from water giving 6: mp 237–238°; ir (KBr) 3380, 1693, 1635 (H₂NCOCO₂⁻), 3190, 1600, and 1310 cm^{-1} (NH₃⁺).

Anal. Calcd for C₁₃H₁₈N₂O₅: C, 55.31; H, 6.43; N, 9.92. Found: C, 54.86; H, 6.56; N, 9.67.

Compound 7f was obtained by five recrystallizations of condensation product in isoamyl alcohol from ethanol (Table VI).

E. General Procedure for Cyclization of Oxamoyl Amino Ketals 2.—A solution of 2 (0.10 mol) in 50–100 ml of a hydrolytic solvent was refluxed for the time indicated in Table II under nitrogen. The reaction mixture was allowed to stand at room temperature, the precipitate was collected, and mother liquor was evaporated to dryness under reduced pressure. The residue was washed with a small amount of water, triturated with hot chloroform, filtered, and recrystallized to give 3 or 8. The physical properties of these compounds are summarized in Table VII.

F. General Procedure for Chlorination of 2,3-Dihydroxypyrazines 3.—A solution of 3 (20 mmol) in 30–50 ml of phosphoryl chloride was heated at 130–180° for the time indicated in Table VIII. The cooled solution was poured into ice–water and extracted with three to five 100-ml portions of ether or chloroform. The combined organic extracts were washed, dried over magnesium sulfate, and evaporated to afford 2,3-dichloropyrazine 9.

G. General Procedure for Amination of 2,3-Dichloropyrazines 9.—A mixture of 9 (2.0 mmol) and ammonium hydroxide (25 ml) or liquid ammonia (40 ml) in the presence of activated

TABLE VII
PHYSICAL PROPERTIES OF CYCLIZATION PRODUCTS 3 AND 8[a]

Material	Mp, °C (lit.)	Uv max (ϵ)	CH₃	Nmr (DMSO-d₆), τ Ring proton	C₆H₅	OH
3a	>360[b] (>350[1])	234 (5,180), 380 (4,860)				
3b	301–303 dec[c]	234 (6,770), 315 (6,470)	8.10 s	3.98 s		−1.08 s
3c	>360[b] (>340[4])	232 (7,240), 324 (6,850)	8.12 s			−1.09 s
3d	288–290 dec[d]	276 (7,240), 323 (7,240)		3.36 s	2.78–2.32 m	−1.52 s
3e	327–328 dec[e]	270 (5,520), 324 (6,960)	8.10 s		2.62 s	−2.11 s
3f	338–339[f] (335–340[6]) (340–342[7])	298 (10,500)			2.81 m	−1.44 s
8d[g]	202–203[e]					
8f[h]	200–201[d]					

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Recrystallized from water, [c] methanol, [d] aqueous acetic acid (1:1 v/v), and [e] ethanol, respectively. [f] Recrystallized from acetic acid and water. The infrared spectrum of this compound was identical with that of an authentic sample.[6] [g] Ir (KBr) 1694, [h] 1691 cm^{-1}.

at room temperature, 30% aqueous sodium hydroxide or water was added to it to redissolve the resulting diketophthazine, and the oily layer was separated. The aqueous layer was extracted in several times with ether. The combined organic portions were worked up in the predescribed manner to give 1. The results and physical properties of 1 are summarized in Tables IV and V.

D. Condensation of Amino Ketals 1 with Ethyl Oxamate.—The general procedure is as follows. A solution of amino ketal 1 (0.10 mol) and ethyl oxamate (0.11 mol) in 100 ml of a solvent was refluxed for the time indicated in Table I. When an insoluble material was formed, it was removed hot by filtration. If ethanol was not used as the solvent, the following pretreatment was carried out: the reaction mixture was evaporated to dryness under reduced pressure and the residue was redissolved in ethanol with heating.

After cooling to 0°, the precipitate was collected by filtration. Into the mother liquor was passed ammonia gas to remove unreacted ethyl oxamate as oxamide, and the resulting solution was boiled and an undissolved matter (oxamide) was removed hot by filtration. The solution was evaporated to dryness under reduced

copper powder (and potassium bromide) was heated in a sealed tube or a stainless steel autoclave (see Table IX). The reaction mixture was allowed to stand at room temperature, and the precipitate was collected, washed with a small amount of water, dried, and recrystallized giving amino product 10 or 11.

TABLE VIII
CHLORINATION OF 2,3-DIHYDROXYPYRAZINES 3[a]

2,3-Dihydroxy-pyrazine	Reaction time, hr	Yield of 9, %	Mp, °C (lit.)
3a	33	63.5	22–25 (22–24)[b]
3b	28	86.1	12[c]
3c	43	70.9	79–80[d] (80–81[4])
3d	90	77.1	106–107[e] (102)[f]
3e	96	79.8	69–70[g]
3f	48	69.9	182[h] (182–183[4])

[a] Satisfactory analytical values (±0.3% for C, H, N, and Cl) were reported for all compounds in the table: Ed. [b] American Cyanamide Co., British Patent 612,385 (1948); *Chem. Abstr.,* **44,** 1537 (1950). [c] Bp 100–101° (20 mm); n^{25}D 1.5498. [d] Recrystallized from hexane and [e] ethanol. [f] S. T. Minovici and V. Th. Bente, *Bull. Sect. Sci. Acad. Roumaine,* **4,** 185 (1915); *Chem. Abstr.,* **10,** 606 (1916). [g] Recrystallized from petroleum ether (bp 30–50°). [h] Recrystallized from acetone.

TABLE IX
AMINATION OF 2,3-DICHLOROPYRAZINES 9[a]

Starting material	Conditions Temp, °C	Time, hr	Product	Yield, %	Mp, °C
9a	130–140[b]	50	11a	61	167[f]
9b	150–160[c]	70	11b	77	113[g]
9b	200–220[d]	60	10b	66	178[h]
9d	200–210[e]	85	10d	59	173[i]
9e	200–220[e]	72	10e	28	167–168[i]

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Amination were carried out with activated copper powder in liquid ammonia, [c] ammonium hydroxide (d 0.880), [d] activated copper powder in ammonium hydroxide (d 0.880), and [e] activated copper powder and potassium bromide in ammonium hydroxide (d 0.880), respectively. [f] Recrystallized from water (lit.[15] mp 169°). The melting point of a mixture with an authentic sample[16] undepressed and ir spectra were identical. The authors are grateful to Mr. T. Kohagizawa for the synthesis of an authentic sample. [g] Recrystallized from ethanol. Mp 113°: G. Palamidassi, *Farmaco, Ed. Sci.,* **18,** 557 (1963); *Chem. Abstr.,* **59,** 13975 (1963). [h] Recrystallized from ethyl acetate and [i] benzene, respectively.

Derivatives of Thiacyclobutene (Thiete). V.[1] Molecular Reorganization in the Reaction of Thiete Sulfone and Tetraphenylcyclopentadienone[2-4]

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Thiete sulfone (1) and tetracyclone react in refluxing *m*-xylene to yield 1,2,6,7-tetraphenylcycloheptatriene (65%, 2) and a bicyclic ketone (15%), 1,5,6,7-tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one (3). When 1,2,3,4-tetraphenylcyclopentadiene and thiete sulfone are refluxed in *m*-xylene, a 77% yield of the Diels–Alder adduct is obtained in addition to 1,5,6,7-tetraphenylbicyclo[3.2.1]octa-2,6-diene (13%). Thiete sulfone and phencyclone give a 69% yield of a cycloheptatriene (4) but no carbonyl compound. An alternate structure (6) for ketone **3** was abandoned on the basis of physical data and the conversion of the ketone to 1,5,6,7-tetraphenylbicyclo-[3.2.1]octene-6 (8). In dioxane a low (8%) yield of the Diels–Alder adduct 9 of thiete sulfone and tetracyclone is obtained. Decomposition of this adduct in refluxing *m*-xylene gives only cycloheptatriene 2. A pathway for formation of bicyclic ketone **3** through the intermediacy of vinyl carbene (or some species which resembles it) derived from thiete sulfone is discussed. Reaction of a vinyl carbenoid species, obtained by the Simmons–Smith procedure from 3,3-dichloro-1-propene, with tetracyclone gives a 4% yield of bicyclic ketone 3.

α,β-Unsaturated sulfones usually react normally as dienophiles in the Diels–Alder cycloaddition reaction[5] and a number of additions to thiete sulfone (thiacyclobutene 1,1-dioxide) (1) proceed normally.[6] A logical

route to thiete sulfones containing a fused benzene ring involves the Diels–Alder addition of tetracyclone (tetraphenylcyclopentadienone) to thiete sulfone followed by loss of carbon monoxide and two hydrogens. In fact, a number of tetraphenylbenzene derivatives are obtained from Diels–Alder adducts of tetracyclone.[7] We have found that butadiene, furan, and 2,5-dimethylfuran, in addition to the dienes reported earlier,[6a] add normally to thiete sulfone. This report is about an anomalous reaction of thiete sulfone with tetracyclone.

Product Identification. A Cycloheptatriene and a Bicyclic Ketone.—When thiete sulfone and tetracyclone were refluxed in *m*-xylene (139°) until the color of tetracyclone was discharged (*ca.* 85 hr), two gases identified as sulfur dioxide and carbon monoxide were produced. The major organic products were two solids of empirical formulas $C_{31}H_{24}$ (65% yield) and

(1) Paper IV: D. C. Dittmer, R. S. Henion, and N. Takashina, *J. Org. Chem.,* **34,** 1310 (1969).

(2) This research was supported in part by National Science Foundation Grants GP 726, 5513 and 8086, and by National Institutes of Health Grant CA 08250, for which the authors are grateful.

(3) A preliminary report on some of this work has been given: D. C. Dittmer and J. M. Balquist, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstract K 37. The structure of compound 3 was given incorrectly at that time.

(4) Taken in part from the Ph.D. thesis of J. M. Balquist, Syracuse University, 1966.

(5) For example, see K. Alder, H. F. Rickert, and E. Windemuth, *Ber.,* **71,** 2451 (1938); H. R. Snyder, H. V. Anderson, and D. P. Hallada, *J. Amer. Chem. Soc.,* **73,** 3258 (1951); H. R. Snyder and D. P. Hallada, *ibid.,* **74,** 5595 (1952).

(6) (a) D. C. Dittmer and M. E. Christy, *ibid.,* **84,** 399 (1962); D. C. Dittmer and N. Takashina, *Tetrahedron Lett.,* 3809 (1964); L. A. Paquette, *J. Org. Chem.,* **30,** 629 (1965); L. A. Paquette and T. R. Phillips, *ibid.,* **30,** 3883 (1965). (b) Cycloaddition of diazoalkanes to thiete sulfone also occurs normally although certain adducts lose sulfur dioxide at 150°: D. C. Dittmer and R. Glassman, *ibid.,* **35,** 999 (1970).

(7) See the review by M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.,* **65,** 261 (1965).

$C_{32}H_{24}O$ (15% yield). These were separated and identified as 1,2,6,7-tetraphenylcycloheptatriene (2) and 1,5,6,7-tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one (3).
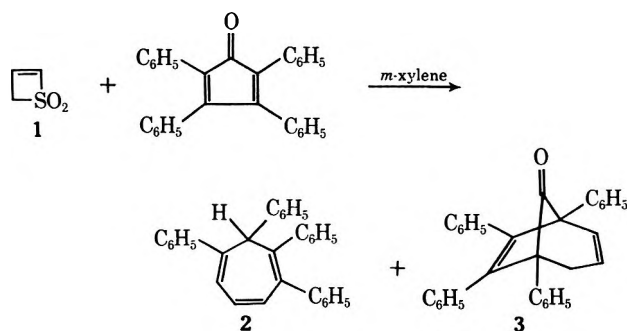
The cycloheptatriene $C_{31}H_{24}$ was dimorphous, exhibiting mp 69–70 and 127–128°.[3] The form melting at 127–128° can be converted to the form melting at 69° by a cycle of melting and solidification. The ultraviolet spectrum in acetonitrile [231 (4.27), 274 (4.29), 324 nm (log ε 3.94)] is similar to that of other cycloheptatrienes, e.g., heptaphenylcycloheptatriene.[9] In the proton nmr spectrum the C-7 proton appears as a singlet, τ 4.40,[10] the C-5 proton appears as a complex multiplet, τ 3.10–3.35, and the C-3 and C-4 protons appear as a complex multiplet, τ 3.35–3.75.

Further evidence for the structure of 2 is obtained by refluxing 2,3,4,5-tetraphenylcycloheptatriene[11] in *m*-xylene. A 1,5-hydrogen shift[12] occurs to give 2.
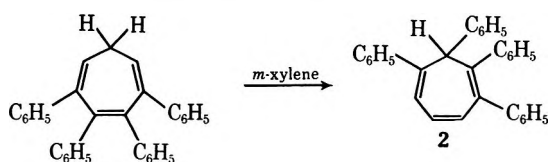
The usefulness of thiete sulfone in the synthesis of tetrasubstituted cycloheptatrienes is illustrated further by the reaction of phencyclone (1,3-diphenyl-2*H*-cyclopenta[*l*]phenanthren-2-one) and thiete sulfone. A 69% yield of cycloheptatriene 4 was obtained. The absence of product from a 1,5-hydrogen migration may be explained by the resistance to disruption of the conjugation in the phenanthrene part of the molecule.

The absorption at 1761 cm^{-1} in the infrared spectrum of the compound of formula $C_{32}H_{24}O$ indicates the pres-

ence of a bridged carbonyl group.[13] Structure 6 was considered in addition to 3. The proton nmr spectrum, in particular, indicated that the structure was not 6, the spectrum, however, being consistent with 3. Double and triple irradiation experiments established that one olefinic proton (absorption centered at τ 4.02) was coupled to the methylene protons, *J* = 3.5 Hz, and to another olefinic proton (centered at τ 3.2), *J* = 9.5 Hz. Decoupling of the methylene protons (–CH$_2$–) absorbing at τ 6.94 reduced the six-line multiplet at τ 4.02 to a doublet, and further irradiation (triple resonance) at τ 3.02 reduced the doublet to a singlet.[14] The pattern and magnitude of the coupling of the protons in the ketone are difficult to interpret on the basis of structure 6. For instance, the large coupling constant of 9.5 Hz between the olefinic protons is about three times greater[15] than is observed normally for a coupling constant between geminal olefinic protons such as occur in 6. The rather low-field absorption (τ 3.02) for the proton at C-2 is an indication of deshielding by the neighboring phenyl group.[16] The mass spectrum of the ketone showed that carbon monoxide was lost readily and that ions corresponding to tropylium ions are formed. Hydrogenation of one double bond in the bicyclic ketone gave a compound which lacked absorption in the infrared at 1370–1385 cm^{-1}, characteristic of the symmetric deformations of a methyl group, and had no absorption in the nmr spectrum which could be attributed to a methyl group.
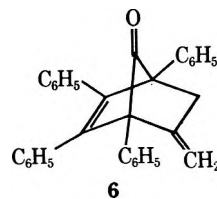
In order to dispose of any ambiguity in the interpretation of the spectra of the bicyclic ketone, compound 7 was prepared; it was *not* identical with the product
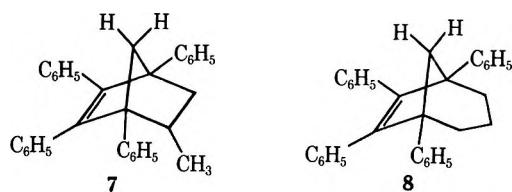
obtained from the bicyclic ketone by reduction of both the carbonyl group and the less conjugated double

(8) X-Ray powder patterns of the two forms are indistinguishable. We wish to thank Professor Harry Brumberger for obtaining these data for us. Infrared, ultraviolet, and proton nmr spectra of both forms are identical.

(9) M. A. Battiste, *Chem. Ind. (London)*, 550 (1961).

(10) The C-7 proton of heptaphenylcycloheptatriene appears at τ 4.73: R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **84**, 1484 (1962).

(11) M. A. Battiste and T. J. Barton, *Tetrahedron Lett.*, 2951 (1968).

(12) A. P. ter Borg, H. Kloosterziel, and N. van Meurs, *Recl. Trav. Chim. Pays-Bas*, **82**, 717 (1963); A. P. ter Borg and H. Kloosterziel, *ibid.*, **82**, 741 (1963).

(13) Absorption of the carbonyl group of bicyclo[3.2.1]octa-2-en-8-one is at 1758 cm^{-1}: N. A. LeBel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964). A structure for the ketone such as **5** is unlikely because dihydrotetracyclone has ir absorption for the carbonyl group at 1709 cm^{-1}: N. O. V. Sonntag, S. Linder, E. I. Becker, and P. E. Spoerri, *J. Amer. Chem. Soc.*, **75**, 2283 (1953).
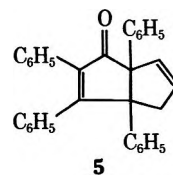
(14) We are indebted to Leroy Johnson of Varian Associates for assistance in obtaining and interpreting the spectra.

(15) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967.

(16) The vinyl protons of 3,6-biphenyl-7,7-dimethylnorbornadiene absorb at τ 2.93: L. A. Paquette and L. M. Leichter, *J. Amer. Chem. Soc.*, **92**, 1765 (1970).

bond. The properties of this product were consistent with structure **8**.

A possible route to the independent synthesis of structure **3** was suggested by the reported rearrangement of *syn*-6-vinyl[3.1.0]bicyclohex-2-ene to bicyclo-[3.2.1]octa-2,6-diene.[17] Accordingly, tetracyclone was treated with the carbenoid species obtained from 3,3-dichloropropene. After 3 days, a 4% yield of a compound identical with the bicyclic ketone, $C_{32}H_{24}O$, was isolated.
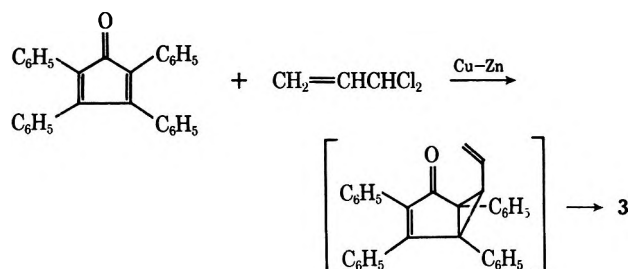
Possible Mechanisms.—The formation of cycloheptatriene **2** and bicyclic ketone **3** conceivably could proceed through the Diels–Alder adduct **9** as a common intermediate (Scheme I).

SCHEME I
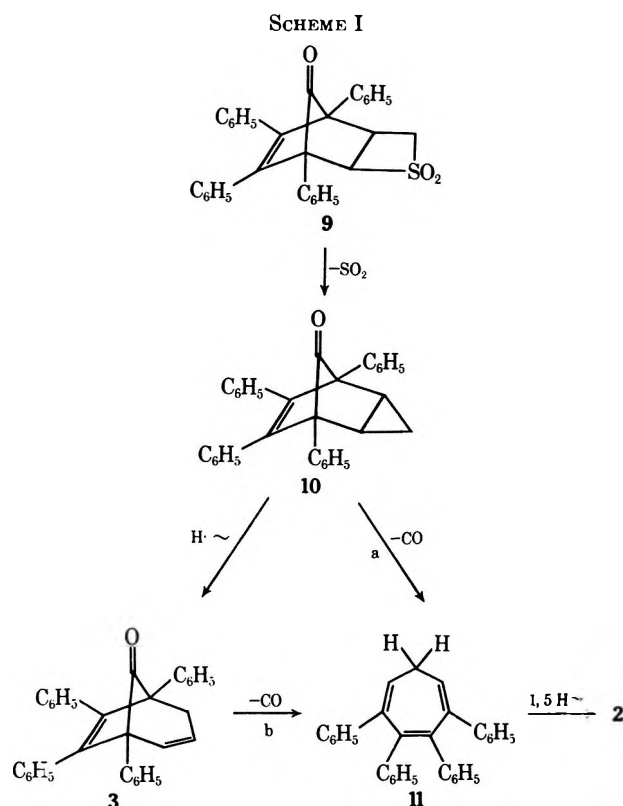
Path b for the formation of the cycloheptatriene, while plausible, is unlikely since **3** did not yield cycloheptatriene **2** when heated. Several products were obtained but none could be identified as **2**. Path a is reasonable since *endo*-1,5,6,7-tetraphenyltricyclo-[3.2.1.0²,⁴]-6-octen-8-one (**10**) yields 2,3,4,5-tetraphenylcycloheptatriene (**11**) in refluxing acetonitrile.[11] This cycloheptatriene derivative gives **2** when it is refluxed in *m*-xylene.

(17) C. Cupas, W. E. Watts, and P. v. R. Schleyer, *Tetrahedron Lett.*, 2503 (1964); J. M. Brown, *Chem. Commun.*, 226 (1965).

Compound **10** (endo) is not an intermediate in the formation of bicyclic ketone **3** since only cycloheptatriene and no ketone is obtained from it. Possibly *exo*-**10** could yield the ketone, except for the report that both *exo*- and *endo*-tricyclo[3.2.1.0²,⁴]-6-octen-8-ones decompose to cycloheptatrienes, the endo decomposing faster.[18] The temperature (139°) at which the reaction of thiete sulfone and tetracyclone was done is sufficiently high so that both isomers would readily decarbonylate according to the rate measurements given in the literature.[18]

In view of these data, divergent pathways must exist for formation of **2** and **3**. To determine if the divergence occurs before or after the formation of the Diels–Alder adduct **9**, this adduct was prepared in dioxane solvent from thiete sulfone and tetracyclone in 8% yield. Decomposition of **9** in refluxing *m*-xylene gave 76% of cycloheptatriene **2**. *No* ketone **3** was detected. Formation of **3** must occur by a pathway which does not involve the Diels–Alder adduct **9**.[19]

Another observation which bears on the mechanism of the reaction is the absence of any cycloheptatriene in the reaction of thiete sulfone and tetraphenylcyclopentadiene. A bicyclic derivative (**12**) analogous to the bicyclic ketone **3** is formed in about the same yield as the latter and a good yield of the Diels–Alder adduct **13** is obtained. The latter is formed in an amount approximately equivalent to the amount of cycloheptatriene **2** produced in the original reaction. Both isomers of **13** were stable at 139°. At 300° they yielded tetraphenylcyclopentadiene, an unidentified substance and tar, but no **12**.

12, 13%   13, 77% (two isomers)
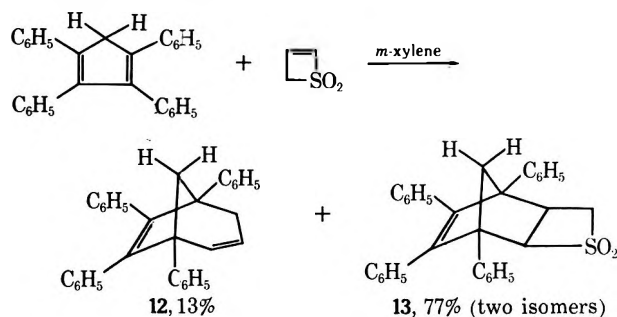
The inference from the above observations is that cycloheptatriene **2** is produced *via* the Diels–Alder adduct **9** while bicyclic ketone **3** and also **12** are not. Scheme II is a rationalization of the reaction path in which cycloheptatriene is produced by decomposition of a Diels–Alder adduct; the bicyclic ketone is formed

(18) B. Halton, M. A. Battiste, R. Rehberg, C. L. Deyrup, and M. E. Brennan, *J. Amer. Chem. Soc.*, 89, 5964 (1967).

(19) The loss of sulfur dioxide and carbon monoxide from adduct 9 is probably thermodynamically sound since three quite stable molecules are formed. We have observed that the Diels–Alder reaction of methyl vinyl sulfone and tetracyclone gives a 77% yield of 1,2,3,4-tetraphenylbenzene, presumably formed in an aromatization by loss of methanesulfinic acid.
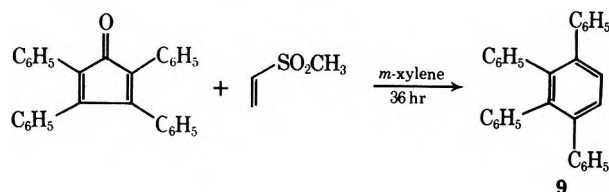
Unfavorable electrostatic interaction between the sulfone group and the carbonyl group in 9 (especially in the exo isomer) may contribute to the instability.

SCHEME II
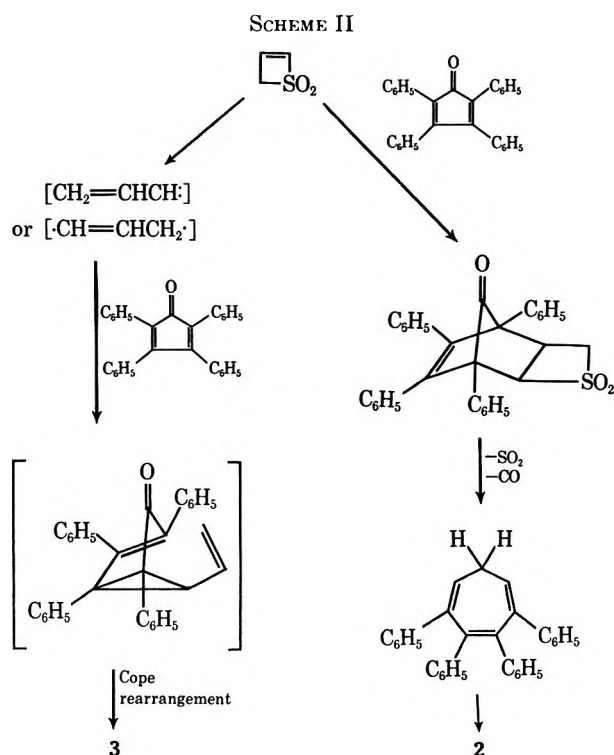
from a diradical or vinyl carbenoid species, C_3H_4, derived from the decomposition of thiete sulfone.[20] Under the reaction conditions, thiete sulfone alone is decomposed completely to tar. Ketone **3** also could be formed from vinyl sulfene[20] *via* its adduct with tetracyclone; the adduct then can undergo loss of sulfur dioxide to give a diradical precursor to **3**.

Experimental Section[21]

Diels-Alder Adducts of Thiete Sulfone. A. With Butadiene.—Butadiene (3 ml) was transferred by means of a vacuum line into a reaction tube containing thiete sulfone[22] (1.04 g, 0.01 mol) in benzene (10 ml); a total of 10 tubes was prepared, sealed *in vacuo* at liquid nitrogen temperature, and placed in an oil bath at 110°. After 60 hr the tubes were opened and the contents combined. Solvent was removed on a rotary evaporator and the residue was treated with 100 ml of methanol to precipitate polymer which was removed by filtration. Evaporation of the methanol left an oil which solidified on standing. Two recrystallizations from ethanol gave 10.3 g (0.065 mol, 65%) of white needles with the structure of 7-thiabicyclo[4.2.0]-3-octene 7,7-dioxide.

Anal. Calcd for $C_7H_{10}O_2S$: C, 53.16; H, 6.37; S, 20.24. Found: C, 53.40; H, 6.42; S, 20.24.

B. With Furan.—Five sealed tubes each containing furan (5 ml) and thiete sulfone (2.08 g, 0.02 mol) in 20 ml of benzene were prepared as in A. After 40 hr in the oil bath at 110°, the tubes were opened, the contents were combined, and the solvent was evaporated. The residue was treated with ethanol and

insoluble material was removed by filtration. The ethanol was removed by evaporation, and the product was recrystallized twice to yield small white crystals (12 g, 0.07 mol, 70%), mp 130°. Spectroscopic data were consistent with the structure, 9-oxa-3-thiatricyclo[4.2.1.0²,⁵]non-7-ene 3,3-dioxide. The stereochemistry (exo or endo) of the product was not determined.

Anal. Calcd for $C_7H_8O_3S$: C, 48.84; H, 4.68; S, 18.60. Found: C, 48.77; H, 4.78; S, 18.67.

C. With 2,5-Dimethylfuran.—Five sealed tubes each containing 2,5-dimethylfuran (5 g) and thiete sulfone (2.08 g, 0.02 mol) in 20 ml of benzene were prepared as in A and placed in an oil bath at 110° for 40 hr. Combination of the reaction mixtures, evaporation of the solvent, and recrystallization from benzene–ethanol gave white crystals, mp 131° (4.55 g, 0.0228 mol, 23%). Spectroscopic data were in accord with the structure, 7,8-dimethyl-9-oxa-3-thiatricyclo[4.2.1.0²,⁵]non-7-ene 3,3-dioxide. The stereochemistry (exo or endo) of the product was not determined.

Anal. Calcd for $C_9H_{12}O_3S$: C, 53.99; H, 6.04; S, 15.99. Found: C, 53.75; H, 6.14; S, 16.15.

Reaction of Thiete Sulfone and Tetracyclone.—A solution of 5.3 g (13.7 mmol) of tetracyclone (Aldrich Chemical Co.), 1.60 g (15.6 mmol) of thiete sulfone,[22] and 75 ml of *m*-xylene (Matheson Coleman and Bell) was refluxed for 85 hr in an apparatus fitted with a gas-tight syringe to collect the evolved gases. During the reaction, the color of the solution changed from purple to yellow. The solution was cooled to room temperature, and an insoluble residue (0.1 g, mp 250°) was removed by filtration. The solvent was removed by means of a rotary evaporator and the residue was chromatographed on a Florisil (Fischer-F-101) column. The first fraction, eluted with a hexane–benzene (2:1) mixture, was identified as 1,2,6,7-tetraphenylcycloheptatriene (**2**) (3.80 g, 65%). Recrystallization from ethanol gave pale yellow crystals, mp 69–70°.

Occasionally, especially with shorter reaction times, a second form of 1,2,6,7-tetraphenylcycloheptatriene, mp 127–128°, was isolated. The infrared spectrum (KBr), ultraviolet spectrum (CH₃CN), proton nmr spectrum (CDCl₃), X-ray powder pattern, and behavior on thin layer chromatography (silica gel sheets, 4:1 petroleum ether–benzene) are identical with those of the lower melting isomer. The high melting polymorph can be converted to the low melting one by melting and resolidification but not vice versa.

Anal. Calcd for $C_{31}H_{24}$: C, 93.90; H, 6.10; mol wt, 396. Found: C, 93.87; H, 6.17; mol wt, 396 (obtained from mass spectrum).

The following spectroscopic observations were made: ir 3047 (sh), 3003 (w), 2959 (sh), 796 (s, C=CH), 747 (s, C_6H_5), 730 (s, C_6H_5), 687 cm⁻¹ (s, HC=CH, C_6H_5); uv (CH₃CN) log ϵ_{274}^{max} 4.27, log ϵ_{274}^{max} 4.29, log ϵ_{324}^{max} 3.94; proton nmr (100 MHz in CDCl₃) τ 2.45–3.03 (multiplet, C_6H_5), 3.03–3.26 (complex multiplet, C-5 H), 3.44–3.65 (complex multiplet, C-3, C-4 H), 4.29–4.42 (singlet, C-7 H); mass spectrum (250°, direct inlet 70 eV)[23] *m/e* 397 (35.5), 396 (100, P), 319 (27, P − C_6H_5), 318 (19, P − C_6H_6), 242 (8, P − $2C_6H_5$), 241 (36, P − $2C_6H_6$ − H), 167 (15, P − $3C_6H_5$), 165 (14.5, P − $3C_6H_6$ − 2H).

The second compound, eluted with benzene, was identified as 1,5,6,7-tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one (**3**) (0.86 g, 2.05 mmol, 15%). Recrystallization from chloroform–ethanol gave colorless crystals, mp 192.5–193.5°.

Anal. Calcd for $C_{32}H_{24}O$: C, 90.63; H, 5.66; mol wt, 424. Found: C, 90.32; H, 5.89; mol wt, 424 (obtained from mass spectrum).

The following spectroscopic observations were made: ir 3074 (sh), 3030 (sh), 3024 (m), 2980 (sh), 1761 (vs, C=O), 1605 (m), 695 cm⁻¹ (vs); uv (CH₃CN) log ϵ_{234}^{max} 3.99, log ϵ_{260}^{max} 4.00, log ϵ_{265}^{max} 4.00, log ϵ_{270}^{max} 4.00; proton nmr (100 MHz in CDCl₃) τ 2.52–3.30 (complex multiplet, 19 H, 18 aromatic protons and one olefinic proton at τ 3.02), 3.37–3.60 (multiplet, 2 H, aromatic protons), 3.84–4.30 (two sets of triplets, J = 9.5, 3.5 Hz, 1 H, C=CH), and 6.79–6.95 (complex multiplet, 2 H, CH₂); mass spectrum (250°, direct inlet, 70 eV)[23] *m/e* 425 (33.3), 424 (100, P), 396 (83.5, P − CO), 395 (13.9, [$C_7H_3(C_6H_5)_4$]⁺), 319 (44.5, [$C_7H_4(C_6H_5)_3$]⁺), 305 (30.5, [$C_6H_3(C_6H_5)_3$]⁺).

The gases which were evolved during the reaction were transferred to a gas infrared cell. An infrared spectrum comparison

(20) Thermal decompositions of thiete sulfones have been reported to yield cyclic sulfinates or sultines: R. W. Hoffmann and W. Sieber, *Angew. Chem., Int. Ed. Engl.*, **4**, 786 (1965); D. C. Dittmer, R. S. Henion, and N. Takashina, Abstracts of Papers, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April, 1967, 101-O and ref 1; J. F. King, K. Piers, D. J. H. Smith, C. L. McIntosh, and P. de Mayo, *Chem. Commun.*, 31 (1969).

(21) Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 or 521 spectrometer and ultraviolet spectra on a Perkin-Elmer Model 202 spectrometer. Nmr spectra were obtained on a Varian A-60 or HA-100 spectrometer with TMS as an internal standard. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU 6 E instrument. Analyses for elements were done by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Alfred Bernhardt Mikroanalytisches Laboratorium in Max Planck Institut für Kohlenforschung, Mulheim, West Germany.

(22) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961); P. L. F. Chang and D. C. Dittmer, *ibid.*, **34**, 2791 (1969).

(23) Percentage of base peak is given in parenthesis. P = parent ion.

showed these gases to be carbon monoxide[24] and sulfur dioxide.[25]

Hydrogenation of 1,5,6,7-Tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one (3).—The bicyclic ketone 3 (0.4 g, 0.94 mmol) and platinum oxide (40 mg) in 50 ml of ethyl acetate were hydrogenated at room temperature under atmospheric pressure. After the hydrogen absorption ceased, the catalyst was removed by filtration and the solvent was removed.

The residue was recrystallized from ethanol-chloroform to give a monoolefinic ketone (0.3 g, 0.7 mmol, 77%): mp 184–186°; uv (CH₃CN) 213 nm (log ε 4.73), 227 (4.34), 250 (4.06), 258 (4.03), 265 (3.99); ir (KBr disk), 3080 (sh), 3063 (w), 3030 (w), 2952 (m), 2870 (m), 1758 (vs, C=O), 1600 (m), 1447 (s, CH₂), 695 cm⁻¹ (vs); proton nmr (60 MHz in CDCl₃) τ 2.68–3.2 (complex multiplet, 20 H) and 7.25–7.85 (complex multiplet, 6 H); mass spectrum (250°, direct inlet, 70 eV) *m/e* 426 (5.4, P).

Anal. Calcd for C₃₂H₂₆O: C, 90.14; H, 6.1. Found: C, 90.25; H, 6.28.

Thermal Rearrangement of 2,3,4,5-Tetraphenylcyclohepta-triene (11) to 1,2,6,7-Tetraphenylcycloheptatriene (2).—2,3,4,5-Tetraphenylcycloheptatriene (11) (0.6 g, 1.48 mmol)[11] was refluxed in *m*-xylene for 1.5 hr. The solvent was removed and the residue was recrystallized from benzene-hexane to yield 11, (0.2 g, 0.5 mmol, 34%), mp 169–170°. The recovered starting material was removed by filtration and the residue was recrystallized from acetone to yield the high melting form of 1,2,6,7-tetraphenylcycloheptatriene (0.2 g, 0.5 mmol, 34%), mp 127–129°.

Conversion of 1,5,6,7-Tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one (3) to 1,5,6,7-Tetraphenylbicyclo[3.2.1]octa-6-ene (8).—The bicyclic ketone 3 (1 g, 2.36 mmol) was dissolved in ethane-dithiol (10 ml). Boron trifluoride etherate (10 ml) was added with cooling by ice-water. The solution immediately became deep red and the mixture was kept at room temperature for 2 days. The precipitate was removed by filtration and washed with methanol to give white crystals (0.3 g, 0.6 mmol, 22.8%), mp 275–278°.

Anal. Calcd for C₃₄H₂₈S₂: C, 81.6; H, 5.6; S, 12.8. Found: C, 81.73; H, 5.78; S, 12.80.

The thioketal was suspended in dioxane (20 ml) and W-5 Raney nickel (5 g) was added. The Ni catalyst was removed after a 14-hr reflux period and the dioxane was removed. The residue was recrystallized from methanol-acetone (50 mg, 0.12 mmol, 20.3%): mp 113–115°; ir (KBr disk) 3080 (sh) 3033 (w), 2950 (m), 2930 (m), 2903 (w), 2862 (w), 1600 (m), 1443 (s, CH₂), and 698 cm⁻¹ (vs); uv (CH₃CN) 225 nm (log ε 4.27), 256 (4.02), and 267 (4.00); nmr (60 MHz in CDCl₃) complex τ 2.54–3.22 (complex multiplet, 20 H), 6.95 (perturbed doublet, 1 H), 7.5–8.25 (complex multiplet, 7 H); mass spectrum (300°, direct inlet, 70 eV) *m/e* 413 (36.7), 412 (100, P), 384 (21.6, P − C₂H₄), 370 (13.3, P − C₃H₆), 306 (30, [C₆H₃(C₆H₅)₃]), 178 (21.6, C₆H₅C≡CC₆H₅), metastable ion at *m/e* 357.9 (P − CH₂=CH₂).

Anal. Calcd for C₃₂H₂₈: C, 93.20; H, 6.79. Found: C, 93.07; H, 6.70.

5-Methyl-1,2,3,4-tetraphenyl-2-norbornene (7). A. 5-Cyano-1,2,3,4-tetraphenyl-2-norbornene.—Tetraphenylcyclopentadiene (8 g, 0.022 mol), acrylonitrile (6 g, 0.14 mol), and a small amount of hydroquinone were heated in benzene solution for 2 days. The solvent was removed and the residue was recrystallized from chloroform-ethanol (8 g, 0.019 mol), mp 187–189°, ir (KBr disk) 2230 cm⁻¹.

Anal. Calcd for C₃₂H₂₅N: C, 90.77; H, 5.91; N, 3.31. Found: C, 91.02; H, 5.89; N, 3.26.

B. 5-Aminomethyl-1,2,3,4-tetraphenyl-2-norbornene.—An equimolar LiAlH₄ ether solution was added at room temperature to the above nitrile (4 g, 9.7 mmol) in dry ether (200 ml). The reaction mixture was refluxed 2 hr and hydrolyzed with 3 N sodium hydroxide solution. The ether layer was separated and the aqueous layer was extracted with benzene. The solvent was removed and the residue was recrystallized from benzene-hexane (3.2 g, 7.5 mmol, 77.5%), mp 80–82°, ir (neat) 3400 cm⁻¹.

Anal. Calcd for C₃₂H₂₉N: C, 89.92; H, 6.79; N, 3.28. Found: C, 89.80; H, 6.67; N, 3.18.

C. 5-N,N-Dimethylaminomethyl-1,2,3,4-tetraphenyl-2-nor-bornene.—The amine prepared in B (7 g, 0.016 mol) was added slowly to formic acid (10 g, 90%) cooled with tap water. Form-

aldehyde (5 ml, 37% solution) was added and the reaction mixture stirred for 2 hr at room temperature and then heated to 90–100° for 14 hr. Hydrochloric acid (2 ml of 4 N) was added, and the solvent was removed by a rotary evaporator. A small amount of water and 2 ml of 18 N sodium hydroxide were added, and the mixture was extracted with benzene. After removal of solvent, the mixture was separated on silica gel (Will, Grade 950, 60–200 mesh). The dimethylated amine was eluted with ether and recrystallized from benzene-acetone (2.5 g, 5.45 mmol, 34%): mp 198–200°; ir (KBr disk) 2880, 2760 cm⁻¹; nmr (60 MHz, CDCl₃) τ 2.5–3.5 (complex multiplet 20 H), 7.5–7.68 (complex multiplet, 5 H), 7.5 (singlet, 6 H), 7.75–8.17 (multiplet, 2 H).

Anal. Calcd for C₃₄H₃₃N: C, 89.92; H, 6.79; N, 3.28. Found: C, 89.80; H, 6.67; N, 3.13.

Another isomer, most probably endo, was eluted with methanol from the silica gel column (2 g, 4.3 mmol, 27%): mp 81–85°; nmr (60 MHz, CDCl₃) τ 2.35–3.6 (complex multiplet, 20 H), complex 6.3–8.4 (complex multiplet, 7 H), 7.83 (singlet, 6 H, endo CH₃).

D. 5-N,N-Dimethylaminomethyl-1,2,3,4-tetraphenyl-2-nor-bornene Methiodide.—The exo-dimethylamine from C (2.5 g, 5.5 mmol) was dissolved in benzene (40 ml). Excess methyl iodide was added and the reaction mixture kept at room temperature for 7 hr, after which a white crystalline precipitate was removed by filtration, washed with benzene, and recrystallized from ethanol-acetone to give 2.7 g (4.45 mmol, 81%) of product, mp 255–260° dec. A methiodide (mp 191–196°) also could be prepared from the endo isomer; the reaction was much slower.

Anal. Calcd for C₃₅H₃₆NI: C, 70.35; H, 6.03; N, 2.34. Found: C, 70.49; H, 6.22; N, 2.48.

E. 5-Methylene-1,2,3,4-tetraphenyl-2-norbornene.—The quaternary ammonium iodide (1 g, 1.6 mmol) was dissolved in tetrahydrofuran and a volume of water equal to the volume of tetrahydrofuran was added. Freshly prepared silver oxide (1 g) was added and stirred for 50 min at room temperature. The excess silver oxide and silver iodide were removed by filtration and the solvent was removed by means of a rotary evaporator. The light brown salt was heated at 240° for 1.5 hr under vacuum (water aspirator). The product mixture was dissolved in benzene and separated on silica gel. The first compound, eluted with hexane-benzene (1:1), was tetraphenylcyclopentadiene (50 mg, 0.13 mmol, 8.4%), mp 181° (lit.[26] mp 180°). The second compound, eluted with the same solvent, was 5-methylene-1,2,3,4-tetraphenyl-2-norbornene (recrystallized from methanol-chloro-form) (0.5 g, 1.21 mmol, 76%): mp 154–156°; ir (KBr disk) 3040, 1658, and 887 cm⁻¹ (C=CH₂); uv (CH₃CN) 221 nm (log ε 4.35), 237 (4.05), 261 (4.05), 340 (3.83); nmr (60 MHz in CDCl₃) τ 2.65–3.5 (complex multiplet, 20 H), 4.77 (apparent doublet, 2 H), 6.95 (broadened singlet, 2 H), 7.26, 7.77 (AB quartet, *J* = 8.5 Hz, 2 H).

Anal. Calcd for C₃₂H₂₆: C, 93.65; H, 6.35. Found: C, 93.67; H, 6.24.

F. Hydrogenation of 5-Methylene-1,2,3,4-tetraphenyl-2-nor-bornene.—The olefin (0.5, 1.2 mmol) was hydrogenated in ethyl acetate (50 ml) with 50 mg of platinum oxide at room temperature and under atmospheric pressure. The reaction was completed in 5 min. The catalyst was removed by filtration and the solvent was removed. The residue was recrystallized from benzene-hexane mixed solvent to give 5-methyl-1,2,3,4-tetraphenyl-2-norbornene (7) (0.28 g, 0.67 mmol, 56%): mp 203°; ir (KBr disk) 2962, 1458, and 1374 cm⁻¹; uv (CH₃CN) 222 nm (log ε 4.31), 237 (4.13), and 273 (3.99); nmr (60 MHz in CDCl₃) τ 2.55–3.5 (complex multiplet, 20 H), 6.52–7.12 (multiplet, 1 H), 7.15–7.65 (complex multiplet, 2 H), 7.95 (doublet, *J* = 9 Hz, 1 H), 8.15–8.5 (complex multiplet, 1 H), 8.59 (doublet, 3 H).

Anal. Calcd for C₃₂H₂₈: C, 93.20; H, 6.79. Found: C, 92.34; H, 6.78.

1,5,6,7-Tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one from Tet-racyclone and 3,3-Dichloropropene.—3,3-Dichloropropene (1.43 g, 0.013 mol) and a trace amount of iodine catalyst were added to 0.91 g (0.014 g-atom) of zinc, treated as described by Shank and Shechter,[27] in 50 ml of ether. The mixture was refluxed for 10 min and tetracyclone (5 g, 0.013 mol) suspended in 150 ml of ether was added. The refluxing was continued for 3 days. The mixture was filtered through Celite, the solvent was removed, and the residue was separated on an alumina column. The

(24) "The Sadtler Standard Spectra," Sadtler Research Laboratories. Philadelphia, Pa., 1965, infrared spectrum 1142.

(25) Reference 24, infrared spectrum 841.

(26) See the paper of Sonntag, *et al.*, cited in ref 13.

(27) R. S. Shank and H. Shechter, *J. Org. Chem.*, **24**, 1825 (1959).

products were mainly recovered tetracyclone (3 g, 7.5 mmol, 60%), a ketone (0.2 g, 0.5 mmol, 4.2%), and an unidentified compound (1 g). The melting point and infrared and nmr spectra of the ketone were identical with those of 1,5,6,7-tetraphenyl-bicyclo[3.2.1]octa-2,6-dien-8-one (3), which was obtained from tetracyclone and thiete sulfone.

1,6,7,8-Tetraphenyl-3-thiatricyclo[4.2.1.0^{2,5}]non-7-en-9-one 3,3-Dioxide (9).—Tetracyclone (3 g, 7.5 mmol) and thiete sulfone (1 g, 9.6 mmol) were refluxed in dioxane (30 ml) for 1 week. The solvent was removed and the residue was separated on a silica gel column. The tetracyclone–thiete sulfone adduct (9) was eluted with ether and recrystallized from benzene–hexane mixed solvent (0.3 g, 0.6 mmol, 7.8%): mp 140–150° (it resolidified at 190–200° followed by decomposition at 220–221°); ir (KBr disk) 1785, 1310, and 1120 cm^{-1}; uv (dioxane) 237 nm (log ε 4.04) and 270 (3.96); nmr (60 MHz in CDCl$_3$) τ 2.7 (singlet, 10 H), 2.9–3.42 (complex multiplet, 10 H), 4.6 (perturbed doublet, 1 H), 5.6–5.96 (multiplet, 1 H), 6.1–6.6 (multiplet, 2 H). Adduct 9 (0.2 g, 0.4 mmol) was refluxed in m-xylene (Eastman Kodak Co.) and the decomposition was followed by thin layer chromatography (silica gel). After 3 hr, the adduct completely decomposed. m-Xylene was removed and the residue was separated on a silica gel column. 1,2,6,7-Tetraphenyl-cycloheptatriene (2) (0.12 g, 0.302 mmol, 76%), mp 64–66°, was eluted with hexane–benzene (2:1).

Anal. Calcd for C$_{32}$H$_{24}$O$_3$S: C, 78.68; H, 4.92; S, 6.56. Found: C, 78.81; H, 5.10; S, 6.38.

Reaction of Tetraphenylcyclopentadiene and Thiete Sulfone.—Tetraphenylcyclopentadiene (5 g, 0.014 mol) and thiete sulfone (1.8 g, 0.015 mol) were refluxed in m-xylene (Eastman Kodak Co.) (70 ml) for 2 days. The solvent was removed by a rotary evaporator, and the residue was dissolved in benzene and chromatographed on silica gel. The first compound, eluted with hexane–benzene (1:1), was 1,5,6,7-tetraphenylbicyclo[3.2.1]-octa-2,6-diene (12) which was recrystallized from ethanol-acetone (1.4 g, 5.2 mmol, 12.7%): mp 140–142°; ir (KBr disk) 3040, 1638, and 904 cm^{-1}; uv (CH$_3$CN) 218 nm (log ε 4.35), 229 (4.27), 235 (4.24), 345 (3.29); nmr (60 MHz in CDCl$_3$) τ 2.6–3.57 (complex multiplet, 21 H), 4.15 (two sets of triplets, J = 10 and 3 Hz, 1 H), 7.36 (quartet, J = 10 Hz, 2 H), 7.45 (complex multiplet, 2 H).

Anal. Calcd for C$_{32}$H$_{26}$: C, 93.65; H, 6.35. Found: C, 93.75; H, 6.28.

The second compound, 1,6,7,8-tetraphenyl-3-thiatricyclo-[4.2.1.0^{2,5}]non-7-en-9-one 3,3-dioxide (13), was eluted with ether and recrystallized from ethanol-acetone (2.4 g, 5.1 mmol, 36.3%): mp 236°; ir (KBr disk) 1323 and 1130 cm^{-1}; uv (CH$_3$CN) 217 nm (log ε 4.24), 235 (shoulder, 4.11), 260 (3.91); nmr (60 MHz in CDCl$_3$) τ 2.6–3.55 (complex multiplet, 20 H), 4.7 (perturbed doublet, 1 H), 5.95-6.8 (complex multiplet, 3 H), 6.89 (singlet, 2 H).

Anal. Calcd for C$_{32}$H$_{26}$O$_2$S: C, 81.01; H, 5.48; S, 6.75. Found: C, 81.16; H, 5.49; S, 6.67.

A third compound was separated from the other sulfone by recrystallization and is an isomer of it (2.7 g, 5.6 mmol, 40.7%): mp 115–120°; uv (CH$_3$CN) 213 nm (log ε 4.27) and 264 (3.88); nmr (60 MHz in CDCl$_3$) τ 2.4–3.6 (complex multiplet, 20 H), 5.6–6.1 (perturbed doublet, 1 H), 6.45–6.95 (complex multiplet, 3 H), 6.95–7.8 (complex multiplet, 2 H). The displacements of some of these absorptions to lower field suggests that this isomer is the exo. The ir spectra of the two sulfones are almost identical.

Anal. Calcd for C$_{32}$H$_{26}$O$_2$S: C, 81.01; H, 5.48; S, 6.75. Found: C, 81.14; H, 5.50; S, 6.51.

Hydrogenation of 1,5,6,7-Tetraphenylbicyclo[3.2.1]octa-2,6-diene (12).—The olefin (0.5 g, 1.2 mmol) was hydrogenated in ethyl acetate solvent over platinum oxide. After 5 min the hydrogenation was complete and the catalyst was separated. The solvent was removed and the residue was recrystallized from ethanol-acetone (0.48 g, 1.15 mmol, 96%). This compound was identical with the Raney nickel reduction product from 1,5,6,7-tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one (3).

Anal. Calcd for C$_{32}$H$_{28}$: C, 93.20; H, 6.79. Found: C, 93.07; H, 6.70.

Reaction of Tetracyclone and Methyl Vinyl Sulfone to Give 1,2,3,4-Tetraphenylbenzene.—A solution of tetracyclone (3.86 g, 10 mmol) and methyl vinyl sulfone (1.59 g, 15 mmol, K and K Laboratories) in m-xylene (100 ml) was refluxed for 36 hr. The reaction mixture was poured into an evaporating dish and allowed to evaporate to dryness. The residue was dissolved in benzene–chloroform and chromatographed on a column of Florisil. Elution with petroleum ether (bp 35–60°) and evaporation of the eluent gave 1,2,3,4-tetraphenylbenzene (2.96 g, 77%), mp 189–190° (lit.[28] mp 190–191°). The infrared and ultraviolet spectra are in accord with data given in the literature.[29]

1,5-Diphenyl-3H-cyclohepta[l]phenanthrene (4).—A solution of thiete sulfone (1.25 g, 12 mmol) and phencyclone[30] (3.82 g, 10 mmol) in m-xylene (100 ml) was refluxed for 12 hr. The m-xylene was removed by evaporation and the residue was chromatographed on a column of Florisil and eluted with 1:1 benzene–petroleum ether (bp 65–75°). The solvent was evaporated and the residue was recrystallized from benzene–ethanol to yield a white, fluorescent product: mp 242–244° (2.75 g, 69%); ir (KBr disk) 3000 (w), 1600 (m), 1480 cm^{-1} (m); uv (CH$_3$CN) 252 nm (log ε 4.75), 261 (4.81), 275 (4.61), 310 (4.06), 340 (3.16); nmr (60 MHz, CDCl$_3$) τ 2.00–3.03 (complex multiplet, 20 H), 3.20–3.56 (triplet, J = 7 Hz, 2 H).

Anal. Calcd for C$_{31}$H$_{22}$: C, 94.38; H, 5.62; mol wt, 394. Found: C, 94.27; H, 5.67; mol wt (osmometric), 400.

Registry No.—1, 7285-32-7; 2, 32513-31-8; 3, 32513-32-9; 4, 32513-33-0; 7, 32513-56-7; 8, 32513-57-8; 9, 32513-58-9; 12, 32513-59-0; endo-13, 32513-60-3; exo-13, 32513-61-4; tetracyclone, 479-33-4; 7-thiabicyclo[4.2.0]-3-octene 7,7-dioxide, 32513-62-5; 9-oxa-3-thiatricyclo[4.2.1.0^{2,5}]non-7-ene 3,3-dioxide, 32476-23-6; 7,8-dimethyl-9-oxa-3-thiatricyclo[4.2.1.-0^{2,5}]non-7-ene 3,3-dioxide, 32513-63-6; monoolefinic ketone from 3, 32506-29-9; thioketal from 3, 32513-64-7; 5-cyano-1,2,3,4-tetraphenyl-2-norbornene, 32513-65-8; 5-aminomethyl-1,2,3,4-tetraphenyl-2-norbornene, 32513-66-9; exo-5-N,N-dimethylaminomethyl 1,2,3,4-tetraphenyl-2-norbornene, 32527-25-6, 32513-68-1 (methiodide); endo - 5 - N,N - dimethylaminomethyl-1,2,3,4-tetraphenyl-2-norbornene, 32513-67-0, 32513-69-2 (methiodide); 5 methylene-1,2,3,4-tetraphenyl-2-norbornene, 32513-70-5.

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Photochemistry of 1,6-Cyclodecadienes. I. 1-Methyl-(E,E)-1,6-cyclodecadiene[1]

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The photochemical behavior of 1-methyl-(E,E)-1,6-cyclodecadiene (4) has been examined. Diene 4 is converted, by direct irradiation in hexane, benzene, or methanol with Vycor- or Corex-filtered light, to a 9:1 mixture of tricyclo[5.3.0.0²,⁶]decanes 6 and 7. None of the isomeric tricyclo[4.4.0.0²,⁷]decane 5 is produced. The same conversion is observed, although in low yield, when 4 is irradiated with Pyrex-filtered light in the presence of benzophenone, naphthalene, or 2-acetonaphthone but not with fluorenone. The E,Z and Z,Z isomers of 4 are not observed as intermediates in the photoreaction. A mechanistic scheme is proposed, based on conformational arguments, for the photochemistry of such 1,6-cyclodecadienes.

The isomeric, tricyclic sesquiterpenes, α-copaene (2)[4] and α-bourbonene (3),[5] could conceivably be derived from the alternate modes of photocycloaddition of a cyclodecatriene such as 1. Several years ago, we undertook an investigation of the photochemistry of 1,6-cyclodecadienes for two reasons. Firstly, such an intramolecular 2 + 2 cycloaddition seemed attractive as a possible synthetic route to the sesquiterpenes 2 and 3. Secondly, the suggestion has been made that the *in vivo* formation of 2 and 3 might involve such a photochemical step.[6,7] Although the problems of chemical synthesis of copaene[8] and bourbonene[7,9] have subsequently been solved in other ways, the possible photochemical conversion of a 1,6-cyclodecadiene to compounds of these two types continued to intrigue us.
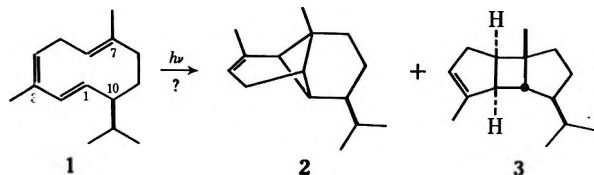
As a logical first step in our investigation of this problem, we decided to examine the photochemical behavior of the known[10] 1-methyl-(E,E)-1,6-cyclodecadiene (4). Diene 4 seemed to be a good model for triene 1 in that the two double bonds postulated to react are similarly substituted. It lacks the isopropyl group and the third double bond of 1. Although the isopropyl group is probably of no electronic consequence in 1, it may be of conformational importance. The absence of the Δ³ double bond is a severe structural change. This linkage will obviously have a profound effect, both conformationally and electronically, in compound 1. The two alternate modes of 2 + 2 cycloaddition of

diene 4 would yield the tricyclic hydrocarbons 5 and 6, the former related to copaene and the latter to bourbonene.

Experimental Section

1-Methyl-(E,E)-1,6-cyclodecadiene (4).—Diene 4 was prepared by the method of Marshall and Bundy.[10] The crude diene was separated from isomeric hydrocarbon impurities by extraction into 10% aqueous silver nitrate solution. The diene was regenerated by the addition of aqueous ammonia. Final purification was accomplished by preparative glpc (6 ft × 0.25 in. SE-30 on Chromosorb W at 145°, retention time of 4, 4 min). The diene so prepared and purified was a water-clear liquid which showed absolutely no impurities by glpc (200 ft × 0.01 in. SF-96 at 90°, 500 ft × 0.03 in. SF-96-50 at 120°, both flame ionization detectors). The uv spectrum of 4, measured in spectroquality hexane, had λ_{max} 180 nm (ϵ 24,700).[11] The absorption, attributable to the $\pi \rightarrow \pi^*$ transitions of the two isolated double bonds, tails strongly toward the red, with measured extinction coefficients as follows: 220 nm (ϵ 1100), 240 (430), and 260 (30).

1-Methyltricyclo[4.4.0.0²,⁷]decane (5).[12]—A solution of 2.5 g of 1-methyltricyclo[4.4.0.0²,⁷]decan-8-one[8] and 20 ml of 85% hydrazine hydrate in 100 ml of freshly distilled ethylene glycol was heated under dry nitrogen for 2.5 hr at 120°. After cooling, 10 g of potassium hydroxide was added and the condenser was replaced by a distilling head. The bath was slowly raised to 210° and kept at this temperature for 2.5 hr. The water which distilled over during this period was retained. The reaction mixture was cooled and diluted with 150 ml of water. The aforementioned water distillate was added and the whole was extracted first with 150 ml of ether, then with 150 ml of hexane. The combined organic extracts were washed with water and dried over magnesium sulfate. Evaporation of the solvent yielded 1.97 g (86%) of hydrocarbon 5 as a clear liquid. The pmr spectrum (in CCl₄) contained complex methylene and methine absorption and had a sharp methyl singlet at τ 9.20.

Anal. Calcd for C₁₁H₁₈: C, 87.93; H, 12.07. Found: C, 88.04; H, 12.16.

cis,anti,cis-2-Methyltricyclo[5.3.0.0²,⁶]decan-5-one.—A solution of 21.8 g of 3-methyl-2-cyclopentenone in 165 g (174 ml) of cyclopentene was degassed for 30 min with a stream of helium and then irradiated with a 440-W Hanovia lamp through Pyrex for 21 hr. The disappearance of the 227-nm band in the uv was used as a measure of the reaction's progress. The reaction appeared to proceed very cleanly; only one major reaction product was seen on glpc analysis. A minor amount of the isomeric cis,syn,cis isomer (approximately 10%) was the sole contaminant. The solvent was removed by distillation at atmospheric pressure through an 18-in. Vigreux column and the residue (27.0 g) was then distilled at reduced pressure through a 6-in. Vigreux column. After collecting a small forerun [1 ml, bp 25–68° (0.25 Torr)], the product (23.2 g, 63%) was collected at 68–70° (0.25 Torr).

The ir spectrum was typical of that expected for a saturated cyclopentanone: 1730 and 1150 cm⁻¹. The pmr spectrum showed only a complex methylene and methine absorption, with a sharp angular methyl singlet emerging at τ 8.99. Glpc analysis (150 ft × 0.01 in. SF-96 at 125°) indicated that the product was

4   **5**   **6**
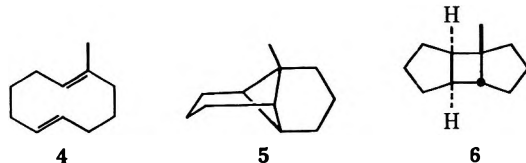
(1) Presented in preliminary form at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 8, 1968.

(2) Fellow of the Alfred P. Sloan Foundation, 1967–1969.

(3) National Institutes of Health Predoctoral Fellow, 1965–1968.

(4) P. de Mayo, R. E. Williams, G. Büchi, and S. H. Feairheller, *Tetrahedron*, **21**, 619 (1965).

(5) J. Krepinsky, Z. Samek, F. Sorm, D. Lamparsky, P. Ochsner, and Y. R. Naves, *ibid.*, **58**, 53 (1966).

(6) R. A. Barnes, *An. Acad. Brasil. Cienc.*, **36**, 238 (1964).

(7) M. Brown, *J. Org. Chem.*, **33**, 162 (1968).

(8) C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

(9) J. D. White and D. N. Gupta, *ibid.*, **90**, 6171 (1968).

(10) J. A. Marshall and G. L. Bundy, *ibid.*, **88**, 4291 (1966).

(11) Measured on a Beckman DK-2A "Ratio-Recording" Spectrophotometer.

(12) This preparation was performed by Mr. Bruce E. Ratcliffe.
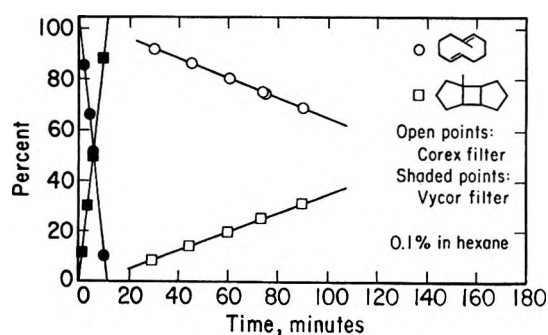
Figure 1.—Irradiation of diene 4.

a mixture of the cis,anti,cis isomer (90.5%) and the cis,syn,cis isomer (9.5%), as expected.[13]

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.11; H, 9.72.

cis,anti,cis-1-**Methyltricyclo[5.3.0.0²,⁶]decane** (6).—Into a 100-ml, three-necked flask were placed 3.25 g of *cis,anti,cis*-1-methyltricyclo[5.3.0.0²,⁶]decan-5-one (*vide supra*), 50 ml of freshly distilled ethylene glycol, and 20 ml of hydrazine hydrate. The mixture was stirred under nitrogen for 5 hr at 125°. Potassium hydroxide (13.0 g) was introduced and water was removed by distillation through a short Vigreux column until the head temperature reached 208°. The distillation column was then replaced by a reflux condenser and the mixture was heated at reflux for 3.25 hr. The cooled, pale-yellow mixture was diluted with 50 ml of ether and extracted with saturated brine (three 20-ml portions). Drying and evaporation of solvent gave only 206 mg of oil. The initial steam distillate, when worked up in the same manner, yielded a further 2.10 g of oily product. The total yield of crude hydrocarbon was thus 2.306 g (81%). Quantitative glpc analysis showed it to be a mixture of the cis,anti,cis isomer 6 (91.3%) and the cis,syn,cis isomer (8.7%). The analytical specimen was obtained by preparative glpc. The ir showed only hydrocarbon absorption; the pmr spectrum (in CCl_4) contained complex methylene and methine absorption and had a sharp angular methyl singlet at τ 9.08.

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.04, 88.31; H, 12.16, 12.02.

Photochemistry of Diene 4.—Solutions of diene 4 were prepared in various spectroquality solvents as follows: 10 mg of 4 (11 μl) in 10 ml of solvent. *n*-Undecane (5 μl) was added to each run as an internal standard for glpc analysis. The solutions were irradiated through the appropriate filter, in a 15-ml capacity quartz apparatus, under helium, with water cooling. Small samples (100 μl) were periodically withdrawn by syringe and analyzed. Analysis was done on an Aerograph 204B instrument with flame ionization detection on the following capillary columns: 150 ft $\times$ 0.01 in. SF-96, 500 ft $\times$ 0.03 in. SF-96. Quantitative analysis was accomplished by disc integrator or by normalized peak height comparison; peak height normalization factors were determined independently to be *n*-$C_{11}H_{24}$, 1; tricyclic hydrocarbon 6, 1.86; diene 4, 0.69.

Results

Irradiation of diene 4 in hexane solution (0.1%, 6.5 $\times 10^{-2}$ *M*) through a Vycor filter led to the rapid production of a 9:1 mixture of tricyclic hydrocarbon 6 and its cis,syn,cis isomer 7 in quantitative yield. The
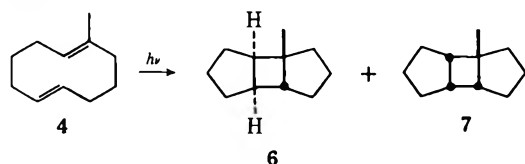
course of the reactions is depicted graphically in Figure 1. No trace of the alternate tricyclic hydrocarbon 5 could be detected. When a similar experiment was done, substituting a Corex D filter (17% transmission

(13) P. E. Eaton, *Accounts Chem. Res.*, 1, 50 (1968).

at 260 nm, 7% transmission at 250 nm), the same result was obtained, albeit at a much slower rate. The time required for one-half conversion in the Vycor experiment was 6 min; in the Corex D experiment it was 278 min. When a Pyrex filter was used, no reaction was observed.

Similar results were obtained when diene 4 was irradiated in benzene through a Corex filter (time for one-half conversion, 35 min) or in methanol through Vycor (time for one-half conversion, 4 min). In the benzene experiment, hydrocarbons 6 and 7 were again produced, in a 9:1 ratio, in quantitative yield. In the methanol experiment, although all the starting diene was consumed, hydrocarbons 6 and 7 were obtained (9:1 ratio) in a total yield of only 83%. The remaining diene was apparently converted to nonvolatile products.

Although diene 4 failed to react when irradiated with Pyrex-filtered light, reaction was observed in the presence of various sensitizers (Table I). In these sensi-

TABLE I

SENSITIZED IRRADIATIONS OF DIENE 4[a]

Sensitizer	E_T, kcal/mol[b]	Yield of 6 + 7, %	Nonvolatile products, %
Benzophenone	68.5	17	81[c]
Naphthalene	60.9	36	64
2-Acetonaphthone	59.3	~10	~90
Fluorenone	53.3	No reaction	

[a] All irradiations were carried out in hexane solution, 0.065 *M* in diene 4 and 0.1% in sensitizer, with Pyrex-filtered light. [b] Data of W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.*, 86, 4537 (1964). [c] In this experiment, four additional volatile products, representing a total yield of 2% (based on diene 4), were produced. None of these products was hydrocarbon 5.

tized experiments, most of the diene was converted to nonvolatile material, although tricyclic hydrocarbons 6 and 7 were produced in measurable quantities with all sensitizers except fluorenone.

In none of the experiments was there any evidence for the build-up of any detectable amount of an intermediate isomer possessing some other double bond geometry (*i.e.*, dienes 8–10). In one experiment, designed
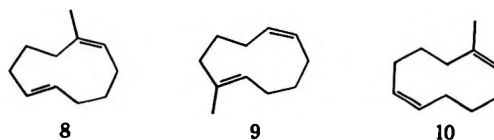
to rule out the possibility that isomers such as 8–10 might be produced, but have the same glpc retention time as 4, and thus escape notice, an irradiation of 4 was interrupted after 15% reaction. The glpc peak corresponding in retention time to 4 was then isolated and examined spectroscopically. It was found to be identical with the starting material.

Discussion

The results clearly show that tricyclo[5.3.0.0²,⁶]decanes 6 and 7 are primary photoproducts of diene 4. In this system, at least, none of the alternate modes of photocyclization, leading to a tricyclo[4.4.0.0²,⁷]decane (5), occurs. Similar results have been reported by Scheffer and Lungle in the irradiation of the unconju-

gated diene–dione 11.[14,15] These workers found that 11 reacts *via* the intermediate *E,Z* isomer to give the cis,anti,cis product 13.
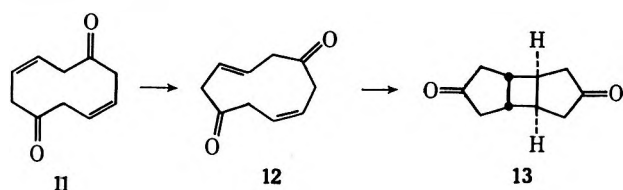
Hirose has reported that germacrene D (14), isolated from a natural source, gives mainly β-bourbonene (15) on irradiation, accompanied by a small amount of β-copaene (16).[17] No mention is made of any cis,syn,cis isomer analogous to compound 7.
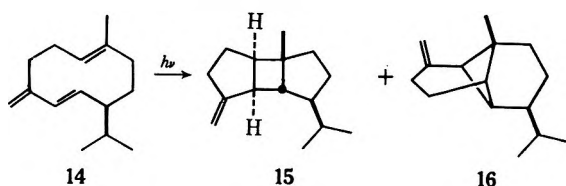
Several interesting features can be noted in the photochemical behavior of diene 4. Firstly, the only mode of cyclization is that leading to the tricyclo[5.3.0.0^{2,6}]-decane skeleton. Thus, the empirical "Rule of Five," discussed by Brown[7] and Srinivasan,[18] is followed. Secondly, both the cis,anti,cis and cis,syn,cis isomers are produced. These observations suggest that the reaction occurs by an nonconcerted path, probably *via* a 1,4-diradical such as 17.
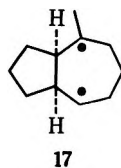
A third interesting feature of the reaction is the apparent absence of *E,Z*, or *Z,Z* intermediates. Moussebois and Dale report that, for 1,6-cyclodecadiene itself, the various double bond isomers are present at equilibrium in the ratio 18:19:20 = 0:4:96.[19] Several attempts to equilibrate diene 4 by the diphenyl disulfide method[20] failed; only nonvolatile products were produced.

As stated above, Scheffer and Lungle established that diene 11 is converted to product 13 *via* its *E,Z* isomer 12. Isomer 12 was shown to give product 13 without the build-up of the *Z,Z* isomer 11. The behavior of these systems can be explained by the following hypothesis.

$$Z,Z \underset{}{\overset{h\nu}{\rightleftharpoons}} A^* \overset{h\nu}{\rightleftharpoons} E,Z \underset{k_1}{\overset{h\nu}{\rightleftharpoons}} B^* \underset{k_2}{\overset{h\nu}{\rightleftharpoons}} E,E$$

$$\downarrow k_3$$

1,4-diradical

$$\downarrow$$

tricyclic product

If excited state A*, reached by excitation of the *Z,Z* or *E,Z* isomer, has a conformation which precludes transannular cyclization, then only double bond isomerization can result. This postulate seems not unlikely in light of established solid-state conformation (21) of diene–dione 11.[21]
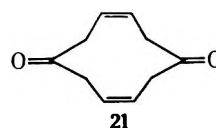
On the other hand, either this *E,Z* or the *E,E* isomer can be excited to a state (B*) which is in a conformation amenable to transannular reaction. A study of models suggests that these isomers must exist in conformations having the two double bonds in rather close proximity, as, for example, 22 and 23. If the rate constant for such a cyclization (k_3) is greater than the rate constant for return to a ground state (k_1 or k_2), then cyclization will be observed to the exclusion of double bond isomerization.

The last noteworthy feature of the reaction is the behavior of diene 4 in the sensitization experiments. When irradiated in benzene through Corex D, the diene is converted into a 9:1 mixture of tricyclic hydrocarbons 6 and 7 in quantitative yield. This result probably represents energy transfer from benzene to the diene. Although no reaction occurs when 4 is irradiated with Pyrex-filtered light, the conversion of 4 to 6 and 7 does occur in the presence of various sensitizers. As shown in Table I, conversion to product occurs when the sensitizer has a triplet energy of >59.3 kcal/mol, but not with fluorenone, which has a triplet energy of 53.3 kcal/mol. If one assumes triplet sensitization, then diene 4 must have an accessible triplet with an energy of less than 59.3 kcal/mol, an extremely low value for isolated double bonds. However, although the absorption maximum for compound 4 occurs at 180 nm, the band tails strongly toward the red; the extinction coefficient at 260 nm is still 30. Thus, 4 may well have a relatively low-lying $\pi \rightarrow \pi^*$ triplet state available. Bischof and Heilbronner have found, by photoelectron spectroscopy, additional evidence for strong interaction between the two double bonds in *trans,trans*-1,6-cyclodecadiene.[22]

On the other hand, the observed reactions of 4 may

(14) J. R. Scheffer and M. L. Lungle, *Tetrahedron Lett.*, 845 (1969).

(15) An earlier report that compound 11 gives a cis,syn,cis tricyclic diketone[15] has been refuted.[14]

(16) A. Shani, *Tetrahedron Lett.*, 5175 (1968).

(17) K. Yoshihara, Y. Ohta, T. Sakai, and Y. Hirose, *ibid.*, 2263 (1969).

(18) R. Srinivasan, Abstracts, 156th National Meeting of the American Chemical Society, San Francisco, Calif., Apr 1968, p 86P.

(19) E. Moussebois and J. Dale, *J. Chem. Soc. C*, 264 (1966).

(20) C. Moussebois and J. Dale, *ibid.*, 260 (1966).

(21) H. L. Carrell, B. W. Roberts, J. Donohue, and J. J. Vollmer, *J. Amer. Chem. Soc.*, **90**, 5263 (1968).

(22) P. Bischof and E. Heilbronner, *Helv. Chim. Acta*, **53**, 1677 (1970).

result from singlet–singlet sensitization, or sensitization by upper triplet states. At the present time, the multiplicity of the excited state responsible for cyclization should be regarded as uncertain.

The reasons for the low yields in the reactions sensitized by benzophenone, 2-acetonaphthone, and naphthalene are unknown. With the carbonyl sensitizers, some 2 + 2 cycloaddition of the sensitizer to the diene may occur. In the case of naphthalene, we have no hypothesis to explain the diminished yield. This question cannot be answered until the nonvolatile reaction products are investigated.

Photochemistry of 1,6-Cyclodecadienes. II. Synthesis and Photochemistry of 6-Methyl-1,6-cyclodecadien-3-one[1]

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6-Methyl-1,6-cyclodecadien-3-one (5) has been synthesized by a multistage route and its photochemical behavior has been examined. Irradiation of dienone 5, with Pyrex-filtered light in either ether or hexane, gives tricyclic ketones 6, 7, and 8. The interesting tricyclo[4.4.0.0²,⁷]decanone 8 arises from a triplet intermediate.

In the previous paper in this series, we reported on the photochemical behavior of 1-methyl-(*E,E*)-1,6-cyclodecadiene (1).[4] Diene 1 was found to undergo photochemical 2 + 2 cycloaddition, probably in a stepwise fashion, yielding only the tricyclo[5.3.0.0²,⁶]decanes 2 and 3. No tricyclo[4.4.0.0²,⁷]decane (*e.g.*, 4) was produced. In the present work, we have prepared and photolyzed the analogous ketone, 5.

1, X = H₂   2, X = H₂   3, X = H₂   4, X = H₂
5, X = O   6, X = O   7, X = O   8, X = O
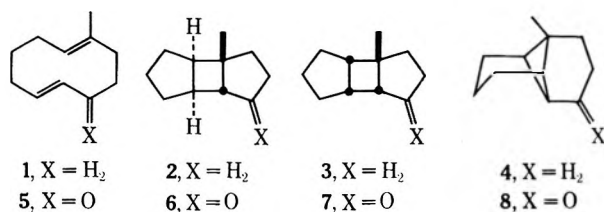
Preparation of Dienone 5.—The starting point for the preparation of dienone 5, outlined in Scheme I, was the readily available Wieland–Miescher diketone (9),[5] which was transformed by established procedures[6] into the ketal acetate 10. Oxidation of 10 with *m*-chloroperbenzoic acid in chloroform gave a 1:1 mixture of epoxides 11 and 12, which could be separated by fractional crystallization. Stereostructures were assigned to compounds 11 and 12 on the basis of their pmr spectra. Williamson has found[7] that angular methyl groups in trans-fused decalins give broader resonance lines ($W_{1/2}$ = 0.80 ± 0.20 Hz) than the corresponding cis-fused isomers ($W_{1/2}$ = 0.25 ± 0.11 Hz). The higher melting isomer, mp 137–139°, was assigned structure 11

since it gave a sharp angular methyl resonance. The lower melting isomer, mp 65.5–66.5°, was assigned the cis structure 12 on the basis of its broad methyl singlet.

Lithium aluminum hydride reduction of 11 and 12 gave corresponding diols 13 (mp 89–90°) and 14 (mp 106–107°), respectively, which were converted, by selective esterification with methanesulfonyl chloride in pyridine, to monomethanesulfonates 15 (mp 104.5–105.5°) and 16 (mp 109–110°). The line widths of the angular methyl resonances in the pmr spectra of compounds 11–14 corroborated the assigned stereostructures.

Base-catalyzed fragmentation[8] of either 15 or 16 (or a mixture of the two) with potassium *tert*-butoxide in *tert*-butyl alcohol gave excellent yields (>95%) of the cyclodecenedione monoketal 17, mp 50.5–51.5°. On the basis of good analogy,[8a] the double bond in 17 can be assigned the *E* configuration. Reduction of 17 with lithium aluminum hydride in ether gave the crystalline hydroxy ketal 18. The overall yield for the eight stages from enedione 9 to intermediate 18 was 37%.

Compound 18 was hydrolyzed by refluxing with an equal weight of oxalic acid in aqueous acetone. The product, β-hydroxy ketone 19, showed surprising resistance to dehydration. Attempts to dehydrate the ketol with basic alumina or methanolic potassium hydroxide led only to recovered starting material, as did vacuum distillation from oxalic acid. Treatment of 19 with even trace amounts of mineral acid gave intense violet solutions from which no tractable products could be isolated.[9]

The corresponding acetate, 20, prepared from 19 by acetylation with acetic anhydride in pyridine, eliminated acetic acid smoothly when warmed to 50° in tri-

(1) This paper was presented in preliminary form at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 8, 1968. See also, C. H. Heathcock and R. A. Badger, *Chem. Commun.*, 1510 (1968).

(2) Fellow of the Alfred P. Sloan Foundation, 1967–1969.

(3) National Institutes of Health Predoctoral Fellow, 1965–1968.

(4) C. H. Heathcock, R. A. Badger, and R. H. Starkey, *J. Org. Chem.*, **37**, 231 (1972).

(5) (a) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950); (b) S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961).

(6) C. H. Heathcock and R. Ratcliffe, *J. Amer. Chem. Soc.*, **93**, 1746 (1971).

(7) K. L. Williamson, T. Howell, and T. A. Spencer, *ibid.*, **88**, 325 (1966).

(8) (a) P. S. Wharton and G. A. Hiegel, *J. Org. Chem.*, **30**, 3254 (1965); (b) H. H. Westen, *Helv. Chim. Acta*, **47**, 575 (1964).

(9) Similar behavior was noted with compounds 17, 18, 20, and 5. The violet color which is produced immediately upon treating a dilute solution of any of these compounds with dilute mineral acid is discharged upon basification.

ethylamine. The product of this reaction was a mixture of the desired α,β-unsaturated ketone 5 (λ_{max} 265 nm; ν_{max} 1665, 1630 cm^{-1}) and its β,γ isomer 21 (ν_{max} 1695 cm^{-1}).

While the trisubstituted double bond in 5 must be assigned the E configuration (*vide supra*), the geometry of the conjugated double bond is uncertain. Attempts to separate dienones 5 and 21 by preparative glpc failed, since only thermal rearrangement products were obtained.[10]

Photochemistry of Dienone 5.—Dienone 5 was irradiated as a 0.1% solution in ether or hexane with Pyrex-filtered light. The irradiation was monitored by observing the diminution of the $\pi \rightarrow \pi^*$ absorption band at 265 nm. The volatile photoproduct was a mixture of compounds containing tricyclic ketones 6, 7, and 8. In ether, products 6, 7, and 8 were formed in
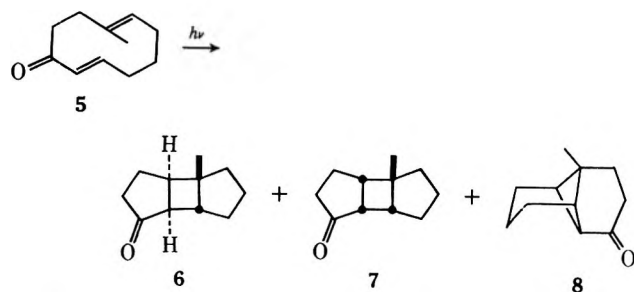
relative yields of 32, 3, and 22%, respectively. Several additional products, totaling 43% of the reaction product, were formed and remain unidentified. In hexane, the reaction is much cleaner, yielding 6, 7, and 8 in relative yields of 60, 6, and 30%, respectively.

In contrast to the situation obtaining in the case of diene 1,[4] dienone 5 yields a significant amount of a product with the tricyclo[4.4.0.0^{2,7}]decane skeleton. In order to test the multiplicity of the reactive state in this case, we carried out the irradiation of 5 in the presence of piperylene, a well-known triplet quencher.[13] Somewhat to our surprise, the relative rate of formation of product 8 was greatly reduced. The ratio of 6 to 8 in this experiment (0.1% solution of 5 in a 20:1 mixture of hexane–piperylene, Pyrex-filtered light) changed from 2:1 to 9:1. Thus, 1-methyltricyclo-[4.4 0.0^{2,7}]decan-8-one (8) must arise from a triplet state. The tricyclo[5.3.0.0^{2,6}]decanones 6 and 7 either

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(10) The thermochemistry of dienone 5 is interesting, although we have not made a rigorous study of it. When the crude mixture of 5 and 21 was injected into any of several glpc columns at 150–200°, several products were formed from thermal rearrangement. The two major products were isolated and examined spectrally. The major product with smaller retention time was identified as the cis,anti,cis tricyclic ketone 6, uncontaminated with any of its cis,syn,cis isomer 7. The other major product, tentatively assigned structure 22 on spectral grounds, is identical spectrally and chromatographically with the minor product isolated from the pyrolysis at 375°

22
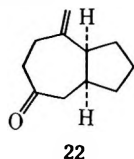
of tricyclic ketone 8.[11] When the mixture of 5 and 21 was pyrolyzed in a sealed Pyrex tube at 200°, the only product formed was compound 22. The thermal lability of 5 is remarkable, in light of the fact that diene 1 is completely stable when heated in a sealed Pyrex tube at 220–240°.[12]

(11) C. H. Heathcock and B. E. Ratcliffe, *J. Org. Chem.*, 33, 3650 (1968).

(12) C. H. Heathcock, unpublished results.

(13) G. S. Hammond, P. A. Leermakers, and N. J. Turro *J. Amer. Chem. Soc.* 83, 2396 (1961).

SCHEME I
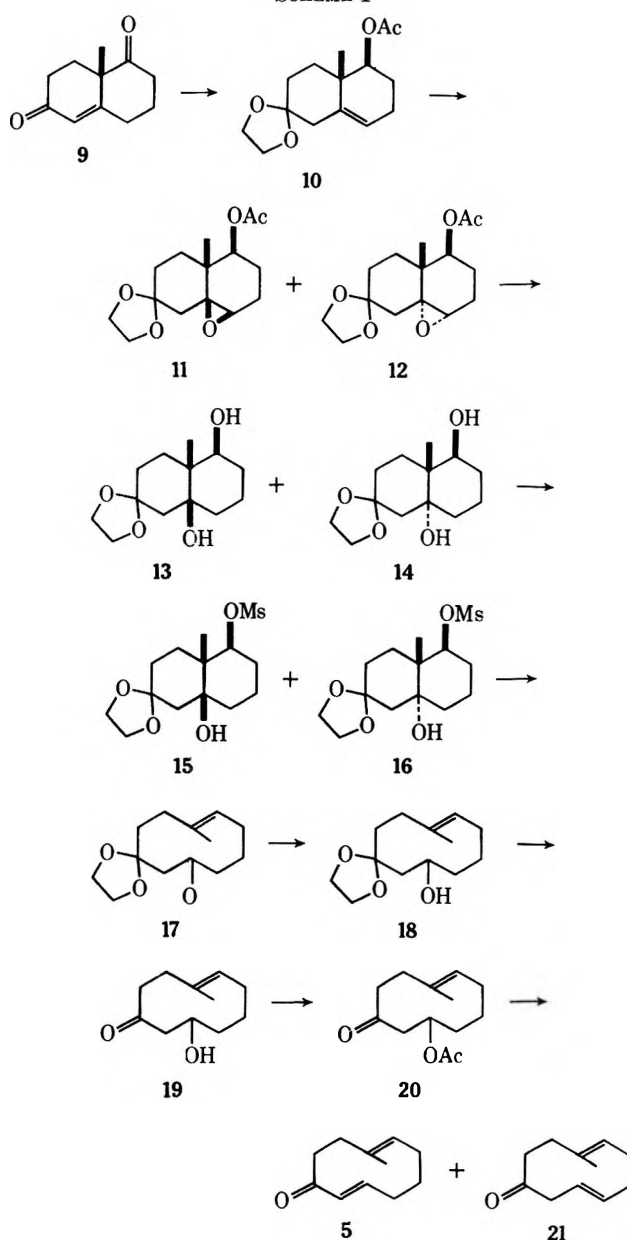
arise from a singlet state or an unquenchable triplet. A tempting hypothesis is that 1,6-cyclodecadienes always give tricyclo[4.4.0.0^{2,7}]decane products from a triplet manifold.[14]

The observation that dienone 5 yields a significant amount of the tricyclo[4.4.0.0^{2,7}]decane product 8 is in striking contrast to the finding by Scheffer and Boire[15] that isogermacrone (23) yields only photoproducts 24 and 25 upon irradiation. The multiplicity of the reacting state in this case has not been reported.

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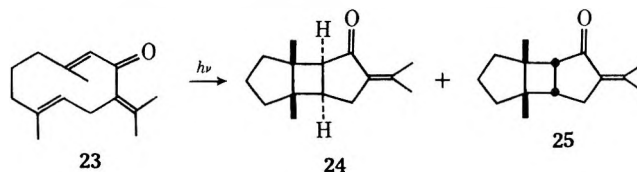
(14) This postulate would require that the observed conversion of diene 1 to products 2 and 3 in the presence of benzophenone, naphthalene, and 2-acetonaphthone[4] be ascribed to singlet–singlet sensitization. Because of concentrations used in that work, this may just be possible. We thank Professor Kurt Schaffner for suggesting this possibility.

(15) J. R. Scheffer and B. A. Boire, *Tetrahedron Lett.*, 4005 (1969).

Experimental Section

Melting points (Pyrex capillary) are uncorrected. Infrared spectra (ir) were recorded on a Perkin-Elmer 237 spectrophotometer. Proton magnetic resonance spectra were taken on Varian A-60 and T-60 spectrometers. Chemical shifts are relative to internal tetramethylsilane and are given on the Tiers τ scale; the multiplicity, peak areas, coupling constant, and proton assignments are given in parentheses. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Department of Chemistry, University of California, Berkeley, Calif.

4aβ-Methyl-5β-acetoxy-8β,8aβ-oxido-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one Ethylene Ketal (11).—A chilled solution of 73.7 g (0.276 mol) of ketal acetate 10[6] in 100 ml of chloroform was treated dropwise with a solution of 55 g (0.320 mol) of 85% m-chloroperbenzoic acid in 500 ml of chloroform. The addition required 42 min. The resulting solution was stirred at 0° for an additional 2 hr and then at room temperature overnight, during which time solid m-chlorobenzoic acid precipitated out. Filtration through sintered glass removed the acid. and the excess peracid was destroyed by stirring the filtrate for 30 min with 300 ml of 30% sodium sulfite solution. The organic layer was separated, washed with 10% sodium hydroxide (two 250-ml portions) and salt solutions (one 300-ml portion), dried, and evaporated to yield 81 g of white, semisolid material, the pmr (CHCl$_3$) of which showed two angular methyl peaks at τ 8.90 and 8.86, in an approximate ratio of 53:47. The slurry was triturated with 50 ml of ether and filtered, giving 39.3 g of white solid, mp 135–138°. Recrystallization from ethyl acetate–ether gave an analytical sample: mp 137–139°; pmr (CCl$_4$) τ 8.86 (s, 3, angular Me), 8.06 (s, 3, acetoxy Me), 6.08 (m, 4, ketal Hs), and 5.04 (m, 1, C-8 H); ir (CCl$_4$) 1730, 1370, 1250, and 1120 cm^{-1}.

Anal. Calcd for C$_{15}$H$_{22}$O$_5$: C, 63.81; H, 7.85. Found: C, 63.76; H, 8.02.

4aβ-Methyl-5β-acetoxy-8α,8aα-oxido-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one Ethylene Ketal (12).—The pmr spectrum of the filtrate above showed that about 90% of the isomer with the lower field angular methyl signal had been removed. Triturating the mother liquors with pentane and ether caused the other isomer to crystallize. Filtration afforded 36.4 g of white solid, mp 63–67°. A small portion was recrystallized from ether: mp 65.5–66.5°; pmr (CHCl$_3$) τ 8.89 (s, 3, angular Me), 8.00 (s, 3, acetoxy Me), 6.17 (s, 4. ketal Hs), and 5.44 (s, 1, C-8 H); ir (CHCl$_3$) 1740, 1355, 1230, 1100, and 835 cm^{-1}.

Anal. Calcd for C$_{15}$H$_{22}$O$_5$: C, 63.81; H, 7.85. Found: C, 63.62; H, 7.69.

For a subsequent preparative-scale reaction, 140.0 g of crystalline ketal acetate in 600 ml of chloroform was chilled to 0°, treated with 105 g of 85% m-chloroperbenzoic acid in 1000 ml of warm chloroform, and allowed to stir at room temperature overnight. After a work-up similar to that described above, 153 g of semisolid was obtained, the pmr spectrum of which showed the two angular methyl peaks in a ratio of 58:42, with the upfield signal again predominating. The crude product was utilized directly in the subsequent reaction.

4aβ-Methyl-5β,8aβ-dihydroxy-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H) Ethylene Ketal (13).—A solution of 20.76 g (74.5 mmol) of crystalline *cis*-epoxy acetate 11, mp 137–139°, in 200 ml of dry tetrahydrofuran was added to a stirring slurry of 12.0 g (316 mmol) of lithium aluminum hydride in 300 ml of tetrahydrofuran. The mixture was heated at reflux under a drying tube for 19 hr. The excess hydride was destroyed with ethyl acetate and the grey slurry was refluxed with 36 ml of 5% potassium hydroxide solution for 30 min. The organic solution was separated from the white slurry by vacuum filtration through sintered glass, dried over magnesium sulfate, refiltered, and evaporated to yield 17.0 g (95.0%) of colorless oil that solidified upon standing. A portion was recrystallized from ether to give a white solid: mp 90–92°; pmr (CCl$_4$) τ 8.90 (s, 3, $W_{1/2}$ = 0.4 Hz, angular Me), 8.34 (broad s, 2), and 6.11 (m, 4, ketal Hs); ir 3650, 3500, 1080 cm^{-1}.

Anal. Calcd for C$_{13}$H$_{22}$O$_4$: C, 64.44; H, 9.15. Found: C, 64.17; H, 9.42.

4aβ-Methyl-5α,8aα-dihydroxy-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H) Ethylene Ketal (14).—To a stirring slurry of 18.0 g (474 mmol) of lithium aluminum hydride in 250 ml of tetrahydrofuran was added a solution of 33.7 g (119 mmol) of crystalline *trans*-epoxy acetate (12) in 200 ml of dry tetrahydro-

furan. Reaction time and work-up procedure were similar to reaction of the cis compound above. The yield of crude trans ketal diol was 25.5 g (88.5%) of colorless oil that crystallized from ether: mp 104–105°; pmr (CHCl$_3$) τ 9.07 (s, 3, $W_{1/2}$ = 0.8 Hz, angular Me) and 6.06 (s, 4, ketal Hs); ir (CHCl$_3$) 3630, 3500, 1090, 1015, and 845 cm^{-1}.

Anal. Calcd for C$_{13}$H$_{22}$O$_4$: C, 64.44; H, 9.15. Found: C, 64.38; H, 9.10.

The crude mixture of 13 and 14 from the large-scale epoxidation (152 g, 538 mmol) was dissolved in 600 ml of dry tetrahydrofuran and added to 40.0 g (1.05 mol) of lithium aluminum hydride in 500 ml of tetrahydrofuran over a period of 50 min. The mixture was stirred at room temperature for 17 hr and then carefully quenched with ethyl acetate until the solvent no longer boiled. Then the mixture was treated with 130 ml of 10% potassium hydroxide solution and heated at reflux for 45 min. Suction filtration removed the white salts which were washed with ether (two 300-ml portions). The organic solution was dried and evaporated to give 107.1 g (82.3%) of pale yellow oil, shown by pmr to be a 58:42 mixture of diols 13 and 14.

4aβ-Methyl-5β,8aβ-dihydroxy-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one Ethylene Ketal 5-Methanesulfonate (15).—A solution of 16.0 g (66 mmol) of *cis*-ketal diol (13) in 250 ml of dry pyridine was treated with 6.00 ml (9.00 g, 78.5 mmol, 19% excess) of methanesulfonyl chloride. The pale yellow solution was allowed to stand at room temperature for 48 hr before being poured into 400 ml of ice water and extracted with chloroform (three 200-ml portions) and ether (one 200-ml portion). The combined organic layers were washed with water (one 200-ml portion), dried, and evaporated to 17.1 g of pale red oil that partially solidified. The crude product was dissolved in ethyl acetate, decolorized with Norit carbon, and chilled to give 7.49 g of white crystals: mp 104.5–105.5°; pmr (CHCl$_3$) τ 9.00 (s, 3, angular Me), 7.12 (s, 3, mesylate Me), and 6.06 (m, 4, ketal Hs); ir (CHCl$_3$) 3580, 1340, 1175, 1100, 1060, 950, and 870 cm^{-1}.

Anal. Calcd for C$_{14}$H$_{22}$O$_6$S: C, 52.45; H, 7.54; S, 9.98. Found: C, 52.52; H, 7.67; S, 9.79.

The mother liquors were concentrated to give 9.5 g of red gum, the pmr spectrum of which displayed two mesyl peaks at τ 7.05 and 7.00 in an approximate ratio of 2:1. After standing at room temperature for several days, a sample of *cis*-mesylate 15 spontaneously decomposed to a red-brown oily solid.

4aβ-Methyl-5β,8aα-dihydroxy-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one Ethylene Ketal 5-Methanesulfonate (16).—In a similar reaction, 20.0 g (82.7 mmol) of crystalline trans diol 14 was allowed to react with 7.0 ml (10.5 g, 92 mmol, 11% excess) of methanesulfonyl chloride in 250 ml of pyridine over a period of 45 hr. After a similar extraction sequence, 26.03 g of pale red oil was obtained. After decolorizing, an ethyl acetate solution afforded 9.52 g of white crystals: mp 98–103°; recrystallization from ethyl acetate–pentane sharpened the melting point range to 109–110°; pmr (CCl$_4$) τ 9.04 (s, 3, angular Me), 7.06 (s, 3, mesylate Me), 6.10 (s, 4, ketal Hs), and 5.20 (m, 1, C-5 H); ir (CCl$_4$) 3500, 3050, 1360, 1220, 1175, 930, and 870 cm^{-1}.

Anal. Calcd for C$_{14}$H$_{24}$O$_6$S: C, 52.45; H, 7.54; S, 9.98. Found: C, 52.34; H, 7.53; S, 9.72.

The crude mixture of ketal diols (13 and 14) (104 g, 440 mmol) was dissolved in 500 ml of pyridine and treated with 35 ml (52.5 g, 460 mmol) of methanesulfonyl chloride. After standing overnight at room temperature, the mixture was poured into 500 ml of ice water and extracted with methylene chloride (three 600-ml portions). The extracts were washed with two 300-ml portions of water, dried over magnesium sulfate, and evaporated under vacuum to give 128 g (94.2%) of red oil that cooled to a glass. The pmr spectrum showed that the product was a mixture of 15 and 16 in a ratio of 54:46.

(E)-6-Methyl-Δ^6-1,3-cyclodecenedione 3-Ethylene Ketal (17).
A.—A lump of potassium metal weighing 897 mg (22.9 mmol) was washed with benzene to remove the protective mineral oil and added to 300 ml of dry distilled *tert*-butyl alcohol (distilled from CaH$_2$). The mixture was heated at reflux under dry nitrogen until the metal completely dissolved. Then the solution was cooled and maintained at 40–42° while a solution of 7.31 g (22.8 mmol) of hydroxy mesylate 15 in 200 ml of *tert*-butyl alcohol was added dropwise over a period of 20 min. A pale yellow color and a fine white precipitate (potassium methanesulfonate) formed at once. The mixture was stirred under nitrogen at 42–52° over a period of 2 hr. Then 400 ml of ice water was added, and the mixture was saturated with salt and extracted with ether (three

400-ml portions). The extracts were washed with saturated salt solution (two 100-ml portions) and then with water (one 100-ml portion), dried, and evaporated to yield 4.54 g (88.8%) of yellow oil. Distillation from an oil-jacketed still at 35–55° (0.2 mm) gave 3.98 g of colorless oil.

B.—The trans-fused isomer 16 (9.13 g, 28.4 mmol), in 200 ml of *tert*-butyl alcohol was added over a period of 12 min to a solution of potassium *tert*-butoxide prepared from 1.11 g (28.4 mmol) of potassium metal dissolved in 250 ml of *tert*-butyl alcohol. The resulting yellow mixture was stirred at 38–44° for 6 hr and then allowed to stand at room temperature overnight. After work-up, 5.75 g (90.5%) of white oil was obtained that solidified when chilled. Recrystallization from petroleum ether (bp 30–60°) gave white crystals with a melting point range of 50.5–51.5°: pmr (CCl₄) τ 9.04 (d, 3, *J* = 1 Hz, C-6 Me), 7.33 (s, 2, C-2 Hs), 6.02 (s, 4, ketal Hs), and 4.88 (m, 1, vinyl H); ir 1715, 1430, 1355, 1075, and 940 cm⁻¹.

Anal. Calcd for C₁₃H₂₀O₃: C, 69.61; H, 8.99. Found: C, 69.50; H, 8.73.

C.—A solution of potassium *tert*-butoxide was prepared under nitrogen by dissolving 15.45 g (396 mmol) of potassium in 1500 ml of dry *tert*-butyl alcohol at reflux. Ten hours was required to completely dissolve the metal. The solution was cooled to 30°, and a solution of 127 g of crude hydroxy mesylate (15 and 16) in 800 ml of warm *tert*-butyl alcohol was added dropwise over a period of 1.5 hr. The temperature of the dark brown solution was maintained at 44° for 12 hr. Ice water (1000 ml) was added, the mixture was saturated with salt and extracted with ether (three 500-ml portions), and the extracts were washed (three 200-ml portions of saturated NaCl and three 200-ml portions of water) until no longer basic to pH paper, dried, and evaporated to give 83.59 g of brown oil (94.0%), the nmr spectrum of which was that of the desired keto ketal. The crude product was dissolved in ether and eluted through 320 g of activity I neutral alumina. Early fractions gave 43.1 g of water-white oil from which 17.6 g of crystals precipitated. Later fractions were distilled at reduced pressure to give 11.35 g of oil that displayed a slightly different nmr spectrum from the pure ketal ketone. Partial cracking to the dione may have occurred, as a small amount of ether-insoluble liquid was produced during the distillation.

A small sample of crystalline 17 (200 mg) in ethanol (2 ml) was treated with 8 ml of 2,4-dinitrophenylhydrazine reagent (0.134 mmol/ml).[16] After 15 min, the initially yellow precipitate darkened to deep red. Filtration and recrystallization afforded 165 mg of brick-red solid, mp 136–138°. On the basis of its empirical formula and its spectra, this derivative has been assigned the pyrazole structure 26. The pmr spectrum (in CDCl₃)

26
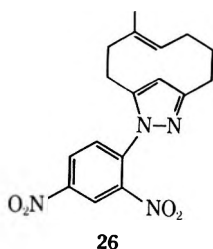
had bands at τ 8.10 (broad s, 3, vinyl Me), 6.41 (m, 1, vinyl H), 3.68 (s, 1, pyrazole ring H), and 2.10 (m, 3, benzene ring Hs); ir (CHCl₃) 3200, 3030, 1625, 1600, 1525, 1430, 1350, 1330, 930, and 835 cm⁻¹.

Anal. Calcd for C₁₇H₁₈N₄O₄: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.64; H, 5.37; M, 16.40.

8-Methyl-3-hydroxy-Δ⁷-cyclodecenone Ethylene Ketal (18).— To a stirring slurry of 2.39 g of lithium aluminum hydride in 100 ml of dry ether was added over a period of 25 min 5.13 g of crystalline ketal ketone 17 in 50 ml of ether. The mixture was stirred for 20 hr at room temperature and then treated carefully with ethyl acetate. When the excess hydride had been destroyed, 10 ml of 10% potassium hydroxide solution was added and the mixture was refluxed for 30 min to precipitate the lithium and aluminum salts. After filtration, drying, and evaporation a pale yellow oil was obtained that crystallized when triturated with petroleum ether. The white solid, which weighed 4.45 g, mp

43.5–45.5°, was recrystallized from ether–pentane to give the analytical sample: mp 46–46.5°; pmr (CCl₄) τ 8.33 (d, 3, *J* = 1 Hz, vinyl Me), 6.10 (s, 4, ketal Hs), and 4.75 (m, 1, C-3 H); ir (CCl₄) 3580, 1120, 1060, and 955 cm⁻¹.

Anal. Calcd for C₁₃H₂₂O₃: C, 68.99; H, 9.80. Found: C, 68.69; H, 9.89.

8-Methyl-3-hydroxy-Δ⁷-cyclodecenone (19).—A solution of 2.711 g of crystalline hydroxy ketal 18 in 150 ml of reagent grade acetone was treated with 2.70 g of oxalic acid dihydrate. The resulting mixture was heated at reflux for 15 hr. The solution was concentrated to 50 ml on a rotary evaporator, neutralized with 35 ml of saturated sodium bicarbonate solution, diluted with ether, and separated. The aqueous layer was extracted with ether (two 80-ml portions) and the organic layers were combined, washed with salt water (two 50-ml portions), and dried over magnesium sulfate. Removal of solvent at reduced pressure yielded 2.109 g (96.3%) of yellow oil. A portion was distilled through a Hickman still, pot temperature 150–180° (0.2 mm), head temperature 100–110°. An ir spectrum of the distillate showed no dehydration. The rest of the crude material was triturated with ether–pentane, chilled on Dry Ice, and scratched to induce crystallization. The collected solid melted at 41.5–43°: pmr (CCl₄) τ 8.28 (s, 3, vinyl Me), 6.06 (m, 1, C-3 H), and 4.75 (m, 1, vinyl H); ir (CCl₄) 3500, 1700, 1120, 1065, and 1050 cm⁻¹.

Anal. Calcd for C₁₁H₁₈O₂: C, 72.49; H, 9.95. Found: C, 72.58; H, 10.19.

8-Methyl-3-acetoxy-Δ⁷-cyclodecenone (20).—A solution of 5.01 g of crystalline hydroxy ketone 19 in 50 ml of acetic anhydride was treated with 2.0 ml of pyridine and allowed to react at room temperature for 22.5 hr. The solvent was removed by rotary evaporation at 60°, and the residue was diluted with 3 ml of pentane. Chilling induced crystallization, and 3.39 g (55.1%) of colorless crystals were collected in two crops. Recrystallization from pentane gave the analytical specimen: mp 42–43°; pmr (CCl₄) τ 8.28 (d, 3, *J* = 1 Hz, vinyl Me), 8.09 (s, 3, acetoxy Me), 4.87 (m, 1, C-3 H) and 5.98 (m, 1, vinyl H), 4.87 (1 H multiplet); ir (CCl₄) 1720, 1705, 1350, 1225, 1020 cm⁻¹.

Anal. Calcd for C₁₃H₂₀O₃: C, 69.61; H, 8.99. Found: C, 69.24; H, 9.02.

8-Methyl-Δ²,Δ⁷-cyclodecadienone (5) and 8-methyl-Δ³,Δ⁷-cyclodecadienone (21).—A solution of 1.80 g of keto acetate 20 in 80 ml of triethylamine was warmed at 53° for 21 hr. The solvent was removed by rotary evaporation and the residue was dissolved in 50 ml of ether. A white flocculent precipitate (polymer?) formed that was removed by filtration. The ether solution was washed with water (two 20-ml portions), dried, and evaporated to give 1.08 g (82.0%) of yellow oil. The infrared spectrum indicated a mixture of α,β- and β,γ-unsaturated ketones: 1665 and 1630 and 1695 cm⁻¹, respectively. The ultraviolet spectra confirmed the presence of a conjugated enone: λ_max 265 nm. When the crude product was injected onto any one of several vpc columns, several products were formed from thermal rearrangement. The two major components were identified as tricyclic ketone 6 and bicyclic enone 22.[10]

Photocyclization of Dienone 5.—Solutions of dienone 5 (0.1% in ether or hexane) were irradiated through a Pyrex filter in a 15-ml capacity quartz apparatus, under helium, with water cooling. Small samples were periodically withdrawn for uv analysis. Within 15 min, the absorption band at 265 nm had disappeared. After evaporation of the solvent, the volatile photoproduct was analyzed by glpc (150 ft × 0.01 in. Carbowax 20M) and by pmr spectroscopy. Quantitative glpc analysis showed that tricyclic ketones 6, 7, and 8 had been produced in the following yields: ether, 6:7:8 = 32:3:22; hexane, 6:7:8 = 60:6:30. In the experiment in ether, there were several additional, unidentified products. The hexane experiment was much cleaner, giving very little of any other product. Since we had found that dienone 5 undergoes thermal rearrangement upon attempted glpc analysis,[10] we also analyzed the crude photoproduct by pmr spectroscopy. Although the angular methyl singlets of tricyclic ketones 6 and 8 coincide when measured in CCl₄ or CHCl₃, they are separated by approximately 3 Hz in pyridine. Pmr analysis of the crude photoproduct in pyridine corroborated the glpc analysis.

In another experiment,[17] a 0.1% solution of dienone 5 in a 20:1 mixture of hexane–piperyline was irradiated in the same manner.

(16) R. I. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1956.

(17) This experiment was kindly performed by Dr. Ronald H. Starkey.

Pmr analysis showed that the 6:8 ratio in this experiment was 9:1.

cis,anti,cis-6-Methyltricyclo[5.3.0.0^{2,6}]decan-3-one (6) and *cis,syn,cis*-6-Methyltricyclo[5.3.0.0^{2,6}]decan-3-one (7).—These tricyclic ketones, needed for comparison with the photoproducts, were prepared as previously outlined.[4]

1-Methyltricyclo[4.4.0.0^{2,7}]decan-8-one (8).—This tricyclic ketone was prepared as previously outlined.[18]

(18) C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

Stereochemistry of Alkaline Cleavage of Some Phospholanium Salts[1]

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The geometric isomers of 1-benzyl-3-methyl-1-phenylphospholanium bromide (5a and 5b) undergo hydroxide cleavage of benzyl which is accompanied by complete retention of configuration at phosphorus yielding pure isomers of 3-methyl-1-phenylphospholane 1-oxide (6a or 6b). Cleavage of either isomer of 1,3-dimethyl-1-phenylphospholanium bromide (7a and 7b) produces identical mixtures of cis and trans isomers of 1,3-dimethylphospholane 1-oxide (2). Base decomposition of the 3-methyl-1,1-diphenylphospholanium salt 8 yields a mixture of about equal parts of 6a and 6b.

The cis or the trans phosphonium salt of 1 will undergo cleavage with aqueous sodium hydroxide to afford the corresponding oxide 2 with complete retention of configuration at phosphorus.[2] Recently it was shown that the cis and trans isomers of 1-benzyl-4-methyl-1-phenylphosphorinanium bromide (3) are decomposed under the same conditions into nonidentical mixtures of the isomeric phosphine oxides (4).[3] For the latter study, the 1-phenyl rather than the 1-methyl compounds were chosen because of synthetic convenience.[4] Since Trippett, *et al.*,[5] report that the base cleavage results of *cis*-1-benzyl-1-phenyl-2,2,3,4,4-pentamethylphosphetanium bromide (11) are different from those of the trans isomer where the two compounds differ *configurationally*, we were cautioned against the assumption that the *substitutionally* different 1-methyl-1-benzyl- and 1-phenyl-1-benzylphospholanium salts (1 and 5, respectively) would behave identically. We were therefore prompted to investigate the stereochemistry of cleavage of the cis and trans isomers of 5 in order to determine conclusively that the dissimilarity in stereochemical behavior between 1 and 3 is indeed due to ring size and *not* differences in substitution at phosphorus.

The stereochemistry of base cleavage of the geometrical isomers of 7 was also investigated to enable a more confident correlation to be made between leaving group ability and stereochemistry of cleavage. Of the two stereochemical studies reported in the phospholane series, benzyl[2] and trichlorosiloxide[6] as leaving

groups give, respectively, retention and inversion of configuration. We have now found that phenyl as a leaving group from *cis*- or *trans*-7 provides identical mixtures of oxides. Since phosphine oxides are known to be configurationally stable toward aqueous sodium hydroxide,[2,3,6,7] it is plausible to assume that *cis*- and *trans*-7 lead to a common intermediate preceding phosphine oxide (2) formation. In fact, we have found that, when either *cis*-7 or *trans*-7 are separately treated with 0.5 equiv of sodium hydroxide under cleavage conditions, the remaining undecomposed salt can be shown to consist of an approximate 1:1 mixture of cis and trans salts. Treatment of either *cis*- or *trans*-7 with a trace of base at room temperature, however, was insufficient to produce stereomutation at phosphorus to a detectible extent.

1, R = CH$_2$Ph
2, R = O$^-$

3, R = CH$_2$Ph
4, R = O$^-$
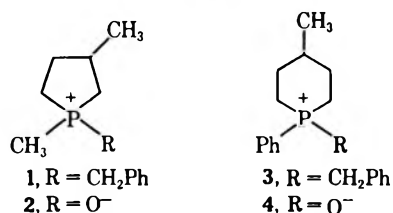
Scheme I summarizes the stereochemical outcome of cleavage reactions of the five pure *P*-phenylphospholanium salts covered by this study.

The retention of configuration at phosphorus for 1 and 5 may be accounted for by (a) equatorial loss of benzyl *via* the conjugate base[8] of the initially formed phosphorane (9),[2] and/or (b) apical loss of benzyl from the conjugate base of 10 after an incomplete pseudorotational process.[9] If formed, 10 would be expected to lose benzyl *via* its conjugate base.[8] Placement of oxygen in the equatorial position of 10 can be

(1) This investigation was supported by National Science Foundation Grants No. GP-7407 and GP-25479. A preliminary account of a portion of this work is found in ref 6.

(2) (a) K. L. Marsi, *Chem. Commun.*, 846 (1968); (b) *J. Amer. Chem. Soc.*, **91**, 4724 (1969).

(3) K. L. Marsi and R. T. Clark, *J. Amer. Chem. Soc.*, **92**, 3791 (1970).

(4) G. Maerkl, *Angew. Chem., Int. Ed. Engl.*, **2**, 620 (1963).

(5) J. R. Corfield, J. R. Shutt, and S. Trippett, *Chem. Commun.*, 789 (1969). The *cis*- and *trans*-1-benzyl-1-methyl-2,2,3,4,4-pentamethylphosphetanium bromides are also reported to give nonidentical products on base cleavage. However, it should be noted that the results of this work are at variance with the work of Cremer, *et al.* (ref 12), on the same systems and under similar conditions.

(6) W. Egan, G. Chauviere, K. Mislow, R. T. Clark, and K. L. Marsi, *Chem. Commun.*, 733 (1970).

(7) K. F. Kumli, W. E. McEwen, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **81**, 3805 (1959). These references give a representative, but not exhaustive, list of such examples.

(8) W. E. McEwen in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1965, Chapter 1.

(9) K. Mislow, *Accounts Chem. Res.*, **3**, 321 (1970).

SCHEME I[a]

cis-5   OH⁻ →   cis-6   + PhCH₃

trans-5   OH⁻ →   trans-6   + PhCH₃

trans-7   OH⁻ →   cis:trans~1:1   OH⁻ ←   cis-7

8   →   cis-6   +   trans-6   + C_6H_6
       50 ± 5%   50 ± 5%
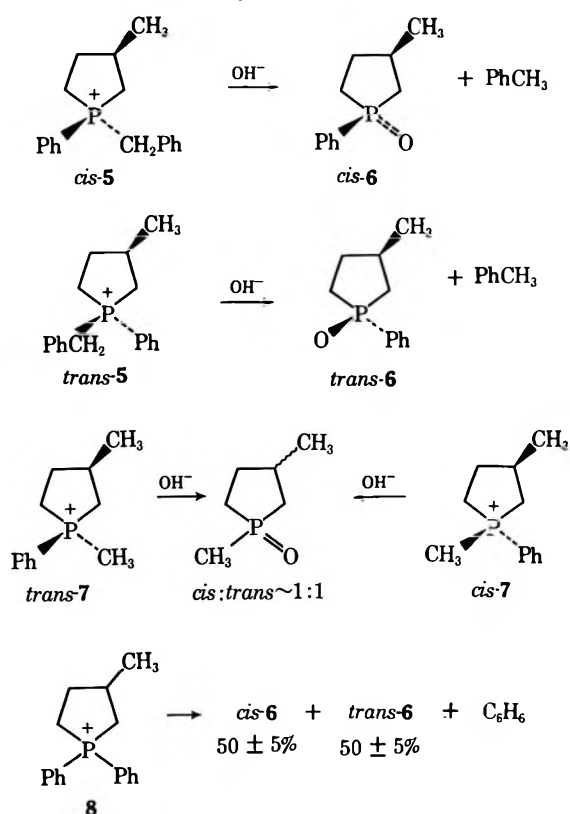
[a] Prefixes cis and trans relate the stereochemistry of the *C*-methyl and the P substituent surviving the cleavage reaction.

defended since it is the less electronegative oxide oxygen which occupies that position in the reactive intermediate.[10]

9   ⇌   10

9   OH⁻ ↘   ↙ OH⁻   10
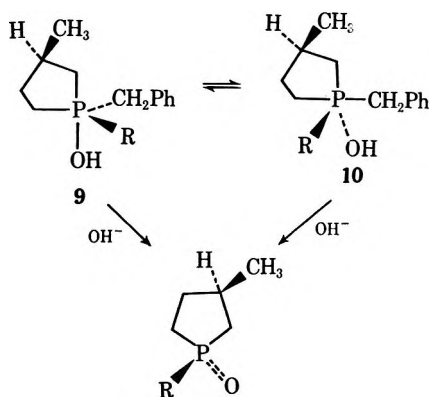
The phosphonium salts 1 and 5 evidently represent examples for which the energy barrier between the initially formed phosphorane (9) and one or more pseudorotational transformations leading to an equilibrium mixture of phosphoranes (and hence to a mixture of diastereomeric oxides) is higher than stereospecific loss of a benzyl group by mechanism a and/or b above. However, in the case of alkaline cleavage of either the cis or trans isomer of 7 the reaction energetics are apparently reversed. For the cleavage of 7 the attainment of equilibrium among pseudorotational forms of the phosphorane intermediate leading to identical mixtures of both isomers of 2 must occur more rapidly than stereospecific loss of phenyl. This

(10) B. R. Ezzell, *J. Org. Chem.*, **35**, 2426 (1970).

is a reasonable explanation since benzyl is known to be a superior leaving group to phenyl.[11]

Similar observations have been made by others in the phosphetanium series. For example, either the cis or trans isomer of 11 is reported to give identical mixtures of phosphetane 1-oxides (13)[12] when treated with aqueous sodium hydroxide, whereas cleavage of the analogous ethoxy isomers (12) occurs stereospecifically with retention of configuration at phosphorus.[13] A rigorous explanation of these phenomena has been advanced by Mislow.[9,13]

11, R = CH₂Ph   14   15
12, R = OC₂H₅
13, R = O⁻
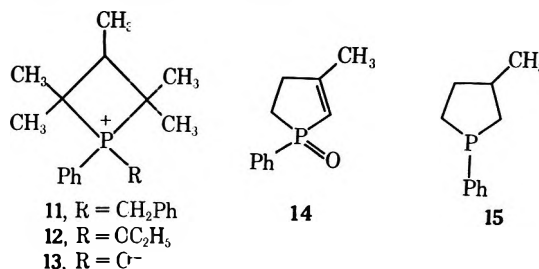
The outcome of the cleavage of 8 may be explained in the same manner as for 7, although, of course, the mixture of oxides could be accounted for without invoking pseudorotation since the phosphorus atom of 8 is achiral. If the latter is true, which seems unlikely in view of the cleavage results of 7, the methyl group exerts no perceptible steric effect on the stereochemistry of cleavage of 8.

Synthetic Procedures.—The ring system of 5 and 7 was constructed by the McCormack cycloaddition reaction[14] of isoprene with phenyldichlorophosphine. After hydrolysis of the adduct, the resulting 3-methyl-1-phenyl-2-phospholene 1-oxide (14)[15] was hydrogenated in the presence of a palladium-on-carbon catalyst, the reduction occurring completely stereospecifically within the limits of pmr detection (about ±5%) to give an oxide (6a), mp 60–61°, bp 115–125° (0.05 mm). This oxide was reduced with phenylsilane, a conversion known to occur stereospecifically with retention of configuration.[2b] The phosphine (15a) thus obtained was quaternized with benzyl bromide or methyl bromide to yield the corresponding phosphonium salts 5a, mp 171.5–172°, or 7a, mp ca. 100°, a reaction known to proceed with retention of configuration at phosphorus.[16] Cleavage of 5a with refluxing 1 N NaOH yielded 6a having the same characteristics as the oxide obtained by hydrogenation of 14. The diastereomeric phosphonium salts 5b, mp 179.5–180°, and 7b, mp 158.5–159°, were obtained by treatment of the oxide 6a with hexachlorodisilane[6,17] followed by careful fractional distillation on a spinning band column of the resulting mixture of diastereomeric phosphines and quaternization of the final fraction with benzyl bromide or methyl bromide.

(11) J. Meisenheimer and L. Lichtenstadt, *Ber.*, **44**, 356 (1911); G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 2342 (1929).

(12) S. E. Cremer, R. J. Chorvat, and B. C. Trivedi, *Chem. Commun.*, 769 (1969).

(13) K. E. DeBruin, G. Zon, K. Naumann, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7027 (1969).

(14) W. B. McCormack, U. S. Patents 2,663,736 and 2,663,737 (Dec 22, 1953); L. D. Quin in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, Chapter 3.

(15) L. D. Quin and T. P. Barket, *Chem. Commun.*, 914 (1967); L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).

(16) L. D. Quin and T. P. Barket, *J. Amer. Chem. Soc.*, **92**, 4303 (1970).

(17) K. Naumann, G. Zon, and K. Mislow, *ibid.*, **91**, 7012 (1969).

Retention of configuration for the base cleavage of the pure salts **5a** and **5b** was established by reduction with phenylsilane of the oxides resulting from cleavage of these salts, quaternizing the resulting phosphine with benzyl bromide, and demonstrating by pmr and mixture melting points the identity of the salts thus obtained with samples of the salts submitted to cleavage. Mixtures of oxides **2a** and **2b** ensuing from the cleavage of pure **7a** and **7b** were analyzed by pmr with advantage being taken of the differences in chemical shifts of the benzyl protons of the diastereomeric salts obtained from benzylation of the phosphine mixtures yielded by phenylsilane reduction of the oxide mixtures. The mixture of oxides **6a** and **6b**, derived from the base decomposition of pure **8**, was similarly analyzed.

Compound **8** was prepared as an eventual alternate route to **15b**, but hexachlorodisilane reduction of **6a** was found to provide a more straightforward access to this compound. The preparation of **8** was accomplished by an adaptation of the Maerkl procedure.[4] The bromide salt of **8** proved to be an intractable oil; therefore, the crystalline hexafluorophosphate[18] salt was prepared, purified, and cleaved.

Experimental Section

General.—Melting points were determined on a Thomas–Hoover 6406-K melting point apparatus in capillary tubes (sealed with silicone grease for hygroscopic materials) and are uncorrected; boiling points are also uncorrected. ¹H nmr spectra were measured at 60 MHz with a Jeolco C-60H spectrometer. Operations involving trivalent phosphorus compounds were conducted in a nitrogen atmosphere. Moisture-reactive halophosphines and very hygroscopic phosphine oxides were handled in a dry atmosphere. Solvents used were dried and/or distilled prior to use. Stereoisomeric compounds used were estimated to be more than 95% isomerically pure as evidenced by nmr analysis.

3-Methyl-1-phenyl-2-phospholene 1-Oxide (14).—This compound was prepared according to the procedure given in ref 15.

3-Methyl-1-phenylphospholane 1-Oxide (6a).—To 121.5 g (0.633 mol) of **14** in 150 ml of absolute ethanol was added 5 g of 5% palladium on carbon, the mixture was hydrogenated in a Paar hydrogenator for 20 hr at 45–49 lb in.⁻², the solution was filtered, the solvent was removed, and the residue was distilled *in vacuo* to yield 122.5 g of a viscous oil, bp 115–125° (0.05 mm), which upon standing formed a crystalline, hygroscopic solid: mp 60–61°; nmr (CCl₄, TMS) δ 1.1 (d, *J* = 6 Hz, CCH₃), 1.23–2.67 (m, ring protons), 7.23–8.1 (m, PC₆H₅).

Anal. Calcd for C₁₁H₁₅PO: C, 68.02; H, 7.79. Found: C, 68.10; H, 8.04.

3-Methyl-1-phenylphospholane (15a).—To 8.0 g (0.041 mol) of **6a** in a 25-ml flask cooled to 0°, 4.43 g (0.041 mol) of phenylsilane was added *via* pipet in a nitrogen atmosphere. The reaction mixture was warmed to 60°. Upon cessation of effervescence, the phosphine was distilled to yield 6.75 g of **15a**: bp 49–51° (0.01 mm); nmr (CCl₄, TMS) δ 1.1 (d, *J* = 6 Hz, CCH₃), 1.23–2.67 (m, ring protons), 7.23–8.1 (m, PC₆H₅).

1-Benzyl-3-methyl-1-phenylphospholanium Bromide (5a).—To 3.1 g (0.0174 mol) of pure **15a** in 10 ml of benzene, 6 g (0.0350 mol) of benzyl bromide dissolved in 10 ml of benzene was added dropwise with stirring. White crystals began separating almost immediately. The mixture was refrigerated overnight and yielded 6.5 g of crude **5a**, mp 169–169.8°. Recrystallization from 1:15 EtOH–EtOAc produced 5.15 g of pure **5a**: mp 171.5–172°; nmr (D₂O, DSS) δ 1.1 (d, *J* = 5.3 Hz, CCH₃), 1.4–3.2 (m, ring protons), 3.95 (d, *J* = 15 Hz, PCH₂Ph), 6.9–7.4 (m, PC₆H₅), 7.4–7.9 (m, PCC₆H₅).

Anal. Calcd for C₁₈H₂₂BrP: C, 54.37; H, 7.02. Found: C, 54.29; H, 7.24.

Reaction of 5a with Sodium Hydroxide.—To a 25-ml flask

containing 2.0 g (0.0057 mol) of **5a** was added 11.5 ml of 1 *N* sodium hydroxide. The resulting solution was refluxed gently for 20 hr. Early formation of an organic layer indicated that the reaction was probably complete within the first 2 hr. Vpc analysis of the organic layer removed by azeotropic distillation showed only toluene. The aqueous residue was saturated with potassium hydroxide and extracted with chloroform. The chloroform solution was concentrated and the residue was distilled at bp 120° (0.01 mm), yielding 0.8 g of liquid **6a**: nmr (CCl₄, TMS) δ 1.1 (d, *J* = 6 Hz, CCH₃), 1.23–2.67 (m, ring protons), 7.23–8.1 (m, PC₆H₅). **6a** was reduced with phenylsilane as described above and the distillate, **15a**, bp 62–68° (0.02 mm), quaternized with benzyl bromide to give crystals identical with **5a** in melting point and nmr.

3-Methyl-1-phenylpholane (15b).—To 26.4 g (0.136 mol) of **6a** in 100 ml of benzene was added dropwise with stirring at room temperature 47.5 g (0.176 mol) of hexachlorodisilane in 50 ml of benzene.[6] Upon completion of the addition, the resulting solution was refluxed for an additional 0.5 hr and cooled to 0° and 100 ml of 30% sodium hydroxide was added dropwise with stirring over a period of 2 hr. A precipitate of white polymeric material separated during this addition. The liquid phase was decanted in a glove bag under nitrogen, the precipitate was washed several times with benzene, and the benzene extracts were combined. After drying over anhydrous sodium sulfate, benzene was removed and the residual phosphine was distilled at reduced pressure, providing 14.55 g of a mixture of **15a** and **15b**, bp 84–88° (0.2 mm). Although attempts to achieve vpc separation of the two isomers were not successful, considerable enrichment was accomplished by use of a Nestor-Faust Auto Annular Teflon spinning band column. Five fractions totaling 13.25 g were collected at 51° (0.02 mm) over a period of 14 hr: nmr (neat, TMS), **15a**, δ 0.93 (d, *J* = 6 Hz); **15b**, δ 0.81 (d, *J* = 6 Hz). Nmr showed that the last three fractions, totaling 6.2 g, were very highly enriched in **15b**.

1-Benzyl-3-methyl-1-phenylphospholanium Bromide (5b).—**15b** (3.53 g), obtained as the last fraction of the preceding experiment, was quaternized in benzene with benzyl bromide in a glove bag under dry nitrogen. Crystals formed immediately and were allowed to stand overnight. The crude crystals (5.7 g), mp 165.5–167°, were recrystallized four times from EtOH–EtOAc to a constant melting point of 179.5–180°. Nmr analysis of the final product indicated complete absence of **5a**: nmr (D₂O, DSS) δ 1.1 (d, *J* = 5.3 Hz, CCH₃), 1.4–3.2 (m, ring protons), 3.98 (d, *J* = 15 Hz, PCH₂Ph), 6.9–7.4 (m, PC₆H₅), 7.4–7.9 (m, PCC₆H₅).

Anal. Calcd for C₁₈H₂₂PBr: C, 61.89; H, 6.32. Found: C, 62.17; H, 6.45.

Reaction of 5b with Sodium Hydroxide.—**5b** (1.96 g) was made to react with 1 *N* sodium hydroxide under the same conditions as described above for **5a**. **6b** (0.52 g), bp 120° (0.01 mm), was obtained: nmr (CCl₄, TMS) δ 1.16 (d, *J* = 5.3 Hz, CCH₃), 1.4–2.6 (m, ring protons), 7.4–8.3 (m, PC₆H₅). Reduction with phenylsilane gave **15b**, bp 62–68° (0.02 mm), which was quaternized with benzyl bromide to provide a crystalline material identical in melting point and nmr with **5b**.

1,3-Dimethyl-1-phenylphospholanium Bromide (7a).—To 7.6 g (0.082 mol) of methyl bromide dissolved in 25 ml of dry benzene was added dropwise with stirring 3.65 g (0.0206 mol) of **15a** in 10 ml of benzene. The reaction mixture was stored in the refrigerator, and the very hygroscopic crystals subsequently were removed in a glove bag under dry nitrogen, yielding 5.45 g (0.0199 mol) of **7a**. The salt oiled out upon attempted recrystallization from dry ethanol and was finally recrystallized from ethyl acetate. Due to its tenacity for traces of water, a sharp melting point could not be obtained for this compound, mp 100–130° (mainly at 100°). However, the nmr spectrum was completely consistent with an isomerically pure salt: nmr (D₂O, DSS) δ 1.26 (d, *J* = 4.5 Hz, CCH₃), 2.3 (d, *J* = 14.3 Hz, PCH₃), 1.5–2.1 (m, ring protons), 7.5–8.1 (m, PC₆H₅).

Anal. Calcd for C₁₂H₁₈PBr·0.15H₂O: C, 52.24; H, 6.69. Found: C, 52.10; H, 6.46.

1,3-Dimethyl-1-phenylphospholanium Bromide (7b).—**15b** (6.2 g, 0.0348 mol), from spinning band fractionation of **15a** and **15b**, was added dropwise to a stirred solution of 13.3 g (0.14 mol) of methyl bromide in 25 ml of benzene; the slightly hygroscopic crystals were filtered in a glove bag, yielding 8.7 g (0.318 mol) of isomerically impure **7b**, mp 155–158°. Seven recrystallizations from 1:5 EtOH–EtOAc yielded pure **7b**, mp 158.5–159°. Nmr analysis verified the absence of **7a**: nmr (D₂O, DSS) δ 1.26

(18) D. B. Denney and S. M. Felton, *J. Amer. Chem. Soc.*, **90**, 183 (1968).

(d, J = 4.5 Hz, CCH₃), 2.3 (d, J = 14.25 Hz, PCH₃), 1.5–2.1 (m, ring protons), 7.5–8.1 (m, PC₆H₅).

Anal. Calcd for C₁₂H₁₈PBr: C, 52.76; H, 6.64 Found: C, 52.51; H, 6.85.

Reactions of **7a** and **7b** with sodium hydroxide were carried out as for **5a**. Vpc analysis of the organic layer obtained by azeotropic distillation of the reaction mixture showed only benzene to be present. Distillation of the oxide mixture derived from 2.0 g of **7a** or **7b** gave 0.40 and 0.45 g, respectively, both of bp 70–80° (0.1 mm) and mp 45–57°. The nmr spectra were identical in every respect: nmr (CCl₄, TMS) δ 1.07 (d, J = 6 Hz, CCH₃), 1.13 (d, J = 5.3 Hz, CCH₃), 1.5 (d, J = 12.5 Hz, PCH₃), 1.3–2.6 (m, ring protons). The two oxide mixtures were separately reduced with phenylsilane and quaternized with benzyl bromide, each giving a phosphonium salt mixture of mp 154–164°. Comparison of the nmr spectra of these mixtures with those of known mixtures prepared from pure cis and trans isomers of 1-benzyl-1,3-dimethylphospholanium bromide[2] showed the unknown mixtures to consist of about equal quantities of the two isomers.

Synthesis of 3-Methyl-1,1-diphenylphospholanium Hexafluorophosphate (8).—A mixture of 50.0 g (0.217 mol) of 1,4-dibromo-2-methylbutane and 40.2 g (0.108 mol) of tetraphenyldiphosphine in 270 ml of o-dichlorobenzene was added dropwise to 750 ml of refluxing o-dichlorobenzene over a period of 3 hr. The solvent (800 ml) was removed by distillation, the residue was extracted with water, and the water extract was evaporated, leaving 41.7 g of a dark, acidic oil, from which crystals could not be obtained. A 27-g portion of this oil was dissolved in water and titrated to neutrality with 70 ml of 1 *N* sodium bicarbonate, extracted with ether and then with chloroform. Evaporation of the chloroform extract yielded 16 g of a dark glassy oil of which a 7-g portion was dissolved in water and to which a saturated solution of 4.0 g of potassium hexafluorophosphate was added.[18] The gummy precipitate formed was triturated with ether. Repeated recrystallizations from absolute ethanol gave a compound of mp 135.5–136.5°.

Anal. Calcd for C₁₇H₂₀P₂F₆: C, 51.01; H, 5.05. Found: C, 51.08; H, 5.31.

Reaction of 8 with Sodium Hydroxide.—Sodium hydroxide (1*N*, 12 ml) was added to a 25-ml flask containing 2.0 g (0.006 mol) of **8**. The resulting suspension (the hexafluorophosphate salt is only slightly soluble in H₂O) was refluxed gently for 43 hr. The oxide mixture was worked up as described for the cleavage reaction of **5a** and yielded 0.62 g of a mixture of oxides **6a** and **6b**, bp 120–125° (0.05 mm). Following previously outlined procedures, the oxide mixture was reduced with phenylsilane and quaternized with benzyl bromide to give a 93% yield of salt mixture of mp 150–156°. Comparative nmr analysis using known mixtures of pure **5a** and **5b** showed this to be an approximately equal mixture of the two isomers.

Base-Catalyzed Isomerization of 7a and 7b.—To a 2-ml pear-shaped flask was added 200 mg (733 μmol) of pure **7a**, 15 mg (375 μmol) of sodium hydroxide, and 0.3 ml of water. The reaction mixture was refluxed gently for a period of 16 hr. The ³¹P nmr spectrum (220 MHz Varian spectrometer) of the reaction mixture provided two peaks of equal area at +95.84 and +96.00 ppm (relative to trimethyl phosphite) as compared with a control solution (100 mg of **7a** in 0.3 ml of water) which showed a single peak at +95.78 ppm.

An identical study was conducted on a mixture of **7a** and **7b** (27% **7a** and 73% **7b**). After base treatment the ³¹P nmr spectrum showed two signals of equal intensity at +95.94 and +96.09 ppm as compared with the untreated mixture (100 mg salt mixture in 0.3 ml water), which showed signals at +95.86 and +96.01 ppm in the ratio of 27:73, respectively.

Thujopsene Rearrangements. The Ring System *via* Methyl Group Migration[1-3]

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Under mild acid conditions, cis-thujopsene rearranges to 1,4,11,11-tetramethylbicyclo[5.4.0]undeca-3,7-diene (**3**). This diene when treated with 0.02 *M* perchloric acid in refluxing acetic acid rearranges to tricyclic olefin **4** whose structure was proved by degradation and by partial synthesis. This extensive rearrangement which involves a ring closure and two methyl group migrations finds its thermodynamic driving force in the low free energy of the product. The mechanism of the rearrangement is discussed and its relationship to the rearrangement of caryophyllene to neoclovene is noted.

Part A

Under mild acidic conditions, 0.02 *M* perchloric acid in aqueous dioxane, the equilibrating cyclopropylcarbinyl and homoallyl cations from cis-thujopsene (**1**) and widdrol (**2**), respectively, are irreversibly converted

by a ring enlargement and angular methyl group migration to the diene **3**.[2] This diene is the major product formed under these acidic conditions and it is stable for long periods, but it is slowly consumed in another reaction. This latter process has now been evaluated by studying the rearrangement of cis-thujopsene under more vigorous reaction conditions, namely, 0.02 *M* perchloric acid in refluxing acetic acid. Under these conditions the rearrangement proceeded past diene **3** and a completely different set of reaction products was formed. Three hydrocarbons in a ratio of 14:4:3 were obtained and in this paper the structure of the major hydrocarbon and its mechanism of formation will be discussed.

Through a series of degradation and synthetic steps, the structure of the major hydrocarbon was established as the tricyclic olefin **4**. A possible pathway for the rearrangement of cis-thujopsene (**1**) to this olefin **4** may conveniently involve the diene **3** as an intermediate.

(1) This work was partially supported by Grant GP-8700, National Science Foundation.

(2) For previous papers in this study see (a) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 2675 (1964); (b) W. G. Dauben and L. E. Friedrich, *ibid.*, 1735 (1967); (c) W. G. Dauben and E. I. Aoyagi, *Tetrahedron*, **26**, 1249 (1970); (d) W. G. Dauben, L. E. Friedrich, P. Oberhänsli, and E. I. Aoyagi, *J. Org. Chem.*, **37**, 9 (1972).

(3) This work appeared in the Abstracts, IUPAC 5th International Symposium on the Chemistry of Natural Products, F-13, London, July 8–13, 1968, p 296.

(4) National Science Foundation Predoctoral Fellow.

Since **3** is not stable indefinitely in acid, the stronger acid conditions used in this present study simply increased the rate of isomerization of **3** to **4**. In this isomerization, protonation of the lesser hindered trisubstituted double bond would generate the tertiary

3 → → **5**

6 → **7** → **8** →

4
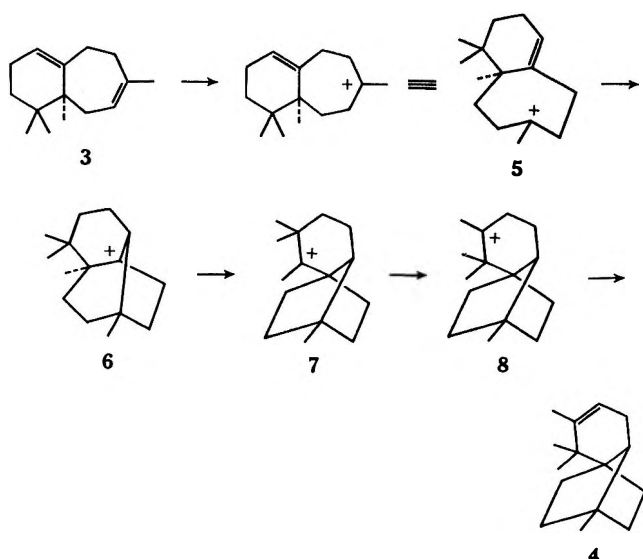
cation **5** which may cyclize to yield the bridgehead cation **6**. This strained cation may undergo a Wagner–Meerwein rearrangement to afford ion **7**, possessing a bicyclo[2.2.1]heptane nucleus and the unstrained tertiary carbonium ion. A subsequent methyl migration would yield the cation **8** which upon loss of a proton would give rise to the tricyclic olefin **4**. The mechanistic pathway employing this series of intermediates does not necessarily provide, step by step, the driving force for the overall rearrangement; the intermediates' only function is to provide a route to the final product whose low free energy content provides the driving force for the overall reaction. Undoubtedly, the major feature of this transformation which accounts for the low free energy content of the tricyclic olefin **4** relative to the diene **3** is the net transformation of one carbon–carbon double bond into two carbon–carbon single bonds. The energy for this conversion may be estimated from the heats of combustion of cyclohexane and cis-2-hexene as 18–20 kcal/mol.[5] This decrease in thermochemical energy must compensate for the increased strain of a bicyclo[2.2.1]heptane nucleus, a strain which is estimated to be 14–18 kcal/mol.[6] The additional differential elements of ring strain, non-bonded atom interactions, torsional strain, and entropy considerations cannot be accurately evaluated.

It is of interest to note that the reaction pathway by which caryophyllene (**9**) is thought to be converted under acidic conditions into neoclovene (**11**) is similar to that postulated for the formation of the tricyclic olefin **4**.[7] In caryophyllene, protonation, ring closure, and rearrangement can give a bicyclo[3.2.1]octyl bridgehead cation **10** which upon subsequent rearrangement leads to neoclovene (**11**) with a bicyclo[2.2.1]hep-

tane ring system. In this specific series of transformations, however, the driving force for the reaction should be much larger than in the thujopsene series because of the strain in the four-membered ring of caryophyllene.

9 → **10** → **11**
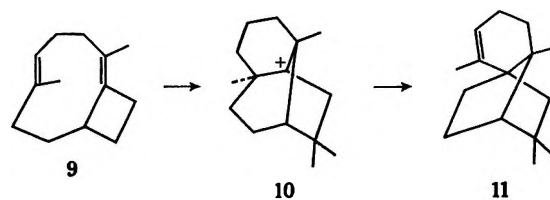
Part B

cis-Thujopsene (**1**) was allowed to react with 0.02 *M* perchloric acid in refluxing acetic acid and the major hydrocarbon formed was purified on a preparative scale by chromatography using a silver nitrate impregnated silica gel column.

Quantitative elemental analysis of the major hyd ⌣ carbon **4** indicated that the compound was isomeric with the starting cis-thujopsene. The nmr spectrum of the hydrocarbon showed one vinyl proton, one vinyl methyl group, and three quaternary methyl groups. The presence of a trisubstituted double bond also was indicated by a maximum at 192 nm,[8] and that this was the only unsaturated linkage in the molecule was indicated by a molar extinction coefficient of 8860. Therefore, since the starting thujopsene was tricyclic with one double bond, this new olefin **4** must also be tricyclic.

Hydroboration of the tricyclic olefin **4** gave alcohol **12**, which was oxidized to the tricyclic ketone **13** with Jones reagent. Alumina chromatography of this ketone gave an isomeric ketone **14**, indicating that hydroboration of the olefin **4** gave an alcohol with an axially oriented methyl group at C-3. The carbonyl absorption in the infrared spectra of ketone **13** and **14** (1713 and 1710 cm^{-1}) established that the double bond of the olefin **4** was most likely located endocyclic in a six-membered ring. Furthermore, a one-proton quartet at δ 2.67 and a two-proton multiplet at δ 1.98–2.31 in the nmr spectrum of the ketone **14** tentatively identify C-2 as a quaternary carbon atom and C-5 as a methylene group.

It was of importance to establish that the alumina chromatography of ketone **13** induced only epimerization and not a skeletal rearrangement. Therefore, the ketone **14** was reduced with LiAlH$_4$ to alcohol **15**. This alcohol was identical with the minor alcohol obtained from the LiAlH$_4$ reduction of epoxide **16**, prepared from the reaction of olefin **4** with m-chloroperbenzoic acid. The major alcohol **17** of this latter reaction was formed by the 1,2-diequatorial opening of the oxirane ring, a result often found with epoxides which are of the secondary–tertiary type.[9] These positional and stereochemical assignments were confirmed by reduction of ketone **13** with LiAlH$_4$ to yield the hydroboration alcohol **12** and a new equatorial tricyclic alcohol **18** in 48 and 33% yield, respectively. Finally, oxidation of alcohol **15** with Jones reagent gave the more stable ketone **14**. The selective formation of alcohol **12** and epoxide **16** from hydroboration and from epoxidation

(5) F. D. Rossini, K. S. Pitzer, R. C. Arnett, R. M. Braun, and G. C. Pimentel, "Selective Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburgh, Pa., 1953, pp 451, 455.

(6) K. B. Wiberg, private communication.

(7) W. Parker, R. A. Raphael, and J. S. Roberts, *J. Chem. Soc. C*, 2634 (1969).

(8) R. A. Micheli and T. H. Applewhite, *J. Org. Chem.*, **27**, 345 (1962).

(9) C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, p 636; N. A. LeBel and G. G. Ecke, *J. Org. Chem.*, **30**, 4316 (1965).
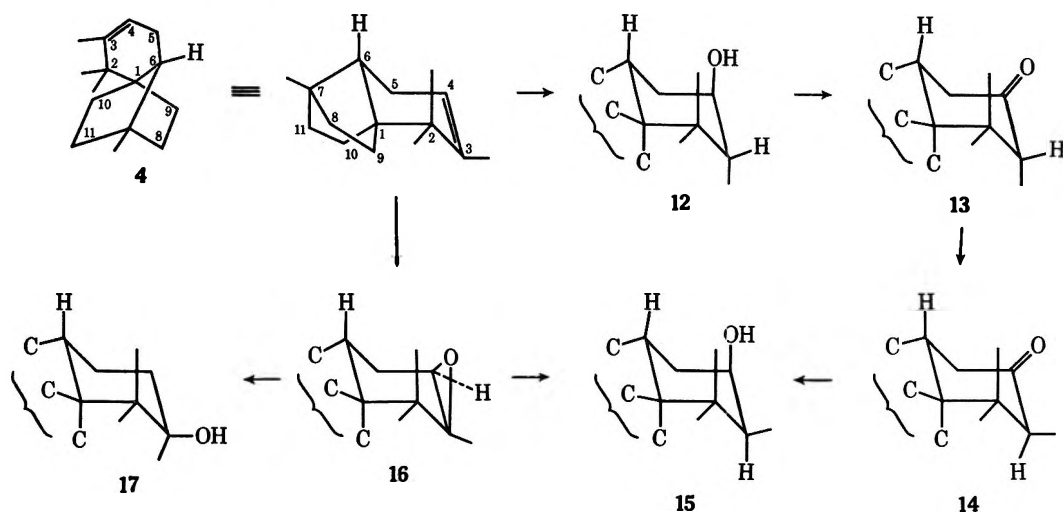
established that the C-8,9-dimethano bridge of the tricyclic hydrocarbon hinders the bottom side of the double bond more than the pseudoaxially oriented methyl group on C-2 hinders the topside of the double bond.

With the substitution and the surroundings of the double bond established, the unsaturated linkage was cleaved *via* the formation of the diol **19** with osmium tetroxide and scission to keto aldehyde **20** with lead tetraacetate. The nmr spectrum of **20** indicated the presence of a methyl ketone (3 H, singlet, δ 2.04) confirming the presence of a vinyl methyl group in the olefin **4**. Also, the one-proton aldehyde triplet (*J* = 1.5 Hz, δ 9.63) confirmed the presence of two protons on C-5.
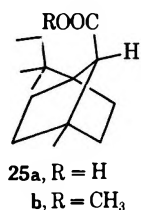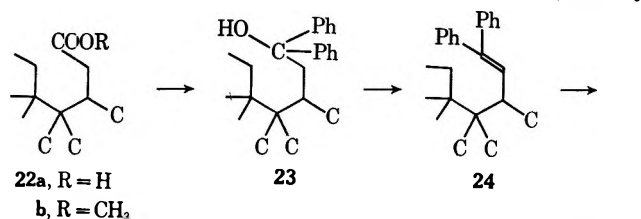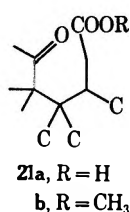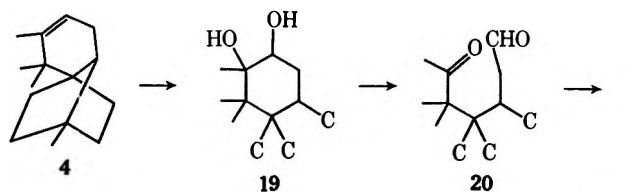
The keto aldehyde **20** was oxidized to the keto acid **21a** with potassium permanganate. This keto acid and its methyl ester **21b** failed to react with 2,4-dinitro-

phenylhydrazine and with trifluoroperacetic acid. This lack of reactivity is characteristic of highly hindered ketones[10] and is in agreement with the placement of the *gem*-dimethyl group at C-2. The keto ester **21b** was reduced under forcing Wolff–Kishner conditions[11] and the acid **22a** after conversion to its methyl ester **22b** was degraded according to the Barbier–Wieland method. Treatment of **22b** with phenylmagnesium bromide yielded the carbinol **23** which was dehydrated to give the diphenyl olefin **24**. The nmr spectrum of **24** showed a one vinyl proton doublet at δ 6.03 coupled to another one-proton doublet at δ 2.07 (*J* = 11 Hz). The absence of further splitting of the allylic proton at δ 2.07 indicated that the neighboring carbons must be quaternary. Oxidation of **24** gave bicyclic acid **25a**.

Summarizing the data available, a partial structure **26** can be formulated. In this structure, three of the
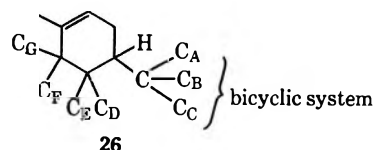
unallocated carbon atoms labeled A–G must be methyl groups, two of which are geminal. The location of these latter two methyl groups was achieved by examination of the changes in chemical shifts of the methyl groups with the various chemical transformations. From the data in Table I, it is seen that the presence of

TABLE I
CHEMICAL SHIFTS OF METHYL GROUPS

Compd	Methyl shifts, δ
21a	1.19, 1.19, 0.93
21b	1.15, 1.15, 0.88
27b	1.27, 1.17, 0.88
22a	0.94, 0.88, 0.83
22b	0.88, 0.88, 0.88

a carbonyl function at C-3 (**21a**, **21b**, **27b**) causes two methyl groups to resonate at an average field of δ 1.19. Removal of the oxygen function (**22a**, **22b**) shifts the average absorption of these two methyl groups upfield by an average of δ 0.3. Such a large shift is commen-

(10) G. Büchi, R. E. Erickson, and H. Wakabayashi, *J. Amer. Chem. Soc.*, **83**, 927 (1961).

(11) D. H. R. Barton, D. A. Ives, and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

surate with two methyl groups substituted at C-2, next to the carbonyl function. In agreement with this assignment is the finding that when the keto ester **21b** was oxidized with concentrated nitric acid in acetic acid, the half ester **27a** was formed. The presence of a geminal methyl group accounts for the stopping of the oxidation with the loss of only one carbon atom.

This placement of the two geminal methyl groups permitted expansion of the partial structure of the tricyclic olefin to **28**. There remained to be located two

27a, R = H
b, R = CH₃

28
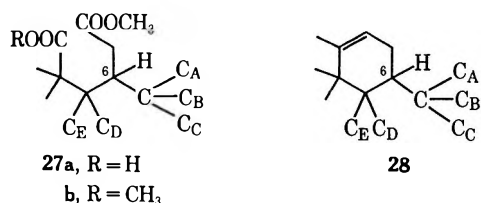
methylene groups and a quaternary methyl group. If the logical assumption is made that no cyclopropane ring would remain under the strong acidic conditions utilized for the formation of the tricyclic olefin **4**, only the structures **29–31** can be formulated for this hydro-

29   30   31
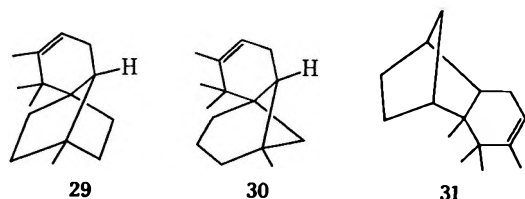
carbon. The evidence required to differentiate these three structures was provided by bromination followed by dehydrobromination of the tricyclic olefin to give the optically active conjugated diene **32**, $[\alpha]$D $-73°$.

32
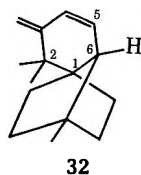
The structure and placement of this new chromophore was readily established by its spectral properties. When the diene was allowed to react with potassium *tert*-butoxide in dimethyl sulfoxide, the starting material was recovered but was partially racemized, $[\alpha]$D $-28°$.[12] To account for these facts, in **29** carbons 1, 2, and 6 must be in a potential symmetry plane of the molecule whereas C-5 is not in the plane. The base-catalyzed removal of the hydrogen on C-6 to yield a carbanion would provide a mechanism to racemize diene **32**. These symmetry demands would not be met by dienes derived from **30** and **31** since base treatment of them would yield only starting material unchanged in optical purity or an isomer, not a mirror image. Thus, compilation of all of these data permits structure **29** to be assigned to the tricyclic olefin **4**.

In view of the extensive structural changes undergone in this acid-catalyzed rearrangement of thujopsene, an unequivocal synthesis of the degradation acid **25a** was

performed. Birch reduction of the known *p*-(*tert*-amyl)toluene (**33**)[13] gave **34** which upon reaction with potassium *tert*-butoxide in dimethyl sulfoxide[14] gave a 86:14 mixture of conjugated diene **35** and nonconjugated diene **34**. Distillation of the crude reaction product gave material of 90% purity, a purity sufficient to permit its use in the Diels–Alder reaction with maleic anhydride. The adduct **36** was obtained in high yield; the anhydride was hydrogenated and hydrolyzed to yield the cis diacid **37**. Reaction of **37** with lead tetraacetate under the Grob oxidative bisdecarboxylation conditions gave olefin **38** in 65% yield. The two vinyl protons of **38** exhibited an AB quartet pattern in the nmr spectrum at δ 6.13 and 5.88 ($J =$ 8 Hz).

Hydroboration of olefin **38** gave the two alcohols **39** and **40**. A minor ($\sim$10%) product of the reaction was a polar product; this material is postulated to be the boronic acid **45** because its infrared spectrum shows oxygen–hydrogen stretching absorptions and a strong band at 1365 cm⁻¹, characteristic of oxygen–boron stretching absorption.[15] Upon standing, this polar major product no longer exhibited the oxygen–hydrogen absorptions in the infrared. These data are consistent with the known facile trimerization of a boronic acid to a boroxine (**46**).[16] This new product when allowed to react with excess alkaline hydrogen peroxide under reflux in tetrahydrofuran solution gave the major alcohol **40** in good yield. The structure assigned to the major alcohol is in analogy with the finding that the major product from the hydroboration of 3,3-dimethyl-1-cyclohexene is the lesser hindered 3,3-dimethylcyclohexan-1-ol.

The mixture of alcohols **39** and **40**, as well as each individual alcohol, was oxidized with Jones reagent to yield ketones **41** and **42**. Each ketone showed an nmr resonance attributable to the methylene protons adjacent to the carbonyl group. The methylene hydrogens of the major ketone **42** absorb at higher field (δ 1.95) than the hydrogens of the minor ketone **41** (δ 2.07). It is to be expected that the *tert*-amyl group would be more shielding than a methyl group,[17] and the structure assignments are in agreement with this postulate.

Both ketones **41** and **42** upon oxidation by selenium dioxide in *o*-xylene gave the diketone **43a**. Upon reaction with *p*-toluenesulfonylhydrazine, the diketone yielded a keto tosylhydrazone **43b** which in chloroform solution was filtered through basic alumina to give the crystalline diazo ketone **43c**. Irradiation through Corex of an aqueous tetrahydrofuran solution of **43c** gave an almost quantitative yield of ketene **44**. The ketene was converted into the bicyclic acid **25a** upon reaction with aqueous acid. The acid and its methyl ester were identical with the bicyclic acid and methyl ester obtained from the degradation of the tricyclic olefin **4**.

Several properties of this acid warrant comment.

(12) The incomplete racemization may be a consequence of the excessive strain in the bond angle C-1:C-6:C-7 which retards the formation of a trigonal carbon at C-6 (see J. P. Schaefer and D. S. Winberg, *J. Org. Chem.*, **30**, 2635 (1961), and references cited therein).

(13) G. W. Hearne, T. W. Evans, V. W. Buls, and C. G. Schwarzer, *Ind. Eng. Chem.*, **47**, 2311 (1955).

(14) W. G. Dauben and P. Oberhänsli, *J. Org. Chem.*, **31**, 315 (1966).

(15) C. N. R. Rao, "Chemical Applications in Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 283.

(16) M. F. Lappert, *Chem. Rev.*, **56**, 959 (1956).

(17) In a related bicyclic system, it has been reported that bridgehead alkyl substituents of several 7-oxabicyclo[2.2.1]heptanes diamagnetically shield neighboring protons; see S. Seltzer, *J. Amer. Chem. Soc.*, **87**, 1534 (1965).

33 34 35 36

40 + 39 ← 38 ← 37

42 + 41 → 43a, R = O
            b, R = NNHTs
            c, R = N₂
→ 44 → 25a, R = H
       b, R = CH₃

45 46 40
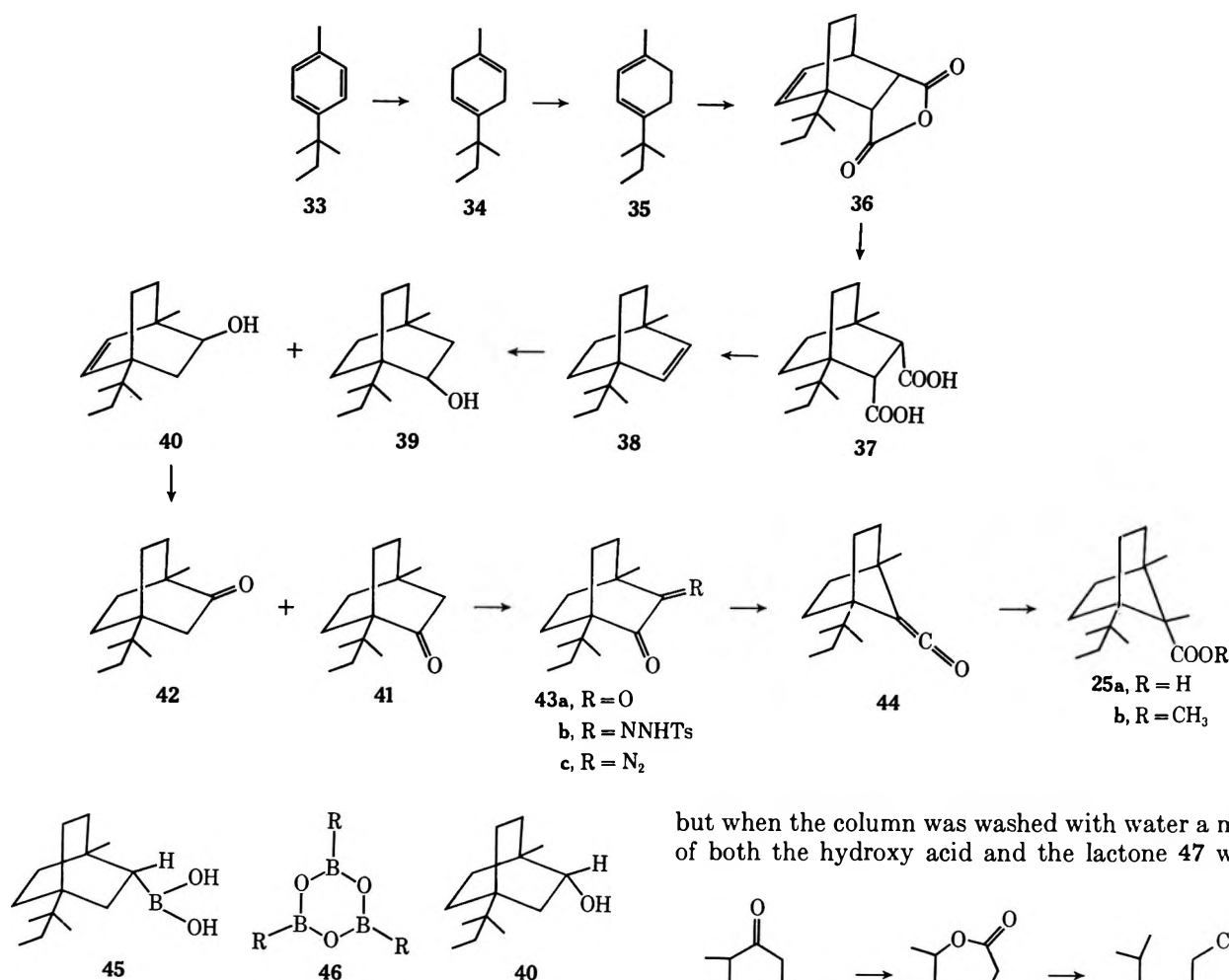
The acid could not be extracted from an ethereal solution with half-saturated aqueous potassium bicarbonate solution. The related methyl ester **25b** could not be hydrolyzed with 1.8 M potassium hydroxide in 90% aqueous methanol at reflux temperature in 7 hr. Also, the ketone **44** was stable to 1 M aqueous potassium hydroxide at room temperature. In contrast, 7-norbornylcarboxylic acid and 7-norbornylketene are much more reactive compounds.[18] These and other facts suggest that the bridgehead alkyl substituents of **25a** abnormally hinder the vicinity of the functional group. This conclusion is confirmed by the low acidity of acid **18a**, $pK^*_{MCS} = 8.44$.[19,20] Secondary aliphatic carboxylic acids are generally more acidic by a factor of ten than the value found for **25a**.[21] This abnormal hindrance by the bridgehead substituents undoubtedly also causes the experimental difficulties found in the hydroboration reaction.

In the course of these degradational studies, a variety of methods was studied in order to ascertain the best way to cleave the unsaturated ring. Of these many reactions the Baeyer–Villiger oxidation of ketone **14** is worthy of special mention. The lactone **47** formed by reaction of **14** with trifluoroperacetic acid was hydrolyzed on an alumina column to its related hydroxy acid

but when the column was washed with water a mixture of both the hydroxy acid and the lactone **47** was ob-

14 47 48
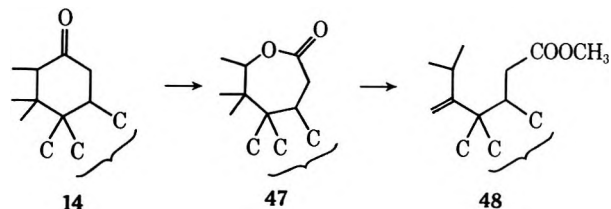
tained. Treatment of the lactone with a solution of boron trifluoride etherate in methanol yielded the rearranged, dehydrated ester **48** whose structure was readily established by its nmr spectrum.

Finally, it is of interest to note the ease of rearrangement of the bicyclo[2.2.1]heptane system. The bromo ester **49**, a 5:3 diastereomeric mixture, was prepared from the acid **22a** in the standard fashion. Dehydrohalogenation of **49** in quinoline gave the unexpected fragmentation product **50** which was characterized on

49 50
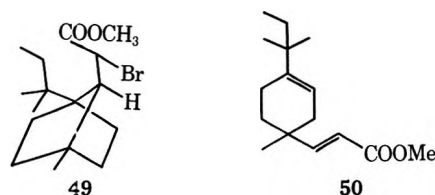
the basis of spectral data. Since the material was optically inactive, the overall elimination of the hydrogen bromide and the ring scission appears to be a stepwise process rather than a concerted fragmentation reaction.[22]

(18) P. Yates and R. J. Crandall, *J. Amer. Chem. Soc.*, **88**, 1292 (1966).

(19) The acidity of acid **18a** was kindly measured by Professor W. Simon, Eidg. Techn. Hochschule, Zurich.

(20) P. F. Sommer, V. P. Arya, and W. Simon, *Tetrahedron Lett.*, 18 (1960); P. F. Sommer, C. Pascual, V. P. Arya, and W. Simon, *Helv. Chim. Acta*, **46**, 1734 (1963).

(21) P. F. Sommer and W. Simon, "Scheinbare Dissociations Konstanten," Band II, Juris–Verlag, Zurich, 1961.

(22) It has been reported by J. Martin, W. Parker, and R. H. Raphael [*J. Chem. Soc. C*, 343 (1967)] that attempts to dehydrate the β-hydroxy ester found in the Reformatsky reaction with 1,5-dimethylbicyclo[3.3.1]nonan-9-one gave the expected unsaturated ester in only 3% yield.

This abnormal dehydrohalogenation reaction was further investigated using α-bromobicyclo[2.2.1]heptane-7-acetic acid and its methyl ester. Using boiling quinoline, conditions under which the desired α,β-unsaturated ester was shown to be stable, the bromo ester yielded only a small amount of reductively debrominated ester; the major amount of starting material was destroyed. Using potassium *tert*-butoxide in *tert*-butyl alcohol, again no dehydrobromination occurred, the only reaction being transesterification to give the *tert*-butyl ester. When the bromo acid was treated with potassium *tert*-butoxide in toluene, a small yield of unsaturated acid was obtained. However, when these conditions were used with the bromo acid found in the degradation study, again only decomposition occurred.

Experimental Section

Infrared spectra were run either with a Perkin-Elmer Model 137 or Model 237 spectrometer. Ultraviolet spectra were recorded with either a Perkin-Elmer Model 202 spectrometer or, when necessary, a nitrogen-flushed Beckman Model DK2-A spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer. Optical rotations at the sodium D line were calculated from the rotations at 546 and 578 nm with the Drude equation; these latter rotations were measured with a Zeiss LEP-A2 photoelectric polarimeter with a 10-cm cell length. Mass spectra were obtained with a modified C.E.C. 21-103C mass spectrometer at the University of California, Berkeley.

Melting points were measured with a Büchi Schmelzpunktbestimmungsapparat; they were obtained in unevacuated melting point tubes and are uncorrected. Boiling points are uncorrected. Vapor phase chromatographies were conducted on a Wilkins Aerograph Model A90-P with a helium carrier gas flow rate between 50 and 150 ml/min, depending on the need. Combustion analyses and molecular weight determinations were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

All extractions were washed with acid or base until neutral, water, and saturated salt solution, and dried over anhydrous sodium sulfate. The solvent was removed either by distillation at reduced pressure or rotary evaporation. All infrared spectra and nmr spectra were taken in CCl₄ unless otherwise noted.

Perchloric Acid–Acetic Acid Treatment of *cis*-Thujopsene.—A mixture of 65.0 g (0.318 mol) of natural *cis*-thujopsene, 500 ml of glacial acetic acid, and 1.00 ml of 70% aqueous perchloric acid was heated under reflux for 48 hr under an atmosphere of nitrogen in the absence of light. The dark brown reaction mixture was diluted with water and extracted with hexane to yield 64.7 g of a brown, fluid oil. Glpc analysis of the crude product, using 3-keto-10-methyl-Δ^4-octalone as an internal standard, indicated that the major product of the reaction was formed in 37% yield (20% DEGS, firebrick, 150°, 5 ft × 0.25 in.) which composed *ca.* 70% of the area of the chromatogram. Infrared and nmr spectral analyses of the crude product did not indicate the formation of acetate or alcoholic products. Extensive polymerization of the product was reduced by a rapid flash distillation of the mixture preceding the slow spinning band distillation. Nevertheless, the major product was not separated from other isomeric impurities in the mixture.

The major product was purified best on a preparative scale by chromatography. Accordingly, 1.00 g of the crude reaction product was chromatographed on 30.0 g of 22% silver nitrate impregnated on silica gel (height to diameter 9.7). The major product was eluted by hexane in fractions 6 through 9 (23 ml/fraction), yield 262 mg, 88% pure (23%). A pure sample of the tricyclic olefin 4 was obtained by preparative glpc (20% DEGS, firebrick, 150°, 5 ft × 0.25 in.): bp 112° (9 mm); [α]²³D −46° (*c* 1.41, CHCl₃); uv max (cyclohexane) 192 nm (ε 8860); nmr δ 5.20 (m, 1), 1.67 (sharp multiplet, 3), 1.00 (s, 3), 0.97 (s, 3), 0.87 (s, 3).

Anal. Calcd for C₁₅H₂₄ (204.34): C, 88.16; H, 11.84. Found: C, 87.94; H, 11.64.

Hydroboration of Tricyclic Olefin 4.—A solution of 10.0 g of tricyclic olefin 4 (70% pure, 0.034 mol) in 125 ml of tetrahydro-

furan, cooled at 0° in an atmosphere of nitrogen, was allowed to react with 0.084 mol of diborane. The reaction mixture allowed to warm to room temperature and stand for an additional 5 hr; then 32 ml of 3 *M* aqueous sodium hydroxide and 32 ml of 30% aqueous hydrogen peroxide were added. The mixture was stirred at 40° for 1 hr, and processed in the standard fashion to yield 10.90 g of residual colorless oil, which was chromatographed on 200 g of Woelm neutral alumina (activity II). Elution with 650 ml of hexane yielded 6.8 g of a fluid oil. The remainder of the product was eluted with 400 ml of diethyl ether to yield 4.0 g of a viscous oil which slowly solidified. The first fraction was rechromatographed to obtain a total of 6.8 g of a waxy solid (90%). Analysis of the original hexane fraction by glpc (20% DEGS, Chromosorb P, 160°, 5 ft × 0.25 in.) indicated that the impurities in the starting material did not react with diborane. An analytical sample of the tricyclic alcohol 12 was prepared by slow recrystallization of a portion of the product from hexane: mp 67–70°; [α]²³D +3° (*c* 6.81, CHCl₃); uv at 210 nm (cyclohexane) (ε 75); nmr δ 3.96 (broad multiplet, 1), 1.17 (s, 3), 1.01 (d, 3, *J* = 7 Hz), 0.98 (s, 3), 0.86 (s, 3).

Anal. Calcd for C₁₅H₂₆O (222.36): C, 81.02; H, 11.79. Found: C, 81.26; H, 11.57.

Oxidation of Tricyclic Alcohol 12.—A solution of 4.04 g (0.018 mol) of crude tricyclic alcohol 12 and 125 ml of acetone was cooled to −20° and 5.0 ml (1.1 equiv) of Jones reagent was slowly added. The mixture was stirred for 15 min, 2 ml of isopropyl alcohol was added, and then the mixture was worked up to yield the crude tricyclic ketone 13: 3.90 g (98%); [α]²³D −110° (*c* 7.02, CHCl₃); ir 1713 cm⁻¹; nmr δ 2.00–2.37 (m, 3), 1.08 (d, 3, *J* = 7 Hz), 1.03 (s, 3), 0.98 (s, 3), 0.83 (s, 3).

A 2,4-dinitrophenylhydrazone derivative was prepared and recrystallized from methyl alcohol, orange crystals, mp 172–183°.

Anal. Calcd for C₂₁H₂₈N₄O₄ (400.46): C, 62.98; H, 7.05; N, 13.99. Found: C, 62.80; H, 6.98; N, 13.90.

The crude tricyclic ketone 13 was filtered through 190 g of Woelm neutral alumina (activity II) with benzene to yield 3.33 g (84%) of tricyclic ketone 14 which solidified after several weeks. A small portion of the material was purified by preparative glpc (20% DEGS, Chromosorb P, 160°, 5 ft × 0.25 in.): mp 40°; [α]²³D −52° (*c* 7.07, CHCl₃); ir 1710 cm⁻¹; nmr δ 2.67 (q, 1, *J* = 7 Hz), 1.98–2.31 (m, 2), 0.96 (s, 3), 0.89 (d, 3, *J* = 7 Hz), 0.88 (s, 3), 0.78 (s, 3).

Anal. Calcd for C₁₅H₂₄O: C, 81.76; H, 10.98. Found: C, 81.54; H, 10.91.

A 2,4-dinitrophenylhydrazone derivative was prepared, yellow solid, mp 180.0–180.5°.

Anal. Calcd for C₂₁H₂₈N₄O₄: C, 62.98; H, 7.05; N, 13.99. Found: C, 63.07; H, 6.76; N, 14.28.

Lithium Aluminum Hydride Reduction of Tricyclic Ketone 13.—A mixture of 300 mg (1.37 mmol) of crude tricyclic ketone 13, 1.02 g (27 mmol) of lithium aluminum hydride, and 100 ml of diethyl ether was stirred for 1.5 hr at room temperature; 266 mg of the crude product was chromatographed on 13 g of Woelm neutral alumina (activity II). Benzene (68 ml) eluted 145 mg (48%) of a white solid. An infrared spectrum of the material was identical with the spectrum of tricyclic alcohol 12. An additional 86 ml of benzene and 60 ml of benzene–diethyl ether (95:5) eluted 101 mg (33%) of tricyclic alcohol 18, mp 123–127°. A small portion of the alcohol was recrystallized from hexane: mp 131–132°; [α]²³D −5° (*c* 2.84, CHCl₃); nmr δ 3.75–4.20 (broad m, 1) 1.03 (s, 3), 1.01 (d, 3, *J* = 7 Hz), 0.98 (s, 3), 0.89 (s, 3).

Anal. Calcd for C₁₅H₂₆O: C, 81.02; H, 11.79. Found: C, 81.20; H, 11.50.

Lithium Aluminum Hydride Reduction of Tricyclic Ketone 14.—A mixture of 109 mg (0.49 mmol) of crude tricyclic ketone 14, 100 mg (2.64 mmol) of lithium aluminum hydride, and 15 ml of diethyl ether was stirred for 13 hr at room temperature; 115 mg (100%) of the crude product was filtered through a small amount of Woelm neutral alumina (activity II) in diethyl ether to yield tricyclic alcohol 15: [α]²³D −5° (*c* 2.07, CHCl₃); nmr δ 3.79 (m, 1), 1.00 (d, 3, *J* = 7 Hz), 0.96 (s, 6), 0.75 (s, 3).

Anal. Calcd for C₁₅H₂₆O: C, 81.02; H, 11.79. Found: C, 81.26; H, 11.57.

Treatment of Tricyclic Olefin 4 with *m*-Chloroperbenzoic Acid.—A solution of 100 mg (0.49 mmol) of 85% *m*-chloroperbenzoic acid in 3 ml of chloroform was slowly added to a solution of 100 mg (0.49 mmol) of greater than 95% pure tricyclic olefin 4 in 2.0 ml of chloroform at 0°. After 13 hr at 0°, the mixture was poured into half-saturated aqueous potassium bicarbonate and

processed to give a residual light yellow oil, 121 mg, which was filtered through 3 g of Woelm neutral alumina (activity II) with hexane to yield 106 mg (99%) of tricyclic epoxide 16: $[\alpha]^{23}D$ −42° (c 0.4367, CHCl₃); nmr δ 2.90 (m, 1), 1.16 (s, 3), 0.94 (s, 6), 0.88 (s, 3).

Anal. Calcd for C₁₅H₂₄O: C, 81.76; H, 10.98. Found: C, 81.70; H, 10.88.

Lithium Aluminum Hydride Reduction of Tricyclic Epoxide 16.—A mixture of 3.50 g (15.9 mmol) of tricyclic epoxide 16, 1.498 g (39.4 mmol) of lithium aluminum hydride, and 125 ml of ethylene glycol dimethyl ether was heated under reflux for 49.5 hr under nitrogen. The mixture was allowed to react for an additional three days at room temperature. After work-up, 3.67 g of a residual oil was chromatographed on 180 g of Woelm neutral alumina (activity II). Hexane (1115 ml) eluted 457 mg of unidentified material which was not investigated. Hexane-benzene (330 ml, increasingly greater amounts of benzene) and finally benzene (1210 ml) eluted two alcohols. Infrared and nmr spectra of the first alcohol, 650 mg (18%), were identical with the spectra of tricyclic alcohol 15. Jones oxidation of this material afforded tricyclic ketone 14, as determined by infrared and nmr spectroscopy. The second alcohol solidified after several weeks to yield 1.432 g (41%) of tricyclic alcohol 17: mp 46–50°; $[\alpha]^{23}D$ +9° (c 2.69, CHCl₃); nmr δ 1.33 (s, 3), 1.04 (s, 3), 0.95 (s, 3), 0.85 (s, 3).

Anal. Calcd for C₁₅H₂₆O: C, 81.02; H, 11.79. Found: C, 80.89; H, 11.62.

Treatment of Tricyclic Olefin 4 with Osmium Tetroxide.—A mixture of 3.34 g (16.3 mmol) of 90% pure tricyclic olefin 4, 175 ml of diethyl ether, 4.17 ml of pyridine, and 4.24 g (16.7 mmol) of osmium tetroxide was allowed to react at room temperature in the absence of light for 1 month (later it was found, 1 week was sufficient); the brown tacky crude osmylate was dissolved in 175 ml of diethyl ether, and reduced with 2.40 g (63 mmol) of lithium aluminum hydride (20 hr). The reaction mixture yielded 4.53 g of a viscous yellow oil which was chromatographed on 175 g of Woelm neutral alumina (activity II). Elution with benzene-diethyl ether (increasingly greater amounts of diethyl ether) yielded 2.13 g of an unidentified oil: nmr δ 4.83 (broad singlet), 1.61 (narrow multiplet), 0.97 (s), 0.92 (s). The tricyclic diol 19 was eluted with pure diethyl ether, yield 2.00 g (51%). A small portion of the product was recrystallized from carbon tetrachloride: mp 124–125°; $[\alpha]^{23}D$ +5° (c 2.10, CHCl₃); nmr δ 3.55 (broad m, 1), 1.21 (s, 3), 0.97 (s, 3), 0.94 (s, 3), 0.91 (s, 3).

Anal. Calcd for C₁₅H₂₆O₂: C, 75.58; H, 10.99. Found: C, 75.41; H, 10.76.

Treatment of Tricyclic Diol 19 with Lead Tetraacetate.—A mixture of 1.944 g (8.2 mmol) of tricyclic diol 19, 175 ml of glacial acetic acid, and 8.80 g (19.80 mmol) of lead tetraacetate was stirred under a nitrogen atmosphere at room temperature for 40 hr. The solution was diluted with water and extracted with four portions of diethyl ether. The combined ethereal solutions were processed in the standard manner to yield 1.88 g (98%) of crude bicyclic keto aldehyde 20. A small portion of this material was rapidly oxidized overnight at room temperature in the atmosphere to bicyclic keto acid 21a. Therefore, the crude keto aldehyde was used directly in the next experiment: ir 2713, 1730, 1703 cm⁻¹; nmr δ 9.63 (t, 1, J = 1.5 Hz), 2.04 (s, 3), 1.13 (s, 6), 0.88 (s, 3).

Oxidation of Bicyclic Keto Aldehyde 20.—A solution of 2.280 g (14.4 mmol) of potassium permanganate in 30 ml of water was slowly added to a solution of 1.80 g (7.6 mmol) of crude bicyclic keto aldehyde 20 in 200 ml of acetone. The mixture was stirred for 3 hr at room temperature, diluted with water containing 2.0 ml of concentrated aqueous hydrochloric acid, extracted with ether, and processed to yield 1.08 g (53% yield from tricyclic diol 19) of bicyclic keto acid 21a. A portion of the material was recrystallized twice from hexane: mp 104–105°; $[\alpha]^{23}D$ +4° (c 4.56, CHCl₃); ir 1706 cm⁻¹; nmr δ 2.08 (s, 3), 1.19 (s, 6), 0.97 (s, 3).

Anal. Calcd for C₁₅H₂₄O₃: C, 71.39; H, 9.59. Found: C, 71.50; H, 9.35.

The product failed to react with 2,4-dinitrophenylhydrazine.

Wolff–Kishner Reduction of Bicyclic Keto Acid 21a.—A solution of 249 mg (10.8 mg-atoms) of sodium metal in 5 ml of distilled diethylene glycol was added to 2 ml (63 mmol) of anhydrous hydrazine[11,23] and 300 mg (1.193 mmol) of bicyclic keto acid 21a and heated under reflux for 35 hr. The excess

hydrazine was distilled from the solution until the temperature in the reaction flask reached 200°. The solution was heated under reflux for 27 hr, and worked up to yield 275 mg (98%) of bicyclic acid 22a which slowly solidified. A small portion of the material was recrystallized twice from hexane: mp 87–88°; $[\alpha]^{23}D$ −7° (c 6.15, CHCl₃); ir 1709 cm⁻¹; nmr δ 2.15–2.75 (m, 2), 0.94 (s, 3), 0.88 (s, 3), 0.84 (s, 3), 0.83 (broad t, 3, J = 7 Hz).

Anal. Calcd for C₁₅H₂₆O₂: C, 75.58; H, 11.00. Found: C, 75.37; H, 10.63.

The acid was esterified with diazomethane and the ester was chromatographed on Woelm neutral alumina (activity II). Elution with hexane yielded the pure ester 22b: $[\alpha]^{23}D$ −5° (c 8.13, CHCl₃); ir 1738 cm⁻¹; nmr δ 3.59 (s, 3), 2.13–2.70 (m, 2), 0.88 (s, 9), 0.83 (broad t, 3, J = 7 Hz).

Anal. Calcd for C₁₆H₂₈O₂: C, 76.14; H, 11.18. Found: C, 75.96; H, 10.88.

Treatment of Bicyclic Ester 22b with Phenylmagnesium Bromide.—To a solution of 86 mmol of phenylmagnesium bromide was added 2.20 g (8.71 mmol) of bicyclic ester 22b in 25 ml of dry ether. The solution was heated under reflux for 9 hr and allowed to react at room temperature for an additional 12 hr. The mixture was processed in the standard fashion and the crude 3.99 g of a yellow oil was chromatographed on 123 g of Woelm neutral alumina (activity II). Hexane eluted 554 mg of unreacted ester. Hexane-diethyl ether (85:15) eluted 2.239 g of the crude diphenylcarbinol 23 which was rechromatographed on 46 g of Woelm neutral alumina (activity II) to yield a total of 989 mg (45%) of unreacted ester and 1.390 g (42%) of crude diphenylcarbinol 23. The unreacted ester was allowed to react with an ethereal solution of 85.5 mmol of phenylmagnesium bromide as previously described. Isolation and alumina chromatography yielded a total of 2.001 g (61%) of crude liquid diphenylcarbinol 23: ir 3597, 3044, 1600, 699 cm⁻¹; nmr δ 7.00–7.57 (m, 10), 0.78 (s, 3), 0.73 (s, 3), 0.48 (s, 3).

Anal. Calcd for C₂₇H₃₆O: C, 86.11; H, 9.64. Found: C, 84.80; H, 9.31.

Dehydration of Diphenylcarbinol 23.—A mixture of 1.75 g (4.7 mmol) of diphenylcarbinol 23, 38 ml of water, and 190 ml of acetic acid was heated at 90° on a steam bath for 2.5 hr, and worked up in the usual way to yield 1.55 g of a yellow oil. The material was chromatographed on 85 g of Woelm neutral alumina (activity I) and the diphenyl olefin 24 was eluted with hexane-diethyl ether (95:5): yield 1.418 g (74%); $[\alpha]^{23}D$ +202° (c 2.85, CHCl₃); nmr δ 6.99–7.53 (m, 10), 6.03 (d, 1, J = 11 Hz), 2.07 (d, 1, J = 11 Hz), 1.03 (s, 3), 0.83 (s, 3), 0.78 (s, 3), 0.75 (broad t, 3, J = 7 Hz).

Anal. Calcd for C₂₇H₃₄: C, 90.44; H, 9.56. Found: C, 90.22; H, 9.77.

Treatment of Diphenyl Olefin 24 with Ruthenium Tetroxide.—A mixture of 1.57 g of sodium metaperiodate, 121 mg (0.905 mmol) of ruthenium dioxide, and 30 ml of water was stirred at 0° for 30 min. An additional 1.60 g of sodium metaperiodate was added to the mixture, followed by the dropwise addition of 1.406 g (3.92 mmol) of diphenyl olefin 24 dissolved in 76 ml of cold acetone (distilled from potassium permanganate). A black precipitate formed immediately. During the next 9 hr at room temperature with vigorous stirring, a total of 12.80 g of sodium metaperiodate was added in 1.60-g portions in order to remove the black precipitate whenever it appeared. The excess ruthenium tetroxide was destroyed by the addition of 16 ml of isopropyl alcohol and the mixture was placed in the refrigerator overnight. The mixture was added to an aqueous sodium chloride solution containing 1.0 ml of concentrated aqueous hydrochloric acid and extracted with ether. The combined ethereal extracts were washed with water and half-saturated aqueous potassium bicarbonate. The basic water solution was washed with diethyl ether, acidified with concentrated aqueous hydrochloric acid, and extracted with four portions of diethyl ether. The combined ethereal extracts were worked up to yield 238 mg of benzoic acid. The original base-washed ethereal solution was washed twice with water and dried, and the solvent was removed under reduced pressure. This material was dissolved in hexane and extracted with 50 ml of 1 M aqueous sodium hydroxide and twice with water. The aqueous extracts were combined, washed with hexane, acidified with concentrated aqueous hydrochloric acid, and extracted with four portions of diethyl ether. The combined ethereal solutions were processed to yield 798 mg (91%) of crude bicyclic acid 25a: $[\alpha]^{23}D$ −19° (c 4.83, CHCl₃); ir 1699 cm⁻¹; nmr δ 1.08 (s, 3), 0.88 (s, 3), 0.85 (s, 3), 0.84 (broad t, 3, J = 7 Hz).

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Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.74; H, 10.73.

The methyl ester was prepared with diazomethane: $[\alpha]^{23}D$ +6° (c 6.46, CHCl$_3$); ir 1737 cm^{-1}; nmr δ 3.58 (s, 3), 0.97 (s, 3), 0.80 (s, 3), 0.78 (broad t, 3, J = 7 Hz), 0.77 (s, 3).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.80; H, 10.88.

Bromination–Dehydrobromination of Tricyclic Olefin 4.—A solution of 120 ml of acetic acid, 6.0 g of sodium acetate, and 6.2 ml (113.5 mmol) of bromine was added over a period of 20 min to a solution of 9.108 g (30.8 mmol) of 70% pure tricyclic olefin 4 in 125 ml of diethyl ether at 0°. The reaction mixture was allowed to react for 0.5 hr at 0° and poured into a solution of 10 g of sodium sulfite in water, and the product was extracted with hexane. The 15.42 g of crude dibromide was dissolved in 125 ml of γ-collidine and heated under reflux for 20 min under a N$_2$ atmosphere. The mixture was processed in the usual manner to yield 11.60 g of a brown oil which was chromatographed on 183 g of Woelm neutral alumina (activity II). Elution of the chromatography column with 570 ml of hexane produced 6.91 g of a fluid oil which was further purified by distillation through a 40 cm long platinum spinning band column (Nester–Faust) to yield 4.61 g of 63% pure tricyclic diene 32, yield 46% by vpc analysis (20% DEGS, Chromosorb P, HMDS, 157°, 5 ft × 0.25 in.). A pure sample of tricyclic diene 32 was obtained by preparative glpc: bp 51° (3.0 mm); $[\alpha]^{23}D$ −73° (c 0.2897, CHCl$_3$); uv max (cyclohexane) 229 nm (ε 15,750), 236 (17,200), 245 (10,900); ir 3086, 3012, 1629, 1594, 889 cm^{-1}; nmr δ 6.05 (q, 1, J = 10, 2.5 Hz), 5.60 (broad d, 1, J = 10 Hz), 4.94 (narrow m, 1), 4.85 (broad s, 1), 1.10 (s, 3), 1.02 (s, 6).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.34; H, 10.72.

Treatment of Tricyclic Diene 32 with Potassium *tert*-Butoxide.—A mixture of 206 mg (0.82 mmol) of 80% pure tricyclic diene 32, 4 ml of dry dimethyl sulfoxide, and 1.134 g (10.1 mmol) of commercial potassium *tert*-butoxide was allowed to react at 40° for 13 hr and then at 52° for 21 hr. The material was poured into aqueous sodium chloride and the product was isolated in the standard fashion. The 174 mg of a residual oil was chromatographed on 15.4 g of Woelm basic alumina (activity II); elution with 10 ml of hexane produced 47 mg of a colorless oil which had a superimposible infrared spectrum with that of the 80% pure starting material. Further elution with 10 ml of hexane produced an additional 97 mg of impure diene 32 (infrared analysis). The tricyclic diene was purified by preparative vpc (20% DEGS, Chromosorb P, HMDS, 157°, 5 ft × 0.25 in.): $[\alpha]^{23}D$ −28° (c 0.2642, CHCl$_3$); uv max (cyclohexane) 229 nm (ε 15,700), 236 (16,600), 245 (10,000).

p-(*tert*-Amyl)toluene (33).—A mixture of 63.7 ml of toluene and 67 ml of concentrated sulfuric acid was stirred under a nitrogen atmosphere at 0° while 16.4 ml (0.15 mol) of *tert*-amyl alcohol was slowly added over a period of 20 min such that the temperature of the mixture did not rise above 10°. The mixture was stirred at 0° for 2 hr, poured onto 1000 g of crushed ice, and the mixture was worked up to yield 24.2 g of a liquid which was distilled through a 40 cm long platinum spinning band column (Nester–Faust). The desired product, 13.98 g (57%), distilled at 93–99° (19 mm). The majority of the material distilled at 99° (19 mm) [lit.[13] 100° (20 mm)]: nmr δ 6.83–7.29 (m, 4), 2.27 (s, 3), 1.62 (q, 2, J = 7 Hz), 1.23 (s, 6), 0.67 (t, 3, J = 7 Hz).

1-Methyl-4-*tert*-amylcyclohexa-1,4-diene (34).—A solution of 900 ml of liquid ammonia (distilled from sodium metal), 400 ml of diethyl ether, 370 ml of isopropyl alcohol, and 13.98 g (86.1 mmol) of p-(*tert*-amyl)toluene was stirred under reflux. A total of 12.9 g (1.86 mol) of lithium metal was added in portions to the reaction mixture over a period of 35 min. After stirring the reaction for an additional 10 min, the dark blue solution became colorless. The mixture was allowed to reflux for 1 additional hr and then 100 ml of methyl alcohol was added over a period of 10 min. Work-up in the standard fashion yielded 13.32 g (97%) of a colorless oil which by nmr spectral analysis was pure and contained no starting material. A portion of the material was further purified by preparative glpc (20% Carbowax 20M, 10% KOH, firebrick, 115°, 5 ft × 0.25 in.): ir 3015 cm^{-1}; nmr δ 5.41 (broad m, 2), 2.56 (broad s, 4), 1.65 (broad s, 3), 1.35 (broad q, 2, J = 7 Hz), 1.00 (s, 6), 0.71 (broad t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.86; H, 12.09.

1-Methyl-4-*t*-amylcyclohexa-1,3-diene (35).—A mixture of 770 ml of dimethyl sulfoxide, 15 ml of benzene, and 13.32 g (81.2

mmol) of 1-methyl-4-*tert*-amylcyclohexa-1,4-diene (34) was stirred at room temperature for 0.5 hr while a nitrogen stream was bubbled through the solution. After addition of 25.2 g (225 mmol) of commercial potassium *tert*-butoxide, the reaction mixture was stirred for 27.75 hr, and worked up in the usual manner to yield 22.71 g of material which contained some hexane. Nmr analysis of the crude product indicated that the ratio of conjugated diene to unconjugated diene is 86:14. The material was distilled through a 40 cm long platinum spinning band column (Nester–Faust), bp 81–86° (10.5 mm), to yield 9.18 g (69%) of 90% pure product: bp 86° (10.5 mm); uv max (cyclohexane) 268 nm (ε 7285); nmr δ 5.53 (s, 2), 2.02 (s, 4), 1.75 (s, 3), 1.37 (broad q, 2, J = 7 Hz), 0.99 (s, 6), 0.72 (broad triplet, 3, J = 7 Hz).

The product rapidly reacted with air under ambient conditions to produce a viscous oil; a sample of the product obtained from the center fraction of the distillation gave the following analyses on successive days.

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 86.46; H, 12.66. *Anal.* Found: C, 79.85; H, 11.02.

1-Methyl-4-*tert*-amylbicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Acid Anhydride (36).—A mixture of 9.00 g (54.8 mmol) of 90% pure 1-methyl-4-*tert*-amylcyclohexa-1,3-diene (35) (10% unconjugated diene), 35 ml of o-xylene (filtered through Woelm neutral alumina, activity I), and 5.50 g (56.1 mmol) of maleic anhydride, mp 53–54°, was heated for 2.7 hr at 135° under 1 atm of nitrogen. The yellow reaction mixture was worked up to yield 12.93 g (100%) of a white solid, mp 66–69°. This material was dissolved in benzene and filtered to remove insoluble material (ca. 50 mg), and the solvent was removed under reduced pressure. The residue had mp 72.5–74.0°; ir 3033, 1845, 1783, 708 cm^{-1}; nmr (benzene) δ 5.02 (d, 1, J = 8 Hz), 5.67 (d, 1, J = 8 Hz), 2.60 (d, 1, J = 9 Hz), 2.22 (d, 1, J = 9 Hz), 1.39 (s, 3), 0.98 (s, 3), 0.90 (s, 3), 0.82 (broad t, 3, J = 7 Hz).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.99; H, 8.30.

1-Methyl-4-*tert*-amylbicyclo[2.2.2]octane-2,3-dicarboxylic Acid (37).—A mixture of 12.12 g (46.2 mmol) of 1-methyl-4-*tert*-amylbicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (36) and 98 mg of prereduced platinum oxide in 60 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was shaken at room temperature under 1 atm of hydrogen gas. The absorption of hydrogen ceased after 6 hr. The mixture was processed to yield 11.46 g (94%) of a viscous oil which solidified overnight, mp 42–50°. A portion of the product was dissolved in hexane, the solution was filtered, and the solvent was removed under reduced pressure from the filtrate. The anhydride had mp 44–47°; ir 1862, 1776 cm^{-1}; nmr δ 3.17 (d, 1, J = 10 Hz), 2.83 (d, 1, J = 10 Hz), 1.13 (s, 3), 0.86 (s, 6), 0.85 (broad t, 3, J = 7 Hz).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.49; H, 9.10.

A mixture of 4.96 g (18.7 mmol) of the crude anhydride and 25 ml of 20% aqueous potassium bicarbonate was stirred on a steam bath for 1 hr, acidified, and extracted with ether. The solvent was rotary evaporated to yield 5.34 g of a light yellow foam. Approximately 70 ml of hexane was added to the foam, and the foam was scratched with a glass stirring rod to produce a white solid and a yellow solution. This mixture was filtered to yield 4.81 g (91%) of diacid 37: mp 144.5–145.5° dec; ir (KBr) 1717 cm^{-1}; nmr (CDCl$_3$) δ 3.24 (d, 1, J = 11.5 Hz), 2.73 (d, 1, J = 11.5 Hz), 0.96 (s, 3), 0.80 (s, 6), 0.78 (broad t, 3, J = 7 Hz).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 86.05; H, 9.28. Found: C, 67.99; H, 8.99.

1-Methyl-4-*tert*-amylbicyclo[2.2.2]octene (38).—A mixture of 10.10 g (38.2 mmol) of cis-1-methyl-4-*tert*-amylbicyclo[2.2.2]-octane-2,3-dicarboxylic acid (37), 70 ml of reagent grade benzene (filtered through Woelm neutral alumina, activity I), 4.93 ml of pyridine (distilled from p-toluenesulfonyl chloride and then potassium hydroxide), and 20.20 g (45.6 mmol) of lead tetraacetate (the material was washed free of acetic acid with dry hexane and the hexane was removed under reduced pressure to yield a white, free-flowing powder) was stirred for 50 min at room temperature under 1 atm of nitrogen. The orange opaque mixture was slowly heated in an oil bath until carbon dioxide began to evolve at 56°. At the end of 1.75 hr, the evolution of carbon dioxide had ceased. At this time, the mixture was heated at 75–80° for 3 hr and allowed to cool to room temperature and stand for an additional 3.75 hr. The mixture was poured into ca. 2 l. of 1.1 M aqueous nitric acid and extracted with diethyl ether until the

aqueous layer was clear and colorless. The combined ethereal solutions were processed to yield 7.76 g of a fluid orange oil. Hexane was added and the mixture was filtered to yield a light yellow solution of the crude product in hexane. The solvent was evaporated under reduced pressure and the residual oil was chromatographed on 180 g of Woelm neutral alumina (activity I). Elution with 160 ml of hexane and evaporation of the solvent under reduced pressure yielded 4.80 g (65%) of the product as a colorless, mobile oil: ir 3021, 697 cm^{-1}; nmr δ 6.13 (d, 1, J = 8 Hz), 5.88 (d, 1, J = 8 Hz), 1.09 (s, 3), 0.85 (s, 6), 0.85 (broad t, 3, J = 7 Hz).

Anal. Calcd for C$_{14}$H$_{24}$: C, 87.42; H, 12.58. Found: C, 87.37; H, 12.30.

1-Methyl-4-*tert*-amylbicyclo[2.2.2]octan-2-ol (40). A.—A 30-ml aliquot of a solution of borane in tetrahydrofuran (1.26 M in boron hydride) was added to a stirred solution of 4.80 g (24.9 mmol) of 1-methyl-4-*tert*-amylbicyclo[2.2.2]octene (38) in 27 ml of tetrahydrofuran at 0°. After 15 min an additional 30 ml of borane solution was added and the mixture was allowed to warm to room temperature and react for 5.25 hr. The excess diborane was decomposed by the addition of 9 ml of water followed by the addition of 14.4 ml of 3 M aqueous sodium hydroxide and 14.4 ml of 30% aqueous hydrogen peroxide (no exothermic reaction). The mixture was stirred for 10 hr at room temperature, diluted with water, and extracted with four portions of diethyl ether. The combined ethereal solutions were worked up in the normal manner to yield 5.250 g of a viscous oil: ir 3635 (weak), 1360 cm^{-1} (strong); nmr δ 3.5–4.2 (multiplet). Vapor phase chromatographic analysis (20% Carbowax 20M, 10% KOH, Chromosorb W, 170°, 5 ft × 0.25 in.) showed three peaks in the ratio 24:64:12. The first peak had the same retention time as the starting bicyclic olefin. The second and third compounds eluted at a much longer retention time. The minor of the latter two compounds had a retention time 1.33 times longer than the major compound. Both of these latter compounds were collected by preparative glpc.

The minor product was a viscous oil, ir 3611 cm^{-1}, and the fingerprint region of the infrared spectrum was similar to that of the major product which was a white solid: mp 46–49°; ir 3611 cm^{-1}; nmr δ 3.97 (q, 1, J = 8.5, 2.5 Hz), 0.80 (broad s, 9), 0.79 (broad triplet, 3, J = 7 Hz). A dilute nmr spectrum of the minor product in carbon tetrachloride showed major absorptions for quaternary methyl groups at δ 0.80 and 0.70.

The remaining portion of the 5.250 g was chromatographed on 150 g of Woelm neutral alumina (activity II). Elution with 435 ml of hexane gave 1.29 g of a slightly viscous oil which had the same glpc retention time as bicyclic olefin 38. Further elution of the chromatography column with 240 ml of diethyl ether yielded 2.07 g of a light yellow, viscous oil, glpc analysis of which showed that over 95% of the chromatogram consisted of the two previously mentioned alcohols in the ratio 4.4:1.0. The minor alcohol had the longer retention time. This mixture of alcohols was collected by preparative glpc.

Anal. Calcd for C$_{14}$H$_{26}$O: C, 79.93; H, 12.46. Found: C, 79.68; H, 12.22.

Further elution of the chromatography column with 100 ml of diethyl ether produced only 0.01 g of a viscous oil which was not investigated. The contents of the chromatography column were added to water, the mixture was extracted with three portions of diethyl ether, and the ethereal solution was processed in the usual manner to yield 0.53 g of a viscous boronic acid 45: ir 3670, 3610, 3552, 3448, 1365 cm^{-1} (strong, broad); nmr δ 5.50 (very weak broad absorption), 1.0–2.0 (multiplet), 0.75 (strong singlet). An nmr spectrum of this material which was run less than 24 hr later showed no absorptions at δ 5.50. The strong singlet at δ 0.75 had been replaced by two strong overlapping broad singlets at δ 0.77 and 0.70 and the infrared spectrum no longer exhibited any oxygen–hydrogen stretching vibrations; these spectral features are characteristic of a boroxine 46.

A solution of 460 mg of this latter material 46 in 10 ml of dry tetrahydrofuran was allowed to react with 1.0 ml of 30% aqueous hydrogen peroxide and 1.0 ml of 3 M aqueous sodium hydroxide under reflux for 2.3 hr. The mixture was diluted with water and extracted with three portions of diethyl ether. The combined ethereal solution was processed to yield 410 mg of a yellow oil. Analysis of the crude product by nmr and infrared spectroscopy showed major absorptions attributable to the major alcohol 40 in addition to a medium–strong absorption at 1365 cm^{-1} and a weak absorption at 3645 cm^{-1}. Glpc analysis showed only one compound, which was collected by preparative vpc. An infrared

spectrum of this product was superimposible with a spectrum of the major alcohol 40.

The remaining portion of the crude alcoholic product was dissolved in 10 ml of reagent grade acetone and treated with 0.5 ml of Jones reagent at 0°. The mixture was stirred and allowed to come to room temperature over a period of 15 min. The mixture was poured into water and the aqueous mixture was worked up in the usual manner to yield 372 mg of a light yellow oil. The nmr spectrum showed major absorptions attributable to ketone 42.

B.—A solution of 5.63 g of 90% pure bicyclic olefin 38 (26.4 mmol) in 10 ml of dry tetrahydrofuran was allowed to react with 41.6 ml of 1.26 M boron hydride in tetrahydrofuran at room temperature for 45.5 hr. The borane adduct was oxidized by the addition of 4.74 ml of 3 M aqueous sodium hydroxide and 4.74 ml of aqueous 30% hydrogen peroxide and heating the mixture at 47° for 1 hr. The solution was processed in the standard manner to yield 6.54 g of a viscous yellow oil. The material was chromatographed on 150 g of Woelm neutral alumina (activity II). Elution with 300 ml of hexane gave 1.63 g of an oil with no nmr absorptions downfield of δ 2.0; only the complex absorptions of hydrogens substituted on non-functionalized carbon atoms were seen between δ 0.6 and 2.0. Further elution with 340 ml of diethyl ether gave 4.11 g of a viscous oil; glpc analysis of the material showed the presence of two alcohols 40 and 39 in the ratio 2.6:1.0 at the same retention times as the two alcohols mentioned in the first experiment; the minor alcohol had the longer retention time.

1-Methyl-4-*tert*-amylbicyclo[2.2.2]octan-2-one 42.—A solution of 848 mg (4.0 mmol) of the mixture of bicyclic alcohols 40 and 39, containing some boroxine from the hydroboration experiment, in 25 ml of acetone at 0° was oxidized with 1.0 ml (1.0 equiv) of Jones reagent to yield 821 mg (98%) of a fluid, light yellow oil. Glpc analysis of the material (10% KOH, 20% Carbowax 6000, firebrick, 172°, 5 ft × 0.25 in.) indicated that two ketones were formed in the ratio 2.0:1.0 (by area); the minor ketone had the longer retention time.

The minor ketone 41 was purified by preparative glpc (same conditions as above): ir 1722 cm^{-1}; nmr δ 2.07 (broad s, 2), 0.87 (s, 3), 0.85 (broad t, 3, J = 7 Hz), 0.78 (s, 6).

The major ketone 42 was purified by preparative glpc: ir 1718 cm^{-1}; nmr δ 1.95 (broad s, 2), 0.92 (s, 3), 0.88 (s, 6), 0.81 (broad t, 3, J = 7 Hz).

Anal. Calcd for C$_{14}$H$_{24}$O: C, 80.71; H, 11.61. Found: C, 80.42; H, 11.31.

1-Methyl-4-*tert*-amylbicyclo[2.2.2]octane-2,3-dione (43a).—A mixture of 1.52 g (7.33 mmol) of the 2.0:1.0 mixture of bicyclic ketones 42 and 41, 11.5 g (104 mmol) of selenium dioxide, and 20 ml of *o*-xylene was stirred for 10 hr in an oil bath at 140–145°. The mixture was processed in the standard fashion and a hexane concentrate was analyzed by glpc (G.E. SF-96, 170°, 5 ft × 0.25 in.; chromatography on 10% KOH, 20% Carbowax 20M, Chromosorb W, 172°, 5 ft × 0.25 in. decomposed the product to a carbonyl-containing compound, ir 1718 cm^{-1}). The hexane solution was evaporated under reduced pressure to yield a brown residual oil which chromatographed on 50 g of silica gel (the product was unstable on Woelm neutral alumina, activity II). The column was eluted with 600 ml of benzene and the solvent was evaporated under reduced pressure to yield 1.508 g of an amber oil which solidified. The material was recrystallized from pentane to yield a total of 697 mg (43%) of product: mp 90–91°; uv max (cyclohexane) 456 nm (ϵ 33); ir 1750, 1732 cm^{-1}; nmr δ 1.00 (s, 3), 0.94 (s, 6), 0.86 (broad t, 3, J = 7 Hz).

Anal. Calcd for C$_{14}$H$_{22}$O$_2$: C, 75.63; H, 9.98. Found: C, 75.48; H, 9.72.

1-Methyl-4-*te-t*-amylbicyclo[2.2.2]octane-2,3-dione 2-*p*-Toluenesulfonylhydrazone (43b).—A mixture of 636 mg (2.86 mmol) of 1-methyl-4-*tert*-amylbicyclo[2.2.2]octane-2,3-dione (43a), 533 mg (2.86 mmol) of *p*-toluenesulfonylhydrazine, and 7.5 ml of chloroform was stirred for 48 hr with the exclusion of light. The mixture was filtered through anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield 981 mg (88%) of bicyclic keto hydrazone 43b. A portion of the product was recrystallized from chloroform–methyl alcohol to yield small, light yellow needles: mp 193° (decomposition with gas evolution); uv max (EtOH) 229 nm (ϵ 9710), 289 (10,400), 397 (242); ir 3218, 1680, 1371, 1166 cm^{-1}; nmr δ 7.83 (broad d, 2, J = 8 Hz), 7.30 (broad d, 2, J = 8 Hz), 2.43 (s, 3) 1.05 (s, 3), 0.92 (s, 6), 0.83 (broad triplet, 3, J = 7 Hz).

Anal. Calcd for $C_{21}H_{30}N_2SO_3$: C, 64.58; H, 7.74; N, 7.17; S, 8.21. Found: C, 64.31; H, 8.03; N, 7.33; S, 8.10.

2-Diazo-1-methyl-4-*tert*-amylbicyclo[2.2.2]octan-3-one (43c). —A solution of 764 mg (1.96 mmol) of 1-methyl-4-*tert*-amylbicyclo[2.2.2]octane-2,3-dione 2-*p*-toluenesulfonylhydrazone (43b) in 10 ml of chloroform was filtered through 21 g of Woelm basic alumina (activity I). The column was eluted with fresh chloroform until appreciable amounts of a yellow eluate were no longer obtained. The chloroform solution was concentrated under reduced pressure. An infrared spectrum of the concentrated solution indicated that some unreacted hydrazone was present in the mixture. The mixture was filtered again through 21 g of Woelm basic alumina (activity I). Fresh chloroform was passed through the column until the yellow diazo ketone no longer eluted from the column. The solvent was removed under reduced pressure to yield 343 mg (75%) of diazo ketone 43c, mp 66–69°. A small portion of the product was recrystallized from hexane at −78° to yield a pure sample of the product as light yellow needles: mp 69–70°; uv max (cyclohexane) 265 nm (ϵ 12,700), 424 (15); ir 2078, 1651 cm^{-1}; nmr δ 1.22 (s, 3), 0.98 (s, 6), 0.85 (broad t, 3, J = 7 Hz).

Anal. Calcd for $C_{14}H_{22}ON_2$: N, 11.96. Found: N, 12.08.

Irradiation of Diazo Ketone 43c in Water.—Nitrogen gas was slowly bubbled through a solution of 118 mg (0.50 mmol) of 2-diazo-1-methyl-4-*tert*-amylbicyclo[2.2.2]octan-2-one (43c) in 25 ml of 70% aqueous tetrahydrofuran (seven parts tetrahydrofuran which had been distilled from lithium aluminum hydride, three parts water, by volume) for 30 min. The solution was irradiated in a quartz irradiation flask with a 679A-36 Hanovia 450-W quartz mercury vapor lamp and a Corex 9700 filter (transmission: 0%, 255 mμ; 50%, 290 mμ) for 20 min under 1 atm of helium gas. After standing for 1 hr at room temperature, the solution was diluted with 75 ml of 1 *M* aqueous potassium hydroxide and extracted with two volumes of diethyl ether. The combined ethereal solutions were washed with water and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to yield 91 mg (95%) of crude 1-methyl-4-*tert*-amylbicyclo[2.2.1]-heptyl-7-ketene (44): uv max (cyclohexane) 222 nm (ϵ 1260), 301 (shoulder), 386 (15); ir 2115 cm^{-1}; nmr δ 1.33 (s, 3), 0.93 (s, 6), 0.88 (broad t, 3, J = 7 Hz).

A portion of this crude product, 44 mg, was heated under reflux for 30 min in a solution of 1.5 ml of ethylene glycol dimethyl ether (distilled from lithium aluminum hydride), 0.5 ml of water, and 180 μl of 70% aqueous perchloric acid. After this time an additional 1.5 ml of ethylene glycol dimethyl ether and 0.5 ml of water were added and the solution was heated under reflux for an additional 30 min. The solution was allowed to stand for 12 hr at 0°, diluted with 30 ml of 1 *M* aqueous potassium hydroxide, and extracted with diethyl ether. The alkaline extracts yielded 35 mg (70% based on diazo ketone 43c) of a colorless oil which solidified. An infrared spectrum of the crude product in carbon tetrachloride was identical with the spectrum of bicyclic acid 25a obtained from the degradation of tricyclic olefin 4. A portion of the material was recrystallized from pentane, mp 80.5–81.5°, pK*$_{MCS}$ 8.44.[21]

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.12; H, 10.55.

A portion of the acidic product was esterified in the usual manner with diazomethane in diethyl ether to yield 78 mg of product. The infrared and nmr spectra of this esterified material were identical in all respects with the spectra of methyl ester 25b which was obtained from the irradiation of diazo ketone 43c in anhydrous methyl alcohol. A portion of this ester, 60 mg, did not hydrolyze in a solution of 9 ml of methyl alcohol, 1 ml of water, and 1.21 g of potassium hydroxide pellets, which was heated under reflux for 6.5 hr.

Treatment of Tricyclic Ketone 14 with Trifluoroperacetic Acid.—A methylene chloride solution of 39.6 mmol of trifluoroperacetic acid was added to a mixture of 1.14 g (5.2 mmol) of tricyclic ketone 14, 12.8 g (90 mmol) of sodium hydrogen phosphate, and 100 ml of methylene chloride. The reaction mixture was stirred and heated under reflux for 8.25 hr. The reaction mixture was worked up in the standard fashion to yield 1.14 g of a light yellow oil which slowly crystallized to yield 280 mg of a white solid, mp 138–140°. The filtrate was concentrated and placed in the refrigerator for 2 days. Filtration gave an additional 102 mg of crude product, mp 100–123°. The total yield of tricyclic lactone 47 was 382 mg (31%). Chromatography of the mother liquors from the recrystallizations on

Woelm neutral alumina (activity II) gave an 11% yield of unreacted ketone and a small yield (4%) of an isomeric lactone, ir 1736 cm^{-1}. In addition a complex mixture of unknown alcohols and ketones were eluted from the chromatography column with hexane–diethyl ether. These products were not investigated.

Tricyclic lactone 47 could not be purified by alumina chromatography because it would not elute from the column with diethyl ether. When the chromatography column was stripped with water, a mixture of lactone 47 and its corresponding hydroxy acid were isolated. A portion of the crude tricyclic lactone was recrystallized two times from hexane: mp 142–143°; [α]^{23}D −40° (*c* 1.11, CHCl$_3$); ir 1729 cm^{-1}; nmr δ 4.67 (q, 1, J = 7 Hz), 1.27 (d, 3, J = 7 Hz), 1.00 (s, 3), 0.88 (s, 3), 0.73 (s, 3).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.39; H, 10.05.

Treatment of Tricyclic Lactone 47 with Boron Trifluoride in Methyl Alcohol.—A mixture of 234 mg (0.99 mmol) of tricyclic lactone 47, 30 ml of dry methyl alcohol, and 1.7 ml of boron trifluoride etherate (freshly distilled) was heated under reflux in 1 atm of nitrogen for 23.5 hr. The solution was cooled to room temperature and allowed to react for an additional 20.5 hr. The solution was worked up in the standard fashion to yield 238 mg of a light yellow, semisolid material which was chromatographed on 10 g of Woelm neutral alumina (activity II). Elution with 104 ml of hexane yielded 124 mg (50%) of bicyclic unsaturated ester 48: [α]^{23}D −2° (*c* 10.74, CHCl$_3$); ir 3086, 1745, 1639, 898 cm^{-1}; nmr δ 4.93 (s, 1, $W_{1/2}$ = 2.0 Hz), 4.79 (m, 1, $W_{1/2}$ = 2.3 Hz), 3.59 (s, 3), 2.35 (septet, 1, J = 7 Hz), 1.08 (s, 3), 0.97 (s, 6).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.76; H, 10.47. Found: C, 77.03; H, 10.64.

Preparation of Bicyclic α-Bromo Esters (49).—A mixture of 263 mg (1.11 mmol) of bicyclic acid 22a, 5 ml of purified thionyl chloride, and 220 mg (1.37 mmol) of bromine was heated under reflux for 10.5 hr. The mixture was cooled and dropped slowly into methyl alcohol at 0°. The methanolic solution was stirred for 12 hr at room temperature, and processed in the usual way to yield 363 mg (99%) of the crude product. The product was a mixture of two diastereoisomers: [α]^{23}D +15° (*c* 1.575, CHCl$_3$); ir 1755, 1728 cm^{-1}; nmr δ 4.80, 4.77, 4.66, 4.58 (the four absorptions integrated to a total of one hydrogen), 3.73, 3.71 (the two absorptions integrated to a total of three hydrogens).

Calcd relative intensities for $C_{14}H_{22}O_2Br^+$: *m/e* 301, 1.000; 303, 0.9923. Found: *m/e* 301, 1.000; 303, 1.00 ± 0.05.

Dehydrohalogenation of α-Bromo Esters 49.—A solution of 347 mg (1.05 mmol) of α-bromo esters 49 in 6 ml of synthetic quinoline was heated at 172° for 2 hr. The mixture was allowed to cool to room temperature and was poured into 0.65 *M* aqueous hydrochloric acid. The mixture was worked up in the usual manner and the residual 186 mg of brownish-red oil was chromatographed on 18 g of Woelm neutral alumina (activity II). Elution with 72 ml of hexane yielded 45 mg of an multicomponent oil and further elution with 80 ml of hexane gave 44 mg (17%) of hydrocarbon 50: [α]^{23}D 0° (*c* 2.71, CHCl$_3$); uv max (cyclohexane) 194 nm (ϵ 14,700), 204 (13,800); ir max 3021, 1725, 1653 cm^{-1}; nmr δ 6.85 (d, 1, J = 16 Hz), 5.63 (d, 1, J = 16 Hz), 5.37 (m, 1), 3.27 (s, 3), 1.80–2.15 (m, 4), 1.05 (s, 3), 0.97 (s, 6), 0.67 (t, 3, J = 7 Hz); mass spectrum *m/e* 250.

Further elution with hexane–diethyl ether yielded an additional 62 mg of material but no fraction contained spectral absorptions characteristic of the desired unrearranged product.

Thujopsene Rearrangements.   The Ring System *via* Ring Contraction[1-3]

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In refluxing acetic acid, *cis*-thujopsene rearranges both to 1,4,11,11-tetramethylbicyclo[5.4.0]undeca-3,7-diene (3) and to α- and β-chamigrenes (11).   When perchloric acid is added, diene 3 is converted to tricyclic olefin 4. β-Chamigrene, however, is mainly converted to two transitory tricyclic olefins 19 and 20 which, in turn, are transformed into the further rearranged but thermodynamically stable tricyclic olefins 5 and 6.   The structures of 5 and 6 were proven by degradation and partial synthesis.   This extensive series of rearrangements is extremely sensitive to the acidic conditions employed and this effect has been studied in detail.   The mechanisms of these rearrangements are discussed and the possible biogenetic significance of this process is evaluated.

Part A

Previous studies with *cis*-thujopsene (1) showed that under mild acidic conditions (0.02 M perchloric acid in 80% aqueous dioxane at reflux) a series of cyclopropyl-carbinyl–homoallyl rearrangements first occurred to yield mainly widdrol (2) and upon prolonged reaction time the methyl migrated diene 3 was the major product.   When *cis*-thujopsene was allowed to react under more acidic conditions (0.02 M perchloric acid in acetic acid at reflux) a mixture of olefins of which 3 was the major product was formed very rapidly and upon prolonged heating a final mixture of three compounds in the ratio of 70:18:12 resulted.   In an earlier study, the structure of the major hydrocarbon was established[2] to be the tricyclic olefin 4.   In this present investigation, the structures of the two lesser abundant hydrocarbons have been shown to be the tricyclic olefins 5 and 6.   The structures of these two materials were proved by degradation and partial synthesis.

It has been found that under the mild acid conditions which convert *cis*-thujopsene to widdrol and diene 3, *trans*-thujopsene (7) retains its stereochemical integrity and yields, first, mainly epiwiddrol (8) and then the diene 9.   When 9 was allowed to react under the more strongly acidic conditions, refluxing 0.02 M HClO₄ in acetic acid, again the three hydrocarbons 4, 5, and 6 were formed but this time in a ratio of 50:30:20. Thus, under these forcing conditions some mixing of the isomeric series occurred but the different ratio of the final products formed from *cis*- and *trans*-thujopsene

suggested that 5 and 6 most likely were derived from a precursor more readily formed from *trans*-thujopsene.
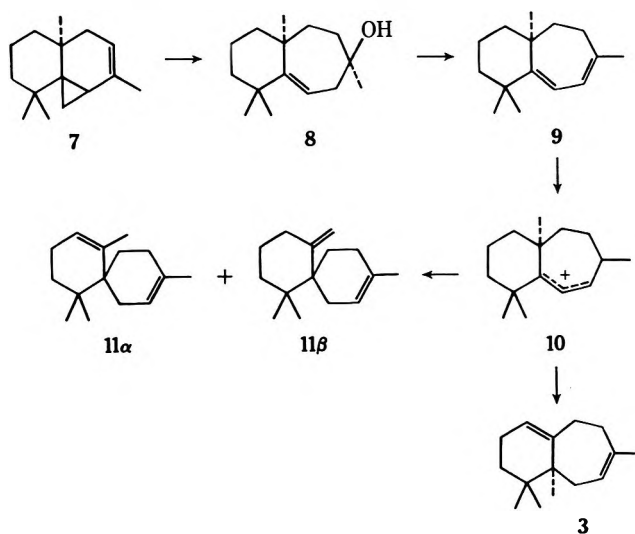
The rearrangements in this series of compounds are very sensitive to the experimental conditions and although minor amounts of many materials are formed under most conditions it is usually possible to find a reaction condition which leads to the accumulation of only a few compounds.   In earlier studies there were indications, by glpc, that β-chamigrene (11β), a naturally occurring hydrocarbon,[5] was formed in the acid-catalyzed rearrangements.   In the present investigation, it was found that when *cis*-thujopsene was heated under reflux in glacial acetic acid, 30% of α-chamigrene, 30% of β-chamigrene, and 40% of methylmigrated diene 3 were formed.[6]   *trans*-Thujopsene (7) under similar conditions yielded these same three materials. Knowing that this trans isomer readily forms diene 9, it is reasonable that its protonation would yield the allyl cation 10 which, in turn, would rearrange to yield 11 and 3.   Previous studies[2] related to the establishment of the pathway of formation of diene 3 have shown that cation 10 is not on the major pathway for the rearrangement of *cis*-thujopsene.   Thus, involvement of cation 10 (or related species) in the rearrangement of *cis*-thujopsene must be minimal.   The facile formation of β-chamigrene from diene 9 (and thus from *trans*-thujop-

(1) This work was supported in part by Grant GP-8700, National Science Foundation.

(2) For the previous paper in this study, see W. G. Dauben and L. F. Friedrich, *J. Org. Chem.*, **37**, 241 (1972).

(3) This work was reported at the 14th Symposium of the Chemistry of Natural Products, Fukuoka, Japan, Oct 28–30, 1970, Abstracts, p 220.

(4) National Institutes of Health Predoctoral Fellow, 1967–1970.

(5) In 1960, S. Nagahama [*Bull. Soc. Chem. Jap.*, **33**, 1467 (1960)] reported that *cis*-thujopsene upon reaction with 0.85 M oxalic acid in 8% aqueous ethanol yielded widdrol and a new hydrocarbon.   During the course of our own related studies, S. Ito [*Chem. Commun.*, 186 (1967)] showed that this new hydrocarbon was the naturally occurring β-chamigrene.

(6) Attention must be given to the analytical method employed since α-chamigrene and diene 3 are only fully separated at 117° using a 500-ft, 0.03-m column coated with PPES plus Igepal.

sene), suggests that the former hydrocarbon is the precursor of **5** and **6**. Indeed, when β-chamigrene (95% pure) was refluxed with 0.02 *M* perchloric acid in acetic acid only olefins **5** and **6** were formed.
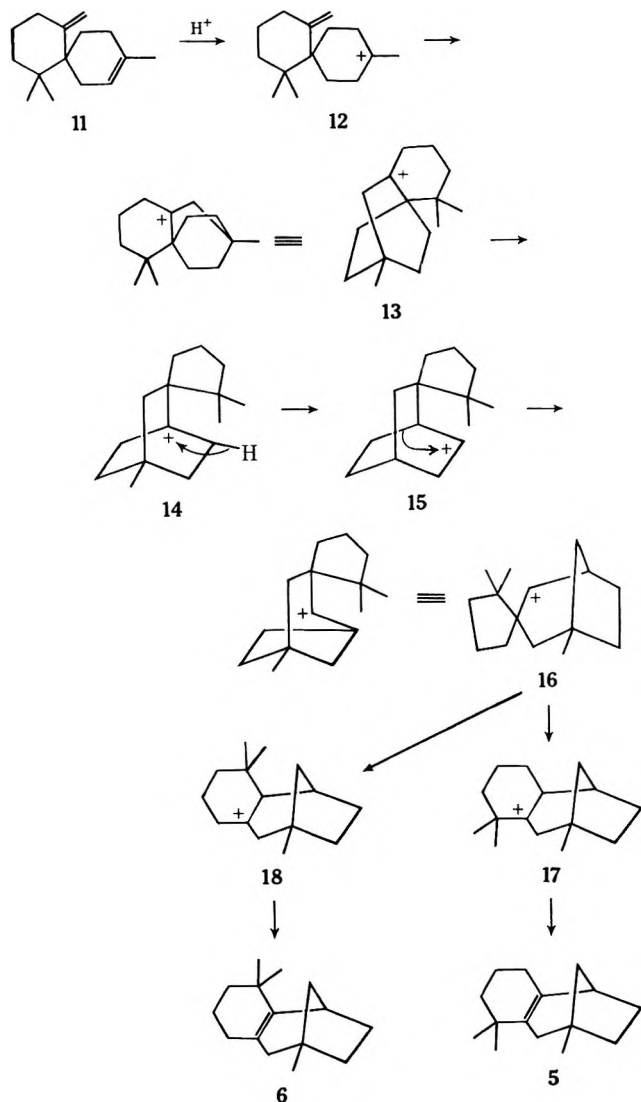
With β-chamigrene identified as an intermediate in the formation of **5** and **6**, a reasonable mechanism for their formation can be postulated. Initial protonation of β-chamigrene at the endocyclic double bond to give the carbonium ion **12** is expected since it is known from the chemistry of the hydrocarbon that it is the lesser hindered double bond.[5] Ring closure to the exocyclic double bond yields the bicyclo[2.2.2]octyl cation **13**. This intermediate (or activated complex), upon Wagner–Meerwein rearrangement to **14**, hydride migration to yield **15** to relieve the strain of the bridgehead carbonium ion, and again a Wagner–Meerwein rearrangement, yields the spirano intermediate **16**. This latter cation has two pathways available to it for rearrangements, one giving the ion **17** and subsequently olefin **5** and the other giving ion **18** and subsequently olefin **6**.

This preferred protonation of β-chamigrene at the endocyclic double bond accounts for the inability of the compound to reverse back to cation **10** which could yield the methyl-migrated diene **3**. Therefore, at this β-chamigrene stage the pathway to olefins **5** and **6** is split off from that leading to **3** and subsequently olefin **4**.

Since this postulated mechanism involves an extensive number of steps, it might be expected that by controlling the reaction conditions it should be possible to build up intermediates of lesser stability which are separated by a high energy barrier from the thermodynamically stable **5** and **6**.

When *cis*-thujopsene was allowed to react at 25° with 0.02 *M* perchloric acid in acetic acid, the results given in Table I were obtained. It is seen that *cis*-thu-

TABLE I

REACTION OF *cis*-THUJOPSENE WITH 0.02 *M* HClO₄ IN ACETIC ACID, 25°

Time, min	Yield of compound, %						
	1	3	11α	11β	4	19	20
5	Trace	62	22	16			
15		61	20	15		4	
30		55	18	13	6	8	
240		20	14	4	38	20	4
720				1	69	18	12

jopsene is rapidly rearranged to methyl-migrated diene **3** and to α- and β-chamigrene. Under these acidic conditions, these compounds undergo further rearrangement. β-Chamigrene is more reactive than methyl-migrated diene **3** or α-chamigrene and is transformed into two new isomeric hydrocarbons, **19** and **20**.[7,8]
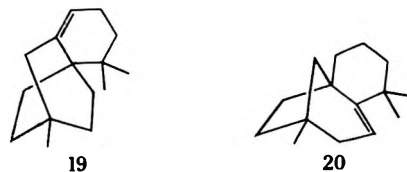
These data again show that β-chamigrene does not cross over to the methyl-migrated diene **3** which leads to **4**. Under these room-temperature conditions, **19** and **20** are stable and no **5** or **6** are formed

This effect of the acidity of the media was further investigated and the results are given in Table II. It is

TABLE II

EFFECT OF ACID CONCENTRATION ON *cis*-THUJOPSENE REARRANGEMENT, 40°, 12 HR

Concn of HClO₄ in HOAc, *M*	Yield of compounds, %	
	4	19 + 20
0.02	55	35
0.1	40	55
0.5	30	65
1.0	25	70

apparent from these data that, as the concentration of perchloric acid increased, products **19** and **20** related to β-chamigrene increased at the expense of tricyclic olefins **4** related to methyl-migrated diene **3**. These results again point to the increased tendency of *cis*-thujopsene to yield chamigrenes as the acidity of the media increases.

(7) The same two compounds also have been prepared from *cis*-thujopsene by G. C. Kitchens, A. R. Hochstettler, and K. Kaiser (private communication) using different acid conditions. The structure of **19** was established by X-ray crystallography and of **20** by chemical transformations and spectra.

(8) After completion of this work, S. Ito and coworkers [Abstracts of 14th Symposium of the Chemistry of Natural Products, Fukuoka, Japan, Oct 28–30, 1970, p. 174; *Tetrahedron Lett.*, 1149 (1971)] reported of these same two hydrocarbons from a reaction mixture obtained by allowing *cis*-thujopsene to react with a special acidic silica gel (Wako gel Q-50). Their structural assignments were made solely on the basis of mechanistic concepts.

SCHEME I
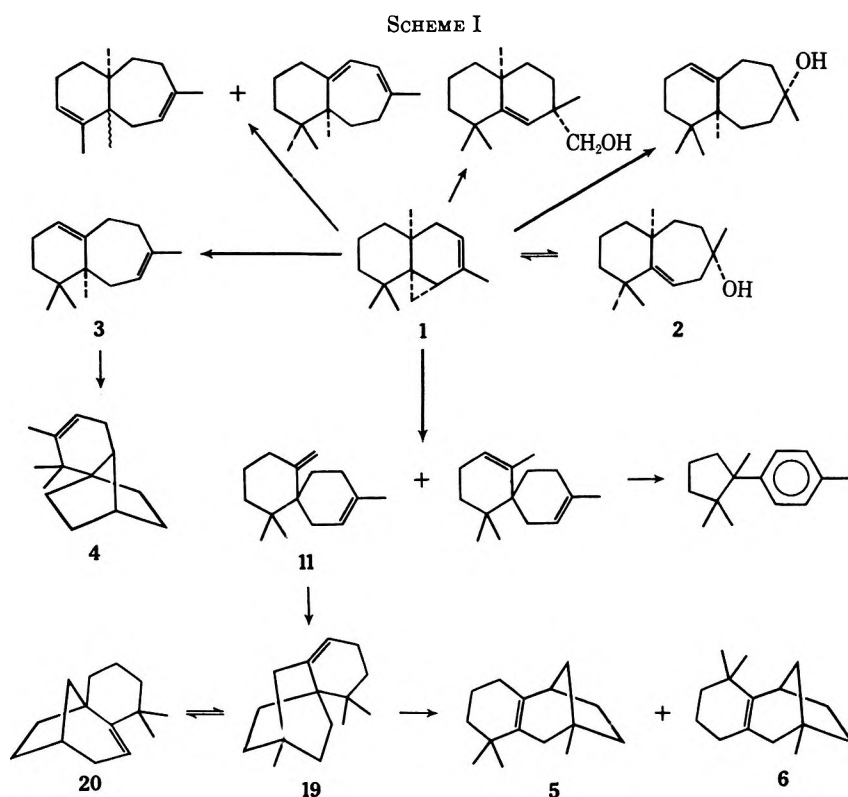
Recalling that β-chamigrene in refluxing 0.02 M perchloric acid–acetic acid only yielded hydrocarbons 5 and 6, the foregoing data indicate that, as postulated earlier, the new olefins 19 and 20 must be intermediates in the rearrangement of β-chamigrene to 5 and 6. Indeed, when β-chamigrene was allowed to react at room temperature with 0.02 M perchloric acid–acetic acid, first 19 was formed which, in turn, yielded a 30:40 mixture of 19 and 20, respectively. When this latter mixture of 19 and 20 was heated, 5 and 6 were formed as the major products.
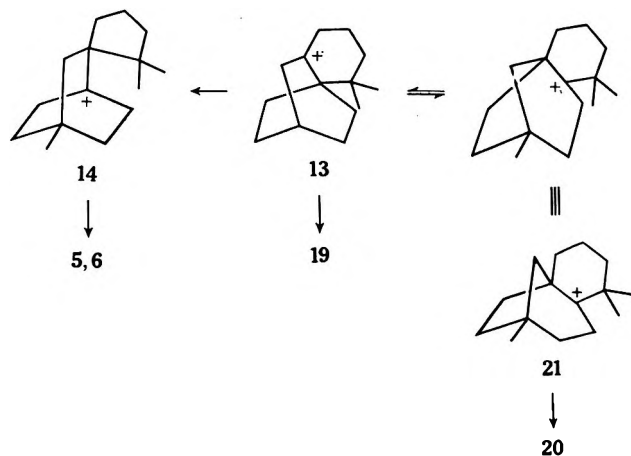
Starting with either pure 19 or 20, the same 60:40 equilibrium mixture of the two compounds was formed. The intermediate (or activated complex) 13 formed from β-chamigrene has two possible pathways for rearrangement, ring expansion to unstrained 21 or ring contraction to the spiran 14. This facile interconversion between 19 and 20 followed by slow formation of 5 and 6 via 14 clearly points to the higher energy barrier for the formation of the bridgehead cation 14 in the bicyclo[2.2.2]octane system.

As with the formation of tricyclic olefin 4 from bicyclic diene 3, the thermodynamic stability of 5 and 6 as compared with that of β-chamigrene arises from the fact that the former compounds are tricyclic with one tetrasubstituted double bond as compared with the latter which is bicyclic with a lesser substituted double bond. In general, a cycloalkene is more stable than its acyclic analog by $\sim$20 kcal/mol. The conversion of two relatively unstrained six-membered rings into a bicyclo[3.2.1]octane nucleus has been estimated to involve a strain increase of $\sim$6–7 kcal/mol.[9] Thus the 18–20 kcal/mol energy gained by ring closure to a tricyclic monoolefin overcomes the slight increase in ring strain energy.

Comment should be made on the reasonableness of postulating a bridgehead carbonium ion as an intermediate (or activated complex) in skeletal rearrangements. In this present study, one is concerned with the bicyclo[2.2.2]octane system 14 and in previous work in the formation of the tricyclic olefin 4 with a bicyclo[3.2.1]octane nucleus. Recently, Wiberg,[9] using rates of solvolysis of appropriate bridgehead derivatives, estimated the strain energy of bridgehead carbonium ions of the bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.1]octane systems to be 31.7, 17.3, and 18.7 kcal/mol, respectively. Clearly, bridgehead cations in the latter two systems are of an energy such that it is reasonable that rearrangements may proceed through them.

With this study of the mechanism of formation of hydrocarbons 4, 5, and 6, the study of the major rearrangements of thujopsene under acid conditions is complete. All the major products which appear during the course of the rearrangements have been identified. However, there are many other materials formed in very small amounts and which thus must be viewed as being de-

(9) K. B. Wiberg, private communication.

rived from minor pathways. The rearrangements of thujopsene so far observed by various workers[2,6,7] are summarized in Scheme I.

As can be seen in Scheme I, the rearrangements of *cis*-thujopsene are perhaps the most extensive in scope of any known sesquiterpene. A study of the isomers derived from *cis*-thujopsene has also shown that, under the proper conditions, many bicyclic materials can easily cyclize to give tricyclic compounds. Such results warrant serious consideration and lead to a conclusion that bicyclic sesquiterpenes can, indeed, be precursors of tricyclic sesquiterpenes. It is apparent that *cis*-thujopsene occupies an important place in the search for intermediates in sesquiterpene biogenesis.

Part B

In a typical preparative experiment using 0.02 *M* perchloric acid in acetic acid at reflux temperature, an 85% recovery of hydrocarbons was obtained, the composition of which was 18% of 5, 12% of 6 and 70% of 4. The new hydrocarbons 5 and 6 boiled at a lower temperature than 4 and by distillation through a gold-plated spinning band column fractions highly enriched in 5 and 6 were obtained. Subsequent distillation through a Teflon spinning band column yielded 5 in greater than 90% purity. Hydrocarbon 6 was more difficult to purify since its boiling point was between those of 5 and 4 and all fractions were contaminated with one or the other of these latter two compounds. The olefin was best purified by silver nitrate–silica gel chromatography of highly enriched distillation fractions.[10] Analytically pure samples of 5 and 6 were obtained by preparative vpc.

Preliminary investigation of the spectral properties of the two materials indicated a close structural relationship. Since hydrocarbon 5 was more readily available, this material was investigated first. The structure elucidation of the closely related 6 was greatly facilitated by the result obtained with 5.

Mass spectral and elemental analyses indicated that 5 was isomeric with thujopsene. The infrared spectrum lacked any bands characteristic of a functional group and there was no vinyl absorption in the nmr spectrum. However, the ultraviolet maximum at 197 nm indicated a possibility of a tetrasubstituted double bond and this was confirmed by a strong absorption at 1650 cm⁻¹ in the Raman spectrum.[11,12] The extinction coefficients of these latter two absorptions allowed for only one double bond and hence the compound must be tricyclic. Furthermore, from the nmr spectrum, there were only three methyl groups all of which are quaternary, indicating that one of the methyl groups of thujopsene was incorporated into a ring during the transformation.

Since the only functional group present in the molecule was a tetrasubstituted double bond, only a limited degradational scheme could be applied. The following degradation scheme (summarized in Scheme II) was carried out and the fragments of the degradation were

(10) A supply of highly enriched 5 and 6 was kindly supplied by Dr. G. C. Kitchens of the Givaudan Corp.

(11) G. F. Bailey, S. Kint, and J. R. Scherer, *Anal. Chem.*, **39**, 1040 (1967).

(12) The authors wish to thank Dr. J. R. Scherer of the U. S. D. A. Western Regional Research Laboratory, Albany, Calif., for obtaining the Raman spectrum.

SCHEME II
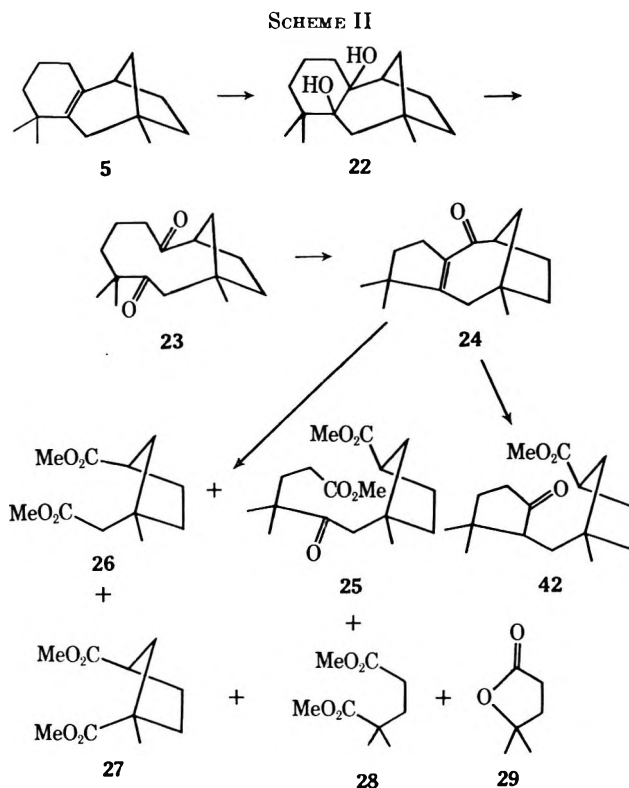
identified either by unambiguous synthesis or by comparison of the spectral data with those of authentic materials.

The hydrocarbon 5 upon reaction with osmium tetroxide yielded the diol 22, which was cleaved with lead tetraacetate in benzene to give the diketone 23. The infrared spectrum of the diketone showed a broad peak at 1705 cm⁻¹ indicating the presence of unstrained carbonyl groups. Since no carbon atoms were lost during the cleavage, the original double bond must have been endocyclic. This result, combined with the fact that all the methyl groups are quaternary, requires that one of the methyl groups must be of the angular (or bridgehead) type and the other two must form a *gem*-dimethyl group on a ring.

Treatment of the diketone 23 with aqueous base gave a good yield of a *single* unsaturated ketone. The infrared absorptions at 1650 and 1620 cm⁻¹ indicated that the carbonyl group was conjugated and unstrained. The ultraviolet absorption at 254 nm and the absence of vinyl proton resonance in the nmr spectrum confirmed the expected presence of a tetrasubstituted double bond in the conjugated enone 24.

The enone was ozonized and treated with hydrogen peroxide, and the acidic material was allowed to react with diazomethane to give the keto diester 25. In addition, lesser amounts of four smaller fragments, 26, 27, 28, and 29, were isolated, the lactone 29 being isolated from the neutral fraction of the ozonolysis. Formation of the smaller fragments upon ozonolysis was most likely due to the buildup of some peracids from the oxygen in the ozone employed and the peracid, in turn, brought about a Baeyer–Villiger type cleavage. Examples of such anomalous ozonolysis reactions have been reported by other workers.[13]

(13) (a) P. R. Story and J. R. Burgess, *Tetrahedron Lett.*, 1287 (1968); (b) R. T. Aplin, R. P. K. Chan, and T. G. Halsall, *J. Chem. Soc. C*, 2322 (1969).

Connecting together the smaller fragments of the ozonolysis, the keto diester could be formulated as **25**, **30**, **31**, or **32**. The nmr spectrum did not permit differentiation between these structures. However, **31** and **32** were eliminated on the following basis. The mass spectrum showed a base peak at m/e 183; a reasonable assignment of this peak is **33** or **34** which can arise by
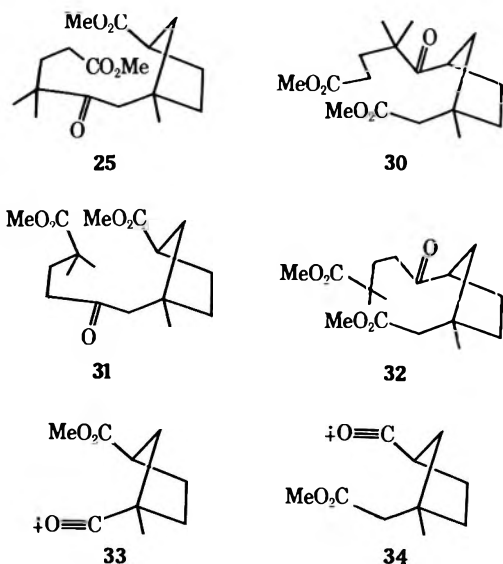
α cleavage of the carbonyl group facilitated by the presence of an α-*gem*-dimethyl group. Compared to the base peak at m/e 183, the peak at m/e 253, which is due to the loss of a carbomethoxy group, is for all practical purposes not present. Although these spectral interpretations are not conclusive, they support the postulate that the *gem*-dimethyl group is α to the carbonyl group and γ to a carbomethoxy group.
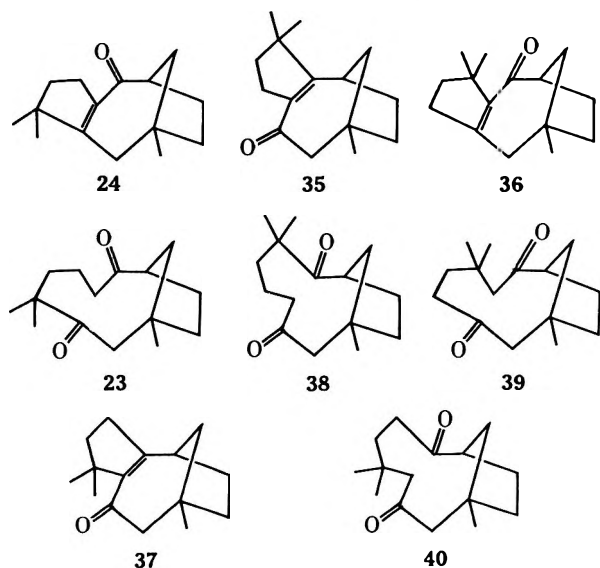
Further evidence for the placement of the *gem*-dimethyl group was found in the formation of a *single* enone from the diketone upon base-induced cyclization. The four possible enones from which the ozonolysis fragments could be obtained are **24**, **35**, **36**, and **37**, which, in turn, could be obtained from the diketones **23**, **38**, **39**, and **40**, respectively. However, **39** and **40** upon cyclization would be expected to yield two enones, since enolization of either carbonyl group can result in ring closure to a bicyclo[3.2.1]octane ring system. On

the other hand, **23** and **38**, having the *gem*-dimethyl group next to one carbonyl group, can only yield one such enone; the other would possess a bicyclo[2.2.1]-heptane ring system which would not be expected due to the extra strain of the ring system.

On the basis of the above arguments, keto diesters **31** and **32** need not be considered at this time. To distinguish between **25** and **30** by further degradation was not feasible, since the amount of material available was too limited. Therefore, possible distinctions between enones **24** and **35** were evaluated. The enone was treated with peracetic acid in buffered acetic acid to give an enol lactone **41**, which was opened with a trace of sulfuric acid in methanol to yield the cyclopentanone ester **42**. The infrared spectrum possessed a broad
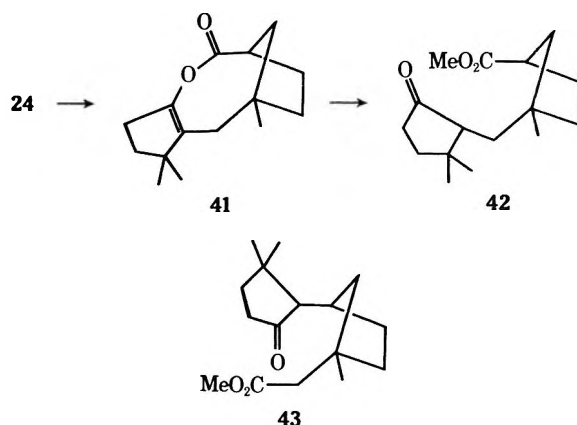
band at 1745 cm^{-1} confirming the presence of a cyclopentanone and an ester grouping. The nmr spectrum showed the continued presence of the three methyl groups but more important the presence of a one-proton quintet (J = 8 Hz) at δ 2.8 for a single proton on the cyclopentane ring α to the carbomethoxy group and a broad three-proton band between δ 1.8–2.5 for the protons adjacent to the carbonyl group. The total of four such α protons is commensurate with the structure **42** derived from enone **24** but not with keto ester **43**, which would be derived from enone **35** and demand the presence of five such protons. With this establishment of structure **24**, following back through the foregoing discussion leads to the establishment of structure **5** for the olefinic hydrocarbon derived from thujopsene.

The structure elucidation of hydrocarbon **6** was carried out in an identical manner as described above for isomer **5** and is outlined in Scheme III. The structural similarities of the two materials were clearly evident throughout the degradation. Again, the diketone **38** derived from cleavage of the double bond yielded only one enone **35** upon cyclization, speaking for the placement of the *gem*-dimethyl grouping. The expected products from the ozonization of the enone were obtained but the new fragment **45** was specially significant, since it showed the position of the carbonyl group in the primary ozonolysis product. This product is formed by a Baeyer–Villiger type of cleavage of **30** followed by hydrolysis and oxidation during the ozonolysis.[14] The nmr spectrum of cyclopentanone ester **43** showed the expected five-proton signals assignable to

(14) Oxidation of alcohols during ozonolysis has been reported previously; see J. von Euw, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, **27**, 821 (1944); E. P. Oliveto, H. W. Smith, C. Gerold, R. Raussen, and E. B. Hershberg, *J. Amer. Chem. Soc.*, **78**, 1414 (1952).

SCHEME III

desired keto ester **45**. Dimethyl α,α-dimethylglutarate was synthesized from 4,4-dimethylcyclohexenone by ozonolysis and esterification and γ,γ-dimethylbutyrolactone was prepared by published procedures.[16]
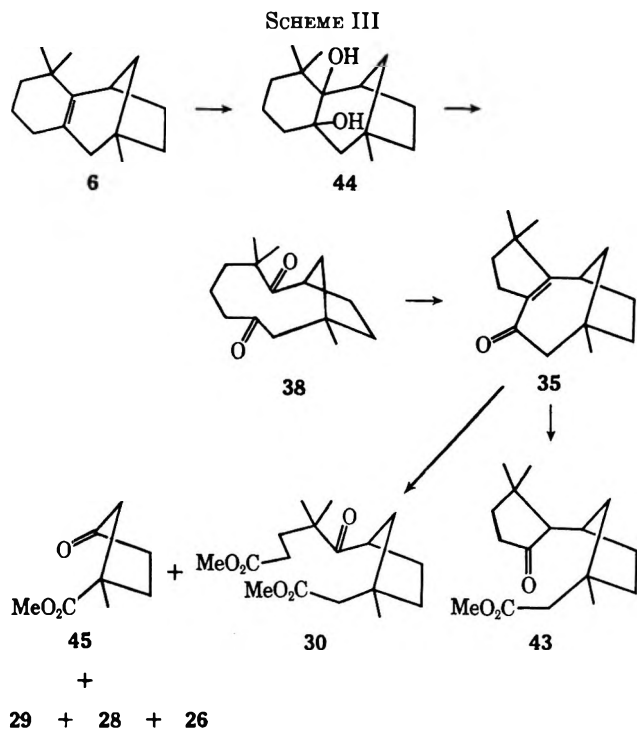
those protons α to the carbonyl and ester groupings. This finding further substantiates the conclusion arrived at with respect to cyclopentanone ester **42**.

The structures of the important smaller fragments from the ozonolysis were first arrived at on the basis of spectral information. The diester **26** was prepared by ozonolysis of bicyclic bromide **48**, which was prepared from 1-methylnorbornene (**46**). Dibromocarbene insertion into **46**[15] followed by lithium aluminum hydride reduction yielded a mixture of bromides **47** and **48** which were not separated, but the mixture was directly ozonized. The resulting diesters **26** and **49** were readily separated and their spectral properties permitted structure assignment.

The diester **27** was prepared by ozonolysis of 1-methylnorbornene followed by esterification of the acid fraction. The cyclopentanone ester **45** also was prepared from this same olefin *via* hydroboration and oxidation to a mixture of ketones **50** and **51**, which upon chromatography was separated into its two components. Peracid oxidation of **51** gave the lactone **52** which was, in turn, converted into hydroxy ester **53** and

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were obtained with either a Perkin-Elmer Model 137 or 237 spectrometer using CCl_4 as solvent. Ultraviolet spectra were taken on a Beckman DK-2A spectrophotometer. Nmr spectra were taken with Varian Models T-60 or HA-100; carbon tetrachloride was used as the solvent, chemical shifts are given in δ with respect to internal TMS. Mass spectra were recorded with either a Varian M-66 cycloidal mass spectrometer, modified CEC type 21-103 C, or a Finigan quadrupole mass spectrometer. Elemental analysis and high-resolution mass spectra were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

Unless otherwise stated the general work-up of a reaction was as follows: after extraction of the desired materials with organic solvents (ether or hexane), the solution was dried ($MgSO_4$ or Na_2SO_4) and concentrated by rotary evaporation of the solvents.

General Procedure of Ozonolysis.—Ozonolysis was carried out by using the Welsbach ozone generator. For the oxidative work-up of the ozonide, reagent grade ethyl acetate saturated with water was used as the solvent. Ozonolysis was carried out at $-10°$ and the solution of crude ozonide was *partially* concentrated by removing *ca.* three-fourths of the solvent on a rotary evaporator. Water and excess 30% hydrogen peroxide (*ca.* 15-fold excess) were added and the resulting mixture was refluxed for 2 hr, diluted with saturated aqueous sodium bicarbonate solution, and extracted with ether. The ether extract was concentrated to give the neutral material, and the bicarbonate solution was acidified with sulfuric acid. Acidic products were back extracted with ether.

Time Study of Rearrangements. A. Refluxing Acetic Acid.—A 0.5 *M* solution of *cis*-thujopsene in glacial acitic acid under a nitrogen atmosphere was refluxed, and at definite time intervals, 0.1 ml of solution was withdrawn and added to a saturated sodium bicarbonate solution. The organic materials were extracted with hexane, the solvent was removed, and the residue was analyzed on a 500 ft × 0.02 in. capillary column coated with PPE 5 and Igepal.

B.   0.02 *M* HClO₄ in Acetic Acid, 25°.—A 0.5 *M* solution of *cis*-thujopsene in 0.02 *M* HClO₄ in acetic acid was kept at 25° (±1°) under a nitrogen atmosphere. At definite time intervals 0.1 ml aliquots were removed and processed and analyzed as above.

Perchloric Acid–Acetic Acid Treatment of *cis*-Thujopsene.—A solution of 1.34 g (6.56 mmol) of *cis*-thujopsene (1) in 14 ml of glacial acetic acid and 20 μl of 70% aqueous perchloric acid was refluxed under nitrogen for 25 hr. The reaction mixture was

(15) C. W. Jefford, S. N. Mahajan, J. Waslyn, and B. Waegell, *J. Amer. Chem. Soc.*, **87**, 2183 (1965).

(16) A. L. J. Beckwith and J. E. Goodrich, *Aust. J. Chem.*, **18**, 1026 (1965).

poured carefully into saturated aqueous potassium carbonate solution, extracted with hexane, and after solvent evaporation the residual oil was chromatographed on Woelm neutral alumina to give 1.1 g (85%) of hydrocarbon mixture. Glpc analysis (5 ft × 0.25 in. KOH, Carbowax 6000, 140°) showed three major materials, **4**, **5**, and **6**, in 13:4:3 ratio. Each compound was purified by preparative glpc for spectra. Hydrocarbon **5**: Raman spectrum 1650 cm^{-1}; nmr 0.91 (s, 3), 0.95 (s, 3), 1.1 (s, 3); uv max (cyclohexane) 197 nm (ϵ 8000); mass spectrum m/e (rel intensity) 204 (M$^+$, 45), 189 (100).

Anal. Calcd for C$_{15}$H$_{24}$: C, 88.16; H, 11.84. Found: C, 87.97; H, 11.68.

Hydrocarbon **6**: Raman spectrum 1650 cm^{-1}; nmr 0.93 (s, 3), 0.99 (s, 3), 1.06 (s, 3), 2.42 (m, 1); uv max (cyclohexane) 197 nm (ϵ 8900); mass spectrum m/e (rel intensity) 204 (M$^+$, 40), 189 (100).

Anal. Calcd for C$_{15}$H$_{24}$: C, 88.16; H, 11.84. Found: C, 87.95; H, 11.66.

Oxidation of 5 with Osmium Tetroxide.—A solution of 582 mg (2.85 mmol) of hydrocarbon **5** in 5 ml of reagent grade pyridine was added slowly to 751 mg (2.85 mmol) of osmium tetroxide in 10 ml of pyridine. The reaction mixture was allowed to stand in the dark for 28 days at room temperature, the pyridine was rotary evaporated, and the residue was taken up in 15 ml of benzene and 15 ml of ethanol. To the brown mixture was added a solution of 10 g of potassium hydroxide, 10 g of mannitol, 30 ml of water, and 60 ml of ethanol, and the resulting mixture was refluxed for 6 hr. The reaction mixture was processed in the usual fashion to yield 450 mg of dark brown diol which was recrystallized from the hexane to give 156 mg of diol **22**. Chromatography of the mother liquor on 30 g of Woelm neutral alumina (activity II) gave an additional 98 mg of the diol. The total yield of diol was 254 mg (37.5%): ir 3660, 3590, 1070, 860 cm^{-1}; nmr 0.88 (s, 3), 1.05 (s, 3), 1.13 (s, 3), 2.75 (d, 1, J = 11 Hz); mass spectrum m/e (rel intensity) 238 (M$^+$, 7), 220 (56), 151 (100), 138 (67).

Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.71; H, 11.13.

Diketone 23.—To a solution of 25 mg (0.105 mmol) of diol **22** in 3 ml of dry benzene was added 50 mg (0.113 mmol) of lead tetraacetate, the mixture was stirred under dry nitrogen at room temperature for 1 hr, and 2 ml of quarter saturated aqueous sodium bicarbonate solution was added. The mixture was quickly extracted with ether and the ether solution was dried. Rotary evaporation of ether gave 22 mg (93%) of white crystalline diketone **23**. Tlc (33% ether–hexane) showed only one spot and the diol **22** was absent. Glpc (2% SE-30, 5 ft × 0.125 in., 155°) showed only one peak. A small portion of the diketone was recrystallized twice from hexane: mp 105–106°; ir 1705 cm^{-1}; nmr 0.97 (s, 3), 1.01 (s, 3), 1.31 (s, 3); mass spectrum m/e 236 (M$^+$), 208.

Enone 24.—A solution of 24 mg (0.11 mmol) of diketone **23** and ca. 12 mg of potassium hydroxide in 80% aqueous methanol was refluxed under nitrogen for 2.5 hr. The solution was diluted with water and worked up for 18 mg (75%) of pale brown oil. Glpc (20% DEGS, 5 ft × 0.25 in., 150°) and tlc (20% ethyl acetate–hexane) showed only one major compound. The physical properties were determined on glpc-collected material: ir 1650, 1620 cm^{-1}; nmr 1.03 (s, 6), 1.21 (s, 3); uv max (95% ethanol) 254 nm (ϵ 10,900); mass spectrum m/e (rel intensity) 218 (M$^+$, 90), 203 (100), 190 (25), 175 (33).

Anal. Calcd for C$_{15}$H$_{22}$O: C, 82.52; H, 10.16. Found: C, 82.44; H, 9.97.

Ozonolysis of Enone 24.—A solution of 350 mg (1.6 mmol) of enone **24** in 50 ml of wet ethyl acetate was ozonized as described before. Glpc analysis (5 ft × 0.25 in., 5% SE-30, 180°) of the neutral residue showed only one major peak. This material was purified by preparative glpc. The spectra (ir and nmr) of the glpc collected material was identical with those of authentic γ,γ-dimethylbutyrolactone (**29**).[16]

Crude acidic material from the ozonolysis was esterified with excess diazomethane to give 351 mg of crude esters which were chromatographed on 50 g of Woelm neutral alumina (activity III). Elution with 220 ml of 10% ether–hexane gave 85 mg of a mixture of three major materials in the ratio of ca. 40:23:20. These compounds were later identified as **28**, **27**, and **26**, respectively, by comparison of their spectra (ir, nmr, and mass spectrum) with the unambiguously synthesized material. Further elution of the chromatography column with 250 ml of 10% ether–hexane gave 154 mg (30%) of oily keto diester **25**. Glpc

examination (10 ft × 0.375 in., 5% SE-30, 225°) of the latter fraction showed only one major peak and the major material was collected from glpc: ir 1740, 1705 cm^{-1}; nmr 1.02 (s, 3), 1.10 (s, 6), 2.52 (s, 2), 2.8 (m, 1), 3.58 (s, 6); mass spectrum m/e (rel intensity) 312 (M$^+$, trace), 249 (12), 183 (100), 155 (24), 95 (52). The absorption peaks in the spectra (ir, nmr) of the glpc collected material are identical with the major absorption peaks in the crude material. The high resolution mass spectrum of the glpc collected material was taken: reference peak 304.9824242, ratio 1.023467, measured peak 312.1943, possible empirical formula C$_{17}$H$_{28}$O$_5$, Δm (mmu) +0.6.

Peracid Treatment of Enone 24.—A solution of 100 mg (0.45 mmol) of enone **24** in 0.4 ml of glacial acetic acid saturated with potassium acetate was maintained at room temperature and 70 ml (0.54 mmol) of commercial 40% peracetic acid in acetic acid was added and stirred for 2.5 hr. Water (3 ml) was added and the mixture was worked up under standard conditions to yield 110 mg of crude material (faint odor of acetic acid). Glpc analysis (5 ft × 0.125 in., 2% SE-30, 155°) showed the presence of starting enone **24** and a new product (retention time ca. 1.1 times that of the enone). The spectra (nmr and ir) indicated that the major material was the unreacted enone. A small amount of enol lactone **41** (ir 1750 cm^{-1}) was present. The crude material was dissolved in 5 ml of dry methanol, 2 drops of concentrated sulfuric acid were added, and the solution was stirred at room temperature under nitrogen overnight. After work-up, there was obtained 130 mg of crude product. Glpc examination indicated the presence of starting enone but the peak at 1.1 times the retention time of the enone was gone and a new peak appeared at a much longer retention time. The crude material was chromatographed on 15 g of Woelm neutral alumina (activity III) to yield 60 mg of the recovered enone **24** and 28 mg (57% based on the recovered starting material) of the keto ester **42**: ir 1745 cm^{-1} (broad); nmr 0.72 (s, 3), 0.92 (s, 3), 1.14 (s, 3), 2.78 (quintet, 1, J = 2.78), 3.58 (s, 3); mass spectrum m/e (rel intensity) 266 (M$^+$, trace), 251 (22), 219 (34), 191 (27), 142 (35), 125 (100), 109 (54), 95 (46). The high-resolution mass spectrum of this material was taken: reference peak 254.9856198, ratio 1.043936, measured peak 266.1887, possible empirical formula C$_{16}$H$_{26}$O$_3$, Δm (mmu) +0.5.

Osmium Tetroxide Oxidation of the Hydrocarbon 6.—A solution of 595 mg (2.92 mmol) of the hydrocarbon **6** and 761 mg (3.0 mmol) of osmium tetroxide in 32 ml of dry ether and 0.75 ml of pyridine was stirred in the dark for 24 days; to the crude osmylation product was added 50 ml of 95% ethanol and 3.0 g (28.8 mmol) of sodium bisulfite (NaHSO$_3$), and the mixture was refluxed for 5 hr. After usual work-up, 605 mg of dark brown residue was obtained. Chromatography of the residue on 60 g of Woelm neutral activity (activity III) gave 396 mg (57%) of the diol **44** which crystallized upon standing. A small portion of the diol was recrystallized from hexane: mp 99–100°; ir 3640, 1005 cm^{-1}; nmr 0.90 (s, 3), 0.98 (s, 3), 1.12 (s, 3), 2.42 (m, 1); mass spectrum m/e (rel intensity) 238 (M$^+$, 1), 220 (40), 151 (100), 138 (69).

Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.85; H, 10.83.

Diketone 38.—Diol **44** (24 mg, 0.104 mmol) was cleaved with lead tetraacetate in a similar manner as described previously for the cleavage of diol **22**. After work-up, 22 mg (90%) of diketone **38** was obtained. The diketone was recrystallized from hexane: mp 132–133°; ir 1710, 1695 cm^{-1}; nmr δ 1.0 (s, 3), 1.25 (s, 3), 1.31 (s, 3), 2.95 (m, 1); mass spectrum m/e (rel intensity) 236 (M$^+$, 17), 218 (3), 208 (8), 193 (22), 154 (78), 126 (100).

Enone 35.—Diketone **38** (20 mg, 0.085 mmol) was treated with base in a similar manner as previously described for the base treatment of diketone **23**. After work-up, 18 mg (97%) of enone **35** (an oil which solidified upon standing) was obtained. The enone was recrystallized from hexane: mp 72–74°; ir 1650, 1620 cm^{-1}; nmr 1.07 (s, 3), 1.10 (s, 3), 2.43 (s, 2), 2.75 (m, 1); uv max (95% ethanol) 258 (ϵ 9500); mass spectrum m/e (rel intensity) 218 (M$^+$, 47), 203 (100), 190 (18), 175 (22).

Anal. Calcd for C$_{15}$H$_{22}$O: C, 82.52; H, 10.16. Found: C, 82.73; H, 9.97.

Ozonolysis of Enone 35.—A solution of 123 mg (0.5 mmol) of enone **35** was ozonized as described previously. Wet neutral residue (27 mg) from the ozonolysis contained γ,γ-dimethylbutyrolactone. Acidic material from the ozonolysis was esterified with diazomethane. The crude esters were chromatographed on 30 g of Woelm neutral alumina (activity III). Elution with 50 ml of 10% ethyl acetate–hexane gave 30 mg of a

mixture of diesters. The major diester (ca. 80%) was **28**. In addition, small amounts of **26** and **45** were isolated. Further elution with 50 ml of 10% ethyl acetate–hexane gave 42 mg (23%) of the keto diester **30**: ir 1745, 1710 cm^{-1}; nmr δ 1.05 (s, 3), 1.1 (s, 6), 2.35 (s, 2), 3.6 (s, 6); mass spectrum (glpc collected) m/e (rel intensity) 312 (M$^+$, trace), 281 (7), 24.9 (5), 183 (100), 155 (28), 123 (35), 95 (46), 81 (67). The spectra (ir and nmr) of the glpc collected material (5 ft × 0.25 in., 5% SE-30, 220°) were identical in major respect with the spectra of the alumina chromatograph fraction 2. The high-resolution mass spectrum of the glpc collected material was taken: reference peak 304.9824242, ratio 1.023645, measured peak 312.1937, possible empirical formula C$_{17}$H$_{28}$O$_5$, Δm (mmu) 0.0.

Peracid Treatment of Enone 35.—Enone **35** (80 mg, 0.37 mmol) was oxidized with peracetic acid in a similar manner as described for the oxidation of enone **24**. After work-up and chromatography, 40 mg (50%) of starting enone **35** was recovered and 15 mg (30% based on recovered starting material) of cyclopentanone ester **43** was obtained: ir 1745 cm^{-1}; nmr 0.99 (s, 3), 1.02 and 1.06 (two s, total 3 H), 1.2 (s, 3), 2.3 (s, 2), 3.6 (s, 3); mass spectrum m/e (rel intensity) 266 (M$^+$, 1), 235 (3), 219 (3), 193 (2), 155 (8), 154 (7), 112 (31), 97 (100), 81 (52); high resolution mass spectrum, reference peak 254.9856198, ratio 1.043935, measured peak 266.1884, possible empirical formula C$_{16}$H$_{26}$O$_3$, Δm (mmu) +0.1. The chromatographed material showed only a single spot on tlc and a single peak on glpc (2% SE-30, 5 ft × 0.125 in., 155°).

1-Methylnorbornene (46).—The procedure is similar to that of Jefford.[15] Methylcyclopentadiene dimer (340 g, 2.12 mol) and 10.0 g of sodium bicarbonate were placed in a hydrogenation bomb with glass liner. The bomb was charged with ca. 1000 psi of ethylene and heated to 190° while shaking. After 7 hr, heating was stopped, the bomb was cooled, and the mixture was processed. Clear liquids distilling between 100 and 115° were collected (20-cm column) in two fractions (282 g, 64%). The earlier fraction (112 g, 36% **46** and 63% 2-methylnorbornene) was further distilled on a Teflon spinning band column to give 20 g of 1-methylnorbornene (**46**) of greater than 90% purity.

Bromides 47 and 48.—Potassium *tert*-butoxide (16.8 g, 150 mmol) was added slowly in small portions to a solution of 6 g (55 mmol) of 1-methylnorbornene and 13 ml (37.8 g, 150 mmol) of bromoform in 70 ml of olefin-free pentane. The resulting yellow paste was stirred at room temperature for 14 hr, and after work-up, 10.9 g of crude product which contained some *tert*-butyl alcohol and bromoform was obtained. The nmr of the crude product indicated the presence of two dibromides as previously reported.[17] The crude dibromides were dissolved in 50 ml of dry ether and added slowly to a suspension of 27 g (71 mmol) of lithium aluminum hydride in 100 ml of dry ether. The reaction mixture was refluxed under nitrogen for 14 hr, a saturated aqueous solution of sodium sulfate was carefully added, and the mixture was processed to yield 3.5 g (32%) of crude bromides, the nmr of which showed the bromides **47** and **48** in ca. 3:2 ratio.

Ozonolysis of the Bromides 47 and 48.—A mixture of bromides **47** and **48** (540 mg, 2.28 mmol) from the preceding experiment was ozonized as described previously. After esterification and work-up, 320 mg (65%) of a mixture of diesters **26** and **49** in ca. 3:2 ratio (glpc, 20% DEGS, 5 ft × 0.25 in., 170°) was obtained. The diesters were separated on glpc. Peak I (shorter retention time and present in lesser amount): ir 1745 cm^{-1} (broad); nmr δ 1.2 (s, 3), 2.0–2.5 (m, 4), 3.54 (s, 3), 3.56 (s, 3); mass spectrum m/e (rel intensity) 214 (M$^+$, 1), 183 (5), 155 (88), 141 (82), 123 (63), 81 (100). Peak II: ir 1745 cm^{-1} (broad); nmr 1.04 (s, 3), 2.28 (s, 2), 2.8 (quintet, 1, $J = 8$ Hz), 3.58 (s, 6); mass spectrum m/e (rel intensity) 183 (66), 154 (51), 141 (100), 77 (81), 81 (75).

Anal. Calcd for C$_{11}$H$_{18}$O$_4$ (Peak II): C, 61.66; H, 8.47. Found: C, 61.77; H, 8.39.

Diester 27.—1-Methylnorbornene (**46**) (1.0 g, 9.25 mmol) was ozonized as described previously. After esterification and work-up 925 mg of crude diester **27** was obtained. The nmr of the crude product showed the presence of acidic proton (δ 10.2); therefore, the crude material was filtered through 60 g of Woelm neutral alumina (activity II) to give a neutral fraction (497 mg) which was ca. 90% in the desired diester **27**. The diester **27** was further purified by preparative glpc (5 ft × 0.25 in., 5% SE-30, 170°): ir 1745 cm^{-1}; nmr 1.22 (s, 3), 2.8 (quintet, 1, $J = 8$ Hz),

3.48 (s, 3), 3.50 (s, 3); mass spectrum m/e (rel intensity) 200 (M$^+$, trace) 169 (12), 147 (57), 140 (48), 109 (60), 81 (100). The structure of the minor material was not determined, but since the starting material contained a small amount of 2-methylnorbornene, the impurity was thought to arise from this material.

Dimethyl 2,2-Dimethylglutarate (28).—A solution of 1.0 g (8.06 mmol) of 4,4-dimethylcyclohexenone[18] was ozonized as described previously. After esterification and work-up, 0.9 g of crude product was obtained. The glpc analysis (5 ft × 0.25 in., 5% SE-30, 180°) showed two major materials (40 and 44%), a trace of starting material, and ca. 5% each of unidentified materials. The two major peaks were collected on glpc. Peak I (shorter retention time and present in 40%): ir 2800, 2700, 1750 cm^{-1}; nmr δ 1.06 (s, 3), 1.78 (s, 2), 2.8 (m, 2), 3.6 (s, 4), 9.36 (s, 1); mass spectrum m/e 130 (39), 129 (20), 127 (46), 97 (55), 74 (100), 69 (97). This material was assigned to be 2,2-dimethyl-4-carbomethoxybutylaldehyde on the basis of the spectral data. Peak II (present in 44%) is the desired diester **28**: ir 1745 cm^{-1}; nmr 1.12 (s, 6), 1.6–2.3 (m, 4), 3.56 (s, 3), 3.58 (s, 3); mass spectrum m/e (rel intensity) 157 (7), 129 (84), 102 (29), 97 (65), 69 (100).

3-Keto-1-methylnorbornane (51).—To a solution of 4.5 g (41.6 mmol) of 85% pure 1-methylnorbornene (the other 15% was 2-methylnorbornene) in 50 ml of tetrahydrofuran at 0° under nitrogen there was added 60 ml (ca. 60 mmol) of ca. 1.0 M solution of disiamyldiborane in tetrahydrofuran. The reaction mixture was stirred at 0° for 30 min and an additional 16 hr at room temperature. Water (20 ml) was added carefully followed by addition of 20 ml of 3 N sodium hydroxide and 20 ml of 30% hydrogen peroxide. The reaction mixture was warmed at 50° for 1 hr and worked up in the standard fashion.

The crude alcohols were dissolved in 40 ml of acetone and oxidized with Jones reagent. After work-up, 4.35 g of crude ketone was obtained. Glpc analysis showed the ratio of 3-keto-1-methylnorbornane (**51**) to 2-keto-1-methylnorbornane (**50**) to be ca. 4:1.[19] The crude product (4.0 g, 90% of the total crude product) was chromatographed on 400 g of silica gel using an automatic fraction collector and 2% ether–hexane as the eluent. 2-Keto compound **50** was eluted first. 3-Keto-1-methylnorbornane (**51**) was obtained in ca. 85% purity after chromatography and was used directly in the next experiment.

Baeyer–Villager Oxidation of 3-Keto-1-methylnorbornane.—To a cooled solution of 611 mg (4.15 mmol, 85% pure) of 3-keto-1-methylnorbornane (**51**) in 2.14 ml of glacial acetic acid and 1.5 ml of concentrated sulfuric acid, there was added 1.04 ml (8.0 mmol) of 40% peracetic acid in acetic acid. The resulting dark solution was stirred at room temperature for 2 hr in the dark, poured into a cold solution of 8.5 g of sodium carbonate in 100 ml of water, and processed to yield 531 mg (91%) of crude lactone **52**. Glpc examination of the crude material indicated the presence of only one major material (91%). The lactone **52** was purified by preparative glpc: ir 1750, 1040, 1028, 1000 cm^{-1}; nmr δ 1.05 (s, 3), 2.35 (s, 2), 4.68 (brd, 1); mass spectrum m/e (rel intensity) 140 (M$^+$, 13), 111 (24), 97 (93), 96 (72), 82 (100).

Similar treatment of the approximate 3:2 mixture of 3-keto- and 2-keto-1-methylnorbornanes gave a crude product whose spectra (ir and nmr) indicated only one major product, that of the lactone **52**. Presumably the lactone formed from 2-keto-1-methylnorbornane is a tertiary butyl type lactone and as such it is unstable in strong acid and opens to an acid which will be lost during alkaline work-up.

Methyl 3-Keto-1-methylcyclopentaneacetate (45).—The crude lactone **52** (450 mg, 3.2 mmol) from the previous experiment was dissolved in 20 ml of reagent-grade methanol and 0.07 ml of concentrated sulfuric acid was added. The reaction mixture was stirred at room temperature for 22 hr, diluted with 30 ml of half-saturated aqueous sodium bicarbonate solution, and processed to yield 410 mg of crude product. The nmr spectrum indicated that the crude product was a mixture of starting lactone **52** and the hydroxy ester **53** in ca. 1:2 ratio. The crude material was dissolved in 10 ml of reagent grade acetone and oxidized with Jones reagent at 0°. After the usual work-up, 380 mg of oily material was obtained. Glpc analysis (20% cyanosilicone, 5 ft × 0.25 in., 180°) of crude product showed two materials in ca. 68% and 32% yield. They were separated by preparative glpc. The minor component (32%) had a glpc retention time and spec-

(17) C. W. Jefford, S. N. Mahajan, and J. Funsher, *Tetrahedron*, **24**, 2921 (1968).

(18) E. L. Eliel and C. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

(19) Using (+)-diisopinocampheylborane, H. C. Brown and coworkers [*J. Amer. Chem. Soc.*, **86**, 397 (1964)] obtained a ratio of isomers of 88:12.

tra (ir and nmr) identical with those of lactone **52**. The major material (68%) had the following physical properties: ir 1750 cm⁻¹ (broad); nmr δ 1.17 (s, 3), 2.06 (AB quartet, 2), 2.33 (s, 2), 3.60 (s, 3); mass spectrum *m/e* (rel intensity) 170 (M⁺, 1), 155 (5), 139 (18), 97 (100). This material was identical with one of the ozonolysis product of enone **35**.

Mirestrol. I. Preparation of the Tricyclic Intermediate

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The synthesis of (±)-6aβ,7,8,9,10,10aα-hexahydro-3-methoxy-10,10-dimethyl-6*H*-dibenzo[*b,d*]pyran-9-one (**3**) from 3-(β-carbethoxyethyl)-4-methyl-7-hydroxycoumarin (**12a**) through **12b**, **2a**, **15a**, **16**, **17a**, **18**, **19a**, **19b**, and **20** (Schemes II and III) is described. This multistep transformation involved ring closure to the tricyclic unsaturated lactone **2a** and conversion to the cyclic ether **17a** followed by the introduction of two methyl groups at C-10 to give **20**.

Mirestrol (**1a**) was isolated[1] from the tuber of *Pueraria mirifica* which has been used locally in southeast Asia as a rejuvenating drug. The highly potent estrogenic activity of mirestrol was reported,[1a,2] but a limited supply of the natural resource has restricted extensive physiological studies. The structure of mirestrol was elucidated[3] by X-ray crystallographic studies on the monobromo derivative **1b**.[4]

1a, R = H
b, R = Br
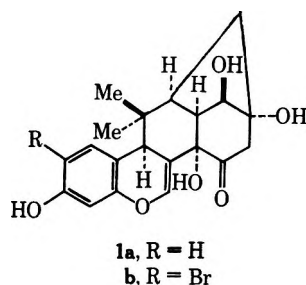
This communication deals with the preparation of the A,B,C ring system of mirestrol, which is properly functionalized for eventual conversion into the pentacyclic ring system of the natural product. The tricyclic lactones of type **2** were the first targets and the conversion of **2a** into **3** was the subsequent objective

2a, R¹ = R² = H
b, R¹ = Me, R² = H
c, R¹ = R² = Me

3

of this study. While all synthetic compounds containing asymmetric carbon are racemic, only one enantiomer is depicted as a matter of convenience.

Preparation of Tricyclic Lactones 2a, 2b, and 2c.—As the most direct approach to obtain **2c**, the Pechmann reaction of resorcinol with **5** was examined. The latter was prepared (Scheme I) by condensation of 2,2-di-

4a, R = H₂
b, R = C(OH)CO₂Et

5

6
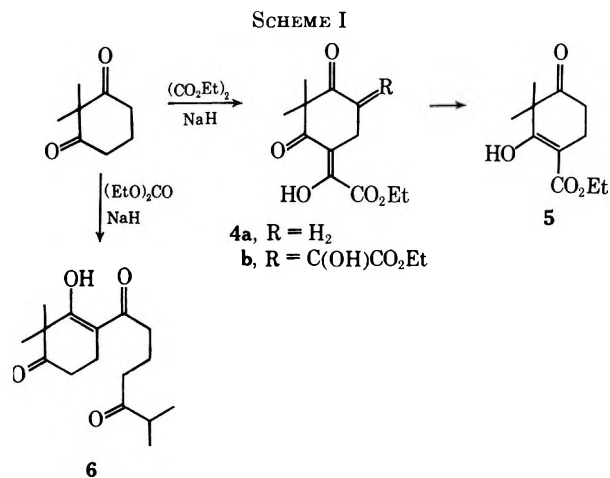
methylcyclohexane-1,3-dione[5] and diethyl oxalate to **4a** followed by pyrolysis. A double condensation product **4b** was obtained as a by-product which gave rise to **7**

7

8
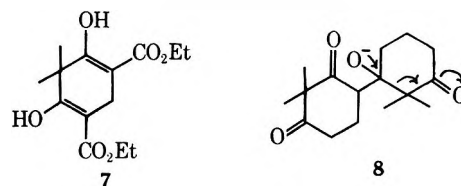
on pyrolysis. Direct carbethoxylation of 2,2-dimethylcyclohexane-1,3-dione with diethyl carbonate in the

(1) (a) W. Schoeller, M. Dohrn, and W. Hohlweg, *Naturwissenschaften*, **33**, 532 (1940); (b) G. S. Pope, H. M. Grundy, H. E. H. Jones, and S. A. S. Tait, *J. Endocrinol.*, **17**, xv (1958); (c) J. C. Cain, *Nature*, **188**, 774 (1960).

(2) (a) H. E. H. Jones and G. S. Pope, *J. Endocrinol.*, **22**, 303 (1961), and references cited therein; (b) L. Terenius, *Acta Pharmacol. Toxicol.*, **26**, 15 (1968), and references cited therein.

(3) N. E. Taylor, D. C. Hodgkin, and J. S. Rollett, *J. Chem. Soc.*, 3685 (1960).

(4) D. G. Bounds and G. S. Pope, *ibid.*, 3696 (1960).

(5) I. N. Nazarov, *Zh. Obshch. Khim.*, **23**, 1703 (1953); *Izv. Akad. Nauk SSSR*, **32** (1956); *ibid.*, 325 (1957); *Chem. Abstr.*, **48**, 13667 (1954); **50**, 13847 (1956); **51**, 14597 (1957).

presence of sodium hydride did not produce 5, but exclusively 6 as the result of an intermolecular aldol condensation followed by an intramolecular retroaldol reaction (see 8). Unfortunately, 5 did not undergo the Pechmann reaction with resorcinol either under standard conditions[6] or under forcing conditions.[7] It was desirable to achieve introduction of the geminal dimethyl group, as well as formation of ring B and ring C in a single reaction, but it was now realized that the steric interference between the geminal dimethyl group and the aromatic ring had been underestimated.

The Pechmann reaction of resorcinol or its monomethyl ether with open-chain β-keto esters followed by ring closure to 2c was subsequently examined, in the hope that the open-chain compounds would be flexible enough to reduce steric interference. While 9a[8] and 9b were obtained by the boron trifluoride procedure, the condensation of resorcinol monomethyl ether with either 11a[9] or 11b did not produce 10a or 10b under a variety of conditions.

9a, R = H
b, R = Me

10a, R = H
b, R = CO₂Et

Me₂CRCOCHCO₂Et
|
CH₂CH₂CO₂Et

11a, R = H
b, R = CO₂Et

Finally 12a,[10] the Pechmann reaction product of resorcinol and diethyl 2-acetylglutarate, was chosen as the starting material and was converted into the methyl ether 12b. The latter could be prepared in one step, though in less satisfactory overall yield, from resorcinol monomethyl ether by the boron trifluoride procedure. The methyl ether 12b was readily cyclized to 2a (see Scheme II). It is worth noting that the double bond in 2a stayed between the aromatic ring and lactone group rather than between the aromatic and ketonic group. Methylation of the potassium

13

14a, R¹ = R² = Me
b, R¹ = Me; R² = H

(6) Sixteen hours in concentrated sulfuric acid or 3 days in ethanol saturated with hydrogen chloride.

(7) (a) Phosphorus oxychloride in boiling toluene; see R. Adams and B. R. Baker, *J. Amer. Chem. Soc.*, **62**, 1401 (1940). (b) Boron trifluoride in refluxing benzene under the continuous removal of water. A modification of the boron trifluoride procedure was first used by Indian workers; see L. G. Shah, G. D. Shah, and R. C. Shah, *J. Indian Chem. Soc.*, **32**, 302 (1955); *Chem. Abstr.*, **50**, 4927 (1956). (c) After this work had been completed, a novel modification of the Pechmann reaction for a sterically hindered coumarin was published which might be applicable in this case. See G. Büchi and S. M. Weinreb, *J. Amer. Chem. Soc.*, **91**, 5408 (1969).

(8) This compound was previously synthesized in three steps: B. B. Dey, *J. Chem. Soc.*, 1633 (1915).

(9) F. Korte, K.-H. Büchel, and L. Schiffer, *Chem. Ber.*, **91**, 763 (1958).

(10) M. M. Shah and R. C. Shah, *Ber.*, **71B**, 2075 (1938).

SCHEME II

12a, R = H
b, R = Me

2a

2b, R¹ = H; R² = Me
c, R¹ = R² = Me

enolate of 2a give rise to a single product 2b. The C-methyl group exhibited a doublet at τ 8.50 (J = 7.5 Hz) excluding all structural alternatives. The subsequent methylation of 2b using similar conditions afforded 2c as the major product (35%), whereas the other C-alkylation product 13, an O-alkylation–oxidation product 14a, and an oxidation product 14b were isolated as minor products. The preferential formation of 2c over 13 is similar to the alkylation of Hagemann's ester.[12]

Preparation of Tricyclic Ketone 3.—The direct transformation of 2c to 3 could not be carried out due to steric interference between the C-1 aromatic hydrogen and the geminal dimethyl group. Once the B ring was opened, all attempts to restore the tricyclic system of 3 were unsuccessful. The synthesis of 3 was finally achieved by the transformation of the less hindered 2a into 17a (see Scheme III) and subsequent introduction of the geminal dimethyl group.

Lithium aluminum hydride reduction of the ethylene ketal 15a, which was readily obtained from 2a in the usual manner, gave 16. The uv spectrum of 16 showed that the aromatic ring and the double bond were not coplanar. Treatment of 16 with refluxing aqueous acetic acid produced an intractable resin. However, when 16 was refluxed in aqueous acetic acid containing a weak base, both 17a and 21a were obtained. Though

21a, R = H
b, R = Me
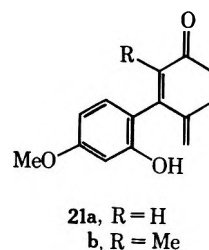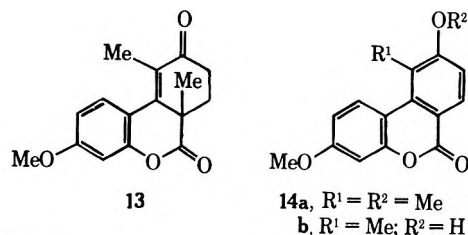
the uv spectrum suggested that the two rings were noncoplanar, 21a could be cyclized to 17a upon treatment with acid–base or with pyridine. The lithium–ammonia reduction of 17a afforded either 22a or 23

(11) A similar cyclization was recorded in the literature: K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Amer. Chem. Soc.*, **88**, 2079 (1966).

(12) (a) C. Th. L. Hagemann, *Ber.*, **26**, 876 (1893); (b) R. B. Turner, O. Buchart, E. Herzog, R. B. Morin, A. Riebel, and M. J. Sanders, *J. Amer. Chem. Soc.*, **88**, 1766 (1966).

SCHEME III

depending upon the reaction conditions. The latter was also obtained by the borohydride reduction of **22a**. Reductive alkylation[13] of **17a** afforded **18**.

The nmr data indicated that the C-10 methyl group of **18** is axial and the B/C ring juncture is trans,[14] as will be discussed later. It is worth emphasizing that the axial methyl group is in the more stable configuration, as it is free from serious steric interaction with the C-1 hydrogen. In agreement with this, **18** was not epimerized upon treatment with either hot hydrochloric acid or hot sodium carbonate solution.

An analogous series of reactions starting from the ketal of **2b** would, in a formal sense, afford **17b** and then **3** by the subsequent reductive alkylation. Actually **17b** could not be isolated, and **21b** and **24** were obtained
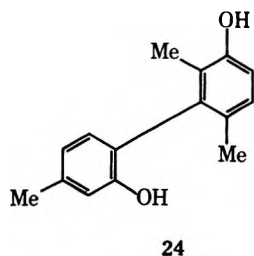
(13) (a) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (b) G. Stork, P. Rosen, and N. L. Goldman, *ibid.*, **83**, 2965 (1961).

(14) The B/C juncture is predicted to be trans based upon theoretical considerations. See ref 13b and G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960); **86**, 1761 (1964).

instead, this result being attributed to serious steric interaction of the C-1 hydrogen and the C-10 methyl in the hypothetical **17b**.

Introduction of the C-10 equatorial methyl group in **18** was the most difficult part of this work, due not only to the steric hindrance, but also to a rather unexpected tendency of **22a**, **18**, and **20** to readily undergo fragmentation giving rise to phenolic substances.

The *n*-butylthiomethylene derivative **22c**, obtained *via* **22b** in the well-known manner,[15] gave rise to the red potassium enolate which reacted with methyl iodide under standard conditions.[15] Subsequent alkaline cleavage of the protecting group to generate **18**, however, resulted in phenolic substances. It was later found that **18** itself was readily decomposed in boiling alkali to phenolic products. This behavior might be rationalized by fragmentations as depicted in **25**. Vari-

ous reagents, both acidic[16] and basic, failed to remove the protecting group without destroying the compound.
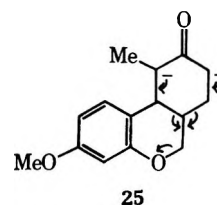
After the *N*-methylanilinomethylene[17] and trimethylene dithioketal groups[18] had been examined, attention was directed to the isopropoxymethylene group of

(15) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615, 1620 (1962).

(16) The original authors[15] suggested a possibility of acid hydrolysis of this protecting group to the hydroxymethylene group. This idea could not be expedited in our hands.

(17) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944).

(18) (a) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. Ives, and R. B. Kelly, *ibid.*, 1131 (1957). (b) For application to saturated ketones, see B. Gaspert, T. G. Halsall, and D. Willis, *ibid.*, 624 (1958).

TABLE I
NMR SPECTRA OF 18, 19a, 3, AND 20[a]
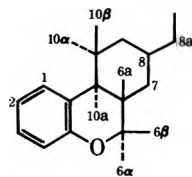
Compd	Solvent	C-1 H (J, Hz)	C-6β H (J, Hz)	C-6α H (J, Hz)	C-10a H (J, Hz)	C-10β Me (J, Hz)	C-10α Me	
18	CDCl₃	3.14 d (8.5)	5.75 q (10.5, 3.5)	6.30 t (10.5)	Overlapped	9.02 d (7)		Methoxy 6.28
	C₆D₆	Overlapped	6.20 q (10.5, 3.5)	6.78 t (10.5)	7.59ᶜ q (11.5, 4.5)	9.29 d (7.5) Δ + 0.27ᵈ		Methoxy 6.70
19a	CDCl₃	3.07 d (8.5)	5.72 q (10.5, 3)	6.28 t (10.5)	Overlapped	9.01 d J 7		Methoxy 6.27 C-8a 1.18, d (1.5)
	C₆H₆	3.35ᵇ d (8.5)	6.11 q (10.5, 3.5)	6.71 t (10.5)	7.66ᶜ q (11, 5)	9.13 d (7) Δ + 0.12ᵈ		Methoxy 6.67 C-8a 1.56, d, (1.0)
3	CDCl₃	2.68ᵇ d (8.5)	5.86 q (10.5, 3.5)	6.40 t (10.5)	7.09ᶜ d (11)	9.08 s	8.47 s	Methoxy 6.28
	C₆D₆	2.80ᵇ d (9)	6.28 q (10.5, 4)	6.82 t (10.5)	7.56ᶜ d (11.5)	9.15 s Δ + 0.07ᵈ	8.59 s	Methoxy 6.69
20	CDCl₃	2.63ᵇ d (8.5)	5.81 q (10, 2.5)	6.34 m	7.25ᶜ Deformed d (10)	9.01 s	8.32 s	Methoxy 6.27 C-8a 1.31, d, (3)
	C₆D₆	2.77ᵇ d (8.5)	6.21 q (10.5, 3.5)	6.75 t (10.5)	7.65ᶜ d (11)	9.05 s Δ + 0.04ᵈ	8.46 s	Methoxy 6.69 C-8a 1.76, d (3)

[a] The 100-MHz nmr spectra were determined on a Varian HA-100 and chemical shifts are reported in τ values downfield from an internal standard of tetramethylsilane. [b] The long-range coupling with the C-10a proton was observed. [c] The long-range coupling with the C-1 proton was observed. [d] Solvent shift δ (CDCl₃) − δ (C₆D₆) or τ (C₆D₆) − τ (CDCl₃).

Johnson and Posvic,[19] which, to the best of our knowledge, has only been used by the original authors. This protecting group, being very sensitive to either weak acids or weakly nucleophilic solvents, was easily removed after the alkylation. Under carefully controlled conditions, the isopropoxymethylene group gave satisfactory results. Thus, the hydroxymethylene ketone 19a, which was readily prepared from 18, was converted into the isopropoxymethylene ketone 19b in the usual manner[19] or by simply recrystallizing 18 from isopropyl alcohol. The potassium enolate was generated at room temperature[20] by treatment of 19b with freshly prepared potassium amide[21] in ether. Alkylation of the enolate with methyl iodide and the subsequent acidic work-up afforded 3 and 20 as the major products and small amounts of 26 and 27. Cleavage of 20 with boiling sodium carbonate solution gave 3 in quantitative yield.

The nmr spectrum (see Table I) of 20 in deuteriobenzene exhibited a C-10a proton (benzylic) signal at τ 7.65 (d, 1, J = 11 Hz), clearly demonstrating the trans juncture. This doublet was broader than other

(19) W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, **69**, 1361 (1947).

(20) At higher temperature, extensive fragmentation to phenolic substances took place.

(21) Commercial potassium amide did not work at all. Sodium hydride, freshly prepared sodium amide, and potassium *tert*-butoxide were examined, but invariably failed to generate the enolate at room temperature.

racemic and/or meso

26

27

signals, indicating the long-range coupling with the C-1 proton which was confirmed by the decoupling experiment. It is very reasonable to assume that 3, 18, 19a, 19b, 20, 22a, 22b, 22c, 26, and 27 all have the same B/C juncture based upon the way of their preparation. The C-10a proton signals of some of these compounds (Table I, see also Experimental Section) confirmed this view.

It has been mentioned that serious steric interference exists between the C-1 proton and the C-10α (equa-

torial) methyl group. In line with this, the C-1 proton signal and the C-10α methyl[22] signal of **3** and **20** appeared at unusually low field because of this steric crowding. The nuclear Overhauser effect confirmed this spacial proximity: irradiation of the methyl signal at τ 8.32 of **20** in deuteriochloroform increased the integration of the C-1 proton at τ 2.63 by as much as 16–20%.

The fact that the C-10 methyl groups of **18** and **19a** are axial (C-10β) could be easily deduced from the chemical shifts as well as from the upfield solvent shifts,[23] that is, positive δ (CDCl₃) − δ (C₆D₆) (Table I). Additional evidence was provided by the normal chemical shift of the C-1 proton as well as by the coupling constant (4.5–5 Hz, suggesting the cis relationship) of the C-10a proton and the C-10α proton.

Lithium in ammonia reduction of **15a** followed by acidic work-up afforded an oily product which was best represented by **28a**, though an alternative structure **29a** could not be excluded.

28a, R¹ = R² = H
b, R¹ = Ac; R² = H
c, R¹ = H; R² = Me

29a, R = H
b, R = Ac
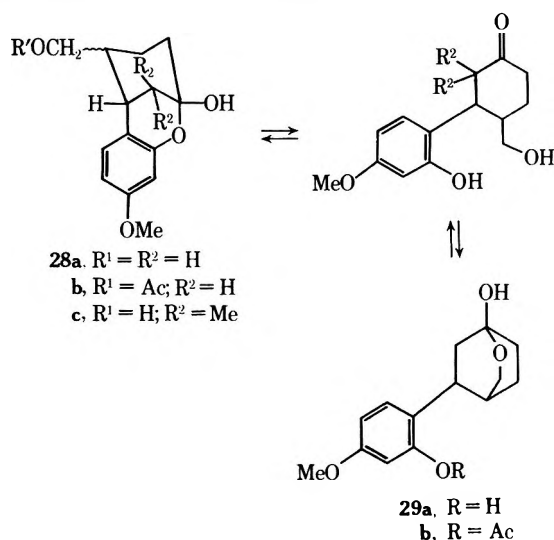
The nmr signal at τ 6.80 (m, 1, $W_{1/2}$ = 12 Hz) suggested that the benzylic proton is equatorial.[24]

A

B

When refluxed in acetic acid–water–pyridine, **28a** gave the crystalline monoacetate **28b**. The downfield shift of 0.4 ppm by the –CH₂O– signal of the latter is better rationalized by **28a → b** than **29a → b**. When nondistilled ammonia was used in the lithium reduction, **28a** was obtained along with a crystalline substance $C_{14}H_{20}O_3$, best formulated as **30a**. The diacetate **30b**, prepared from **30a** by acetic anhydride in pyridine,

30a, R = H
b, R = Ac
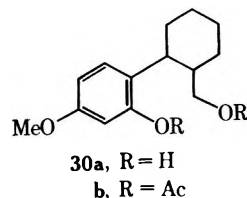
was also crystalline. Wolff–Kishner reduction of **28a** gave **30a**, thus interrelating the two products. The hydrogenolysis of the ethylene ketal group in undistilled ammonia may be due to the presence of lithium amide,[25,26] which would have catalyzed a transient formation of i.

15a

i

ii
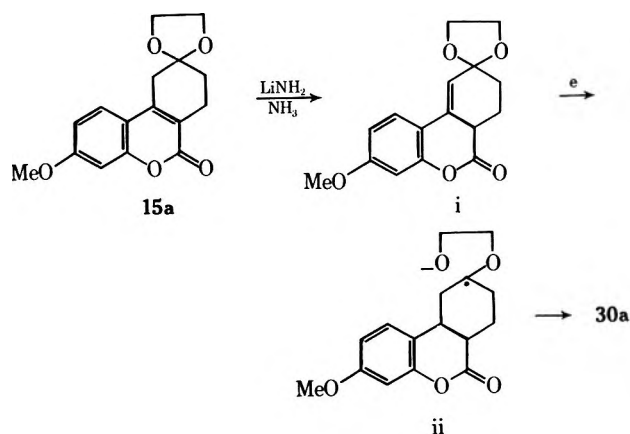
A similar reduction of **15b** in distilled ammonia gave **28c**, whose nmr signal at τ 7.29 (d, 1, J = 2.5 Hz) indicated that the benzylic proton is equatorial.

Attempted cyclization of **28a** or **28c** to **31a** or **31b** has so far been unsuccessful.

31a, R = H
b, R = Me
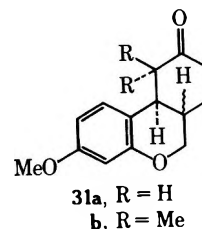
Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover Unimelt. All melting and boiling points are uncorrected. The nmr spectra were taken on a Varian A-60 spectrometer with TMS as an internal reference and the data are given in τ values (ppm). Unless otherwise stated, concentrations were carried out *in vacuo* (water pump pressure).

(22) The downfield shift of the C-10α methyl group may be partially due to deshielding by the aromatic ring.

(23) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 169; (b) R. S. Matthews, P. K. Hyer, and E. A. Folkers, *Chem. Commun.*, 38 (1970).

(24) The aromatic ring and hydroxymethyl group in **28a** and **28c** are more likely to be cis than trans, considering the transition states of protonation (by ethanol) leading to cis (A) and trans (B) isomers.

(25) Traces of iron present in undistilled ammonia catalyze the formation of the alkaline metal amide or the metal alkoxide; for instance, see C. R. Hauser and W. H. Peterbaugh, *J. Amer. Chem. Soc.*, **75**, 1068 (1964).

(26) The undistilled ammonia contains traces of iron. See H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

2,2-Dimethyl-4-ethoxalylcyclohexane-1,3-dione (4a). A.— To a suspension of 4.3 g of 56% sodium hydride mineral oil in 250 ml of anhydrous ether was added a mixture of 14.0 g of 2,2-dimethylcyclohexane-1,3-dione[5] and 29 g of diethyl oxalate. The mixture was stirred under reflux for 3 hr. In case the reaction did not start after 30 min of refluxing, 2 drops of ethanol were added as an initiator. The reaction mixture was cooled with an ice bath, neutralized with aqueous acetic acid, and extracted with ether. The ethereal extract was washed with bicarbonate solution containing sodium chloride. The bicarbonate washing was acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate, and concentrated, and the residue was distilled. The fraction boiling at 120–145° (0.5–1.0 mm) was collected (7.9 g) and redistilled, giving 6.7 g (29%) of 4a: bp 120–121° (0.25 mm); uv max (MeOH) 312 mμ (ϵ 10,600); ir (CHCl$_3$) 1734, 1726, 1623, 1577 cm^{-1}; nmr (CDCl$_3$) τ 8.58 (s, 6), 7.22 (m, 4, H-5 and -6), 2.61 (s, 1, enolic H).

Anal. Calcd for C$_{12}$H$_{16}$O$_5$: C, 59.99; H, 6.71. Found: C, 59.74; H, 6.51.

The neutral fraction gave 6.5 g of ethyl 4-keto-5-methylhexane-1-carboxylate:[27] bp 65–67° (0.25 mm); ir (CHCl$_3$) 1733 (ester), 1710 cm^{-1} (ketone); nmr (CDCl$_3$) τ 8.90 (d, 6, J = 7 Hz).

B.—To a solution of 88.8 g of 2,2-dimethylcyclohexane-1,3-dione[5] and 200 g of diethyl oxalate in 300 ml of anhydrous ether was added 27.5 g of 56% sodium hydride in mineral oil. The mixture was refluxed gently (39–42°) for 2 hr and worked up as described above. The bicarbonate-soluble fraction gave 24.7 g (16.3%) of 4a boiling at 125° (0.4–0.5 mm) and 10 g of higher boiling [130–180° (0.8 mm)] material which was mostly 4b. The latter was decarbonylated without purification.

2,2-Dimethyl-4-(2-methyl-3,7-heptanedione)cyclohexane-1,3-dione (6).—A suspension of 8.6 g of 56% sodium hydride mineral oil in 150 ml of benzene containing 40 g of diethyl carbonate was heated to 90°, to which a solution of 14.6 g of 2,2-dimethylcyclohexane-1,3-dione[5] in 100 ml of benzene was added during 1 hr. The mixture was stirred at 85–90° for an additional 1.5 hr, cooled, neutralized with 15 ml of acetic acid, decomposed with 150 ml of water, and extracted with ether. The ethereal extract was washed with bicarbonate solution, dried on sodium sulfate, and concentrated to an oily residue, which was distilled through a 20-cm column, giving 11.0 g (80%) of 6: bp 168–170° (0.5 mm); uv max (MeOH) 288 mμ (ϵ 8480); ir (CHCl$_3$) 1720 (ketones), 1560–1640 cm^{-1} (enolic β-diketone); nmr (CDCl$_3$) τ 8.91 (d, 6, J = 7 Hz), 8.67 (s, 6), 7.40 (s, 4, H-5 and -6, this peak was transformed to m in pyridine), 1.96 (s, 1, enolic H).

Anal. Calcd for C$_{16}$H$_{24}$O$_4$: C, 68.54; H, 8.62. Found: C, 68.85; H, 8.93.

2,2-Dimethyl-4-carbethoxycyclohexane-1,3-dione (5).—4a (15 g) was distilled in the presence of 0.5 g of soft glass powder and a trace (less than 1 mg) of iron powder at a bath temperature of 180°. The fraction (7.4 g) boiling at 135–145° (12 mm) was redistilled through a 20-cm column, giving pure 5: bp 93° (0.5 mm); uv max (MeOH) 254.5 mμ (ϵ 9340); ir (CHCl$_3$) 1723 (ketone), 1653 (ester), 1613 cm^{-1} (enolic C=C); nmr (CDCl$_3$) τ 8.65 (s, 6), 7.43 (s, 4, H-5 and -6), −2.6 (s, 1, enolic H).

Anal. Calcd for C$_{11}$H$_{16}$O$_4$: C, 62.25; H, 7.60. Found: C, 62.50; H, 7.76.

2,2-Dimethyl-4,6-dicarbethoxycyclohexane-1,3-dione (7).— The higher boiling fraction (4b) obtained in the preparation of 4a was distilled in the presence of soft glass powder. The distillate, containing long needles, was filtered and the crystals were purified by recrystallization from cyclohexane and sublimation at 100° (0.05 mm) to give 7: mp 159–161°; uv max (MeOH) 242 mμ (ϵ 18,480); ir (CHCl$_3$) 2560–3570 (broad, enolic OH), 1681, 1652, 1612, 1241 cm^{-1} (strongest band); nmr (CDCl$_3$) τ 8.65 (t, 6, J = 7.5 Hz), 8.53 (s, 6), 6.94 (s, 2, H-4), 5.69 (q, 4, J = 7.5 Hz), −2.6 (s, 2, enolic H).

Anal. Calcd for C$_{14}$H$_{20}$O$_6$: C, 59.14; H, 7.09. Found: C, 59.07; H, 7.26.

Ethyl 7-Methoxycoumarin-4-acetate (9a).—A solution of 3.7 g of resorcinol monomethyl ether, 6.0 g of diethyl acetonedicarboxylate, and 4.2 g of boron trifluoride etherate in 30 ml of

(27) S. Eskola, A. Auvienen, A. Hirvines, T. Rinne, and R. Waris, *Suom. Kemistilehti,* **27B**, 88 (1954); *Chem. Abstr.,* **50**, 5559 (1956). Undoubtedly

formed by the reversed Claisen condensation.

benzene was refluxed for 3 hr under continuous water separation. Most of the water (totally 0.5 ml) was separated during the first 1 hr. The reaction mixture was poured into bicarbonate solution, stirred for 2 hr, and extracted with additional benzene. The benzene extract was washed with water, dried over sodium sulfate, and concentrated. Crystallization of the residue from 25 ml of benzene–cyclohexane (1 : 1) yielded 4.3 g (55%) of 9a: mp 101.5–103° (lit.[8] mp 101.5–103°); uv max (MeOH) 220 mμ (ϵ 17,400), 323.5 (14,130).

Ethyl 7-Methoxycoumarin-4-(2-isobutyrate) (9b).—A solution of 7.4 g of resorcinol monomethyl ether, 8.7 g of diethyl 2,2-dimethyl-3-ketoglutarate,[28,29] and 4.2 g of boron trifluoride etherate in 30 ml of benzene was refluxed for 16 hr under continuous water separation. Totally 0.6 ml of water was separated. The reaction mixture was poured into bicarbonate solution, stirred for 2 hr, and extracted with benzene. The benzene solution was washed with 2% aqueous potassium hydroxide, washed with water, dried over sodium sulfate, and concentrated. The material remaining was recrystallized from benzene–cyclohexane (1 : 1) to give 1.0 g (11%) of 9b: mp 171.5°; uv max (MeOH) 220 mμ (ϵ 19,250), 322 (13,600); ir (CHCl$_3$) 1725 (broad), 1616 cm^{-1}; nmr (CDCl$_3$) τ 8.37 (s, 6, gem dimethyl), 6.13 (s, 3, methoxy), 3.69 (s, 1, H-3).

Anal. Calcd for C$_{16}$H$_{18}$O$_5$: C, 66.19; H, 6.25. Found: C, 66.01; H, 6.17.

Diethyl 2,2-Dimethyl-3-oxo-4-carbethoxyheptane-1,7-dioate (11b).—To a solution of 3 g of potassium *tert*-butoxide in 18 ml of ethanol was added 92 g of diethyl 2,2-dimethyl-3-ketoglutarate,[28,29] and the solution was heated to 85°. Ethyl acrylate (40 g) was then added and the mixture was stirred at 85–90° for 4 hr. After cooling, the reaction mixture was poured into iced dilute sulfuric acid and extracted with ether. The ethereal extract was washed with bicarbonate solution, dried over sodium sulfate, concentrated, and distilled, giving 106 g (80%) of 11b: bp 131–132° (0.2 mm); ir (CHCl$_3$) 1721–1755 cm^{-1} (C=O, broad); nmr (CDCl$_3$) τ 8.58 (s, 3), 8.55 (s, 3).

Anal. Calcd for C$_{16}$H$_{26}$O$_7$: C, 58.17; H, 7.93. Found: C, 58.37; H, 7.96.

Ethyl 7-Methoxy-4-methylcoumarin-3-propionate (12b). A.— To a solution of 300 g of ethyl 7-hydroxy-4-methylcoumarin-3-propionate (12a)[10] and 425 g of methyl iodide in 1 l. of acetone was added 240 g of potassium carbonate and the mixture was stirred under reflux for 3.5 hr. An additional 280 g of potassium carbonate and 240 g of methyl iodide were added and the mixture was refluxed for another 4 hr. The reaction mixture was filtered to remove inorganic substances and the filtrate was concentrated and then dissolved in ether. The ethereal solution was washed with aqueous alkali, washed with water, dried over potassium carbonate, and concentrated to 500 ml. Colorless needles were collected and washed with ether, giving 282.7 g of 12b, mp 74–75.5°. The second crop (25.8 g, mp 72–73.5°) was obtained on concentration of the mother liquor. Occasionally, the product did not crystallize, in which case it could be distilled to give colorless oil, bp 195–197° (0.08 mm). The oily material showed identical spectral data with the crystalline one and crystallized upon seeding: uv max (MeOH) 322 mμ (ϵ 17,820); ir (CHCl$_3$) 1711 (broad), 1610 cm^{-1} (C=C); nmr (CDCl$_3$) τ 7.58 (s, 3, CMe), 7.23 (AB type m, 4, methylenes), 6.14 (s, 3, OMe).

Anal. Calcd for C$_{16}$H$_{18}$O$_5$: C, 66.19; H, 6.25. Found: C, 66.38; H, 6.09.

B.—A solution of 3.7 g of resorcinol monomethyl ether, 6.9 g of diethyl α-acetoglutarate, and 4.2 g of boron trifluoride etherate in 40 ml of benzene was refluxed for 9 hr under continuous water separation. The reaction mixture was worked up in the usual manner (see preparation 9b) to give 3.5 g (41%) of 12b, bp 205–210° (0.5 mm). This product crystallized upon seeding and exhibited identical spectra with the specimen prepared by procedure A.

2-(2-Hydroxy-4-methoxyphenyl)-4-oxo-1-cyclohexene-1-carboxylic Acid Lactone (2a).—To a solution of 100 g of 12b in 400 ml of dimethyl sulfoxide was added 15 g of 56% sodium hydride mineral oil and the solution was stirred for 2 hr without external heating. The dark brown solution was neutralized with 25 ml of acetic acid and decomposed with 500 ml of water to produce a voluminous precipitate. The crystals were filtered with suction, then washed with water followed by ether. The yellowish needles (67.4 g, 80.2%), mp 222–224°, were recrystal-
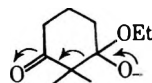
(28) W. H. Perkin, Jr., and A. E. Smith, *J. Chem. Soc.,* **83**, 12 (1903).
(29) L. I. Smith and W. W. Prichard, *J. Org. Chem.,* **4**, 348 (1939).

lized from 1 1. of dioxane giving 51.8 g of **2a**: mp 228.5°; uv max (MeOH) 319 mμ (ε 16,240); ir (CHCl₃) 1720 (C=O), 1620 cm⁻¹ (C=C).

Anal. Calcd for C₁₄H₁₂O₄: C, 68.84; H, 4.95. Found: C, 68.75; H, 4.69.

2-(2-Hydroxy-4-methoxyphenyl)-3-methyl-4-oxo-1-cyclohexene-1-carboxylic Acid Lactone (2b).—To a solution of 25.3 g of **2a** and 13.5 g of potassium *tert*-butoxide in 250 ml cf dimethyl sulfoxide and 60 ml of *tert*-butyl alcohol was added 100 ml of methyl iodide. The solution was heated to gentle reflux for 15 min, evacuated to remove excess methyl iodide, poured into 500 ml of ice-water, and refrigerated overnight. Yellow crystals were collected, washed with water, triturated with 250 ml of acetone, and filtered to remove 3.8 g of recovered starting material. The acetone filtrate was concentrated and the residue was recrystallized from methanol to give 17.1 g of pale yellow **2b**: mp 135°; uv max (MeOH) 322 mμ (ε 15,000); ir (CHCl₃) 1720 (C=O), 1614 cm⁻¹ (C=C); nmr (CDCl₃) τ 8.50 (d, 3, *J* = 7.5 Hz, *C*-Me), 6.30 (q, 1, *J* = 7.5 Hz), 6.11 (s, 3, OMe).

Anal. Calcd for C₁₅H₁₄O₄: C, 69.75; H, 5.46. Found: C, 69.54; H, 5.54.

Upon heating the methanol solution, this material was partially converted into the dimethyl ketal: mp 159° (recrystallized from acetone); uv max (MeOH) 319.5 mμ (ε 16,430); ir (CHCl₃) 1712, 1611 cm⁻¹; nmr (CDCl₃) τ 8.72 (d, 3, *J* = 7.5 Hz, *C*-Me), 6.76 (s, 3, acetal OMe), 6.65 (s, 3, acetal OMe), 6.13 (s, 3, phenolic OMe).

Anal. Calcd for C₁₇H₂₀O₅: C, 67.09; H, 6.62; OMe, 30.60. Found: C, 67.14; H, 6.61; OMe, 29.89.

2-(2-Hydroxy-4-methoxyphenyl)-3,3-dimethyl-4-oxo-1-cyclohexene-1-carboxylic Acid Lactone (2c), 13, 14a, and 14b.—To a solution of 5.2 g of **2b** in 70 ml of dimethyl sulfoxide was added 2.4 g of potassium *tert*-butoxide and the mixture was stirred for 15 min to dissolve the starting material. A mixture of 15 ml of *tert*-butyl alcohol and 20 ml of methyl iodide was added. The resulting solution was stirred for 30 min at room temperature, heated to gentle reflux for 20 min, cooled, poured into ice water, and finally extracted with ether. The ethereal extract was washed twice with 3% potassium hydroxide solution, washed with water, and dried over potassium carbonate. After evaporation of the solvent, recrystallization of the residue from chloroform-ether gave 1.9 g of **2c**: mp 186.5–188°; uv max (MeOH) 321 mμ (ε 15,000) ir (CHCl₃) 1723, 1626, 1610 cm⁻¹; nmr (CDCl₃) τ 8.27 (s, 6, gem dimethyl), 7.14 (m, 4, methylenes), 6.12 (s, 3, OMe).

Anal. Calcd for C₁₆H₁₆O₄: C, 70.57; H, 5.92. Found: C, 70.40; H, 5.82.

The mother liquor (2.5 g) was adsorbed on 175 g of silica gel, washed with benzene, and eluted with 5% ethyl acetate-benzene and then with 10% ethyl acetate-benzene. The 5% ethyl acetate fractions gave successively **14a**, **13**, and **2c** (0.4 g). The 10% ethyl acetate fractions gave **14b**. Recrystallization from benzene-cyclohexane afforded pure **14a**: mp 189°; uv max (MeOH) 260, 287, 299, 325 mμ (ε 53,500, 12,500, 12,500, 6200); ir (KBr) 1741 cm⁻¹ (C=O).

Anal. Calcd for C₁₆H₁₄O₄: C, 71.10; H, 5.22; methoxy, 22.96. Found: C, 70.85; H, 5.07; methoxy 22.00.

Recrystallization from benzene afforded pure **13**: mp 156.5°; uv max (MeOH) 229 mμ (ε 18,200), 317 (10,200); ir (CHCl₃) 1770 (lactone), 1678 (ketone), 1621 cm⁻¹ (C=C); nmr (CDCl₃) τ 8.58 (s, 3), 7.91 (s, 3), 6.10 (s, 3).

Anal. Calcd for C₁₆H₁₆O₄: C, 70.98; H, 5.86. Found: C, 70.57; H, 5.92.

Recrystallization from benzene afforded pure **14b**: mp 257.5°; uv max (MeOH) 260.5, 287.5, 299.5, 326 mμ (ε 53,300, 12,500, 12,600, 6830); ir (KBr) 3245 (OH), 1708 cm⁻¹ (C=O).

Anal. Calcd for C₁₅H₁₂O₄: C, 70.30; H, 4.72. Found: C, 70.39; H, 4.74.

7,8,9,10-Tetrahydro-3-methoxyspiro(6H-dibenzo[b,d]pyran-9,2′-[1,3]dioxolan)-6-one (15a).—A suspension of 150 g of **2a** and 1 g of *p*-toluenesulfonic acid in a mixture of 230 ml of ethylene glycol and 1.5 l. of benzene was refluxed for 8 hr under continuous water separation. The reaction mixture was washed with potassium carbonate solution, dried over sodium sulfate, and concentrated at atmospheric pressure to 600 ml. Stout, transparent crystals of mp 145.5° were obtained (130.5 g). The second crop (21.0 g) was obtained upon concentration to 200 ml: uv max (MeOH) 319 mμ (ε 17,300); ir (CHCl₃) 1717 (C=O), 1613 cm⁻¹ (C=C); nmr (CDCl₃) τ 8.07 (t, 2, *J* = 6.5 Hz, H-8), 7.20 (t, 2, *J* = 6.5 Hz, H-7), 7.05 (s, 2, H-10), 6.14 (s, 3), 5.92 (s, 4, ethylenedioxy).

Anal. Calcd for C₁₆H₁₆O₅: C, 66.66; H, 5.59. Found: C, 66.76; H, 5.64.

7,8,9,10-Tetrahydro-3-methoxy-10,10-dimethylspiro(6H-dibenzo[b,d]pyran-9,2′-[1,3]dioxolan)-6-one (15b).—A suspension of 18 g of **2c** and 0.5 of *p*-toluenesulfonic acid in 50 ml of ethylene glycol and 500 ml of benzene was refluxed for 48 hr. Work-up in the usual manner furnished 18.7 g of **15b**: mp 179–180°; uv max (MeOH) 319 mμ (ε 14,600); ir (CHCl₃) 1725 (C=O), 1626 cm⁻¹ (C=C); nmr (CDCl₃) τ 8.42 (s, 6, gem dimethyl), 8.09 (t, 2, *J* = 6.5 Hz, H-8), 7.25 (t, 2, *J* = 6.5 Hz, H-7), 6.14 (s, 3), 5.92 (s, 4, ethylene ketal).

Anal. Calcd for C₁₈H₂₀O₅: C, 68.34; H, 6.37. Found: C, 68.16; H, 6.37.

2-(2-Hydroxy-4-methoxyphenyl)-4-ethylenedioxy-1-cyclohexene-1-methanol (16).—A suspension of 20.0 g of **15a** and 7.0 g of lithium aluminum hydride in 1 l. of ether was refluxed for 12 hr. To the ice-cooled reaction mixture was added, under nitrogen, a solution of 20 ml of 95.5% sulfuric acid and 6 ml of acetic acid in 500 ml of water to decompose excess hydride, and the reaction mixture was extracted with ether. The ethereal extract was washed with water, washed with bicarbonate, dried over sodium sulfate, and concentrated, giving glassy **16** in quantitative yield: uv max (MeOH) 281.5 mμ (ε 2980); ir (CHCl₃) 3675 (OH), 3480 (OH), 1628 cm⁻¹ (C=C); nmr (CDCl₃) τ 6.23 (s, 3, OMe), 6.05 (broad s, 2, -CH₂O-), 5.99 (s, 4, methylenedioxy). This material was used in the next step without purification.

6,6a,7,8-Tetrahydro-3-methoxy-9H-dibenzo[b,d]pyran-9-one (17a) and 3-(2-Hydroxy-4-methoxyphenyl)-4-methylene-2-cyclohexen-1-one (21a). A.—The crude diol **16**, prepared from 10 g of **15a**, was dissolved in a mixture of 250 ml of acetic acid, 200 ml of water, and 50 ml of pyridine and refluxed for 29 hr. The reaction mixture was concentrated, diluted with water, and extracted with ether. The ethereal extract was washed successively with water, cold dilute potassium hydroxide solution, and water and dried over sodium sulfate. The alkaline washing was acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed with water and dried over sodium sulfate. After removal of the solvent, the neutral fraction was dissolved in the minimum amount of chloroform and crystallized by addition of ether to yield 1.9 g of **17a**: mp 126°; uv max (MeOH) 247.5, 303, 346 mμ (ε 6900, 12,000, 20,100); ir (CHCl₃) 1666 (C=O), 1600 cm⁻¹ (C=C); nmr (CDCl₃) τ 6.27 (q, 1, *J* = 10.5 and 12 Hz, H-6α), 6.19 (s, 3, OMe), 5.63 (q, 1, *J* = 10.5 and 5 Hz, H-6β) 2.45 (d, 1, H-1).

Anal. Calcd for C₁₄H₁₄O₃: C, 73.02; H, 6.13. Found: C, 73.02; H, 6.18.

The phenolic fraction was concentrated and the residue was recrystallized from benzene to give 1.45 g of **21a**: mp 116.5–117.5°; uv max (MeOH) 276 mμ (ε 11,500);[30] ir (CHCl₃) 1667 (C=O), 1622 cm⁻¹ (C=C); nmr (CDCl₃) τ 7.26 (m, 4, A₂B₂ type), 6.21 (s, 3, OMe), 4.80 (broad s, 1, vinylic), 4.53 (broad s, 1, vinylic, 3.81 (s, 1, olefinic).

Anal. Calcd for C₁₄H₁₄O₃: C, 73.02; H, 6.13. Found: C, 73.13; H, 5.96.

B.—A heterogeneous mixture consisting of **16** (prepared from 26.6 g of **15a**), 750 ml of acetic acid, 600 ml of water, 150 ml of pyrrolidine, and 800 ml of toluene was refluxed for 20 hr. The organic layer was separated. The aqueous layer was refluxed again with 800 ml of fresh toluene for 20 hr. Both toluene solutions were combined, washed successively with water, dilute hydrochloric acid, water, dilute alkali, and water, dried over sodium sulfate, and concentrated, giving 16.7 g (78%) of **17a**.

C.—The dihydroxy compound **16**, prepared from 10 g of **15a**, was dissolved in a mixture of 20 g of potassium hydroxide, 250 ml of acetic acid, and 200 ml of water and refluxed for 30 hr. Work-up in the usual manner gave 1.9 g of **17a** and 1.2 g of **21a**.

Transformation of 21a to 17a.—A solution of 1 g of **21a** and 2 g of pyridine hydrochloride in 30 ml of pyridine was refluxed for 5 hr. The reaction mixture was poured into ice water, and after the usual work-up (see procedure A for preparation of **17a**) gave 0.2 g of **17a**.

A solution of 1 g of **21a** and 3 ml of acetic acid in pyridine was refluxed for 5 hr. Work-up in the usual manner afforded 0.25 g of **17a**.

2-Methyl-3-(2-hydroxy-4-methoxyphenyl)-4-methylene-2-cyclohexen-1-one (21b) and 2-Hydroxy-4-methoxy-2′,6′-dimethyl-3′-hydroxybiphenyl (24).—A suspension of 4.6 g of the dimethyl

(30) The uv maximum is in good accordance with the calculated value assuming that the benzene ring is not coplanar: 215 + 30 + 12 + 18 + 5 = 280.

ketal of **2b** and 2.0 g of lithium aluminum hydride in 400 ml of ether was refluxed for 7 hr, cooled, and decomposed with a solution of 20 ml of 95.5% sulfuric acid and 3 ml of acetic acid in 500 ml of water. The ether extract was washed with water, washed with bicarbonate solution, dried over sodium sulfate, and concentrated to a colorless glass. The glass was dissolved in a mixture of 250 ml of acetic acid, 200 ml of water, and 20 g of potassium hydroxide and refluxed for 45 hr. The reaction mixture was worked up in the usual manner (see experiment for **17a** and **21a**). The neutral fraction contained only a trace of material and gave no hypothetical compound **17b**. The phenolic fraction (3.4 g) was chromatographed on 272 g of silica gel starting with benzene and continuing with increasing amounts of ethyl acetate. The biphenyl product was eluted quickly with 10% ethyl acetate–benzene and recrystallized from chloroform–benzene to give 86 mg of **24**: mp 126.5°; uv max (MeOH) 281.5 mμ (ϵ 6100); ir (CHCl$_3$) 3635 (OH), 3570 cm^{-1} (OH); nmr (CDCl$_3$) τ 8.03 (s, 6, CMe), 6.17 (s, 3, OMe).

Anal. Calcd for C$_{15}$H$_{16}$O$_3$: C, 73.75; H, 6.60. Found: C, 73.84; H, 6.57.

The ketonic substance was eluted slowly with the same solvent and recrystallized from benzene to afford 703 mg of **21b**: mp 142.5–144°; uv max (MeOH) 280 mμ (ϵ 14,400); ir (CHCl$_3$) 3595 (OH), 3340 (OH), 1680 (C=O), 1630 (C=C), 915 cm^{-1} (C=CH$_2$); nmr (CDCl$_3$) τ 8.29 (s, 3, C-Me), 7.25 (m, 4, A$_2$B$_2$ type), 6.18 (s, 3, OMe), 5.10 (broad s, 1, vinylic), 4.70 (broad s, 1, vinylic).

Anal. Calcd for C$_{15}$H$_{16}$O$_3$: C, 73.75; H, 6.60. Found: C, 73.57; H, 6.56.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-6H-dibenzo[b,d]pyran-9-one (22a).—To a suspension of 2.3 g of **17a** in 100 ml of ether and 250 ml of ammonia was added 0.5 g of lithium wire. The mixture was stirred under reflux for 1 hr, cooled with Dry Ice–acetone, decomposed with 6 g of ammonium chloride (added in one portion), and set aside to evaporate ammonia. The residue was taken up in ether, and the solution was washed thoroughly with water, dried over sodium sulfate, and concentrated. Recrystallization of the residue from chloroform–ether separated 1.7 g of **22a**: mp 129–130.5°; uv max (MeOH) 281.5 mμ (ϵ 3160), 287.5 mμ (ϵ 2720); ir (CHCl$_3$) 1721 cm^{-1} (C=O); nmr (CDCl$_3$) τ 6.93 (q, 1, $J_{6a,10a} = 12.5$, $J_{10a,10\beta} = 3$ Hz, $J_{10a,10\alpha} = $ small, benzylic H-10a), 6.24 (s, 3, OMe), 6.20 (t, 1, $J = 10.5$ Hz, H-6α), 5.67 (q, 1, $J_{6\alpha,6\beta} = 10.5$, $J_{6\beta,6a} = 3.5$ Hz, H-6β), 3.04 (d, 1, H-1).

Anal. Calcd for C$_{14}$H$_{16}$O$_3$: C, 72.39; H, 6.94. Found: C, 72.18; H, 6.86.

6a,7,8,9,10a-Hexahydro-3-methoxy-6H-dibenzo[b,d]pyran-9-ol (23). A.—The reaction conditions were the same as for **22a** (see above) except that the ammonium chloride was added portionwise. The residue was recrystallized from chloroform–ether, giving **23**: mp 104–105;[31] uv max (MeOH) 281.5 mμ (ϵ 2940), 287.5 (2730); ir (CHCl$_3$) 3700 (OH), 3532 cm^{-1} (OH); nmr (CDCl$_3$) τ 6.28 (m, 1, H-9), 6.28 (t, 1, $J = 10.5$ Hz, H-6α), 6.26 (s, 3, OMe), 5.80 (q, 1, $J = 10$ and 3.5 Hz, H-6β), 2.96 (broad d, 1, $J = 8.5$ Hz, H-1).

Anal. Calcd for C$_{14}$H$_{18}$O$_3$: C, 71.77; H, 7.74. Found: C, 71.70; H, 7.84.

B.—The identical substance was obtained by sodium borohydride reduction of **22a** in methanol.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-10-methyl-6H-dibenzo-[b,d]pyran-9-one (18). A. **Reductive Methylation of 17a.**—To a suspension of 13.8 g of **17a** in 200 ml of ether and 300 ml of ammonia was added 1 g of lithium wire. After 25 min at reflux temperature the blue color disappeared. A piece of lithium was added and the mixture was stirred for 20 min (still blue), cooled with a Dry Ice–acetone bath, and treated with 20 ml of methyl iodide. The cooling bath was removed, and the mixture was stirred for 4 hr under reflux, set aside overnight to evaporate ammonia, and then taken up with ether. The ethereal extract was treated with potassium hydroxide solution, water, and 5% hydrochloric acid, and filtered to remove the precipitate. The filtrate was washed with water, dried over potassium carbonate, and concentrated at atmospheric pressure to about 15 ml. Colorless needles (5.4–7 g) of mp 92° were obtained which were used for the next step without further purification. Pure **18** was obtained by recrystallization from chloroform–ether: mp 95°;

uv max (MeOH) 282.5 mμ (ϵ 3040), 288 (2790); ir (CHCl$_3$) 1712 cm^{-1} (C=O); nmr (CDCl$_3$) τ 9.00 (d, 3, $J = 7$ Hz, Me-10β), 6.27 (t, 1, $J = 10.5$ Hz, H-6α), 6.23 (s, 3, OMe), 5.70 (q, 1, $J = 10.5$ and 3.5 Hz, H-6β), 3.07 (d, 1, H-1).

Anal. Calcd for C$_{15}$H$_{18}$O$_3$: C, 73.14; H, 7.37. Found: C, 72.88; H, 7.30.

B. **Recovery from 19a.**—A solution of 300 mg of **19a** in 50 ml of 20% aqueous sodium carbonate was refluxed for 2 hr, cooled, and extracted with ether. After evaporation the residue was recrystallized from ether to afford 200 mg of **18**, mp 93°. The mixture melting point with an authentic sample was 93–94°.

Fragmentation and Equilibrium of 18.—When 300 mg of **18** in a mixture of 25 ml of diethylene glycol and 25 ml of 25% potassium hydroxide solution was refluxed for 7 hr, the majority of the material was transformed into phenolic substances, presumably owing to fragmentation (see **25**).

A suspension of 300 mg of **18** in 50 ml of 20% sodium carbonate was refluxed for 24 hr. The oil crystallized (mp 85°, mixture melting point with the starting material 93°) on cooling and was recrystallized from chloroform–ether to give the pure starting material, mp 95°.

A suspension of 1 g of **18** in 100 ml of 10% hydrochloric acid was refluxed for 30 min. The starting material was recovered unchanged.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-hydroxymethylene-6H-dibenzo[b,d]pyran-9-one (22b).—To a solution of 2.3 g of **22a** and 2.0 g of ethyl formate in 30 ml of benzene was added 2.3 g of potassium *tert*-butoxide. The mixture was stirred at room temperature under nitrogen for 5 hr, set aside overnight, and decomposed with ice water. The aqueous layer was washed with ether, acidified with hydrochloric acid to pH 3, and refrigerated. The crystals were collected, washed with water, dried, and recrystallized from benzene to give 2.3 g of **22b**: mp 156–156.5°; uv max (MeOH) 289 mμ (ϵ 9300), 313 (14,300); ir (CHCl$_3$) 2855 (broad, OH), 1656 cm^{-1} (C=O); nmr (CDCl$_3$) τ 6.23 (s, 3, OMe), 6.20 (t, 1, $J = 10.5$ Hz, H-6α), 5.67 (q, 1, $J = 10.5$ and 3 Hz, H-6β), 2.96 (d, 1, $J = 8.5$ Hz, H-1), 1.22 (s, 1, H-8a).

Anal. Calcd for C$_{15}$H$_{16}$O$_4$: C, 69.21; H, 6.20. Found: C, 69.43; H, 6.23.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-hydroxymethylene-10-methyl-6H-dibenz[b,d]pyran-9-one (19a).—This substance was prepared in the usual manner (see preparation of **22b**) and recrystallized from benzene–cyclohexane: mp 126°; uv max (MeOH) 282.5 mμ (ϵ 11,200), 288.5 (11,100); ir (CHCl$_3$) 2775 (broad, OH), 1646 cm^{-1} (broad, C=O); nmr (CDCl$_3$) τ 9.00 (d, 3, $J = 7$ Hz, Me-10β), 6.27 (t, 1, $J = 10.5$ Hz, H-6α), 6.22 (s, 3, OMe), 5.69 (q, 1, $J = 10.5$ and 3 Hz, H-6β), 3.00 d, 1, $J = 8.5$ Hz, H-1), 1.32 (s, 1, H-8a).

Anal. Calcd for C$_{16}$H$_{18}$O$_4$: C, 70.05; H, 6.61. Found: C, 70.13; H, 6.62.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-n-butylthiomethylene-6H-dibenzo[b,d]pyran-9-one (22c).—A solution of 2.6 g of **22b**, 1.1 g of n-butylmercaptan, and 40 mg of p-toluenesulfonic acid in 40 ml of benzene was refluxed for 2 hr under continuous water separation. The reaction mixture was diluted with benzene, washed with bicarbonate and then with salt solution, dried over sodium sulfate, and concentrated. The residue was recrystallized from benzene–cyclohexane to yield 2.6 g of **22c**: mp 142.5–143°; uv max (MeOH) 312 mμ (ϵ 19,000); ir (CHCl$_3$) 1664 (C=O), 1546 cm^{-1} (C=C); nmr (CDCl$_3$) τ 9.05 (t, 3, $J = 6$ Hz, CMe), 6.24 (s, 3, OMe), 6.19 (t, 1, $J = 10$ Hz, H-6α), 5.63 (q, 1, $J = 10.5$ and 3 Hz, H-6β), 2.96 (d, 1, $J = 8.5$ Hz, H-1), 2.20 (m, 1, $W_{1/2} = 4.5$ Hz, H-8a).

Anal. Calcd for C$_{19}$H$_{24}$SO$_3$: C, 68.64; H, 7.28; S, 9.64. Found: C, 68.47; H, 7.24; S, 9.77.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-isopropyloxymethylene-10-methyl-6H-dibenzo[b,d]pyran-9-one (19b).—A mixture of 2.7 g of **19a**, 2.7 g of potassium carbonate, and 3.4 g of 2-iodopropane in 50 ml of methyl ethyl ketone was refluxed for 6 hr. After cooling, ice water was added, and the mixture was extracted with ether. The ethereal extract was washed twice with cold potassium hydroxide solution, washed with water, dried over potassium carbonate, and concentrated under nitrogen. The material which remained was crystallized from cyclohexane–Skelly A to give 2.3 g of **19b**: mp 135°; uv max (MeOH) 281.5 mμ (ϵ 18,900); ir (CHCl$_3$) 1670 (C=O), 1582 cm^{-1} (C=C); nmr (CDCl$_3$) τ 9.07 (d, 3, $J = 7$ Hz, Me-10β), 8.67 (d, 6, $J = 6$ Hz, isopropyl), 6.28 (t, 1, $J = 10$ Hz, H-6α), 6.25 (s, 3 OMe), 5.80 (m, 1, H-6β, overlapped with OCHMe$_2$), 3.04 (d, 1, $J = 8$ Hz, H-1), 2.47 (t, 1, $J = 1.5$ Hz, H-8a).

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(31) Some preparations melted at 118.5°. The mixture melting point of 105 and 118.5° specimens was 118.5°.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.05; H, 7.71.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-hydroxymethylene-10,10-dimethyl-6H-dibenzo[b,d]pyran-9-one (20). A.—This entire operation was carried out under a nitrogen stream. To 250 ml of ammonia containing a few pieces of ferric nitrate was added 10 g of potassium in several portions. After the blue color disappeared, the reflux condenser (Dry Ice-acetone) was removed and 250 ml of anhydrous ether was added to the ammonia solution with vigorous stirring. The bulk of the ammonia was evaporated on an acetone-water bath (0-25°) under continuous stirring. More anhydrous ether (250 ml) was added to the potassium amide suspension and a slow stream of nitrogen was bubbled overnight through the suspension to remove traces of ammonia. The volume of the suspension was then adjusted to 500 ml with anhydrous ether (about 250 ml was needed). To the cool (0-5°) and vigorously stirred potassium amide suspension was added a solution of 20 g of 19b in 125 ml of dioxane and a rapid stream of nitrogen was passed through to remove ammonia as soon as it was formed. The mixture was warmed and stirred vigorously at 22-25° for 20 min. The deep red solution was cooled to 0° and 145 g of methyl iodide was added during 5 min. The reaction mixture was stirred at 0-5° for 30 min and then at room temperature for 3 hr, while a moderate stream of nitrogen was being introduced to evaporate methylamine as soon as it was formed. The reaction mixture was cooled, decomposed with 250 ml of water, and filtered to remove a yellow, crystalline substance (1.5 g) and the filtrate was taken up in ether. The ethereal extract was washed with cold dilute hydrochloric acid, washed with 2% salt solution, dried over sodium sulfate, and concentrated, and the residue was dissolved in a mixture of 75 ml of water and 250 ml of tetrahydrofuran. This solution was acidified with concentrated hydrochloric acid, set aside for 24 hr, poured into cold water, and extracted with ether. The ethereal solution was washed with iced 2% potassium hydroxide, followed by 2% salt solution, and dried over sodium sulfate. The cold alkaline washing was acidified and extracted with ether. The ether extract was washed with 2% salt solution, dried over sodium sulfate, and concentrated. The product which remained was recrystallized from ethyl acetate to give 9.55 g (52%) of 20: mp 155°; uv max (MeOH) 288.5 mμ (ϵ 10,500); ir (CHCl$_3$) 1621, 1584, 1511 cm^{-1}; nmr (CDCl$_3$) τ 8.98 (s, 3, Me-10β), 8.29 (s, 3, Me-10α), 7.21 (m, 1, H-10a), 6.32 (t, 1, J = 10.5 Hz, H-6α), 6.24 (s, 3, OMe), 5.77 (q, 1, J = 10 and 2.5 Hz, H-6β), 2.55 (d, 1, H-1), 1.27 (d, 1, J = 3 Hz, H-8a).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.62; H, 6.91.

The yellow crystalline product which separated from the original reaction mixture was repeatedly recrystallized from warm chloroform-dioxane to give 26: mp 287° dec; uv max (MeOH) 281.5 mμ (ϵ 8900), 384 (46,000); ir (CHCl$_3$) 1667, 1642, 1617, 1573, 1505 cm^{-1}, nmr (CDCl$_3$) τ 9.09 (s, 3, Me-10β), 9.04 (s, 3, Me-10β), 8.42 (s, 3, Me-10α), 8.32 s, 3, Me-10α), 6.21 (s, 6, OMe).

Anal. Calcd for $C_{34}H_{39}O_6N$: C, 73.22; H, 7.05; N, 2.51. Found: C, 73.16; H, 7.20; N, 2.57.

The neutral fraction was adsorbed on SilicAR CC-7 and the column was eluted with benzene. The earlier fractions contained complex mixtures of trimethylated compounds which were not fully characterized. Further elution with benzene produced a crystalline product which was triturated with cold ether and then recrystallized from benzene-hexane to afford colorless crystals of 27: mp 122-123°; ir (CHCl$_3$) 1714, 1622, 1581, 1509, 1168 cm^{-1}; uv max (MeOH) 282, 288 mμ (ϵ 3300, 2980); nmr (CDCl$_3$) τ 3.08 (d, 1, J = 8 Hz), 6.25 (s, 3), 8.90 (d, 2, J = 6.5 Hz), 9.00 (d, 2, J = 7 Hz).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.87; H, 7.74.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-10,10-dimethyl-6H-dibenzo[b,d]pyran-9-one (3). A.—A solution of 2.5 g of 20 in 250 ml of 20% aqueous sodium carbonate was refluxed for 2 hr, cooled, and extracted with ether. The ethereal extract was dried over sodium sulfate and concentrated and the residual material was recrystallized from chloroform-ether to deposit 2.1 g of 3: mp 94°; uv max (MeOH) 282 mμ (3490), 288 (3120); ir (CHCl$_3$) 1719 cm^{-1} (C=O); nmr (CDCl$_3$) τ 9.05 (s, 3, Me-10β), 8.45 (s, 3, Me-10α), 7.05 (d, 1, J = 11 Hz, H-10a), 6.37 (t, 1, J = 10.5 Hz, H-6α), 6.25 (s, 3, OMe), 5.83 (q, 1, J = 10.5 and 3.5 Hz, H-6β), 2.62 (d, 1, J = 10 Hz, H-1).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.87; H, 7.99.

B.—A suspension of 9.7 g of crude 26 in 200 ml of toluene and 200 ml of 10% hydrochloric acid was refluxed for 24 hr. The toluene layer was washed and separated into enolic and neutral fractions in the usual manner. The enolic fraction gave 4.0 g of 20, mp 147.5-150°. The neutral fraction (3.2 g) was chromatographed to give 1.5 g of 3.

3-(2-Hydroxy-4-methoxyphenyl)-4-hydroxymethyl-1-cyclohexanone Hemiketal (28a).—To a suspension of 5.8 g of 15a in 350 ml of distilled ammonia was added 1.0 g of lithium wire. After stirring under reflux for 3 hr the reaction mixture was cooled with Dry Ice-acetone and 12 g of ammonium chloride (or 38 ml of ethanol) was added. After evaporation of ammonia the residue was taken up with ether, washed with water, and extracted with dilute potassium hydroxide solution. The alkaline washing was acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed, dried over sodium sulfate, and concentrated. The product (3.0 g of colorless glass) was chromatographed on 200 g of silica gel using benzene with increasing amounts of ethyl acetate. The major fraction was eluted with 30% ethyl acetate to give 1.5 g of 28a: ir (CHCl$_3$) 3635 (OH), 3580 (OH), 3425 cm^{-1} (OH); nmr (CDCl$_3$) τ 6.80 (m, 1, $W_{1/2}$ = 12 Hz, benzylic H), 6.65 (d, 2, J = 7.5 Hz, -CH$_2$O-), 6.27 (s, 3, OMe).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.20; H, 7.60.

3-(2-Hydroxy-4-methoxyphenyl)-4-acetoxymethyl-1-cyclohexanone Hemiketal (28b).—A solution of 13.2 g of 28a in a mixture of 100 ml of acetic acid, 80 ml of water, and 20 ml of pyridine was refluxed for 45 hr, cooled, and extracted with ether. The ethereal extract was washed successively with water, dilute hydrochloride acid, water, and bicarbonate solution, and dried over potassium carbonate. Concentration of the dried extract gave 4.4 g of crystalline substance which was recrystallized from benzene to afford 28b: mp 113-113.5°; uv max (MeOH) 281 mμ (ϵ 3360), 287 mμ (ϵ 3100); ir (CHCl$_3$) 3480 (OH), 3445 (OH), 1735 cm^{-1} (ester); nmr (CDCl$_3$) τ 7.90 (s, 3, acetyl), 6.24 (s, 3, OMe), 6.88 (m, 1, $W_{1/2}$ = 11 Hz).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.46; H, 6.99.

2,2-Dimethyl-3-(2-hydroxy-4-methoxyphenyl)-4-hydroxymethyl-1-cyclohexanone Hemiketal (28c).—A suspension of 3.2 g of 15b in 350 ml of ammonia was reduced with 2 g of lithium and worked up as described for 28a. The product gave a major spot on tlc (silica gel, ethyl acetate) accompanied by two minor spots. Purification of this material was not attempted. However, spectral similarity to 28a led to the tentative structure 28c: uv max (MeOH) 281 mμ (ϵ 3970), 287 (3650); ir (CHCl$_3$) 3650 (OH), 3280 cm^{-1} (OH); nmr (CDCl$_3$) τ 9.08 (s, 3, CMe), 8.72 (s, 3, CMe), 7.29 (d, 1, J = 2.5 Hz, benzylic H), 6.67 (d, 2, J = 7 Hz, -CH$_2$O-), 6.23 (s, 3, OMe).

2-(2-Hydroxy-4-methoxyphenyl)cyclohexane-1-methanol (30a). A.—A suspension of 5.8 g of 15a in 300 ml of ether and 400 ml of undistilled ammonia was reduced with 3.0 g of lithium, then treated with 33 ml of ethanol and worked up as described for 28a. The phenolic fraction (5.6 g) gave rise to a crystalline mass which was triturated with 50% methanol, filtered, and recrystallized from acetone-benzene to yield 1.4 g of 30a: mp 140-141.5°; uv max (MeOH) 280.5 mμ (ϵ 2920), 286.5 (2480); ir (CHCl$_3$) 3650 (OH), 3300 cm^{-1} (OH); nmr (DMSO-d_6) τ 6.32 (s, 3, OMe).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.37.

B.—A solution of 0.8 g of 28b and 1.0 ml of hydrazine hydrate in 30 ml of diethylene glycol was set aside for 2 days, then heated to 180-190° in the presence of 1.5 g of potassium hydroxide for 3 hr. The reaction mixture was poured into 500 ml of water, acidified with hydrochloric acid, and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate, and concentrated. The residue was recrystallized from acetone-benzene to give 0.5 g of 30a, mp 142-143° (no depression upon admixture with 30a obtained by procedure A).

C.—Hemiketal (28a) was reduced in an analogous manner to give 30a, mp 142-143°.

2-(2-Acetoxy-4-methoxyphenyl)cyclohexane-1-methanol Acetate (30b).—The dihydroxy compound 30a was acetylated with acetic anhydride and pyridine in the usual manner to obtain 30b: mp 71°; ir (CHCl$_3$) 1766 (aromatic acetoxy), 1736 cm^{-1} (aliphatic acetoxy); nmr (CDCl$_3$) τ 8.13 (s, 3, acetoxy), 7.68 (s, 3,

acetoxy), 7.68 (s, 3, acetoxy), 6.23 (q, 1, J = 11 and 9 Hz, one of -CH$_2$O-), 5.95 (q, 1, J = 11 and 5.5 Hz, one of -CH$_2$O-).

Anal. Calcd for C$_{18}$H$_{24}$O$_5$: C, 67.48; H, 7.55. Found: C, 67.36; H, 7.40.

Mirestrol. II.[1]   A Synthesis of a New Tricyclic System

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As a model experiment to construct the C,D,E ring system of mirestrol (1), the unequivocal synthesis of (±)-2β,4β-ethano-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2α-ol-11-one (2b) from 2,2-dimethylcyclohexanone is described in Schemes I and II. This sequence involved elaboration of the starting material to the γ-keto ester 4b, followed by introduction of an acetonyl side chain to obtain 6b. The latter underwent an aldol condensation to the unsaturated bicyclic keto acid 7, which was reduced catalytically to the *cis*-hydrindanone 18a. Conversion of 18a to the diketone 23a and the subsequent intramolecular aldol ring closure gave the desired ketol 2b.

As a part of our effort to synthesize mirestrol (1)[2] and related substances from the tricyclic ketone 2a,[1] we explored an unambiguous synthesis of the new tricyclic ring system incorporated in the C,D,E rings of the natural product. To determine the feasibility of constructing such a ring system, we chose to convert a
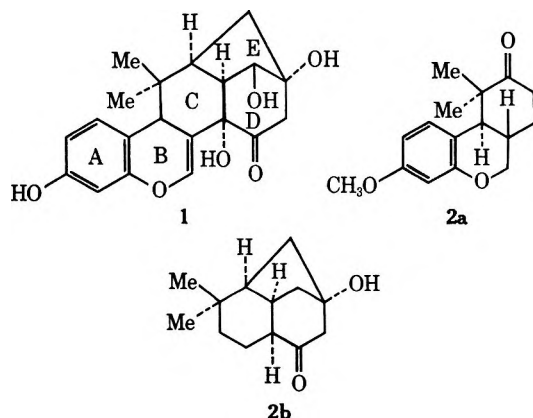
simple analog of compound 2a into the ketol 2b, and the successful synthesis of the latter compound is the subject of this paper. Although all synthetic compounds containing a chiral carbon atom are racemic, only one enantiomer is depicted for convenience.

2,2-Dimethylcyclohexanone, an obvious model for 2a, was transformed by conventional methods (see Scheme I) into 6,6-dimethylcyclohexanone-3-carboxylic acid (4a), which was identical with the authentic speci-

men[3] prepared from camphoric anhydride by a series of known procedures.[3a]

Our next objective, the formation of the five-membered ring, was initiated by alkylation of the methyl ester 4b with methallyl iodide[4] in the presence of potassium *tert*-butoxide to afford a mixture of *trans*- and *cis*-2-methallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (5) (see also 8a and 9a) in about a 3:1 ratio. Since further treatment of this mixture with sodium methoxide in refluxing methanol did not significantly alter the ratio of the isomers, the major product (lower boiling[5]) was suspected to be the more stable trans compound 8a. This assumption was supported by conformational analysis, which indicated that 9a is 0.55 kcal[6] less stable than 8a. The mixture 5 was partially separated by distillation and more effective purification was achieved by preparative thin layer chromatography (see Experimental Section). The nmr spectrum of the more abundant isomer possessed a broad multiplet at τ 6.83 representing the hydrogen attached to C-2; the observed half-height width of 22 Hz is consistent with a diaxial coupling of H-2 and H-3, and the major epimer was designated trans as in 8a. The cis isomer 9a was obtained as a low-melting solid whose nmr displayed a

(1) Part I: M. Miyano and C. R. Dorn, *J. Org. Chem.*, **36**, 259 (1971).

(2) (a) N. E. Taylor, D. C. Hodgkin, and J. S. Rollett, *J. Chem. Soc.*, 3685 (1960); (b) D. G. Bounds and G. S. Pope, *ibid.*, 3696 (1960).

(3) (a) W. H. Perkin, *ibid.*, **73**, 796 (1898); (b) G. Blanc, *Bull. Soc. Chim. Fr.*, [3] **15**, 1193 (1896); [3] **21**, 835 (1899).

(4) For a similar procedure, see L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos, and G. E. Arth, *J. Amer. Chem. Soc.*, **75**, 2112 (1953).

(5) The von Auwers–Skita rule suggests the trans isomer to boil lower than the cis. See, for example, E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 216.

(6) The conformational energy (1.1 kcal) of the axial carbomethoxy group was divided by two. See E. L. Eliel, N. L. Allinger, J. S. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 441.

SCHEME I

interactions and therefore is unlikely to be formed under such mild conditions.

Periodate cleavage of **5** in the presence of osmium tetroxide[7] afforded **6a**, which was saponified to **6b**. The latter could also be obtained from **5** by ozonation and the subsequent alkaline work-up. Purification of the acetonyl derivatives **6a** and **6b** resulted in substantial loss of material and was not rigorously pursued, since the crude products gave acceptable results.

The cyclization of **6a** to **12a** was complicated by the hindered nature of the six-membered ketone. Even

a simpler model, 2-acetonyl-6,6-dimethylcyclohexanone,[8] upon forced cyclization afforded a furan **14** along with the five-membered ketone **13**. Upon treatment with potassium *tert*-butoxide, the methyl ester **6a** gave rise to the triketone **15**, while on the other hand the acid **6b** yielded the cyclization–migration product **7**, rather than the expected unsaturated ketone **12b**. The nmr spectrum of **7** revealed a narrow triplet at τ 4.17 which can be rationalized by the weak coupling of the olefinic proton with the two allylic protons at C-4 and C-8 (see **16**). In addition, the hydrogen at C-4 (multiplet at τ 6.64) was slowly replaced by deuterium on treatment with deuterium oxide, thus collapsing the triplet at τ 4.17 to a narrow doublet ($J \cong 2$ Hz).

broad signal at τ 6.85 with a width at half-height of only 7 Hz.

In contrast to the ester **4b**, alkylation of the free acid **4a** under similar conditions proceeded less efficiently and gave rise to the isomeric acids **8b** and **9b**, accompanied by appreciable amounts of starting material. The noncrystalline trans acid **8b** was again the predominant epimer and could be converted to **8a** by treatment with diazomethane. During chromatographic separation of the cis–trans mixture of γ-keto acids **8b** and **9b**, a neutral compound with spectral data (see Experimental Section) in agreement with **10** was isolated. The data were also consistent with **11**, although this "trans" lactone contains two significant nonbonded

Vigorous evolution of gas was noted as compound **7** was heated above its melting point, also suggesting the presence of a vinylogous β-keto acid. Considering the reaction conditions employed, the formation of **7** was apparently subject to thermodynamic control and the carboxyl group should be equatorial as in **16**.

Hydrindenones of type **7** generally yield cis-fused products upon catalytic hydrogenation[9] and presumably the catalyst would approach compound **7** predominantly from the side opposite of the β-oriented carboxyl group to afford the all-cis saturated acid **18a**. This was indeed the case, although the hindered nature of the

(7) For a general procedure, see R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 473 (1956).

(8) Prepared by methallylation of 2,2-dimethylcyclohexanone followed by ozonation.

(9) R. L. Augustine and A. D. Broom, *J. Org. Chem.*, **25**, 802 (1960).

SCHEME II
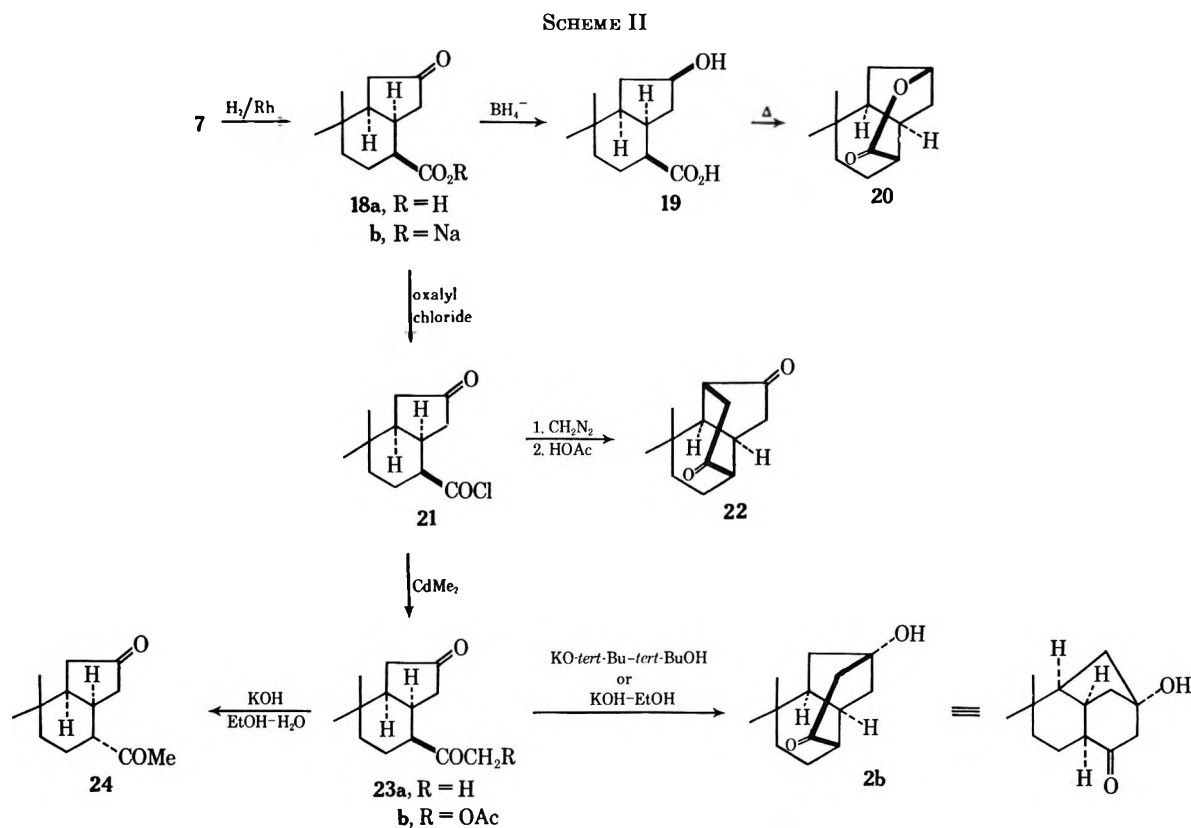
double bond caused some difficulty. For example, hydrogenation in the presence of 5% rhodium on alumina was sluggish and gave erratic results, while, if 10% palladium on carbon was employed as the catalyst, reduction of **7** gave reproducible yields of **18a** (about 50%) (Scheme II), but significant quantities of the hydrogenolysis product **17** resulted and some starting material was recovered. The nmr spectrum[10a] of **18a** could not be properly interpreted in terms of a single conformation like **26a**, **26b**, **27a**, **27b**,[10b] or **28**. It therefore seemed likely that **18a** is a conformational mixture of **26a** and **26b**. In agreement with the proposed stereochemistry, **18a** gave rise to the all-cis hydroxy acid **19**. A β orientation of the hydroxyl group is expected since the axial carboxyl group in **26a** and the axial methyl group in **26b** would hinder β-face attack of the reducing agent. Chemical evidence for the structure of **19** was demonstrated by its facile conversion (briefly heating above its melting point) to the tricyclic lactone **20**.

An attempted preparation of the methyl ketone **23a** from **18a** in the usual manner[11] was unsuccessful; that

(10) (a) One of the methylene protons of the six-membered ring appeared as an irregular triplet ($J = 4$ Hz) in benzene solution, which may be compatible with rapidly equilibrating conformational isomers **26a** and **26b**, but not with conformers **27a** and **27b** (see footnote 10b) or the fixed structure **28**. For a similar situation, see protons a and b in N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "Nmr Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, No. 469. (b) Although **26a** contains a greater number of significant 1,3 nonbonded interactions than **26b**, this may be somewhat compensated by the more severe interaction of the C-7 axial methyl group and the C-9 methylene in **26b** as compared to the diaxial interaction of the C-4 carboxyl and the C-8 methylene in **26a**. Since the energies of **26a** and **26b** are roughly comparable, the prospect for equally populated species is reasonable. The situation for **27a** and its flipped form **27b** is different. Conformer **27b** possesses a very serious interaction between the axial methyl and the C-9 methylene which is not present in **27a**. The axial C-4 carboxyl group in **27b** also gives rise to significant 1,3 nonbonded interactions and one would predict that **27b** has a much higher energy content than **27a**. Conformational analysis indicates that at equilibrium the mixture contains at least 99% of **27a** at room temperature.

(11) G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961).

is, the sodium salt **18b** was converted into the acyl chloride **21**, which upon treatment with excess diazomethane followed by warm acetic acid failed to produce the acetoxymethyl ketone **23b**. Instead, the product was a tricyclic substance containing a five-membered ketone as well as a six-membered ketone (ir bands at 1748 and 1710 cm⁻¹). Taking into account the mechanism of formation (see **29**), compound **22** appeared to be the logical structure, thus providing additional evidence for the stereochemical assignment of **18a**.

The conversion of the carboxyl group in **18a** to an acetyl group in **23a** was effected in good yield by treat-

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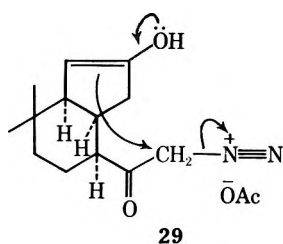
ing the acid chloride **21** with dimethylcadmium in benzene. It is worth mentioning that the methyl ketone **23a** still retained the acetyl group in the configuration which was necessary for the subsequent cyclization. The fact that this was indeed the less stable configuration was demonstrated by the epimerization of **23a** to the more stable isomer **24** upon treatment with potassium hydroxide in aqueous ethanol.

Finally, the desired cyclization of **23a** to ketol **2b** was accomplished in modest yield by means of potassium hydroxide in ethanol, or more efficiently, by potassium *tert*-butoxide in 50% *tert*-butyl alcohol–benzene. Inspection of the spectral data of **2b** left no doubt concerning the structure of the intramolecular aldol condensation product; the signals of the methyl ketone at τ 7.83 (s, 3), the α-methylene protons of the five-membered ring at τ 7.23 (m, 4), and the five-membered ring ketone absorption at 1742 cm^{-1} present in **23a** all disappeared completely and were replaced by the signal of the newly formed six-membered ring α-methylene protons at τ 7.38 (broad s, 2) and a strong absorption of the newly formed hydroxyl group at 3610 cm^{-1}.

Experimental Section

Melting points were taken on a Fisher-Johns block and are uncorrected. Unless otherwise stated, infrared spectra were obtained as 3% solutions in chloroform. The nmr spectra were determined in deuteriochloroform (unless otherwise stated) on a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. The expression "worked up in the usual manner" involved the washing of an organic extract with dilute aqueous sodium chloride, drying the extract over anhydrous sodium sulfate, removal of the drying agent by filtration, and evaporation of the solvent under aspirator pressure. All reactions utilizing strongly basic reagents were conducted under nitrogen.

6,6-Dimethyl-2-cyclohexen-1-one.—A cold stirred solution of 63 g of 2,2-dimethylcyclohexanone[12] in 500 ml of tetrahydrofuran was treated with 80 g of bromine in 75 ml of methylene chloride over a period of 30 min, keeping the temperature of the reaction mixture below 10°. The yellow solution was stirred for an additional 10 min, then diluted with 650 ml of 10% aqueous sodium bicarbonate and poured into 2 l. of cold water. The mixture was extracted several times with methylene chloride and the combined organic extracts were washed with water, dried, and concentrated. The crude bromo ketone was dissolved in 75 ml of dimethylformamide and added to a hot (140°) suspension of 26 g of magnesium oxide in 750 ml of dimethylformamide. The mixture was stirred under a nitrogen atmosphere at 140° for 1 hr, then cooled in an ice bath as 1.5 l. of cold dilute hydrochloric acid was added. After all of the magnesium oxide dissolved, the mixture was diluted with about 1.5 l. of ice water and extracted several times with ether. The ether extracts were washed with aqueous sodium chloride, saturated sodium bicarbonate, and finally with saturated sodium chloride. After drying, the ether was distilled off at atmospheric pressure and the residue was fractionated (20 mm) through a 10-in. Vigreux column to yield 57 g of almost colorless unsaturated ketone, bp 55–60°. Spectral properties were consistent with the literature:[13] ir 1685, 1642, 1390 cm^{-1}; uv max

(12) Prepared by methylation of 2-methylanilinomethylene-6-methyl-cyclohexanone in the presence of potassium *tert*-butoxide followed by removal of the protecting group; see A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944).

(13) J. Warkentin and L. K. M. Lam, *Can. J. Chem.*, **42**, 1676 (1964).

(MeOH) 225 mμ (ε 9150); nmr τ 3.11 (sextet, 1), 4.07 (d, 2), 7.61 (m, 1), 8.15 (t, 2), 8.90 (s, 6).

3-Cyano-6,6-dimethylcyclohexanone (3).—To a solution of 56 g of potassium cyanide and 35 g of ammonium chloride in 300 ml of water was added 56 g of 6,6-dimethyl-2-cyclohexen-1-one dissolved in 600 ml of dimethylformamide. After stirring at 100° for 8 hr, the wine red reaction mixture was cooled, diluted with water, and extracted several times with ether. The combined organic solutions were washed with saturated sodium chloride, dried, and evaporated under reduced pressure. The residue was distilled at 20 mm to give 33 g of colorless nitrile boiling at 135–142°: ir 2250 (CN), 1725 cm^{-1}; nmr τ 8.81 (s, 3), 8.88 (s, 3). *Anal.* Calcd for C$_9$H$_{13}$NO: C, 71.49; H, 8.67. Found: C, 71.35; H, 8.79.

6,6-Dimethylcyclohexanone-3-carboxylic Acid (4a).—A solution of 11 g of the nitrile **3** in 40 ml of dioxane and 220 ml of 10% aqueous sodium hydroxide was stirred and refluxed for 4.5 hr. The reaction mixture was cooled and diluted with water and ether. The aqueous layer was separated, washed with ether, acidified with dilute hydrochloric acid, and finally extracted with ether. The extract was worked up in the usual manner to produce a crystalline residue, which was recrystallized from ether–pentane to afford 8.5 g of colorless crystals, mp 82–85°. Recrystallization from the same solvent pair gave the pure sample: mp 87–89° (lit.[3a] mp 88–89°); ir 1710 cm^{-1}; nmr τ −0.93 (s, 1), 8.83 (s, 3), 8.91 (s, 3).

3-Carbomethoxy-6,6-dimethylcyclohexanone (4b).—A cold solution of 30 g of acid 4a in 1.5 l. of ether was treated with a cold ethereal solution of diazomethane, prepared from 40 g of *N*-nitrosomethylurea. After a period of 30 min, a few milliliters of glacial acetic acid was carefully added to destroy excess diazomethane. The almost colorless solution was washed with water, aqueous sodium bicarbonate, and again with water, then dried and concentrated. The residue was distilled at 20 mm to give 28.8 g of pure, colorless ester: bp 120–124°; ir 1745, 1718, 1295, 1227, 1147 cm^{-1}; nmr τ 6.31 (s, 3), 8.83 (s, 3), 8.93 (s, 3). *Anal.* Calcd for C$_{10}$H$_{16}$O$_3$: C, 65.19; H, 8.75. Found: C, 65.36; H, 8.92.

2-Methylallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (5).—A total of 7.3 g of potassium metal was dissolved in 220 ml of hot *tert*-butyl alcohol under an atmosphere of nitrogen. The solution was cooled to room temperature and diluted with 440 ml of benzene followed by 27.6 g of the ester **4b**. With rapid stirring, 45 g of methallyl iodide[4] was added in one portion; the temperature of the reaction mixture rose to 40° as potassium iodide was immediately precipitated. Stirring was continued for about an hour and then the reaction mixture was allowed to stand overnight at room temperature. Water was carefully added and the mixture was extracted several times with ether. The organic solutions were washed with water, dilute aqueous sodium thiosulfate, and again with water, dried and concentrated. The residue was distilled under reduced pressure (2 mm) through a 10-in. Vigreux column. After a small forerun, the main fraction amounted to 22.3 g of colorless **5** boiling at 122–126°. Gas chromatography (4-ft column packed with 8% SE-30 on Diatoport S) indicated that this material contained 73.4% of the trans isomer and 26.5% of the cis isomer (see below for separation). The oil **5** had the following spectral properties: ir 1736, 1712, 1650 cm^{-1}; nmr τ 5.25 (m, 1), 5.36 (m, 1), 6.32 and 6.34 (two singlets for a total of three protons, the signal at 6.32 being the major peak), 8.29 (s, 3), 8.73, 8.78, 8.85, and 8.92 (four singlets for a total of six protons with the signals at 8.73 and 8.92 having much greater intensities). *Anal.* Calcd for C$_{14}$H$_{22}$O$_3$: C, 70.55; H, 9.31. Found: C, 70.76; H, 9.55.

Further distillation at 124–129° (2 mm) yielded an additional 5.1 g of colorless oil (56.2% trans and 43.8% cis by vpc). The ratio of isomers remained essentially the same after refluxing with sodium methoxide in methanol.

Separation of the epimers was effected by preparative tlc (silica gel; 95% benzene–5% ethyl acetate). The slightly less polar component was a colorless liquid identified as *trans*-2-methylallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (8a): ir 1737, 1718, 1650, 898 cm^{-1}; nmr τ 5.30 (m, 1), 5.38 (m, 1), 6.32 (s, 3), 6.83 (m, 1, $W_{1/2}$ = 22 Hz), 8.30 (s, 3), 8.75 (s, 3), 8.92 (s, 3). *Anal.* Calcd for C$_{14}$H$_{22}$O$_3$: C, 70.55; H, 9.38. Found: C, 70.77; H, 9.63.

The minor isomer was isolated as an oil which slowly solidified to a crystalline mass. Recrystallization from a small amount of

pentane gave white crystals of *cis*-2-methylallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (9a): mp 50–51°; ir 1732, 1710, 1650, 1174, 897 cm^{-1}; nmr τ 5.26 (m, 1), 5.43 (m, 1), 6.35 (s, 3), 6.85 (m, 1, $W_{1/2}$ = 8 Hz), 8.31 (s, 3), 8.80 (s, 3), 8.88 (s, 3).

Anal. Calcd for C$_{14}$H$_{22}$O$_3$: C, 70.55; H, 9.38. Found: C, 70.59; H, 9.33.

Alkylation of 4a.—A stirred solution of potassium *tert*-butoxide (prepared from 3.4 g of potassium) in 110 ml of *tert*-butyl alcohol was treated with 5.8 g of 4a in 200 ml of benzene, followed by 17 g of methallyl iodide. The temperature of the reaction mixture rose only slightly and after about 5 min potassium iodide began to slowly precipitate. Stirring was continued for 2 hr, and after standing overnight, the mixture was cooled, treated with 250 ml of cold water, and finally washed with ether. The aqueous solution was chilled, acidified with cold dilute hydrochloric acid, and extracted with ether. Washing of the organic extract with dilute aqueous sodium thiosulfate followed by the usual work-up yielded a yellow oil weighing about 8 g. The crude product was taken up in benzene and chromatographed on 800 g of silica. Elution of the column with 5% ethyl acetate produced 2.7 g of oil which crystallized slowly from pentane to give 315 mg of colorless cis acid (9b), mp 128–132°. Further elution with 10% ethyl acetate yielded 1.3 g of starting acid 4a. Recrystallization of 9b from ether–pentane gave analytically pure *cis*-2-methallyl-6,6-dimethylcyclohexanone-3-carboxylic acid: mp 133–134°; ir 1752, 1723, 1651, 900 cm^{-1}; nmr τ 5.20 (m, 1), 5.34 (m, 1), 6.82 (m, 1, $W_{1/2}$ = 6 Hz), 8.30 (s, 3), 8.81 (s, 3), 8.90 (s, 3).

Anal. Calcd for C$_{13}$H$_{20}$O$_3$: C, 69.61; H, 8.99. Found: C, 69.69; H, 9.06.

Upon prolonged refrigeration the pentane mother liquor from the crystallization of 9b deposited 120 mg of hard, colorless prisms, mp 75–77°. Examination of the nmr spectrum revealed that this product did not contain a methallyl group (no signal near τ 5.30), but possessed four distinct methyl peaks in addition to a pair of isolated protons (bridgeheads) appearing in the τ 7.15–7.45 region. The infrared spectrum showed a single carbonyl absorption at 1776 cm^{-1} (five-membered lactone) and the substance was tentatively identified as 10: ir 1776, 1272, 1185, 1120 cm^{-1}; nmr τ 8.58 (s, 3), 8.74 (s, 3), 8.88 (s, 3), 8.95 (s, 3).

Anal. Calcd for C$_{13}$H$_{20}$O$_3$: C, 69.61; H, 8.99. Found: C, 69.91; H, 9.16.

The filtrate obtained after the removal of 10 (see above) was examined by tlc (silica gel; benzene–ethyl acetate–acetic acid 30:10:1) and found to contain two spots with slightly different mobilities; the slower moving material (minor amount) had the same R_f value as the cis acid 9b. Separation of the major isomer was eventually achieved by preparative tlc (SilicAR CC-4; 98.75% chloroform, 1% ethyl acetate, 0.25% acetic acid) affording *trans*-2-methallyl-6,6-dimethylcyclohexanone-3-carboxylic acid (8b) as a nonmobile oil: ir 1750, 1718, 1650, 898 cm^{-1}; nmr τ 5.27 (m, 1), 5.33 (m, 1), 6.85 (m, 1 $W_{1/2}$ = 20 Hz), 8.28 (s, 3), 8.75 (s, 3), 9.15 (s, 3).

Anal. Calcd for C$_{13}$H$_{20}$O$_3$: C, 69.61; H, 8.99. Found: C, 69.33; H, 8.98.

Esterification of 8b and 9b with diazomethane gave 8a and 9a, respectively.

2-Acetonyl-3-carbomethoxy-6,6-dimethylcyclohexanone (6a).— The methallyl compound 5 (10 g) was dissolved in 134 ml of dioxane and 40 ml of water and treated with 25.6 g of sodium metaperiodate followed by 3 ml of 4% osmium tetroxide in dioxane. The reaction flask was flushed with nitrogen, tightly stoppered, and stirred magnetically for 19 hr. The precipitated sodium iodate was filtered and washed well with ether. The resulting solution was washed with water, several times with dilute sodium thiosulfate, and twice more with water. The usual work-up left 7.5 g of brown oil which showed several spots on tlc (silica gel; benzene–ethyl acetate 5:1). Neither distillation nor chromatography separated all of the impurities, but it was found that the crude material was suitable for further modification. Partial purification could be achieved by chromatography on silica; elution with benzene containing 2% ethyl acetate gave 6a as a yellow oil: ir 1732, 1715, 1382 cm^{-1}; nmr τ 6.30 and 6.32 (two singlets for a total of three protons), 7.75 and 7.77 (two singlets for a total of three protons), 8.85, 8.80, 8.90 and 8.93 (four singlets for six protons).

2-Acetonyl-6,6-dimethylcyclohexanone-3-carboxylic acid (6b). A.—The crude ester 6a (3 g) was dissolved in 5 ml of dioxane and mixed with 10 ml of 30% aqueous sodium hydroxide. After standing overnight, the mixture was cooled in ice, acidified with 5 ml of concentrated hydrochloric acid, and extracted several

times with chloroform. Washing of the extracts with saturated sodium chloride was followed by the usual work-up to give 2 g of dark brown oil. Although tlc (benzene–ethyl acetate–acetic acid 30:10:1) revealed that 6b was impure, the crude product gave satisfactory results upon further transformation: ir 1718 cm^{-1}; nmr τ 6.55 (broad m, 1), 7.78 (s, 3), 8.74, 8.78, 8.93 (three singlets for a total of six protons).

B.—The methallyl ester 5 (24 g) in 200 ml of methanol and 100 ml of methylene chloride was cooled to −70° as a stream of ozonized oxygen was bubbled through the rapidly stirred solution for 105 min. At this point the initially colorless solution became blue. Excess ozone was removed under a stream of oxygen and the reaction mixture was poured into 2 l. of 2% aqueous sodium hydroxide and stirred for 1 hr at room temperature. About 500 ml of solvent was removed under aspirator pressure and the remaining aqueous solution was heated on the steam bath for 2 hr and finally allowed to stand overnight at room temperature. The orange reaction mixture was washed with ether, carefully acidified with cold dilute hydrochloric acid, saturated with sodium chloride, and then extracted with ether. The combined extracts were washed three times with saturated sodium chloride, dried, and concentrated to dryness. The residual oil amounted to 13 g and was comparable to 6b prepared by saponification of 6a.

6,6-Dimethyldecahydronaphthalene-1,3,5-trione (15).—A mixture of 4 g of crude 6a in 25 ml of benzene was treated with a solution of 50 ml of *tert*-butyl alcohol containing 1.5 g of dissolved potassium. After stirring at room temperature for 2 days, the dark red solution was poured into 400 ml of ice water and 7 ml of concentrated hydrochloric acid. Ether extraction and the usual work-up produced about 3 g of dark green oil, which was triturated with ether to give 700 mg of tan crystals, mp 150–160°. Two recrystallizations from ethyl acetate gave material melting at 145–158°: ir (KBr) 1715 (C=O), 1613 (C=O of enol form[14]), 1563 (C=C of enol[14]), 1227 cm^{-1}; uv max (0.1 N HCl in MeOH) 251.5 mμ (ϵ 13,000); uv max (0.1 N NaOH in MeOH) 282 mμ (ϵ 23,000).

Anal. Calcd for C$_{12}$H$_{16}$O$_3$: C, 69.21; H, 7.74. Found: C, 69.00; H, 7.72.

Chromatography of the mother liquors on silica yielded intractable mixtures.

4,5,6,7-Tetrahydro-8α(H)-7,7-dimethyl-2-oxo-$\Delta^{3(9)}$-indene-4β-carboxylic Acid (7).[15]—Crude diketone 6b (30 g) in 300 ml of benzene was added to 600 ml of *tert*-butyl alcohol containing 20 g of dissolved potassium. The resulting mixture was stirred for 20 hr at room temperature, poured into about 2 l. of ice water, acidified with dilute hydrochloric acid, and extracted with ether. The usual work-up yielded a crystalline residue, which was triturated with ether to afford 15 g of slightly yellow crystals, mp 160–167° dec. The analytical sample was obtained by recrystallization from ethyl acetate: mp 170–172° dec; ir (KBr) 1736, 1667, 1603, 1410, 1190 cm^{-1}; uv max (MeOH) 232 mμ (ϵ 14,500); nmr (CD$_3$SOCD$_3$) τ 4.17 (t, 1, $J \approx$ 2 Hz), 6.64 (m, 1), 9.03 (s, 3), 9.37 (s, 3).

Anal. Calcd for C$_{12}$H$_{16}$O$_3$: C, 69.21; H, 7.74. Found: C, 69.49; H, 7.87.

4,5,6,7,8α,9α-Hexahydro-7,7-dimethyl-2-oxoindan-4β-carboxylic Acid (18a). A.—The unsaturated ketone 7 (1 g) was dissolved in 150 ml of methanol and hydrogenated in the presence of 200 mg of 5% rhodium on alumina for 29 hr at atmospheric pressure and room temperature. After removal of the catalyst by filtration, the filtrate was evaporated to an oil which was dissolved in benzene and chromatographed on 150 g of SilicAR CC-4. The column was washed with increasing percentages of ethyl acetate and the fractions eluted with 10% ethyl acetate were concentrated and then crystallized from ether–pentane to give 290 mg of tan crystals, mp 97–102°. Two recrystallizations from the

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(14) For a discussion on the infrared spectra of cyclic β-diketones, see K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, San Francisco, Calif., 1962, p 65.

(15) For the sake of uniformity, all of the compounds depicted in Scheme II are designated by the following numbering system.
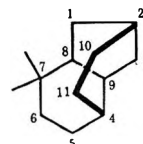
same solvent mixture furnished colorless **18a**: mp 110–112°; ir 1745, 1712 cm⁻¹; nmr τ −0.35 (s, 1), 9.07 (s, 3), 9.20 (s, 3).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.54.

B.—A solution of 10.4 g of **7** in 250 ml of isopropyl alcohol was shaken in an atmosphere of hydrogen with 6 g of 10% palladium on carbon for 18 hr. Removal of the catalyst followed by concentration gave about 11 g of orange oil, which was taken up in benzene and placed on 1000 g of SilicAR CC-4. Elution with 2% ethyl acetate yielded about 800 mg of solid, which was recrystallized from aqueous ethanol to give colorless crystals of **7,7-dimethyl-5,6,7,8-tetrahydroindan-4-carboxylic acid** (**17**), mp 158–162°. The analytical sample of the hydrogenolysis product was obtained by recrystallization from aqueous ethanol: mp 162–163°; ir 1686 (conjugated acid), 1645, 1282 cm⁻¹; uv max (MeOH) 231.5 mμ (ε 11,250); nmr τ −1.79 (s, 1), 8.98 (s, 3), 9.28 (s, 3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.36; H, 9.41.

The material obtained from the 15% ethyl acetate fractions was recrystallized from ether–pentane to yield 5 g of product, mp 108–110°, which was identical with **18a**. Continued elution of the above column with 50% ethyl acetate gave about 1 g of the starting ketone **7**.

4,5,6,7,8α,9α-Hexahydro-7,7-dimethyl-2β-hydroxyindan-4β-carboxylic Acid (19).—A solution of 208 mg of keto acid **18a** was dissolved in 2 ml of ethanol and neutralized with 0.1 N aqueous sodium hydroxide to a phenolphthalein end point. The solution was cooled in an ice bath as 500 mg of solid sodium borohydride was added portionwise. The mixture was allowed to warm to room temperature and stand overnight, then cooled and carefully acidified with saturated aqueous citric acid. The precipitate was filtered, washed with water, and air dried to give 185 mg of solid, mp 185–188°. Recrystallization from methanol–ethyl acetate separated 157 mg of pure **19**: mp 187–189°; ir (KBr) 3450, 1710 cm⁻¹; nmr (CD₃SOCD₃) τ 5.80 (m, 1), 9.09 (s, 3), 9.18 (s, 3).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.09; H, 9.58.

4,5,6,7,8α,9α-Hexahydro-7,7-dimethyl-2β-hydroxyindan-4β-carboxylic Acid 4β → 2β-Lactone (20).—The hydroxy acid **19** (72 mg) was heated with an oil bath at 190–195° for 1 min. The product was cooled and taken up in ether, and the solution was washed with 3% aqueous sodium bicarbonate. Drying and removal of the solvent produced 63 mg of crystalline residue which gave a single spot on tlc (silica gel; 80% benzene–20% ethyl acetate). Recrystallization from pentane followed by sublimation (20 mm at a bath temperature of 120°) yielded colorless crystals: mp 61–62°; ir 1727, 1380, 1148, 992 cm⁻¹; nmr τ 5.22 (m, 1), 7.30 (m, 1), 8.98 (s, 3), 9.11 (s, 3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.94; H, 9.44.

1β,4β-Ethano-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2,11-dione (22).—The saturated ketone **18a** (800 mg) was dissolved in 10 ml of 95% ethanol and slowly treated with 0.1 N aqueous sodium hydroxide to a phenolphthalein end point. The solution was allowed to evaporate at room temperature (or concentrated under high vacuum) and the solid residue was powdered and dried at 65° under high vacuum to a constant weight. The dried sodium salt **18b**, amounting to 770 mg, was suspended in 10 ml of dry benzene containing 3 drops of pyridine. The suspension was stirred and cooled in a cold water bath as 2.5 ml of oxalyl chloride was introduced. After the vigorous reaction subsided, the cooling bath was removed and the reaction mixture was stirred at room temperature for about 1 hr. The mixture was concentrated; 5 ml of benzene was added and the evaporation was repeated. The residue was mixed with 10 ml of benzene and filtered, and the solution of the acid chloride **21** was immediately added to a cold ethereal solution of excess diazomethane (prepared from N-nitrosomethylurea and dried over potassium hydroxide pellets). There was an immediate evolution of gas and the yellow solution was allowed to stand in an ice bath for 2 hr. At this point, glacial acetic acid was added dropwise and when gas evolution ceased, the mixture was gradually poured into 20 ml of warm (60°) glacial acetic acid. The solution was heated at 60° for 1 hr, then concentrated under a stream of nitrogen to a partially crystalline residue. An nmr spectrum of this crude material indicated that the acetoxy ketone **23b** was not formed (no signal in the τ 5.00 region). Preparative tlc (silica; 50% benzene–ethyl acetate)

yielded a solid which was recrystallized from ether–pentane to give colorless crystals of **22**: mp 70–71°; ir 1748 (five-membered ketone), 1710 cm⁻¹ (six-membered ketone); nmr τ 6.76 (d of m, 1), 7.12 (m, 1), 8.94 (s, 3), 9.26 (s, 3).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.00; H, 8.94.

4β-Acetyl-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2-one (23a).—A mixture of dimethylcadmium[16] (prepared from 20 ml of 3.0 M methylmagnesium bromide in diethyl ether and 6.0 g of anhydrous cadmium chloride) in 35 ml of benzene was stirred and cooled in a cold water bath as a benzene solution of the crude acid chloride **21** (prepared from 3 g of **18a** as described above) was added rapidly. The cooling bath was removed and the mixture was refluxed for 30 min, cooled, and poured into ice-cold dilute hydrochloric acid. The product was isolated by ether extraction and recrystallized from ether–pentane to give 2.2 g of pure **23a**: mp 84–86°; ir 1742, 1711, 1150 cm⁻¹; nmr τ 7.23 (m, 1), 7.83 (s, 3), 9.08 (s, 3), 9.23 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.85; H, 9.76.

4α-Acetyl-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2-one (24).—Diketone **23a** (82 mg), dissolved in 8 ml of methanol, was mixed with 8 ml of 1.0 N aqueous potassium hydroxide and the resulting solution was allowed to stand overnight at room temperature under nitrogen. The mixture was acidified with dilute acetic acid and extracted with ether. The organic extract was washed several times with aqueous sodium chloride, dried, and evaporated to an almost colorless oil weighing 75 mg. This product showed a single spot which migrated slightly faster than the starting ketone on tlc (silica gel; benzene–ethyl acetate–acetic acid 30:10:1): ir 1749, 1712, 1360, 1158 cm⁻¹; nmr τ 7.85 (s, 3), 8.93 (s, 3), 9.10 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.32; H, 9.59.

2β,4β-Ethano-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2α-ol-11-one (2b). A.—A solution of 1.25 g of **23a** in 20 ml of benzene was added to 20 ml of *tert*-butyl alcohol containing 350 mg of dissolved potassium metal. After standing at room temperature for 3 hr, the deep red solution was poured into ice water, acidified with cold, dilute hydrochloric acid, and extracted twice with ether. The extract was treated in the usual manner to afford a partially crystalline residue, which upon recrystallization from ether–pentane yielded 510 mg of yellow crystals, mp 100–103°. Chromatography of the mother liquor on 60 g of SilicAR CC-4 gave an additional 150 mg of material upon elution with 30% ethyl acetate–benzene. The analytical sample of colorless **2b** was prepared by recrystallization from ether–pentane: mp 103–104°; ir 3610, 1709, 1086 cm⁻¹; nmr τ 7.38 (broad s, 2) 9.02 (s, 3), 9.20 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.46.

B.—The diketone **23a** (76 mg) was dissolved in 1 ml of anhydrous ethanol and mixed with 3.5 ml of 4.0 N ethanolic potassium hydroxide. The resulting solution was allowed to stand at room temperature for 2 days, then acidified with dilute aqueous acetic acid and extracted with ether. The usual work-up and recrystallization of the product from ether–pentane yielded 21 mg of tan crystals, mp 100–103°. This compound exhibited spectra data identical with those of **2b**.

(16) J. Cason and F. S. Prout, *J. Amer. Chem. Soc.*, **66**, 46 (1944).

and Mrs. Joyann Serauskas. Column chromatography and thin layer chromatography were accomplished under the direction of Mr. R. T. Nicholson and Mr. B. G. Smith, Mr. W. W. Aksamit and staff provided the vpc results. We are grateful to Dr. J. W. Ahlberg and staff for both spectral data and elemental analyses.

Badgerin, a New Germacranolide from *Artemisia arbuscula* ssp. *arbuscula*

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Samples of *Artemisia arbuscula* ssp. *arbuscula*, collected in Montana, contained tatridin-A (1) and a new germacranolide which was named badgerin. Structure 2 was assigned to the new lactone on the basis of its spectral properties and chemical reactions.

The sesquiterpene lactones of three subspecies of big sagebrush (*Artemisia tridentata*) were investigated[2] in this laboratory as a part of our program on chemical constitutents of sagebrush in Montana.[2-4] One of the subspecies, *A. tridentata* ssp. *vaseyana*, collected from several locations in this state gave the same sesquiterpene lactones that have been isolated from *A. arbuscula* Nutt. ssp. *arbuscula* collected in another location.[5] This prompted us to investigate the sesquiterpene lactones of a Montana plant known as *A. arbuscula* ssp. *arbuscula*.

Results and Discussion

Different samples of this plant were collected from a 1 square mile area near Badger Pass and extracted with chloroform. Tlc analysis of the extracts gave a consistent pattern for the sesquiterpene lactone contents, which were quite different from those reported earlier for *A. arbuscula* ssp. *arbuscula*.[5]

Extensive chromatographic separation of the lactones from the combined chloroform extracts resulted in the isolation of two pure crystalline lactones along with some gummy fractions and a crystalline mixture. One of the two crystalline lactones was identified as tatridin-A[6] (1) by its physical constants, spectral properties and ultimately by tlc and mixture melting point with an authentic sample. The other crystalline lactone was an unknown compound. It was named badgerin and assigned the structure 2 on the basis of the following considerations.

1

2, $R_1 = R_2 = H$
3, $R_1 = R_2 = Si(Me)_3$
4, $R_1 = Ac; R_2 = H$
5, $R_1 = R_2 = Ac$

Composition and Functional Groups.—Mass spectroscopy and elemental analysis showed the molecular weight of 280 and the empirical formula of $C_{15}H_{20}O_5$. The compound had an α,β-unsaturated γ-lactone, as shown by uv end absorption, ir bands at 1766 and 1639 cm^{-1}, and the nmr spectrum discussed later (see Table I, 2). There were two hydroxyl groups, with an ir band at 3378 cm^{-1}, which formed a di(trimethylsilyl) ether derivative (3). One of these hydroxyl groups was readily acetylated to give a monoacetate compound (4) and was proved to be secondary (see Table I and the following nmr discussions). The monoacetate showed an ir band at 3510 cm^{-1} for a free hydroxyl group. However, it could not be oxidized by chromium trioxide–acetic acid[7,8] or by Jones[9] reagent, indicating the tertiary nature of the remaining hydroxyl group.

The lactone moiety and the hydroxyl groups account for four of the five oxygen atoms present. Since no other functional group could be detected it became evident that the fifth oxygen must form an oxide ring. The oxide ring could not be cleaved on treatment with acetic anhydride and p-toluenesulfonic acid,[10] or acetic anhydride and sulfuric acid,[11] indicating the presence of an unusually stable ring structure. This almost ruled out the possibility of a labile epoxide ring in favor of a more stable structure such as a pyran derivative. Under the employed drastic acetylating conditions, however, the free hydroxyl groups in badgerin were acetylated to give a crystalline diacetate (5).

Badgerin was not oxidized by sodium metaperiodate even after 48 hr, nor did it form a benzeneboronate derivative on treatment with benzeneboronic acid,[12] showing that the two hydroxyl groups are neither adjacent nor are likely to be 1,3-diaxially oriented.

Other than the methylene group conjugated to the lactone carbonyl function, badgerin had another double bond and on hydrogenation it absorbed 2 mol of hydrogen. The hydrogenation product, which lacked olefinic protons in its nmr spectrum, unfortunately proved
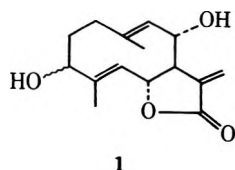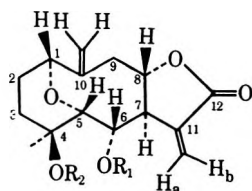
(1) Established through a grant from Hoerner–Waldorf Corp. of Montana.

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TABLE I
NMR Spectral Data for Badgerin and Derivatives[a]

Compd	C-13 H_b	C-13 H_a	C-10 $=CH_2$	C-8 H	C-7 H	C-6 H	C-5 H	C-4 CH_3	C-1 H	Miscellaneous
2[b]	6.13 (d, 3.5)	6.07 (d, 3.5)	5.18, 4.99 (bs, $W_{1/2}$ = 4)	3.95 (td, 10, 2)	3.36 (br)	4.40 (dd, 8.5, 2)	2.85 (d, 2)	1.60 (s)	4.33 (nr)	2.00 hydroxyls
3[c]	6.16 (d, 3.5)	5.75 (d, 3.5)	5.28, 5.03 (bs, $W_{1/2}$ = 4)	4.07 (td, 10, 2)	3.21 (br)	4.32 (dd, 8.5, 2)	2.67 (d, 2)	1.43 (s)	4.37 (nr)	0.10, 0.20 [OSi(Me)₃]₂ (s)
4[c]	6.15 (d, 3.5)	5.42 (mx)	5.42, 5.15 (mx) (d, 2)	4.21 (td, 10, 2)	3.65 (br)	5.35 (mx)	3.03 (d, 2)	1.27 (s)	4.48 (nr)	2.22 acetate
4[b]	6.10 (d, 3.5)	5.47 (d, 3.5)	5.22, 5.03 (bs, $W_{1/2}$ = 4) (d, 2)	4.10 (td, 10, 2)	3.60 (br)	5.80 (dd, 8.5, 2)	3.07 (d, 2)	1.50 (s)	4.37 (nr)	2.10 acetate
5[c]	6.12 (d, 3.5)	5.40 (mx)	5.40, 5.13 (mx) (d, 2)	4.20 (td, 10, 2)	3.50 (br)	5.62 (dd, 8.5, 2)	3.48 (d, 2)	1.48 (s)	4.47 (nr)	2.10, 1.96 acetates

[a] These data were obtained with a Varian HA-60 nmr spectrometer. TMS was used as an internal standard for compounds 2, 4, and 5 and CHCl₃ for 3. Chemical shifts are quoted in δ (parts per million) and the signals are denoted by s, singlet; d, doublet; dd, doublet of doublets; td, triplet of doublets; br, broad signal; nr, narrow signal; bs, broad singlet; mx, mixed signal. Figures in parenthesis denote coupling constants in cycles per second. [b] Pyridine-d_5 was used as the solvent. [c] CDCl₃ was used as the solvent for these spectra and in the double irradiation experiments.

to be a mixture and could not be isolated as pure isomers.

The nmr spectrum of badgerin (see Table I, 2) showed the following features: a low-field pair of doublets at 6.13 and 6.07 ppm (2 H, J = 3.5 Hz) for methylene protons of the α,β-unsaturated γ-lactone[2,5,13] (C-13 H_b and C-13 H_a); two broad singlets at 5.18 and 4.99 ppm (2H, $W_{1/2}$ = 4 Hz), characteristic of unconjugated exo-methylene vinyl protons[2,8] (C-10 $=CH_2$); three protons which appeared to represent OCH groups including a triplet of doublets at 3.95 ppm (J = 10, 2 Hz) for the lactone proton (C-8 H) and a doublet of doublets at 4.40 ppm (J = 8.5, 2 Hz for C-6 H) on a narrow signal at 4.33 ppm (C-1 H); a broad signal centered at 3.36 ppm (C-7 H); a doublet at 2.85 ppm (1 H, J = 2 Hz) also representing an OCH group as discussed later (C-5 H); a narrow singlet at 2 ppm which collapsed on D₂O exchange signifying the hydroxyl proton(s); and a sharp singlet at 1.60 ppm (3 H) indicating a methyl group on a carbon attached to oxygen (C-4 CH_3).

The above data indicated a germacranolide structure (2) with the following groups: an α,β-unsaturated lactone, one secondary hydroxyl group, one tertiary hydroxyl group, one oxide ring, and an unconjugated exo-methylene.

Position of the Lactone Ring and the Secondary Hydroxyl Group.—The biosynthetic pathways involved in the conversion of trans-farnesyl pyrophosphate to sesquiterpene lactones including eudesmanolides, guaianolides, and germacranolides generally lead to lactone ring enclosure at C-6 or C-8.[14]

As noted before, the conjugated methylene protons, C-13 H_b and C-13 H_a, in badgerin gave characteristic nmr signals at 6.13 and 6.07 ppm. In the nmr spectra of the disilyl compound, the monoacetate, and the diacetate (see Table I, 3, 4, and 5), the signal from one of the methylene protons, C-13 H_b, remained almost unchanged, while the position of the other proton, C-13 H_a, shifted upfield to 5.75, 5.42, and 5.40 ppm, respectively. The near equivalence of C-13 protons in badgerin and the upfield shift of one of them after the substitution is characteristic of an α-oriented hydroxyl

group in the β position to the lactone methylene group in a variety of sesquiterpene lactones investigated.[15] Although in most of these compounds the lactone ring is enclosed at C-6 and the free hydroxyl group is at C-8, the possibility of the reverse situation, that is, lactone closure at C-8 and the free hydroxyl group at C-6, should be also considered.

The doublet of doublets at 4.40 ppm in badgerin representing an OCH proton shifted downfield in the monoacetate derivative (4, Table I) and merged with other signals at 5.42 ppm so that only a part of it could be seen as a narrow doublet at 5.35 ppm. This characteristic downfield shift indicated that the proton (C-6 H) is located under a secondary hydroxyl group that has been acetylated.[16] The coupling constants of the lactone proton (C-8 H, J = 10, 2 Hz, Table I) and the proton under the adjacent secondary hydroxyl group (C-6 H, J = 8.5, 2 Hz, Table I) indicated the presence of either C-8 α-hydroxyl and C-6 α-lactone or C-6 α-hydroxyl and C-8 α-lactone. In the former case opening and reclosing of the lactone should result in changing to the more stable C8 enclosure, while the latter structure should remain unchanged.[17] Badgerin was recovered unchanged on opening and reclosing of the lactone moiety, thus showing that the lactone is enclosed at C-8 and the secondary hydroxyl group is at C-6.

Positions of the Tertiary Hydroxyl, the Unconjugated Methylene, and the Methyl Functions.—The C-6 proton showed a doublet of doublets (J = 8.5, 2) suggesting that it had only two neighboring protons, one at C-7 and the other at C-5. The narrow doublet at 2.85 ppm in badgerin which shifted to 3.03 ppm in the monoacetate was assigned to C-5 H because irradiation of this proton in the monoacetate collapsed the C-6 H doublet to a singlet and vice versa.

The C-5 H doublet shifted further downfield to 3.48 ppm in the diacetate.[10] These shifts, which are more clearly observed by comparing the spectra of the disilyl,

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(17) H. Yoshioka, W. Renold, and T. J. Mabry, *Chem. Commun.*, 147 (1970).

the monoacetate and the diacetate compounds in chloroform solution [Table I, 3, 4 (in CDCl₃) and 5], indicated that the C-5 proton is located between the two hydroxyl groups. This means that the tertiary hydroxyl group is at C-4. In the germacranolide skeleton the methyl and methylene groups could be either at C-4 or C-10. The presence of the tertiary hydroxyl group at C-4 leads to the assignments of methyl group to the same position and the methylene group to C-10.

Position of the Oxide Ring.—The nmr spectrum of badgerin showed three protons between 3.7 and 4.6 ppm and one proton at 2.85 ppm which could be attributed to an OCH system. Two protons at 3.95 and 4.40 ppm have been assigned to C-8 H and C-6 H, respectively. This leaves the C-5 proton at 2.85 ppm and another proton (C-1 H) at 4.33 ppm for the two ends of the oxide bridge. Irradiation of the latter proton in the diacetate compound affected the C-10 methylene protons, indicating that it is located at C-1 or C-9 allylic positions. Position 9 was eliminated because the lactone proton, C-8 H, showed a triplet of doublets which on irradiation of C-7 H in the diacetate collapsed to another complex signal[18] indicating the presence of two protons at C-9. This showed that the oxide ring must form a bridge between C-1 and C-5.

The C-1 and C-5 protons gave narrow signals, indicative of equatorially (or pseudoequatorially) oriented bonds. Construction of a chemical model showed that these equatorially oriented protons have the β configuration and the oxide bridge involves C-1α,C-5α bonds.

The above data account for configuration of all the asymmetric centers except C-4. The configuration of the hydroxyl group at C-4 was determined from solvent-induced chemical shifts of the C-6 H and C-4 CH₃ signals in the nmr spectra of the monoacetate compounds.

In CDCl₃ (see 4, Table I) the signals for C-6 H and C-4 CH₃ appeared at 5.35 and 1.27 ppm, respectively. However, when pyridine-d₅ (see 4, Table I) was used as the solvent, the C-6 H signal showed a downfield shift of 0.45 ppm to appear at 5.80 ppm, and the C-4 CH₃ signal showed a downfield shift of 0.23 ppm to appear at 1.5 ppm. These solvent shifts indicated that the C-6 H and C-4 CH₃ bonds must lie in the same planes as the C-4 O and C-6 O bonds respectively.[19,20] In other words the hydroxyl groups at C-4 and C-6 are trans. Since the C-6 OH, as noted before, is α, the C-4 OH, or the tertiary hydroxyl group, must be β oriented. The trans configuration of the hydroxyl group explained the failure of badgerin to form a benzeneboronate derivative. Also, it could be seen from a chemical model that the eclipsed conformation of C-6 H and C-4 OH forms a dihedral angle of somewhat more than 60° between C-6 H and C-5 H which is consistent with the observed weak coupling (J = 2 Hz) between these protons.

Absolute Configuration.—The above data give the structure of badgerin and the relative configuration of all the asymmetric centers. However, they do not establish the absolute configuration of the compounds

because all the spectroscopic and chemical properties that have been considered are equally applicable to the mirror image of the proposed structure.

It is interesting to note that the above structure is based on the application of the relactonization rule[17] established for germacranolides. It could be argued that the new compound with an oxygen bridge between C-1 and C-5 may behave differently so that the relactonization rule is no longer applicable. Under these circumstances the alternative possibility, that is, lactone closure to C-6, must be considered. If the lactone ring is closed at C-6, then the other functional groups on the germacranolide skeleton must be located as shown in structure 6 in order to accommodate the ob-

6
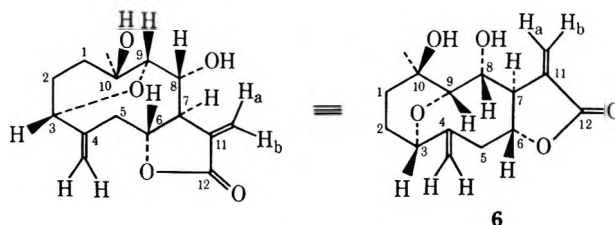
served chemical and spectroscopic properties. At the first sight structure 6 seems totally different from the proposed structure of badgerin (2). However, closer observation indicates that despite the differences in numbering, structures 2 and 6 are actually mirror images. Consequently, the position of the lactone ring will be known when one of the enantiomers is related to a compound with known absolute configuration or *vice versa*. This situation is remarkably similar to the configurational relationships that were used by Emil Fischer at the turn of the century for determining the stereoisomerism of the monosaccharides.

Isolation of Tatridin-A (1).—Three samples of *A. arbuscula* ssp. *arbuscula*[22] were collected from a one square mile area near Badger Pass, Montana (T. 7 S, R. 11 W, Section 11, elevation 6319 ft), in August 1970. Dried twigs and foliage of the samples (400 g each) were separately extracted with chloroform and worked up in the usual manner.[2,23] The resulting crude dark syrups, about 25 g from each sample, were found to have the same sesquiterpene lactone pattern by tlc and were combined together. The combined syrup was dissolved in a small amount of benzene and chromatographed over 1 kg of silica gel, using benzene and benzene–ethyl acetate mixtures of increasing polarity as the eluents. The first 4 l. of benzene and 9 l. of the solvent mixtures (9:1, 8:2, 7:3) eluted colored gums. The following eight 150-ml aliquots of the mixed solvents (6:4) furnished a gum which crystallized from chloroform–ether and gave a mixture of two compounds. The next ten 150-ml aliquots of benzene–ethyl acetate (1:1) contained a transparent gum which crystallized from chloroform–ether to give 800 mg of colorless needles of tatridin-A, mp 150–160°. Azeotropic removal of the crystallization solvent and recrystallization from methanol gave another crystalline form, mp 176–177°, alone or in admixture with an authentic sample:[24] [α]¹⁸D −49° (c 1.1, EtOH); mass spectrum m/e 264 (M⁺); uv end absorption; ir bands at 3333 (hydroxyl), 1762 (γ-lactone), 1666, 1647, 890 cm⁻¹ (unsaturation); nmr spectrum in pyridine-d₅, doublets of doublets at 6.50, 6.35 ppm

(18) M. F. L'Homme, T. A. Geissman, H. Yoshioka, T. H. Porter, W. Renold, and T. J. Mabry, *Tetrahedron Lett.*, 3161 (1969).

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(21) All melting points are uncorrected. The uv and ir spectra were recorded on Coleman–Hitachi EPS-3T and Beckman IR-5 spectrophotometers, respectively.

(22) Samples were collected and identified by M. S. Morris, Professor of Range Management, University of Montana.

(23) T. A. Geissman, T. Stewart, and M. A. Irwin, *Phytochemistry*, 6, 901 (1967).

(24) The authentic sample was obtained from Professor T. A. Geissman as the methanol solvate, mp 178–179°.

(1 H each, J = 3, 1.5 Hz, C-11 =CH$_2$) situated on a broad base of hydroxyl signals from 6.0 to 6.7 ppm, broad doublets at 5.20 and 5.32 ppm (1 H each, J = 9.5 Hz, C-5 H and C-9 H), a complex signal from 4.4 to 5.1 ppm (3 H, C-3 H, C-6 H, C-8 H), a broad signal at 3.0 ppm (1 H, C-7 H), and two narrow doublets at 1.88 and 1.68 ppm (3 H each, J = 1.5 Hz, C-4 and C-10 CH$_3$).

Isolation of Badgerin (2).—The materials remaining in the chromatographic column after removal of tatridin-A were further eluted with ten 150-ml portions of the same solvent mixture. The tlc analysis of the eluents showed a single spot, but the gummy product, 5 g, obtained on removal of the solvents could not be crystallized and glc analysis of a silylated sample indicated the presence of two closely related components which remain unidentified.

Continued elution in the same manner gave 1.5 g of a transparent gum, which crystallized from chloroform–ether to give 200 mg of needles of badgerin: mp 207–208°; $[\alpha]^{18}$D +8.50 (c 1.165, EtOH), mass spectrum m/e 280 (M$^+$), 262 (M − 18); uv end absorption; ir bands at 3378 (hydroxyl), 1766 (γ-lactone), 1639 cm^{-1} (unsaturation).

Anal. Calcd for C$_{15}$H$_{20}$O$_5$: C, 64.28; H, 7.14. Found: C, 64.05; H, 7.27.

A solution of badgerin in pyridine-d_5 gave the nmr spectrum recorded in Table I. Further elutions of the column gave colored gums which could not be crystallized.

Di(trimethylsilyl) Derivative of Badgerin (3).—Badgerin (50 mg) was treated with Tri-Sil reagent (3 ml). The resulting solution was warmed for a few minutes and allowed to stand for 1 hr. The excess solvent was then removed under reduced pressure and the residue was extracted with carbon tetrachloride. Removal of the solvent from the filtered extract left a residue which was used for the spectroscopic investigations. The nmr spectrum of this compound is given in Table I.

Badgerin Monoacetate (4).—Badgerin (50 mg) was dissolved in pyridine (2 ml) and acetic anhydride (2 ml) and kept overnight. Removal of solvents under reduced pressure and crystallization of the residue from methanol afforded a monoacetate derivative (4): yield 40 mg; mp 197–199°; ir bands at 3510 (hydroxyl), 1766 (γ-lactone), 1718, 1245 cm^{-1} (acetate).

Anal. Calcd for C$_{17}$H$_{22}$O$_6$: C, 63.35; H, 6.83. Found: C, 63.57; H, 6.88.

Badgerin Diacetate (5).—A solution of 50 mg of badgerin in 10 ml of acetic anhydride was treated with a drop of concentrated sulfuric acid.[10] After a few minutes the solution was poured over crushed ice and allowed to stand for 1 hr. It was then extracted with chloroform (five 20-ml portions). The extract was washed with sodium bicarbonate solution and water. Removal of the solvent left a solid which was recrystallized from ethanol to give 40 mg of a diacetate (5): mp 189–190°; mass spectrum m/e 364 (M$^+$); ir bands at 1776 (γ-lactone), 1740 and 1250 cm^{-1} (acetate).

Anal. Calcd for C$_{19}$H$_{24}$O$_7$: C, 62.63; H, 6.59. Found: C, 62.29; H, 6.68.

This compound was also obtained in good yield when badgerin (40 mg) was refluxed in acetic anhydride (5 ml) with p-toluenesulfonic acid[10] (30 mg) for 1.5 hr.

Hydrogenation of Badgerin.—A solution of 56 mg of badgerin in 25 ml of ethanol was stirred with 10% Pd/C catalyst in a hydrogen atmosphere. The reaction was complete in 2 hr after

absorption of 2 mol of hydrogen. The catalyst was then filtered and the filtrate was concentrated to a residue which showed three overlapping tlc spots. The nmr spectrum of this mixture lacked signals for olefinic protons.

Relactonization of Badgerin.[25]—Badgerin ($\sim$10 mg) was dissolved in 1 ml of 10% aqueous sodium hydroxide solution by gentle warming. The solution was then cooled in ice and the solvent was removed under vacuum without heating. The solid residue was dissolved in 2 ml of glacial acetic acid and the solution was again evaporated under high vacuum without heating. The residue obtained was taken in cold water and extracted repeatedly with chloroform. Removal of chloroform under vacuum gave badgerin quantitatively.

Attempted Oxidation of Badgerin Monoacetate. A.—The monoacetate (28 mg) was dissolved in 4 ml of glacial acetic acid and treated with 10 mg of chromium trioxide.[7,8] The reaction mixture was monitored by tlc. There was no change after 8 hr, when the reagent was destroyed by methanol and the starting monoacetate was recovered quantitatively.

B.—The monoacetate recovered from the above experiment (25 mg) was dissolved in 20 ml of acetone (purified by distillation from KMnO$_4$ and stored over K$_2$CO$_3$) and Jones reagent[9] was added dropwise with stirring until a persistent orange color developed. Stirring was continued for 20 min, after which the excess reagent was destroyed with methanol and the starting monoacetate was recovered quantitatively.

Attempted Periodate Oxidation of Badgerin.—Badgerin (14 mg, 0.5 × 10^{-4} mol) was suspended in a solution of sodium metaperiodate (21.4 mg, 1 × 10^{-4} mol) in distilled water (10 ml). The reaction was monitored by periodic titrations of the mixture and a blank. No appreciable amount of periodate was consumed in 48 hr. The reaction mixture was then extracted with CHCl$_3$ (5 × 10 ml) and removal of the solvent left a residue which was identical with the starting material.

Attempted Preparation of Benzeneboronate Derivative.—Badgerin (42 mg) and benzeneboronic acid (22 mg) were added to 30 ml of benzene and refluxed for 8 hr in a Dean–Stark apparatus.[12] The main bulk of benzene was then removed and dry ligroin was added to the remaining solution. This gave a fine precipitate that was filtered and identified as badgerin.

(25) W. Renold, H. Yoshioka, and T. J. Mabry, *J. Org. Chem.*, **35**, 4264 (1970).

Thermal Degradation of 1,6-Anhydro-β-D-glucopyranose

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Thermal degradation of 1,6-anhydro-β-D-glucopyranose-1-^{14}C, -2-^{14}C, and -6-^{14}C gave carbon dioxide, carbon monoxide, and a variety of carbonyl compounds that were isolated and traced to the labeled positions. Variations of the yields and radiochemical patterns of the products on addition of sodium hydroxide or zinc chloride indicated the nature of the complex consecutive and concurrent reactions involved.

A variety of mechanisms have been suggested for the thermal degradation of cellulose and related model compounds to low-molecular-weight products.[2-5] These mechanisms are generally based on the isolation and identification of the products assuming the formation of either free-radical[3] or carbonium ion intermediates[4] without sufficient evidence. Furthermore, they entail a single pathway for the formation of each product, which is very unlikely under the pyrolytic conditions, when the molecule is physically torn into pieces.[2] To gain further insight into the complex nature of the pyrolytic transformations, a systematic approach has been adapted in this laboratory involving combinations of thermal analysis methods (differential thermal analysis, thermogravimetric analysis, and derivatography) and parallel chemical studies.[6-10] These investigations have shown that heating of carbohydrates results in transition of the crystalline structure, anomerization of free sugar, cleavage of the glycosidic bond, condensation of the glycosyl group, and ultimately degradation of the molecule through acid- and alkali-catalyzed reactions. Analysis of the products obtained from the pyrolysis of 1,6-anhydro-β-D-glucopyranose (levoglucosan), before and after treatment with zinc chloride or sodium hydroxide, is shown in Table I.[7] This table shows that addition of zinc chloride promotes the formation of char, water, and 2-furaldehyde, which are the expected products of an acid-catalyzed dehydration reaction,[11,12] whereas the addition of alkali promotes the production of low-molecular-weight carbonyl compounds, which may be accounted for by base-catalyzed rearrangement and fragmentation reactions of carbohydrates.[13]

These data have been combined with the radiochemical patterns obtained by tracing the individual products to different segments of specifically labeled samples

TABLE I
PYROLYSIS PRODUCTS OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE

Product	Neat	+ZnCl₂	+NaOH
Acetaldehyde	1.1	0.3	7.3
Furan	1.0	1.3	1.6
Acrolein	1.7	<0.1	2.6
Methanol	0.3	0.4	0.7
2,3-Butanedione	0.5	0.8	1.6
2-Butenal	0.7	0.2	2.2
1-Hydroxy-2-propanone	0.8	<0.1	1.1
Glyoxal	1.4	<0.1	4.9
Acetic acid	1.7	0.7	1.5
2-Furaldehyde	0.9	3.0	0.4
5-Methyl-2-furaldehyde	0.1	0.3	
Carbon dioxide	2.9	6.8	5.7
Water	8.7	20.1	14.1
Char	3.9	29.0	16.0
Balance (tar)	74.3	36.8	40.3

of 1,6-anhydro-β-D-glucopyranose-^{14}C to obtain more precise information about mechanisms of pyrolytic reactions.

Results and Discussion

Samples of 1,6-anhydro-β-D-glucopyranose-1-^{14}C, -2-^{14}C, and -6-^{14}C were prepared from the corresponding labeled D-glucose by the standard method[14] involving alkaline hydrolysis of phenyl β-D-glucopyranosides. The products were pyrolyzed without any additive and in the presence of 5% sodium hydroxide or 5% zinc chloride. In one experiment 1,6-anhydro-β-D-glucopyranose was prepolymerized in the presence of 5% zinc chloride before pyrolysis. These experiments gave several samples of carbon dioxide, carbon monoxide, and aqueous pyrolysate containing a variety of carbonyl compounds. Samples of carbon dioxide were converted to barium carbonate. The carbon monoxide samples were oxidized to carbon dioxide by iodine pentoxide[15] and also recovered as barium carbonate. The carbonyl compounds present in the pyrolysates were converted to the 2,4-dinitrophenylhydrazone (DNPH) derivatives, by treatment with acidic 2,4-dinitrophenylhydrazine, and the resulting DNPH mixtures were separated by thin layer chromatography.[16] The separation gave sufficient quantities of the DNPH derivatives of 2-furaldehyde, 2,3-butanedione, pyruvaldehyde, acetaldehyde, and glyoxal for radioanalysis. All these carbonyl compounds and some of the related hydroxy

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TABLE II

SPECIFIC RADIOACTIVITIES OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE-1-^{14}C, -2-^{14}C, AND -6-^{14}C,
AND THEIR PYROLYSIS PRODUCTS IN 10^2 μCi/MOL

Compd	Neat			5% NaOH			5% ZnCl₂			5% ZnCl₂, polymerized		
	1-^{14}C	2-^{14}C	6-^{14}C	1-^{14}C	2-^{14}C	6-^{14}C	1-^{14}C	2-^{14}C	6-^{14}C	1-^{14}C	2-^{14}C	6-^{14}C
1,6-Anhydro-β-D-glucopyranose	6.08	3.53	5.42	6.08	3.53	5.42	6.08	3.53	5.42	6.08	3.53	5.42
2-Furaldehyde	3.70	3.65	1.94	1.84	3.55	3.97	5.20	3.36	0.90	4.88	3.42	1.17
2,3-Butanedione	1.51	1.93	1.70	1.00	1.09	3.07	3.90	2.02	1.46			
Pyruvaldehyde	1.66	0.93	1.04	1.41	1.48	1.67	3.01	1.65	1.61	2.40	1.63	2.06
Acetaldehyde	0.61	1.08	1.96	0.038	1.03	3.00	0.026	0.026	1.62			
Glyoxal	0.93	0.68	0.038	1.54	1.70	1.96	1.78	1.00	1.54	2.17	1.18	1.44
Carbon dioxide	2.08	0.87	0.034	1.90	0.62	0.048	2.65	1.17	0.052	3.03	1.00	0.53
Carbon monoxide	1.28	0.67	0.92	2.32	0.63	0.07	2.22	0.97	0.62	2.88	0.88	0.66

TABLE III

PERCENTAGE OF THE PYROLYSIS PRODUCTS TRACED TO THE LABELED CARBONS OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE

Compd	Neat			5% NaOH			5% ZnCl₂			5% ZnCl₂, polymerized		
	1-^{14}C	2-^{14}C	6-^{14}C	1-^{14}C	2-^{14}C	6-^{14}C	1-^{14}C	2-^{14}C	6-^{14}C	1-^{14}C	2-^{14}C	6-^{14}C
2-Furaldehyde	60.8	103.4	35.8	30.2	100.7	73.0	86.0	95.8	16.6	80.3	96.9	21.6
2,3-Butanedione	24.8	54.6	31.3	16.5	31.0	56.5	64.8	57.7	26.9			
Pyruvaldehyde	27.3	26.3	19.1	23.3	42.0	30.7	49.7	46.7	29.6	39.5	46.2	38.0
Acetaldehyde	10.1	30.5	36.0	6.3	29.2	55.1	4.4	7.3	29.8			
Glyoxal	15.4	19.2	6.9	25.5	48.3	36.0	29.5	28.2	28.2	35.7	33.4	26.6
Carbon dioxide	34.3	24.5	6.3	31.2	17.7	8.9	43.7	33.3	9.5	49.8	28.3	9.8
Carbon monoxide	21.1	18.9	16.8	38.4	18.0	13.7	36.7	27.6	11.4	47.4	24.9	12.2

derivatives have been previously identified among the pyrolysis products of cellulose and levoglucosan.[2,7,17,18] The last three bis-DNPH derivatives could have also been obtained from the corresponding α-hydroxycarbonyl compounds under the employed experimental conditions.[16] Thus, the 2,3-butanedione bis-DNPH may have been also derived from 2-hydroxy-3-butanone, the pyruvaldehyde bis-DNPH from 1-hydroxy-2-propanone or 2-hydroxypropanal, and the glyoxal bis-DNPH from glycolaldehyde. Quantitative analysis of these products carried out by gas chromatography is shown in Table I.

The specific radioactivity of the labeled levoglucosan samples and the isolated products given in Table II were determined by the standard liquid scintillation and gel-suspension counting techniques.[19] The radiochemical data gave the percentage of each product originating from C-1, C-2, and C-6 positions of the sugar molecule (see Table III). The resulting data on radiochemical patterns and the yields of each product, on pyrolysis of the anhydro sugar under the acidic, neat, alkaline, and prepolymerized conditions, were used for unravelling the nature of the reactions involved.

2-Furaldehyde.—Furan compounds are generally formed from the acid-catalyzed dehydration of carbohydrates[11,12] and are not very likely to involve recombinations of the sugar fragments. On this basis 2-furaldehyde could have been derived either from the first or the last five carbons of the anhydro sugar. The formation of 2-furaldehyde from these fragments is confirmed by the radiochemical data which, within ±4% experimental error, show that in all cases it contains 100% of C-2. However, under the acidic condition this product originates about 86% from the first five carbons and 17% from the last. Under the alkaline condition the situation is reversed and about 30% originates from

the first five carbons and 73% from the last. In the absence of any additives the results obtained are more similar to the acid-catalyzed rather than the base-catalyzed condition.

Formation of 2-furaldehyde from C-1 to C-5 is consistent with the acid-catalyzed degradation pathway of carbohydrates involving the conversion of the enolic forms of intermediate 3-deoxyglycosuloses to furan compounds.[12] It is also consistent with the observations of Kato and coworkers,[5] who have identified 3-deoxyglycosuloses among the pyrolysis products of cellulose, D-glucose, D-fructose, and D-xylose and have shown that 5-(hydroxymethyl)-2-furaldehyde could form 2-furaldehyde. The 3-deoxyglycosuloses are produced by a general acid- and alkali-catalyzed reaction of carbohydrates.[12,13,20] They are even formed during the processing and storage of food.[21−23]

Considering that cleavage of the glycosidic bond, reversible polymerization, and opening of the ring structure could readily take place under the pyrolytic conditions,[6] the reactions in Scheme I account for the formation of 2-furaldehyde from C-1 to C-5 of 1,6-anhydro-β-D-glucopyranose. According to this scheme, 2-furaldehyde may be formed either directly from 1,6-anhydro-β-D-glucopyranose or from its polymerization product. Since it is known that the anhydro sugar is readily polymerized on heating in presence of an acidic catalyst[7,24,25] and the polymeric material provides the same product and isotopic pattern as the anhydro sugar, the latter possibility cannot be ignored.

The competing pathway which is the main source of 2-furaldehyde under the alkaline condition is related

(17) R. G. Schwenker, Jr., and L. R. Beck, Jr., *J. Polym. Sci., Part C*, (2), 331 (1963).

(18) S. Glassner and A. R. Pierce, III, *Anal. Chem.*, **37**, 525 (1965).

(19) J. C. Turner, *Int. J. Appl. Radiat. Isotopes*, **20**, 761 (1969).

(20) J. C. Speck, Jr., *Advan. Carbohyd. Chem.*, **13**, 63 (1958).

(21) A. A. El-Dash and J. E. Hodge, *Carbohyd. Res.*, **18**, 259 (1971).

(22) H. Kato and Y. Sakurai, *Nippon Nogeikagaku Kaishi*, **38**, 536 (1964); *Agr. Biol. Chem.*, **28**, No. 12, A46 (1964).

(23) S. Oka, *Agr. Biol. Chem.*, **33**, 554 (1969).

(24) M. L. Wolfrom, A. Thompson, and R. B. Ward, *J. Amer. Chem. Soc.*, **81**, 4623 (1959).

(25) J. da S. Carvalho, W. Prins, and C. Schuerch, *ibid.*, **81**, 4054 (1959).

SCHEME I[a]

CH   CHOR   CHOR   CHO
HCOH HCOH   COH   COH
HOCH HOCH → CH   → $+ H_2O →$ CH $+ ROH$
HCOH HCOH   HCOH   HCOH
HCO   HCO   HCO   HCOH
±OCH₂ CH₂OH   CH₂OH   CH₂OH
H

CHO   CHO   CHO   CHO
C   C   C=O   C=O
HC ← CH ← CH   CH₂
HC   CH   CH   HCOH
HCO   CO   HCOH   HCOH
+   CH₂OH
CO ← CH₂O CH₂OH CH₂OH

CHO   CO
C=O → +
CH₃   CHO
+   CH₃
CO
+
CHO
CH₃

CO   CHO   CHO   CHO
+   C=O   COH   HCOH
CHO ← CH₃ ← CH₂ ← CH₂OH
CH₃

[a] R = H or D-glucose units.
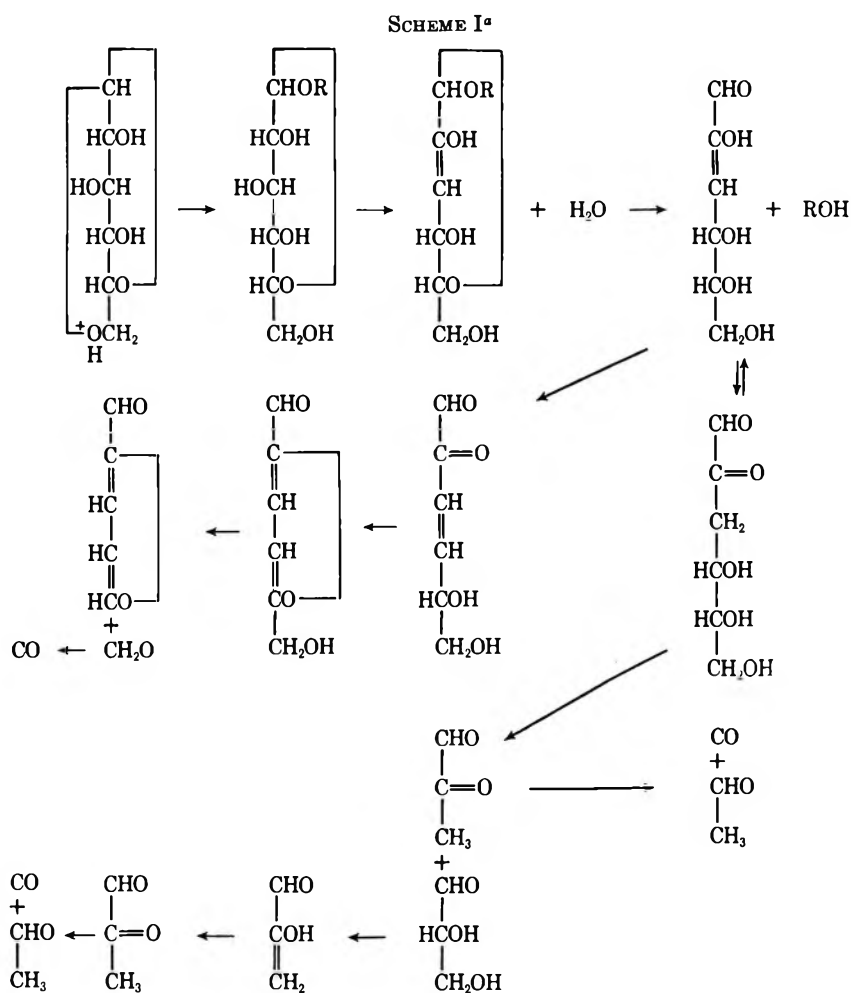
to the observation of Gardiner,[26] who has isolated 2-furyl hydroxymethyl ketone from the pyrolysis of cellulose, 3,6-anhydro-D-glucose, and other sugars. In this pathway (Scheme II), formation of the 3,6-anhydro ring leads to production of 2-furyl hydroxymethyl ketone, which on degradation gives 2-furaldehyde from the C-2–C-6 fraction of the original compound.
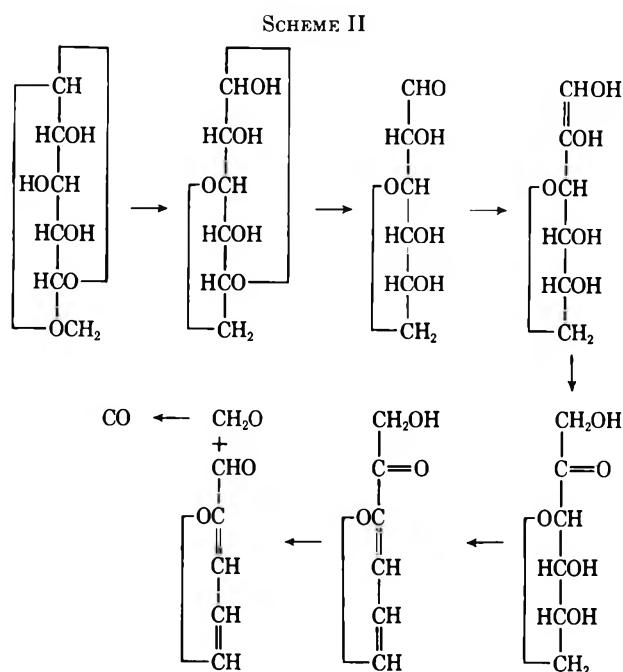
Since, as shown in Table I, the yield of 2-furaldehyde is substantially increased in the presence of zinc chloride and reduced with addition of sodium hydroxide, it could be surmised that the former pathway is enhanced by acidic conditions, whereas the latter pathway is not promoted by alkali and merely becomes dominant because the competing mechanism is hindered.

The two competing pathways even apply to aqueous reactions, because minor quantities of 2-furyl hydroxymethyl ketone have been obtained from the treatment of sucrose and D-fructose with aqueous acid, which results mainly in the formation of 5-(hydroxymethyl)-2-furaldehyde.[27] Although the formation of furan derivatives is catalyzed by acids, the 3-deoxy precursor, as noted before, is produced under both acidic and alkaline conditions.[12,20] Under the alkaline condition, however, it more readily undergoes dealdolization and other degradation reactions.

2,3-Butanedione.—This compound also follows the pattern shown by 2-furaldehyde. Under the acidic condition it is derived mainly from C-1 (65%) and under the alkaline condition mainly from the C-6 (56%). However, in contrast to 2-furaldehyde the radiochemical data indicate some fragment recombination which in this case is quite feasible and may be

SCHEME II

CH   CHOH   CHO   CHOH
HCOH   HCOH   HCOH   COH
HOCH → OCH → OCH → OCH
HCOH   HCOH   HCOH   HCOH
HCO   HCO   HCOH   HCOH
OCH₂   CH₂   CH₂   CH₂

CO   CH₂O   CH₂OH   CH₂OH
+   CHO   C=O   C=O
CHO ← OC ← OC ←   OCH
      CH   CH   HCOH
      CH   CH   HCOH
      CH   CH   CH₂

(26) D. Gardiner, *J. Chem. Soc. C*, 1473 (1966).

(27) R. E. Miller and S. M. Cantor, *J. Amer. Chem. Soc.*, **74** 5236 (1952).

due to aldol condensation or combination of CH₃CO·
free radicals.[2,3] If no fragment recombination had
occurred, all of the product should have been derived
from C-1–C-4 (25%), C-2–C-5 (30%), and C-3–C-6
(31%). This leads to a discrepancy of about 14%,
which must be accounted for by the recombination of
nonradioactive carbon fragments from C-3 to C-5.

The same logic also applies to the radiochemical data
obtained under the alkaline and acidic conditions.
Recombination of free radical fragments is also sup-
ported by detection of esr signals and investigations of
Heyns and Klier,[28] who have shown that pyrolysis of
glyceraldehyde gives acetaldehyde and 2,3-butanedione
as the first and second largest products. However,
these authors also have shown that 2,3-butanedione is
the major pyrolysis product of D-erythrose and the
radiochemical patterns show a high degree of specificity
rather than randomness expected from extensive frag-
ment recombination. Therefore, it seems very likely
that the observed patterns result from the breakdown
of the sugar moiety into a four-carbon fragment.

Scheme III shows cleavage of the sugar molecule
under alkaline condition to D-erythrose that is converted
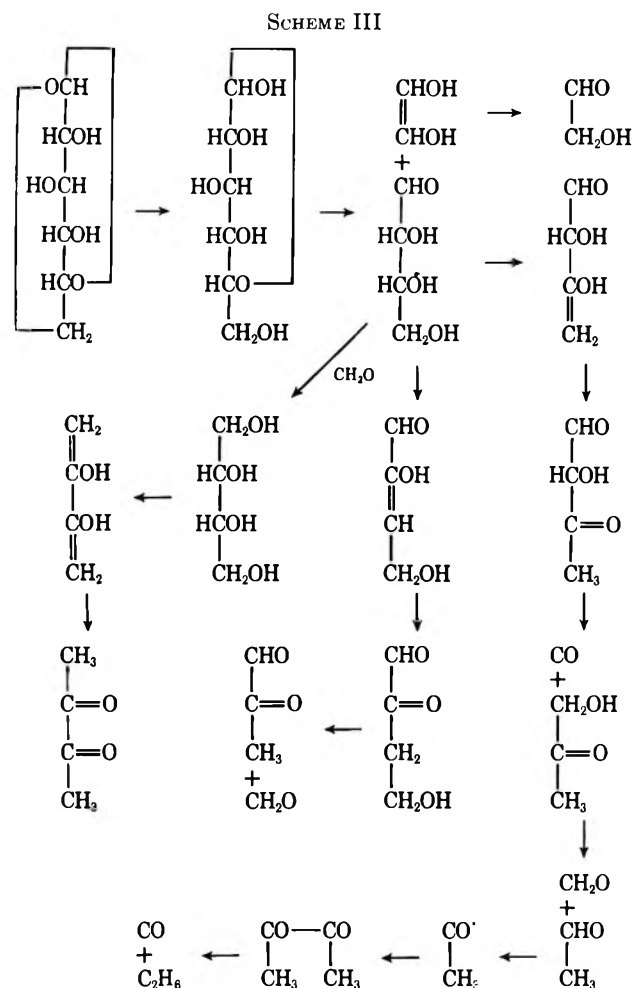
to the enolic form of glycolaldehyde and D-erythrose.
Opening of the anhydro ring conforms with the estab-
lished alkaline hydrolysis of the glycosidic bond at high
temperatures,[29] but under pyrolytic conditions it is
accompanied by degradation of the molecule. Fur-
ther transformation of glycolaldehyde and D-erythrose
gives glyoxal from C-1–C-2 and 2,3-butanedione, 1-
hydroxy-2-propanone (isolated as pyruvaldehyde),
and acetaldehyde carrying the C-6 label.

Pyruvaldehyde.—Assuming that pyruvaldehyde and
1-hydroxy-2-propanone are formed only through pri-
mary fragmentation of the sugar, the results given
in Table III could be further analyzed to show the con-
tribution of the central fragment C-3–C-5 which
amounts to 54% for uncatalyzed, 28% for the alkali,
and 20% for the acid-catalyzed conditions. This in-
dicates that pyruvaldehyde is derived mainly from
C-3–C-5 under the uncatalyzed condition and from
C-1–C-3 and C-4–C-6 under the acidic condition.
Under the alkali condition it is formed in a more random
fashion from C-1–C-3, C-2–C-4, C-3–C-5, and C-4–C-6.

The radiochemical pattern of pyruvaldehyde under
the acidic condition may be attributed to the degrada-
tion of 3-deoxy-D-*erythro*-hexosulose. As seen in
Scheme I, this compound could break to pyruvaldehyde
and glyceraldehyde, which is further pyrolyzed to
pyruvaldehyde, acetaldehyde, and 2,3-butanedione
carrying the C-6 label.

The same reactions could take place under the alka-
line condition. However, in these cases the D-glucose
moiety formed after opening of the anhydro ring could
also break down through Scheme III or more randomly
through dealdolization (Scheme IV), to give three

SCHEME III

SCHEME IV

directly or indirectly into 2,3-butanedione and other
products. The direct conversion should involve inter-
molecular disproportionation of the aldotetrose. Ac-
cording to Scheme III the anhydro ring is first opened
and the resulting D-glucose moiety then breaks down
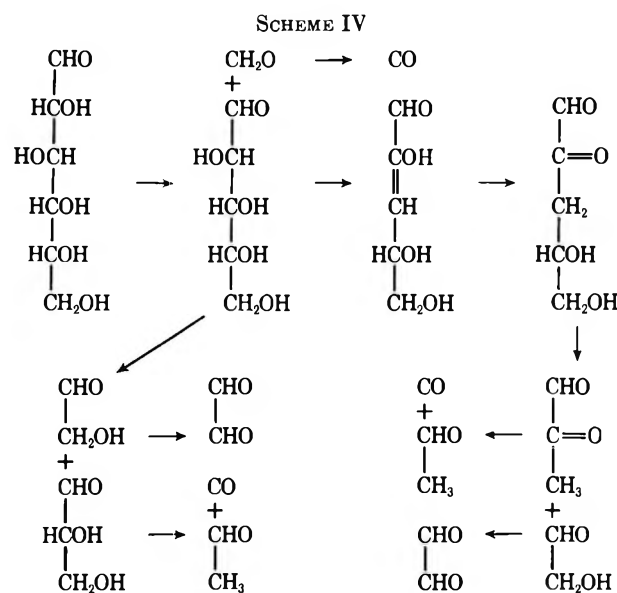
carbon fragments which are readily rearranged to
pyruvaldehyde.

Acetaldehyde.—This compound is formed heavily
from C-6 and lightly from C-1. Under the alkaline
condition more than half (55%) of the acetaldehyde
contains the terminal carbon atom of the anhydro
sugar. The high radiochemical yields of acetaldehyde
from C-6 under acidic, neat, and alkaline conditions

(28) K. Heyns and M. Klier, *Carbohyd. Res.*, **6**, 436 (1968).

(29) Elizabeth Dryselius, B. Lindberg, and O. Theander, *Acta Chem. Scand.*, **12**, 340 (1958); A. Dyfverman and B. Lindberg, *ibid.*, **4**, 879 (1950).

and its partial formation from C-2 under the last two conditions are consistent with the thermal degradation pathways presented by Schemes I and III.

Glyoxal.—The radiochemical data indicate that glyoxal and its precursor, glycolaldehyde, are derived from all the positions, although under the alkaline and acidic conditions the terminal carbons are more favored. Schemes I, III and IV show how these compounds could be formed from the different fragments.

It should be noted that the yields of acetaldehyde, glyoxal, and 1-hydroxy-2-propanone are substantially increased with the addition of sodium hydroxide.[7] The increased formation of these carbonyl compounds under alkaline condition strongly confirms the proposed dealdolization mechanisms, which have many counterparts among the normal alkaline degradation reaction of carbohydrates.[13,20]

Carbon Dioxide.—This compound originates mainly from C-1 and C-2 positions in all cases. However, the specificity is highest under acid condition and lowest under alkali condition.

Formation of carbon dioxide from C-1 may be attributed to the benzylic acid rearrangement of the 3-deoxy-D-*erythro*-hexosulose and pyruvaldehyde to 3-deoxy-D-hexonic acids (metasaccharinic acid) and lactic acid followed by decarboxylation. However, since relatively large quantities of carbon dioxide are formed from both acid and alkaline conditions and the reaction takes place even under mi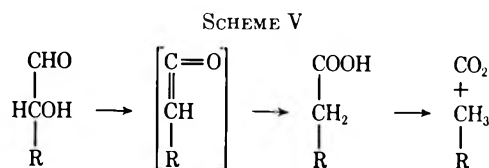ld pyrolytic conditions with cellulose[2] and other carbohydrates, including D-glucose,[30] it seems that a more direct pathway should be involved. A dehydration and rehydration rearrangement at C-1 and C-2 of the original sugar and decarboxylation of the product according to Scheme V could

<div align="center">SCHEME V</div>

$$\begin{array}{ccc} \begin{matrix} CHO \\ | \\ HCOH \\ | \\ R \end{matrix} & \longrightarrow & \begin{bmatrix} C{=}O \\ \| \\ CH \\ | \\ R \end{bmatrix} & \longrightarrow & \begin{matrix} COOH \\ | \\ CH_2 \\ | \\ R \end{matrix} & \longrightarrow & \begin{matrix} CO_2 \\ + \\ CH_3 \\ | \\ R \end{matrix} \end{array}$$

readily account for the carbon dioxide formation. This arrangement proceeds through a ketene intermediate to form a carboxylic acid that is decarboxylated under the pyrolytic conditions. Although to our knowledge there is no known precedent for this reaction with carbohydrates, the formation of ketenes from carbonyl compounds under the pyrolytic conditions is well known.[31]

Various aldehydes, particularly acetaldehyde, could also form carboxylic acids and primary alcohols through intermolecular disproportionation involving a hydride shift. Formation of methanol and acetic acid shown in Table I and erythritol postulated in Scheme III confirm this hypothesis.

Carbon Monoxide.—The radiochemical patterns obtained for carbon monoxide are very similar to those of carbon dioxide. The relatively heavier formation of this compound from C-1 and C-2 is consistent with the proposed schemes in which carbon monoxide is

derived by decarbonylation of the various aldehydes[32,33] and decomposition of formaldehyde, under the pyrolytic conditions.[34]

The carboxylic acids derived from the rearrangement or disproportionation reactions could also provide carbon monoxide through decarbonylation.[35,36] Formation of both carbon dioxide and carbon monoxide from C-1 of the aldehydes is further confirmed by the closely similar isotopic patterns that have been obtained for the two compounds.

The above schemes by no means represent all the reactions which take place on pyrolysis of carbohydrates. However, they clearly indicate the nature and mechanism of the reactions involved and lead to the following general conclusions.

Pyrolysis of carbohydrates not only provides a variety of products but also leads to the formation of the individual products from different positions of the sugar molecule, through competing pathways which fall short of complete randomization.

Within each pathway the individual transformations are remarkably similar to known aqueous reactions, especially the acid- and alkali-catalyzed degradation of carbohydrates, but the products formed by the combination of these reactions are further randomized by decarboxylation, decarbonylation, disproportionation, and other molecular rearrangements which are more prevalent at high temperatures.

In the absence of solvent the compelling forces for molecular rearrangements are provided more by an overabundance of energy than by the normal intermolecular and ionic interactions. Thermal anomerization of α-D-xylose, which proceeds as the crystalline material is melted,[6] clearly shows this point. A variety of ionic and solvent interactions have been proposed for cleavage of the cyclic structure in solution which are not applicable to the molten state.[37]

The competing pathways are controlled by ionic species present and the statistical possibility for the first point of attack or cleavage within the glycosyl unit. Under the acidic conditions the molecule or its polymerization product degrades by eliminations of various bonds and hydroxyl groups yielding substantial amounts of water and char (see Table I). Under the alkaline conditions cleavage of the anhydro ring and breakdown of the sugar mainly through reverse aldolization gives a variety of carbonyl compounds. There is no clear line of demarcation between the two types of pathways and both of them take place in the absence of additives. The pattern for pyrolysis of the neat substrate, however, is closer to the acidic conditions, presumably due to the formation of carboxylic acids.

Since the above reactions are of a general nature, the pyrolysis products of homologous carbohydrate compounds like cellulose, starch, 1,6-anhydro-β-D-glucose, D-glucosides, and D-glucose should be similar. There is a considerable amount of experimental support for this conclusion,[2,7,18] although it does not jibe with

(30) Y. Houminer and S. Patai, *Tetrahedron Lett.*, 1297 (1967).

(31) J. W. Williams and C. D. Hurd, *J. Org. Chem.*, **5**, 122 (1940).

(32) H. Burkett, W. M. Schubert, F. Schultz, R. B. Murphy, and R. Talbott, *J. Amer. Chem. Soc.*, **81**, 3923 (1959).

(33) J. F. Bunnett, J. H. Miles, and K. V. Nahabedian, *ibid.*, **83**, 2512 (1961).

(34) A. R. Hall, J. C. McCoubrey, and H. G. Wolfhard, *Combust. Flame*, **1**, 53 (1957).

(35) E. O. Wilg, *J. Amer. Chem. Soc.*, **52**, 4729 (1930).

(36) G. A. Ropp, *ibid.*, **82**, 842 (1960).

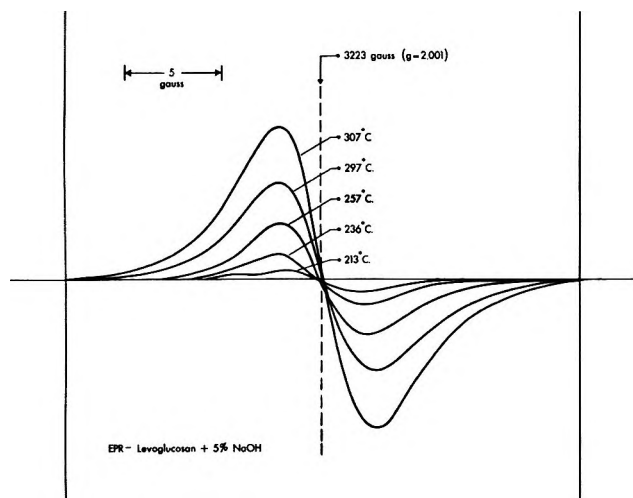(37) H. S. Isbell and W. Pigman, *Advan. Carbohyd. Chem.*, **24**, 13 (1969).

Figure 1.—The esr signals of 1,6-anhydro-β-D-glucopyranose treated with 5% sodium hydroxide and pyrolyzed at different temperatures.
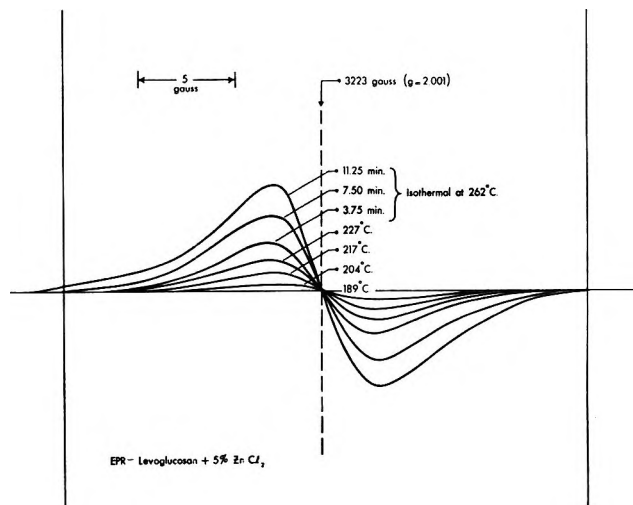

Figure 2.—The esr signals of 1,6-anhydro-β-D-glucopyranose treated with 5% zinc chloride and pyrolyzed under different conditions.

all the data reported by Heyns and Klier.[28] Development of almost the same products[7] and isotopic patterns from the anhydro sugar and its polymerization product in the presence of zinc chloride also confirms this conclusion.

Other than the ionic reactions, homolytic cleavage also plays a significant role in the pyrolytic degradation. However, the signals detected by esr spectroscopy (see Figures 1 and 2) are mainly associated with the stable carbonacious residue, rather than transient free radical intermediates. Some aspects of the free radical formations and the kinetics of the pyrolytic reactions will be discussed in a following report. The subjects that are currently under investigation should also shed some light on the significance of levoglucosan as a model compound for thermal degradation of starch and cellulose and provide a comparison between the pyrolytic reactions and field ionization which takes place on mass spectroscopy.

Experimental Section

Preparation of Samples.—1,6-Anhydro-β-D-glucopyranose labeled at positions 1, 2, or 6 was prepared by standard methods[14] from commercially available D-glucose-*1*-[14]*C*, -*2*-[14]*C*, and -*6*-[14]*C* diluted with nonradioactive materials (5 g). Small portions of the product were dissolved in methanol and mixed with calculated amounts of a solution of sodium hydroxide in methanol or zinc chloride in tetrahydrofuran. The solvents were then removed under vacuum at 50° to give samples of 1,6-anhydro-β-D-glucopyranose containing 5% sodium hydroxide or zinc chloride. The dried materials were kept under anhydrous condition.

Polymerization of the anhydro sugars containing 5% zinc chloride was carried out by heating 100-mg portions at 150° for 30 min in ampoules sealed under a nitrogen atmosphere.[25] Examination of nonradioactive samples showed the presence of 30% of a polymer which precipitated from 85% ethyl alcohol and the absence of any monomeric material that could be detected by tlc. The entire sample of the polymerized radioactive material in each ampoule was used for the pyrolysis experiments.

Pyrolysis.—Samples of treated and untreated ^{14}C-labeled 1,6-anhydro-β-D-glucopyranose (100 mg) were placed in small vials which were introduced into the pyrolysis apparatus consisting of a modified Sargent microcombustion unit attached to a series of receptacles. The system was thoroughly flushed with nitrogen and the sample was pyrolyzed by heating for 8 min at 600°. The pyrolysis products were swept through the system for 3 hr with a gentle stream of nitrogen. The pyrolysate containing carbonyl compounds was condensed in a small flask cooled in a Dry

Ice–acetone bath. The carbon dioxide was recovered as barium carbonate in traps containing barium hydroxide solution.[38] The carbon monoxide remaining in the stream was dried by passing through drying tubes (CaCl₂ and P₂O₅), oxidized with iodine pentoxide,[15] and collected as barium carbonate in the last traps.

Isolation of the Pyrolysis Products.—The pyrolysate condensed in the cooled flask was combined with washings from the adjoining tubes (5 ml) and treated at room temperature with 10 ml of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* HCl[39] for 18 hr. The precipitate of mixed DNPH derivatives was filtered, washed with water, and dried, yield 12 mg. The mixture was dissolved in 6 ml of chloroform, and 1-ml portions of the solution were placed as a line on Baker-flex silica gel IB-F tlc sheet and were developed in three stages with benzene. This gave six major zones in addition to the original strip. The top five zones from chromatograms were collected and extracted with chloroform. The extract was concentrated and rechromatographed, and the developed zones were processed to provide the compounds listed in Table IV.[40–42]

Radiochemical Assay.—The samples were counted with the Tri-Carb liquid scintillation spectrometer model 314 E operated at 6° using a scintillation mixture (Permablend I consisting of 91% PPO and 9% Dimethyl POPOP) produced by Packard Instrument Co. Before counting, the samples were stored in the counter for 20 min to eliminate the effect of light. Duplicate samples were counted five times, each time for 10 min to reduce the random counting error to less than 2%.

Samples of ^{14}C-labeled 1,6-anhydro-β-D-glucopyranose (1 mg) were weighed in a scintillation vial and dissolved in 10 ml of a toluene–methanol mixture (8:2) containing 0.4% of Permablend I. The solutions were counted using toluene-[14]*C* as a reference, with the counting efficiency of 61.76%.

The gel-suspension technique[19] was employed for counting the samples of barium carbonate and DNPH derivatives absorbed on tlc silica gel. The barium carbonate sample (~0.5 mg) and 400 mg of Cab-O-Sil gel forming reagent were weighed in a scintillation vial. The mixture was shaken with 10 ml of toluene containing 1% of Permablend I to form a gel. The gel was counted using standard ^{14}C-labeled barium carbonate as a reference, with the counting efficiency of 40.2%.

The DNPH derivatives absorbed on silica were collected from tlc zones and homogenized. A sample of the homogenized material (0.2 g) was extracted with 25 ml of chloroform and the solution was used for determining the concentration of the DNPH derivative by uv spectroscopy. Another sample of the silica powder containing a DNPH derivative (300 mg) was used for preparation of the gel suspension as before. The DNPH deriva-

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TABLE IV

PHYSICAL PROPERTIES OF 2,4-DINITROPHENYLHYDRAZONE DERIVATIVES ISOLATED FROM THE PYROLYSIS PRODUCTS

| | | Found | | | | Literature | | |
| | | | Uv (CHCl₃) | | | Uv (CHCl₃) | | |
	R_f^b	Mp, °C	λ_{max}, mμ^a	$\epsilon \times 10^{-4}$	Mp, °C	λ_{max}, mμ	$\epsilon \times 10^{-4}$	Ref
2-Furaldehyde	0.32	222–224	388*	2.90	225	386	2.65	40
2,3-Butanedione (bis)	0.16	312–314	394*, 442	2.92	314–315			41
Pyruvaldehyde (bis)	0.11	298–301	394*, 444	3.81	299–300			41
					304–305			42
Acetaldehyde	0.30	164–165	354*	2.22	167	354	2.22	40
Glyoxal (bis)	0.07	330–333	390, 445*	2.42	326–328			41
					336–338			42

^{a} Starred wavelengths denote major maxima. ^{b} In benzene.

tives produced a strong quenching effect on scintillation that was measured by using ^{14}C-labeled toluene as an internal standard. The counting efficiency varied within the range of 10–30% according to the sample and concentration.

Esr Spectroscopy.—Samples of the anhydro sugar (1 part) were mixed with ground glass .(9 parts) and ground together thoroughly to ensure uniform mixing. The ground samples (4–7 mg) were accurately weighed into a 2-mm capillary tube. The tube was placed into the cavity of a Varian E-3 esr spectrometer heated with a specially designed variable-temperature accessory.

Studies on the Vilsmeier–Haack Reaction. IV.[1] Convenient Synthesis of 2,2′-Anhydro-1-β-D-arabinofuranosylcytosine (2,2′-Cyclocytidine) and Its Derivatives[2]

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A carcinostatic nucleoside, 2,2′-anhydro-1-β-D-arabinofuranosylcytosine (2,2′-cyclocytidine) (5), was prepared in a yield of 55% by treatment of cytidine (4) with Vilsmeier–Haack reagent 1 or 2. 5′-Chloro-5′-deoxy-2,2′-anhydro-1-β-D-arabinofuranosylcytosine (6) and 2′,5′-dichloro-2′,5′-dideoxycytidine (7) were also prepared by prolonged treatment of 4 with 1. Treatment of 5 and 6 with mild alkali gave 1-β-D-arabinofuranosylcytosine (9) and 5′-chloro-5′-deoxy-1-β-D-arabinofuranosylcytosine (10), respectively, whereas treatment of either of 6 and 7 with strong alkali gave 2′,5′-anhydro-1-β-D-arabinofuranosylcytosine (11).

2,2′-Anhydro-1-β-D-arabinofuranosylcytosine (2,2′-cyclocytidine) (5) has been shown to be an intermediate[3–5] for the synthesis of a carcinostatic nucleoside, 1-β-D-arabinofuranosylcytosine (9),[6] and by itself a potent carcinostatic agent.[7] 1-β-D-Arabinofuranosylcytosine (9) has been synthesized by several procedures, such as (a) from cytidine via 2,2′-anhydro intermediates,[3,8,9] (b) from 1-β-D-arabinofuranosyluracil,[10] or (c) from the appropriate sugars,[11–13] but most of these in-

volve tedious steps. Recently, 5 and 9 were successfully synthesized[14] directly from 4 by use of a partially hydrolyzed phosphorus oxychloride.[15] We wish to report an improved method to prepare 5, 9, and their derivatives.

N,N′-Dimethylformamide (DMF) combines with inorganic acid halides to form active reagents (Vilsmeier–Haack reagents),[16–18] which are useful as formylating, halogenating, and dehydroxylating agents.[19] Thus, phosphorus oxychloride and thionyl chloride react with DMF to form the complex 1[18] and the complex 2,[17] respectively (Scheme I). The latter may be converted into the crystalline complex 3 by removal of sulfur dioxide,[17] and 3 re-forms 2 on addition of sulfur dioxide.[20] The reaction of nucleosides with the com-

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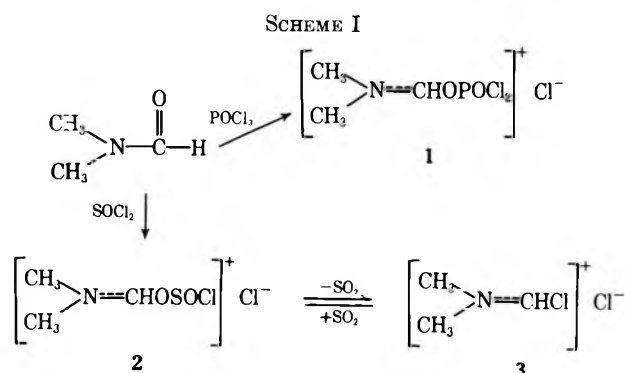(16) A. Vilsmeier and A. Haack, *Chem. Ber.*, **60**, 119 (1927).

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SCHEME I

plex **3** have been studied by several researchers, affording nucleosides chlorinated at the base[21] or the sugar moiety.[22] This time, we studied the reaction of **1** or **2** with cytidine (**4**) and obtained the anhydro nucleoside **5** and its derivatives, **6** and **7**.

Cytidine (**4**) was treated with the complex **1** in DMF at room temperature for 3 hr and then the mixture was treated with water. Paper chromatography showed a major spot corresponding to the anhydro nucleoside **5**. It was isolated as a formate **5a** and then converted to a hydrochloride **5b** (yield 55%) by use of ion exchange column chromatographies. The product **5b** was identified as 2,2'-anhydro-1-β-D-arabinofuranosylcytosine hydrochloride by comparison of the physicochemical properties with those of the authentic sample.[3-5]

When **5b** was hydrolyzed with ammonia, **9** was obtained quantitatively. The yield of **9** from **4** can be increased to 60% by omitting the isolation of the intermediate **5**. Thus, this procedure constitutes a simple method to synthesize 1-β-D-arabinofuranosylcytosine (**9**) in contrast to other complicated methods.

Treatment of cytidine (**4**) with **1** was performed at room temperature for 24 hr (Scheme II). Paper chromatography showed another spot having an R_f value larger than that of **5**. The new product (**6**) was isolated from the aqueous reaction mixture in a yield of 65% by use of successive cation and anion exchange columns. The product (**6**) was identified as the 5'-chloro-5'-deoxy derivative of the anhydro nucleoside **5**. It is known that the 5'-hydroxyl function of nucleosides can be readily replaced by halogen atoms.[22,23] Treatment of **6** with mild alkali gave a monochlorinated 1-β-D-arabinofuranosylcytosine (**10**), which could be further converted into the compound **11** by treatment with strong alkali. Elemental analysis and ultraviolet absorption spectrum suggested that **11** was 2',5'-anhydropentofuranosylcytosine. The compound **11** could be converted into the known 2',5'-anhydro-1-β-D-arabinofuranosyluracil (**12**)[24] by treatment with nitrous acid. Hence the structure of **11** was firmly established to be 2',5'-anhydro-1-β-D-arabinofuranosylcytosine. Thus, the structures of the reaction products, **6** and **10**, were elucidated to be 5'-chloro-5'-deoxy-2,2'-anhydro-1-β-D-arabinofuranosylcytosine hydrochloride and 5'-chloro-5'-deoxy-1-β-D-arabinofuranosylcytosine, respectively.

Treatment of cytidine (**4**) with **1** for 240 hr gave a new product (**7**) containing two chlorine atoms in a yield of 70%. When **7** was heated at 80° for 1 hr in water, it was quantitatively converted into the anhydro compound **6**. Since 2'-chloro-2'-deoxycytidine can be easily converted into the anhydro nucleoside **5**,[4] the structure of **7** must be 2',5'-dichloro-2',5'-dideoxycytidine. Physicochemical properties of **7** supported the above structure. Treatment of **7** with ammonia afforded **10**, probably *via* the anhydro intermediate **6**, and with strong alkali afforded 2',5'-anhydro compound **11** quantitatively.

Thus, cytidine (**4**) undergoes the transformation with **1** in the following sequence: (1) anhydro bond formation between the 2 and 2' positions; (2) chlorination at the 5' position; (3) cleavage of the 2,2'-anhydro bond with chlorine.

Treatment of cytidine (**4**) with the complex **2** also afforded **5-7**. In this case, however, 5'-chloro-5'-deoxycytidine (**8**), whose structure was established by comparison with the authentic sample,[23] was also produced. Thus, the yield of the anhydro compound **5** obtained was lower than that obtained by the complex **1**. Reaction of cytidine (**4**) with the crystalline complex **3** was also attempted, but no reaction was observed.

In order to prepare 5'-substituted derivatives of 1-β-D-arabinofuranosylcytosine, replacement of the 5' chlorine atom of **10** with nucleophiles was attempted but was unsuccessful because it was readily attacked by the 2'-hydroxyl function affording **11**. Treatment of the anhydro compound **11** with acid gave cytosine (**13**) instead of **9**. This observation was not unexpected in view of the known lability of the glycosidic linkage of **12** toward acid affording uracil (**14**).[24] Cleavage of the anhydro ring of **11** by halide, azide, or benzylthio ion failed, although it is known that the anhydro ring in the 3',5'-anhydroxylofuranosyl nucleosides can be attacked by these nucleophiles.[25]

Experimental Section[26]

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(26) Melting points were determined on a Büchi Schmerzpunktbestimmung-sapparat nach Dr. Tottli and not corrected. Ultraviolet absorption was measured with a Hitachi recording spectrophotometer, ESP-3T. Optical rotations were obtained with a JASCO automatic polarimeter, Model DIP-SL. Paper chromatograms were run by the ascending technique on Toyo Roshi No. 51A paper, using the following solvent systems: (1) i-PrOH–1 M NH₄OAc (pH 4.0) (7:3); (2) n-BuOH–H₂O (84:16); (3) 5 M NH₄OAc–0.5 M EDTA·Na₄-saturated Na₂B₄O₇–EtOH (12:0.3:48:132);[27] (4) i-PrOH–NH₄OH–H₂O (7:1:2). The spots were detected under uv light and was represented by the symbol R_f with suffix corresponding to the number of the solvents. Paper electrophoresis was carried out in the borate buffer system (pH 6.0),[28] and the mobility was represented by the relative value to that of cytidine (**4**). TOD is total optical density.

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(29) The complex **1** could be isolated as a gummy solid when POCl₃ was treated with an equimolar amount of DMF in anhydrous ether.[18] When **4** was treated with this gummy solid in DMF the same results as described here were obtained.

SCHEME II
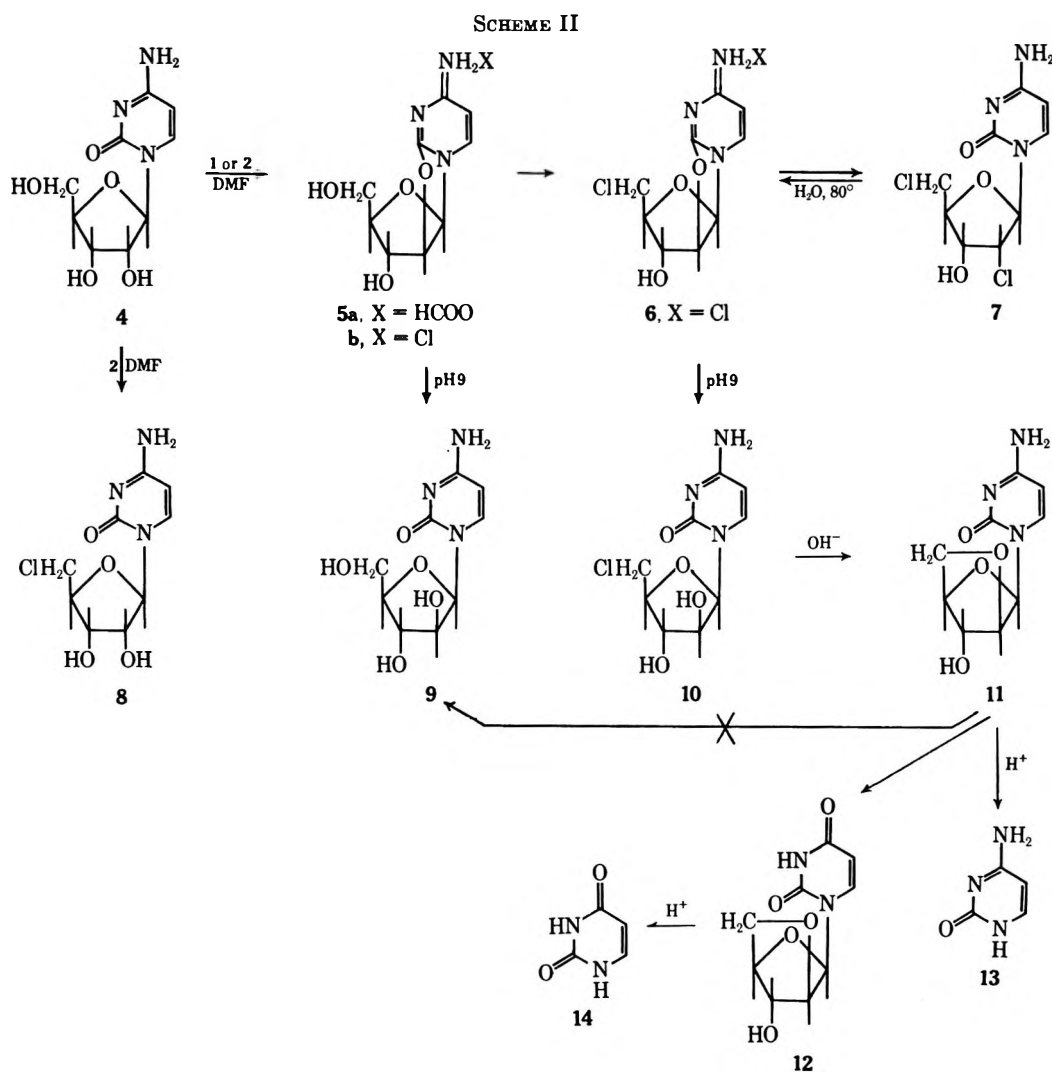
(4.1 mmol) of cytidine (4) and the mixture was stirred at room temperature for 3 hr, then poured into 100 ml of water to destroy the reagent. The ultraviolet absorption spectrum of the aqueous reaction mixture showed the maxima at 260 and 320 nm, and the latter maximum completely disappeared after 3 hr standing at room temperature.[30] Paper chromatography showed one main spot having R_{f_1} 0.58 and R_{f_3} 0.73, an aqueous extract of which showed the absorption maxima at 232 and 262 nm (pH 1-6). The aqueous reaction mixture [$TOD_{280 \text{ nm}}$ (pH 1) 50,500] was applied to a Dowex 50 × 4 (pyridinium form) column (2.5 × 40 cm). The column was eluted with 0.1 M pyridinium formate (pH 4.8) to give 4 at the 1700-2300-ml fraction, and subsequently with 0.4 M pyridinium formate (pH 4.8) to give the product 5 at the 500-1300-ml fraction. The fraction containing the product 5 [$TOD_{280 \text{ nm}}$ (pH 1) 13,000] was evaporated to dryness after the pH of the solution was adjusted to 4.0 with formic acid in order to avoid the degradation of the product. Repeated evaporation of the residue with EtOH gave a gum. Crystallization from EtOH gave 5a as granules which melted at 173-174° dec and weighed 735 mg, uv max (pH 1-6) 232 and 263 nm. It was redissolved in 20 ml of water and passed through a Dowex 1 × 4 (Cl⁻) column (2 × 3 cm). The column was washed with 100 ml of water. The combined effluent and washings were evaporated to dryness to give a crystalline material. Recrystallization from aqueous EtOH gave 5b as white needles which melted at 262-264° dec and weighed 615 mg (55%): uv max (pH 1-6) 231 nm (ϵ 9600), 263 (10,900), min (pH 1-6) 218 (7000), 243 (6600), shoulder (pH 1-6) 282 (3200); $[\alpha]^{20}$D −21.0° (c 2, H_2O) [lit.³ mp 248-250°; uv max (pH 1-7) 231 nm (ϵ 9400), 262 (10,600), min (pH 1-7) 243 (6500); $[\alpha]^{23}$D −21.8° (c 2, H_2O)]; R_{f_1} 0.58, R_{f_2} 0.05, R_{f_3} 0.73.

(30) The substance having the characteristic absorption maxima at 260 and 320 nm could not be isolated because of its instability. Thus, it seemed that the initial reaction of 4 with 1 afforded the unstable substitution at the cytosine moiety.

Anal. Calcd for $C_9H_{11}O_4N_3 \cdot HCl$: C, 41.32; H, 4.63; N, 16.07. Found: C, 41.44; H, 4.45; N, 16.30.

1-β-D-Arabinofuranosylcytosine (9). A. From 2,2′-Anhydro-1-β-D-arabinofuranosylcytosine (5b).—The compound 5b (100 mg) was dissolved in 2 ml of water and the solution was adjusted to pH 9 with ammonia. The mixture was allowed to stand at room temperature for 15 min, acidified with HCl, and applied to a column (1 × 1.5 cm) of Dowex 50 × 4 (H⁺). The column, which was washed well with water, was eluted with 50 ml of 1 N NH_4OH. The effluent was evaporated *in vacuo*. Crystallization of the residue from EtOH afforded 78 mg (90%) of the pure material of 9: mp 210-212° dec; uv max (pH 1) 282 nm (ϵ 13,400), min (pH 1) 241 (1600), max (pH 7) 271 (9700), min (pH 7) 251 (6500); $[\alpha]^{20}$D +158° (c 0.5, H_2O) [lit.⁸ mp 212-213° dec; uv max (pH 1) 280 nm (ϵ 13,400), max (pH 13) 273.5 (10,000); $[\alpha]^{25}$D +151° (c 0.5, H_2O)]; R_{f_2} 0.18, R_{f_3} 0.71; paper electrophoretic mobility +0.45.

Anal. Calcd for $C_9H_{13}O_5N_3$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.65; H, 5.21; N, 17.08.

B. By the Reaction of Cytidine (4) with 1.—The reaction mixture, containing 6.0 g of $POCl_3$, 1.0 g of 4, and 20 ml of DMF, was stirred at room temperature for 3 hr. It was poured into 100 ml of water and the aqueous mixture was treated with ammonia at pH 9 and room temperature for 15 min. The mixture was reacidified with HCl and was applied to a column (2.5 × 40 cm) of Dowex 50 × 4 (H⁺). The column, which was washed well with water, was eluted with 1.0 l. of 1 N NH_4OH. The eluate was evaporated *in vacuo* to dryness, giving a gummy residue. It was crystallized from EtOH to afford 604 mg (60%) of 9, mp 208-211° dec.

5′-Chloro-5′-deoxy-2,2′-anhydro-1-β-D-arabinofuranosylcytosine (6). A. By the Reaction of Cytidine (4) with 1.—The reaction mixture, containing 6.0 g of $POCl_3$, 1.0 g of 4, and 20 ml of DMF, was stirred at room temperature for 24 hr. Paper chromatography showed two spots having R_{f_1} 0.58 and 0.67, corre-

sponding to **5** and **6**, respectively. An aqueous extract of both of these spots showed identical absorption maxima at 232 and 264 nm (pH 1–6). To the reaction mixture was added 100 ml of water. The solution was then applied to a column of Dowex 50 × 4 (pyridinium form). The column was eluted with 0.1 *M* pyridinium formate (pH 4.8) to give two peaks at the 2500–4500-ml fraction (**5**) and at the 6000–8000-ml fraction (**6**). The fraction containing **6** was evaporated to dryness, and the residue was dissolved in 5 ml of water. The solution was passed through a column (2 × 3 cm) of Dowex 1 × 4 (Cl⁻). The column was eluted with 50 ml of water. Effluent and washings were combined and evaporated to dryness. The residue was crystallized from EtOH to afford 750 mg (65%) of fine needles of **6**. Recrystallization from aqueous EtOH gave a pure sample of **6**: mp 263–265° dec; uv max (pH 1–7) 233 nm (ε 9900), 263 (11,300) min (pH 1–7) 244 (7800); [α]²⁰D −25.3° (c 0.5, H₂O); R_{f_1} 0.67, R_{f_2} 0.11, R_{f_3} 0.78.

B. From 2',5'-Dichloro-2',5'-dideoxycytidine (7).—2',5'-Dichloro-2',5'-dideoxycytidine (**7**) (100 mg) was dissolved in 2 ml of water and heated at 80° for 1 hr. The mixture was evaporated to dryness *in vacuo*, and a crystalline residue was obtained. Recrystallization from aqueous EtOH gave 80 mg (80%) of fine needles of **6**: mp 263–265° dec; uv max (pH 1–7) 231, 263 nm; R_{f_1} 0.67, R_{f_2} 0.11, R_{f_3} 0.78.

Anal. Calcd for C₉H₁₀O₃N₃Cl·HCl: C, 38.60; H, 3.96; N, 15.01; Cl, 25.33. Found: C, 38.82; H, 4.00; N, 15.23; Cl, 24.97.

2',5'-Dichloro-2',5'-dideoxycytidine (7).—The reaction mixture, containing 12.0 g of POCl₃, 2.0 g of **4**, and 40 ml of DMF, was stored at room temperature for 240 hr. Paper chromatography showed a major spot having R_{f_1} 0.84, an aqueous extract of which showed an absorption maximum at 280 nm (pH 1). The reaction mixture was mixed with 2000 ml of water and was applied to a column of Dowex 50 × 4 (pyridinium form). The column was eluted with 0.1 *M* pyridinium formate (pH 4.0) to give a major peak at the 5000–8000-ml fraction. The fraction was evaporated to dryness *in vacuo* at below 40°. Repeated evaporation with EtOH gave a gummy residue which was crystallized from aqueous EtOH to give 1.61 g (70%) of **7**. Recrystallization from aqueous EtOH gave fine needles of **7**: mp 242–245° dec; uv max (pH 1) 282 nm (ε 13,500), max (pH 7) 272 (9600); [α]²⁵D +29° (c 0.25, H₂O); R_{f_1} 0.85, R_{f_2} 0.66, R_{f_3} 0.82; paper electrophoretic mobility 0.0.

Anal. Calcd for C₉H₁₁O₃N₃Cl₂·¹/₂H₂O: C, 37.40; H, 4.19; N, 14.54; Cl, 24.54. Found: C, 37.54; H, 4.18; N, 14.59; Cl, 24.18.

The compound is negative to HIO₄–benzidine reagent.[31]

5'-Chloro-5'-deoxy-1-β-D-arabinofuranosylcytosine (10). A. By the Reaction of Cytidine (4) with 1.—The reaction mixture, containing 6.0 g of POCl₃, 1.0 g of **4**, and 20 ml of DMF, was kept at room temperature for 240 hr. The mixture was treated with water and then with ammonia, and desalted as in method B of the preparation of **9**, affording a residual gum. Paper chromatography of the residue showed a major spot having R_{f_2} 0.52 corresponding to **10** and two minor spots having R_{f_2} 0.66 and 0.26, corresponding to **7** and **11**, respectively. Compound **10** was isolated from the residue in a yield of 55% (590 mg) by use of a cellulose column (1.8 × 57 cm) with the elution solvent, *n*-BuOH–H₂O (84:16). Recrystallization from aqueous EtOH gave white needles of **10**: mp 202–204.5° dec; uv max (pH 1) 281 nm (ε 13,550), min (pH 1) 241 (1580), max (pH 7) 272 (9650), min (pH 7) 251 (6270); [α]²⁰D +163.8° (c 0.5, H₂O); R_{f_1} 0.72, R_{f_2} 0.52, R_{f_3} 0.78.

Anal. Calcd for C₉H₁₂O₄N₃Cl: C, 41.30; H, 4.62; N, 16.06; Cl, 13.55. Found: C, 41.05; H, 4.59; N, 16.16; Cl, 13.16.

B. From 5'-Chloro-5'-deoxy-2,2'-anhydro-1-β-D-arabinofuranosylcytosine (6).—5'-Chloro-5'-deoxy-2,2'-anhydro-1-β-D-arabinofuranosylcytosine (**6**) (100 mg) was dissolved in 5 ml of water and the mixture was adjusted to pH 9 with ammonia. After standing at room temperature for 15 min it was evaporated to dryness. Crystallization from aqueous EtOH afforded 65 mg of **10**, mp 202–204° dec.

2',5'-Anhydro-1-β-D-arabinofuranosylcytosine (11). A. By the Reaction of Cytidine (4) with 1.—The desalted reaction mixture obtained as in method A of the preparation of **10** was applied

to a column (2.5 × 40 cm) of Dowex 1 × 4 (OH⁻),[32] which was eluted with 30% MeOH. From the 2000–3000-ml fraction 740 mg (80.0%) of **11** was obtained. Recrystallization from aqueous EtOH gave pure needles of **11**: mp 257–258° dec; uv max (pH 1) 282.5 nm (ε 13 400), min (pH 1) 242 (1300), max (pH 7) 273 (9300), min (pH 7) 250 (5000); [α]²⁰D +232.3° (c 0.5, H₂O); R_{f_1} 0.57, R_{f_2} 0.26, R_{f_3} 0.72, R_{f_4} 0.63; paper electrophoretic mobility 0.0.

Anal. Calcd for C₉H₁₁O₄N₃: C, 47.99; H, 4.93; N, 18.66. Found: C, 48.17; H, 5.17; N, 18.27.

The compound is negative to HIO₄–benzidine reagent.[31]

B. From 5'-Chloro-5'-deoxy-1-β-D-arabinofuranosylcytosine (10).—5'-Chloro-5'-deoxy-1-β-D-arabinofuranosylcytosine (**10**) (100 mg) was dissolved in 2 ml of 2 *N* NaOH and heated at 80° for 1 hr. The mixture was acidified with HCl and absorbed to a Dowex 50 × 4 (H⁺) column (2 × 3 cm). The column, which was washed well with water, was eluted with 20 ml of 1 *N* NH₄OH, and the effluent was evaporated to dryness. Crystallization from EtOH gave 70 mg of white needles of **11**, mp 257–258° dec.

2',5'-Anhydro-1-β-D-arabinofuranosyluracil (12).—2',5'-Anhydro-1-β-D-arabinofuranosylcytosine (**11**) (300 mg) was treated with 1.5 g of NaNO₂, 2.2 ml of AcOH, and 5 ml of water at room temperature for 3 hr. After the mixture was diluted with 10 ml of water, it was passed successively through columns of Dowex 50 × 4 (20 ml) and Dowex 1 × 4 (HCO₃⁻) (5 ml). Combined eluate and washings (about 100 ml) were evaporated to dryness, affording 254 mg (85%) of the crystalline product **12**. Recrystallization from aqueous EtOH gave white needles of **12**: mp 258–259.5° dec; uv max (pH 7) 265 nm (ε 10,500), min (pH 7) 233 (2000), max (pH 13) 265 (8500), min (pH 13) 242 (4600); [α]²⁰D +206.3° (c 0.3, H₂O) [lit.²⁴ mp 260–262° eff dec; uv max (pH 6.9) 264 nm (ε 10,700), min (pH 7) 231 (1900), max (1 *N* NaOH) 264 (8400), min (1 *N* NaOH) 240 (4270); [α]²³D +193° (c 0.3, H₂O)]; R_{f_2} 0.34.

Anal. Calcd for C₉H₁₀O₅N₂: C, 47.79; H, 4.42; N, 12.39. Found: C, 47.91; H, 4.31; N, 12.40.

A mixture of **12** and an authentic compound,²⁴ mp 257–259° dec, melted at 257–258.5° dec.

Reaction of Cytidine (4) with 2.³³—Thionyl chloride (3.0 ml) was dissolved in 20 ml of DMF and the mixture was set aside at room temperature for 30 min. To the solution was added 2.0 g of **4** and the mixture was stirred at room temperature for 3 hr. It was then poured into about 50 ml of water and the aqueous solution was stirred for 1 hr to remove sulfur dioxide that evolved by the decomposition of the reagent. The product (**5a**) was isolated in a yield of 30% by a procedure similar to that described in the preparation of **5a** using **1**. **5a** was converted into **5b**, which melted at 262–264° dec: uv max (pH 1–6) 231 nm (ε 9600), 262.5 (10,800), min (pH 1–6) 218 (7100), 243 (6700), shoulder (pH 1–6) 282 (3300); [α]²⁰D −22° (c 2, H₂O); R_{f_1} 0.58, R_{f_2} 0.05.

The reaction mixture, containing 3 ml of SOCl₂, 2 g of **4**, and 20 ml of DMF, was allowed to stand at room temperature for 240 hr. After addition of water, the mixture was absorbed to Dowex 50 × 4 (H⁺) (2.5 × 40 cm). The column was eluted with 1 *N* NH₄OH, and the effluent was evaporated to dryness *in vacuo*. Paper chromatography of the residue showed four spots having R_{f_2} 0.26, 0.34, 0.52, and 0.66 corresponding to **11**, **8**, **10**, and **7**, respectively. From the gummy residue 5'-chloro-5'-deoxycytidine (**8**), which melted at 167–170° dec, was isolated in a yield of 20%. Paper chromatographic comparison of **8** (R_{f_2} 0.34) with the authentic sample,³³ and the mixed fusion test confirmed the structure of **8**. From the mother liquor, 2',5'-anhydro compound **11**, which melted at 257–258° dec, was isolated in a yield of 35% by use of a Dowex 1 × 4 (OH⁻)³² column.

Attempted Cleavage of the Anhydro Ring of 11.—2',5'-Anhydro-1-β-D-arabinofuranosylcytosine (**11**) (10 mg) was treated with 0.15 ml of 0.4 *N* H₂SO₄ at 100° for 2.5 hr. Paper chromatography revealed a spot having R_{f_4} 0.53, identical with that of cytosine **13**, an aqueous extract of which showed the absorption maxima at 268 (pH 7) and 282 nm (pH 13). Several attempts to open the anhydro ring of **11** by nucleophiles such as NaI–AcOH, complex 3–CHCl₃, LiN₃–DMF, and NaSCH₂Ph–MeOH under heated conditions were made but they were unsuccessful.

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(33) The complex **2** could also be formed by the addition of sulfur dioxide to the complex **3**.²¹ When **4** was treated with this fuming liquid in DMF, the same results were obtained.

Nucleoside Peptides. III. The Synthesis of *N*-[1-(9-Adenyl)-β-D-ribofuranuronosyl] Derivatives of Certain Amino Acids and Peptides

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Benzyl esters of several amino acids and peptides have now been successfully coupled with 1-(9-adenyl)-2,3-*O*-isopropylidene-β-D-ribofuranuronic acid (1) by the DCC method to afford *N*-[1-(9-adenyl)-2,3-*O*-isopropylidene-β-D-ribofuranuronosyl]amino acid and peptide benzyl esters. Concomitant acylurea side-product formation was inhibited by the addition of *N*-hydroxysuccinimide. The title compounds were produced in excellent yields when the isopropylidene and benzyl blocking groups were removed by acid hydrolysis and catalytic hydrogenolysis, respectively. These procedures provide a general method for the attachment of the amino terminus of an amino acid or peptide to a carboxylic acid moiety of a nucleoside.

Recently there has been a great deal of interest in the isolation and synthesis of nucleoside amino acids and peptides.[1-3] Reasons for the preparation and study of this class of compounds has been outlined in an earlier publication submitted from these laboratories.[4] Most syntheses of nucleoside peptides have involved either the coupling of an amino[1,2,4] or hydroxyl[5] group of a nucleoside to the carboxyl group of a blocked amino acid or displacement of a leaving group on a nucleoside by the amino group of an amino acid.[6] In one report[7] purine and pyrimidine ribofuranoic acids have been coupled to unblocked high molecular weight polypeptides in yields ranging from 2 to 10%. The work described in this article has provided a general method for the coupling of the amino terminus of an amino acid or peptide to a free carboxylic acid moiety of a nucleoside in good yield.

1-(9-Adenyl)-2,3-*O*-isopropylidene-β-D-ribofuranuronic acid (1) was selected as the nucleoside reagent because of its solubility properties and ease of preparation.[8a,b] *N*,*N*'-Dicyclohexylcarbodiimide (DCC) was chosen to effect coupling, since it has been known to provide peptide linkages in high yield with little or no racemization.[9] When 1 was coupled to various amino acid benzyl esters by the action of DCC, yields ranging from 40 to 50% of the desired products (2) were obtained (Scheme I). Purification was complicated by the presence of a second product (3), 15–30% yields, from which 2 could not be readily separated. Consideration of the mechanism of action of

DCC proposed by Khorana and coworkers[10,11] led to the assumption that this by-product could be the acylurea adduct[12,13] of 1 and DCC. This assumption was substantiated by elemental analysis. Examination of its infrared spectrum, which exhibited a strong band at 1640 cm⁻¹ (-NHCONH, ~1660 cm⁻¹),[14] suggested that this by-product was actually *N*-acylurea (3) rather than the *O*-acylisourea.[10]

Attempts to suppress the formation of acylurea by-product by changing the solvent medium to methylene chloride[12] were without success. Addition of *N*-hydroxysuccinimide (NHS) with DCC has been shown to improve the yields in peptide syntheses[15] without increasing racemization;[16] therefore 1 was coupled to glycine benzyl ester in the presence of DCC and NHS and gave a 91% yield of *N*-[1-(9-adenyl)-2,3-*O*-isopropylidene-β-D-ribofuranuronosyl]glycine benzyl ester (2a). Under these conditions only a trace of the side product was detected in the reaction mixture. Similarly, compounds 2b, 2c, and 2d benzyl ester were prepared in high yield by treating 1 with the benzyl esters of L-alanine, L-phenylalanine, and L-glutamic acid (Scheme I).

Hydrolysis of the isopropylidene blocking groups with 88% formic acid was very slow at room temperature. When the temperature was raised to 60–65° the reaction was complete in 2–4 hr. *N*-[1-(9-Adenyl)-β-D-ribofuranuronosyl]glycine benzyl ester (4a), -L-alanine benzyl ester (4b), -L-phenylalanine benzyl ester (4c), and -L-glutamic acid dibenzyl ester (4d) were produced in good yields by this procedure. Facile hydrogenolysis of the benzyl blocking groups of 4a–d was accomplished utilizing palladium on charcoal as catalyst. The title compounds *N*-[1-(9-adenyl)-β-D-ribofuran-

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Scheme I

B = 9-β-adenyl

a, R = H; R₁ = CH₂C₆H₅
b, R = CH₃; R₁ = CH₂C₆H₅
c, R = CH₂C₆H₅; R₁ = CH₂C₆H₅

d, R = CH₂CH₂COOH; R₁ = CH₂C₆H₅
e, R = (CH₂)₄NHCbz; R₁ = CH₃
f, R = (CH₂)₄NHCbz; R₁ = H
g, R = (CH₂)₄NH₂
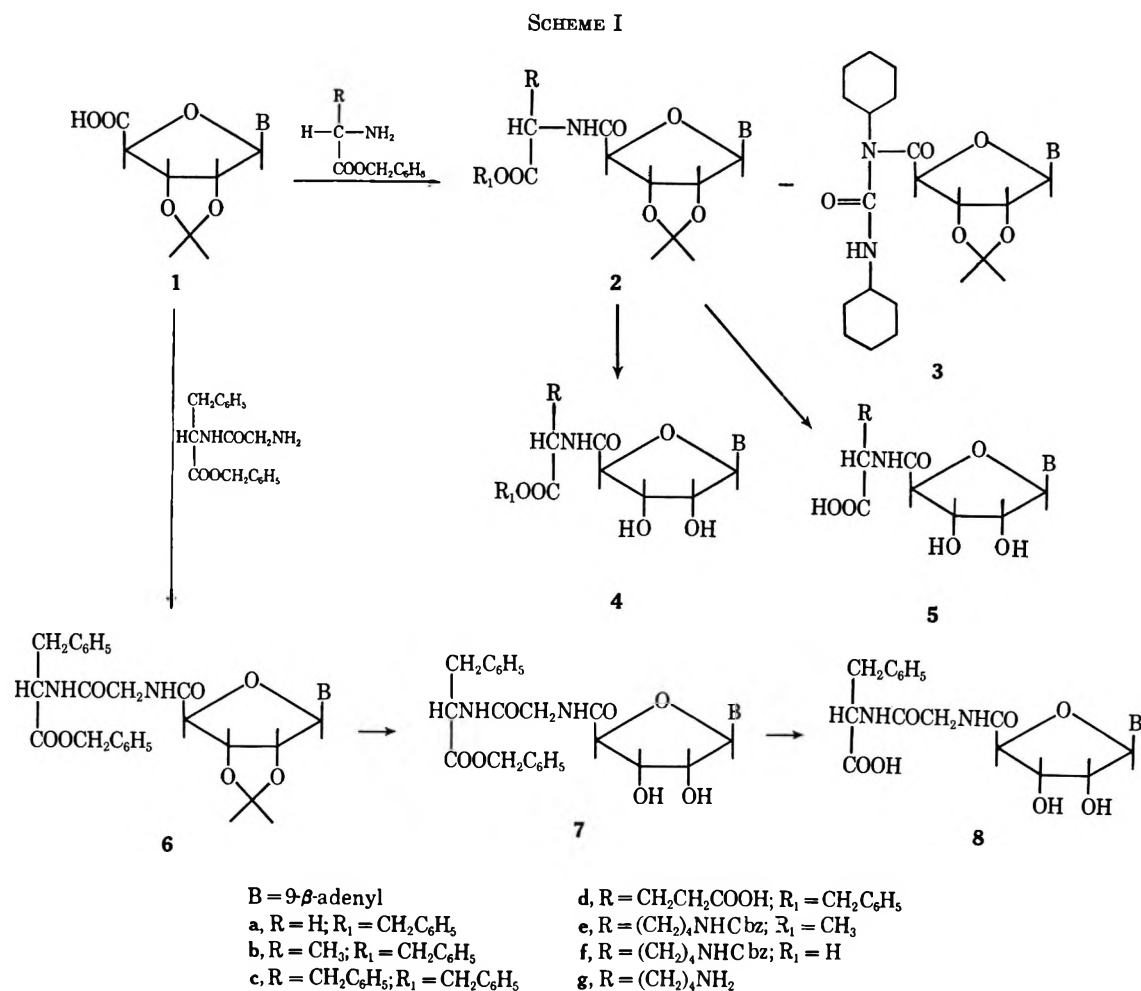
uronosyl]glycine (5a), N-[1-(9-adenyl)-β-D-ribofuran-uronosyl]-L-alanine (5b), N-[1-(9-adenyl)-β-D-ribo-furanuronosyl]-L-phenylalanine (5c), and N-[-1-(9-adenyl)-β-D-ribofuranuronosyl]-L-glutamic acid (5d) were produced by this method in yields of 58, 71, 89, and 73%, respectively.

When 1 was coupled to N^ϵ-carbobenzyloxy-L-lysine methyl ester, N^α-[1-(9-adenyl)-2,3-O-isopropylidene-β-D-ribofuranuronosyl]-N^ϵ-carbobenzyloxy-L-lysine methyl ester (2e) was formed in 91% yield. Removal of the methyl ester with potassium hydroxide gave 2f while subsequent treatment with 88% formic acid removed the isopropylidene blocking group and afforded N^α-[1-(9-adenyl)-β-D-ribofuranuronosyl]-N^ϵ-carbobenzyloxy-L-lysine (4f). Attempts to remove the carbobenzyloxy group by catalytic hydrogenolysis were unsuccessful, since 4f was insoluble in the common solvents used for hydrogenolysis. The desired product, N^α-[1-(9-adenyl)-β-D-ribofuranuronosyl]-L-lysine (5g), was prepared in 79% yield by catalytic hydrogenolysis of 2e in 88% formic acid.

The dipeptide, glycyl-L-phenylalanine benzyl ester, was also coupled with 1 in the presence of DCC and NHS. This afforded a 93% yield of N-[1-(9-adenyl)-2,3-O-isopropylidene-β-D-ribofuranuronosyl]glycyl-L-phenylalanine benzyl ester (6). Removal of the isopropylidene and benzyl blocking groups gave the desired product N-[1-(9-adenyl)-β-D-ribofuranuronosyl]-glycyl-L-phenylalanine (8) in good yield.

Confirmation that little or no racemization of the amino acid moieties had occurred was ascertained by tlc, since the products at each step were found to be homogenous in several solvent systems.

Experimental Section[17]

(17) Physical properties were determined with the following instruments: melting points, Thomas–Hoover apparatus (uncorrected); uv spectra, Cary 15 uv spectrometer (pH 1, pH 11, and MeOH); specific rotations, Perkin-Elmer Model 141 polarimeter; and ir spectra, Perkin-Elmer Model 257 (KBr). Where indicated by elemental analyses, solvation was verified by nmr spectroscopy in absolute DMSO-d_6 and in the case of hydration, by exchange with addition of D₂O and reintegration of the spectral area where the D₂O peak had occurred.

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TABLE I

Compd	Method	Purification	Yield, %	Formula	Calcd, % C	H	N	Found, %[d] C	H	N
2a	A	Column chromatography[a]	91	$C_{22}H_{24}N_6O_6 \cdot 0.5H_2O$[17]	55.34	5.27	17.60	55.41	5.16	17.55
2b	A	EtOAc[b]	63	$C_{23}H_{26}N_6O_6$	57.25	5.43	17.41	56.99	5.72	17.18
2c	A	EtOAc-n-heptane[b]	71	$C_{29}H_{30}N_6O_6$	62.35	5.41	15.05	62.28	5.34	15.07
2d	A	Column chromatography[a]	92	$C_{32}H_{34}N_6O_8 \cdot H_2O$	59.25	5.59	12.95	59.27	5.61	12.94
4a	B	MeOH[b]	56	$C_{19}H_{20}N_6O_6$	53.26	4.70	19.61	53.23	5.09	19.64
4b	B	EtOH-H2O[b]	82	$C_{20}H_{22}N_6O_6 \cdot H_2O$	52.17	5.27		52.40	5.56	
4c	B	Column chromatography[c]	67	$C_{26}H_{26}N_6O_6$	60.22	5.05	16.20	60.22	4.95	15.97
4d	B	Column chromatography[c]	72	$C_{29}H_{30}N_6O_8$	58.97	5.12	14.23	58.99	5.24	14.36
5a	C	MeOH[b]	58	$C_{12}H_{14}N_6O_6$	42.60	4.17	24.84	42.69	4.58	24.58
5b	C	EtOH-H2O[b]	71	$C_{13}H_{16}N_6O_6$	44.32	4.57	23.85	44.61	4.71	24.01
5c	C	EtOH-H2O[b]	89	$C_{19}H_{20}N_6O_6 \cdot 0.5H_2O$	52.17	4.83	19.21	52.21	4.86	19.28
5d	C	EtOH-H2O[b]	73	$C_{15}H_{18}N_6O_8$	43.90	4.42	20.48	43.87	4.54	20.51

[a] Silica gel column, packed and eluted with EtOAc-n-heptane-CHCl3 (8:1:1). [b] Recrystallization solvent. [c] Silica gel column, packed and eluted with EtOAc-CHCl3-EtOH (6:3:1). [d] Compounds were dried (P2O5) *in vacuo* at 56° for 4 hr before analytical determinations.

TABLE II

PHYSICAL CONSTANTS OF CERTAIN N-[1-(9-ADENYL)-β-D-RIBOFURANURONOSYL] AMINO ACIDS AND PEPTIDES

Compd	Mp, °C	$\lambda_{max}^{pH\ 1}$, nm (ϵ)	$\lambda_{max}^{pH\ 11}$, nm (ϵ)	λ_{max}^{MeOH}, nm (ϵ)	Chromatographic mobilities[a] 5% NH4HCO3	EtOH-1 N NH4OAc (7:3)	n-PrOH-concd NH4OH-H2O (6:3:1)
2a	Glass	257 (13,300)	258 (13,400)	259 (16,400)			
2b	~90	255 (15,800)	257 (17,700)	257 (16,000)			
2c	134–135	257 (13,200)	257 (13,700)	259 (14,500)			
2d	Glass	257 (13,200)	258 (11,600)	258 (13,900)			
4a	109–110	256 (14,500)	258 (15,500)	259 (15,400)			
4b	139 softens 148 dec	255 (14,400)	257 (19,900)	258 (14,800)			
4c	Glass	258 (13,100)	258 (14,400)	259 (14,800)			
4d	Glass	258 (11,900)	259 (9,600)	260 (13,900)			
5a		257 (17,400)	258 (18,100)	258 (17,800)	0.62	0.29	0.39
5b	262–263	256 (16,500)	259 (17,100)	259 (16,000)	0.70	0.37	0.45
5c		257 (14,300)	259 (14,900)	254 (15,700)	0.69	0.48	0.59
5d	229–232	257 (14,400)	258 (14,700)	259 (14,800)	0.80	0.18	0.23

[a] Chromatograms were developed by the descending technique utilizing Whatman No. 1 chromatographic paper and spots were detected with short-wave uv light.

General Procedure B (Table I) for the Removal of Isopropylidene Groups. Preparation of Compounds 4a–d.—A solution of the respective isopropylidene blocked compounds (2a–d) in 88% formic acid (6 ml) was heated at 60–65° (bath temperature) for 3–4 hr. The solvent was removed by repeated coevaporation with EtOH–MeOH *in vacuo* to give an amorphous residue. The residue was treated according to Table I.

General Procedure C (Table I) for the Removal of the Benzyl Blocking Groups by Catalytic Hydrogenation. Preparation of Compounds 5a–d.—A cooled solution of the respective benzyl ester compound (4a–d, 2.0 mmol) in the appropriate solvent under nitrogen atmosphere was hydrogenated using Pd/C (150 mg) at room temperature and on a Parr apparatus at 45 psi for 20 hr. The resulting precipitate was dissolved by heating [water (40 ml) had to be added to dissolve the precipitate in the preparation of 5b], the catalyst was removed by filtration (Celite pad) and washed with methanol, and the filtrate and washings were evaporated to dryness. The residue was recrystallized from the appropriate solvent (Table I).

N-[1-(9-Adenyl)-2,3-O-isopropylidene-β-D-ribofuranuronosyl]-N,N'-dicyclohexylurea (3).—A mixture of 1 (1.9 g, 6 mmol) and L-phenylalanine benzyl ester[19] (1.5 g, 6 mmol) in DMF (20 ml) was treated with DCC (1.36 g, 6.6 mmol) in the absence of NHS in a manner similar to that used in the preparation of 2a. A solution of the crude product in CHCl3 was chromatographed over a silica gel column (200 g, 4.2 cm). Elution was effected with ethyl acetate–n-heptane–chloroform (8:1:1), and 100-ml fractions were collected. Fractions 7–16 contained 2c (1.85 g, 55%). Fractions 23–24 were combined, and the solvent was

removed to give 3 (680 mg, 22%) as an amorphous foam, which was crystallized from isopropyl alcohol: mp 210–211° (sintered); $[\alpha]^{25}$D +0.3° (c 2, CHCl3); $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 15,700), $\lambda_{max}^{pH\ 11}$ 259 (15,200), λ_{max}^{MeOH} 259 (16,100); ir 1640 cm^{-1} (-NHCONH-).

Anal. Calcd for $C_{28}H_{37}N_7O_5$: C, 59.18; H, 7.06; N, 18.58. Found: C, 59.23; H, 7.17; N, 18.60.

N^α-[1-(9-Adenyl)-2,3-O-isopropylidene-β-D-ribofuranuronosyl]-N^ϵ-carbobenzyloxy-L-lysine Methyl Ester (2e).—A mixture of 1 (321 mg, 1 mmol), N^ϵ-carbobenzyloxy-L-lysine methyl ester[20] (294 mg, 1 mmol), and NHS (115 mg, 1 mmol) in DMF (5 ml) was treated with DCC (227 mg, 1.1 mmol) in a manner similar to that used in the preparation of 2a; aqueous saturated NaHCO3 was used instead of 5% Na2CO3. The crude product (2e, 560 mg, 91%) was obtained as a colorless solid, which could be utilized in further reactions.

The analytical sample was prepared by purification with a silica gel column using ligroin–ethyl acetate–methanol (6:3:1) to elute the desired product. The uv-absorbing fractions were collected and concentrated to yield an amorphous solid (dried over P2O5 at 80° *in vacuo* for 4 hr): $[\alpha]^{25}$D –9.0° (c 1, CHCl3); $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 14,300), $\lambda_{max}^{pH\ 11}$ 259 (14,000), λ_{max}^{MeOH} 259 (14,300).

Anal. Calcd for $C_{28}H_{35}N_7O_8 \cdot H_2O$: C, 54.62; H, 6.05; N, 15.92. Found: C, 55.01; H, 6.22; N, 15.52.

N-[1-(9-Adenyl)-2,3-O-isopropylidene-β-D-ribofuranuronosyl]-N^ϵ-carbobenzyloxy-L-lysine (2f).—To a solution of 2e (230 mg, 0.37 mmol) in methanol (5 ml) was added a solution of KOH

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(34 mg) in methanol (5 ml) and water (0.2 ml), and the mixture was stirred at room temperature. After 24 hr, KOH (11 mg) was added, and the stirring was continued for another 6 hr; the reaction was monitored by a silica gel tlc using chloroform-methanol (9:1). After evaporation of the solvent, the residue was taken in water (10 ml), and the undissolved material was removed by filtration. The filtrate was cooled in an ice-water bath, stirred, and acidified to pH 3.5–4 with 20% formic acid. The resulting precipitate was filtered, washed with water, and dried over P_2O_5.

This compound was crystallized from ethanol-water to give fine needles of 2f (120 mg, 56%): mp 224–226° dec; $[\alpha]^{25}D$ −16.5° (c 1, DMSO); $\lambda_{max}^{pH\ 1}$ 256 nm (ϵ 13,800), $\lambda_{max}^{pH\ 11}$ 259 (13,800), λ_{max}^{MeOH} 259 (13,900).

Anal. Calcd for $C_{27}H_{33}N_7O_8$: C, 55.56; H, 5.69; N, 16.80. Found: C, 55.63; H, 5.63; N, 16.98.

N^α-[1-(9-Adenyl)-β-D-ribofuranuronosyl]-N^ϵ-carbobenzyloxy-L-lysine (4f).—A solution of 2f (250 mg, 0.43 mmol) in 88% formic acid (3 ml) was heated at 60–65° (bath temperature) for 2.3 hr. The solvent was removed by repeated coevaporation with ethanol. The residue was dissolved in refluxing ethanol (10 ml) and the wall of the vessel was scratched to induce crystallization of 4f (200 mg, 86%). This compound was recrystallized from DMF-water and dried at 110° over P_2O_5 *in vacuo* for 10 hr to afford an analytically pure sample: mp 230° (partly melted), 244–246° dec; $[\alpha]^{25}D$ −23.9° (c 1, DMSO); $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 13,700), $\lambda_{max}^{pH\ 11}$ 259 (13,900), $\lambda_{max}^{pH\ 7}$ 259 (13,900).

Anal. Calcd for $C_{24}H_{29}N_7O_8$: C, 53.03; H, 5.37; N, 18.03. Found: C, 52.90; H, 5.52; N, 18.10.

N^α-[1-(9-Adenyl)-β-D-ribofuranuronosyl]-L-lysine (5g).—To a cooled solution of 2f (430 mg, 0.74 mmol) in 88% formic acid (20 ml) was added 10% palladium on charcoal (150 mg) under nitrogen atmosphere. The mixture was treated with hydrogen at room temperature with a Parr apparatus at 45 psi for 18 hr. The catalyst was removed *via* filtration utilizing a Celite pad. Then it was washed with cold water. The combined filtrate and washings were concentrated to dryness by coevaporation with ethanol. The resulting amorphous solid was dissolved in water (1 ml), and ethanol (15 ml) was added to give a gummy precipitate, which was scratched until a solid was obtained. After the mixture had been allowed to stand at 5° overnight, the solid was collected, washed with ethanol, and dried to yield 260 mg (79%) of 5g.

The analytical sample was obtained by reprecipitation from ethanol-water to give an amorphous solid (dried over P_2O_5 at 80° *in vacuo* for 4 hr); $[\alpha]^{25}D$ −19.3° (c 1, H_2O); $\lambda_{max}^{pH\ 1}$ 256 nm (ϵ 14,800), $\lambda_{max}^{pH\ 11}$ 259 (14,600), λ_{max}^{MeOH} 258 (14,800).

Anal. Calcd for $C_{16}H_{23}N_7O_6\cdot 2H_2O$: C, 43.14; H, 6.11; N, 22.01. Found: C, 43.23; H, 6.14; N, 21.83.

N-[1-(9-Adenyl)-2,3-*O*-isopropylidene-β-D-ribofuranuronosyl]-glycyl-L-phenylananine Benzyl Ester (6).—A mixture of glycyl-L-phenylalanine[21] (6.17 g, 28 mmol), *p*-toluenesulfonic acid monohydrate (5.4 g, 28.6 mmol), benzene (50 ml), and benzyl alcohol (50 ml) was refluxed into a Dean-Stark distillation apparatus.[22] After the azeotropic distillation of water had ceased (1.5 hr) the solution was allowed to cool to room tempera-

(21) K. R. Rao, S. M. Birnbaum, R. B. Kingsley, and J. P. Greenstein *J. Biol. Chem.*, **198**, 507 (1952).

(22) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, p 940.

ture, diethyl ether (800 ml) was added, and the cloudy mixture was allowed to stand at 4° overnight. The excess solvents were decanted and the residual syrup was twice crystallized from ethanol-petroleum ether (bp 30–60°) to give glycyl-L-phenylalanine benzyl ester *p*-toluenesulfonate salt (3.5 g). This salt (2.96 g, 6.1 mmol) was added to a solution of Na_2CO_3 (647 mg) in water (40 ml) and the solution was extracted with dichloromethane (three 40-ml portions) and dried ($MgSO_4$) and the organic phase was evaporated *in vacuo*. The residue was treated with 1 (1.93 g, 6.0 mmol), NHS (690 mg, 6.0 mmol), and DCC (1.36 g, 6.6 mmol), in a manner similar to that used in the preparation of 2a affording 3.5 g (93%) of the crude product 6.

The analytical sample was obtained by silica gel chromatography using ethyl acetate-chloroform-methanol (6:3:1) as a developer. The uv-absorbing band yielded an amorphous foam (dried over P_2O_5 at 80° *in vacuo* for 5 hr): $[\alpha]^{25}D$ −15.7° (c 1, $CHCl_3$); $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 14,600), $\lambda_{max}^{pH\ 11}$ 259 (15,000), λ_{max}^{MeOH} 259 (14,900).

Anal. Calcd for $C_{31}H_{33}N_7O_7\cdot 0.5H_2O$: C, 59.60; H, 5.48; N, 15.69. Found: C, 59.47; H, 5.45; N, 15.72.

N-[1-(9-Adenyl)-β-D-ribofuranuronosyl]glycyl-L-phenylalanine Benzyl Ester (7).—A solution of 6 (2.8 g, 4.48 mmol) in 88% formic acid (24 ml) was heated at 60–65° (bath temperature) for 2 hr. The solvent was removed by coevaporation with ethanol to give an amorphous foam, which was dissolved in a small amount of chloroform-methanol. The solution was applied to a silica gel column (200 g, 4.2 cm) packed with ethyl acetate-chloroform-methanol (5:3:2). Elution was effected with the same solvent system, 50-ml fractions being collected. Fractions 15–19 were combined and evaporation of the solvent gave colorless solids (1.5 g, 56%).

The analytical sample was obtained by crystallization from ethanol: mp 138–140°; $[\alpha]^{25}D$ −36.5° (c 1, DMSO); $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 14,500), $\lambda_{max}^{pH\ 11}$ 259 (14,500), λ_{max}^{MeOH} 260 (15,100).

Anal. Calcd for $C_{28}H_{29}N_7O_7\cdot 1.5H_2O$: C, 55.80; H, 5.35; N, 16.27. Found: C, 55.79; H, 5.44; N, 16.50.

N-[1-(9-Adenyl)-β-D-ribofuranuronosyl]glycyl-L-phenylalanine (8).—The benzyl ester (7, 500 mg, 0.83 mmol) was dissolved in hot methanol (150 ml). To the cooled solution was added a suspension of 10% palladium on charcoal (300 mg) in water (10 ml), and the mixture was hydrogenated at room temperature on a Parr apparatus at 45 psi for 20 hr. The catalyst was removed by filtration with a Celite pad and washed with methanol. The combined filtrate and washings were evaporated to dryness to give a colorless solid in a yield of 370 mg (92%).

The analytical sample was prepared by recrystallization twice from ethanol-water and dried over P_2O_5 at 110° *in vacuo* for 2 hr: mp 242–244° dec; $[\alpha]^{25}D$ −30.8° (c 1, DMSO); $\lambda_{max}^{pH\ 1}$ 258 nm (ϵ 14,300), $\lambda_{max}^{pH\ 11}$ 260 (14,400), λ_{max}^{MeOH} 259 (15,700).

Anal. Calcd for $C_{21}H_{23}N_7O_7$: C, 51.95; H, 4.77; N, 20.19. Found: C, 51.89; H, 4.82; N, 20.37.

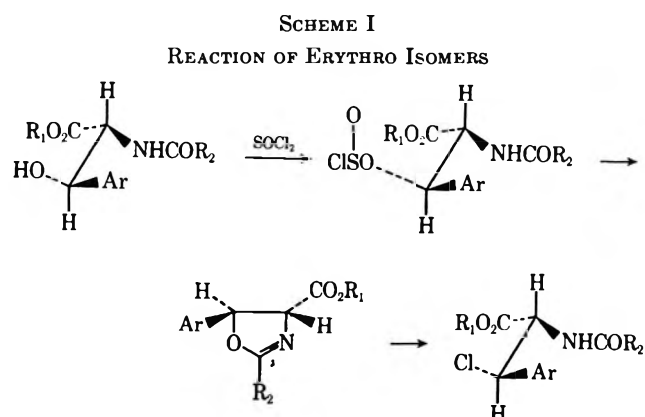# Substituent Effects in the Reaction of *N*-Benzoyl-β-arylserinates with Thionyl Chloride

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Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065
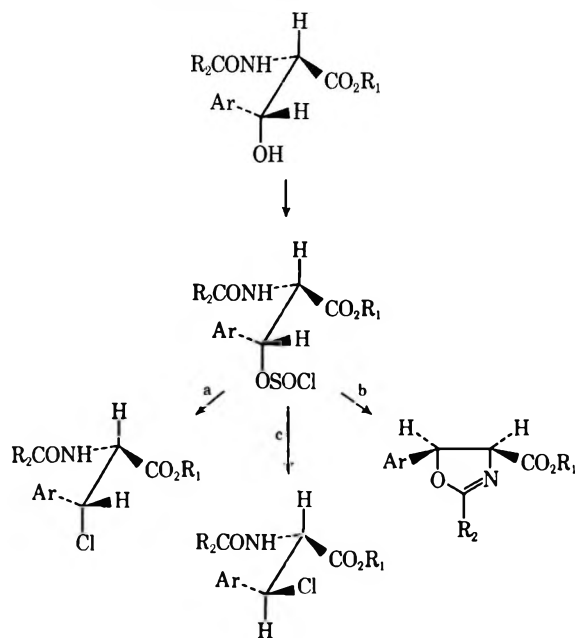
The reaction of several pairs of *N*-benzoyl-β-arylserine methyl esters with thionyl chloride has been studied by nmr and product isolation. The erythro isomers rapidly form trans oxazolines which react further to give *erythro*-β-chloro-β-arylalaninates. The reactions of the threo isomers depend upon the electrical effects of the aryl substituents. Thus, internal displacement of chlorosulfite is observed in the case of strongly deactivating groups (*m*-nitro and *p*-cyano) giving cis oxazolines which *do not* react further. SNi reaction occurs in the case of the *threo-p*-chlorophenyl analog yielding a *threo*-β-chloro-β-arylalaninate *without* intervention of an oxazoline. *threo*-*m*-Chlorophenylserinate undergoes both the above reactions as well as SN2 displacement. Both *erythro*- and *threo-p*-methoxyphenylserinates give evidence of an additional SN1 mechanism.

Previously, we reported on the reaction of some arylserine derivatives with thionyl chloride.[1] The *erythro-N*-acyl-phenylserinate and *p*-nitrophenylserinate esters were shown to undergo rapid ring closure to trans oxazolines, followed by a slower nucleophile initiated conversion to corresponding β-aryl-β-chloroalaninates of the same (erythro) configuration (Scheme I). Each of these steps occurred cleanly with inversion at the benzylic center.

SCHEME I
REACTION OF ERYTHRO ISOMERS

The threo isomers reacted differently, reflecting the steric interactions of two eclipsing bulky groups in the ensuing transition state which would lead to cis oxazolines. *threo-N*-Acylphenylserine esters underwent SNi reaction to give *threo*-β-chloro-β-phenylalaninates without intervention of an oxazoline (Scheme II, path a). On the other hand, *threo-p*-nitrophenylserinates slowly cyclized to cis oxazolines which did not open to β-chloro-β-(*p*-nitrophenyl)alaninates under the same reaction conditions (Scheme II, path b).

We suggested[1] that the marked difference in reactivity between *threo*-phenyl- and *threo-p*-nitrophenylserinates was attributable to the electron withdrawing effect of the ring substituent. In the case of the *p*-nitrophenylserinates, such an effect deters breaking of the benzylic C–O bond and invites participation of the neighboring amide group.[2] Participation of the amide group in the reaction of the erythro isomers is not unexpected, since a sterically favored conformer of the chlorosulfite ester would place the amide anti-coplanar to the departing group.

SCHEME II
REACTION OF THREO ISOMERS

The results summarized briefly above, and their rationalization prompted an extension of this research. Specifically, if the above attribution is correct, then there should exist *threo*-arylserinates which react with thionyl chloride by mechanisms of *both* path a and path b, Scheme II, to give both the cis oxazoline (participation) and the *threo*-β-chloroalaninate (SNi) products. Likely candidates would be those whose substituent(s) lie between H and NO₂ in electronegativity. A further aim was to extend the scope of the reaction beyond the "H" end of the scale with an electron-*donating* substituent, where the incipient benzylic ion would be more stabilized. For this latter goal, the *p*-methoxy substituent seemed ideal.

Starting amido esters were made by known methods. Each was chromotographically and spectroscopically (nmr) free of its diastereomer. We verified the stereochemistry on the basis of reaction with thionyl chloride in all cases except the *p*-methoxy derivative, (a special case, which is discussed separately, below.) Those isomers which rapidly and cleanly formed trans oxazolines (Scheme I) were the erythro isomers. Incidentally, the amino acids from which they derive all showed lower r_f vis-a-vis their diastereomers in the

(1) S. H. Pines, M. A. Kozlowski, and S. Karady, *J. Org. Chem.*, **34**, 1621 (1969).

(2) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952).

chromatographic system of Shaw and Fox.[3] Assignment of stereochemistry on the basis of the presence or absence of ir absorption at 11.90–11.95 μ, first suggested by Bolhofer[4] and subsequently supported by Greenstein and Winitz,[5] is not a reliable criterion with some of the serines used in this work.

The stereochemistry of the two p-methoxyphenylserinates was provisionally assigned on the basis of tlc behavior[3] of the parent serines. Reaction of the methyl ester of the erythro isomer with benziminoethyl ether hydrochloride,[6] a procedure which does not affect the stereochemistry of the chiral centers, gave *cis*-4-carbomethoxy-5-p-methoxyphenyl-2-phenyl-2-oxazoline, as shown by its distinctive nmr spectrum. The threo ester gave the trans oxazoline as the major product in similar reaction with the imino ether. These results substantiated the original assignment.

Results

As indicated above, all erythro isomers of the derivatized serines, with the exception of p-methoxyphenylserine (*vide infra*), reacted with thionyl chloride according to Scheme I, cleanly and rapidly forming trans oxazolines which opened more slowly to form *erythro*-β-chloroalaninates. This behavior was expected from our previous study.

The threo isomers, on the other hand, showed an even greater variety of reactions than was previously encountered.[7] *threo-m*-Nitrophenyl- and p-cyanophenylserinates gave cis oxazolines slowly according to the mechanism of path b, Scheme II.

threo-p-Chlorophenylserinate was converted to the β-chloroalaninate (path a, Scheme II) via $S_N i$ reaction. As we had hoped,[8] *threo-m*-chlorophenylserinate gave products corresponding to both mechanisms. What was not anticipated, however, was that this substrate also gave a sizable amount of the isomeric *erythro*-β-chloroalaninate! Specifically, the three products, *threo*-β-chloroalaninate, cis oxazoline, and *erythro*-β-chloroalaninate, were formed in the approximate ratio[9] of 50:30:20 when the reaction was carried out in deuteriochloroform. Similar ratios (52:32:16) were measured when the reaction was run neat in thionyl chloride.

Both *erythro*- and *threo-N*-benzoyl-β-p-methoxyphenylserine methyl esters gave the *same* major reaction product, *threo-N*-benzoyl-β-chloro-β-(p-methoxy-

phenyl)alanine methyl ester. Other reaction products of these two starting materials were identified and their identity bears on the nature of the reaction mechanism(s) in this exceptional case.

Finally, the accumulated evidence of this and our previous work allows statement of some nmr spectral distinctions between the isomeric oxazolines, β-chloroalaninates, and amido alcohols. The cis oxazolines show the larger coupling constant of the C_4–C_5 protons 10.5–11 Hz *vs.* 7.5–8 for trans, and a markedly higher field signal for the ester methoxyl, δ ~3.2–3.3 *vs.* ~3.9 for trans. The threo linear compounds show the higher J_{HCNH}, 8.5–9 Hz *vs.* 7–7.5 Hz for the erythro isomers. Coupling constants between their vicinal aliphatic protons are too close to be definitive by themselves, but are slightly larger for the erythro member of a given pair.

Discussion

Reaction of erythro isomers with thionyl chloride according to Scheme I may now be accepted as general in view of the results reported here, our earlier report,[1] and some references cited therein. The exceptional case which is observed with the p-methoxy analog is discussed separately below. The conversions at each step were clean and essentially complete. The trans oxazolines, all but one of which are oils, were separated from traces of starting material or already formed β-chloro compounds by chromatography to obtain analytical samples, thus sacrificing isolation yield for purity. The latter *erythro*-β-chloroalaninates were obtained in near pure form (tlc, nmr) in quantitative yield. Simple recrystallization was sufficient for analysis.

Participation of the neighboring amide group in displacing the leaving group, –OSOCl, is reasonable in view of the sterically favored anticoplanar conformer of the intermediate chlorosulfite ester. Nucleophilic opening of the thus formed oxazoline in the anhydrous system is an unexceptional second step, and requires little elaboration. Fry, for example, used the nucleophilic opening of oxazoline-4-carboxylate with thiobenzoic acid as the key step in a synthesis of cystine. He also commented on the possibility of competition of Cl^- with the thiobenzoate under his reaction conditions.[10]

The results obtained with the threo isomers support our earlier views concerning the importance of the aryl substituent on the reaction mechanism. The p-cyano and m-nitro substituents, both strongly electronegative, destabilize the potential benzylic cation in the same way as did the p-nitro group,[1] and accordingly, could be expected to promote product formation *via* participation of the neighboring amide group.[2] Finding the cis oxazolines as the essential products in these instances (according to Scheme IIb) is consonant with this view. In the case of the p-chloro substituent, the stabilizing resonance effect apparently outweighs the negative inductive effect of Cl, and the product predicted by path a (Scheme II) ($S_N i$ reaction) is formed quantitatively.

The m-chloro substituent provides the first clear case for multiple reaction pathway. In this case,

(3) K. N. F. Shaw and Sidney W. Fox, *J. Amer. Chem. Soc.*, **75**, 3421 (1953). The relationship r_f (threo) > r_f (erythro) holds also for the unsubstituted phenylserines and p-nitrophenylserines. Our chromatograms were run on cellulose plates rather than paper. See also R. Wichert, *Ark. Kemi*, **25**, 231 (1966).

(4) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **76**, 1322 (1954).

(5) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, New York, N. Y., 1961, p 2599.

(6) By the procedure of M. Viscontini and E. Fuchs, *Helv. Chim. Acta*, **36**, 1 (1953); also ref 1.

(7) The discussion is restricted to the truly dominant products of reaction. Close examination of the various nmr spectra of the $SOCl_2$ reactions of threo isomers, including those of our previous work,[1] revealed small methoxy peaks which could be attributed to some of the "mechanistically excluded" products. In the case of the *threo-m*-nitrophenylserinate reaction, for example, the by-product was estimated at 5–8% of the total reaction. Its two major constituents were identified as *erythro-N*-benzoyl-β-chloro-β-(m-nitrophenyl)-alanine methyl ester (by ir, melting point, and tlc), and *trans*-4-carbomethoxy-5-m-nitrophenyl-2-phenyl-2-oxazoline (by ir and tlc). The *threo*-β-chloroalaninate was not found. Similar or lesser amounts of by-products were estimated for the phenyl,[1] p-nitrophenyl,[1] p-chlorophenyl, and p-cyanophenyl cases.

(8) See footnote 17, ref 1.

(9) Ratios from nmr integration.

(10) E. M. Fry, *J. Org. Chem.*, **15**, 438 (1950).

the moderate $-I$ effect is not overly destabilizing, nor are there counteractive resonance contributions. Thus, about 30% conversion to a cis oxazoline is found. The remaining mixture of *threo-* and *erythro-β*-chloroalaninates can be accounted for by the usual Sni reaction for the former, and a heretofore unobserved Sn2 displacement of -OSOCl by chloride (path c, Scheme II). An alternative carbonium ion mechanism is rejected on the basis of the findings with the *p*-methoxyphenyl analog (where Sn1 reaction is suggested) which differ dramatically from these, especially with regard to formation of appreciable amounts of the trans oxazoline.

Both the erythro and threo isomers of *N*-benzoyl-*β*-*p*-methoxyphenylserine methyl ester react rapidly at ice temperature with thionyl chloride, giving *threo-β*-chloroalaninate, trans oxazoline, and *erythro-β*-chloroalaninate in that order of importance. Even though the conversion of trans oxazoline to erythro-*β*-chloroalaninate casts doubt on the meaningfulness of rigid yield figures, nevertheless, a crude estimate of yields from a rapid, cold reaction is instructive. Thus, after 10 min reaction at 0° with the erythro starting material, we find approximately 42, 35, and 15% of *threo-β*-chloroalaninate, trans oxazoline, and *erythro-β*-chloroalaninate, respectively. In the case of the threo starting material, the comparable numbers are ∼70, 15, and 5%. In neither case is any intermediate chlorosulfite ester observed in the nmr. A trace of the cis oxazoline can be seen in the mother liquors remaining from isolation of the major product of the threo reaction.

The pattern and rate of product formation clearly distinguishes this pair of serinates from all the others we have studied, and suggests that a common ionic intermediate plays a role. Studies of the *p*-anisyl carbonium ion are all too familiar to require citation, and, in reactions such as these, its implication seems a foregone conclusion.

The ionic pathway to products might be an even more attractive explanation were the yields from both erythro and threo starting materials similar. The raw yield data suggest that reaction occurs not only through the carbonium ion intermediate, but also through some of the pathways cited previously. The strongest arguments for ionization are (a) formation of a *threo-β*-chloroalaninate from an erythro starting material, and (b) formation of a trans oxazoline from a threo starting material. One might argue that the former result could be explained by an Sn2 reaction of Cl attacking the intermediate -OSOCl in a very rapid reaction. We suggest that, if this argument is valid, we should have seen some evidence for the same reaction with erythro starting materials. We did not.

Experimental Section[11]

threo-β-p-Chlorophenylserine.—Prepared from *p*-chlorobenzaldehyde and glycine according to the method of Holland and Nayler,[12] the crystals showed mp 186° dec (lit[12] 179° dec).

Anal. Calcd for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; N, 6.50. Found: C, 49.47; H, 4.66; N, 6.44.

erythro-β-p-Chlorophenylserine.—Isolated from acid hydrolysis of the corresponding methyl ester (see below), this isomer appeared somewhat hygroscopic: mp 185° dec, unsharp; dta endotherms at 179 and 196° dec (lit.[12] 178° dec for "hemihydrate").

Anal. Found: C, 49.92; H, 4.55; N, 6.43.

threo-β-p-Methoxyphenylserine.—To 15 g (0.2 mol) of glycine and 54.5 g (0.4 mol) of anisaldehyde in 50% ethanol (160 ml) was added a solution of 28 g (0.7 mol) of sodium hydroxide in 80 ml of water. The reaction was stirred overnight, then acidified to pH 4 (HCl) and extracted with chloroform. The aqueous layer was taken to dryness, and the residue crystallized from 200 ml of water. The solids, after recrystallization from hot water, gave 1.7 g of almost pure (tlc) *threo-p*-methoxyphenylserine. The analytical sample, from water, showed (dta) an endotherm at 203° dec.[13]

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.50; H, 6.25; N, 6.57.

erythro-β-p-Methoxyphenylserine.—The original mother liquor from the isolation of the threo isomer (above) was allowed to stand several days. There was deposited 1.7 g of almost pure *erythro-β-p*-methoxyphenylserine. The analytical sample from water showed (dta) an endotherm at 198° dec.

Anal. Found: C, 56.67; H, 6.25; N, 6.87.

erythro-β-p-Chlorophenylserine Methyl Ester Hydrochloride.— A solution of 10.4 g (83 mmol) of glycine methyl ester hydrochloride, 23.2 g (166 mmol) of *p*-chlorobenzaldehyde and 11.7 ml (84 mmol) of triethylamine in 40 ml of methanol was stirred 2 days. The crystalline product separated after saturating the solution with anhydrous hydrogen chloride. Recrystallization of the crude (mp 177°) from ethanol, then methanol, gave an analytical sample, mp 188–189° dec.

Anal. Calcd for $C_{10}H_{13}Cl_2NO_3$: C, 45.13; H, 4.92; N, 5.26. Found: C, 45.05; H, 5.05; N, 5.38.

erythro-β-m-Nitrophenylserine Methyl Ester Hydrochloride.— This compound was prepared from *m*-nitrobenzaldehyde in the same way as reported directly above for the *p*-chlorophenyl analog. The analytical sample showed mp 184–185° dec (MeOH) (lit.[14] mp 190° dec.

Anal. Calcd for $C_{10}H_{13}N_2O_5Cl$: C, 43.4; H, 4.74; N, 10.13. Found: C, 43.36; H, 4.88; N, 10.10.

erythro-β-p-Cyanophenylserine Methyl Ester Hydrochloride.— A solution of 10 g (76 mmol) of *p*-cyanobenzaldehyde, 4.78 g (38 mmol) of glycine methyl ester hydrochloride, and 3.84 g (38 mmol) of triethylamine in 100 ml of methanol was stirred for 18 hr. The volatiles were removed, and the residue was warmed in dioxane to form a fluid slurry. After cooling, the crystalline triethylamine hydrochloride was removed, and the filtrate acidified with 6.5 ml of 6 N hydrochloric acid. The slurry was stirred in an ice bath for 2 hr and the product collected, 2.6 g of almost pure (nmr) *erythro-β-p*-cyanophenylserine methyl ester hydrochloride, mp 194–197° dec.

threo-β-p-Cyanophenylserine Methyl Ester Hydrochloride.— When the mother liquor solids from the previous experiment were stirred in tetrahydrofuran, a crude mixture (5.2 g), mp 153–157° dec, was isolated. This solid contained the title compound, contaminated with, *inter alia*, the erythro isomer, and glycine methyl ester. Nevertheless, it was satisfactory for benzoylation.

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systems reported in the experimental section allowed separation of the specific compound from its diastereomer. Cellulose plates (Analtech) were used for the serines, and in each case the isomers were shown to be separable *via* the Shaw–Fox[3] solvent system. Where the free serines were not directly isolated, acid hydrolysates of the corresponding esters were examined. The "usual work-up" involves aqueous extractions, drying over sodium sulfate, and evaporation *in vacuo* to dryness. Preparative chromatography was carried out either in columns (silica gel H, E. Merck) or on purchased preparative plates. (b) The generalizations in the "Results" section of this paper taken in conjunction with the nmr data of Table IV, ref 1 (the entry for trans-**10**, however, should read $H_A = 362$) characterize the structural features of the compounds of this work. Presentation of further tables of nmr data seems unwarranted.

(12) D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, 273 (1953).

(13) K. W. Rosenmund and H. Dornsaft [*Ber.*, **52**, 1734 (1919)] reported mp 185–186°, as did S. Kanao and K. Shinozuka [*J. Pharm. Soc. Jap.*, **67**, 218 (1947); *Chem. Abstr.*, **45**, 9508h (1951)]. P. B. Mahajani and J. N. Ray [*Current Sci. (India)*, **22**, 146 (1953); *Chem. Abstr.*, **48**, 6964g (1954)] reported mp 155°.

(14) E. D. Bergmann, H. Bendas, and C. Resnick, *J. Chem. Soc.*, 2564 (1953).

TABLE I

N-Benzoyl-β-arylserine Methyl Esters

Phenyl substituent	Isomer[a]	Registry no.	Mp °C[b]	Formula	Calcd % C	H	N	Found % C	H	N
p-Chloro	e	32721-54-3	151.1-154.5[c]	$C_{17}H_{16}ClNO_4$	61.17	4.83	4.20	61.34	4.95	4.23
	t	32721-55-4	142-144[c,d]					60.87	4.80	4.18
m-Chloro	e	32721-56-5	134-136.5[e]					60.95	4.69	4.12
	t	32721-57-6	99.5-101.5[c,d,f]					60.98	4.77	4.27
p-Cyano	e	32721-58-7	161-165[c]	$C_{18}H_{16}N_2O_4$	66.66	4.97	8.64	66.44	4.93	8.74
	t	32721-59-8	101-104[c,d,f]					66.71	5.05	8.73
p-Methoxy	e	32721-60-1	154-155.5[g]	$C_{18}H_{19}NO_5$	65.64	5.82	4.25	65.43	5.78	4.22
	t	32721-61-2	143.5-145[c]					65.44	5.65	4.23
m-Nitro	e	32721-62-3	138.5-140.5[c]	$C_{17}H_{16}N_2O_6$	59.30	4.68	8.14	59.20	4.70	7.99
	t	32721-64-5	117-120[c,f]					59.00	4.52	8.08

[a] e = erythro, t = threo. [b] Superscripts[c]–[g] denote recrystallization solvent or solvent combinations: c = ethyl acetate, d = ether, e = aqueous ethanol, f = hexane, g = acetonitrile.

TABLE II

4-Carbomethoxy-5-aryl-2-phenyl-2-oxazolines

Phenyl substituent	Isomer	Registry no.	Mp °C[a,b]	Formula	Calcd % C	H	N	Found % C	H	N
p-Chloro	Trans			$C_{17}H_{14}ClNO_3$	64.67	4.47	4.44	64.69	4.54	4.39
m-Chloro	Trans							64.64	4.40	4.69
	Cis	32721-64-5	86.5-89[d,f]					64.80	4.51	4.39
p-Cyano	Trans	32721-65-6	104.5-106.5[d]	$C_{18}H_{14}N_2O_3$	70.58	4.61	9.15	70.60	4.39	8.93
	Cis	32721-66-7	132-135[c]					70.38	4.70	9.05
p-Methoxy	Trans			$C_{18}H_{17}NO_4$	69.44	5.50	4.50	69.55	5.77	4.74
	Cis	32721-67-8	93-95[c,d]					69.20	5.57	4.42
m-Nitro	Trans			$C_{17}H_{14}N_2O_5$	62.57	4.32	8.59	62.97	4.45	8.50
	Cis	32721-68-9	103-105[c,f]					62.55	4.38	8.45

[a] Where no melting point is given, the compound was an oil. [b] Superscripts[c]–[f] denote recrystallization solvent or solvent combinations: c = ethyl acetate, d = ether, f = hexane.

_erythro-β-m-_Chlorophenylserine Methyl Ester Hydrochloride.— This compound was made from m-chlorobenzaldehyde in the same way described for the _erythro-p_-cyano ester. After recrystallization from ethanol, mp 183-185° dec, the product was pure (nmr).

Amido Esters.—The above compounds were all converted to their N-benzoyl derivatives by the previously mentioned procedure;[1] i.e., Fischer esterification, where necessary, was followed by treatment of the ester hydrochloride in ethyl acetate with 2.2 equiv of triethylamine and 1.2 equiv of benzoyl chloride. In the case of the crude _threo-β-p_-cyanophenylserine methyl ester hydrochloride, some of the less soluble _erythro_ amido ester was removed by crystallization (ether-ethyl acetate) before the threo isomer was obtained. The compounds are listed in Table I.

The two remaining amido esters were obtained via hydrolysis of the corresponding trans oxazolines. The procedure was the same in both cases, and is described only for the _threo-m_-nitro analog. The second one (_threo-m_-chloro) did not form a stable solvate. Characterization data are in Table I, also.

threo-N-Benzoyl-β-m-nitrophenylserine Methyl Ester.—A solution of 1.7 g (5.2 mmol) of _trans_-4-carbomethoxy-5-m-nitrophenyl-2-phenyl-2-oxazoline in 20 ml of dioxane, 1 ml of water, and 2 ml (5 mmol) of 2.5 N HCl was stirred for 3 hr at room temperature. Sodium bicarbonate (500 mg) was added with a few milliliters of water and the mixture stirred overnight. After removal of the dioxane in vacuo, the residue was work up in the usual way with ethyl acetate. Crystallization from isopropyl alcohol gave 1.5 g of an isopropyl alcohol solvate of the title compound, mp 74-78°. The analytical sample showed two endotherms (dta) at 79 and 113°. Nmr showed a 1:1 mole ratio of the desired compound with isopropyl alcohol.

Anal. Calcd for $C_{17}H_{16}N_2O_6 \cdot C_3H_8O$: C, 59.40; H, 5.98; N, 6.93; volatiles, 14.85%. Found: C, 59.71; H, 5.48; N, 7.14; volatiles (by tga), 14.5%.

When the solvate was stirred overnight in water containing a few drops of _tert_-butyl alcohol (as surfactant), the unsolvated product was obtained.

Reactions with Thionyl Chloride.—All reactions were initially followed in an nmr tube to determine the reaction times most appropriate for isolation of the various products. Product identities for oxazolines could be made on the basis of these initial spectra. Thus, formation of a trans oxazoline was characterized

by shift of the ester $-OCH_3$ signal downfield to δ ~3.9 and the appearance of two doublets between 5 and 6.5 (J = 7.5-8 Hz) representing the C_4 and C_5 protons; a cis oxazoline showed an upfield shift of the ester $-OCH_3$ signal to 3.2-3.3 (aromatic shielding[1]) and more widely split C_4 and C_5 protons (J = 10.5-11 Hz). The stereochemistry of the β-chloro compounds was assigned after isolation of the pure product, and in conjunction with the mode of formation.[1] Preparative runs were made in chloroform, ~5-10% concentration, with about 5-10-fold excess thionyl chloride unless otherwise stated. Reaction times are listed in each case below. In some cases, the volatiles were removed in vacuo to provide the product (method A); in others, the reaction was quenched into ice-water, and the usual work-up (of footnote 11) was followed (method B). Physical constants and elemental analyses of the oxazolines and β-chloroalaninates which were formed are found in Tables II and III.

A. With _erythro-N_-Benzoyl-β-p-chlorophenylserine Methyl Ester.—After room temperature reaction for 10 min and work-up by method B, the pure _trans_-4-carbomethoxy-5-p-chlorophenyl-2-phenyl-2-oxazoline, an oil, was obtained by chromatography ($CHCl_3$ containing 1.5% ether).

When extended over the weekend, the same reaction gave (method A) crystalline _erythro-N_-benzoyl-β-chloro-β-(p-chlorophenyl)alanine methyl ester, which had been a very minor impurity of the 10-min reaction.

B. With _threo-N_-Benzoyl-β-p-chlorophenylserine Methyl Ester.—After 10 min at room temperature, method A work-up gave _threo-N_-benzoyl-β-chloro-β-(p-chlorophenyl)alanine methyl ester, mp 163-136°.

C. With _erythro-N_-Benzoyl-β-m-chlorophenylserine Methyl Ester.—Reaction for 1.5 min at room temperature and method B work-up gave almost complete reaction (tlc). Chromatography (9:1 benzene-ether) gave pure _trans_-4-carbomethoxy-5-m-chlorophenyl-2-phenyl-2-oxazoline, an oil.

Work-up of a 10-min reaction (method A) gave crystalline _erythro-N_-benzoyl-β-chloro-β-(m-chlorophenyl)alanine methyl ester.

D. With _threo-N_-Benzoyl-β-m-chlorophenylserine Methyl Ester.—A solution of 1.8 g of the title compound in 20 ml of chloroform was stirred for 20 hr with a 1 ml of thionyl chloride. The residue after removal of volatiles was chromatographed on 100 g of silica (benzene-ether 8:1). From the earlier fractions

TABLE III

N-BENZOYL-β-CHLORO-β-ARYLALANINE METHYL ESTERS

Phenyl substituent	Isomer[a]	Registry no.	Mp °C[b]	Formula	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
p-Chloro	e	32721-69-0	110–112.5[d]	C₁₇H₁₅Cl₂NO₃	57.97	4.29	3.98	57.87	4.17	4.04
	t	32721-70-3	163.5–165.5[c]					58.24	4.45	3.92
m-Chloro	e	32721-71-4	148–151.5[c]					57.76	4.25	3.95
	t	32721-72-5	106–108[c,d]					58.05	4.19	3.99
p-Cyano	e	32721-73-6	119–121[c]	C₁₈H₁₅ClN₂O₃	63.07	4.41	8.17	62.81	4.43	8.07
p-Methoxy	t	32721-74-7	155–156[c]	C₁₈H₁₈ClNO₄	62.16	5.22	4.03	62.17	5.17	3.97
m-Nitro	e	32721-75-8	155–157[c]	C₁₇H₁₅ClN₂O₅	56.28	4.16	7.72	56.45	4.20	7.92

a e = erythro, t = threo. *b* Superscripts[c,d] denote recrystallization solvent or solvent combinations: c = ethyl acetate, d = ether.

was obtained *erythro-N*-benzoyl-β-chloro-β-(*m*-chlorophenyl)alanine methyl ester, mp 145–149°, undepressed on admixture with the product from the 10-min thionyl chloride reaction with the corresponding erythro amido ester C above). Nmr, ir, and tlc all support the assignment. Next in increasing polarity was *threo-N*-benzoyl-β-chloro-β-(*m*-chlorophenyl)alanine methyl ester.

The next fraction eluted, 500 mg, consisted mainly of methyl-α-benzamido-*m*-chlorocinnamate, an analytical sample of which showed mp 113.5–115.5° (EtOAc–Et₂O); uv max (EtOH) 278 nm (log ε 4.2), 221 (4.35).

Anal. Calcd for C₁₇H₁₄ClNO₃: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.77; H, 4.37; N, 4.60.

Close examination of the nmr spectrum of the original mixture revealed but a trace of this component. In all likelihood, and in conformity with the integration values determined on the reaction mixture prior to isolation, the cinnamate was generated during the chromatography.

More polar yet was *cis*-4-carbomethoxy-5-*m*-chlorophenyl-2-phenyl-2-oxazoline, which was eluted after the cinnamate.

E. With *erythro-N*-**Benzoyl-β-*p*-cyanophenylserine Methyl Ester.**—Reaction was for 3 min at room temperature. Chromatography (CHCl₃–1% acetone) after method B work-up gave the desired *trans*-4-carbomethoxy-5-*p*-cyanophenyl-2-phenyl-2-oxazoline.

The same reaction extended for 2 days gave directly (method A) crystalline *erythro-N*-benzoyl-β-chloro-β-(*p*-cyanophenyl)alanine methyl ester, mp 114–117°.

F. With *threo-N*-**Benzoyl-β-*p*-cyanophenylserine Methyl Ester.**—Two-day room temperature reaction, work-up by method B gave almost pure *cis*-4-carbomethoxy-5-*p*-cyanophenyl-2-phenyl-2-oxazoline, mp 125° from ether.

G. With *erythro-N*-**Benzoyl-β-*p*-methoxyphenylserine Methyl Ester.**—To a stirred suspension of 100 mg of the title compound in 1 ml of methylene chloride at 0–5° was added 0.2 ml of thionyl chloride. Solution was achieved in 2–3 min. After a total of 10 min, the reaction was quenched on ice and worked up by method B. Crystallization of the residue from ethyl acetate–ether gave 44.6 mg (42%) of single spot *threo-N*-benzoyl-β-chloro-β-(*p*-methoxyphenyl)alanine methyl ester, mp 152–153° dec.

The mother liquor solids, 60 mg, were examined by nmr. Two components accounted for essentially the entire spectrum, *trans*-4-carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline (~60%) and *erythro-N*-benzoyl-β-chloro-β-(*p*-methoxyphenyl)-alanine methyl ester (~30%). A small amount of the *threo-β*-chloro compound also remained.

A similar reaction extended for 1.5 hr at room temperature and worked up by method A gave a 47% yield of *threo-β*-chloro compound, mp 147–149° dec.

The mother liquors resulting from the isolation of the *threo-β*-chloro compound were chromatographed on preparative silica plates using 6:1 benzene–ether, then 2% methanol in benzene. The faster moving compound was *trans*-4-carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline, identical (ir, tlc, nmr) with that formed from the reaction of *threo-β-p*-methoxyphenyl-serine methyl ester and benziminoethyl ether hydrochloride (see below). The slower moving material was not the *erythro-N*-benzoyl-β-chloro-β-(*p*-methoxylphenyl)alanine methyl ester, but its dehydrochlorination product, methyl-α-benzamido-*p*-methoxycinnamate (characterization below).

When the reaction was run in an nmr probe (CDCl₃, T ~ 5°) the first spectrum obtained showed methoxyl signals equivalent to at least three species, two of which were clearly the trans oxazoline and the *threo-β*-chloro compound. The former amounted to approximately 40–45% of the total. It was not

possible to quantify the others. After 90 min, the oxazoline had decayed to about 30%, and, after an additional hour (now at room temperature or slightly above), the signals for the oxazoline were considerably diminished. Observation over the following days showed a steadily increasing complexity of the methoxyl region and the growth of a signal attributable to methyl chloride. Ultimately, crystalline 4-*p*-methoxybenzylidene-2-phenyl-2-oxazolin-5-one deposited,[1] and was recovered: mp 156–157° (methanol) (lit.[15] mp 158–159°); uv max (methanol)[16] 252 nm (log ε 4.18) 259 (4.22), 383 (4.59).

H. With *threo-N*-**Benzoyl-β-*p*-methoxyphenylserine Methyl Ester.**—The identical 10-min reaction in the cold as described above (G) for the erythro isomer gave 75 mg (71%) of *threo-N*-benzoyl-β-chloro-β-(*p*-methoxyphenyl)alanine methyl ester, mp 152–153° dec from ethyl acetate–ether. The mother liquor residue when examined by nmr showed lines clearly attributable to trans oxazoline (~60%) and the *erythro-β*-chloro compound (~15–20%). Up to 10% of cis-oxazoline was present.

Extended reaction (1.5 hr at room temperature) gave 64% *threo-β*-chloro compound. From the mother liquors there was isolated (by thick plate chromatography) both the trans oxazoline (ir and tlc), and methyl α-benzamido-*p*-methoxycinnamate: mp 149–152° from aqueous methanol (lit.[17] mp 141–142°); uv max (CH₃OH) 311 nm (log ε 4.4), 228 (4.3).

Anal. Calcd for C₁₈H₁₇NO₄: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.59; H, 5.59; N, 4.48.

This product, obtained in 14% yield was probably formed by dehydrochlorination of the *erythro-β*-chloroalaninate during the chromatography.

In the nmr probe (CDCl₃, T ~ 3°) the earliest spectra represented about 70% *threo-β*-chloro compound, with no evidence for the chlorosulfite ester of the starting material. A methoxyl signal attributable to the trans oxazoline ester could be seen, amounting to no more than 10–15% of the total. The signal corresponding to the cis oxazoline ester methyl group was not discernible.

I. With *erythro-N*-**Benzoyl-β-*m*-nitrophenylserine Methyl Ester.**—To 3.35 g of the title compound in 42 ml of chloroform was added 5 ml of thionyl chloride. After 5-min stirring, the reaction was quenched into ice water. After usual work-up, the residue was chromatographed (benzene–ether, 95:5). There was obtained 2.3 g of pure *trans*-4-carbomethoxy-5-*m*-nitrophenyl-2-phenyl-2-oxazoline, an oil.

Overnight reaction at room temperature, followed by method A work-up, gave crystalline *erythro-N*-benzoyl-β-chloro-β-(*m*-nitrophenyl)alanine methyl ester, mp 148–153°.

J. With *threo-N*-**Benzoyl-β-*m*-nitrophenylserine Methyl Ester.**—A mixture of 200 mg of the title compound in 5 ml of chloroform was stirred at 40° overnight with 1 ml of thionyl chloride. After method A work-up, the crystalline residue was triturated with ether containing ethyl acetate. Filtration gave 174 mg of solids (a) and mother liquors containing 37 mg of residue (b).

The mixture (a) consisted of *cis*-4-carbomethoxy-5-*m*-nitrophenyl-2-phenyl-2-oxazoline and its hydrochloride, as evidenced by its single spot tlc (6:1 C₆H₆–Et₂O, then 2% MeOH in C₆H₆). The ethyl acetate soluble portion gave an analytical sample.

When the hydrochloride-containing portion (+AgNO₃ test, ir) was dissolved in methanol and chromatographed on a prepara-

(15) H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, **178**, 403 (1949).

(16) D. A. Bassi, V. Deulofeu, and F. A. F. Ortega [*J. Amer. Chem. Soc.*, **75**, 171 (1953)] reported very similar values from ethanol.

(17) N. K. Kochetkov, E. I. Budovskii, R. M. Khomutov, and M. Ya. Karpeiskii, *J. Gen. Chem. U.S.S.R.*, **29**, 70 (1959).

tive plate (2% MeOH in C₆H₆), there was obtained, in addition to more cis oxazoline, a small amount of *erythro-N*-benzoyl-β-*m*-nitrophenylserine methyl ester, mp 135–137°, which arose from oxazoline hydrolysis (and O → N acyl migration) during work-up. This component was not present in the original crystalline precipitate (a).

The residue (b), which consisted of three major components was separated on thick plates (6:1 C₆H₆-Et₂O, then 2% MeOH in C₆H₆). The most polar of the three was cis oxazoline, the major reaction product. Next was the isomeric trans oxazoline (ir, tlc), and least polar was *erythro-N*-benzoyl-β-chloro-β-(*m*-nitrophenyl)alanine methyl ester (melting point, ir, tlc).

cis-4-Carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline.—An intimate mixture of 200 mg of *erythro-p*-methoxyphenylserine methyl ester, made by Fisher esterification of the more polar of the two *p*-methoxyphenylserines, and 200 mg of benziminoethyl ether hydrochloride was heated on the steam bath for 30 min.[6] Chromatography (3.5% MeOH in C₆H₆) gave 110 mg of crude product, the nmr of which clearly established the configuration as the cis oxazoline. The product was crystallized from ether–hexane. The same chromatography gave a vivid yellow fraction which was shown to be 4-*p*-methoxybenzylidene-2-phenyl-2-imidazolin-5-one: mp 295° dec from isopropyl alcohol (lit.[18] mp 289–290°); uv max (MeOH) 254 nm (log ε 4.39), 394 (4.54); M⁺ 278, C₁₇H₁₄N₂O₂, mol wt 278.3.

trans-4-Carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline.—When 400 mg of the threo isomer of *p*-methoxyphenyl-

(18) A. R. Kidwai and G. M. Devasia, *J. Org. Chem.*, **27**, 4527 (1962).

serine methyl ester underwent the same reaction as described directly above, there was obtained 124 mg of the title product, a light yellow oil, after chromatography on silica gel plates with 6·1 benzene–ether, then 2% methanol in benzene.

# Synthetic Indole Alkaloids. I. Synthesis of a Pentacyclic Lactam[1]

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1,2,3,4,6,7,12,12b-Octahydro-2,4-diketoindolo[2,3-*a*]quinolizine (3), a tetracyclic keto lactam, has been prepared as an intermediate in the synthesis of pentacyclic indole alkaloids from tryptamine (2a) and citric acid. 6-Methoxytryptamine (2b) has also been used in place of 2a. 3 has been reacted with carbethoxy methyl vinyl ketone (15) to produce the expected cyclized adduct, 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[*g*]-1-carbethoxy-2,5-diketoindolo[2,3-*a*]quinolizine (16). 16 reduces smoothly with Pt and H₂ to produce the tetrahydro adduct 18. Lithium aluminum hydride reduction of 18 produces a pentacyclic diol 21. The stereochemistry of 21 is discussed.

Most of the total synthesis work in the reserpine[2] and the yohimbine[3] areas[4] (1) has involved preconstruction of the stereochemical relationships of the D/E rings before condensation with tryptamine (2a) or 6-methoxytryptamine (2b) to form the pentacyclic skeleton.
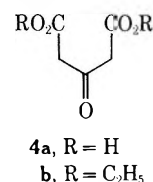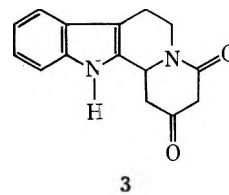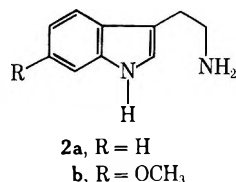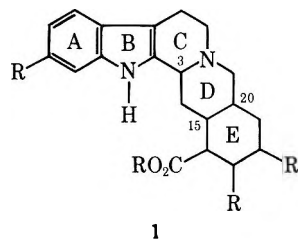
In this paper a stepwise construction of rings A through E is explored. In outline, it was envisaged that 2a or 2b might be combined with a modified β-oxoglutaric acid to yield a keto lactam of type 3 which then could be alkylated with a substituted methyl vinyl ketone and cyclized to yield a pentacyclic precursor of 1.

2a, R = H
b, R = OCH₃

1

3

4a, R = H
b, R = C₂H₅

Synthesis Results.—Citric acid, an inexpensive starting material, was readily converted[5] to β-oxoglutaric acid (4a) which in turn was esterified[6] to yield 4b as a preliminary to preparing the desired aldehydo ester 5. To obtain 5, 4b was converted to the ketal ester 6a which was converted to its disodium salt 6b, and then cyclized with oxalyl chloride to give the anhydride 7.[7] 7 was then transformed with ethanol to the acid es-

(1) (a) Supported in part by the National Institute of Mental Health. (b) Presented in part before the Division of Organic Chemistry, 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, Abstracts, No. ORGN 15.

(2) R. B. Woodward, F. Bader, H. Bickel, and R. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(3) E. Van Tamelen, M. Shamma, A. Burgstahler, J. Wolinsky, R. Tamm, and P. Aldrich, *J. Amer. Chem. Soc.*, **80**, 5006 (1958); **91**, 7315 (1969).

(4) (a) J. Poisson, *Ann. Chim. (Paris)*, **9**, 99 (1964); (b) R. H. F. Manske in "The Alkaloids, Chemistry and Physiology," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1965, p 694; (c) E. Schlittler in "The Alkaloids, Chemistry and Physiology," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1965, p 287; (d) I. Ernest and B. Kakac, *Chem. Ind. (London)*, 513 (1965); (e) for a different stepwise approach, see Cs. Szantay, L. Toke, and K. Honti, *Tetrahedron Lett.*, No. **22**, 1665 (1965).

(5) R. Adams, E. M. Chiles, and C. F. Rassweiler, *Org. Syn.*, **5**, 5 (1925).

(6) R. Adams and H. M. Chiles, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1947, p 237.

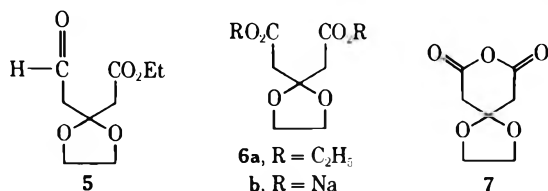(7) R. Adams, *J. Amer. Chem. Soc.*, **42**, 599 (1920).

ter **8a** which on treatment, without purification, with oxalyl chloride gave **8b**. Rosenmund reduction[8] of **8b** again without purification gave the blocked aldehydo ester **5**.

nolic ferric chloride test[14] and that its ir spectrum in KBr had a good ketone peak at 1724 cm^{-1} certainly indicative of little if any enolic character under these conditions. However, **3** dissolved readily in aqueous base and also was converted with acetic anhydride to the enol acetate **14**.

Condensation of **5** and tryptamine (**2a**) then proceeded smoothly without purification of intermediates to yield the keto lactam **3**. Thus **5** and **2a** reacted in glacial acetic acid to give a red gum whose infrared peaks indicated an ester at 1720 cm^{-1}, a ketal at 946 cm^{-1}, and a strong peak at 1626 cm^{-1} due to a C=N vibration. Solution of this Schiff's base in ethanolic hydrogen chloride and subsequent treatment with boiling 10% sulfuric acid converted it to **3** in an overall yield from **5** of 35%.
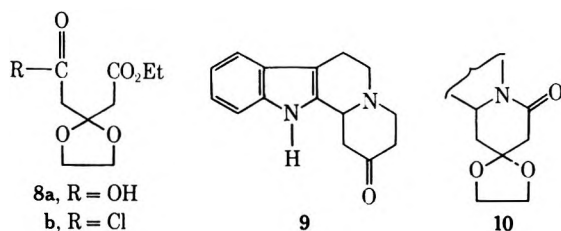
As a structure proof **3** seemed readily convertible to **9**, which had been earlier prepared by Swan[9] using a different route. Accordingly the keto lactam **3** was blocked to give the ketal **10**, which was then reduced to **11** and hydrolyzed to give **9** identical in every respect with an authentic sample kindly supplied by Dr. G. A. Swan. An additional sodium borohydride reduction of **3** gave the expected hydroxy lactam **12**. Our interest in the 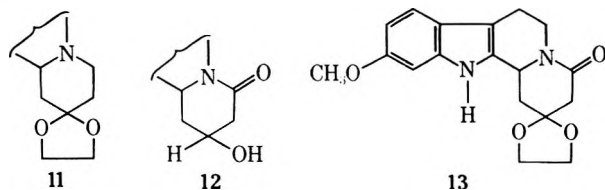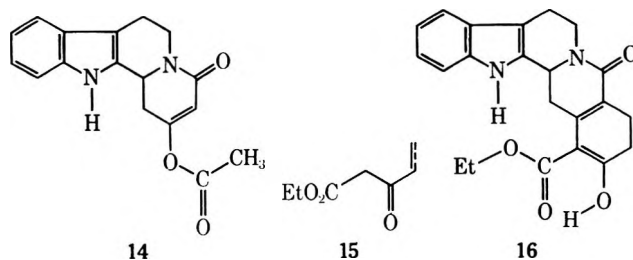reserpine series led us to condense 6-methoxytryptamine (**2b**) and **5** under slightly different conditions to give the lactam **13** but with the ketal group still intact.[10]

Although the physical properties of the tetracyclic keto lactam **3** generally corresponded closely to its assigned structure, it was most interesting to note that its β-dicarbonyl system failed to give a positive metha-

Reaction with Carbethoxymethyl Vinyl Ketone (15).—

The tetracyclic keto lactam (**3**), carbethoxymethyl vinyl ketone (**15**),[15] and a basic catalyst, potassium hydroxide in methanol,[16] were allowed to react in refluxing methanol to give after standing overnight a crystalline product which in time was shown to be the pentacyclic Michael adduct **16**. The ir spectrum of **16** had the peculiar property of having no carbonyl absorption[17] above 1635 cm^{-1}. Thus the saturated ester and ketone absorptions of **3** and **15** were replaced by strong absorptions at 1635, 1592, and 1558 cm^{-1}. The 1635 and 1592 cm^{-1} bands were interpreted to be representative of the chelated enol **16** in accordance with the work of Rhoads[18] on enolizable cyclic β-keto esters. The absence of higher frequency absorption associated with the keto form was rationalizable in terms of the report of Albright and Goldman[19] that α-yohimbinone (**17**) was completely enolic and had no absorption above 1642 cm^{-1}. **16** did have a peak in its nmr spectrum at δ 13.5 ppm which could be assigned to an enolic hydrogen,[19] but its mass spectrum was indeterminate since it decomposed in the instrument to low molecular weight fragments.

Hydrogenation of **16** proceeded smoothly with platinum oxide,[20] apparently accompanied by the uptake of four atoms of hydrogen, since the mass spectrum of the product **18** had a strong parent peak at 382 mass units corresponding to the molecular weight of **18**. The ir spectrum of the tetrahydro adduct **18** showed two strong saturated carbonyl absorptions at 1722 and

(8) E. Mosettig and R. Mozingo, *Org. React.*, **4**, 362 (1948).

(9) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).

(10) Several other approaches which did not lead to **3** or a variation of it include attempted reaction of diethyl ethylenedioxyglutarate (**6a**) or the corresponding dimethyl ester with tryptamine (**2a**) under a wide variety of conditions. Starting materials were generally recovered except in a sealed tube where the ditryptamide of β-ethylenedioxyglutaric acid was obtained in a low yield.[11] Reaction of tryptamine (**2a**) with β-ethylenedioxyglutaric anhydride (**7**) gave the expected glutaramic acid but it, or its ester or the derived glutarimide, could not be cyclized to form ring C.[12,13]

(11) E. Besthorn and E. Garben, *Ber.*, **33**, 3442 (1900).

(12) E. Schlittler and T. Allemann, *Helv. Chim. Acta*, **31**, 128 (1948).

(13) N. Itoh and S. Sugasawa, *Tetrahedron*, **1**, 45 (1957).

(14) R. L. Shriner, R. C. Fuson, and D. T. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 127.

(15) N. Nazarov and S. I. Zavylov, *J. Gen. Chem. USSR*, **23**, 1701 (1953).

(16) S. I. Zavylov, G. V. Kondratina, and L. F. Kudryantseva, *ibid.*, **31**, 3449 (1961); R. Hohenlohe-Oehingen, *Monatsh. Chem.*, **93**, 576 (1962); E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *J. Amer. Chem. Soc.*, **86**, 2038 (1964); S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *ibid.*, **90**, 2889 (1968).

(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 34.

(18) S. J. Rhoads, A. W. Decora, J. C. Gilbert, T. Garland, M. J. Urbigkit, and R. J. Spangler, *Tetrahedron*, **19**, 1625 (1963). They also report that enolizable cyclic β-keto esters develop an instantaneous and intense blue to blue-purple coloration with Henecka's ferric chloride reagent. **16** gave an immediate dark blue color with this reagent. **3** gave no color at all and **15** was wine red. Rhoads, *et al.*, also reported a dark green color formed with ethanolic cupric acetate and their β-keto esters. **16** gave a similar dark green color with this reagent.

(19) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1007 (1965).

(20) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6082, 6087 (1960). The double bond common to rings D and E at C$_{15}$ and C$_{20}$ in **16** might be expected to reduce smoothly cis under these conditions in view of the experiments of F. L. Weisenborn, *ibid.*, **79**, 4818 (1957), leading to synthetic 17-desmethoxydeserpidine.

1610 cm^{-1} corresponding to a saturated ester and lactam, respectively. Since **18** had a secondary alcohol, back oxidation using the modified[19] *N,N'*-dicyclohexylcarbodiimide method of Pfitzer and Moffatt[21] produced the ketone **19**. **19** had no saturated carbonyl

17

18   19
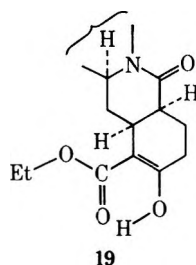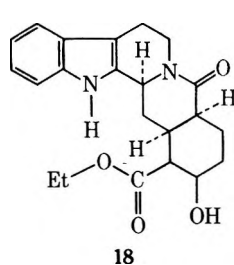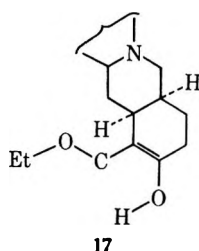
absorption at all, but rather a strong doublet at 1641 and 1617 cm^{-1} consistent with an enolized β-keto ester. This result, following Albright and Goldman,[19,22] can be used to assign a cis D/E ring junction in 19 and also in **18**. The mass spectrum of **19** had no parent peak; however, this was not surprising since the other β-keto ester **16** also had none. Reduction of **19** with platinum oxide and hydrogen, although on an extremely small scale, gave a dihydro-**19** which was identical in all respects with the tetrahydro Michael adduct **18**. Regeneration of **18** this way suggests that similar steric factors may be operating in the reduction of **18** and the Michael adduct **16**. If α-cis addition of hydrogen to the hindered enol is favored, as molecular models seem to indicate, then the carbethoxyl and hydroxyl groups would be β-cis. This conclusion, coupled with the likelihood that D/E in **18** is cis fused, places **18** in the alloyohimbine (**20**) family. If the C$_3$ hydrogen of **18** is α then it would be oriented as in alloyohimbine (**20**), but if it is β it would be as in epialloyohimbine.

CH$_3$O$_2$C   HOH$_2$C   CH$_3$O$_2$C

20   21   22

In order to get some idea as to the orientation of the C$_3$ hydrogen and also to remove the lactam carbonyl group at C$_{21}$,[23] the lithium aluminum hydride reduc-

tion of **18** to yield **21** was accomplished. The crystalline diol **21** showed no absorption in the carbonyl region but had two bands in the CH region at 2805 and 2755 cm^{-1} which were not in **18**. These so-called Bohlmann bands have been suggested,[24,25] not without dissent,[26] to be indicative of an axial α-C$_3$ hydrogen. Since Wenkert[27] has suggested that a β-C$_3$ hydrogen might have an nmr peak at δ 4.6 ppm, the nmr spectrum of **21** was scrutinized. No peak other than from the deuterated dimethyl sulfoxide at 2.5 and 3.7 ppm could be found from 3.4 to 7 ppm, again indicating that the C$_3$ hydrogen of **21** was α. While the mass spectrum of **21** showed a parent peak equal to the molecular weight of the diol and the isotopic analysis was consistent with its empirical formula, it was of considerable importance to note the appearance of a large *m/e* M − 1 peak characteristic of yohimbine-like alkaloids[28] and arising from loss of the C$_3$ hydrogen. The elemental analysis required inclusion of 0.75 mol of ethanol to fit the combustion analysis. Solvation of this sort is also characteristic of the diols from yohimbine[29] and α-yohimbine.[30]

If the stereochemistry of the diol is that shown in *dl*-**21**, then alloyohimbine (**20**) is that alkaloid which should reduce to optically active **21**. Unfortunately it was not available. α-yohimbine (**22**) was, however, and, although the C$_{17}$ hydroxyl was now α, the rest of the molecule was similar to **20**. Reduction of **22** yielded the diol **23**, which had the expected Bohlmann bands at 2795 and 2745 cm^{-1}; however, the rest of the ir spectrum of **23** showed that it was definitely different from synthetic diol **21**. Since the mass spectra of **21** and the diol from α-yohimbine **23** should be very similar, they were compared and found to be nearly

HOH$_2$C

23
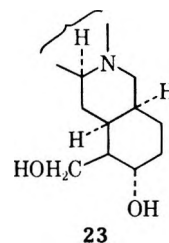
identical. However, there were definite slight differences in intensity of the peaks due in part to the slightly different stereochemistry and also to possible impurity differences.

Although other experiments were attempted, especially on the initial Michael adduct **16** or its immediate transformation products, they were indefinite due presumably to the two D/E double bonds in **16**. This generally mirrors the reported instability even toward recrystallization of Δ$^{15(20)}$-yohimbine[31] due most likely to the double bond common to the D/E rings.

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(22) Albright and Goldman[19] oxidized yohimbine, which has D/E trans, to yohimbinone and observed no enolic character, but α-yohimbine (**22**) with D/E cis on oxidation to a α-yohimbinone (**17**) was highly enolic.

(23) In this synthetic scheme the lactam carbonyl at C$_{21}$ through its enol at C$_{21}$–C$_{20}$ represents a way of converting the D/E junction from cis to trans and thereby entering, with the proper substituents, the reserpine and the yohimbine areas using a common synthetic plan.

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Experimental Section

All microanalyses were obtained from the Galbraith Laboratories, Knoxville, Tenn., or from Dr. Alfred Bernhardt, Microanalytical Laboratory, Max Planck Institute, Ruhr, West Germany. The melting points of all compounds up to and including 13 were determined on a calibrated apparatus heated at 1 deg/min and are corrected. All others were obtained on a Hoover-Thomas melting point apparatus heated at 1 deg/min and have not been corrected. All boiling points are uncorrected. The ir spectra were run on a Perkin-Elmer Infracord or Model 21, 421, or 521 recording ir spectrophotometer. The nmr spectra were run on a Varian HA-60 or HR-60 nmr instrument. The uv spectra were run on a Cary 14 recording uv spectrophotometer. The mass spectra were obtained from Morgan Schaffer Corp., Montreal, Canada.

Starting Materials.—Tryptamine (2a) was prepared from indole by the Brutcher and Vanderwerff modification [*J. Org. Chem.*, **23**, 146 (1958)] of the Speeter and Anthony[32] synthesis of substituted tryptamines. 6-Methoxytryptamine (2b) was synthesized using the Woodward method.[2] Conversion of citric acid to diethyl β-ethylenedioxyglutarate (6a)[33] was routine.[5,6]

Disodium β-Ethylenedioxyglutarate (6b).—A solution of 35.6 g (0.89 mol) of sodium hydroxide in 400 ml of hot absolute ethanol was added dropwise with stirring to a hot solution of 73.1 g (0.297 mol) of diethyl β-ethylenedioxyglutarate (6a) in 400 ml of ethanol over a 1-hr period. The mixture was refluxed for an additional hour, filtered hot through a sintered glass funnel, and washed with hot ethanol to give 67.7g (97.2%) of 6b as a snow-white powder. Recrystallization from water–ethanol afforded colorless blades.

Anal. Calcd for $C_7H_8O_6Na_2$: C, 35.91; H, 3.44. Found: C, 35.61; H, 3.42.

β-Ethylenedioxyglutaric Anhydride (7).—To a suspension of 52.8 g (0.22 mol) of the crude disodium salt 6b in 1 l. of chloroform was added, with rapid stirring, a solution of 38.1 ml (0.45 mol) of oxalyl chloride in 300 ml of chloroform over a 5-min period. The mixture was maintained at 45–50° (water bath) for 1 hr, filtered hot through Celite, concentrated to one-third volume under vacuum, and heated to boiling followed by saturation with low-boiling petroleum ether (bp 30–60°) and chilling to yield 29.5 g of 7. Concentration of the liquors yielded 3.3 g more of 7 for a combined yield of 85%. 7 on recrystallization from chloroform–petroleum ether gave colorless needles: mp 112–113°; ir (CHCl₃) 1828, 1779 (anhydride C=O), 1055 (CO), 952 cm⁻¹ (ketal COC).

Anal. Calcd for $C_7H_8O_5$: C, 48.87; H, 4.67. Found: C, 48.86; H, 4.59.

4-Carbethoxy-3-ethylenedioxybutyric Acid (8a).—A mixture of 21.85 g (0.127 mol) of β-ethylenedioxyglutaric anhydride (7) and 14.8 ml (0.254 mol) of absolute ethanol was gently refluxed for 24 hr. After removal of the excess ethanol under vacuum there remained 26.58 g (96.0%) of the half-acid ester as a colorless, viscous oil which was always used for further reactions without purification. 8a had in the ir spectrum (CHCl₃) 1720 (acid and ester C=O), 1365 (CH₃), 1035 (ester CO), and 950 cm⁻¹ (ketal COC).

4-Carbethoxy-3-ethylenedioxybutyryl Chloride (8b).—To a solution of 26.58 g (0.12 mol) of unpurified half-acid ester 8a in 250 ml of dry benzene was added 27 ml (0.30 mol) of oxalyl chloride and the mixture was refluxed for 2 hr, after which the solvent was removed under vacuum. The resulting oil was triturated several times with a total of 1 l. of low-boiling petroleum ether. The triturants were combined, treated with Darco, and filtered and the petroleum ether was removed under a stream of dry air on a water bath to yield 19.66 g (68.5%) of the acid chloride 8b as a mobile, pale yellow liquid: ir (CHCl₃) 1785 (acid chloride C=O), 1720 (ester C=O), 1365 (CH₃), 1030 (ester CO), and 950 cm⁻¹ (ketal COC). 8b suffered complete decomposition on attempted distillation and was used further without purification.

4-Carbethoxy-3-ethylenedioxybutyraldehyde (5).—A mixture of 200 ml of dry xylene, 4.0 g of 5% palladium on barium sulfate,[8] and 40 mg of "quinoline sulfur"[8] was heated under a stream of hydrogen to remove traces of water, then cooled; 19.66 g (0.083 mol) of the unpurified acid chloride 8b was added and the mixture was heated to reflux. When hydrogen chloride evolution ceased after 1 hr, the mixture was cooled and filtered through Celite and the solvent was removed under vacuum. There remained a residue

which was distilled to yield 10.31 g (61.4%) of the almost colorless aldehyde 5: bp 120–122° (1.3 mm); ir (CHCl₃) 1720 (ester and aldehyde C=O), 1360 (CH₃), 1030 (ester CO), 948 (ketal COC). The 2,4-dinitrophenylhydrazone of 5 after two recrystallizations from ethanol had mp 111.5–113.0°.

Anal. Calcd for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.74; N, 14.66. Found: C, 47.35; H, 4.72; N, 14.55.

1,2,3,4,6,7,12,12b-Octahydro-2,4-diketoindolo[2,3-a]quinolizene (3). A. **N-[β-(3-Indolyl)ethyl]-4-carbethoxy-2-ethylenebutylimine (Schiff's Base).**—To a hot solution of 3.20 g (0.02 mol) of tryptamine (2a) in 25 ml of glacial acetic acid was added at once a solution of 4.04 g (0.02 mol) of the aldehyde ester 5 in 25 ml of glacial acetic acid. The mixture was refluxed for 2 hr, then cooled and poured into a large volume of ice-water. It was then extracted twice with chloroform using added sodium acetate to reduce emulsion formation, washed twice with water, dried (Na₂SO₄), and stripped of solvent under vacuum to give 5.18 g (75.2%) of the Schiff base as a red-orange oil which could not be crystallized: ir (CHCl₃) 1732 (ester C=O), 1638 (C=N), 1040 (ester CO), 948 cm⁻¹ (ketal COC).

B.—To 5.18 g (0.015 mol) of the above Schiff's base in a 250-ml beaker was added 150 ml of 10% sulfuric acid. The mixture was heated on a hot plate with constant stirring until, after a few minutes of ebullition, the keto lactam product 3 began to precipitate. Heating was continued until this ceased and then the mixture was cooled, filtered, and washed (H₂O). The keto lactam 3 was freed from traces of the Schiff's base by trituration with cold ethanol. After final filtration and washing with ethanol, 0.96 g (25.2%) of 3 was obtained as a white solid. Recrystallization from ethanol–water gave 3 as clusters of colorless needles: mp 242° dec; ir (KBr) 1724 (ketone C=O), 1644, 1622 cm⁻¹ (lactam C=O).

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.81; H, 5.74; N, 11.04.

The phenylhydrazone recrystallized from ethanol–water had mp 219° dec.

Anal. Calcd for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.27; H, 6.08; N, 16.27.

A solution of 2.67 g (0.00775 mol) of the above Schiff's base in a minimum amount of 20% ethanolic hydrogen chloride was allowed to stand for 24 hr at room temperature. The resulting tan crystals were filtered, washed first with ethanol and the with ether. to yield 1.19 g of an unstable tan intermediate. This product readily dissolved in 100 ml of 10% sulfuric acid, which was then heated on a hot plate for 10 min with accompanying ebullition. At the end of that time reasonable pure white crystalline keto lactam 3 separated out. Filtration and washing with water yielded 0.90 g (46%) of 3. Recrystallization from ethanol–water yielded 3 as white, flocculent crystals, mp 243–244° dec.

1,2,3,4,6,7,12,12b-Octahydro-2-ethylenedioxy-4-ketoindolo-[2,3-a]quinolizine (10).—A solution of 1.00 g (0.00393 mol) of the keto lactam 3 and 40 mg of *p*-toluenesulfonic acid in 100 ml of tetrahydrofuran and 50 ml of 2-methyl-2-ethyl-1,3-dioxolane, prepared by a previously described method,[34] was refluxed for 21 hr, cooled, poured into benzene, washed twice with 10% sodium carbonate and twice with water, and dried (Na₂SO₄), and the solvent was removed under vacuum to give 0.20 g (17%) of the ketal 10 as a yellow, granular solid: ir (CHCl₃) 1628 (lactam C=O), 946 cm⁻¹ (ketal COC). Further purification was not attempted.

1,2,3,4,6,7,12,12b-Octahydro-2-ketoindolo[2,3-a]quinolizine (9).—To a refluxing suspension of 0.5 g of lithium aluminum hydride in 50 ml of diethyl ether was added slowly a solution of 0.11 g (0.00037 mol) of the crude ketal 10 in 100 ml of diethyl ether. The mixture was refluxed for 1 hr and after cooling water was cautiously added. The resulting mixture was filtered through Celite and the filter cake was triturated several times with diethyl ether. After the combined filtrate and triturants were evaporated to dryness, the crude reduction product was dissolved in 10% sulfuric acid, refluxed for 18 hr, cooled, made basic with sodium hydroxide, extracted with chloroform, washed (H₂O), and dried (Na₂SO₄), and the solvent was removed under vacuum to give 0.02 g of the ketone 9. Recrystallization from benzene–low boiling petroleum ether afforded 9 as yellow needles, mp 178.5–179° (lit.[9] mp 180–180.5°). A mixture melting point with an authentic sample of 9 kindly supplied by Dr. Swan[9] had a value of 181.5–182.2° and was therefore undepressed.

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(34) H. J. Dauben, B. Löken, and H. J. Ringold, *J. Amer. Chem. Soc.*, **76**, 1359 (1954).

dl-1,2,3,4,6,7,12,12b-Octahydro-2-hydroxy-4-ketoindolo[2,3-*a*]quinolizine (12).—To a solution of 0.50 g (0.00197 mol) of the keto lactam **3** in 55 ml of absolute ethanol was added 0.50 g of sodium borohydride. The mixture was heated briefly to effect solution of the hydride and then allowed to stand for 45 min. A small volume of water was then added and the mixture was cautiously heated to boiling to destroy the excess hydride. While ebullition was maintained, 100 ml of water was added gradually to displace the ethanol. The solution was chilled, filtered to remove a faint cloudiness, and allowed to stand overnight, whereupon 0.19 g (40%) of colorless crystals of **12** were deposited. Recrystallization from ethanol–water gave colorless, feathery needles: mp 144–146° dec; ir (KBr) 1650, 1580 cm⁻¹ (lactam C=O).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.35; H, 6.36; N, 10.99.

1,2,3,4,6,7,12,12-b-Octahydro-2-ethylenedioxy-4-keto-10-methoxyindolo[2,3-*a*]quinolizine (13).—Solutions of 0.42 g (0.00221 mol) of 6-methoxytryptamine (**2b**) prepared by the method of Woodward[2] and 0.45 g (0.00221 mol) of the ester aldehyde **3** each in 25 ml of benzene were combined and refluxed for 18 hr, 5 mg of *p*-toluenesulfonic acid was added, and the mixture was refluxed for another 2.5 hr. The solution was filtered hot, and the filtrate on standing deposited 0.19 g (26%) of **13** as tan granular crystals. Recrystallization of **13** from chloroform–low boiling petroleum ether gave **13** as clusters of almost white needles: mp 231–232°; ir (KBr) 1620 (lactam C=O), 945 cm⁻¹ (ketal COC).

Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.60; H, 6.31; N, 8.42.

N-[β-(3-Indolyl)ethyl]-β-ethylenedioxyglutaramic Acid.—To a refluxing solution of 10.69 g (0.0667 mol) of tryptamine (**2a**) in 800 ml of chloroform was added dropwise with stirring over a 2 hr period a solution of 11.49 g (0.0667 mol) of β-ethylenedioxyglutaric anhydride (**7**) in 500 ml of chloroform. The mixture was then stirred for 2 hr with occasional application of heat to maintain the temperature just below reflux. Finally 700 ml of low-boiling petroleum ether was added and the mixture was chilled to give 21.39 g (96.6%) of the glutaramic acid which on recrystallization from ethyl acetate–petroleum ether gave almost white crystals: mp 166–167° dec; ir (KBr) 1721 (acid C=O), 1620, 1567 (amide C=O, 956 cm⁻¹ (ketal COC).

Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.43. Found: C, 61.40; H, 6.03; N, 8.33.

N-[β-(3-Indolylethyl)]-β-ethylenedioxyglutarimide.—To a mixture of 50 g of phosphorus pentoxide and 250 g of sand suspended in 500 ml of dry pyridine at 75° (water bath) was added dropwise with vigorous stirring a solution of 5.00 g of the above glutaramic acid in 250 ml of pyridine over a period of 1 hr. During this time the temperature was increased to 85–90°. The mixture was stirred at this temperature for an additional 4 hr, then filtered hot, and the residue was washed with hot pyridine. The combined filtrate and washings were stripped of solvent under vacuum and the resulting oil was triturated with cold, saturated sodium bicarbonate solution. The resulting tan, granular product was filtered, washed, and dried to give 3.28 g (69.4%) of the glutarimide, which upon recrystallization from benzene–low boiling petroleum ether gave colorless crystals: mp 155.5–156°; ir (CHCl₃) 1734, 1681 (imide C=O), 948 cm⁻¹ (ketal COC).

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.99; H, 5.60; N, 8.74.

1,2,4,6,7,12,12b-Hexahydro-2-acetyl-4-ketoindolo[2,3-*a*]quinolizine (14).—To a mixture of 0.2 g (7.9 × 10⁻⁴ mol) of keto lactam and 0.2 g (2. 6 × 10⁻³ mol) of sodium acetate was added 10 ml (0.09 mol) of acetic anhydride. The mixture was stirred overnight at room temperature and in the morning it was added to 40 ml of ice–water, stirred for 0.5 hr, and extracted twice with 50-ml portions of diethyl ether. The ether solution was dried over sodium sulfate, filtered, and concentrated on a Rotovap to yield finally 0.085 g (39.8%) of the crude enol acetate (14). **14** was recrystallized from anhydrous ether to give colorless, cubic crystals: mp 196–197 dec; ir (KBr) 1766 (acetyl C=O), 1652 (C=C), 1637, 1598 cm⁻¹ (lactam C=O); uv max (95% EtOH) 289 mμ (ε 8.0 × 10³), 282 (10.5 × 10³), 273 (10.9 × 10³), 223 (43.0 × 10³).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.42. Found: C, 69.04; H, 5.51; N, 9.33.

1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[*g*]-1-carbethoxy-2,5-diketoindolo[2,3-*a*]quinolizine (16).—To a solution of 1.0 g (3.9 × 10⁻³ mol) of keto lactam **3** in 50 ml of hot methanol was

added first a solution of 0.03 g (5.2 × 10⁻⁴ mol) of potassium hydroxide in several milliters of methanol and then 0.60 g (4 × 10⁻³ mol) of freshly prepared carbethoxymethyl vinyl ketone (15). The solution formed was gently refluxed under nitrogen for 0.5 hr and then allowed to cool overnight. In the morning the crystalline product was filtered, washed with 20 ml of cold methanol, and recrystallized from ethanol–water to yield 0.65 g (42.2%) of rhomboidlike crystals of the keto lactam adduct (16): mp 195° dec; ir (KBr) 1635, 1595, 1560 cm⁻¹ (lactam and keto ester C=O, C=C); uv max (95% MeOH) 224 mμ (ε 46,000), 269 (17,000), 289 (10,000), 338 (6700); nmr (C₂D₆SO) δ 1.25 (t, 3), 2.6 (d, 3), 4.28 (d, 2), 7.25 (d, 2), 11.01 (s, 1), 13.4 (s, 1).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.83; H, 5.61; N, 7.48.

1,2,3,4,4a,5,7,8,13,13b,14,14a-Dodecahydrobenz[*g*]-1-carbethoxy-2-hydroxy-5-ketoindolo[2,3-*a*]quinolizine (18).—To a solution of 0.50 g (1.32 × 10⁻³ mol) of the keto lactam adduct 16 in 250 ml of absolute ethanol was added 50 mg of platinum oxide. The mixture was placed in a Parr hydrogenator, flushed with hydrogen four times, and shaken under 55 lb of pressure at room temperature for 12 hr. After filtration, the filtrate was concentrated on a Rotovap and the crude solid was then dissolved in hot methanol, treated with Darco, filtered, and allowed to crystallize. There was obtained 0.10 g (20.5%) of the tetrahydro adduct 18 as white rhomboid needles: mp 228–231° dec; ir (KBr) 3290 (indole NH), 1722 (ester C=O), 1610 cm⁻¹ (lactam C=O); uv max 224 mμ (ε 40.000), 273 (8000), 283 (8700), 289 (6900); nmr (C₂D₆SO) δ 0.8 (t, 2), 1.54 (t, 3), 2.77 (d, 3), 3.68 (s, 3), 4.75 (s, 2), 7.05 (t, 1), 7.3 (m, 1); mass spectrum *m/e* 382, 364, 335, 291, 186, 170, 169, 144, 91, 55, 18.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.96; H, 6.75; N, 7.41.

1,2,3,4,4a,5,7,8,13,13b,14,14a-Dodecabenz[*g*]-1-carbethoxy-2,5-diketoindolo[2,3-*a*]quinolizine (19).—To 0.1 g (5.2 × 10⁻⁴ mol) of 18 was added 0.5 g (0.0024 mol) of *N*,*N*'-dicyclohexylcarbodiimide, 0.12 g (0.0012 mol) of crystalline orthophosphoric acid, and 0.3 ml of dimethyl sulfoxide, and the mixture was stirred for 24 hr at room temperature. To the orange-tan mixture was then added 5 ml of methanol–water (3:2) and stirring was continued for an additional 0.5 hr. The resulting slurry was filtered and the filter cake was washed with 5 ml more of the methanol–water solution. The filtrate was diluted with 40 ml of ice–water, made basic with aqueous ammonia, and filtered. The resulting filter cake was washed with water, dried, dissolved in hot methanol, treated with Darco, filtered, and allowed to crystallize to yield 0.035 g (34.1%) of the keto ester of the dihydro adduct 19 as white needles: mp 139–142°; ir (KBr) 3290 (indole NH), 1617 cm⁻¹ (ester ketone, lactam C=O, C=C).

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36. Found: C, 69.32; H, 6.42.

1,2,3,4,4a,5,7,8,13,13b,14,14a-Dodecabenz[*g*]-1-hydroxymethyl-2-hydroxy[2,3-*a*]quinolizine (21).—21 was obtained by the following precedure.

A solution of 0.1 g (2.62 × 10⁻⁴ mol) of tetrahydro adduct 18 in 15 ml of purified tetrahydrofuran was added dropwise to a stirred mixture of 0.1 g (0.004 mol) of LiAlH₄ in 25 ml of tetrahydrofuran under a nitrogen bed. The mixture, which turned pea-green, was refluxed for 1 hr, cooled, cautiously treated with 5 ml of water–tetrahydrofuran, and then refluxed for an additional 0.5 hr. It was then filtered hot through a Celite bed to give a filtrate which was dried (Na₂SO₄) and concentrated on a Rotovap. The crude solid residue was dissolved in hot ethanol, treated with Darco, filtered, and allowed to crystallize to give 0.061 g (71.5%) of the pentacyclic diol 21 as white crystals: mp 189–191° dec; ir (KBr) 3280 (indole NH), 2805 and 2755 cm⁻¹ (Bohlmann[24] bands); uv max 224 mμ (ε 33,000), 275 (7100), 283 (7500), 289 (6100).

Anal. Calcd for $C_{20}H_{26}N_2O_2$·³/₄EtOH: C, 71.54; H, 8.52; N, 7.76. Found: C, 71.42; H, 8.51; N, 7.77.

Registry No.—3, 32296-83-6; 3 phenylhydrazone, 32296-84-7; **5**, 32296-85-8; 5 2,4-DNP, 32296-86-9; 6b, 32296-87-0; 7, 32296-88-1; 8a, 32296-89-2; 8b, 32367-46-7; 10, 32296-90-5; 12, 32296-91-6; 13, 32296-92-7; 14, 32296-93-8; 16, 32296-94-9; 18, 32296-95-0; 19, 32296-96-1; 21, 32296-97-2; *N*-[β-(3-indolyl)ethyl]-β-ethylenedioxyglutaramic acid, 32296-

98-3; *N*-[β-(3-indolylethyl)]-β-ethylenedioxyglutar-imide, 32367-47-8.

The Condensation of Aldehydes and Ketones with Dipeptides[1]

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The interaction of simple peptides and carbonyl compounds has been investigated and found to be a fairly general reaction in weakly alkaline media. The reaction appears to be reversible and the most stable products have been obtained using alicyclic and acyclic ketones and acyclic aldehydes. In the present work, the sodium salts of several dipeptides were treated with ketones or aldehydes in refluxing methanolic or aqueous solutions. The products were shown to be imidazolidinyl peptides. This is apparently the first general investigation of what appears to be a common reaction of peptides.

The condensations of aldehydes and ketones with substances containing both amide and amine functional groups have been reported in the literature. The products of these reactions are generally heterocyclic compounds which have both the amide and amine nitrogen atoms in the new ring system.

Davis and Levy[2] described the condensation of acetone with the α-phenylglycine amide (1) to yield an oxazolidine 2, which rearranged, after treatment with pyridine, to a 4-imidazolidinone 3. Similarly, other
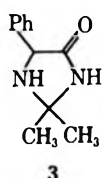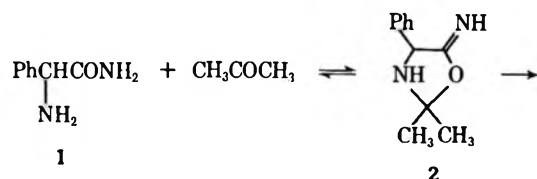
workers[3] found that isobutyraldehyde, benzaldehyde, and cyclohexanone reacted with the amides of carbobenzoxyamino acids 4 in the presence of a sulfonic acid catalyst to afford 1-carbobenzoxy-4-imidazolidinones 5 and other products. Primary and secondary amides
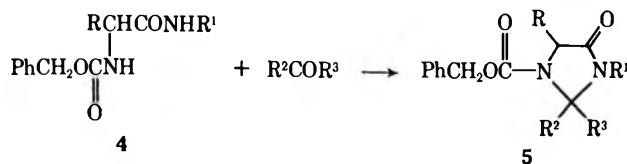
of 2-aminobenzoic acids 6 undergo the same type of condensation reaction with aldehydes[4] and ketones.[5] 1,2,3,4-Tetrahydro-4-quinazolones 8 were obtained after isomerization of the initially formed imine 7. An

imidazolidinone known as hetacillin (10) has been reported in other work.[6] It was prepared by the action of acetone on the commercially important penicillin,
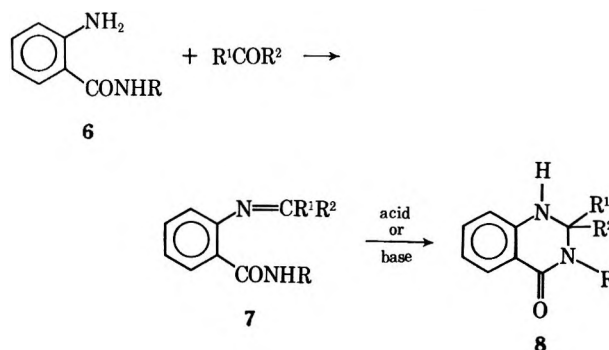
ampicillin (9), in a weakly basic aqueous medium. Aldehydes and other ketones were also successfully condensed with 9.
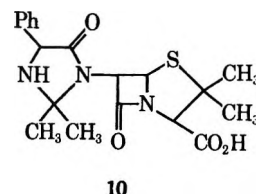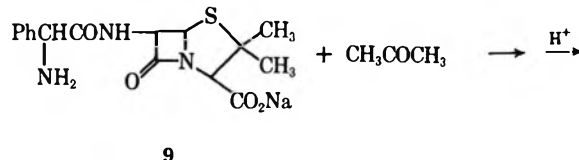
The reaction of formaldehyde with proteins and peptides has been reviewed[7] and the formation of 4-imidazolidinone derivatives was postulated in some of the cases. Aside from this work, however, there has been no systematic and thorough study of the interaction of carbonyl compounds with peptides.

In this paper, we report on what appears to be a general condensation reaction of aldehydes and ketones with a variety of dipeptides. The reaction is appar-

(1) Presented at the Joint Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970.

(2) A. C. Davis and A. L. Levy, *J. Chem. Soc.*, 3479 (1951).

(3) U. Zehavi and D. Ben-Ishai, *J. Org. Chem.*, **26**, 1097 (1961).

(4) T. A. K. Smith and H. Stephen. *Tetrahedron*, **1**, 38 (1957).

(5) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 777 (1971).

(6) G. A. Hardcastle, Jr., D. A. Johnson, and C. A. Panetta, *ibid.*, **31**, 897 (1966).

(7) D. French and J. T. Edsall, *Advan. Protein Chem.*, **2**, 277 (1945).

TABLE I

IMIDAZOLIDINYL PEPTIDES 12

Dipeptide sodium salt 11	Carbonyl compd	Registry no.	R₁	R₂	R₃	R₄	Mp, °C	Infrared^c carbonyl absorption frequency,^{a} —cm⁻¹—		Calcd, %^{b} C	H	N	Found, %^{b} C	H	N
Diglycine	Acetone	32380-90-8	H	H	CH₃	CH₃	120–125	1675	1601	43.29	5.67	14.43	43.16	5.78	14.28
Glycyl-DL-phenyl-alanine	Acetone	32380-96-4	H	bz	CH₃	CH₃	175–180	1670	1605	59.15	5.98	9.86	58.95	6.15	10.02
L-Leucylglycine	Acetone	32319-33-8	i-Bu	H	CH₃	CH₃	85–90	1670	1601	52.80	7.60	11.20	52.95	7.73	11.11
DL-Alanylglycine	Acetone	32319-34-9	CH₃	H	CH₃	CH₃	150–155	1675	1602	46.15	6.25	13.46	46.28	6.41	13.32
Diglycine	Cyclohexanone	32380-97-5	H	H	–(CH₂)₅–		210–215	1660	1610	51.20	6.45	11.95	51.14	6.39	11.84
Diglycine	Isobutyralde-hyde	32319-35-0	H	H	i-Bu	H	195–200	1675	1602	44.15^d	6.45^d	12.90^d	44.51	6.45	12.46
Diglycine	Cyclopentanone	32319-36-1	H	H	–(CH₂)₄–		162–167	1675	1610	46.60^e	6.22^e	12.10^e	46.65	5.92	12.40

^{a} All products show no amide II band in region 1525–1565 cm⁻¹. ^{b} Microanalyses were performed by Alfred Bernhardt, 5251 Elbach, Germany. ^{c} Infrared spectra were prepared using Nujol mull. ^{d} Calculations based on the hemihydrate of the imidazolidinyl peptide. ^{e} Calculation based on the two-thirds hydrate of the imidazolidinyl peptide.

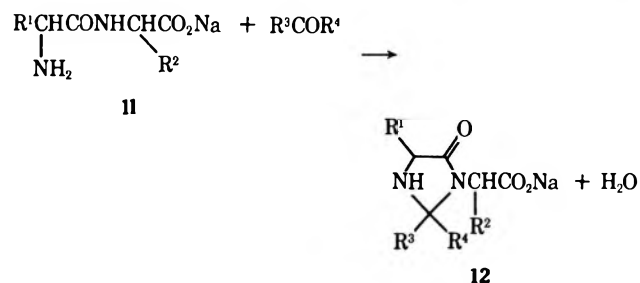ently reversible and the products are 4-imidazolidinones according to elemental analysis, spectral properties, and comparison with products obtained in previous and related work (some of which is cited above).

Alkali metal salts of several dipeptides 11 were

R¹CHCONHCHCO₂Na + R³COR⁴ ⟶
| |
NH₂ R²

11

12

treated with carbonyl compounds in methanolic or aqueous solution. The salt was probably necessary in order to keep the concentration of the zwitterionic form of the dipeptide as low as possible. This postulation was supported by the observation that little or no condensation occurred when the reaction was attempted in weakly alkaline solution.

The reactivity of the carbonyl compounds used in this condensation reaction varied greatly depending on certain structural features of these reagents. For example, acetaldehyde reacted exothermically and almost violently with diglycine (11, R¹, R² = H) to yield a very complex reaction mixture that resisted attempts to separate it into its components. Acetone, cyclopentanone, cyclohexanone, and isobutyraldehyde condensed readily with several dipeptides to afford stable and characterizable imidazolidinyl peptides 12. Benzaldehyde, p-nitrobenzaldehyde, and acetophenone were reactive toward diglycine but the products were labile and easily reverted to the starting materials when attempts were made to isolate and identify them. Fluorenone and camphor did not react with diglycine at any observable rate.

The nature of the groups R¹ and R² in the dipeptide 11 also show a marked influence on the rate of the condensation reaction. If R¹ was smaller in size than R² [DL-alanyl-DL-phenylalanine (11, R¹ = CH₃; R² = PhCH₂); glycyl-L-leucine (11, R¹ = H; R² = (CH₃)₂CHCH₂); and glycyl-DL-alanine (11, R¹ = H; R² = CH₃)], the reaction resulted in a complex mixture and the products were unstable and/or not easily isolated. An exception to this was glycyl-DL-phenylalanine (11, R¹ = H; R² = PhCH₂), which produced a stable

imidazolidinyl peptide with acetone (see Table I). On the other hand, if R¹ was the same size as, or larger in size than R² [diglycine (11, R¹, R² = H); L-leucylglycine (11, R¹ = (CH₃)₂CHCH₂; R² = H); DL-alanylglycine (11, R¹ = CH₃; R² = H)], the reaction mixture contained essentially one product which was usually, but not always, easy to isolate and purify. DL-Phenylalanyl-DL-alanine (11, R¹ = PhCH₂; R² = CH₃) was an exception to this rule. This was not completely unexpected since it is a mixture of diastereoisomers. These results appear to indicate the bulky R² groups offer steric hindrance to the formation of a bond with the amide nitrogen atom and thus prevent the formation of stable cyclic products. Alternatively, large R¹ groups facilitate the cyclization process.[8]

Table I lists all of the condensation products that were stable enough to be isolated in pure form and characterized. The imidazolidinone ring structure was supported mainly by infrared spectra. All of the compounds showed a carbonyl stretching band for a cyclic tertiary amide (amide I band) at about 1675 cm⁻¹. This frequency was in agreement with that (1695 cm⁻¹) reported for the γ-lactam carbonyl stretching band of the potassium salt of hetacillin (10).[6] The carbonyl stretching absorption for the carboxylate group appeared at about 1605 cm⁻¹ (1620, 1610 cm⁻¹ in the potassium salt of hetacillin[6]) and the amide II band[9] (amide NH deformation), which was a strong band found between 1525 and 1565 cm⁻¹ in the spectra of the dipeptide starting materials 11, was significantly absent in those of the products 12.

The nmr spectra of the imidazolidinyl peptides 12, were prepared and were in agreement with the types and numbers of protons found in the proposed structures. Unlike the infrared data, however, the nmr information could not be used to exclude the possibility that the products had the Schiffs base (imine) structure.

The present research has uncovered a new class of group-specific reagents for use in peptide and, possibly, in protein chemistry. These reagents are simple aldehydes (isobutyraldehyde) and ketones (acetone, cyclopentanone, cyclohexanone) and the group for which they are specific is the α-aminoamide moiety found in almost all peptides and proteins. Group-specific rea-

(8) For a review of the literature concerning the beneficial effect of alkyl substituents on the ease of ring closure, see B. Capon, *Quart. Rev. Chem. Soc.*, **18**, 109 (1964).

(9) L. J. Bellamy "Advances in Infrared Group Frequencies," Methuen and Co., 1968, pp 285, 287.

gents have been chiefly responsible for the elucidation of structure-activity correlations in proteins.

Continuing work on this project is concerned with the stereochemistry of the products 12 which have been prepared from optically active carbonyl compounds and dipeptides 11.

Experimental Section[10]

General Procedure for the Preparation of Imidazolidinyl Peptides (12).—This procedure was used for the preparation of all of the imidazolidinyl peptides listed in Table I except that prepared from diglycine and cyclopentanone. The dipeptide free acid (10.0 mmol) was dissolved (or suspended) in a small amount of water and the resultant mixture was treated with 10 ml of 1 N NaOH. The aqueous solvent was removed by distillation under reduced pressure and the residual solid (dipeptide sodium salt, 11) was found to be homogeneous by thin layer chromatography (the R_f of 11 was always greater than that of the dipeptide-free acid). The dipeptide sodium salt 11 (10.0 mmol) was dissolved in about 30 ml of methanol. The resultant solution was then treated with 20–25 mmol of the appropriate aldehyde or ketone and this was followed by heating of the reaction mixture to the reflux temperature for 3 hr. Thin layer chromatographic inspection indicated that an equilibrium between the reactants and the products was established during this time period and that further heating beyond 3 hr did not increase the yield of the products (usually two new tlc zones were observed with larger R_f values than those of the reactants). The reaction mixture (now light yellow to dark brown) was concentrated by distillation under reduced pressure until all of the solvent was removed. The oily residue was then dissolved in a minimum amount of

MeOH–EtOAc or MeOH–acetone (both 50:50) and this solution was placed on a column of silica gel (E. Merck, 70–375 mesh). The column was eluted with the same solvent that was used to dissolve the oily residue. The w/w ratio of adsorbent to sample was about 66 to 1. The column fractions were collected and combined according to their thin layer chromatograms. Usually the original oily reaction product which was placed on the column was separated into two homogeneous products, one of which was obtained in a much greater yield than the other. The foregoing manipulations were performed as quickly as possible in order to avoid undue decomposition which was known to occur spontaneously with some of the products. The major product eluted from the column was usually an oil. It was stored in a desiccator (hygroscopic) for several hours, during which time it usually crystallized. Recrystallization was accomplished from a mixture of methanol and petroleum ether (bp 30–60°). Infrared, elemental analysis, and melting point data for the products are listed in Table I. Accurate calculations of yields were made in the experiments involving diglycine–isobutyraldehyde (57.5%), diglycine–cyclohexanone (36.0%), and diglycine–acetone (40.2%). The yields of products from the other experiments were estimated to be in the same range.

Condensation of Diglycine and Cyclopentanone. Preparation of an Imidazolidinyl Peptide in an Aqueous Medium.—Diglycine (10.0 mmol) and an equimolar amount of CH_3ONa were mixed and stirred in a small amount of dry methanol for a few minutes. The methanol was removed under reduced pressure and the residual solid (11, R^1, R^2 = H) was homogeneous according to tlc. This diglycine sodium salt and 10.0 mmol of cyclopentanone were added to 15 ml of distilled water and the resultant mixture was stirred at room temperature for 24 hr. After this time, the brownish-red product was isolated, chromatographed, crystallized, and recrystallized exactly as described in the general procedure. The physical constants for this product are listed in Table I. The estimated yield was similar to the yields obtained in the general procedure.

(10) Thin layer chromatograms of the reactions mixtures were run on 20 × 20 cm glass plates coated with a 250-μ thick layer of silica gel (Camag DF-5). Spotting was performed using 2 μl of a 1% solution and the developing solvent system was one of the following: methylene chloride–methanol (70–30 or 50–50) or ethyl acetate–methanol (50–50). The eluted zones were detected as colored areas after spraying with a 0.3% solution of ninhydrin in 1-butanol-2,4,6-collidine (95–5) followed by heating.

Reactions of 7-*tert*-Butylnorbornadiene. Synthesis of syn- and anti-7-*tert*-Butylnorbornenes[1]

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7-*tert*-Butylnorbornadiene was synthesized from the corresponding 7-*tert*-butoxy compound and *tert*-butyllithium. Hydroboration and oxymercuration of the *tert*-butyldiene occurred exclusively with the sterically unencumbered anti double bond *via* exo,cis addition. Diimide reduction and catalytic hydrogenation occurred preferentially with the anti double bond even though both exo,cis and endo,cis additions were involved. The study of these various reactions has provided synthetic routes from the *tert*-butyl diene to the isomeric syn- and anti-7-*tert*-butylnorbornenes. The chemistry of 7-*tert*-butylnorbornadiene has been contrasted with that of norbornadienes substituted in the 7 position with an oxygen radical.

Previous papers from these and other laboratories have illustrated the preference of norbornadienes and norbornenes substituted in the 7 position with an oxygen-bearing substituent to experience electrophilic addition to the syn double bond[2-7] (eq 1). This preference has been ascribed to "chelation" of the entering electrophile by the syn double bond and the 7 sub-

stituent, which stabilizes the transition state.[3-5] In this way, the potentially adverse steric inhibition presented by the syn-7 substituents was overcome by this electronic effect.

The proposition was subsequently advanced that, in reactions where this electronic effect was nonoperative, steric factors would become dominant.[4] Catalytic hydrogenation of the syn and anti isomers was shown to be controlled by steric parameters ($k_{anti} \gg k_{syn}$); similar reduction of the norbornadiene derivatives was less sensitive to steric control and was influenced primarily by coordination control.[8,9]

(1) Presented in part at the 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, Abstract PETR 103.

(2) B. Franzus and E. I. Snyder, *J. Amer. Chem. Soc.*, **87**, 3423 (1965).

(3) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *ibid.*, **89**, 410 (1967).

(4) B. Franzus, W. C. Baird, Jr., E. I. Snyder, and J. H. Surridge, *J. Org. Chem.*, **32**, 2845 (1967).

(5) W. C. Baird, Jr. and M. Buza, *ibid.*, **33**, 4105 (1968).

(6) G. W. Klumpp, A. H. Veefkind, W. L. de Graff, and F. Bickelhaupt, *Justus Liebigs Ann. Chem.*, **706**, 47 (1967).

(7) J. Haywood-Farmer, R. E. Pincock, and J. I. Wells, *Tetrahedron*, **22**, 2007 (1966).

(8) B. Franzus, W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **33**, 1288 (1968).

(9) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *ibid.*, **34**, 2944 (1969).

Scheme (eq 1):

X—[norbornadiene] →(AB)→ A,B—[addition product]

X = OH, OOCCH$_3$, OC(CH$_3$)$_3$

syn —(AB)→ $k_{syn} > k_{anti}$

anti

(1)
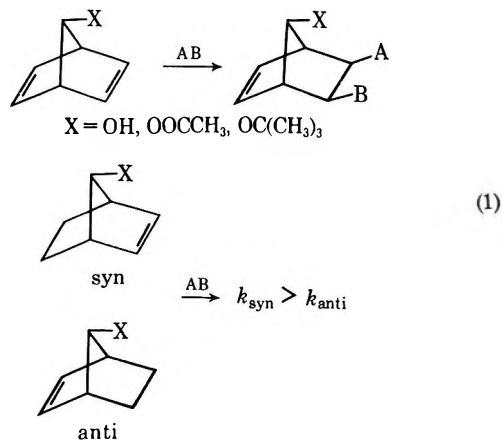
Against this background an investigation of the reactions of norbornenes and norbornadiene substituted in the 7 position by a group that possessed a large steric requirement but no polar functionality was undertaken. This study was made possible by the availability of 7-tert-butylnorbornadiene[10] and by the development of synthetic routes to syn- and anti-7-tert-butylnorbornenes. This paper describes these syntheses and the various addition reactions of 7-tert-butylnorbornadiene that led to them. A subsequent paper will discuss the chemistry of the isomeric tert-butylnorbornenes.

Results and Discussion

7-tert-Butylnorbornadiene (1) was synthesized from 7-tert-butoxynorbornadiene and tert-butyllithium according to the procedure described by Wittig and Otten;[10] isolated yields ranged from 50 to 60%. The nmr spectrum of 1 (Table I) exhibited two features requiring comment. In contrast to other 7-substituted norbornadienes, both the syn (δ 6.34) and the anti (δ 6.80) vinyl hydrogens appeared as triplets; i.e., the syn vinyl protons were not split by the anti-7 hydrogen as had been previously observed.[11] Since this long-range coupling was also absent in the spectrum of syn-7-tert-butylnorbornene (2), it was concluded that this criterion for configurational assignment of the 7 substituent with respect to the double bonds is not applicable to the 7-tert-butyl compounds. Secondly, the syn vinyl protons of 1 experienced a 24-Hz diamagnetic shift relative to the vinyl resonance of norbornadiene compared to an average shift of ~10 Hz for other 7-substituted norbornadienes.[10,11] The chemical shift difference between the syn and anti vinyl hydrogens of 1 was 27.6 Hz compared to an average value of 6 Hz. These spectral data clearly indicated that the 7-tert-butyl diene possessed unique structural features.

Catalytic hydrogenation, demonstrated previously to be sensitive to steric factors,[4,8,9] seemed a reasonable approach to the synthesis of syn-7-tert-butylnorbornene (2). Hydrogenation of 7-tert-butylnorbornadiene (1) proceeded as illustrated in Scheme I; product distribution as a function of catalyst is summarized in Table II. Unlike hydrogenation of the previously studied norbornadienes, reduction of the 7-tert-butyl compound yielded syn-7-tert-butylnorbornene (2) as the exclusive olefinic product. No anti isomer (3) was detected (within the limits of vpc analysis) at any time during

(10) G. Wittig and J. Otten, Tetrahedron Lett., 601 (1963).
(11) E. I. Snyder and B. Franzus, J. Amer. Chem. Soc., 86, 1166 (1964).

TABLE I
NMR SPECTRA OF 7-tert-BUTYL COMPOUNDS

Compd	Proton type, δ (pattern, relative area, [J])						% exo,cis addition	% endo,cis addition
	HC=CH	CH	Exo >C<H/H	HC-tert-Bu	Endo >C<H/H	(CH$_3$)$_3$C		
7-tert-Butylnorbornadiene (1)[a]	Anti 6.80 (t, 2 [5]), Syn 6.34 (t, 2 [5])	3.40 (m, 2)		2.48 (m, 1)		0.80 (s, 9)		
syn-7-tert-Butylnorbornene[a] (2)	5.66 (t, 2 [5])	2.68 (m, 2)	1.46–1.72 (m, 2)	1.39 (m, 1)	0.82–1.00 (m, 2)	0.78 (s, 9)		
anti-7-tert-Butylnorbornene (3)	6.10 (t, 2 [5])	2.71 (m, 2)	1.61–1.90 (m, 2)	1.38 (m, 1)	0.93–1.08 (m, 2)	0.88 (s, 9)		
7-tert-Butylnorbornane (4)		2.06 (m, 2)	1.36–1.90 (m, 4)	1.26 (m, 1)	1.00–1.20 (m, 4)	0.92 (s, 9)	40	60
3-tert-Butylnortricyclane (5)		1.80 (m, 1)	1.52–1.62 (m, 1)	1.14–1.24 (m, 5)[b]	0.95–1.04 (m, 2)	0.86 (s, 9)	60[c]	40[c]
5,6-Dideuterio-syn-7-tert-butyl-norbornene (6)	5.75 (t, 2)	2.72 (m, 2)	1.63 (m, 1.2), (m, 0.8)[c]	1.41 (m, 1)	0.89 (m, 0.8), (m, 1.2)[c]	0.80 (s, 9)	30	70
2,3,5,6-Tetradeuterio-7-tert-butylnorbornane (7)		2.07 (m, 2)	1.40–1.76 (m, 2.8), 1.68 (m, 1.4)[c]	1.26 (m, 1)	1.06 (m, 1.2)	0.93 (s, 9)	65[c]	35[c]
5,7-Dideuterio-3-tert-butyl-nortricyclane (8)		1.80 (m, 1)	1.55 (m, 1)	1.00–1.22 (m, 5)[b]	1.04–1.14 (m, 2.6)[c]	0.87 (s, 9)	0	100

[a] Nmr on neat samples; all others in CDCl$_3$. [b] exo >CH$_2$ (1), HC-tert-Bu (1), cyclopropyl H's (3). [c] Values from diimide reduction.

SCHEME I

REACTIONS OF 7-*tert*-BUTYLNORBORNADIENE

bornadiene also failed to produce any anti isomer, thereby providing additional evidence for the absence of this potential reduction product.

Homoconjugative hydrogenation of 7-*tert*-butylnorbornadiene (1) produced 3-*tert*-butylnortricyclane (5) in amounts ranging from ~10% over platinum and nonprereduced palladium catalysts to ~30% over prereduced palladium. These yields and catalyst sensitivities were comparable to those observed for nortricyclene formation during the reduction of 7-acetoxy- and 7-*tert*-butoxynorbornadiene.[9] Such homoconjugative reduction is most reasonably ascribed to endocyclic catalyst–diene complexation followed by hydrogen transfer through a π-homoallylic metal–olefin complex.[14-16]

The stereochemistry of the hydrogenation of 7-*tert*-butylnorbornadiene (1) was assessed by utilizing deuterium as the reducing gas. The course of deuterium addition is summarized by eq 2, where the values in

$$(2)$$

		% D₂ distribution	
	6	7	8
exo,cis	40 (72)	30 (60)	
endo,cis	60 (28)	70 (40)	100 (100)

TABLE II

HYDROGENATION OF 7-*tert*-BUTYLNORBORNADIENE

	Product composition, %				
Catalyst	Diene 1	Syn 2	Satd 4	Nortricyclane 5	Method
Pd/C	17	57	14	12	*a*
HPd/C	33	38	7	22	*a, b*
HPd/C	3	91	0	7	*a, b, c*
Pd/C	0	0	88	12	*d*
HPd/C	0	0	72	28	*e*
PtO₂	21	58	18	2	*a*

a Gas buret, H₂ consumption, 50–60% of theory. *b* Prereduced catalyst. *c* Norbornadiene present. *d* Parr hydrogenator, 30 psig, 100% reaction. *e* Brown hydrogenator, prereduced catalyst, 100% reaction.
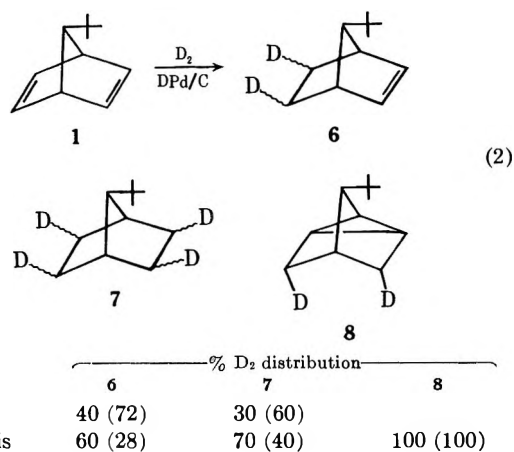
the reaction, a reflection of remarkable selectivity for the sterically unhindered anti double bond of the diene. The failure to observe any anti isomer cannot be ascribed to its rapid reduction to 7-*tert*-butylnorbornane (4). The competitive rates of reduction of *syn-* and *anti*-7-*tert*-butylnorbornenes, $k_{anti}/k_{syn} \cong 9.6$, are too close to permit total destruction of any initially formed anti isomer by this process.[12,13]

The production of *syn*-7-*tert*-butylnorbornene (2) by hydrogenation was maximized by the addition of norbornadiene, or norbornene, to the reaction (Table II, line 3).[8,9] The relative rates of reduction of norbornene and 2 (~40:1) completely suppressed the hydrogenation of the latter to saturated product 4. The synthesis of *syn*-7-*tert*-butylnorbornene by this procedure has provided isolated yields of 60–70%. Hydrogenation of the *tert*-butyl diene 1 in the presence of nor-

parentheses are for corresponding 7-acetoxy compounds.[9] The direction of deuterium addition was determined by nmr analysis (Table I).[17] Inspection of this comparative data has shown that this reduction has involved predominantly endo,cis addition. The results represent a departure from those obtained from the 7-acetoxy derivatives in that the roles of steric and coordination control have been reversed. The high level of endo,cis reduction of the anti olefinic bond of 1 was indicative of endocyclic coordination of this site with the catalyst. The preference of the anti bond for endo reduction is believed to reflect the development of structural strain in the exocyclic catalyst complex; the source of such strain may be bond angle deformation, or nonbonded interaction between the 7-*tert*-butyl group and the syn π orbitals. In view of this degree of endo reduction it was particularly significant that no endo,cis addition to the syn bond of the diene 1 to give *anti*-7-*tert*-butylnorbornene occurred. The failure to observe anti product is attributed to the desire to avoid steric repulsion between the *tert*-butyl group and the exo,cis 5,6 hydrogens generated by endocyclic reduction of the syn double bond.

The reduction of *syn*-7-*tert*-butylnorbornene (6) to tetradeuterated norbornane (7) was clearly sterically

(12) Anti product was present in cases where $k_{anti}/k_{syn} \cong 17$. See ref 9.

(13) For comparison, when the 7 substituent was methyl, $k_{anti}/k_{syn} \cong 2$: V. A. Mironov, B. D. Polkovinkov, E. P. Mikos, T. M. Fadeeva, and A. A. Akhrem, *Izv. Akad. Nauk SSSR, Ser. Khim. Nauk*, 118 (1970).

(14) D. R. Coulson, *J. Amer. Chem. Soc.*, **91**, 200 (1969).

(15) M. Green and R. I. Hancock, *J. Chem. Soc. A*, 2054 (1967).

(16) H. A. Quinn, M. A. McKervey, W. R. Jackson, and J. J. Rooney, *J. Amer. Chem. Soc.*, **92**, 2922 (1970).

(17) For pertinent background, see ref 9, footnotes 12–15.

controlled and gave 80% endo,cis deuteration. The comparable reaction in the 7-acetate series occurred with 60% exo,cis addition.[9] In both cases the formation of the nortricyclic derivative was totally endocyclic.

Since the parent olefin, norbornadiene, did not experience either endocyclic or homoconjugative hydrogenation,[9] the presence of a 7 substituent must be a necessary condition for these reactions. A rationale for this behavior is suggested by eq 3, where the reacting system is considered to comprise equilibria between two isomeric exocyclic complexes and an endocyclic complex. In the case of norbornadiene (X = H), k_1 and $k_2 \gg k_3$, and homoconjugative and endocyclic reduction are not competitive. When X is acetoxy,

$$X = H, OOCCH_3, OC(CH_3)_3, (CH_3)_3C$$
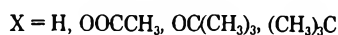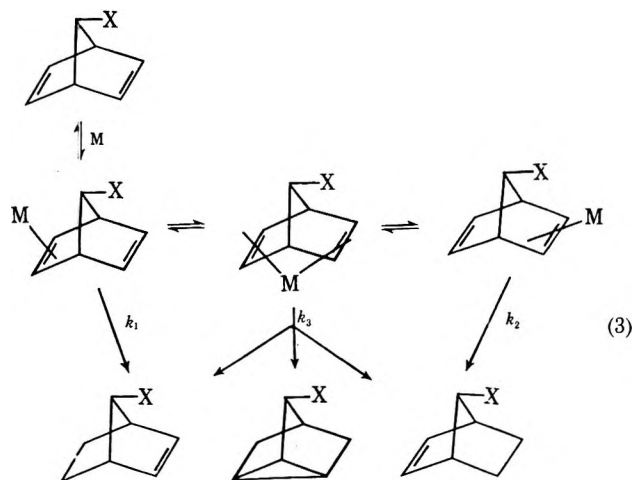
tert-butoxy, or *tert*-butyl, this kinetic relationship is altered to the extent that k_3 becomes competitive and even dominant. The effect of the 7-oxy radicals on this situation may be ascribed to steric hindrance to reaction of the syn double bond and deactivation of the anti double bond through electron delocalization.[4,5] For 7-*tert*-butylnorbornadiene and other 7-alkyl derivatives,[13,18] steric shielding of the syn bond is obviously important; the influence of the 7-*tert*-butyl group on the reactivity of the anti bond cannot be ascribed to delocalization and must involve the strain factors cited above.

The reduction of 7-*tert*-butylnorbornadiene (1) to *syn*-7-*tert*-butylnorbornene (2) in 84% selectivity was accomplished with the chemical reducing agent diimide (Scheme I). While this high degree of selectivity was in accord with the sensitivity of diimide reduction to steric approach control,[19] the formation of *anti*-7-*tert*-butylnorbornene (3) and 7-*tert*-butylnorbornane (4) as by-products was totally unexpected. Control experiments showed that, although the syn olefin 2 was passive to diimide, the anti isomer 3 was reduced to 7-*tert*-butylnorbornane (4).

In order to study this reaction in detail the reduction was carried out using dideuteriodiimide;[3] eq 4 illustrates the results. The observed level of endo,cis reduction was without precedent and represented a

| | % D₂ distribution | | |
	6	9	7
exo,cis	60	30	65
endo,cis	40	70	35
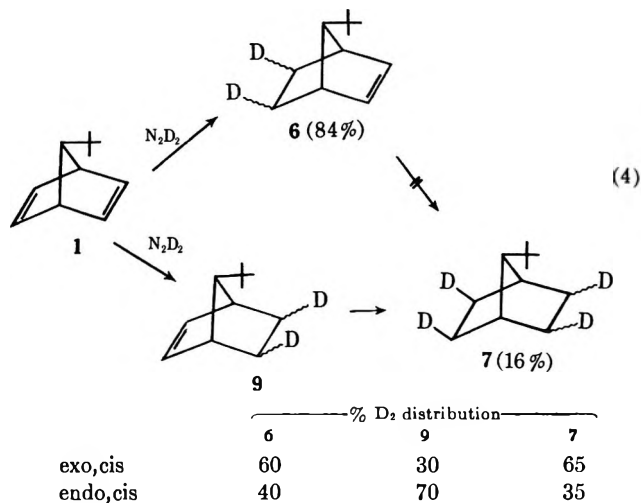
complete departure from normal diimide reactions. The deuterium distribution in **6** has shown that the reduction of the *tert*-butyl diene has involved endocyclic diimide attack in addition to the anticipated exocyclic reaction. While **6** was not the precursor of **7**, it has been demonstrated that this endocyclic reaction produced *anti*-7-*tert*-butylnorbornene, which was subsequently rapidly reduced to saturated product.[20] Control experiments have shown that the anti isomer is reduced with 100% exo,cis addition (eq 4). This fact, coupled with the overall deuterium distribution found in tetradeuterio-7-*tert*-butylnorbornane (**7**), has indicated that the formation of dideuterio-*anti*-7-*tert*-butylnornornene (**9**) has involved both endocyclic (70%) and exocyclic (30%) reduction of the syn double bond of the diene.

The failure of *syn*-7-*tert*-butylnorbornene (**2**) to yield 7-*tert*-butylnorbornane (**4**) is ascribed to the hindrance to exo attack by the *tert*-butyl group and to endo attack by the endo 5,6 hydrogens. That the syn double bond of the diene **1** did experience a small degree of exocyclic reduction (5% of the total reaction) is believed to reflect a more favorable geometric disposition between the *tert*-butyl group and the six-membered cyclic transition state involved in diimide reductions.[21,22]

Since direct conversion of 7-*tert*-butylnorbornadiene (**1**) to *anti*-7-*tert*-butylnorbornene (**3**) by chemical or catalytic reduction was clearly not feasible, the reaction sequence shown in Scheme I was selected as a route to this olefin. Oxymercuration of norbornenes and norbornadienes had been shown to occur exo,cis, to be free of rearrangements, and to occur on the less hindered side of the molecule;[23] consequently, oxymercuration appeared to provide a useful synthesis of *exo*-5-hydroxy-*syn*-7-*tert*-butylnorbornene-2 (**11**). While nmr experiments[24] confirmed that the oxymercuration reaction had occurred exo,cis with the anti double bond of the *tert*-butyl diene, borohydride reduction of the

(18) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 201 (1970).

(19) For reviews on the chemistry of diimide, see (a) C. E. Miller, *J. Chem. Educ.*, **42**, 254 (1965); (b) S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem., Int. Ed. Engl.*, **4**, 271 (1965); (c) F. Aylward and M. Sawistowska *Chem. Ind. (London)*, 484 (1962).

(20) Such a sequence has been observed in the 7-acetoxy series.[3]

(21) E. J. Corey, W. L. Mock, and D. J. Pasto, *J. Amer. Chem. Soc.*, **83**, 2957 (1961).

(22) Diimide reduction of 7,7-dimethylnorbornene also gave exo,cis addition: H. C. Brown, J. H. Kawakami, and K.-T. Liu, unpublished results. The authors thank Professor Brown for a preprint of these data.

(23) (a) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967); (b) H. C. Brown and W. J. Hammar, *ibid.*, **89**, 1524 (1967); (c) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **89**, 1525 (1967); (d) T. G. Traylor and A. W. Baker, *ibid.*, **85**, 2746 (1963).

(24) H. C. Brown, M.-H. Rei, and K.-T. Liu, *ibid.*, **92**, 1760 (1970).

organomercurial[23a] did not yield any of the desired alcohol (**11**). The reaction had proceeded as shown by eq 5 to give an 80% yield of *endo-5-tert*-butyl-*anti*-7-

X = H or Ac
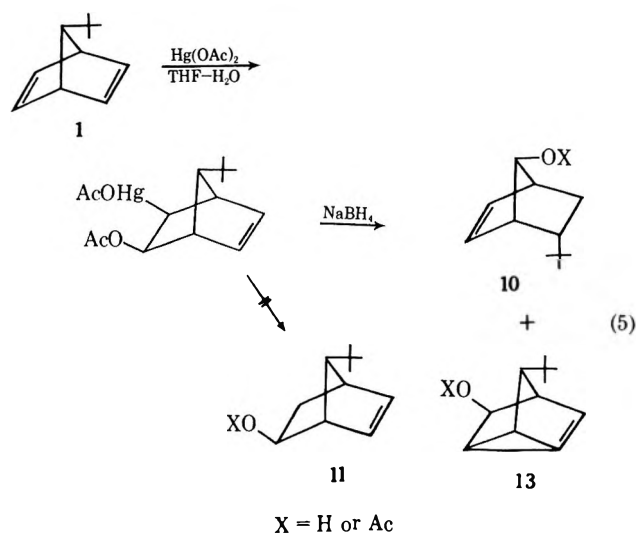
hydroxynorbornene-2 (**10**), a product of the now well-established radical rearrangement encountered in the borohydride reduction of such norbornenyl mercurials.[25] A 12% yield of by-product was also formed, which has been arbitrarily assigned the nortricyclic structure **13**; a sample of sufficient purity to permit accurate identification could not be obtained, but the formation of **13** would be consistent with known chemistry.[5,25,26] The exclusion of **11** from the product mixture and the sixfold dominance of **10** over **13** have not been observed in the previous studies cited. Since the products are derived from hydrogen transfer to rapidly equilibrating norbornenyl $\rightleftharpoons$ nortricyclyl radicals,[25d] it was apparent that in this case the radical precursor to **10** was the preferred thermodynamic species by virtue of being the least strained configuration.

Hydroboration of 7-*tert*-butylnorbornadiene (**1**) with 9-BBN[27] produced the desired exo 5-alcohol **11** (Scheme I) in 90% yield. Catalytic hydrogenation and tosylation gave the exo tosylate of **12** in 81% yield. Attempts to induce elimination with potassium *tert*-butoxide in dimethyl sulfoxide were unsuccessful. Dehydrotosylation with the potassium salt of 2-cyclohexylcyclohexanol[28] gave a 47% yield of *anti*-7-*tert*-butylnorbornene (**3**); the overall yield from 7-*tert*-butylnorbornadiene was 34%.

In summary, synthetic routes to *syn*- and *anti*-7-*tert*-butylnorbornenes from a common precursor, 7-*tert*-butylnorbornadiene, have been realized. In general, additions to the *tert*-butyl diene have shown a marked preference for the sterically unhindered anti double bond in contrast to the syn double bond reactions experienced by 7-oxy substituted norbornadienes. Additions to the anti double bond involving cyclic transition states (hydrogenation, diimide reduction) have exhibited both exocyclic and endocyclic stereo-

chemistry, the degree of each being determined by the steric and strain demands of the reacting species. Hydroboration with 9-BBN, which also involves a cyclic mechanism, occurred only exo due to the reluctance of the system to accommodate such a bulky reagent in an endocyclic configuration. Finally, these results have reinforced the view that the principles governing the reactions of the parent olefin, norbornadiene, cannot be applied indiscriminately to those of its derivatives.[9]

Experimental Section

Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Nmr spectra were recorded on Jeol Minimar, Varian Associates A-60, and Varian Associates HA-100 spectrometers using tetramethylsilane as an internal standard. Analytical vapor phase chromatography (vpc) was performed on a Perkin-Elmer 154D fractometer and a Perkin-Elmer Model 226 capillary gas chromatograph. Preparative scale vpc was performed on a Varian Aerograph Model A-700. Melting points and boiling points are not corrected. All reagents were obtained from commercial sources and were used as received.

7-*tert*-Butylnorbornadiene (1).[10]—To a 500-ml round-bottom flask equipped with a stirrer, a thermometer, a dropping funnel, and a reflux condenser were added under nitrogen 81 ml of a 1.24 *M* solution of *tert*-butyllithium in *n*-pentane (0.1 mol)[29] and 160 ml of dry *n*-pentane. A solution of 16.4 g (0.1 mol) of 7-*tert*-butoxynorbornadiene[30] in 100 ml of dry *n*-heptane was added dropwise with stirring at −20° over a period of 2 hr. The reaction mixture was allowed to warm to room temperature. The pentane was removed by distillation, and simultaneously 100 ml of dry *n*-heptane was added. The reaction was stirred and refluxed for 2 hr. The reaction was cooled to 0° and 10 ml of isopropyl alcohol was added. The heptane solution was washed twice with 125-ml portions of water and dried over magnesium sulfate. The solvent was removed on a rotary evaporator at 40° (50 mm), and the residue was distilled through a Monel spiral Todd column to give 8.0 g (54%) of 7-*tert*-butylnorbornadiene, bp 98–100° (85 mm), n^{20}D 1.4702 (lit.[10] n^{20}D 1.4718). Vpc analysis (4 m × 0.25 in. 20% squalane column, 160°, 70 ml/min helium) gave a single peak, retention time 25 min, purity 98%.

Anal. Calcd for $C_{11}H_{16}$: C, 89.18; H, 10.82. Found: C, 89.12; H, 10.86.

The nmr spectrum is included in Table I.

Hydrogenation of 7-*tert*-Butylnorbornadiene.—Into a gas buret hydrogenation assembly were placed 8 ml of methanol and 106 mg of 10% palladium on charcoal. The catalyst was exposed to hydrogen, and a solution of 2.34 g (14.2 mmol) of 7-*tert*-butylnorbornadiene in 10 ml of methanol was injected through a septum. After ∼73% of the theoretical quantity of hydrogen had been absorbed, a 7-ml sample was withdrawn. The vpc analysis of the product is given in Table III.

TABLE III

	Retention time —(min from air)—		Per
Compd	a	b	cent
7-*tert*-Butylnorbornadiene (1)	25.0	14.2	0
syn-7-*tert*-Butylnorbornene (2)	26.5	13.7	57
3-*tert*-Butylnortricyclane (5)	35.0	16.5	29
7-*tert*-Butylnorbornane (4)	38.5	17.0	14

a 4 m × 0.25 in. 20% squalane, 160°, 70 ml/min. *b* 300 ft × 0.01 in. DC-550 silicone, 115°, 30 psig.

No *anti*-7-*tert*-butylnorbornene (**3**) was detected in an amount exceeding 1%. The syn isomer (retention time 26.5 min) was separated in >98% purity on a 12 ft × 0.375 in. 20% SE-30 silicone column at 160° and 110 ml/min and was shown to be identical with an authentic sample.

The remainder of the reaction mixture was hydrogenated to completion to give a mixture of 3-*tert*-butylnortricyclane (29%)

(25) (a) G. A. Gray and W. R. Jackson, *J. Amer. Chem. Soc.*, **91**, 6205 (1969); (b) G. M. Whitesides and J. San Filippo, Jr., *ibid.*, **92**, 6611 (1970); (c) V. M. A. Chambers, W. R. Jackson, and G. W. Young, *Chem. Commun.*, 1275 (1970); (d) G. A. Gray, W. R. Jackson, and V. M. A. Chambers, *J. Chem. Soc. C*, 200 (1971).

(26) K. Pande and S. Winstein, *Tetrahedron Lett.*, 3393 (1964).

(27) E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5200 (1968).

(28) H. C. Brown, J. H. Kawakami, and S. Misumi, *J. Org. Chem.*, **35**, 1360 (1970).

(29) Foote Mineral Co., Exton, Pa.

(30) Frinton Laboratories, Vineland, N. J.

and 7-*tert*-butylnorbornane (71%). The two hydrocarbons were separated by preparative vpc (20 ft × 0.375 in. 20% squalane column, 160°, 110 ml/min) to give samples of >98% purity. The nmr data are presented in Table I.

7-*tert*-Butylnorbornane (4) had n^{20}D 1.4650. *Anal.* Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.47; H, 13.50.

3-*tert*-Butylnortricyclane (5) had n^{20}D 1.4666. *Anal.* Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.70; H, 12.27.

The influence of various catalysts and catalyst prereduction on the hydrogenation of 7-*tert*-butylnorbornadiene was evaluated by previously described techniques.[4] Representative data are shown in Table II.

A sample of the 7-*tert*-butyl diene (1) was reduced with deuterium according to the procedure described above. The products were separated by preparative vpc to provide individual samples of the deuterated hydrocarbons 6, 7, and 8 in 98% purity. The nmr data are summarized in Table I. Analysis of the exo,endo proton areas gave a measure of the relative amounts of exo,cis and endo,cis deuterium addition;[17] these values are listed in Table I.

syn-7-*tert*-Butylnorbornene (2).—In a gas buret apparatus a mixture of 215 mg of 10% palladium on charcoal, 4.0 g (43.5 mmol) of norbornadiene, and 3.0 g (20.2 mmol) of 7-*tert*-butylnorbornadiene (1) in 50 ml of methanol was hydrogenated at ambient conditions. The hydrogenation was taken to ~70% of completion (~2.2 l. of hydrogen). In a duplicate run 2.5 g (17.0 mmol) of 1 was reduced. The combined reaction mixtures were filtered, and the filtrate was added to 250 ml of water. The hydrocarbons were extracted with pentane (three 50-ml portions), and the combined extracts were dried over magnesium sulfate. The pentane, norbornene, and norbornane were removed by distillation through a Monel spiral Todd column. The residue (3.7 g) was heated at 100°(90 mm) on the Todd assembly to sublime residual norbornane. Distillation of the residue gave 3.5 g (64%) of syn-7-*tert*-butylnorbornene, bp 102° (90 mm), n^{20}D 1.4654. Vpc analysis on a capillary column (see above) gave a product peak at 13.7 min, purity 89.5%. The nmr spectrum is presented in Table I.

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.63; H, 12.30.

Diimide Reduction of 7-*tert*-Butylnorbornadiene.—To a stirred solution of 2.0 g (13.5 mmol) of 7-*tert*-butylnorbornadiene (1) and 2.9 g (15.0 mmol) of potassium azodicarboxylate in 5 ml of methanol-d_1 was added dropwise a solution of 1.85 g (30 mmol) of acetic acid-d_1 in 10 ml of methanol-d_1. The reaction was stirred at room temperature under nitrogen for 30 min; a second charge of diimide (7.5 mmol of potassium azodicarboxylate and 15 mmol of acetic acid-d_1) was added to ensure total reduction of the diene. The reaction was poured into water and extracted with pentane. Removal of the pentane by distillation gave 1.43 g (71%) of product which contained 83.5% 5,6-dideuterio-syn-7-*tert*-butylnorbornene (6) and 16.5% 2,3,5,6-tetradeuterio-7-*tert*-butylnorbornane (7). The two hydrocarbons were separated by vpc (SE-30 silicone column) to give individual samples of 99% purity. The nmr spectra are given in Table I with the deuterium distribution noted.

To a mixture of 3.0 g (20.3 mmol) of 7-*tert*-butylnorbornadiene and 5.8 g (30.0 mmol) of potassium azodicarboxylate in 15 ml of methanol was added a solution of 3.6 g (60 mmol) of acetic acid in 15 ml of methanol. The acetic acid solution was added in three equal portions, and a sample of the reaction was withdrawn subsequent to each addition. The sample was shaken with water and pentane, and the pentane layer was analyzed by vpc (200 ft × 0.02 in., 50% phenylsilicone–50% nitrile silicone column, 70°, 16 psig). The results are summarized in Table IV.

TABLE IV

| Sample | Diene (1) | Product distribution, %[c] | | |
		syn (2)	anti (3)	Satd (4)
1	50	41	5	4
2	32	57	4	7
3	21	65	3	11
4[a]	0	83	2	15
5[b]	0	84	0	16

[a] Sampled 30 min after sample 3. [b] Additional 0.5 g of potassium azodicarboxylate added. [c] Retention time, minutes from C_6H_{12}: diene, 11.0; syn, 10.5; anti, 12.5; satd, 13.5.

The reaction mixture was added to 25 ml of water and was extracted twice with pentane. The extract yielded 2.4 g of product.

Hydroboration of 7-*tert*-Butylnorbornadiene.—To 40 ml of 0.78 *M* 9-BBN[27] in tetrahydrofuran was added dropwise a solution of 4.5 g (30.4 mmol) of *tert*-butyl diene (1) in 15 ml of tetrahydrofuran. The reaction was stirred under nitrogen for 20 min at room temperature; 15 ml of 6 *N* sodium hydroxide and 12 ml of 30% hydrogen peroxide were added, and the reaction was refluxed for 1 hr. The reaction mixture was saturated with sodium chloride, and the tetrahydrofuran layer was separated and dried over magnesium sulfate. The ether was removed by distillation, and the residue was slurried with pentane. The slurry was washed with water, and the pentane layer was separated and dried. The pentane was removed by distillation to give 4.5 g (90%) of exo-5-hydroxy-syn-7-*tert*-butylnorbornene-2 (11), crude mp 64–69°. Purification by sublimation at 80° (150 mm) gave white needles, mp 63.5–64.5°.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.34; H, 10.90. Found: C, 79.13; H, 10.72. Nmr (CDCl₃) δ 5.85 (m, 2, HC=CH), 3.80 (m, 1, *J* = 11.3 Hz, endo HCO), 2.56 (s, 1, OH), 2.50–2.83 (m, 2, >CH), 2.14 (m, 1, exo >CH₂), 1.20–1.66 (m, 2, endo >CH₂, HC-*tert*-Bu), 0.85 [s, 9, (CH₃)₃C].

exo-2-Hydroxy-anti-7-*tert*-butylnorbornane (12).—The unsaturated alcohol (4.5 g) was hydrogenated in 75 ml of methanol over 200 mg of 10% palladium on charcoal. The product was isolated by dilution with water and pentane extraction; the yield of saturated alcohol was 4.3 g (98%), mp 84.5–85.5° (after sublimation). Acetylation with acetyl chloride–pyridine gave a single ester, retention time 21 min (from CDCl₃) on a 300 ft × 0.01 in. DC-550 silicone column, 150°, 30 psig.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.30; H, 11.71. Nmr (CDCl₃) δ 3.68 (m, 1, *J* = 11.5 Hz, HCO), 2.16 (s, 1, OH), 1.94–2.28 (m, 2, >CH), 1.03–1.91 (m, 7, exo >CH₂, endo >CH₂, HC-*tert*-Bu), 1.00 [s, 9, (CH₃)₃C].

A solution of 3.6 g (21.4 mmol) of exo-2-hydroxy-anti-7-*tert*-butylnorbornane (12) in 60 ml of pyridine was cooled to 0°, and freshly purified tosyl chloride (8.4 g, 44 mmol) was added with stirring. The mixture was stored at 0° for 16 hr, poured into 200 ml of water, and extracted with ether (four 50-ml portions). The combined extracts were washed with cold 10% hydrochloric acid and water and were dried over magnesium sulfate. The ether was removed *in vacuo* at 30° to give 5.6 g (82%) of the tosylate as a viscous, pale yellow oil. The tosylate was recrystallized with difficulty from pentane at −60°; the tosylate was insufficiently stable to permit accurate elemental analysis. Nmr (CDCl₃) δ 7.76, 7.30 (m, 4, aromatic H's), 4.32 (m, 1, *J* = 11.5 Hz, HCO), 2.41 (s, 3, CH₃–), 2.19 (m, 2, >CH), 0.95–2.00 (m, 7, exo,endo >CH₂, HC-*tert*-Bu), 0.90 [s, 9, (CH₃)₃C].

anti-7-*tert*-Butylnorbornene (3).—For preparative purposes the tosylate described above was stored at 0° in ethereal solution until needed. The dehydrotosylation was a modification of the procedure described by Brown.[28] To 20 g of 2-cyclohexylcyclohexanol and 10 ml of 1,4-diisopropylbenzene was added 2.6 g of potassium. The reaction was heated at 130° until all of the potassium had dissolved. The solution was cooled to room temperature, and a solution of the tosylate prepared from 4.7 g (28 mmol) of 12 in 10 ml of 1,4-diisopropylbenzene was added. The reaction was stirred vigorously and was rapidly heated to 140° and maintained at this temperature for 1 hr. The cooled reaction mixture was poured into 150 ml of water and extracted three times with 50-ml portions of pentane. The extract was dried over magnesium sulfate, and the pentane was removed by distillation. The residue was distilled at 130° (60 mm) through a Monel spiral Todd column; 11–12 ml of distillate was collected and redistilled to give 1.95 g of anti-7-*tert*-butylnorbornene, bp 107° (87 mm), vpc purity 85%. The olefin was purified by preparative vpc (10 ft × 0.375 in. 3% Dowfax on Chromosorb W, 120°, injector and detector at 250°, 200 ml/min helium) to give 1.2 g of 97% pure material, n^{20}D 1.4721. Vpc (2 m × 0.25 in. 20% polypropylene glycol column, 175°, 80 ml/min) gave a single peak, retention time 5.4 min. The yield based on starting alcohol was 47%. The nmr spectrum is listed in Table I.

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.05; H, 12.07.

Oxymercuration of 7-*tert*-Butylnorbornadiene.—To a stirred suspension of 1.6 g (5 mmol) of mercury(II) acetate in 5 ml of water and 2.5 ml of tetrahydrofuran was added 700 mg (4.7 mmol) of 7-*tert*-butylnorbornadiene in 2.5 ml of tetrahydrofuran. The reaction decolorized in ~60 sec; stirring was continued for

15 min. The reaction was decomposed with sodium hydroxide–sodium borohydride[23a] and worked up in the usual manner.[5] The crude product was acetylated with acetyl chloride–pyridine to give 900 mg (92%) of acetate ester. Vpc analysis (300 ft × 0.01 in. DC-550 silicone column, 115°, 30 psig) gave a mixture of two esters, retention time 30.0 min (87%) and 34.5 min (13%). Neither ester was shown by comparative vpc to be *exo-5-acetoxy-syn-7-tert*-butylnorbornene-2 (11), retention time 27.5 min (from hydroboration of 1). A pure sample of the major ester was separated by preparative vpc (10 ft × 0.375 in. 20% FFAP column, 170°, 110 ml/min) and was shown by nmr to be *endo-5-tert*-butyl-*anti*-7-acetoxynorbornene-2 (10).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.68; H, 9.57. Nmr (CDCl$_3$) δ 5.96 (m, 2, HC=CH), 4.26 (m, 1, $J = 5$ Hz, HCO), 2.50–2.88 (m, 2, >CH), 2.03 (s, 3, CH$_3$CO), 1.60–1.88 (m, 2, exo >CH$_2$), 0.95 (s, 1, endo >CH$_2$), 0.80 [s, 9, (CH$_3$)$_3$C].[31]

(31) The position and stereochemistry of the *anti*-7-acetoxy group was established by comparative nmr with other acetoxynorbornenes.[11]

The reaction of the 7-*tert*-butyldiene with mercury(II) trifluoroacetate in benzene-d_6 was studied by nmr.[24] The spectrum of the diene was immediately replaced by that of the exo,cis mercuration adduct of the anti double bond: δ 5.80 (dq, 2, HC=CH), 4.85 (d, 1, HCO, $J = 8$ Hz), 2.93 (m, 2, >CH), 2.30 (d, 1, HgCH, $J = 8$ Hz), 2.20 (s, 1, HC-*tert*-Bu), 0.86 [s, 9, (CH$_3$)$_3$C]. An identical experiment with norbornadiene gave the following nmr spectrum: δ 6.00 (dq, 2, HC=CH), 4.88 (d, 1, HCO, $J = 8$ Hz), 2.90 (m, 2, >CH), 2.18 (d, 1, HCHg, $J = 10$ Hz), 1.50 (s, 2, >CH$_2$). Both spectra were unchanged after 24 hr at room temperature.[32]

Notes

Formation of (Alkoxymethylene)dimethylimmonium Halides in the Reactions of Triphenylphosphine Dihalides with Alcohols in Dimethylformamide

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The reaction of triphenylphosphine dihalides with alcohols to give halides[1] is a useful synthetic procedure.[2] The reaction mechanism in acetonitrile has been proposed as shown in eq 1.[3] The reaction may also pro-

$$R_3PX_2 + R'OH \xrightarrow{\text{fast}} R_3\overset{+}{P}OR' + \overset{-}{X}HX \xrightarrow{\text{slow}}$$
$$R_3P=O + R'X + HX \quad (1)$$
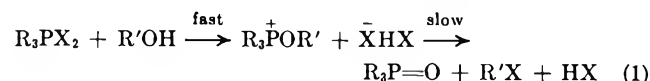
ceed satisfactorily when dimethylformamide (DMF) is used as the solvent.[1,2] We report here a second pathway followed by this reaction when done in DMF.

When N-benzoyl-N-methyl-4-hydroxyadamantan-1-amine[4] (1) is allowed to react with triphenylphosphine dibromide in DMF at ice-bath temperatures, a crystalline precipitate forms. The spectral and analytical properties of this relatively stable product were not consistent with the expected bromide structure 4. Instead, elemental analysis showed that, in addition to bromine, the empirical formula had also gained the elements of C_3H_6N. The nmr spectrum suggested that

part of this gain could be accounted for by two methyl groups attached to a heteroatom such as nitrogen. The infrared spectrum showed the absence of an OH bond and a new strong absorption band at 1710 cm^{-1}. These data suggested that the product had structure 2a, an (alkoxymethylene)dimethylimmonium bromide. Structure 2 is, in fact, an immonium ether halide, a structural type for which considerable precedent exists.[5] For example, an analogous structure has been assigned to the salts obtained from the reaction of dimethylformiminium chloride with either *tert*-butyl alcohol or dimethylbenzylcarbinol, although the products were characterized by elemental analyses only.[5c] Related structures have frequently been postulated[6] and occasionally isolated[7] as intermediates in Vilsmeyer formylation reactions.

Consistent with structure 2a was the observation that the compound was water soluble and was rapidly hydrolyzed, giving formate ester 3 as the product. The structure of 3 was apparent from the elemental analyses and the infrared spectrum (ester carbonyl at 1730 cm^{-1}), as well as the fact that it underwent further hydrolysis under alkaline conditions to give the starting alcohol 1. The latter result shows that the configuration of the oxygen substituent in 1 has been retained throughout these transformations.

An (alkoxymethylene)dimethylimmonium iodide intermediate (2b) also formed when iodine was used in the reaction instead of bromine. Formate ester 3 was also obtained from this intermediate upon hydrolysis.

An intermediate of the above type apparently formed when the diol 1-benzoyl-1-methyl-4,6-dihyroxyadaman-

(1) G. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

(2) *Cf.* L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, N. Y., 1967, pp 1247–1249.

(3) G. A. Wiley, B. M. Rein, and R. L. Hershkowitz, *Tetrahedron Lett.*, 2509 (1964).

(4) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3201 (1968).

(5) *Cf.* (a) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961); (b) F. H. Suydam, W. E. Greth, and N. R. Langerman, *J. Org. Chem.*, **34**, 292 (1969); (c) Z. Arnold, *Collect Czech. Chem. Commun.*, **26**, 1723 (1961).

(6) *Cf.* H. J. Bestmann, J. Lienert, and L. Mott, *Justus Liebigs Ann. Chem.*, **718**, 24 (1968). NOTE ADDED IN PROOF.—See also T. Dahl, R. Stevenson, and N. S. Bhacca, *J. Org. Chem.*, **36**, 3243 (1971).

(7) *Cf.* G. Ferré and A.-L. Palomo, *Tetrahedron Lett.*, 2161 (1969).

1

2a, X = Br
b, X = I

3

4
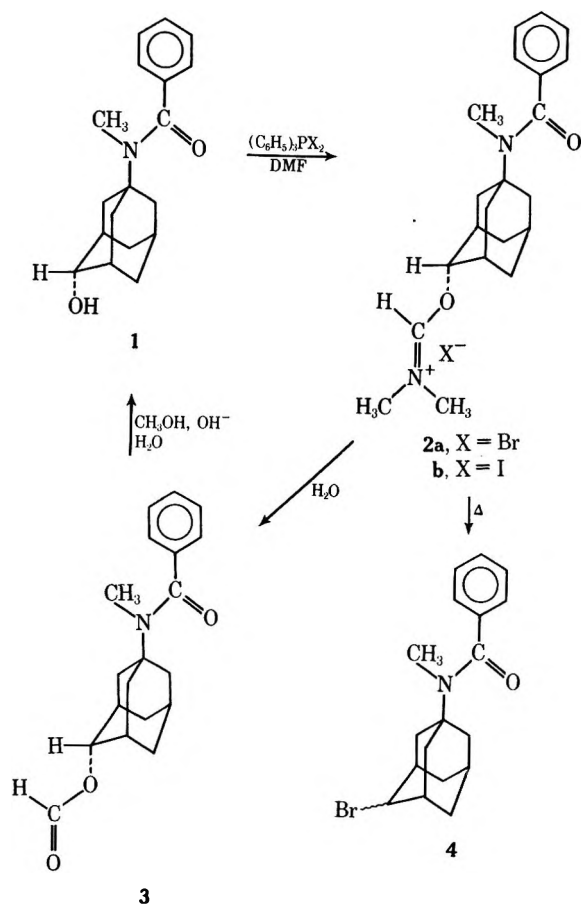
tan-1-amine (5) was allowed to react with triphenyl-
phosphine dibromide in DMF. The product actually
isolated from work-up of the reaction, which involved
aqueous conditions, was the diformate ester 6. Saponi-
fication of 6 gave starting diol 5.

5, R = H
6, R = —CH
‖
O
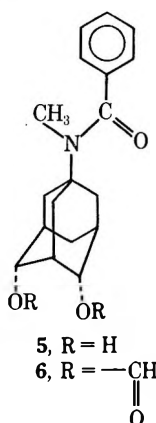
Conversion of the salt 2a to bromide 4 was attempted
by refluxing in toluene, but it remained unchanged.
However, when fused at its melting point, 2a was con-
verted into 4 in good yield. Thin layer chromato-
graphic analysis of 4 showed it to consist of two compo-
nents, suggesting that a mixture of epimeric C-4 bro-
mides had been obtained.

Attempts to isolate intermediates such as 2 from re-
action of triphenylphosphine dihalides with other al-
cohols under the same conditions have not been suc-
cessful. In still another case, the reaction of 4-(4'-
hydroxycyclohexyl)cyclohexanone (7)[8] with triphenyl-

(8) G. S. Fonken, M. E. Herr, and H. C. Murray, U. S. Patent 3,281,330
(Oct 25, 1966).

phosphine diiodide, both the iodide 8 and the formate
9 were detected among the reaction products.

7

8

9
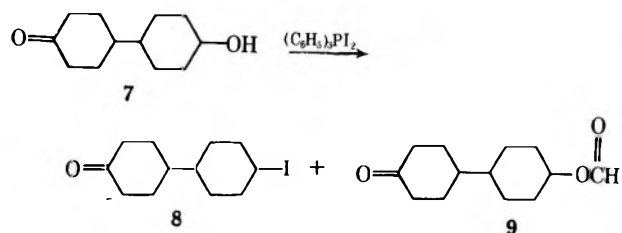
It seems plausible that a mechanism similar to that
postulated for the formation of the Vilsmeyer reaction
intermediates[6] is involved here also. Such a sequence
is shown in eq 2. It may be noted that no inversion of

(2)
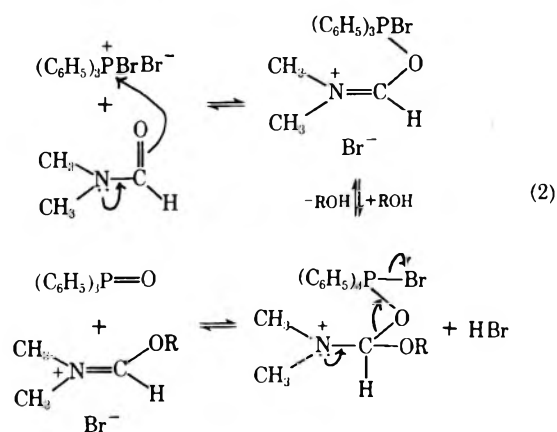
the alcohol configuration is required by this mechanism.
We have not studied the effect of other variables on
this reaction.

Experimental Section

**4-(N-Benzoyl-N-methyl-1-aminoadamantoxymethylene)di-
methylimmonium Bromide (2a).**—A mixture of 28.5 g of N-
benzoyl-N-methyl-1-adamantanamin-4α-ol (1), 150 ml of di-
methylformamide, and 27.5 g of triphenylphosphine in a nitrogen
atmosphere and with ice cooling was stirred and treated dropwise
with 16.0 g of bromine during 15 min. During this addition, the
original solids dissolved and a precipitate separated. The
product was recovered by filtration, washed quickly with ether
and placed in a vacuum desiccator, yield 33.34 g, mp 187–192°
dec. For analysis a sample was recrystallized from methylene
chloride–hexane: mp 195–198° dec; ir (Nujol) 1710 (CH=N),
1650 cm^{-1} (amide); nmr (CDCl$_3$) δ 10.35 (s, 1, N=CHO), 7.33
(s, 5, C$_6$H$_5$), 5.55 (m, 1, CHOC=N), 3.64 (s, 3, C=NCH$_3$), 3.29
(s, 3, C=NCH$_3$), 2.81 (s, 3, NCH$_3$).

Anal. Calcd for C$_{21}$H$_{29}$N$_2$O$_2$Br: C, 59.85; H, 6.94; N, 6.65;
Br, 18.97. Found: C, 59.46; H, 6.77; N, 6.63; Br, 19.45.

N-Benzoyl-N-methyl-1-adamantanamin-4α-ol Formate (3).—
The compound 2a (1.5 g) was dissolved in 10 ml of water; crystals
began to separate almost immediately; and, after 1 hr, these
were collected, washed with water, and dried, yield 1.04 g, mp
93–95°. The analytical sample obtained from aqueous acetone
melted at 95–97°: ir (Nujol) 1730 (formate), 1630 cm^{-1}
(amide); nmr (CDCl$_3$) δ 8.08 (s, 1, HC=O), 7.35 (s, 5, C$_6$H$_5$),
5.1 (m, 1, CHO–), 2.83 (s, 3, NCH$_3$).

Anal. Calcd for C$_{19}$H$_{23}$NO$_3$: C, 72.82; H, 7.40; N, 4.47.
Found: C, 72.60; H, 7.36; N, 4.27.

**Hydrolysis to N-Benzoyl-N-methyl-1-adamantanamin-4α-ol
(1).**—A sample of the formate ester 3 was heated with methanol
and 10% aqueous sodium hydroxide to give 1 identical in all re-
spects with authentic material.

N-Benzoyl-*N*-methyl-1-adamantanamine-4α,6α-diol Diformate (6).—A mixture of 3.01 g of *N*-benzoyl-*N*-methyl-1-adamantanamine-4α,6α-diol (5), 20 ml of dimethylformamide, and 5.5 g of triphenylphosphine under nitrogen was stirred in an ice bath and treated dropwise with bromine until an orange color persisted. After 1 hr, the mixture was diluted with water and extracted with methylene chloride; the extract was washed with 5% sodium bicarbonate solution and dried (Na₂SO₄). The solvent was removed and the residue was recrystallized from acetone–water: yield 1.20 g; mp 142–144°; ir (Nujol) 1730 (formate), 1630 cm⁻¹ (amide); nmr (CDCl₃) δ 7.96 (s, 2, HC=O), 7.25 (s, 5, C₆H₅), 5.08 (m, 2, CHO–), 2.79 (s, 3, NCH₃).

Anal. Calcd for C₂₀H₂₃NO₅: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.31; H, 6.64; N, 4.56.

Hydrolysis to *N*-Benzoyl-*N*-methyl-1-adamantanamine-4α,6α-diol (5).—A sample of the diformate ester 6 was converted to the free diol by warming in methanol and 10% aqueous sodium hydroxide solution. This product was identical in all respects with compound 5.

4-(*N*-Benzoyl-*N*-methyl-1-aminoadamantoxymethylene)dimethylimmonium Iodide (2b).—When iodine was substituted in place of bromine in the above reaction with 1, the product isolated was the iodide salt 2b: mp 150° dec; ir (Nujol) 1695 (CH=N), 1640 cm⁻¹ (amide).

Anal. Calcd for C₂₁H₂₉N₂O₂I: C, 53.85; H, 6.24; N, 5.98; I, 27.10. Found: C, 53.82; H, 6.22; N, 5.82; I, 27.00.

N-Benzoyl-*N*-methyl-4ε-bromo-1-adamantanamine (4).—The compound 2a, 5.59 g, was heated in an oil bath at 200–205° for 15 min. The mixture was cooled, treated with 25 ml of water, and extracted with methylene chloride; the extract was washed with water and dried (Na₂SO₄); the extract residue was chromatographed over 200 g of Florisil by the gradient elution method with 4 l. of solvent SSB containing increasing proportions of acetone from 0 to 25%; cuts of 70 ml each were collected. Residues from fractions 15–20 contained the C₄-bromo product 4. Tlc of this material on a silica gel microplate developed ten times with 10% acetone in Skellysolve B showed this to be a mixture of 4α- and 4β-bromo compounds. A sample recrystallized from ether–pentane melted at 96–99°.

Anal. Calcd for C₁₈H₂₂NOBr: C, 62.07; H, 6.37; N, 4.02; Br, 22.95. Found: C, 62.38; H, 6.36; N, 4.19; Br, 22.81.

Reaction of 4-(4'-Hydroxy)cyclohexylcyclohexanone (7) with Triphenylphosphine Diiodide.—Triphenylphosphine (5.80 g, 0.022 mol) and 4-(4'-hydroxy)cyclohexylcyclohexanone (7)⁸ (3.92 g, 0.020 mol) were dissolved in dimethylformamide (55 ml). Iodine crystals (5.06 g, 0.020 mol) were added to the solution over a period of 20 min at room temperature. After stirring at room temperature for 5 hr, the solution was light yellow. Methanol (5 drops) was added, causing most of the color to disappear. The solution was poured into water (300 ml) and the resulting cloudy mixture was extracted with ether (five 60-ml portions). The ether solution was washed with 5% NaHCO₃ solution (100 ml) and with water, then dried over MgSO₄. The dry ether solution was concentrated under reduced pressure, giving a mixture of liquid and crystals. This mixture was lixiviated with Skellysolve B (four times) and the solution was concentrated under reduced pressure. The residue was passed through silica gel (300 g) in 1:1 ethyl acetate–Skellysolve B, separating the products (fractions 1 and 2) from triphenylphosphine oxide. The presence of a formate ester (9) in the product mixture (fraction 2) was suggested by spectral evidence (a signal at δ 8.00 in the nmr and a band at 1720 cm⁻¹ in the ir spectrum). Hydrolysis (5 ml of 5% NaHCO₃ plus 50 ml of CH₃OH) of the product mixture (fractions 1 and 2, reflux for 20 min) caused disappearance of one product (on tlc) and appearance of starting keto alcohol 7, some of which crystallized and was recovered. The remaining product mixture was chromatographed on silica gel (300 g, 3.5 cm column) packed with 20% ethyl acetate in Skellysolve B. Elution with the same solvent (335-ml fractions) gave fraction 1, crystalline triphenylphosphine, identified by ir spectrum; fraction 2, triphenylphosphine and an olefinic component, δ 7.3 and 5.65, respectively, in the nmr spectrum; fraction 3, olefinic component plus 4-(4'-iodo)cyclohexylcyclohexanone; fraction 4, 4-(4'-iodo)cyclohexylcyclohexanone (8), δ 4.84 in the nmr for ICH, 0.551 g of viscous oil.

Registry No.—DMF, 68-12-2; 2a, 32653-72-8; 2b, 32653-73-9; 3, 32653-74-0; 4α, 32653-75-1; 4β, 32653-76-2; 6, 32653-77-3; 8, 32670-59-0.

## Transannular Reactions of Heptamethylenimine Derivatives

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Microbial oxygenation of *N*-benzoylheptamethylenimine has provided a source of the 5-oxo derivative 1, which can be modified to molecules that undergo transannular reactions.[1] Described below are two additional, unusual transannular reactions encountered in work with compounds derived from 1.

Interception of Ketal Hydrolysis by Transannular Amine.—A large variety of nucleophiles other than water participate in reactions with acetals and ketals. Under anhydrous conditions, the acid-catalyzed exchange with alcohols is well known,[2] while other reports have demonstrated reaction with hydride,[3] Grignard reagents,[3b,4] imide nitrogen,[5] and amine nitrogen.[6] Participation of oxygen[7] and sulfur[8] in the hydrolysis of acetals has also been observed.

With the exception of the unusual example cited above, amine ketals generally form stable acid salts[9] under anhydrous conditions. We have hydrolyzed several amine ketals with no apparent anomalies.[1] However, when the amine ketal 3, prepared from 1 *via* 2
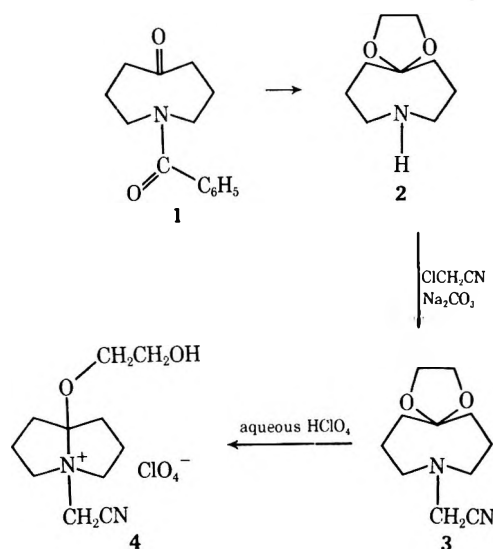
(1) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3187 (1968).

(2) *Cf.* E. H. Cordes, *Prog. Phys. Org. Chem.*, **4**, 1 (1967).

(3) *Cf.* (a) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962); (b) P. C. Loewen, W. W. Zajac, Jr., and R. K. Brown, *Can. J. Chem.*, **47**, 4059 (1969), and earlier papers cited therein.

(4) (a) M. R. Kulibekov, *Dokl. Akad. Nauk Azerb. SSR*, **20**, 15 (1964); *Chem. Abstr.*, **61**, 10579h (1964); (b) R. A. Mallory, S. Rovinski, and I. Scheer, *Proc. Chem. Soc.*, 416 (1964); R. A. Mallory, S. Rovinski, F. Kohen, and I. Scheer, *J. Org. Chem.*, **32**, 1417 (1967); (c) D. Lednicer, *ibid.*, **29**, 2480 (1964).

(5) H. E. Johnson and D. G. Crosby, *ibid.*, **27**, 2077 (1962).

(6) G. Bianchetti, D. Pocar, P. D. Croci, G. G. Gallo, and A. Vigevani, *Tetrahedron Lett.*, 1637 (1966).

(7) B. Capon and D. Thacker, *J. Amer. Chem. Soc.*, **87**, 4200 (1965).

(8) J. C. Speck, Jr., D. J. Rynbrandt, and I. H. Kochevar, *ibid.*, **87**, 4979 (1965).

(9) *Cf.* W. R. Hardie, J. Hidalgo, I. F. Halverstadt, and R. E. Allen, *J. Med. Chem.*, **9**, 127 (1966).

by a known procedure,[10] was allowed to react with aqueous (70%) perchloric acid in ethanol at temperatures of 10–30°, a water-soluble salt **4** was obtained after 15 min. The infrared spectrum (see Experimental Section) of the salt shows the presence of a hydroxyl group, and the nmr spectrum shows that the ethylene glycol moiety remains in the molecule. A structure fitting these requirements, and those of the elemental analysis, is the one that results from interception by the amine nitrogen of an intermediate ion during the hydrolysis of the ketal.

It seems probable that the reduced basicity[11] of the cyanomethyl-substituted amine **3** allows protonation of a ketal oxygen to compete with protonation of the nitrogen. The proximity of the nitrogen to the potential ketal carbonium ion permits the nitrogen to intercept the hydrolysis either by attack as the carbonium ion
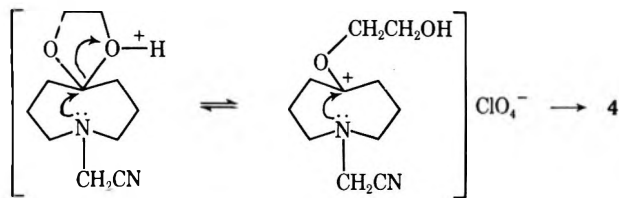
forms or in a concerted attack on the carbon as the oxonium ion forms and the C–O bond breaks. The latter pathway may be expected to accelerate the rate of the hydrolysis reaction.

Transannular Enamine.—We were curious as to whether an enamine could conveniently be prepared from intermediate **1** and would undergo transannular reaction. To this end, a Wittig reaction of **1** with methyltriphenylphosphonium bromide was carried out. The resulting methylene amide **5** was reduced with lithium aluminum hydride, giving the transannularily disposed enamine **6**.
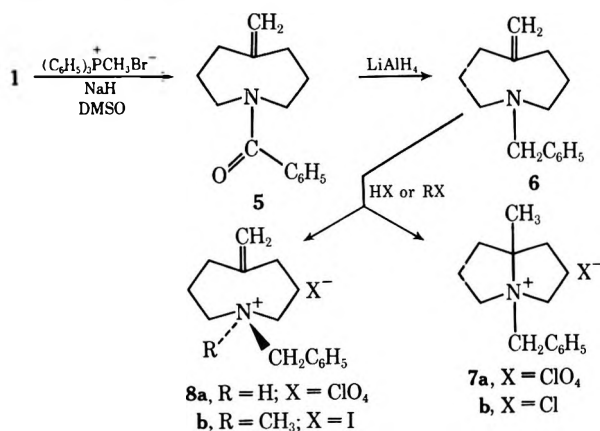
Several experiments show that **6** may react as either a transannular enamine or as a typical amine. Thus, from reaction with 70% aqueous perchloric acid, there was obtained a crystalline salt having the properties of structure **7a** and a residual mixture containing **7a** and tertiary amine perchlorate, **8a**. Reaction of **6** with either benzoyl chloride or acetyl chloride in dioxane resulted in formation of crystalline salt **7b** in yields of 78

and 69%, respectively. Formation of this salt undoubtedly resulted from the presence of hydrogen chloride in the reaction, even though efforts were made to maintain anhydrous conditions. Finally, reaction of **6** with methyl iodide resulted in isolation of salt **8b** in low yield.

A few related transannular enamine reactions have been reported previously. Transannular cyclization of nitrogen to a styrenelike olefinic bond has been studied,[12] as has been cyclization to the olefinic bond of unsaturated lactams.[13] More recently, cyclization to an exocyclic methylene group has been noted.[14]

Experimental Section

1,4-Dioxa-9-azaspiro[4.7]dodec-9-ylacetonitrile (3).—A solution of 1,4-dioxa-9-azaspiro[4.7]dodecane (2)[1] (10.215 g, 0.0597 mol) in benzene (25 ml) was added slowly to a stirred mixture of chloroacetonitrile (6.0 g, 0.0795 mol) in benzene (125 ml) and anhydrous sodium carbonate (4.0 g). During the course of addition (15 min), the mixture was warmed to near the reflux temperature and then was heated to reflux with stirring for 18 hr, giving a light yellow solution over a brown and white precipitate. The precipitate was dissolved in dilute aqueous sodium bicarbonate solution. The benzene layer was washed twice with water and dried over magnesium sulfate. Concentration of the benzene under reduced pressure gave an oil which crystallized upon cooling. The crystalline material dissolved in hot Skellysolve B, leaving a small amount of gummy, yellow residue and giving a colorless solution. Cooling gave colorless crystals (8.960 g), mp 77–78°. A second crop, mp 75–77° (1.726 g, total 10.686 g, 0.0508 mol, 85%), was obtained from the concentrated filtrate. Recrystallization from Skellysolve B gave colorless needles, mp 78–79°, $\nu_{C\equiv N}$ 2220 cm^{-1} in Nujol.

Anal. Calcd for $C_{11}H_{18}N_2O_2$ (210.27): C, 62.83; H, 8.63; N, 13.32. Found: C, 62.44, 63.24; H, 8.35, 9.02; N, 13.80, 13.74.

4-Cyanomethylhexahydro-7a-(β-hydroxy)ethoxy-1H-pyrrolizinium Perchlorate (4).—Aqueous 70% perchloric acid (5 drops) was added to a solution of **3** (0.105 g, 0.000500 mol) in absolute ethanol (2.0 ml), which was kept cold on an ice bath. An oily precipitate formed, which solidified. Ether (6.0 ml) was added to the mixture, which was kept at room temperature overnight. The solid, mp 160–170° (0.122 g, 0.000393 mol, 78%) was collected by filtration and washed with ethanol (3.0 ml). Two recrystallizations from ethanol gave colorless crystals: mp 184–186°; ν_{OH} 3540 cm^{-1} in Nujol; nmr (DMF-d_7) δ 4.83 (s, NCH₂CN), 4.59 (OH), 3.91 (m, 8 H, N⁺CH₂–, –OCH₂–), 2.42 (m, 8 H, CCH₂C).

Anal. Calcd for $C_{11}H_{19}N_2O_6Cl$ (310.74): C, 42.51; H, 6.16; N, 9.02. Found: C, 42.85; H, 6.26; N, 9.13.

At temperatures lower than 10°, a solid precipitated immediately upon addition of the perchloric acid to **3**. The solids obtained in this way varied from having weak hydroxyl absorption to strong absorption at 3350 cm^{-1} and exhibited wide melting point ranges, probably the result of varying degrees of ketal hydrolysis at the lower temperatures.

1-Benzoyl-5-methyleneheptamethylenimine (5).—Sodium hydride (0.0700 mol) was washed with pentane (three 50-ml portions), the flask was flushed with nitrogen until the hydride was dry, and dimethyl sulfoxide (100 ml) was added. The mixture was stirred and heated to 75–80°. After 15–20 min at this temperature, bubbling stopped and a clear, yellowish solution was obtained. The solution was cooled on an ice bath and methyltriphenylphosphonium bromide (25.0 g, 0.070 mol) was added, giving a yellow-orange solution. After 10 min, a solution of 1-benzoylhexahydro-5(2H)-azocinone (1)[1] (12.35 g, 0.0534 mol) in dimethyl sulfoxide (50 ml) was added, causing the resulting solution to become warm. The solution was stirred at room temperature for 16 hr and poured into water (80 ml). The aqueous solution was extracted with pentane (five 75-ml portions).

(10) R. P. Mull, M. E. Edbert, and M. R. Dopero, *J. Org. Chem.*, **25**, 1953 (1960).

(11) G. W. Stevenson and D. J. Williamson, *J. Amer. Chem. Soc.*, **80**, 5943 (1958), report that 1-cyanomethylpiperidine has pK_a 4.55 while 1-methylpiperidine has pK_a 10.08.

(12) F. L. Pyman, *J. Chem. Soc.*, 817 (1913).

(13) L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965).

(14) D. W. Brown, S. F. Dyke, G. Hardy, and M. Sainsbury, *Tetrahedron Lett.*, 2609 (1968); M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron*, **25**, 1881 (1969).

The pentane solution was washed with 1:1 dimethyl sulfoxide-water (two 50-ml portions) and with 50% aqueous sodium chloride. The pentane solution was dried over magnesium sulfate and concentrated to a colorless oil, which crystallized when kept in the refrigerator overnight. Recrystallization from cold Skellysolve B gave 5.05 g (0.022 mol, 41%) of crystals, mp 36–37°. Two recrystallizations from cold Skellysolve B gave colorless crystals: mp 36–37°; $\nu_{C=O}$ 1625, $\nu_{C=C}$ 1600, 1575, 1495, $\nu_{=CH_2}$ 880, ν_{Ph} 780, 730, 700 cm^{-1} in Nujol; nmr (CDCl$_3$) δ 7.33 (s, 5 H, C$_6$H$_5$), 4.86 (s, 2 H, =CH$_2$), 3.8–3.15 (m, 4 H, NCH$_2$), 2.45–1.50 (m, 8 H, –CH$_2$–).

Anal. Calcd for C$_{15}$H$_{19}$NO: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.10; H, 8.32; N, 6.51.

1-Benzyl-5-methyleneheptamethylenimine (6).—A solution of 5 (5.05 g, 0.0220 mol) in ether (50 ml) was added to a mixture of lithium aluminum hydride (3.5 g) and ether (200 ml). The mixture was heated at reflux temperature for 5 hr. Ethyl acetate and water were added to consume the excess hydride and the inorganic solids were collected by filtration. The ether filtrate was dried over magnesium sulfate and concentrated to an oil. The oil was transferred to a 10-ml distillation flask with ether and distilled, giving 3.687 g (0.0171 mol, 78%) of colorless oil: bp 78–80° (0.05 mm); λ_{max} in 95% ethanol 258 mμ (ϵ 508), 263 (362), 268 (254); $\nu_{=CH}$ 3060, 3020, $\nu_{C=C}$ 1630, 1595, 1490, ν_{Ph} 724, 700 cm^{-1} on the oil; nmr (CDCl$_3$) δ 7.29 (m, 5 H, C$_6$H$_5$), 4.76 (s, 2 H, =CH$_2$), 3.61 (s, 2 H, NCH$_2$C$_6$H$_5$).

Anal. Calcd for C$_{15}$H$_{21}$N: C, 83.66; H, 9.83; N, 6.51. Found: C, 84.14, 82.96; H, 10.53, 9.93; N, 5.44, 6.18.

4-Benzylhexahydro-7a-methyl-1H-pyrrolizinium Perchlorate (7a). Aqueous perchloric acid (70%, 20 drops) was added to a solution of 6 (0.42 g, 0.0195 mol) in absolute ethanol (5.0 ml). The solution was heated to reflux for 90 min. Addition of ether (25 ml) caused rapid separation of a first crop of 0.148 g of colorless crystals, mp 195–198°. Recrystallization from absolute ethanol gave colorless crystals: mp 215–216°; $\nu_{C=C}$ 1580, 1495, ν_{Ph} 770, 710 cm^{-1} in Nujol; nmr (DMF-d_7) δ 4.53 (s, PhCH$_2$N), 3.63 (m, –CH$_2$NCH$_2$–), 2.32, 2.26 (s, –CH$_2$–), 1.75 (s, –CH$_3$).

Anal. Calcd for C$_{15}$H$_{22}$NO$_4$Cl: C, 57.05; H, 7.02; N, 4.44. Found: C, 56.79; H, 7.10; N, 4.85.

The filtrate from the isolation of product above was kept in the freezer overnight. Colorless crystals, appearing to be a mixture of 7a and 8a, mp 60–80°, 140–145° (0.269 g), formed and were collected: $\nu_{=CH}$ 3140, $\nu_{C=C}$ 1630, 1575, 1492, ν_{Ph} 751, 697 cm^{-1} in Nujol. Two recrystallizations from ethanol–ether gave colorless crystals, softening at 90–100°, mp 140–145°. Recrystallization of 0.16 g from absolute ethanol, preceded by heating in refluxing ethanol for 1 hr, gave colorless crystals (0.03 g), partial softening at 140–150°, mp 190–205°.

4-Benzylhexahydro-7a-methyl-1H-pyrrolizinium Chloride (7b).
A. From Attempted Benzoylation of 1-Benzyl-5-methyleneheptamethylenimine.—A solution of 6 (0.314 g, 0.00146 mol) in dioxane (reagent grade, 5.0 ml) was added to a solution of benzoyl chloride (0.218 g, 0.00156 mol) in dioxane (5.0 ml). Crystals began forming after 30 min at room temperature and were collected after 22 hr, giving 0.289 g (0.00115 mol, 78%) of product, mp 282–284° dec. Two recrystallizations from ethanol–ether, the last preceded by decolorization with activated charcoal, gave colorless crystals: mp 295–296 subl; $\nu_{C=C}$ 1600, 1580, 1495, ν_{Ph} 770, 720 cm^{-1} in Nujol; nmr PhCH$_2$N (δ 4.68, singlet), –CH$_2$– (2.35, 2.29, singlets), –CH$_3$ (1.82, singlet) in dimethylformamide-d_7 at 95°.

Anal. Calcd for C$_{15}$H$_{22}$NCl: C, 71.54; H, 8.81; N, 5.56. Found: C, 71.46; H, 8.99; N, 5.79.

B. From Attempted Acetylation of 1-Benzyl-5-methyleneheptamethylenimine.—The above compound (7b) was obtained from addition of a solution of 6 (0.387 g, 0.0018 mol) in dioxane (dried over sodium, 5.0 ml) to a solution of acetyl chloride (0.153 g, 0.00195 mol) in dioxane (5.0 ml), giving, after 6 hr, 0.313 g (0.00125 mol, 69%) of product, mp 272–275° dec. The infrared spectrum in Nujol is identical with that of the above product.

1-Benzyl-1-methyl-5-methyleneheptamethyleneiminium Iodide (8b).—Excess methyl iodide was added to a solution of 6 (0.143 g, 0.665 mol) in methanol (5 ml). After 3 days at room temperature, the now yellow solution was partially concentrated by evaporation on the steam bath. Ether was added to the solution, which became cloudy. Crystals slowly formed and, after cooling the mixture in the refrigerator, were collected, mp 187–189°. Two recrystallizations from methanol–ether gave color-

less crystals of 8b: mp 184–186°; nmr (CDCl$_3$) δ 7.7 (m, 5 H, –C$_6$H$_5$), 5.00 (s, 2 H, =CH$_2$ or –NCH$_2$Ph), 4.93 (s, 2 H, =CH$_2$ or NCH$_2$Ph), 3.66 (m, 4 H, –NCH$_2$–), 3.18 (s, 3 H, –CH$_3$), 2.35 (m, 8 H, –CH$_2$–).

Anal. Calcd for C$_{16}$H$_{24}$NI: C, 53.78; H, 6.77; N, 3.92. Found: C, 53.73; H, 6.75; N, 4.36.

Registry No.—**3**, 32674-93-4; **4**, 32674-94-5; **5**, 32674-95-6; **6**, 32674-96-7; **7a**, 32674-97-8; **7b**, 32670-60-3; **8a**, 32670-61-4; **8b**, 32653-78-4.


Reaction of Cyanide Ion with Aromatic Nitriles and Aromatic Heterocyclic Compounds in Dipolar Aprotic Solvents. Cyanide Exchange[1]

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The cyanation of electronegatively substituted aromatic compounds and of unsaturated hydrocarbons containing extended π systems by treatment with sodium cyanide and an oxidizing agent in aprotic solvents offers attractive synthetic possibilities.[2] The reaction has been considered to proceed *via* reversible addition of cyanide ion to the substrate to yield a carbanion (*e.g.*, 1, from 9-cyanoanthracene) which is then
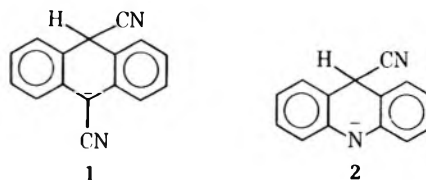
converted to the cyanation product by the action of the oxidizing agent. A similar addition of cyanide ion to a heterocyclic aromatic system has been proposed by Happ and Janzen[3] to account for the esr spectrum observed when acridine is treated with cyanide ion in air-saturated dimethylformamide (DMF); the spectrum is that of the radical anion resulting from the action of oxygen on the carbanion 2. These authors have also studied the esr spectrum of the radical anion formed by the attack of oxygen on the 9-cyanoanthracene adduct (1). In the present study, undertaken before the publication of the work of Happ and Janzen, the oxidizing agent (sodium anthraquinone-α-sulfonate, α-SAS) preferred for the conversion of 9-cyanoanthracene and cyanide ion to 9,10-dicyanoanthracene has been found highly effective for the conversion of acridine and sodium cyanide to 9-cyanoacridine. This result is in accord with the postulation of the similar intermediates 1 and 2. Further evidence for intermediates such as 1 and 2 has been sought by the use of labeled cyanide ion in reactions with electronegatively substituted aromatic compounds. The use of labeled cyanide in the

(1) Grateful acknowledgment is made to the U. S. Army Research Office for partial support of this work [Grant DA-ARO(D)-G857].

(2) (a) B. E. Galbraith, K. E. Whitaker, and H. R. Snyder, *J. Org. Chem.*, **34**, 1411 (1969); (b) K. E. Whitaker and H. R. Snyder, *ibid.*, **35**, 30 (1970).

(3) E. H. Janzen and J. W. Happ, *ibid.*, **35**, 96 (1970).

TABLE I

CYANIDE EXCHANGE

Registry no.	Run	Substrate (S)	Mole ratio of KCN[a]:S	Temp,[b] °C	Time, hr	Radio-activity[c]	Recovery, %
1210-12-4	1	9-Cyanoanthracene	4:1	80	2	0.91	30
	2	9-Cyanoanthracene	4:1	23	5	0.348	70
	3	9-Cyanoanthracene	1:1	80	0.75	0.626	80
	4	9-Cyanoanthracene	2:1	80	0.75	0.755	69
1217-45-4	5	9,10-Dicyanoanthracene	4:1	80	5	1.09	60
5326-19-2	6	9-Cyanoacridine	4:1	65	20	0.800	67
2510-55-6	7	9-Cyanophenanthrene	4:1	100	24	0.970	70
16001-13-1	8	9-Cyano-10-phenyl-anthracene	4:1	100	24	0.060	65
1467-01-2	9	9-Cyano-10-methyl-anthracene	4:1	100	24	0.020	30
3029-30-9	10	1,4-Dicyanonaphthalene	4:1	100	3	0.068	38
	11	1,4-Dicyanonaphthalene	4:1	100	8	0.180	28
	12	4,4'-Dicyanobiphenyl	4:1	130	24	0	82
	13	1-Cyanonaphthalene	4:1	100	24	0	51
	14	2-Cyanonaphthalene	4:1	100	24	0	
	15	1,3-Dicyanobenzene	4:1	100	24	0	31
	16	1,4-Dicyanobenzene	4:1	100	24	0	
	17	1,4-Dicyanocyclohexane	4:1	100	24	0	42
	18	Stearonitrile	4:1	100	24	0	35
110-61-2	19	Succinonitrile	4:1	100	24	0.97	15

[a] The radioactivity of the potassium cyanide was 2.00 μCi of ^{14}C/mmol of the compound. [b] ±5°. [c] Radioactivity is expressed in microcuries of ^{14}C/mmol of compound. Measurements are done by liquid scintillation and are accurate to ±2%.

cyanation reactions also promises to afford a very simple means of introducing labeled cyano groups into certain aromatic and heterocyclic systems.

Treatment of 9-cyanoanthracene with 2 mol of carbon-14 labeled potassium cyanide in the presence of 1 mol of the quinone α-SAS at 80° for 2 hr produced an 80% yield of 9,10-dicyanoanthracene with the same millimolar radioactivity as that of the cyanide employed. A reaction run for 4 hr at 100° yielded a product of millimolar radioactivity 1.34 times that of the cyanide employed. These results would be expected if exchange occurs with the product, 9,10-dicyanoanthracene, and not with the organic reagent, 9-cyanoanthracene, under the conditions employed.

In the absence of oxidizing agent, 9-cyanoanthracene undergoes exchange with cyanide ion (run 1, Table I). Also, under the conditions used, DMF solutions of 9-cyanoanthracene and cyanide ion generate the 9,10-dicyano compound, presumably as a result of electron transfer between the carbanion formed and the parent aromatic compound.[2b] In runs 2-4, the per cent recovery and the extent of exchange are shown to depend upon the temperature, the cyanide concentration, and the duration of the reaction. As more drastic conditions are employed, the amount of labeled 9-cyanoanthracene becomes smaller and the extent of exchange becomes greater.

If the exchange reaction proceeds by the attack of cyanide ion on the carbon atom attached to the cyano group, then there should be very little difference in reactivity between 9-cyanoanthracene and 9-cyano-10-methylanthracene or between 9-cyanoanthracene and 9-cyano-10-phenylanthracene. However, the methyl- and phenyl-substituted compounds proved to be very unreactive (runs 8 and 9).

Therefore, it is most likely that the exchange reaction with 9-cyanoanthracene proceeds through the same carbanion (1) postulated as the intermediate for

the cyanation reaction. The exchange might result from a proton migration in the carbanion, followed by loss of the cyanide ion; alternatively, protonation of the carbanion during the aqueous work-up, followed by the loss of hydrogen cyanide, would give the same result.
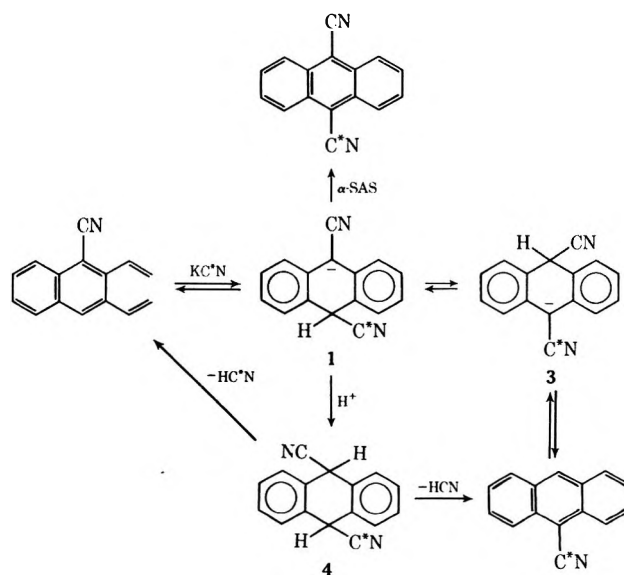
In the latter pathway, the 9,10-dicyano-9,10-dihydro derivative, 4, corresponds to the hydrocyanation products which have been obtained in good yields from some highly unsaturated hydrocarbons by the same experimental procedure.[2a] If the exchange reaction occurs by this pathway, then the use of deuterated or tritiated water in the final hydrolysis of the reaction mixture prepared from 9-cyanoanthracene and so-

dium cyanide should result in the formation of deuterium or tritium labeled compounds. A solution containing 4 equiv of cyanide and 1 equiv of 9-cyanoanthracene was heated at 80° for 2 hr before the reaction mixture was added to tritiated water. The 9-cyanoanthracene was recovered in radiochemically pure form and the 10 position was found to be labeled with tritium to the extent of 39%. In a similar experiment in which deuterium oxide was used in place of tritiated water, the 10 position of 9-cyanoanthracene was found to be labeled with deuterium to the extent of 41%, as determined by deuterium analysis and nmr and mass spectral data. It thus appears that about 80% of the recovered 9-cyanoanthracene is derived from the dihydro derivative (4).

It would, of course, be desirable to isolate 9,10-dicyano-9,10-dihydroanthracene and study its dehydrocyanation. Severin and Schmitz have reported that 9-nitroanthracene reacts with sodium borohydride in DMF to give a solution which upon treatment with an ion exchange resin (acid form) generates 9,10-di-hydro-9-nitroanthracene.[4] We have found that this process applied to 9-cyanoanthracene gives a 65% yield of 9,10-dihydro-9-cyanoanthracene, but with 9,10-dicyanoanthracene the only product isolated other than starting material was 9-cyanoanthracene, which was obtained in 50% yield. The fact that none of the reduction product of 9-cyanoanthracene was found suggests that 9-cyanoanthracene is not formed until after the excess borohydride has been destroyed by the acid treatment. It seems quite likely that the dihydrocyano compound is its precursor.

The observations mentioned above support the view that the carbanion 1 is involved in the cyanation and exchange reactions of 9-cyanoanthracene. This carbanion is formed reversibly, and in the presence of the quinone, α-SAS, it is converted to the cyanation product. Exchange does not occur with 9-cyanoanthracene in the presence of oxidizing agent, since in the aprotic reaction medium protonation of 1 cannot occur to give the dihydro intermediate 4, as demonstrated in the initial synthesis of labeled 9,10-dicyanoanthracene, in which the millimolar radioactivity of the dicyano compound is the same as that of the K[14]CN used initially. However, under more drastic conditions it was found that both addition and exchange with the product occurred, as evidenced by the increased millimolar radioactivity in the dicyano compound. In run 5, the dinitrile was heated with a fourfold excess of labeled cyanide at 80° for 5 hr; exchange did, indeed, occur, as 27% of the cyano groups were replaced.

In the absence of added oxidizing agent the carbanion slowly undergoes electron transfer with 9-cyanoanthracene, and 9,10-dicyanoanthracene and as yet unknown reduction products are formed. Also the portion of the carbanion surviving to the end of the reaction period is converted by hydrolysis to 9,10-dicyano-9,10-dihydroanthracene, which loses hydrogen cyanide to regenerate 9-cyanoanthracene. This is the route by which exchange with radioactive cyanide occurs, but there is substantial loss in the process because of the formation of 9,10-dicyanoanthracene. The best method of preparing labeled

9-cyanoanthracene by the exchange process requires the use of highly radioactive cyanide and short reaction periods.

In other experiments (runs 6–19), various aromatic and aliphatic nitriles were treated with carbon-14 labeled potassium cyanide. Of the aromatic nitriles studied, only 9-cyanoacridine, 9-cyanophenanthrene, and 1,4-dicyanonaphthalene were found to undergo the exchange reaction. In the reaction with 9-cyanophenanthrene, none of the dicyano compound was detected; the phenanthrene derivative does not appear to undergo the electron transfer process which occurs with 9-cyanoanthracene.[2b] Of the aliphatic nitriles studied, only succinonitrile was found to undergo exchange with labeled cyanide. Since the cyanide ion is a very strong base in dipolar aprotic solvents, the reaction with succinonitrile may be explained by proton abstraction, followed by loss of cyanide and then by hydrocyanation to give labeled succinonitrile.

The reactivity of aromatic nitriles in cyanide exchange seems to depend on the ability of the substrate to form a Meisenheimer-like complex. In turn, formation of this complex depends on the ability of the cyano group to stabilize the carbanion sufficiently to compensate for the loss in aromaticity. The relative ease of addition to aromatic nuclei, anthracene > phenanthrene > naphthalene > benzene, has been correlated with the amount of stabilization energy lost in forming the adduct.[5] Thus, for example, the stabilization energy lost in going from anthracene to 9,10-dihydroanthracene is less than the loss with phenanthrene. Because the formation of a Meisenheimer complex also involves a certain loss in aromaticity, a similar argument can be made for the reactivity of simple aromatic nitriles toward exchange. This argument can also be employed to explain the successful cyanation of acridine and the unsuccessful reactions with quinoline, isoquinoline, and pyridine. For the latter compounds, the stabilization of the anionic intermediates is insufficient to compensate for the loss in aromaticity.

Experimental Section

Melting points are uncorrected and were determined with a Kofler micro hot stage apparatus. Infrared spectra were obtained by use of potassium bromide discs and a Perkin-Elmer 521 infrared spectrophotometer. Microanalyses for carbon, hydrogen, and deuterium were performed by Mr. J. Nemeth and associates. Yellow carbon-14 labeled compounds were burned to carbon-14 carbon dioxide and water. The radioactive carbon dioxide was absorbed in Hyamine hydroxide before adding a toluene scintillator and counting with a Packard liquid scintillation spectrometer. Radioactive samples which did not give colored solutions were dissolved in a toluene scintillator and counted. Yellow tritium-labeled compounds were also burned to carbon dioxide and tritium water. The radioactive water was dissolved in a dioxane-based scintillator and counted. The Bush Channels ratio method was used to correct for quenching in all radioactive samples assayed.[6]

Materials.—Unless otherwise specified, commercially available reagents were used without purification. The dimethylformamide was stored over Linde Type 4A Molecular Sieve for 2 weeks before use. Finely divided sodium cyanide (98%), potassium cyanide-^{14}C, and α-SAS were dried for 24 hr at 110° under vacuum and stored over calcium sulfate in a tightly closed container.

(4) T. Severin and R. Schmitz, *Chem. Ber.*, **95**, 1417 (1962).

(5) F. G. Bordwell, "Organic Chemistry," Macmillan, New York, N. Y., 1963, p 540.

(6) E. T. Bush, *Anal. Chem.*, **36**, 1082 (1964).

The millimolar radioactivity of the potassium cyanide-^{14}C was 2.00 μCi of ^{14}C/mmol of compound.

General Procedure for Cyanide Exchange.—A mixture of substrate (1.0 mmol) and potassium cyanide-^{14}C (0.26 g, 4.0 mmol) in DMF (25 ml) was stirred under dry nitrogen in a 50-ml, three-necked flask equipped with a gas inlet tube dipping into the liquid, a reflux condenser with a calcium sulfate drying tube, and a thermometer. After the mixture had been heated at a specified temperature and for a specified time (see Table I), it was poured into 150 ml of a 1:1 solution of water and saturated ammonium chloride. The aqueous mixture was filtered. If the substrate was appreciably soluble in water, a chloroform extraction was used, followed by evaporation of the chloroform. Purification was accomplished by column chromatography with silica gel (20 g) and elution with cyclohexane, mixtures of cyclohexane-benzene, and finally benzene. Identification of the compounds was done by comparison with the known compounds by tlc, melting point, ir, and elemental analysis.

Preparation of 9,10-Dicyanoanthracene with Potassium Cyanide-^{14}C.—A mixture of 9-cyanoanthracene (0.20 g, 1.0 mmol), labeled potassium cyanide (0.13 g, 2.0 mmol), and α-SAS (0.31 g, 1.0 mmol) in 25 ml of DMF was heated at 80° for 2 hr. The reaction mixture was poured into water and filtered hot. The solid product (0.18 g, 80%) was purified by recrystallization from chloroform and by column chromatography. The melting point (335°) and the infrared spectrum were identical with those of 9,10-dicyanoanthracene.[2b] A sample was combusted and analyzed by liquid scintillation counting. The measured radioactivity was 2.00 μCi of ^{14}C/mmol of compound.

An identical experiment was run at 100° for 4 hr. The radioactivity of the purified 9,10-dicyanoanthracene was 2.68 μCi of ^{14}C/mmol of compound.

Preparation of 9-Phenyl-10-cyanoanthracene.—To a solution of 9-phenylanthracene (0.508 g, 2.0 mmol) in 25 ml of carbon disulfide in a 50-ml, three-necked, round-bottomed flask equipped with thermometer, addition funnel, and reflux condenser, bromine (0.32 g, 2.0 mmol) in 25 ml of carbon disulfide was added dropwise over a 30-min period at 23°. Stirring was continued for 3 hr. The excess bromine and carbon disulfide were removed by evaporation to yield a yellow solid (0.50 g) which was mixed with cuprous cyanide (1.7 g, 20 mmol) in 80 ml of DMSO and heated under reflux for 4 hr. The reaction mixture was poured into 500 ml of a 1:1 solution of water and concentrated ammonium hydroxide. The aqueous mixture was filtered to yield a brownish precipitate, which was dried. The product was extracted from the solid with chloroform to separate it from the residual cuprous cyanide. An intensely yellow solid was obtained after evaporation of the chloroform. Tlc showed two spots, one of which corresponded to 9-phenylanthracene. The mixture was separated by silica gel chromatography to give 9-phenyl-10-cyanoanthracene, mp 198–200° (lit.[7] mp 199–200°), in an overall yield of 65%.

Preparation of 9-Methyl-10-cyanoanthracene.—The method of Calas and Lalande[8] was used to prepare 9-methyl-10-cyanoanthracene from 9-methylanthracene by bromination in carbon disulfide, followed by treatment with cuprous cyanide. The latter reaction was carried out in DMSO. A yellow solid, mp 204–205 (lit.[8] mp 205°), was obtained after silica gel chromatography and crystallization from ethanol.

Hydrolysis of Reaction Mixture with Tritiated Water.—A mixture of 9-cyanoanthracene (0.20 g, 1.0 mmol) and sodium cyanide (0.20 g, 4.0 mmol) in 25 ml of DMF was heated for 2 hr at 80°. The reaction mixture was then poured into 100 ml of tritiated water (0.484 μCi of tritium/mmol of water). After purification of the yellow solid obtained, a 45% recovery of starting material was found. Combustion of a sample, followed by a liquid scintillation measurement of the water obtained, showed that the compound contained 0.19 μCi of tritium/mmol of compound.

Hydrolysis of Reaction Mixture with Deuterium Oxide.—The reaction was performed exactly as the preceding one, except that deuterium oxide (100 g) was used in the work-up. Analysis of the water obtained from a burned sample showed that 4.5% of the hydrogen present in the compound was deuterium. A mass spectrum showed a similar increase in the 204 peak; an nmr spectrum also showed a reduction in the peak at δ 8.55.

Reaction of 9-Cyanoanthracene with Sodium Borohydride.—In a three-necked, 100-ml, round-bottomed flask equpped with a reflux condenser, gas inlet, and 50-ml dropping funnel were placed 1.0 g (5.0 mmol) of 9-cyanoanthracene and 30 ml of DMF. Nitrogen was bubbled through the mixture. A solution of sodium borohydride (0.38 g, 10 mmol) in 25 ml of DMF was then added dropwise over a 0.5 hr period. The purple mixture was then stirred for an additional 2 hr at room temperature and then poured onto 50 ml of Dowex 50W-X8 acid resin which had been washed with DMF. After hydrogen evolution ceased, approximately 0.5 hr, the DMF solution was separated from the resin by suction filtration and then poured into a solution prepared from 275 ml of water and 25 ml of saturated ammonium chloride solution. The mixture was allowed to stand overnight and was then filtered to give 0.85 g of a pale yellow solid, mp 110–113°. Recrystallization from heptane gave 0.65 g of white needles, mp 115–116°.

Anal. Calcd for $C_{15}H_{11}N$: C, 87.80; H, 5.37; N, 6.83. Found: C, 87.85; H, 5.32; N, 6.73.

Reaction of 9,10-Dicyanoanthracene with Sodium Borohydride.—In a three-necked, 100-ml, round-bottomed flask equipped with a reflux condenser, gas inlet, and 50-ml dropping funnel were placed 0.228 g (1.0 mmol) of 9,10-dicyanoanthracene and 35 ml of DMF. The mixture was heated to 60°, as nitrogen was bubbled through the solution. After the 9,10-dicyanoanthracene had dissolved, a solution of sodium borohydride (0.076 g, 2.0 mmol) in 10 ml of DMF was added dropwise over a 0.5-hr period. The purple mixture was then stirred for 2 hr at 60° and poured onto 20 ml of Dowex 50W-X8 acid resin which had been washed with DMF. After hydrogen evolution had ceased, approximately 15 min, the DMF solution was separated from the resin by suction filtration. Some of the 9,10-dicyanoanthracene was lost because of its insolubility in DMF. The DMF solution was then poured into 300 ml of water containing 25 ml of saturated ammonium chloride solution. After a few minutes the mixture was filtered, and the solid obtained (0.13 g) was dried and dissolved in chloroform. The solution was then evaporated onto silica gel and put on top of a 15-g column. Elution with 1:1 benzene–cyclohexane gave 0.10 g (50%) of 9-cyanoanthracene and 0.025 g of 9,10-dicyanoanthracene.

Cyanation of Acridine.—In a 50-ml, round-bottomed flask equipped with a gas inlet, condenser, and thermometer were placed acridine (1.78 g, 10 mmol), sodium cyanide (1.0 g, 20 mmol), α-SAS (3.41 g, 10 mmol), and 40 ml of DMSO. The mixture was heated for 3 hr at 90° and was then poured into 300 ml of water containing 25 ml of 10% sodium hydroxide. After a few minutes, the mixture was filtered while it was still warm. After thorough washing, the solid was dried and dissolved in 200 ml of chloroform; decolorizing charcoal and anhydrous magnesium sulfate were added to the solution. Filtration and evaporation of the solvent gave 1.66 g (83%) of a yellow solid: mp 181–182° (lit.[9] mp 180–181°); ir 2220, 1630, 1520, 1150, 750 cm^{-1}.

Anal. Calcd for $C_{14}H_8N_2$: C, 82.35; H, 3.92; N, 13.73. Found: C, 82.36; H, 3.98; N, 13.46; mol wt, 204 (mass spectrum).

Hydrolysis of 9-Cyanoacridine-^{14}C to 9-Acridinecarbamide-^{14}C.—A mixture of the labeled 9-cyanoacridine (0.13 g, 0.800 μCi of ^{14}C/mmol of compound) and 3 ml of 90% H_2SO_4 was heated on a steam bath for 3 hr. The mixture was then poured into 200 ml of water and a 10% KOH solution was added until the pH of the solution was 11. The solid (0.146 g) was collected, washed with water, and then dried. The material was recrystallized twice from ethanol. The purified samples gave a melting point of 264–265° (lit.[10] mp 263–264°). Radioassay gave a value of 0.786 μCi of ^{14}C/mmol of 9-acridinecarbamide.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.68; H, 4.50; N, 12.61. Found: C, 75.42; H, 4.39; N, 12.47.

(7) C. Dufraisse and J. Mathieu, *Bull. Soc. Chim. Fr.*, 302 (1947).

(8) R. Calas and R. Lalande, *ibid.*, 770 (1959).

(9) N. S. Brozdov and O. M. Cherntsoz, *Zh. Obshch. Khim.*, **21**, 1918 (1951).

(10) G. I. Braz and S. A. Kore, *ibid.*, **23**, 868 (1953).

Aroylmethylamine Synthesis by Stephen Reduction of Aroyl Cyanides

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The Stephen reduction of nitriles normally gives rise to an aldimine complex that affords the aldehyde on hydrolysis.[1] Wibaut and Overhoff isolated 2,6-dichloro-4-aminomethylpyridine as the end product of the Stephen reduction of 2,6-dichloro-4-cyanopyridine.[2]

In the course of the synthesis of sympathomimetic amines, we observed that the reduction of aroyl cyanides by the Stephen method leads to the corresponding aroylmethylamine hydrochlorides in good yields. Table I summarizes the results.

TABLE I

STEPHEN REDUCTION OF AROYL CYANIDES

ArCOCN Ar⁻	—ArCOCH₂NH₃⁺ Cl⁻— Yield, %	Mp, °C
Phenyl[a]	67	184–186 dec[b]
2-Methylphenyl[c]	78	160–161 dec[b]
3-Methylphenyl[c]	50	174–175 dec[d]
4-Methylphenyl[c]	62	208–210 dec[d]
4-Methoxyphenyl[e]	60	197–199 dec[f]
3,4,5-Trimethoxyphenyl[g]	56	254–255 dec[h]
2-Furyl[i]	50	249–250 dec[j]

[a] T. S. Oakwood and C. A. Weisgerber, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1958, p 112.   [b] S. Cheng, S. Jonsson, and F. T. Semeniuk, *J. Pharm. Sci.*, **51**, 108 (1962).   [c] F. Asinger, A. Saus, H. Offermanns, and H. D. Hahn, *Justus Liebigs Ann. Chem.*, **691**, 92 (1966).   [d] G. Jones, *J. Chem. Soc.*, 1918 (1960).   [e] J. F. Eastman and S. Selman, *J. Org. Chem.*, **26**, 293 (1961).   [f] H. E. Baumgarten and J. M. Petersen, *J. Amer. Chem. Soc.*, **82**, 459 (1960).   [g] G. P. Schiemenz and H. Engelhard, *Chem. Ber.*, **92**, 1336 (1959).   [h] A. Sonn, *ibid.*, **58**, 1103 (1925).   [i] E. Fischer and F. Brauns, *ibid.*, **46**, 892 (1913).   [j] O. Dann, H. Ulrich, and E. E. Moeller, *Z. Naturforsch.*, **7b**, 344 (1952).

The amino ketones can be reduced to amino alcohols with hydrogen in the presence of a palladium-on-carbon catalyst;[3] however, direct reduction of acyl cyanides to amino alcohols is perferred.[4]

Experimental Section

Reduction Procedure.—Anhydrous stannous chloride (28.0 g, 0.15 mol) in 100 ml of anhydrous ether was saturated with hydrogen chloride at room temperature. While the mixture was stirred in an ice–water bath, 0.1 mol of the aroyl cyanide was added dropwise. After 3 hr the mixture was filtered and the residue was washed with anhydrous ether. The residue was suspended in 500 ml of water containing 5 ml of hydrochloric acid, and was then saturated with H₂S. The tin sulfides were removed by filtration and the filtrate was evaporated in a rotary still. The residual aroymethylamine hydrochloride was purified by crystallization from acetone–ether.

(1) E. Mossetig, *Org. React.*, **8**, 246 (1954).
(2) J. P. Wibaut and J. Overhoff, *Recl. Trav. Chim. Pays-Bas*, **52**, 55 (1933).
(3) G. N. Walker and M. A. Moore, *J. Org. Chem.*, **26**, 432 (1961).
(4) A. Burger and E. D. Hombaker, *J. Amer. Chem. Soc.*, **74**, 5514 (1952).

The Action of Hydrazine and Its Derivatives on the Addition Products of Allyl Isothiocyanate and Dimethyl Malonate. A Correction

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In connection with some other work, we needed samples of I and II, the preparation of which has been described by Worrell.[1]

I   IIa, X = Cl   III
                 b, X = Br
                 c, X = I
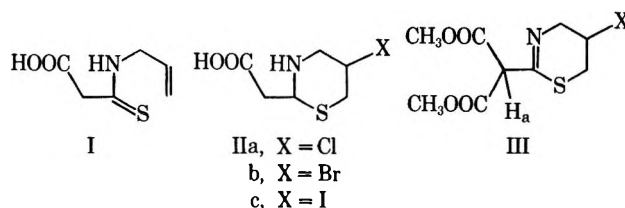
Condensation of dimethyl malonate and allyl isothiocyanate gave IV. Hydrazinolysis of IV, followed by reaction with hydrochloric acid, did not, however, yield I, mp 120–121°, as described, but the hydrazide VI, mp 120–121° (Scheme I). No attempt was made

SCHEME I
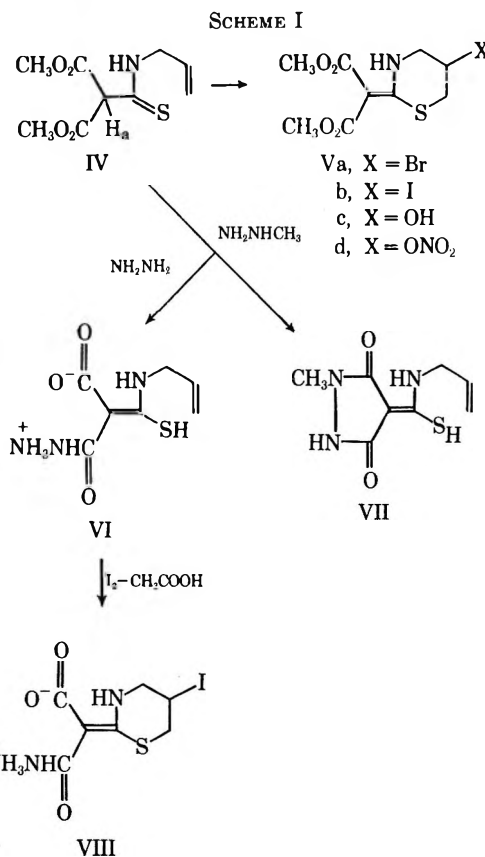
to differentiate between the two possible geometric isomers.

The structure of I had been based on its sulfur analysis (Calcd for C₆H₉O₂NS·2H₂O: S, 16.4. Found:

(1) D. E. Worrell, *J. Amer. Chem. Soc.*, **54**, 2061 (1932).

S, 16.4), which is close to that of VI (S, 15.95). Microanalysis indicated formula $C_7H_{11}O_2N_3S$ rather than $C_6H_{13}O_4NS$. The nmr spectrum of VI showed bands characteristic of the allyl group, which were in the same position as in the starting material IV, one low-field exchangeable proton at 10.1 ppm, and a broad band (5 H), the position of which was concentration dependent ($NH-N^+H_3$, NH, and SH). The major feature of the infrared spectrum was a very broad band at 3500–2300 cm^{-1}, typical of an amine salt.

Reaction of VI with iodine gave, as described, a compound, mp 213–214°, which does not have the structure of IIc, but VIII.[2]

In order to confirm the structure of the hydrazinolysis product VI, diester IV was treated in an analogous manner with methylhydrazine. The unstable product obtained appeared to have the cyclic structure VII,[2] as evidenced by its elemental analysis and nmr spectrum, which indicated the presence of an *N*-methyl group (δ 3.2 ppm, singlet), an allyl group, and only three exchangeable protons (D_2O).

Worrell's conversion of IV to Va and Vb could be duplicated. However, treatment of Va with alcoholic silver nitrate did not give the alcohol Vc as described,[1] but nitrate Vd. Compound Vd gave a positive test for the nitrate group (diphenylamine and sulfuric acid).[3]

It appears that the position of the double bond in Va and Vb is exocyclic and not endocyclic (III), as had been described. The assignment for the position of the double bond is based mainly on the nmr spectra of Va and Vb, which do not show the low-field proton H_a of compound IV (δ 5.6 ppm, singlet), but indicate the presence of a typical N–H proton at 3.0–6.0 ppm (broad band). In addition, Va and Vb absorb at longer wavelength [λ_{max}^{EtOH} 285 nm (ϵ 12,500)] than IV [λ_{max}^{EtOH} 274 nm (ϵ 13,400)].

The position of the double bond in VI and VII is based on the fact that both compounds form a cuprous salt (thiol),[4] and both show secondary amine absorption in their ir spectra. No experimental work was done to find out why reaction of IV with hydrazine and methylhydrazine gave the hydrazido acid VI and the pyrazolidinedione VII, respectively.

Experimental Section

Melting points were determined on a Gallenkamp block and are uncorrected. Mass spectra were obtained on an AE1-MS-902 mass spectrometer at 70 eV using a direct-insertion probe. Nmr spectra were recorded on a Varian Associates T-60 spectrometer. Ir spectra were obtained on a Unicam SP1000 and a Perkin-Elmer 257 infrared spectrophotometer. Ultraviolet spectra were determined with a Unicam SP-800 spectrophotometer. Microanalyses were carried out by A. Bernhardt Mikroanalytisches Laboratorium, Elbach uber Engelskirchen, and C. Daessle, Montreal.

Carbomethoxy Methyl Malonate Monothioallylamide (IV).—This compound was prepared according to the procedure of Worrell[1] with the following modification: the mixture of the sodium salt of dimethyl malonate and allyl isothiocyanate was refluxed for 24 hr with vigorous stirring. This ensured that most of the sodium metal had reacted and minimized the possibility of any large excess of sodium igniting when the mixture was poured

into ice water. After recrystallization from ethyl alcohol–water, a 56% yield of IV was obtained: mp 42–43° (lit.[1] yield 66%; mp 42–43°); ir (KBr) 3335, 3385 (NH), 1750, 1715 cm^{-1} (C=O); nmr (CDCl$_3$) δ 3.9 (s, 6), 4.4 (t, 2), 5.6 (s, 1), 5.2–6.4 (m, 3), 4.0–6.0 (s, broad, NH); uv max (95% C$_2$H$_5$OH) 274 nm (ϵ 13,400); mass spectrum (70 eV) *m/e* 231 (M$^+$).

Anal. Calcd for $C_9H_{13}O_4NS$: C, 46.75; H, 5.62; N, 6.06; S, 13.85. Found: C, 47.03; H, 5.48; N, 5.87; S, 14.03.

Reaction of IV with Bromine (Va).—The procedure of Worrell was followed exactly: yield 68%; mp 152–154° (lit.[1] yield 68%; mp 153–154°); ir (KBr) 3200, 1615, 1650 cm^{-1}; nmr (DMSO-d_6) δ 3.9 (s, 6), 4.1 (m, 2), 3.6 (m, 3), 3.0–6.0 (broad, 1, NH); uv max (95% ethanol) 285 nm (ϵ 12,500); mass spectrum (70 eV) *m/e* 309 (M$^+$), 311 (M$^+$ + 2).

Anal. Calcd for $C_9H_{12}O_4NSBr$: C, 34.95; H, 3.88; N, 4.53; S, 10.36; Br, 25.85. Found: C, 34.92; H, 3.83; N, 4.53; S, 10.61; Br, 25.96.

The iodo derivative Vb was prepared in a similar manner, mp 156–157° (lit.[1] mp 156–157°).

Reaction of Va with Silver Nitrate (Vd).—This compound was prepared according to Worrell: yield 65%; mp 104–105° (lit.[1] mp 104–105°) (after drying under vacuum at 40°, mp 81–82°); ir (KBr) 3220, 1650, 1660, 1630 (ONO$_2$), 1285, 870–855 cm^{-1} (ON); nmr (DMSO-d_6) δ 3.8 (s, 6), 3.95 (m, 3), 4.7 (m, 2), 9.8 (broad, 1, NH); mass spectrum (70 eV) *m/e* 292 (M$^+$), 229 (M$^+$ − HNO$_3$). It was difficult to obtain good analytical values because of the unstability of Vd.

Anal. Calcd for $C_9H_{12}O_7N_2S$: C, 36.99; H, 4.11; N, 9.59; S, 10.95. Found: C, 37.48; H, 4.29; N, 9.63; S, 10.87.

Reaction of IV with Hydrazine (VI).—The procedure of Worrell was followed except for the following modification in the work-up: the concentrated deep red solution was added slowly, with vigorous stirring, to an iced solution of 5 *N* hydrochloric acid. If this was not strictly followed an intractable gum was obtained which could not be crystallized. During the reaction a strong odor of hydrogen sulfide was detected, probably due to gross decomposition of the thioamide. A 20% yield of crystalline product was obtained. It turned yellow upon standing for several weeks. Water of hydration was removed by drying the compound under vacuum at 60° for 4–6 days: mp 120–121°; ir (KBr) 3300, 3000–2300 (NH$_3^+$ str), 1630–1520 (C–O str), 1480, 1430, 1230, 1040, 1000, 940, 775 cm^{-1}; nmr (DMSO-d_6) δ 4.3 (t, 2), 5.35 (m, 1), 5.1 (m, 1), 6.0 (m, 1), 3.0–6.0 (broad, 5), 10.1 (broad, 1); uv max (95% C$_2$H$_5$OH) 293 nm (ϵ 16,500), 255 (14,300).

Anal. Calcd for $C_7H_{11}O_3N_3S$: C, 41.79; H, 5.47; N, 20.89; S, 15.95. Found: C, 42.02; H, 5.27; N, 21.16; S, 15.72.

Reaction of IV with Methylhydrazine (VII).—VII was prepared according to the procedure described for VI, except that the deep red solution was worked up after 2–3 hours. The resulting crystalline solid (25%) was recrystallized from ether–hexane: mp 186–188° (dried under vacuum at 40° overnight); ir (KBr) 3320, 2800–2700 (NCH$_3$); nmr (DMSO-d_6) δ 3.2 (s, 3), 4.5 (t, 2), 5.3 (m, 1), 5.6 (m, 1), 5.9 (m, 1), 4.0–9.0 (broad, 3, exchangeable with D$_2$O); uv max (95% EtOH) 295 nm (ϵ 18,800), 258 (16,000).

Anal. Calcd for $C_8H_{11}O_2N_3S$: C, 45.07; H, 5.16; N, 19.72; S, 15.02. Found: C, 45.53, 44.51; H, 5.13, 5.31; N, 19.96; S, 14.83.

Reaction of VI with Iodine (VIII).—The compound was prepared according to the published procedure.[1] The product was dried overnight under vacuum at 100° to yield 75% of a colorless, crystalline product: mp 213–214° (lit.[1] 213–214°); ir (KBr) 3300, 3000–250C (NH$_3^+$), 1640 cm^{-1}; nmr (DMSO-d_6) δ 3.0 (m, 2), 3.3 (m, 2), 3.6 (m, 1), 5.0–10.0 (broad, 5, exchangeable with D$_2$O); uv max (95% EtOH) 295 nm (ϵ 22,400).

Anal. Calcd for $C_7H_{10}O_3N_3SI$: C, 24.50; H, 2.94; N, 12.25; S, 9.33; I, 37.01. Found: C, 24.67; H, 2.97; N, 12.43; S, 9.60; I, 37.11.

Registry No.—IV, 32444-37-4; Va, 32444-38-5; Vb, 32444-39-6; Vd, 32444-40-9; VI, 32444-41-0; VII, 32444-42-1; VIII, 32444-43-2; hydrazine, 302-01-2.

(2) See Experimental Section.
(3) F. Feigl, "Spot Tests in Organic Analysis," 7th ed, Elsevier, New York, N. Y., 1966, p 178.
(4) Reference 3, p 222.

7-Nitro-1,3,5-triazaadamantane and Derivatives. Reactions of Azaadamantanes with Anhydrides

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The preparations of 7-nitro-1,3,5-triazaadamantane (**4**) and of 1,3,5-triaza-7-adamantylamine (**7**) are disclosed in a U. S. Patent.[1] We had been studying the preparation and properties of **4** before the cited patent came to our attention, and we wish to submit our results at this time.

Previously,[1] compound **4** was prepared by heating a mixture of ethanol, paraformaldehyde, ammonium acetate, and nitromethane. We found that **4** could also be prepared from tris(hydroxymethyl)nitromethane, ammonium hydroxide, and paraformaldehyde.

Some reactions carried out with **4** are shown in Scheme I. Of these, perhaps the only ones requiring comment are reactions of **4** and of 1,3,5-triaza-7-adamantylamine (**7**) with acetic anhydride and of **7** with isopropenyl acetate. On attempted acetylation of **7** with acetic anhydride, 5-acetamido-3,7-diacetyl-1,3,7-triazabicyclo[3.3.1]nonane (**9**) was isolated rather than the expected 7-acetamido-1,3,5-triazaadamantane (**10**). Compound **10** was finally prepared by long refluxing of **7** in isopropenyl acetate.

After **9** had been identified, the reaction of **4** with acetic anhydride was studied, and was found to lead to a good yield of 3,7-diacetyl-5-nitro-1,3,7-triazabicyclo-[3.3.1]nonane (**2**). Similar products were formed from benzoic and propionic anhydrides. The bicyclononanes were identified by analysis and by nmr. The formaldehyde formed was identified by its distinctive odor.

The nmr spectrum of **4**, taken in trifluoroacetic acid, is simple, and consists of a sharp peak at δ 4.23 (6 H) and an AB system at δ 4.75 and 5.07 (6 H, J_{AB} = 13 Hz). The single peak is attributed to the six hydrogen atoms on carbon atoms 6, 8, and 10, while the AB system is formed by splitting between the axial and equatorial hydrogen atoms on carbon atoms 2, 4, and 9.

The nmr spectrum of 3,7-diacetyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane (**2**), taken in dimethyl-d_6 sulfoxide, is complex, although the methyl peak (6 H) at δ 2.11 is easily identified. Based on six hydrogen atoms for the methyl groups, the rest of the peaks integrate for a total of ten hydrogen atoms.

The course of the reaction forming **2** is not known, but does not involve splitting out formaldehyde as methylene acetate. When methylene acetate was added to a reaction mixture of **4** and acetic anhydride a new peak appeared at δ 5.70 in the nmr spectrum.

The formation of **2** from **4** and acetic anhydride is similar to the reaction of 1,3-diazaadamantane with nitrous acid and tosyl chloride,[2] in which formaldehyde is split out and the corresponding dinitroso and ditosyl derivatives are formed. It is also similar to these and other reactions of hexamethylenetetramine which lead

Scheme I
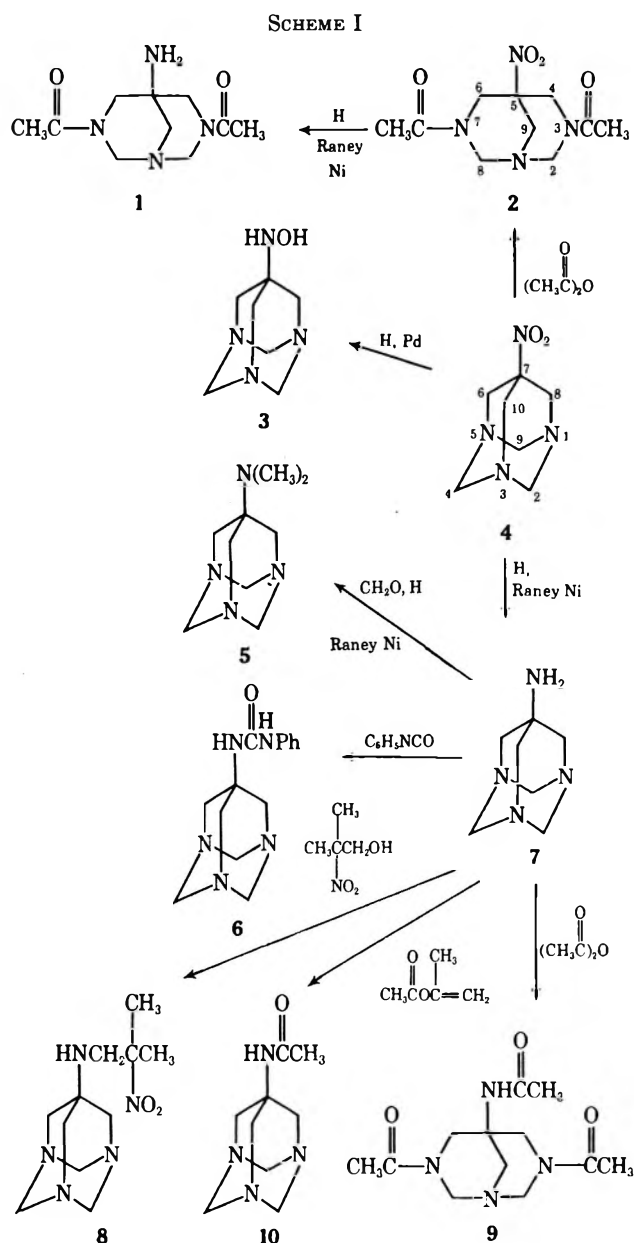
to 3,7 derivatives of 1,3,5,7-tetraazabicyclo[3.3.1]-nonane,[3] and particularly to that of acetic anhydride with hexamethylenetetramine, which was found to lead to a 6.5% yield of 3,7-diacetyl-1,3,5,7-tetraazabicyclo-[3.3.1]nonane.[4]

We have found that the reaction of hexamethylenetetramine and acetic anhydride at room temperature for 4 min gives a 45% yield of 3,7-diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane, but at 90° for 45 min only 9% of the bicyclic product was isolated. Presumably further reaction leading to the tetraacetyltetrazocine occurs, but the bicyclic diacetyl compound crystallizes preferentially. However, with propionic anhydride at 90° for 2 hr, a 39% yield of 1,3,5,7-tetrapropionyloctahydrotetrazocine was isolated. The nmr spectrum (CDCl₃) consisted of a strong peak at δ 5.34 (8 H), a quartet at δ 2.60 (8 H), and a triplet at δ 1.15

(1) N. W. Gabel, U. S. Patent 3,301,854 (Jan 31, 1967).

(2) H. Stettler and R. Merten, *Chem. Ber.*, **90**, 868 (1957).

(3) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms" Part Two, Interscience, New York, N. Y., 1961, pp 1393–1398.

(4) E. Aristoff, J. A. Graham, R. H. Meen, G. S. Myers, and G. F. Wright, *Can. J. Res.*, **27B**, 520–544 (1949). See also M. Dominikiewicz, *Arch. Chem. Farm.*, **2**, 78 (1935); *Chem. Abstr.*, **30**, 1029⁸ (1936).

(12 H). A Dreiding model of this compound indicated it to be a very flexible ring.

Experimental Section

All melting points were taken in open capillary tubes and are uncorrected. The nmr spectra were determined using a Varian A-60A spectrometer, and ir spectra were taken on a Perkin-Elmer Model 21 spectrometer using a KBr disk.

7-Nitro-1,3,5-triazaadamantane (4).—To 150 ml of 28% ammonium hydroxide was added 75.0 g of tris(hydroxymethyl)-nitromethane. The solution was heated in a 40° bath and stirred with a magnetic stirrer. After 30 min seven 15-ml portions of 38% formaldehyde solution were added at 15-min intervals. Cooling and filtration gave 26.0 g of product (28%). This was recrystallized from 700 ml of water using 2.0 g of decolorizing carbon to give 18.9 g of white crystalline product. In a sealed capillary 4 decomposed over the range 260–310° (lit.[1] mp 315°).

Following the procedure in ref 1, a mixture of 125 ml of ethanol, 15 g of nitromethane, 50 g of paraformaldehyde, and 58 g of ammonium acetate was stirred and refluxed for 6 hr. The reaction mixture after 12 hr cooling was filtered to give 8.7 g of product. This is in contrast to the 35 g of sublimed product reported in ref 1.

The above procedure was modified by adding only 23 g of paraformaldehyde to the other ingredients, stirring and refluxing for 1 hr, adding 11 g of paraformaldehyde, stirring and refluxing for 1 hr, adding another 11-g portion of paraformaldehyde, and then stirring and refluxing for 6 hr. Cooling and filtration gave 20.8 g (45%).

1,3,5-Triaza-7-adamantylamine (7).—To 700 ml of methanol was added 100.0 g of 4. This mixture was reduced for 4 hr at 50° under a hydrogen pressure of 1000 psi in a stainless steel rocking bomb using 30 g of a slurry of Raney nickel in methanol as catalyst. The reaction mixture was cooled, filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in 800 ml of hot benzene, and the solution was concentrated to 300 ml. Cooling and filtration yielded 74 g of product melting at 213–217°. This was recrystallized from 600 ml of benzene to give 58 g of white crystals melting at 218–220° (lit.[1] mp 300–310°). *Anal.* Calcd for $C_7H_{14}N_4$: C, 54.52; H, 9.15; N, 36.33. Found: C, 54.80; H, 9.29; N, 36.11.

1,3,5-Triaza-7-adamantylhydroxylamine (3).—A mixture of 50.0 g of 4, 600 ml of water, and 1.0 g of 5% palladized carbon was reduced at 30° in a stainless steel rocking bomb for 2 hr under 1000 psi of hydrogen. The mixture was filtered and evaporated to dryness *in vacuo*. Then 600 ml of *n*-butyl alcohol was added, and the solution was concentrated to 100 ml. Cooling for 12 hr followed by filtration gave 39.4 g of product, mp 221–223°. Recrystallization from 90% *n*-butyl alcohol–10% water raised the mp to 227–229°. *Anal.* Calcd for $C_7H_{14}N_4O$: C, 49.39; H, 8.28. Found: C, 49.61; H, 8.17.

1,3,5-Triaza-7-adamantyldimethylamine (5).—To 150 ml of methanol was added 9.2 g of 7, 9 ml of 37% formaldehyde solution, and about 5.0 g of a suspension of Raney nickel in water. This mixture was reduced for 4 hr at room temperature and 50 psi of hydrogen in a Parr hydrogenation apparatus. After concentration *in vacuo* the residue was dissolved in 50 ml of acetone, mixed with 20 ml of cyclohexane, and then evaporated to 20 ml. Filtration gave 6.3 g, mp 100–108°. Recrystallization from cyclohexane raised the mp to 106–108°. *Anal.* Calcd for $C_9H_{18}N_4$: C, 59.30; H, 9.95. Found: C, 59.12; H, 10.04.

N-Phenyl-N'-(1,3,5-triaza-7-adamantyl)urea (6).—The residue from the reduction of 9.2 g (0.05 mol) of 4 with Raney nickel was dissolved in 100 ml of hot benzene. After cooling, 6 ml of phenyl isocyanate were added; the mixture was stirred for 5 hr and then filtered. The product was recrystallized twice from nitromethane to give 5.3 g of product which decomposed above 200°. *Anal.* Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.42; H, 7.00; N, 25.77.

N-(2-Nitroisobutyl)-1,3,5-triaza-7-adamantylamine (8).—To 7.7 g (0.05 mol) of 7 in 150 ml of methanol was added 5.0 g of 2-methyl-2-nitro-1-propanol. The solution was refluxed for 1 hr, then evaporated to dryness. The residue was crystallized from 100 ml of cyclohexane plus 20 ml of ethanol to give 2.9 g, mp 213–216°. *Anal.* Calcd for $C_{11}H_{21}N_5O_2$: C, 51.74; H, 8.30; N, 27.43. Found: C, 51.63; H, 8.32; N, 27.43.

7-Acetamido-1,3,5-triazaadamantane (10).—To 50 ml of isopropenyl acetate was added 6.0 g of 7, and the mixture was re-

fluxed for 24 hr. After cooling for 12 hr, 5.8 g of product was recovered, mp 182–188°. The ir spectrum of this product was identical with that of a small amount previously prepared using a 6-hr refluxing period. This product melted at 188–191°. *Anal.* Calcd for $C_9H_{16}N_4O$: C, 55.08; H, 8.22; N, 28.55. Found: C, 55.09; H, 8.07; N, 28.71.

5-Acetamido-3,7-diacetyl-1,3,7-triazabicyclo[3.3.1]nonane (9).—A mixture of 10 ml of acetic anhydride and 3.0 g of 7 was heated on the steam bath for 30 min, then mixed with 100 ml of water. The solution was then evaporated to dryness *in vacuo*. The residue was crystallized from 25 ml of isopropyl alcohol to give 0.7 g, mp 232–236°. *Anal.* Calcd for $C_{12}H_{20}N_4O_3$: C, 53.71; H, 7.52; N, 20.88. Found: C, 53.80; H, 7.57; N, 20.73.

3,7-Diacetyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane (2).—The previous experiment was repeated using 4 in place of 7, and crystallizing the product from 40 ml of isopropyl alcohol. This gave 2.9 g of product, mp 158–161°. *Anal.* Calcd for $C_{10}H_{16}N_4O_4$: C, 46.87; H, 6.29. Found: C, 46.92; H, 6.57.

5-Amino-3,7-diacetyl-1,3,7-triazabicyclo[3.3.1]nonane (1).—2 (10 g) was reduced for 4 hr at 50 psi and room temperature in 150 ml of methanol using about 5 g of a suspension of Raney nickel in water. Recrystallization from methanol plus acetone gave 4.4 g, mp 180–182°. *Anal.* Calcd for $C_{10}H_{18}N_4O_2$: C, 53.08; H, 8.02; N, 24.76. Found: C, 53.20; H, 8.03; N, 25.00.

5-Nitro-3,7-dipropionyl-1,3,7-triazabicyclo[3.3.1]nonane.—To 50 ml of propionic anhydride was added 10 g of 4, and the mixture was heated for 45 min on the steam bath. It was then stirred with 200 ml of ice water and concentrated to dryness *in vacuo*. The residue was crystallized twice from isopropyl alcohol (100 ml and 75 ml) to give 10.6 g, mp 145–147°. *Anal.* Calcd for $C_{12}H_{20}N_4O_4$: C, 50.69; H, 7.09. Found: C, 50.89; H, 7.22.

3,7-Dibenzoyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane.—A mixture of 9.2 g of 4 and 19.6 g of benzoic anhydride was heated for 4 hr on the steam bath. The mixture was then treated with 50 ml of hot isopropyl alcohol and filtered. Addition of 40 ml of water to the filtrate, followed by cooling overnight, gave 8.2 g of crystals, mp 160–189°. Recrystallization from aqueous isopropyl alcohol gave 5.1 g, mp 239–240°. *Anal.* Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30. Found: C, 62.95; H, 5.53.

1,3,5,7-Tetrapropionyloctahydrotetrazocine.—A mixture of 50 ml of propionic anhydride and 10 g of hexamethylenetetramine was heated for 2 hr on the steam bath. It was then cooled and mixed with 200 ml of water. After 30 min this mixture was concentrated *in vacuo*, and the residue was crystallized twice from 50 ml of isopropyl alcohol to give 7.3 g, mp 152–154°. *Anal.* Calcd for $C_{16}H_{28}N_4O_4$: C, 56.46; H, 8.29; N, 16.46. Found: C, 56.56; H, 8.35; N, 16.37.

3,7-Diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane.—To 50 ml of acetic anhydride was added 10 g of hexamethylenetetramine. The solution was heated on the steam bath for 15 min, then mixed with 200 ml of ice water. This mixture was then concentrated *in vacuo*, and the residue was taken up in 100 ml of hot ethyl acetate. On cooling and filtering 2.2 g of crystals were obtained, mp 190–196°. Recrystallization from an ethanol–ethyl acetate solution raised the mp to 193–195°. Similar experiments with reaction times of 45 min (steam bath) and 4 min (room temperature) gave, respectively, 1.4 and 6.8 g. *Anal.* Calcd for $C_9H_{16}N_4O_2$: C, 50.92; H, 7.60. Found: C, 51.17; H, 7.60.

A Convenient Procedure for the Preparation of 2-Arylazirines

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In connection with studies on the synthesis and reactions of 3-aryl-1-azabicyclobutanes,[1] a series of 2-(para-substituted)phenylazirines was required. We have found that several simple modifications of Smolinsky's original route[2] to 2-phenylazirine result in a convenient procedure for the preparation of large quantities of these substances in consistently high overall yield. Continuing interest in the reactions[1,3] and photochemistry[4] of azirines prompts us to record this procedure which has been in use in our laboratory for several years.

The original route[2] from 1a to 5a involves conversion of 2a into 3a using NaN_3 in dimethylformamide, isolation and treatment of crude 3a with potassium *tert*-butylate in benzene to yield 4a (after work-up and chromatography), and finally a pyrolysis of 4a which was accomplished by passing a stream of its vapor in nitrogen through a hot tube at 350° and 20 mm to produce crude 5a in about 60% overall yield.

Our attempts to prepare 5a in comparable yield on a large scale failed, primarily as a result of losses incurred during the lengthy pyrolysis step due to polymerization of the vinyl azide 4a in the reservoir. The difficulty was overcome by heating a solution of 4a in refluxing toluene for about 1.5 hr.[5] However, the azirine 5a obtained in this manner (~70% yield) was contaminated with about 5% of 1-bromostyrene from which it could be separated only by careful fractional distillation.

Further studies indicated that the bromostyrene impurity arose from dehydrohalogenation of 2a which was always present in the crude bromo azide 3a (along with small amounts of vinyl azide 4a) when the specified *equimolar* amounts[2] of 2a and NaN_3 were used to convert 2a to 3a. It could be demonstrated[6] that azide ion is a sufficiently strong base to effect dehydrohalogenation of some of the azido bromide 3a as it is formed; consequently, some of the limited quantity of azide ion used in this step is converted to hydrazoic acid which is ineffective in converting the remaining 2a to 3a. It

(1) (a) A. G. Hortmann and D. A. Robertson, *J. Amer. Chem. Soc.*, **89**, 5974 (1967); (b) J. L. Kurz, B. K. Gillard, D. A. Robertson, and A. G. Hortmann, *ibid.*, **92**, 5008 (1970).

(2) G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).

(3) G. Smolinsky and B. I. Feuer, *ibid.*, **31**, 1423 (1966); S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **40**, 1014 (1967); N. J. Leonard and B. Zwanenburg, *J. Amer. Chem. Soc.*, **89**, 4456 (1967); A. Hassner and F. W. Fowler, *ibid.*, **90**, 2869 (1968); J. Ciabattoni and M. Cabell, Jr., *ibid.*, **93**, 1482 (1971).

(4) A. Padwa and J. Smolanoff, *ibid.*, **93**, 548 (1971); B. Singh and E. F. Ullman, *ibid.*, **88**, 1844 (1966); F. P. Woerner, H. Reimlinger, and D. R. Arnold, *Angew. Chem., Int. Ed. Engl.*, **7**, 130 (1968).

(5) Formation of azirines upon pyrolysis of vinyl azides in refluxing aprotic solvents has also been observed by others; see F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967); K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968); F. P. Woerner and H. Reimlinger, *Chem. Ber.*, **103**, 1908 (1970).

(6) The reactions were studied by withdrawal of aliquots from the reaction mixtures and assay of the organic products by nmr spectroscopy after isolation *via* a normal work-up procedure.

was found that, if instead a large excess of NaN_3 (>2.1 equiv) is used, then complete conversion of 2a to 3a and further conversion of 3a to 4a could be effected almost completely at room temperature without requiring the use of any other base. However, the method, as a direct route from 2a-f to 4a-f necessitated long reaction times for complete conversion, and thus an alternate procedure (Scheme I) was developed whereby

SCHEME I
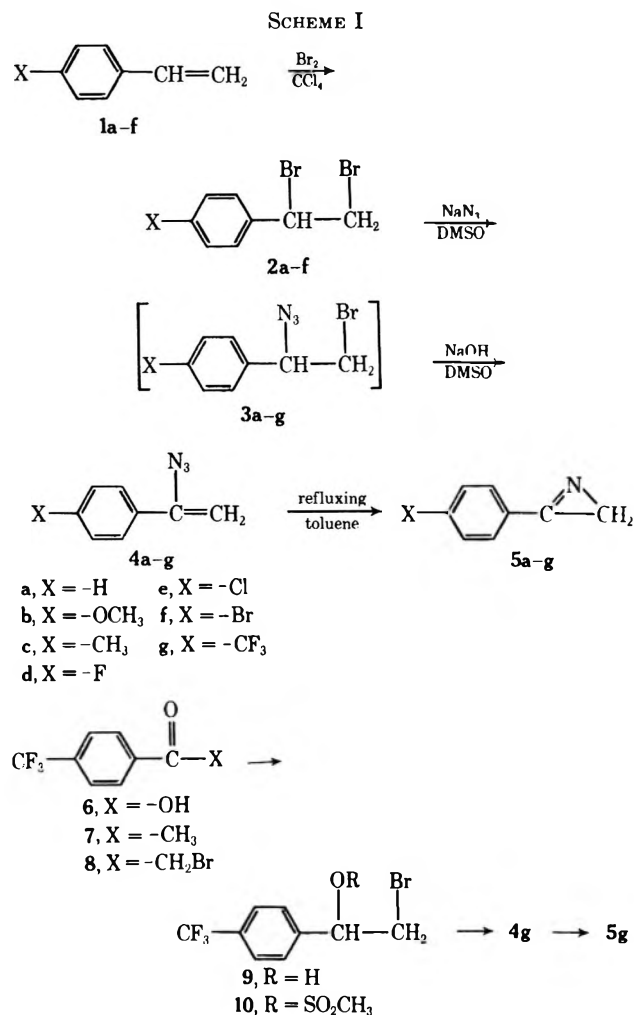
the dibromides 2a-f were dissolved in DMSO and treated with about 1.5 mol equiv of NaN_3 followed after 12–24 hr by addition of NaOH directly to the DMSO solutions in the form of either pellets or (preferably) 50% aqueous solution to hasten the dehydrohalogenation. Pyrolysis of the crude azidostryenes 4a-f in refluxing toluene afforded the azirines 5a-f in 55–65% overall yield from 1a-f after simple distillation.

The commercial nonavailability of *p*-trifluoromethylstyrene prompted the development of an alternate route to 5g (6 → 7 → 8 → 9 → 10 → [3g] → 4g → 5g). Interestingly, only 10 and 4g were in evidence as the reaction between 10 and NaN_3 proceeded;[6] none of the intermediate azido bromide 3g could be detected.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra (ir) were recorded on a Perkin-Elmer Model 457 spectrophotometer; nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60A instrument using TMS (δ = 0.00) as an internal standard. Basic alumina (Alcoa F-20; 100–200 mesh) was used

for column chromatography. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

2-Phenyl-1-azirine (5a).—Bromine (80 g, 0.50 mol) in 100 ml of CCl₄ was added slowly to a stirred and cooled (15–20°) solution of styrene (52.1 g, 0.50 mol) in 400 ml of CCl₄. After the addition was complete, the CCl₄ was removed *in vacuo* and the remaining residue of crystalline 1,2-dibromostyrene (2a) was dissolved in 750 ml of dimethyl sulfoxide (Fisher, certified). The resulting solution was placed in a three-necked flask fitted with a heavy-duty mechanical stirrer and a gas inlet tube. A slow stream of N₂ was passed through the apparatus. With the aid of an ice bath, the solution was maintained at 15–20° during the addition of 49 g (0.75 mol) of sodium azide and for 45 min afterward. The mixture became thick with precipitated azido bromide 3a and was stirred for a further 13 hr at 24–26°.[7] After cooling to 12° the reaction mixture was treated with a solution of 20.0 g (0.50 mol) of NaOH in 20 ml of H₂O. The temperature rose to 19°. Stirring was continued at ambient temperature (24–26°) for 24 hr. The mixture was poured into 2 l. of 2% aqueous NaHCO₃ solution and extracted with CH₂Cl₂ (technical). The combined extracts were washed with H₂O, filtered through cotton (premoistened with CH₂Cl₂), and evaporated to yield crude 1-azidostyrene 4a as a red oil: nmr (CCl₄) δ 4.82 (d, 1, *J* = 2.1 Hz), 5.27 (d, 1, *J* = 2.1 Hz), and 7.1–7.6 (m, 5).[8] The oil was diluted with 200 ml of petroleum ether (bp 63–69°) and passed through a column of alumina (200 g) using an additional 800 ml of the same solvent as an eluent. The eluate was evaporated and the residual pale yellow oil was dissolved in toluene (1.2 l., reagent grade). The solution was refluxed until the evolution of nitrogen ceased (1.5 hr). Removal of the solvent and distillation of the crude product, using a 6-in. Vigreux column, afforded 36.7 g (63%) of 2-phenyl-1-azirine (5a), bp 58.0–58.5° (2.8 mm). The azirine was ~97–98% pure, as determined by comparison of the integrated area of the peaks in the phenyl region (215 units) *vs.* the area of the 2 H singlet at δ 1.61 (84 units).

2-(4'-Methoxyphenyl)-1-azirine (5b).—Azirine 5b was prepared essentially as described for 5a, starting with dibromide 2b prepared from 16.78 g (0.125 mol) of 4-methoxystyrene (1b) (Borden Chemical Co.) and reducing the quantities of other reagents accordingly. A solution of 2b in 180 ml of DMSO was stirred for 20 hr after the addition of NaN₃ (12.35 g, 0.188 mol) and for 7.5 hr after the addition of NaOH [6.75 ml, 0.125 mol, 1:1 (w/w) solution in H₂O]; the usual work-up procedure (including filtration of crude 4b through 50 g of alumina) was followed by refluxing a solution of 4b in toluene (600 ml) for 1.5 hr. Distillation afforded 9.93 g (54%) of 5b as a pale yellow liquid, bp 101–102.5° (2.8 mm), which readily solidified. An nmr assay indicated that the distilled product was of ≥97% purity.

A sample of 5b obtained earlier using the procedure described by Smolinsky for the preparation of 5a exhibited mp 29–31°; ir (CCl₄) 1730, 1610, 1500, 1450, 1440, 1320, 1300, 1280, 1240, 1160, 1030, 980, and 830 cm⁻¹; nmr (CCl₄) δ 1.64 (s, 2), 3.87 (s, 3), and 6.9–8.0 (m, 4).

Anal. Calcd for C₉H₉NO: C, 73.45; H, 6.16; N, 9.62. Found: C, 73.40; H, 6.08; N, 9.70.

2-(4'-Methylphenyl)-1-azirine (5c).—Azirine 5c was prepared essentially as described for 5a, starting with dibromide 2c obtained from 29.5 g (0.25 mol) of 4-methylstyrene (2a) (Borden Chemical Co.). A solution of 2c in 350 ml of DMSO was stirred for 21 hr after the addition of 24.7 g (0.38 mol) of NaN₃ and for 60 hr after addition of 10 g (0.25 mol) of NaOH (pellets). The usual work-up procedure followed by filtration through alumina, pyrolysis, and distillation, as described for 5a, afforded 18.7 g (57%) of 5c: bp 74.8–76.3° (5 mm); nmr (CCl₄) δ 1.60 (s, 2), 2.37 (s, 3), and an A₂B₂ pattern centered at δ 7.25 and 7.70. An nmr assay indicated that the distilled product was of ~96% purity.

2-(4'-Fluorophenyl)-1-azirine (5d).—Azirine 5d was prepared as described for 5a, starting with 24.4 g (0.20 mol) of 4-fluorostyrene (Sigma Chemical Co.) and reducing the quantities of other reagents accordingly to yield 16.9 g (63%) of distilled azirine 5d of >95% purity (nmr assay) after two distillations:

bp 63–66° (5.5 mm); nmr (CCl₄) δ 1.63 (s, 2), 7.13 (~t, 2, *J* ~ 8.3 Hz), and 7.80 (~dd, 2, *J* ~ 5.5, 8.3 Hz).

2-(4'-Chlorophenyl)-1-azirine (5e).—Azirine 5e was prepared as described for 5c, starting with 34.5 g (0.25 mol) of 4-chlorostyrene (Borden Chemical Co.) and yielding 22.7 g (60%) of distilled product, bp 86–88° (5.5 mm), which was 87% pure by nmr assay. Sublimation at 40° (0.3 mm) afforded crystalline material (mp 42.5–44.5°) of ≥95% purity: nmr (CCl₄) δ 1.65 (s, 2) and 7.3–7.8 (sym A₂B₂ pattern, 4).

2-(4'-Bromophenyl)-1-azirine (5f).—Azirine 5f was prepared on an 0.05-mol scale essentially as described for 5c. The product (≥98% pure) was isolated in 54% yield by preparative sublimation: mp 72–73.7°; nmr (CCl₄) δ 1.66 (s, 2) and 7.61 (s, 4). A thrice-sublimed sample exhibited mp 73–74.5°.

4'-Trifluoromethylacetophenone (7).—A 300-ml three-necked flask containing a magnetic stirring bar was charged with 150 ml of anhydrous ether and 10.0 g (0.0525 mol) of 4-trifluoromethylbenzoic acid (6) (Pierce Chemical Co.). The solution was placed under N₂ and methyllithium [50 ml of a 2.1 *M* solution in ether (Alfa Inorganics)] was added dropwise at 0–5° over a period of 45 min. The reaction solution was poured onto ice and washed with H₂O until the washes were neutral, dried (Na₂SO₄), and evaporated to yield 9.6 g (99%) of crude ketone 7. Chromatography on alumina using CHCl₃–petroleum ether (bp 63–69°) (1:4 by volume) as eluent afforded pure 4'-trifluoromethylacetophenone (7): mp 30–33° [lit. bp 79–80° (8 mm);[9] bp 81–84° (8–9 mm)[10]]; nmr (CCl₄) 2.56 (s, 3) and 7.55–8.14 ppm (m, 4); ir (CCl₄) 1695, 850, 720, and 610 cm⁻¹.

2-Bromo-1-(4'-trifluoromethylphenyl)ethanol (9).—Crude 2-bromo-4'-trifluoromethylacetophenone (8)[10] (7.5 g, 0.028 mol; contained about 2 mol % each of the corresponding dibrominated and unbrominated ketone by nmr analysis) was dissolved in 100 ml of CH₃OH. The solution was cooled in an ice bath and H₂O was added to the point of cloudiness (about 10–20 ml). A solution of 0.28 g (0.0074 mol) of sodium borohydride in ethanol (the minimum volume that would give complete solution) was added dropwise with stirring and continued cooling. Ten minutes after the addition was complete, the solution was concentrated to half volume *in vacuo*. The concentrated solution was diluted with 250 ml of H₂O and extracted with CH₂Cl₂. The extracts were dried (Na₂SO₄) and evaporated *in vacuo* leaving 7.4 g (98%) of crude 2-bromo-1-(4'-trifluoromethylphenyl)ethanol (9) as a mixture of diastereomers: nmr (CCl₄) 3.35–3.95 (m, 3), 4.70–5.05 (m, 1), and 7.2–7.7 ppm (m, 4); ir (neat) 3400, 1620, 1480, 1420, 1325, 1110–1180, 1070, 1025, 850, and 680 cm⁻¹.

2-(4'-Trifluoromethylphenyl)-1-azirine (5g).—Crude 2-bromo-1-(4'-trifluoromethylphenyl)ethanol (9) (20.6 g, 0.077 mol) was dissolved in 80 ml of anhydrous pyridine and 7 ml (0.090 mol) of methanesulfonyl chloride was added. The solution was cooled (ice bath) for 1 hr and allowed to stand at ambient temperature for 3 hr. The reaction solution was diluted with 150 ml of benzene and washed successively with water, 10% HCl, H₂O, 5% Na₂CO₃, and H₂O. The benzene solution was dried (Na₂SO₄) and concentrated *in vacuo* leaving 21.3 g (68%) of a mixture of crude 2-bromo-1-(4'-trifluoromethylphenyl)ethanol methanesulfonates (10): nmr (CCl₄) 2.92 (m, 0.72), 3.55–3.73 (m, 0.35), 5.60–5.90 (m, 0.25), and 7.4–7.9 ppm (m, 1.00).[11] The crude mixture of methanesulfonates (21.3 g, 0.061 mol) was dissolved in 100 ml of *N,N*-dimethylformamide and 4.5 g (0.069 mol) of sodium azide was added. The solution was stirred for 26 hr at ambient temperature. The reaction solution was diluted with H₂O (500 ml) and extracted with petroleum ether (bp 35–40°) until the extracts were colorless. The combined extracts were dried (Na₂SO₄) and evaporated *in vacuo* leaving 16 g of red oil. The nmr spectrum of the crude product indicated that the reaction was incomplete. The crude product was again dissolved in *N,N*-dimethylformamide (80 ml) containing 0.9 g (0.014 mol) of sodium azide. After 18 hr the reaction was worked up as before yielding 13.0 g (100%) of crude 1-azido-4'-trifluoromethylstyrene (4g). The crude product was chromatographed on alumina with petroleum ether (bp 63–69°) as eluent yielding 10.5 g (63%) of 95% pure 1-azido-4'-trifluoromethylstyrene (4g): bp 40–45° (1.8 mm); nmr (CCl₄) 5.01 (d, 1, *J* = 2.5 Hz), 5.47 (d, 1, *J* = 2.5 Hz), and 7.41 ppm (s, 4); ir (CCl₄)

(7) An aliquot withdrawn from the mixture at this time contained **3a** and **4a** in a ratio 1.0:1.0; none of the starting dibromide **2a** could be detected. The azido bromide **3a** exhibits nmr δ (CCl₄) 3.45 (d, 2, *J* = 6.5 Hz), 4.67 (t, 1, *J* = 6.5 Hz), and 7.3 ppm (s, 5).

(8) The description of the nmr spectrum of **4a** as "two single sharp lines at τ 5.68 and 4.68 . . . " in ref 2 is apparently in error.

(9) E. T. McBee, S. Resconich, L. R. Belohlav, and H. P. Braendlin, *J. Org. Chem.,* **28**, 3579 (1963).

(10) W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.,* **75**, 5884 (1953).

(11) Since the product is impure, the integrated peak areas do not simplify to a ratio of whole numbers of protons.

2200, 2140, 2110, 1615, 1410, 1320, 1295, 1175, 1140, 1120, 1095, 1070, 1020, 910, 850, and 620 cm^{-1}. The impurity in the azidostyrene was assumed to be another 1-substituted styrene: nmr (CCl$_4$) 5.60 (d, 1, J = 2.1 Hz) and 5.80 ppm (d, 1, J = 2.1 Hz).

The partially purified 1-azido-4'-trifluoromethylstyrene (4g) (4.6 g, 0.0216 mol) was refluxed in toluene (300 ml) until the evolution of nitrogen ceased (1 hr). The toluene was evaporated *in vacuo* and the residue was distilled yielding 2.8 g (70%) of 2-(4'-trifluoromethylphenyl)-1-azirine (5g): bp 42–44° (1.2 mm); nmr (CCl$_4$) 1.74 (s, 2) and 7.6–8.2 ppm (m, 4); ir (CCl$_4$) 1750, 1735, 1620, 1420, 1325, 1180, 1140, 1110, 1070, 1020, 995, 850, and 600 cm^{-1}.

Anal. Calcd for C$_9$H$_6$NF$_3$: C, 58.30; H, 3.26; N, 7.55. Found: C, 58.12; H, 3.20; N, 7.33.

The azirine 5g also contained about 4 mol % of the same impurity (1-substituted styrene) which was present in the azidostyrene 4g. The impurity could not be removed by repeated recrystallization of the azirine 5g from petroleum ether at −40°.

Registry No.—3a, 29847-04-9; 4a, 16717-64-9; 4g, 32654-71-0; 5a, 7654-06-0; 5b, 32687-32-4; 5c, 32687-33-5; 5d, 32687-34-6; 5e, 32687-35-7; 5f, 17631-26-4; 5g, 32687-37-9; 7, 709-63-7; 9, 32687-39-1; 10, 32687-40-4.


Stereochemistry of Tropane Quaternizations[1]

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In 1964, MacGillavry and Fodor[3] reported the results of an X-ray diffraction study of an N-ethyltropinium bromide which indicated that the major products from reactions of N-ethylnortropine (1b) and tropine (1a) with methyl and ethyl iodide, respectively,
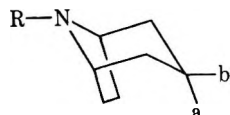
1, a = OH; b = H   a, R = CH$_3$
2, a = H; b = OH   b, R = C$_2$H$_5$
3, a, b = O   c, R = PhCH$_2$
4, a = b = H

are formed by equatorial attack. Three years later, a group at Sheffield[4] questioned MacGillavry and Fodor's results and suggested that these major quaternization products, as well as the main products from other quaternizations of tropanes and 3-substituted tropanes,[5] are formed by axial attack. The following year, Fodor,

Medina, and Mandava[6] reported that empirical correlations of nmr chemical shifts of exo α hydrogens indicated that the main products from reactions of tropine and pseudotropine (2a) with ethyl iodide are formed by different stereochemical pathways, namely, equatorial attack on tropine and axial attack on pseudotropine.[7] In that same year, two of us[11a] and Fodor and Mandava[11b] reported that hydrolysis of the lactone formed from pseudotropine bromoacetate gave the same N-carboxymethylpseudotropinium bromide as is formed by hydrolysis of the main product from quaternization of pseudotropine (2a) with ethyl bromoacetate. Because the lactone was formed by inter- rather than intramolecular reaction,[8] these results[11] led to the *erroneous conclusions* (1) that the N-carboxymethylpseudotropinium bromides were formed by axial attack on nitrogen and, therefore, (2) that the structural assignments originally made by Fodor, Koczka, and Lestyán[5] to the ethoxycarbonylmethylation products were incorrect.

Results described here and in a recent paper by Fodor and coworkers[8] establish conclusively that the predominant pathway for ethylation as well as methylation (or deuteriomethylation), alkoxycarbonylmethylation, and other quaternizations of tropine (1a), pseudotropine (2a), tropinone (3a), and several related compounds is by equatorial attack.

The major product from pseudotropine (2a) and ethyl bromide was obtained in >98% purity (nmr) by two crystallizations from methanol of the 74:26 mixture of diastereomers with δ_{NCH_3} 3.12 and 2.98 ppm, respectively.[12] The crystals are orthorhombic, space group *Pbca*, with unit cell dimensions a = 11.93, b = 14.15, c = 13.32 ± 0.004 Å, d_{obsd} (flotation) 1.45, d_{calcd} 1.45, Z = 8. A crystal was ground to a sphere of diameter 0.31 mm, and intensities were measured on a Picker automatic diffractometer using Ni-filtered Cu Kα radiation (λ 1.5418) and the θ–2θ scan mode to a value of 2θ = 133°. Out of 1952 measured reflections, 1648 were considered to be observed. The data were corrected for absorption effects (μR = 0.784) in addition to the usual data treatment. The position of the bromine atom was found from a three-dimensional Patterson map. A Fourier summation phased on the bromine atom immediately revealed the

(1) Supported in part by Grant CA-05528 from the National Cancer Institute, U. S. Public Health Service.

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(3) C. H. MacGillavry and G. Fodor, *J. Chem. Soc.*, 597 (1964); see also P. Benci, C. H. Stam, and C. H. MacGillavry, *Tetrahedron Lett.*, 243 (1971).

(4) D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc. B*, 1184 (1967).

(5) G. Fodor, K. Koczka, and J. Lestyán, *Magy. Kem. Foly.*, 59, 242 (1953); *J. Chem. Soc.*, 1411 (1956).

(6) G. Fodor, J. D. Medina, and N. Mandava, *Chem. Commun.*, 581 (1968).

(7) This incorrect tentative conclusion concerning the stereochemistry of quanternization of pseudotropine with ethyl iodide resulted from misassignment of the band due to the hydroxyl group to the equatorial methyl group. In the solvent used for examination of the nmr spectra of the diastereomeric N-ethylpseudotropinium salts, the two N-methyl bands are coincident. Our results and those of Fodor, *et al.*,[8] confirm the conclusion reached by Closs[9] in 1959 that exo α hydrogens of N substituents in the equatorial configuration of tropane and 3-substituted tropane salts are more shielded than when in the axial configuration. The opposite is generally the case for piperidine salts.[10]

(8) G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, 93, 403 (1971). We thank Professor Fodor for informing us of their results prior to publication.

(9) G. L. Closs, *ibid.*, 81, 5456 (1959).

(10) For examples, see (a) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 218 (1962); (b) H. O. House and C. G. Pitt, *J. Org. Chem.*, 31, 1062 (1966); (c) A. T. Bottini and M. K. O'Rell, *Tetrahedron Lett.*, 429 (1967).

(11) (a) C. C. Thut and A. T. Bottini, *J. Amer. Chem. Soc.*, 90, 4752 (1968); (b) N. Mandava and G. Fodor, Abstracts, 51st Annual Conference of the Chemical Institute of Canada, Vancouver, B. C., June 1968, p 56.

(12) Both samples had mp >300°. The melting point is a poor criterion of purity for salts of 1a and 1b. *Cf.* S. P. Findlay, *J. Amer. Chem. Soc.*, 75, 3204 (1953); G. Fodor, *Acad. Chim. Acad. Sci. Hung.*, 5, 379 (1955). See also K. Zeile and W. Schulz, *Chem. Ber.*, 88, 1078 (1955).

positions of the atoms heavier than hydrogen and showed that the ethyl group was equatorial. After three cycles of full-matrix least-squares refinement with independent isotropic temperature factors, the R index was 0 15.[13] A perspective drawing of the conformation of the molecule is shown in Figure 1.

Oxidation with ruthenium oxide[14] of the 74:26 mixture of N-ethylpseudotropinium bromides and of the 72:28 mixture of diastereomeric salts obtained from the reaction of ethyl bromide with tropine (δ_{NCH_3} 3.01 and 2.98 ppm, respectively, in dry DMSO-d_6; δ 3.02 ppm in D$_2$O) gave 74:26 and 71:29 mixtures of N-ethyltropinonium bromides with δ_{NCH_3} 3.32 and 3.18 ppm. Treatment of tropinone (3a) with a tenfold excess of ethyl bromide in acetonitrile gave a 75:25 mixture of the same salts, the major product being identical with the major product from the above oxidations. Thus, quaternizations with ethyl bromide of tropine and tropinone, as well as pseudotropine, occur predominantly by equatorial attack.

We have also related the stereochemistry of quaternizations of 1a, 2a, and 3a with deuteriomethyl benzenesulfonate and with ethyl bromoacetate. The *ca.* 70:30 (δ_{NCH_3} 3.02 and 2.98 ppm in DMSO-d_6; 3.00 ppm in D$_2$O) and 72:28 (δ_{NCH_3} 3.18 and 3.03 ppm) mixtures obtained from tropine and pseudotropine, respectively, and deuteriomethyl benzenesulfonate gave on oxidation with ruthenium oxide corresponding mixtures of the N-deuteriomethyltropinonium benzenesulfonates with δ_{NCH_3} 3.38 and 3.21 ppm. The major product from each of these oxidations was identical with the major product obtained directly from tropinone and deuteriomethyl benzenesulfonate. Similar oxidations of the 92:8 (δ_{NCH_3} 3.25 and 3.16 ppm) and 91:9 (δ_{NCH_3} 3.38 and 3.00 ppm) mixtures of diastereomers obtained from tropine and pseudotropine, respectively, and ethyl bromoacetate gave 92:8 and 90:10 mixtures of the same salts with δ_{NCH_3} 3.57 and 3.34 ppm obtained directly from tropinone and ethyl bromoacetate in a ratio of 82:18.

We also examined quaternizations of tropine (1a), pseudotropine (2a), and tropane (4a) with ethyl brosylate, ethyl chloride, ethyl iodide, ethyl chloroacetate, and ethyl iodoacetate. Under otherwise identical reaction conditions, the stereochemical results of these alkylations did not differ significantly from those obtained when bromide was the leaving group. Further, under otherwise identical reaction conditions, the stereochemistry of these quaternizations was not changed significantly when the solvent was acetonitrile, benzene, or methanol.

Fodor and coworkers[8] carried out an X-ray crystal structure analysis of the dihydrate of N-carboxymethylpseudotropinium bromide prepared from the major product from pseudotropine and ethyl bromoacetate, and they found that the carboxymethyl group is equatorial. These workers also used chemical methods to correlate the stereochemistry of the predominant product from tropine and ethyl bromoacetate with that
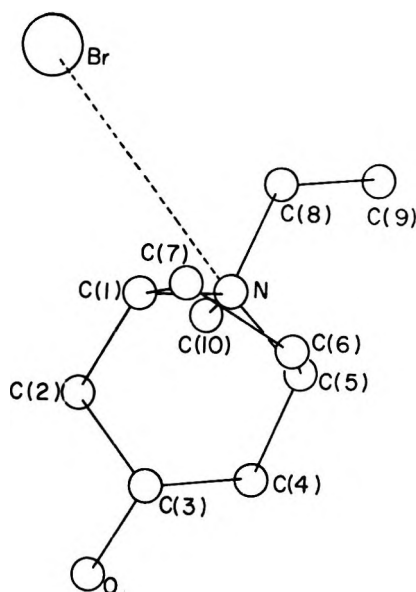

Figure 1.—Perspective of the major product from pseudotropine and ethyl bromide.

of the major products from pseudotropine (2a), tropinone (3a), and tropane (4a) with ethyl bromoacetate as well as the major products from 1a, 2a, and 4a with ethyl bromide and 1a with deuteriomethyl iodide.

Thus, our results and the X-ray structural determination of Fodor and coworkers[8] confirm their chemical correlations of the stereochemistry of the major ethoxycarbonylmethylation and ethylation products. In addition, our results with the deuteriomethylation products, together with Fodor and coworkers' correlation by chemical means of the stereochemistry of the major products from tropine with deuteriomethyl iodide and ethyl bromoacetate,[8] establish that deuteriomethylation of pseudotropine and tropinone also occurs predominantly by equatorial attack.

During the course of this work, we observed that product ratios obtained from quaternizations of tropinone (3a) change as the reactions proceed. For example, quaternization of 3a (0.5 M) with deuteriomethyl benzenesulfonate (0.5 M) at 30° in acetonitrile-d_3 gave a product ratio of 88:12 after 30 min, when the reaction was 70% complete, and this ratio decreased to a constant value of 77:23 after 24 hr, when the reaction was complete. Addition of either tropinone or pyridine resulted in a further gradual change of this ratio to 50:50. A possible mechanism for this and similar equilibrations involves opening of the bicyclic quaternary salt by the weak base[15] to the corresponding 6-dialkylamino-2-cycloheptenone, followed by Michael-type addition to give one or the other of the diastereomeric salts.[16] This mechanism gains support from the observation that dimethylamine hydrochloride, in the presence of dimethylamine, adds to 2,6-cycloheptadienone to give N-methyltropinonium chloride in good yield.[17]

Significantly, treatment with pyridine of the 87:13

(13) Listings of structure factors, conformational parameters, coordinates, and isotropic temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfilm.

(14) H. O. House and B. A. Tefertiller, *J. Org. Chem.*, **31**, 1068 (1966).

(15) Treatment with stronger base under more vigorous conditions gives a mixture of cycloheptadienones; see J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *J. Amer. Chem. Soc.*, **77**, 4401 (1955).

(16) A possible alternative mechanism is mentioned briefly in ref 8.

(17) A. T. Bottini and J. Gal, *J. Org. Chem.*, **36**, 1718 (1971).

and 37:63 (δ_{NCH_2} 4.42 and 4.47 ppm) mixtures of diastereomeric salts obtained, respectively, from quaternizations of tropinone (3a) with benzyl brosylate and N-benzylnortropinone (3c)[17] with methyl brosylate gave the same 72:28 mixture, the predominant isomer being the major product of the benzylation. Essentially the same product ratio was obtained on addition of N-methylbenzylamine hydrochloride to 2,6-cycloheptadienone. If one allows that the N-benzyltropinonium salt with the benzyl group equatorial is the more stable, these results indicate that quaternizations of tropinone with benzyl brosylate and N-benzylnortropinone with methyl brosylate also occur predominantly by equatorial attack. As reactions of benzyl brosylate with tropine (1a), pseudotropine (2a), and tropane (4a) give product ratios (90:10) similar to that obtained with tropinone (3a), and, in view of the similar stereochemistry seen in alkoxycarbonylmethylations, deuteriomethylations, or ethylations of the four bases, it seems likely that the benzylations of 1a, 2a, and 4a also occur mainly by equatorial attack.

Experimental Section[18]

Amines and quaternizing agents used were either obtained commercially or prepared following well-described procedures. Unless noted otherwise, quaternary salts were prepared at 30° from equimolar amounts of amine and quaternizing agent. Preparative runs were carried out in acetonitrile with initial concentrations of 0.2–0.5 M; for other runs, initial concentrations were 0.07–0.10 M.

Nmr spectra were determined with a Varian A-60A system of 10–20% solutions of the quaternary salts in deuterium oxide, dimethyl-d_6 sulfoxide, or equal volumes of these solvents containing 1% 3-trimethylsilyl-1-propanesulfonic acid sodium salt. Several reactions in acetonitrile containing 1% TMS were also followed directly by nmr. The ratio of the diastereomeric salts was taken as equal to the intensity ratio of the bands due to the N-methyl protons and, when possible, the N-benzyl protons. At least eight determinations of product compositions from reactions with high ($\gtrsim$7:1) and moderate ($\sim$3:1) degrees of stereoselectivity gave average deviations of 3 and 2%, respectively. Chemical shifts of the bands used for analysis were not changed significantly ($\pm$2 cps) when the anion was changed from bromide to chloride or iodide; change of anion from bromide to brosylate resulted in similar upfield shifts of these bands (cf. ref 10b and 10c). Assignment of bands in the nmr spectra of salts other than bromides was confirmed by examination of the spectra of mixtures of these salts and the corresponding bromides.

Ruthenium oxide solutions were prepared as described by House and Tefertiller,[14] and oxidations were carried out with approximately 200 mg of mixed quaternary salts. Yields of crude products, which were analyzed by nmr, ranged from 92–99%.

The N-benzyltropinonium brosylates and N-deuteriomethyl benzenesulfonates, as 0.3–0.5 M solutions, were equilibrated in 12–96 hr at 39° in 0.15 M solutions of pyridine in either acetonitrile-d_3 or deuterium oxide. Attempts to equilibrate the N-ethoxycarbonylmethyltropinonium bromides with pyridine in acetonitrile-d_3 were complicated by rapid saponification, as indicated by the appearance in the nmr spectrum of the upfield bands due to ethanol.

N-Benzyltropinonium chloride was prepared in 67% yield by allowing a mixture prepared from 206 mg (1.9 mmol) of 2,6-cycloheptadienone, 300 mg (1.9 mmol) of N-methylbenzylamine hydrochloride, 20 μl of N-methylbenzylamine, and 1 ml of methanol to stand at room temperature for 58 hr.

Registry No.—1a, 120-29-6; 2a, 135-97-7; 3a, 532-24-1; 2a reaction product with ethyl bromide, 32515-65-7.

(18) For details of most of the work summarized here, see C. C. Thut, Ph.D. thesis, University of California, Davis, 1970.

A Nuclear Magnetic Resonance Study of 2,4-Dinitrohalobenzenes and 2,4-Dinitrohalonaphthalenes

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The three spin system of trisubstituted benzenes has been extensively studied,[2] but little data on substituted naphthalenes have appeared. The spectra of 2,4-dinitrohalobenzenes are simple first-order spectra which may be compared to the classic data of the halobenzenes. We anticipated finding more complex AB-CD spectra for the 2,4-dinitrohalonaphthalenes and looked for similar comparisons with the halobenzene spectra.

Experimental Section

The 2,4-dinitrohalobenzenes were samples prepared for previous work.[3] Similarly, the preparation and purification of the 2,4-dinitrohalonaphthalenes are described.[4] The nmr spectra of the 2,4-dinitrohalobenzene series were observed with a Varian T-60, in 10% solution (acetone solvent) with TMS as an internal standard. The T-60 was calibrated against the Jungnickel[5] standard solution. The naphthalene series spectra were observed on a Varian HA-100.[6] The naphthalene samples were run in degassed dioxane solution; the solutions were less than 10% by weight. The chemical shifts and coupling constants were calculated on a control Data Corp. computer, CDC-6400 with the LAOCN3 program, as modified by J. T. Gerig.[7]

Results and Discussion

The calculated chemical shifts and coupling constants are presented in Tables I, II, and III. Comparison of

TABLE I
CHEMICAL SHIFTS FOR
1-X-2,4-DINITRONAPHTHALENES IN DIOXANE

Proton no.	Chemical shift from dioxane at 100 Mc, Hz		
	X = Cl	X = Br	X = I
3	512.60 ± 0.00	504.7 ± 0.00	493.3 ± 0.00
5	494.80 ± 0.02	419.35 ± 0.02	483.21 ± 0.02
6	436.23 ± 0.03	433.23 ± 0.02	428.77 ± 0.03
7	431.97 ± 0.03	429.98 ± 0.02	424.09 ± 0.03
8	506.67 ± 0.02	503.07 ± 0.02	496.10 ± 0.02

our data with that of Smith and Ihrig indicates that there is reasonable agreement (Table III). We believe that the maximum error in absolute chemical shift will be ±1 Hz. The benzene series gave first-order spectra, but the napthalene series gave complex spectra.

(1) Taken (in part) from the Senior Independent Study Thesis of A. H. Kappelman, The College of Wooster, 1970.

(2) L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy to Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, pp 94, 173, 205, 306.

(3) J. D. Reinheimer, R. C. Taylor, and P. E. Rohrbaugh, *J. Amer. Chem. Soc.*, **83**, 835 (1961).

(4) R. C. Krauss and J. D. Reinheimer, *Can. J. Chem.*, **45**, 77 (1967).

(5) J. L. Jungnickel, *Anal. Chem.*, **35**, 1985 (1963).

(6) We gratefully acknowledge the support of Dr. Brian Kieth and Dr. Henry Sable of Case Western Reserve for these spectra.

(7) LAOCN3, A. A. Bothner-By and S. M. Castellano, as modified by J. T. Gerig, personal communication.

J	X = Cl	X = Br	X = I
3,5	0	0	0
5,6	8.64 ± 0.04	8.49 ± 0.03	8.56 ± 0.04
5,7	1.17 ± 0.04	1.29 ± 0.03	1.05 ± 0.04
5,8	0.75 ± 0.03	0.57 ± 0.02	0.58 ± 0.03
6,7	7.16 ± 0.03	6.91 ± 0.02	6.93 ± 0.03
6,8	1.20 ± 0.04	1.12 ± 0.04	0.98 ± 0.04
7,8	8.59 ± 0.04	8.66 ± 0.04	8.56 ± 0.04

TABLE III

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR
1-X-2,4-DINITROBENZENES IN ACETONE

Sub-stituent	Chemical shift			Coupling constant		
	ν_3	ν_5	ν_6	$J_{3,5}$	$J_{3,6}$	$J_{5,6}$
F^a	530.2	515.7	466.1	3.0	0.2	9.3
Cl	530.8	512.6	483.4	2.49	0.10	8.85
Cl^b	529.8	512.3	483.2	2.70	0.36	8.81
Br	527.9	506.6	494.0	2.63	0.26	8.76
I	523.5	495.4	510.7	2.54	0.02	8.80

^{a} T. Schaefer, *Can. J. Chem.*, **40**, 431 (1962). ^{b} S. L. Smith and A. M. Ihrig, *J. Mol. Spectrosc.*, **22**, 241 (1967).

With the data of Spiesecki and Schneider,[8] a plot was made of the chemical shift of the halobenzene protons *vs.* the Pauling electronegativity of the halogen. The same type plot for the chemical shifts of the 2,4-dinitrohalobenzenes shows striking similarities. The H_3 and H_5 in the 2,4-dinitrohalobenzenes series are qualitatively similar to the meta protons of the halobenzene series; H_6 corresponds to the ortho protons in the halobenzenes. The two nitro groups affect the magnitude of the chemical shift, but the nature of the halogen still controls the relative chemical shift within the series.

The 2,4-dinitrohalonaphthalenes gave a much more complex spectra than the benzene series. H_3 appears as an intense singlet with a complex ABCD spectrum for the other protons, H_5, H_6, H_7, and H_8. Since the α protons of naphthalene have a greater chemical shift than β, the assignment of H_5 and H_8 to the downfield portion of the spectra is obvious. Since there is *no* coupling between the substituted and unsubstituted rings, the correct assignment of *one* of the protons (H_5 or H_8) is essential. From this one correct assignment, all other shifts and coupling constants are calculated *via* LAOCN3. The assignment of H_8 to the lower field is based on the data of Wells.[9] The effect of the nitro groups on H_5, H_6, H_7, and H_8 can be calculated.[9] These calculations indicate that ν_8 = 510, ν_5 = 503, ν_6 = 499, and ν_7 = 437 Hz. In other words, the order is H_8 > H_5 > H_6 > H_7. The data of Table I follow this pattern. If one draws resonance structures of the 1-halo-2,4-dinitronaphthalenes, both the 2- and the 4-nitro groups show resonance forms with + charges on the 6 and 8 positions. If electronegativity is the major factor in chemical shifts, these two protons should be downfield with respect to protons 5 and 7. The above argument has the implicit assumption that the halogens do not greatly affect the shift, and that their effect is a perturbation on the major effect of the nitro groups. Is this assumption correct or can we arrive at a satisfactory assignment on other bases? An alternative method is to apply the chemical shift changes of halogens in the ortho, meta, and para positions in benzene to the naphthalene series. If H_8 is regarded as meta to the halogen and H_5 as para, we arrive at the following qualitative result:

1-chloro	ν_8 = 510 (for NO$_2$ groups)	(−2)	(*m*-Cl)	= 508 Hz
	ν_5 = 503 (for NO$_2$ groups)	(−8)	(*p*-Cl)	= 495 Hz
1-bromo	ν_8 = 510	(−6)	(*m*-Br)	= 504 Hz
	ν_5 = 503	(−2)	(*p*-Br)	= 501 Hz
1-iodo	ν_8 = 510	(−15)	(*m*-I)	= 495 Hz
	ν_5 = 503	(−3)	(*p*-I)	= 500 Hz

These assumptions give the same qualitative order as the previous assumptions for the chloro and bromo compounds, but not for iodo. The iodine atom is large, and the peri positions of naphthalene are closer than the meta positions of the benzene. It is probable that the contributions of both the *m*-Br (−6) and the *m*-I (−15) are too negative; their real contribution would be more toward the ortho halogens, which are positive. This approach, though somewhat argumentative, supports the first. The peri effect has been discussed by Zweig, Lancaster, and Neglia.[10] The effect of a peri substituent is to shift that proton downfield; the low-field proton is always at the α position peri to the substituent. In our compounds, H_8 is the α and peri position and should be the low-field proton. Hence, the assignments ν_8 > ν_5 and ν_6 > ν_7 were accepted.

Comparison of the 2,4-dinitrohalonaphthalene series with the benzene series shows the meta pattern is followed. In each case, the chemical shift of the chloro compound is slightly greater than the bromo, which, in turn, is considerably greater than the iodo compounds.

Coupling constants do not vary much with respect to change in halogen. The ortho coupling constants, $J_{5,6}$ and $J_{7,8}$, are about equal (8.5 Hz) and greater than $J_{6,7}$ (7.0 Hz). The meta coupling constants, $J_{5,7}$ and $J_{6,7}$, show no pronounced trends and have the value of (1.0-1.3) Hz. The para coupling constants range from 0.75 to 0.6 Hz.

(10) A. Zweig, J. E. Lancaster, and M. T. Neglia, *Tetrahedron*, **23**, 2577 (1967).

Stepwise Synthesis of Oligopeptides with N-Carboxy-α-Amino Acid Anhydrides. IV. Glycine NCA

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A successful procedure for peptide synthesis using the controlled reaction of N-carboxy α-amino acid anhydrides (NCA's) in an aqueous system has been

(8) H. Spiesecki and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).
(9) R. P. Wells, *J. Chem. Soc.*, 1967 (1963).

TABLE I

RESULTS OF SYNTHESES OF N-GLYCYL PEPTIDES

Peptide	Yield, %	$[\alpha]_D$, deg	Calcd, % C	H	N	Found, % C	H	N
Gly-Gly	90		36.36	6.11	21.20	36.55	6.20	21.50
Gly-L-Ala	87	−59.0 (*c* 2.5, 0.5 N HCl)[a]	41.08	6.91	19.17	40.75	7.12	19.34
Gly-L-Val	91	−19.5 (*c* 2.0. water)[b]	48.25	8.12	16.08	48.33	8.25	16.26
Gly-L-Leu	92	−36.4 (*c* 2.5, water)[c]	51.04	8.58	14.88	51.12	8.61	14.80
Gly-L-Phe	89	41.0 (*c* 2.5, water)[d]	59.45	6.35	12.60	59.60	6.46	12.55
Gly-L-Leu-L-Ala	86	−59.2 (*c* 2.4, water)[e]	50.94	8.18	16.21	51.05	8.20	16.14

[a] −59.3° (*c* 2, 0.5 N HCl): B. F. Erlanger and E. Brand, *J. Amer. Chem. Soc.*, **73**, 3508 (1951).   [b] −19.9° (*c* 2, water): K. R. Rao, S. M. Birnbaum, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **198**, 507 (1952).   [c] −36.3° (*c* 2, water): F. H. Carpenter and D. T. Gish, *J. Amer. Chem. Soc.*, **74**, 3818 (1952).   [d] 40.8° (*c* 2.5, water): ref 2.   [e] −59.0° (*c* 2.5 water): E. Abderhalden and A. Fodor, *Z. Phys. Chem.*, **81**, 1 (1912).

developed by the Merck group.[1,2] The procedure was satisfactorily used by Koppel and coworkers[3] to prepare some oligopeptides. The usefulness of this synthetic method was demonstrated by the total synthesis of the S protein of RNase A.[4-8] In the aqueous system, however, glycine NCA reacted with an amino acid as a nucleophile to give hydantoic acid as a side product to the extent of more than 20% even at the optimal pH of 10.2. 2,5-Thiazolidinedione (glycine NTA), therefore, was used to avoid the formation of the hydantoic acid.[9,10]

Another NCA method for peptide synthesis using the heterogeneous system acetonitrile–water has been reported by us.[11,12] With ordinary stirring and addition of sodium carbonate, the method permitted the synthesis of peptides without such side reactions as polymerization and hydrolysis of the NCA.

A distinct difference in the formation of the hydantoic acid was found between the NCA method in the aqueous system and that in the heterogeneous system. In the reaction of NCA with an amino acid or a peptide in our previous synthesis,[11] attention was not paid to the formation of the hydantoic acid because the desired peptide was obtained in high yield[12,13] and the by-product, if it had been formed, could not react with

(1) R. G. Denkewalter, H. Schwam, R. G. Strachan, T. E. Beesley, D. F. Veber, E. F. Schoenewaldt, H. Barkemeyer, W. J. Paleveda, Jr., T. A. Jacob, and R. Hirschmann, *J. Amer. Chem. Soc.*, **88**, 3163 (1966).

(2) R. Hirschmann, R. G. Strachan, H. Schwam, E F. Schoenewaldt, H. Joshua, B. Barkemeyer, D. F. Veber, W. J. Paleveda, Jr., T. A. Jacob, T. E. Beesley, and R. G. Denkewalter, *J. Org. Chem.*, **32**, 3415 (1967).

(3) K. D. Kopple, T. Saito, and M. Ohnishi, *ibid.*, **34**, 1631 (1969).

(4) R. G. Denkewalter, D. F. Veber, F W. Holly, and R. Hirschmann, *J. Amer. Chem. Soc.*, **91**, 502 (1969).

(5) R. G. Strachan, W. J. Paleveda, Jr., R. F. Nutt, R. A. Vitali, D. F. Veber, M. J. Dickinson, V. Garsky, J. E. Deak, E. Walton, S. R. Jenkins, F. W. Holly, and R. Hirschmann, *ibid.*, **91**, 503 (1969).

(6) S. R. Jenkins, R. F. Nutt, R. S. Dewey, D. F. Veber, F. W. Holly, W. J. Paleveda, Jr., T. Lanza, Jr., R. G. Strachan, E. F. Schoenewaldt, H. Barkemeyer, M. J. Dickinson, J. Sondey, R. Hirschmann, and E. Walton, *ibid.*, **91**, 505 (1969).

(7) D. F. Veber, S. L. Varga, J. D. Milkowski, H. Joshua, J. B. Conn, R. Hirschmann, and R. G. Denkewalter, *ibid.*, **91**, 506 (1969).

(8) R. Hirschmann, R. F. Nutt, D. F. Veber, R. A. Vitali, S. L. Varga, T. A. Jacob, F. W. Holly, and R. G. Denkewalter, *ibid.*, **91**, 507 (1969).
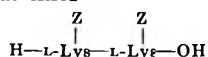
(9) R. S. Dewey, E. F. Schoenewaldt, H. Joshua, W. J. Paleveda, Jr., H. Schwam, H. Barkemeyer, B. H. Arison, D. F. Veber, R. G. Denkewalter, and R. Hirschmann, *ibid.*, **90**, 3254 (1968).

(10) D. F. Veber, R. Hirschmann, and R. G. Denkewalter, *J. Org. Chem.*, **34**, 753 (1969).

(11) Y. Iwakura, K. Uno, M. Oya, and R. Katakai, *Biopolymers*, **9**, 1419 (1970).

(12) R. Katakai, M. Oya, K. Uno, and Y. Iwakura, *ibid.*, in press.

(13) Izumiya, *et al.*, synthesized

$$\underset{\text{H—L-Lys—L-Lys—OH}}{\overset{\text{Z} \qquad \text{Z}}{}}$$

in 87% yield by the NCA method in the heterogeneous system: N. Mitsuyasu, S. Terada, K. Noda, M. Waki, T. Kato, and N. Izumiya, Proceedings of the 8th Symposium on Peptide Chemistry, Osaka, Japan, 1970, p 5.

NCA. In the reaction of glycine NCA with glycine in heterogeneous system, glycylglycine was obtained in 90% yield. Such a yield could not be expected from the results in the aqueous system reported by the Merck group. Glycyl-L-leucine was also obtained in 92% yield by the reaction of L-leucine in the heterogeneous system acetonitrile–water containing sodium carbonate with glycine NCA in acetonitrile. A tripeptide with N-terminal glycine, glycyl-L-leucyl-L-alanine, was also synthesized by the NCA method in the heterogeneous system. The sodium salt of L-alanine was treated with L-leucine NCA and the dipeptide formed was treated with glycine NCA. The resulting tripeptide was recrystallized from aqueous ethanol to give pure tripeptide (86% overall yield). Some N-glycyl dipeptides were also prepared in high yields in the heterogeneous system and these results are summarized in Table I.

These results strongly suggest that few side reactions occurred in the heterogeneous system. This was demonstrated by the synthesis of glycyl-L-tryptophan. After the reaction of glycine NCA with L-tryptophan in the heterogeneous system, the aqueous layer of the system was analyzed by thin layer chromatography. All of the Ehrlich positive components detected on silica gel were ninhydrin positive. No component that was Ehrlich positive and ninhydrin negative could be detected by tlc. These components were quantitatively determined as unreacted L-tryptophan (1%), glycyl-L-tryptophan (96.5%), and glycylglycyl-L-tryptophan (2.5%).

The formation of N-terminal glycyl peptides in high yields without formation of hydantoic acid is consistent with our previous suggestion[11] that the NCA in the heterogeneous system may be protected from side reactions by the acetonitrile layer. The hydantoic acid formed in the homogeneous system may be derived from the isocyanate III formed from the NCA anion II.[2]

The rapid polymerization of NCA (a side reaction in the peptide synthesis by the NCA method) *via* the NCA anion[2,14] does not occur in acetonitrile[15] or in the heter-

(14) M. Goodman and J. Hutchison, *J. Amer. Chem. Soc.*, **88**, 3627 (1966).

(15) Y. Iwakura, K. Uno, and M. Oya, *J. Polym. Sci.*, *Part A-1*, **6**, 2165 (1968).

ogeneous system of acetonitrile–water. Since glycine NCA cannot be transformed to the isocyanate through the NCA anion in the heterogeneous system, hydantoic acid is not formed in this system.

Experimental Section

Glycine NCA.[16]—Into a suspension of 10 g of finely powdered glycine in 400 ml of dry tetrahydrofuran, dry phosgene was bubbled at 45° with magnetical stirring. A clear solution was obtained after 2 hr. The solution was concentrated at reduced pressure at 30°, then glycine NCA crystallized out. To the residue was added 200 ml of n-hexane in order to crystallize out the NCA completely. The crystals of the product were filtered off and dried over P_2O_5 in a vacuum desiccator. The crude product was recrystallized twice from ethyl acetate to yield 9.8 g (73%) of the chlorine-free NCA,[17] mp 100° (lit.[18] 100°).

General Procedure for Synthesis of Glycyl Dipeptides.—To a solution of 0.01 mol of α-amino acid and 1 g of sodium carbonate in 10 ml of 1 N sodium hydroxide and 40 ml of water was added 40 ml of acetonitrile and the system was cooled to −10°. A solution of 1.2 g (0.012 mol) of glycine NCA in 24 ml of acetonitrile was added to the system and allowed to react for 3 hr at −10° with stirring. The aqueous layer of the system was washed with 50 ml of acetonitrile under cooling and neutralized with concentrated sulfuric acid. Sodium sulfate was removed by addition of 200 ml of ethanol followed by filtration and the alcoholic solution was concentrated *in vacuo* at 35°. Addition of 50 ml of ethanol and 100 ml of diethyl ether to the residue gave a crystalline product. The crude product was recrystallized from aqueous methanol to yield a crystalline dipeptide.

Glycyl-L-leucyl-L-alanine.—To a heterogeneous system of 50 ml of acetonitrile and 50 ml of 0.2 N sodium hydroxide containing 0.89 g (0.01 mol) of L-alanine and 1 g of sodium carbonate was added a solution of 1.73 g (0.011 mol) of L-leucine NCA in 17.3 ml of acetonitrile. The condensation reaction was allowed for 2 hr at −10° with stirring. After the reaction the acetonitrile layer of the system was separated off and the aqueous layer was washed with 100 ml of acetonitrile under cooling. The solution was warmed to 40° for 5 min. Then 50 ml of acetonitrile and 20 ml of 0.2 N sodium hydroxide were added to the solution and the system was cooled again to −10°. After the addition of 1.2 g (0.012 mol) of glycine NCA in 24 ml of acetonitrile, the system was kept at −10° for 3 hr with stirring. The aqueous layer of the system was treated by the same manner as above, washing, neutralization, and condensation. The crude product was recrystallized from aqueous ethanol.

Reaction of Glycine NCA with L-Tryptophan.—To a solution of 2.05 g (0.01 mol) of L-tryptophan and 1 g of sodium carbonate in 10 ml of 1 N sodium hydroxide and 40 ml of water, 40 ml of acetonitrile was added and the system was cooled to −10°. After the addition of 1.2 g of glycine NCA in 24 ml of acetonitrile the system was allowed to stand for 3 hr with stirring. The aqueous layer of the system was washed with 50 ml of acetonitrile and diluted with water to a volume of 50 ml. A 40-μl sample of the solution was analyzed by tlc on silica gel in pyridine–water (4:1). A strip showed three ninhydrin-positive spots, unreacted L-tryptophan (R_f 0.57), glycyl-L-tryptophan (R_f 0.39), and glycylglycyl-L-tryptophan (R_f 0.18). Three Ehrlich-positive spots were detected on another strip, L-tryptophan (R_f 0.57), glycyl-L-tryptophan (R_f 0.39), and glycylglycyl-L-tryptophan (R_f 0.18). Then the pertinent areas of the tlc developed anew were scraped off and extracted with 100 ml of water. The transmittancy of the extracts was measured at 280 mμ.[19] The residual sample was treated as above to isolate the dipeptide. The crude product was recrystallized from methanol to yield 2.33 g (89%) of a pure dipeptide: [α]D 33.5° (c 2.5, 5 N HCl) [lit.[20] [α]D 34.3°

(c 2, 5 N HCl)]. *Anal.* Calcd for $C_{13}H_{15}N_3O_3$: C, 59.75; H, 5.80; N, 16.08. Found: C, 59.94; H, 6.06; N, 16.15.

Registry No.—Glycine NCA, 2185-00-4; Gly-Gly, 556-50-3; Gly-L-Ala, 3695-73-6; Gly-L-Val, 1963-21-9; Gly-L-Leu, 869-19-2; Gly-L-Phe, 3321-03-7; Gly-L-Leu-L-Ala, 32557-24-7; Gly-L-tryptophan, 2390-74-1.


A Convenient Synthesis of 5-Fluorouracil

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Communication No. 54[1] from the Research Institute for Medicine and Chemistry, Cambridge, Massachusetts 02142

5-Fluorouracil (1) is a cytotoxic analog of uracil of use in biochemical research and also of a certain value in medicine.[2] This derivative of uracil is typically prepared by a total synthesis as expressed in Chart I[3]

CHART I
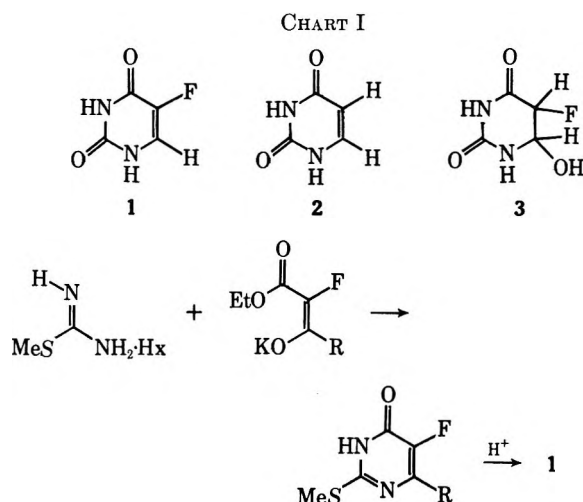
which requires the use of a persistent and insidious toxin, fluoroacetic acid. The discovery that fluoroxytrifluoromethane (CF_3OF) is a useful reagent for the heretofore difficult direct electrophilic fluorination of aromatic compounds[4] led us to consider that the reaction of CF_3OF with uracil (2) (or an appropriate derivative thereof) might lead directly to 5-fluorouracil (or a derivative thereof) and thus constitute a convenient synthesis of such compounds. We now report that the direct conversion of uracil to 5-fluorouracil may be accomplished in high yield by electrophilic fluorination.

Electrophilic substitution at the 5 position of the pyrimidine ring is well known.[5] Uracil itself undergoes nitration at position 5 without complication,[6] and

(16) Y. Iwakura K. Uno, and S. Kang, *J. Org. Chem.*, **30**, 1158 (1965). We synthesized glycine NCA by the reaction of glycine with phosgene in tetrahydrofuran. The reaction time needed in phosgenation of the amino acid was shorter in this solvent than in any other solvents. High yield and high purity of the product were obtained in this solvent.

(17) M. Oya, K. Uno, and Y. Iwakura, *Kogyo Kagaku Zasshi*, **69**, 741 (1966).

(18) H. Leuchs, *Ber.*, **39**, 857 (1906).

(19) Uv spectra of peptides were measured with Shimazu MPS-50 L and Hitachi Perkin-Elmer 139 spectrophotometers.

(20) K. R. Rao, S. M. Birnbaum, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **198**, 507 (1952).

(1) For no. 53, see D. H. R. Barton, T. J. Bentley, R. H. Hesse, F. Mutterer, and M. M. Pechet, *Chem. Commun.*, 912 (1971).

(2) G. Ramirez, *et al.*, *Amer. J. Surg.*, **120**, 400 (1970); J. Dule, *Bull. Soc. Fr. Dermatol. Syphiligr.*, **77**, 218 (1970); L. Y. Deemarsky, *et al.*, *Cancer*, **26**, 771 (1970); M. S. Mitchell, *et al.*, *ibid.*, **26**, 884 (1970); M. Hursthouse, *Brit. J. Dermatol.*, **82**, 218 (1970).

(3) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957).

(4) D. H. R. Barton, *et al.*, *Chem. Commun.*, 806 (1968).

(5) C. W. Kenner and A. Todd in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp 235 ff.

(6) T. B. Johnson, *J. Amer. Chem. Soc.*, **30**, 19 (1908); *Chem. Abstr.*, **2**, 2792 (1909).

reacts with halogens to afford at least initially 5-substituted products.[7] Although the latter reactions are often further complicated by addition of halogen to the initial substitution product,[7a] successful monohalogenation can be achieved.[7b] We find that uracil dissolved in water, trifluoroacetic acid, or preferably a mixture thereof, reacts slowly but cleanly with CF_3OF to afford a mixture of 5-fluorouracil and a second substance in variable proportions. The companion product, which is quite unstable, may be smoothly converted to 5-fluorouracil by heating. Indeed, heating *in vacuo* of the total crude reaction product leads to isolation by sublimation of 5-fluorouracil in approximately 85% yield.

The precursor of I shows no high-intensity absorption in the uv, no $-OCF_3$ or CF_3CO- absorption in the infrared or ^{19}F nmr spectra, and exhibits a complex series of resonances at δ 5–6 ppm in the ^{1}H nmr spectrum. These characteristics, together with the thermal conversion to 5-fluorouracil, suggest that this material is an addition product of uracil. The ^{19}F nmr spectrum, which consists of a doublet (J = 45 Hz) at ϕ^* 207.6, and the composition, $C_4H_5N_2O_3F$, lead to expression **3** for this product.[8] The formation of adduct **3** at the expense of 5-fluorouracil is promoted as expected by the presence of water in the reaction medium. This is fortunate, as, while **1** undergoes some reaction with CF_3OF to afford overfluorinated by-products, adduct **3** is essentially inert to CF_3OF and an aqueous medium thus ensures a very clean reaction product.

While we have found uracil inert to exposure to perchloryl fluoride ($FClO_3$) under conditions considerably more forceful than required to ensure reaction with CF_3OF, this substrate does react avidly with elemental fluorine. Although little 5-fluorouracil is formed in the reaction of uracil with F_2, heating the reaction mixture *in vacuo* leads to the sublimation and isolation of 5-fluorouracil in approximately 60% yield. The spectral and chromatographic properties of the progenitor of 5-fluorouracil formed in this reaction suggest that it is analogous with or identical with **3**. Therefore, while it is possible that the direct fluorination of uracil with elemental fluorine may afford yields of 5-fluorouracil comparable to those achieved by fluorination with CF_3OF, the reaction with the latter reagent is more easily controlled and the reagent itself is more amenable to utilization with usual laboratory techniques.

It is appropriate to point out that, as methods are extant for the conversion of 5-fluorouracil to other 5-fluoropyrimidine derivatives,[9] the method described in this paper provides a synthesis of such derivatives, particularly the important 5-fluorocytosine.

Experimental Section

All melting points were taken on the Kofler hot stage and are reported uncorrected. [1]H nmr spectra were obtained at 60 MHz using a Varian T-60 spectrometer and are reported as shifts downfield from internal tetramethylsilane (δ). [19]F nmr spectra were obtained at 56.4 MHz on the above instrument and are reported as shifts from internal $CFCl_3$ (ϕ^*). Ir spectra were obtained with a Perkin-Elmer Model 137 spectrometer. Solutions of CF_3OF were prepared by passing the gaseous reagent into

CFCl₃ at $-78°$; aliquots were treated with an excess of aqueous KI and the concentration of CF_3OF was estimated by titration of the I_2 liberated ($CF_3OF + 2KI + H_2O \rightarrow I_2 + 2KF + 2HF + CO_2$).

CF_3OF is a powerful oxidant and while we have experienced no difficulty with its use certain precautions are indicated: all reactions should be conducted with adequate shielding, accumulation of the reagent in the presence of oxidizable substances should be avoided, material for handling of the reagent should consist of glass, Teflon, Kel-F, or passivated metals. *On no account should PVC, rubber, polyethylene or similar substances be used.*

Fluorination of Uracil with CF_3OF—Uracil (0.336 g, 3 mmol) in a mixture of trifluoroacetic acid (6 cc) and water (20 cc) was added to a solution of CF_3OF (4.5 mmol) in CFCl₃ (50 cc) at $-78°$ in a pressure bottle. The precipitated uracil redissolved in the aqueous layer when the mixture was warmed up to room temperature. The mixture was vigorously stirred for 15 hr. The excess CF_3OF was removed with nitrogen and solvent was removed under reduced pressure. The solid residue was sublimed at 210–230° under reduced pressure (0.5 mm) to give crude 5-fluorouracil (0.365 g, 94%), mp 260–270°. Recrystallization from methanol–ether gave pure 5-fluorouracil (0.33 g, 85%), mp 282–283°, mmp (with authentic 5-fluorouracil) 282–283°. [1]H nmr, ^{19}F nmr, ir, and uv spectra were identical with those of authentic 5-fluorouracil.

In a companion fluorination as above, the crude products were not subjected to heat, but instead separated by preparative tlc (silica gel GF 254; methanol–chloroform 20:80) into a fraction having R_f 0.5 (5-fluorouracil) and a fraction having R_f 0.3 (adduct **3** which on heating was quantitatively converted to 5-fluorouracil): ν (KBr) 3300 (s), 1720 (s), 1475 (m), 1250 (m), 1140 (m), 1080 (m), 880 (m), 800 cm⁻¹ (m). The proton nmr showed a complex pattern of resonances at δ 5–6 ppm (AB pattern of an ABX system). The ^{19}F nmr had ϕ^* = 207.6 ppm (broad doublet, J = 45 Hz). The mass spectrum had a molecular ion at m/e 148⁺; accurate mass, m/e 148.0291 (calcd for $C_4H_5FN_2O_3$, m/e 148.0284). *Anal.* Calcd for $C_4H_5FN_2O_3$: C, 32.45; H, 3.40; N, 18.92; F, 12.83. Found: C, 32.26; H, 3.5; N, 18.90; F, 13.84.

Fluorination of Uracil with Fluorine.—Fluorine gas diluted liberally with nitrogen was passed at room temperature into a vigorously stirred solution of uracil (150 mg, 1.34 mmol) in water (50 cc). After the disappearance of starting material (nmr control; *ca.* 2.5 mmol F_2) the solvent was removed under reduced pressure and the residue was sublimed to give 5-fluorouracil (95 mg, 0.74 mmol, 55% yield) identified by comparison with authentic 5-fluorouracil.

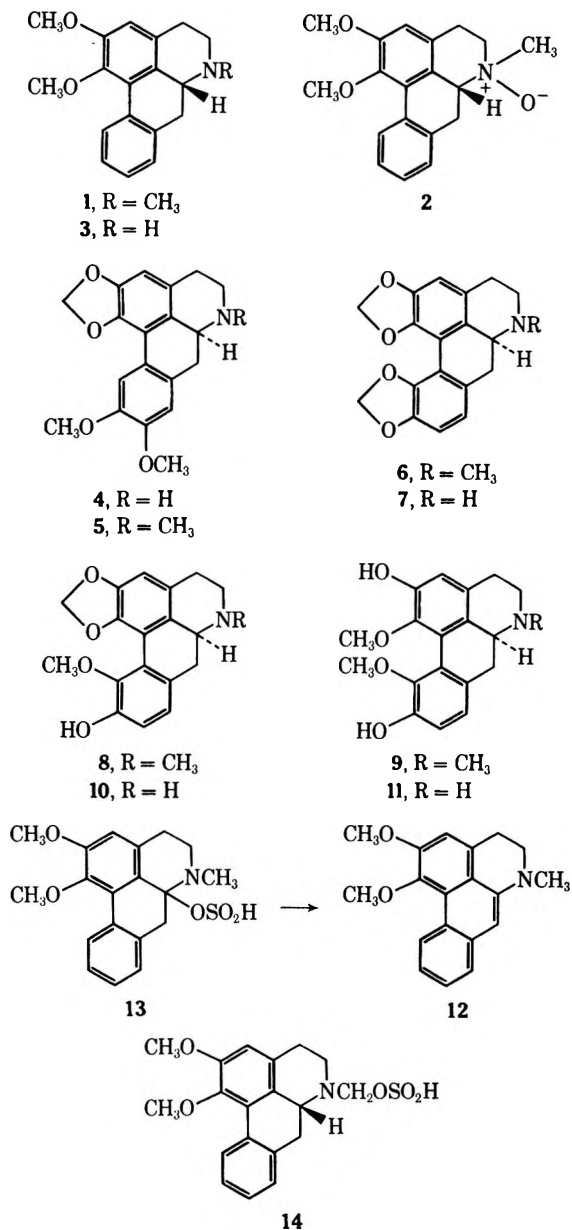## Conversion of Aporphines into *N*-Noraporphine Alkaloids

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The *N*-noraporphines constitute an important subgroup of alkaloids corresponding to the more widely found N-methylated bases, the aporphines.[1] The aporphines may be obtained not only by total synthesis but, when practical, also by the N-methylation of *N*-noraporphines. On the other hand, *N*-noraporphines have been available only by isolation and by total synthesis *via* their *N*-benzyl derivatives. We now report the first procedure for the conversion of aporphines into the corresponding *N*-noraporphine bases.

(7) (a) T. B. Johnson, *J. Amer. Chem. Soc.,* **65,** 1218 (1943). (b) T. Nishiwaki, *Tetrahedron,* **22,** 2401 (1966).

(8) Microanalysis suggest that **3** may be accompanied by 5–10% of the analogous 5,6-difluoro-5,6-dihydrouracil adduct.

(9) K. Undheim and M. Gacek, *Acta Chem. Scand.,* **23,** 294 (1969).

(1) For recent reviews of the aporphine alkaloids, see (a) M. Shamma in "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 1; (b) M. P. Cava and A. Venkateswarlu, *Annu. Rep. Med. Chem.,* 331 (1968). Earlier reviews are cited in these references.

A recent study of the mechanism of the reductive demethylation of trimethylamine *N*-oxide by sulfur dioxide[2] led us to investigate the applicability of this reaction to the aporphine series. Thus, (−)-nuciferine (**1**) was treated with hydrogen peroxide in aqueous methanol at room temperature to give the corresponding *N*-oxide **2**. Reductive demethylation of **2** to (−)-nornuciferine (**3**) was achieved in fair yield (34%) by

1, R = CH₃
3, R = H

2

4, R = H
5, R = CH₃

6, R = CH₃
7, R = H

8, R = CH₃
10, R = H

9, R = CH₃
11, R = H

13

12

14

reaction with liquid sulfur dioxide, followed by hydrolysis with hydrochloric acid; under these conditions very little nuciferine was regenerated and the product was readily purified. Under similar conditions, the rare alkaloid (+)-nordicentrine (**4**) was obtained in 32% yield from the relatively common aporphine, (+)-dicentrine (**5**). Also, (+)-*N*-methylovigerine (**6**) was demethylated in 28% yield to (+)-ovigerine (**7**). Since racemic **6** has been synthesized,[3] this conversion completes the formal total synthesis of natural ovigerine except for the resolution of racemic **6**.

(2) J. C. Craig and K. K. Purushothaman, *Tetrahedron Lett.*, 5305 (1969). Earlier work is cited in this reference.

(3) M. P. Cava and M. Srinivasan, *Tetrahedron*, **26**, 4649 (1970).

The reaction conditions employed proved to be sufficiently mild to allow the N-demethylation of two representative phenolic aporphines to be carried out, although yields were not so good as with the nonphenolic examples. Thus, (+)-*N*-methylnandigerine (**8**) and (+)-*N*-methylhernovine (**9**) afforded (+)-nandigerine (**10**) and (+)-hernovine (**11**) in 22 and 18% yields, respectively.

Since the objective of this study was a simple preparative conversion of aporphines into *N*-noraporphines, we were interested in avoiding procedures which afforded mixtures of water-insoluble reaction products. It was found, indeed, that such mixtures were produced from (−)-nuciferine *N*-oxide (**2**) under a variety of conditions. For example, reaction of **2** with sulfur dioxide in methanol–benzene, followed by hydrolysis with dilute acid, gave a 5:2 mixture of (−)-nuciferine and (−)-nornuciferine. A similar reaction, followed by dilute base hydrolysis, gave a mixture of (−)-nuciferine, (−)-nornuciferine, and dehydronuciferine (**12**) in a ratio of about 8:2:5. The formation of dehydronuciferine in the alkaline hydrolysis reaction is rather interesting, since it probably arises by way of a base-catalyzed elimination of an intermediate of structure **13**; the isomeric structure **14** is the expected intermediate which gives rise to (−)-*N*-nornuciferine, on the basis of what is known concerning the mechanism of the corresponding demethylation of trimethylamine *N*-oxide.[2]

Experimental Section[4]

(−)-**Nornuciferine** (**3**) from (−)-**Nuciferine** (**1**).—A solution of (−)-nuciferine (**1**, 0.100 g) in methanol (10 ml) and 30% hydrogen peroxide (2 ml) was stirred at room temperature overnight, after which time tlc showed the complete disappearance of **1**. A suspension of 5% Pd on charcoal (0.020 g) was added and the mixture was stirred for 2 hr in order to decompose excess hydrogen peroxide. The filtered solution was saturated with sodium chloride and extracted with chloroform. Evaporation of the dried (Na₂SO₄) extract gave an oil, which was further dried by repeated addition of 2:5 methanol–benzene and evaporation *in vacuo* to give a foam of *N*-oxide **2** (0.100 g). To this foam was added liquid sulfur dioxide (10 ml), followed by *N*,*N*-dimethylacetamide (1 ml). After 48 hr at about −70°, excess liquid SO₂ was removed, concentrated hydrochloric acid (1 ml) was added, and the mixture was heated (steam bath) until SO₂ was no longer evolved. Basification with aqueous ammonia, followed by chloroform extraction, yielded a crude product (0.043 g) which was purified by chromatography on silica. Elution with chloroform gave a few milligrams of recovered **1**, after which chloroform–methanol (99:1) eluted the major product, which was converted to the hydrochloride. After several crystallizations from methanol–ethyl acetate there was obtained 0.039 g (34%) of pure (−)-nornuciferine hydrochloride, mp 268–270° dec (lit.[5] mp 264–266°), [α]²⁵ᴅ (EtOH) −122°.

(+)-**Nordicentrine** (**4**) from (+)-**Dicentrine** (**5**).—The N-oxidation and subsequent demethylation of **5** were carried out as in the nuciferine case to give **4** in 32% yield. The product was crystallized from methanol as its hydrobromide, mp 262–265° dec (lit.[6] mp 278° dec), [α]²⁵ᴅ (EtOH) +34°.

(+)-**Ovigerine** (**7**) from (+)-*N*-**Methylovigerine** (**6**).—The usual conditions afforded **7** (28% from **6**), isolated as the crys-

(4) Melting points are uncorrected and were determined using a Thomas–Hoover apparatus. Infrared spectra were determined in KBr using a Perkin-Elmer Model 137 instrument. Tlc analyses were carried out using 9:1 chloroform–methanol with silica plates. The identity of all products was confirmed by ir and tlc comparison with authentic alkaloids from natural sources.

(5) S. M. Kupchan, B. Dasgupta, E. Fujita, and M. L. King, *Tetrahedron*, **19**, 227 (1963).

(6) A. Venkateswarlu, Ph.D. Dissertation, Wayne State University, 1969.

talline hydrochloride, mp 298–300° dec (lit.[7] mp 300° dec), [α]²⁵D (EtOH) +207°.

(+)-Nandigerine (10) from (+)-N-Methylnandigerine (8).— The usual conditions afforded 10 (22% from 8), isolated as the crystalline hydrochloride, mp 242–245° dec (lit.[7] mp 245–247° dec), [α]²⁵D (EtOH) +240°.

(+)-Hernovine (11) from (+)-N-Methylhernovine (9).—The usual conditions afforded 11 (18% from 9) as crystals, mp 235–237° dec (lit.[7] mp 236–240° dec), [α]²⁵D (EtOH) +253°.

Reaction of N-Oxide 2 with Sulfur Dioxide in Methanol–Benzene.—Dried N-oxide 2 (50 mg) was dissolved in 1:1 methanol–benzene (20 ml) and SO₂ was passed into the mixture for 0.5 hr. Aqueous hydrochloric acid (2 N, 10 ml) was added and the solution was refluxed for 3 hr. Basification with ammonia, followed by chloroform extraction, gave a crude product (40 mg), shown by tlc to contain only nuciferine (1) and nornuciferine (3). Chromatography on neutral alumina gave 1 (25 mg) and 3 (10 mg).

The above experiment was repeated, with the modification that the N-oxide SO₂ complex was refluxed not with acid, but with 5% aqueous sodium hydroxide. Preparative tlc (2% MeOH in CHCl₃, Al₂O₃) gave 1 (38 mg), 3 (18 mg), and dehydronuciferine (12, 25 mg).

Registry No.—3, 32557-14-5; 4, 25394-59-6; 7, 6410-87-3; 10, 5544-70-7; 11, 5544-69-4.

(7) M. P. Cava, K. Bessho, B. Douglas, S. Markey, R. F. Raffauf, and J. A. Weisbach, *Tetrahedron Lett.*, 1577 (1966).

Inductive Effects on Molecular Ionization Potentials. IV. Hydrogen Sulfide and Mercaptans

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The ionization potentials of alkyl free radicals, R·, have been correlated[1] with the polar substituent constants, σ*, and we have shown recently that the ionization energies of alcohols,[2] ethers,[3] and amines[4] are linear functions of both σ* and the inductive substituent constants, σI.

We now demonstrate that the ionization energies of thiols, RSH, are also linear functions[5] of both σ* and σI. The gas-phase expulsion of an electron from the nonbonding lone pair on the sulfur atom of a mercaptan molecule is in accord with the equation

$$R-\overset{..}{\underset{..}{S}}-H \xrightarrow{E_I} R-\overset{.\,+}{\underset{..}{S}}-H + e^-$$
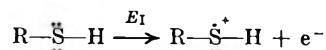
and the ionization potential, E_I, of course, corresponds approximately to the energy of the highest occupied molecular orbital.[6-8] The entire chemistry of thiols,

in fact, is dependent upon the behavior of the 3p sulfur lone pair electrons. Electron-releasing alkyl groups bonded to the S atom of a thiol molecule should obviously facilitate the electron removal, and thereby lower the E_I; and the presence of electron-withdrawing groups should likewise cause an increase in the requisite ionization energy.[9] It is interesting that we are able to include hydrogen sulfide as the simplest thiol in the series.

Table I presents the σ* and the σI[10] values together with the photoionization potentials[11] (eV) for various aliphatic mercaptans and hydrogen sulfide.

Figure 1.—A plot of ionization potentials, E_I, of the thiols vs. the inductive substituent constants, σI, of the corresponding R groups.

TABLE I

Thiol	σ*	σI	E_I, eV (exptl)[a]	E_I, eV (eq 1a)	E_I, eV (eq 2)
H₂S	+0.49	0	10.46	10.46	10.46
MeSH	0	−0.046	9.44	9.45	9.44
EtSH	−0.10	−0.055	9.29	9.25	9.24
n-PrSH	−0.12	−0.058	9.20	9.18	9.17
n-BuSH	−0.13	−0.060[b]	9.14	9.14	9.13
i-PrSH	−0.19	−0.064	c	9.05	9.04
tert-BuSH	−0.30	−0.074	8.79	8.77	8.81

a Reference 11. b Value suggested in ref 3. c Experimental value not available.

An excellent correlation is shown in Figure 1 where the E_I values are plotted vs. σI. The equation for the correlation line is given by

$$E_{RSH} = E_{H_2S} + a_I\sigma_I \tag{1}$$

The slope, a_I, is found to be 22.2 and therefore we have

$$E_{RSH} = 10.46 + 22.2\sigma_I \tag{1a}$$

(1) A. Streitwieser, Jr., *Progr. Phys. Org. Chem.*, **1**, 1 (1963).

(2) L. S. Levitt and B. W. Levitt, *Chem. Ind. (London)*, 990 (1970).

(3) B. W. Levitt and L. S. Levitt, *Experientia*, **26**, 1183 (1970).

(4) B. W. Levitt and L. S. Levitt, *Israel J. Chem.*, **9**, 71 (1971).

(5) The ionization potentials of X–SH have been correlated with the three-parameter extended Hammett equation: $E_I = 3.22\sigma_I + 9.06\sigma_R + 10.37$ [M. Charton and B. I. Charton, *J. Org. Chem.*, **34**, 1882 (1969)].

(6) R. S. Mulliken, *J. Chem. Phys.*, **3**, 564 (1935).

(7) T. Koopmans, *Physica*, **1**, 104 (1933).

(8) J. C. Lorquet, *Rev. Mod. Phys.*, **32**, 312 (1960).

(9) The same effect manifests itself in a greater basicity, the greater is the electron density at the S atom of the mercaptan molecule, similar to that recently demonstrated for alcohols: L. S. Levitt and B. W. Levitt, *J. Phys. Chem.*, **74**, 1812 (1970); also *Tetrahedron*, **27**, 3777 (1971).

(10) R. W. Taft, Jr., and I. C. Lewis, *ibid.*, **5**, 210 (1959).

(11) K. Watanabe, T. Nakayama, and J. Mottl, *J. Quant. Spectrosc. Radiat. Transfer*, **2**, 369 (1962).

It is seen that this relation is much simpler than that obtained in ref 5.

Using the polar substituent constants, σ^*, one obtains a correlation from which it is found

$$E_{RSH} = E_{MeSH} + a^*\sigma^* = 9.44 + 2.08\sigma^* \quad (2)$$

These correlations indicate that the effect of alkyl substituents on the S atom is primarily an inductive one.

In the last two columns of Table I we show a comparison between the experimental ionization energies and those calculated using eq 1a and 2. The agreement is excellent. A calculated value is also given for Me_2CHSH for which an experimental value has not yet been obtained.

The a_I and the a^* constants are, of course, analogous to the reaction constants ρ_I and ρ^*, and are a measure of the susceptibility of the reaction site (the S atom) to substituent effects. The a_I value of 22.2 obtained here may be compared to those observed in the correlation of E_I's of alcohols[2] ($a_I = 37.5$) and for ethers[3] ($a_I = 28.0$). These comparisons show that the S atom is considerably less sensitive to inductive effects than is the O atom, probably due to the larger radius of the S atom.

Registry No.—Hydrogen sulfide, 7783-06-4; methanethiol, 74-93-1; ethanethiol, 75-08-1; 1-propanethiol, 107-03-9; 1-butanethiol, 109-79-5; 2-propanethiol, 75-33-2; 2-methyl-2-propanethiol, 75-66-1.

Silver-Assisted Displacements on Sulfur. A New Thiolsulfonate Ester Synthesis

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Kice[2,3] has recently described the dramatic effects of cooperative electrophilic–nucleophilic assistance in scission of sulfur–sulfur bonds. In the present paper, we report a probable member of this mechanistic class, the facile cleavage of alkyl disulfides by silver nitrate and sodium methanesulfinate to produce thiolsulfonate esters in high yield.

We have found that addition of a solution of silver nitrate in aqueous acetone to a solution of equivalent quantities of sodium methanesulfinate and alkyl disulfide in the same solvent leads to rapid formation of thiol ester and insoluble silver alkylmercaptide according to eq 1.

$$RSSR + AgNO_3 + CH_3SO_2Na \longrightarrow$$
$$\underset{\underset{O}{\parallel}}{\overset{\overset{O}{\parallel}}{CH_3SSR}} + RSAg + NaNO_3 \quad (1)$$

$$R = CH_3, C_2H_5, \text{ or } (CH_3)_2CH$$

(1) Author to whom correspondence should be addressed.

(2) John L. Kice, *Accounts Chem. Res.*, **1**, 58 (1968).

(3) John L. Kice, "Sulfur in Organic and Inorganic Chemistry," A. Senning, Ed., Marcel Dekker, New York, N. Y., 1971, p 197.
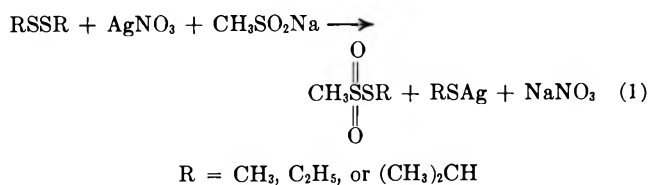
In the case of di-*tert*-butyl disulfide, the corresponding thiol ester was not obtained after heating the reaction mixture under reflux either 2 hr in aqueous acetone or 4 hr in aqueous dioxane. A black silver sulfide precipitate slowly formed and isobutylene was detected in the gas phase above the reaction mixture. The large steric factor associated with the *tert*-butyl groups apparently prevents nucleophilic displacement by the methanesulfinate anion and elimination slowly occurs instead.

Although we have not yet applied kinetic techniques to elucidate the mechanism of this reaction, it seems reasonable to postulate that the transformation is initiated by silver ion–disulfide complex formation followed by nucleophilic displacement on sulfur (eq 2, 3).

$$RSSR + Ag^+ \rightleftharpoons \overset{\overset{Ag^+}{|}}{RSSR} \quad (2)$$

$$\overset{\overset{Ag^+}{|}}{R-S-S-R} + \overset{\overset{\cdot\ddot{O}\cdot}{}}{\underset{\underset{O}{\parallel}}{S-CH_3}} \longrightarrow RSAg + \underset{\underset{O}{\parallel}}{\overset{\overset{O}{\parallel}}{CH_3SSR}} \quad (3)$$
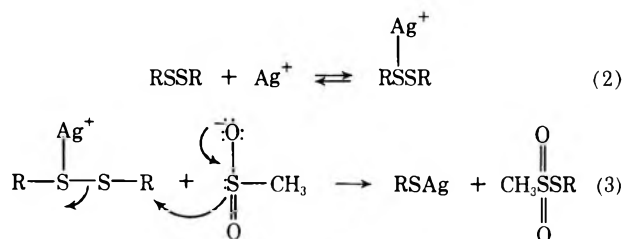
The disulfide sulfur on which the attack occurs would be rendered more electrophilic by metal ion coordination by the adjacent sulfur, while the very insoluble silver mercaptide would become an effective leaving group.

An alternate pathway (eq 4–6) is not ruled out, but

$$RSSR + Ag^+ \rightleftharpoons \overset{\overset{Ag^+}{|}}{RSSR} \quad (4)$$

$$\overset{\overset{Ag^+}{|}}{RS-S-R} \longrightarrow RSAg + RS^+ \quad (5)$$

$$RS^+ + CH_3SO_2^- \longrightarrow \underset{\underset{O}{\parallel}}{\overset{\overset{O}{\parallel}}{R-S-S-CH_3}} \quad (6)$$
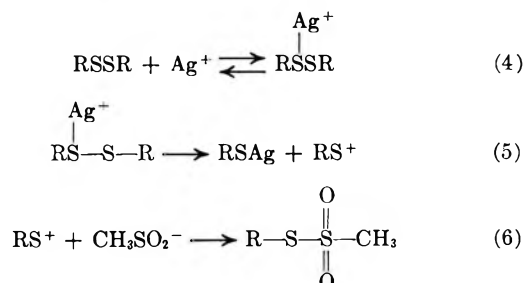
seems less likely since there was no evidence of alkanesulfenic acid formation (*i.e.*, disproportionation products) which should occur by competitive nucleophilic attack on the sulfenium ion by water.

The isolation of solid silver nitrate–alkyl disulfide complexes has been reported.[4] In several instances, we have observed formation of a white precipitate, probably the disulfide complex, which rapidly disappeared with formation of the yellow alkyl mercaptide. The silver mercaptides, identified by gas chromatography of the mercaptans formed by acidification of the salts with concentrated HCl, were formed quantitatively and there was no evidence for the presence of silver ion–disulfide complex in the final product mixtures.

It is significant that no alkyl sulfenylmethanesulfinates (I) could be detected as products of our reac-
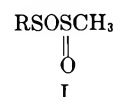
$$\underset{\underset{O}{\parallel}}{RSOSCH_3}$$
$$I$$

(4) P. C. Ray, N. Adhikari, and H. Ray, *J. Indian Chem. Soc.*, **8**, 689 (1931).

tions. These would have occurred *via* nucleophilic displacement by sulfinate oxygen, rather than sulfinate sulfur, on the silver ion–disulfide complex. This observation is consistent with the recent study of Meek and Fowler[5] on alkylation of the ambident *p*-toluenesulfinate anion, where it was shown that alkylation with hard alkylating agents yielded esters while similar reaction with soft alkylating agents resulted in sulfone formation.

Experimental Section

Methyl Methanethiolsulfonate.—To a solution of dimethyl disulfide [0.5 g, 0.0053 mol, bp 108° (1 atm)] in 20 ml of 75% acetone–water was added a solution of silver nitrate (Fisher-ACS, 0.99 g, 0.00585 mol) and sodium methanesulfinate[6,7] (0.542 g, 0.0053 mol) in 20 ml of water. A bright yellow precipitate formed immediately. The mixture was stirred at room temperature for 30 min and the silver methylmercaptide was separated by suction filtration. The filtrate was diluted with water and extracted with several portions of ether. The combined ethereal extracts were dried over sodium sulfate and the ether was evaporated under reduced pressure to yield a colorless oil (0.63 g, 94%) whose ir and nmr spectra were identical with those of authentic methyl methanethiolsulfonate. In addition, the compound exhibited a parent peak in the mass spectrum at *m/e* 126 and was also shown to be pure by gas chromatography on a 6 ft Triton-X305 column at 160°.

Ethyl Methanethiolsulfonate.—To a solution of 2.44 g (0.02 mol) of diethyl disulfide in 75 ml of a 50% aqueous acetone solution was added 75 ml of a 50% aqueous acetone solution containing 4.25 g (0.025 mol) of silver nitrate and 2.53 g (0.025 mol) of sodium methanesulfinate. A white precipitate formed immediately. The mixture was brought to reflux temperature and the precipitate rapidly became bright yellow. Heating at reflux was continued for 4 hr and the product mixture was filtered. The cooled filtrate was extracted several times with ether and the combined ethereal extracts were dried (Na$_2$SO$_4$) and evaporated to yield 2.6 g (93%) of a colorless oil whose nmr spectrum in CDCl$_3$ (δ 3.37, s, 3 H; 3.21, q, J = 7.5 Hz, 2 H; 1.45 t, J = 7.5 Hz, 3 H) was consistent with that expected for pure ethyl methanethiolsulfonate. The distilled ester, bp 101° (4 mm), had a refractive index, $n^{25}D$ 1.5005. The mass spectrum showed a parent peak at *m/e* 140 and the ir spectrum exhibited strong absorptions at 1310, 1130, 955, and 750 cm^{-1}. *Anal.* Calcd for C$_3$H$_8$O$_2$S$_2$: C, 25.76; H, 5.75; S, 45.74. Found: C, 25.88; H, 5.72; S, 45.88.

Isopropyl Methanethiolsulfonate.—The procedure used was similar to that described for ethyl methanethiolsulfonate with the modification that the mixture was heated under reflux for 6 hr. From 3.0 g (0.02 mol) of diisopropyl disulfide (K and K) was obtained 2.5 g of product whose nmr in CDCl$_3$ (δ 1.47, d, J = 7 Hz, 6 H; 3.32, s, 3 H; 3.70, h, J = 7 Hz, 1 H) was consistent with that expected for isopropyl methanethiolsulfonate. The ester, distilled at 102° (5 mm), exhibited a refractive index ($n^{25}D$) of 1.4910. The ir spectrum (neat) consisted of strong absorptions at 2980, 2940, 1320, 1130 ,1055, and 750 cm^{-1}, and the mass spectrum exhibited a parent peak at *m/e* 154. *Anal.* Calcd for C$_4$H$_{10}$O$_2$S$_2$: C, 31.14; H, 6.53; S, 41.58. Found: C, 31.23; H, 6.54; S, 41.71.

(5) John S. Meek and Joanna S. Fowler, *J. Org. Chem.*, **33**, 3422 (1968).

(6) I. B. Douglass, *ibid.*, **30**, 633 (1965).

(7) Richard V. Norton, Gordon M. Beverly, and Irwin B. Douglass, *ibid.*, **32**, 3645 (1967).

Synthesis of *N*-Fluoronitramines[1]

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Little work has been reported on the synthesis and reactions of *N*-halo-*N*-nitro amine derivatives. *N*,*N*'-Dichloro-*N*,*N*'-dinitro-1,2-ethylenediamine, isolated by Smart and Wright[2] in 1948, remained the sole example of this class of compounds until the recently reported synthesis of simple *N*-chloro-*N*-nitroalkylamines by the chlorination of aqueous salts of alkylnitramines.[3] The synthesis of *N*-chloro-*N*-nitrocarbamates by this method was reported by Thomas[4] in 1955. *N*-Bromo-*N*-nitro amine derivatives have not been reported. *N*-Chloro-*N*-nitro amines and *N*-chloro-*N*-nitrocarbamates are explosive compounds[2] and decompose rapidly on storage.[4]

We have synthesized *N*-fluoro-*N*-nitrobutylamine, the first *N*-fluoronitramine, by two independent, generally applicable procedures. The compound was obtained in 84% yield in the fluorination of aqueous alkali salts of butylnitramine under reaction conditions similar to those employed in the fluorination of aqueous nitronate salts[5] and carboxylic acid salts (eq 1).[6] The

$$\text{C}_4\text{H}_9\text{NNO}_2{}^-\text{K}^+ + \text{F}_2 \longrightarrow \text{C}_4\text{H}_9\text{NFNO}_2 + \text{KF} \qquad (1)$$
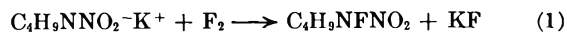
compound was characterized by elemental analysis as well as infrared and nmr spectra. Its fluorine nmr spectrum exhibited a triplet at ϕ −1.10. *N*-Fluoro-*N*-nitrobutylamine was stored at room temperature for several months without apparent decomposition. On the other hand, in one instance a sample of the compound exploded on distillation at 60°. This method of preparation of *N*-fluoro-*N*-nitro amines is of general utility. Graff, *et al.*,[7] used our general procedure[8] to synthesize other *N*-fluoronitramines for thermal stability studies.

N-fluoro-*N*-nitrobutylamine was also synthesized by treating methyl *N*-butyl-N-fluorocarbamate with 100% nitric acid (eq 2). Since *N*-alkyl-*N*-fluorocarbamates

$$\text{C}_4\text{H}_9\text{NFCOOCH}_3 + \text{HNO}_3 \longrightarrow$$
$$\text{C}_4\text{H}_9\text{NFNO}_2 + \text{CO}_2 + \text{CH}_3\text{ONO}_2 \quad (2)$$
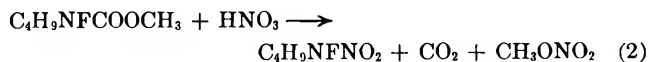
are readily available by the fluorination of alkylcarbamates,[9] this route to *N*-fluoro-*N*-nitro amines is also of general synthetic utility.

(1) This work was supported by the Office of Naval Research. The experimental work was carried out at the Aerojet-General Corp., Azusa, Calif.

(2) G. N. R. Smart and G. F. Wright, *Can. J. Res.*, **26B**, 257 (1948).

(3) V. P. Ivshin, A. L. Fridman, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 640 (1970).

(4) G. R. Thomas, U. S. Patent 2,772,306 (Nov 27, 1956).

(5) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

(6) V. Grakauskas, *ibid.*, **34**, 2446 (1969).

(7) M. Graff, C. Gotzmer, Jr., and W. E. McQuistion, *ibid.*, **32**, 3827 (1967); *J. Chem. Eng. Data*, **14**, 513 (1969).
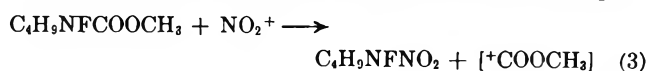
(8) Private communication prior to their work of ref 7.

(9) V. Grakauskas and K. Baum, *J. Org. Chem.*, **34**, 2840 (1969).

The nitrolysis of *N*-butyl-*N*-fluorocarbamate most likely proceeds by the electrophilic displacement of carbomethoxycarbonium ion by nitronium ion (eq 3).

$$C_4H_9NFCOOCH_3 + NO_2^+ \longrightarrow$$
$$C_4H_9NFNO_2 + [^+COOCH_3] \quad (3)$$

This mechanism is analogous to that proposed for the fluorinalysis of *N*-alkyl-*N*-fluorocarbamates to the corresponding *N,N*-difluoroalkylamines.[9] The nitrolysis of *N,N*-dialkylformamides has also been reported.[10]

Experimental Section

Fluorinations were conducted in a three-necked flask following the previously described technique.[5,6] *Adequate safety shielding should be used when handling N-fluoro-N-nitrobutylamine.*

Fluorination of Butylnitramine.—Butylnitramine (11.8 g, 0.1 mol) and 0.1 mol of potassium hydroxide in 250 ml of water were fluorinated with 0.1 mol of fluorine over a period of 45 min. A yellow liquid separated. The product was extracted with 70 ml of methylene chloride, and was washed with 75 ml of cold saturated aqueous sodium bicarbonate and 75 ml of water. The methylene chloride solution was dried with sodium sulfate and distilled to give 11.5 g (86% yield) of *N*-fluoro-*N*-nitrobutylamine: bp 40° (25 mm); proton nmr (CCl₄) δ 0.98 (m, CH₃), 1.62 (m, two internal CH₂'s), and 6.07 (d, t, J_{HF} = 35, J_{HH} = 11 Hz, –CH₂); fluorine nmr ϕ −1.10 (t, J_{HF} = 33.5 Hz); ir 3.39 (m), 3.50 (m), 6.18 (sh), 6.35 (sh), 6.84 (w), 7.01 (w), 7.25 (w), 7.55 (sh), 7.76 (s), 7.93 (sh), 8.14 (w), 8.96 (w), 9.40 (w), 9.61 (w), 10.05 (w), 11.35 (m), and 12.10 μ (m).

Anal. Calcd for C₄H₉N₂FO₂: C, 35.3; H, 6.7; N, 20.6; F, 14.0. Found: C, 35.0; H, 6.3; N, 21.2; F, 14.3.

Nitration of Methyl *N*-Butyl-*N*-fluorocarbamate.—Methyl *N*-butyl-*N*-fluorocarbamate (4.0 g, 0.027 mol) was added dropwise over a 15-min period to 25 ml of 100% nitric acid at −5°. Carbon dioxide was evolved. The mixture was stirred for 20 min and then poured on 100 g of crushed ice. The product was extracted with two 20-ml portions of methylene chloride, dried over sodium sulfate, and distilled to give 3.1 g (84% yield) of *N*-fluoro-*N*-nitrobutylamine, bp 40° (25 mm).

Registry No.—*N*-Fluoro-*N*-nitrobutylamine, 14233-86-4.

(10) J. H. Robson, *J. Amer. Chem. Soc.*, **77**, 107 (1955).

Amine Hydrochlorides by Reduction in the Presence of Chloroform[1]

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We have developed a new method for the preparation of amine hydrochlorides from azides, nitriles, oximes, and nitro compounds. Catalytic reduction of these compounds in a solvent containing a small amount of chloroform leads directly to the corresponding amine hydrochlorides. In addition to trapping unstable amines as the hydrochloride, an important advantage of the present procedure lies in the fact that it provides a method for the preparation of amine hydrochlorides that contain functional groups which might be unstable to reduction conditions employing acidic media. As can be seen from Table I, reduction in the presence of

TABLE I
REDUCTION DATA[a]

Compd	Proton source	Catalyst	Time, hr	Yield, %
1	CHCl₃	Pd/C	1.5	92
n-PrCN	CHCl₃	PtO₂	4	96
	HCl	PtO₂	1.75	95
C₆H₅CN	CHCl₃	PtO₂	2	98
	HCl	PtO₂	1.5	97
p-CH₃C₆H₅NO₂	CHCl₃	Pd/C	1.5	89[b]
	HCl	Pd/C	1.5	93[c]
n-PrNO₂	CHCl₃	PtO₂	18	40[d]
	CHCl₃	PtO₂	15	61[e]
	HCl	PtO₂	24	59[f]
n-C₆H₁₃CH=NOH	CHCl₃	PtO₂	1	97
	HCl	PtO₂	2	60

[a] Standard conditions are 3 atm, 2 mmol of starting material, 50 ml of absolute EtOH, 1 ml of CHCl₃ or 1 ml of concentrated HCl, 100 mg of 10% Pd/C or 50 mg of PtO₂, except as noted.[g] [b] 83% after sublimation. [c] After sublimation. [d] 0.2 ml of CHCl₃. [e] 0.1 ml of CHCl₃. [f] 0.2 ml of concentrated HCl. [g] Only 1.0 mmol of 1 was employed.

chloroform affords comparable yields to those afforded by reduction in the presence of hydrochloric acid.

Methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (1),[3] which contains the acid-labile isopropylidene and acetal functions, was found to be reduced cleanly in the presence of chloroform to the corresponding amine hydrochloride 2 without affecting
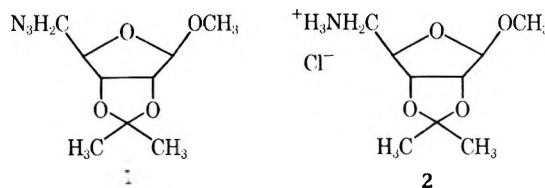
either of these acid-sensitive groups. By contrast, reduction in the presence of methanolic hydrogen chloride also resulted in removal of the isopropylidene group and anomerization, as judged by nmr. Attempts at reduction of 1 under similar conditions in ether containing hydrogen chloride resulted in recovery of unchanged 1.

Reduction of aromatic and aliphatic nitriles as well as *p*-nitrotoluene occurred readily in the presence of either chloroform or hydrochloric acid. In the absence of a proton source the reduction of 1-nitropropane produced propylamine, characterized as the hydrochloride, in 95% yield after 1.75 hr. Under the standard conditions with either chloroform or hydrochloric acid, 1-nitropropane was not reduced to any appreciable extent.[4] Upon decreasing the quantity of chloroform and hydrochloric acid, however, reduction was facilitated.

Heptaldoxime was reduced readily in the presence of either chloroform or hydrochloric acid, although the yield in hydrochloric acid was considerably lower. In both cases an additional ether-soluble product was formed.

As a mechanistic test, a blank solution of absolute ethanol, chloroform, and catalyst was hydrogenated for 1 hr. The resulting solution gave a positive silver ni-

(3) J. A. Secrist III and N. J. Leonard, *J. Amer. Chem. Soc.*, in press.

(4) Nitroalkanes are known to be reduced with difficulty in the presence of acids; see P. N Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967, pp 168-174.

trate test,[5] indicating the presence of ionic chloride. It appears, therefore, that the reaction occurs by hydrogenolysis of the chloroform to produce very small quantities of hydrogen chloride, which combines immediately with the amine as it is formed by reduction.

Experimental Section[6]

General Procedure.—The hydrogenations were carried out on a Parr apparatus as indicated in Table I followed by filtration through Hyflo-Supercel and evaporation of the solvent under reduced pressure. Unless otherwise indicated, the material left after evaporation to dryness was used for characterization.

Methyl 5-amino-5-deoxy-2,3,-*O*-isopropylidene-β-D-ribofuranoside hydrochloride (2) was obtained as a colorless solid, mp 189.5–190° dec. Recrystallization from absolute EtOH gave **2**, mp 200.5–201.5° dec (lit.[7] 201.5–202°).

***n*-Propylamine hydrochloride, *n*-butylamine hydrochloride, and benzylamine hydrochloride** were obtained as colorless solids, mp 153–154° (lit.[8] 155–158°), 201–203° (lit.[9,10] 195 and 215°), and 253–254° (lit.[11] 255–256°), respectively.

***p*-Toluidine hydrochloride** was obtained as a gray solid, mp 233.5–237.5°. Sublimation gave colorless material, mp 238.5–239.5° (lit.[12] 238–240°).

***n*-Heptylamine Hydrochloride.**—After filtration of the hydrogenation mixture through Hyflo-Supercel, the filtrate was evaporated to dryness. The residue was then washed with ether to give a colorless solid, which turned to a gel (200°) and became fluid at 256–259°. An authentic sample prepared by a Gabriel synthesis behaved identically.

Registry No.—2, 14131-79-2; chloroform, 67-66-3; *n*-propylamine HCl, 556-53-6; *n*-butylamine HCl, 3858-78-4; benzylamine HCl, 3287-99-8; *p*-toluidine HCl, 540-23-8; *n*-heptylamine HCl, 142-93-8.

(5) Pretested chloroform gave a negative silver nitrate test.

(6) All melting points were determined on a Thomas–Hoover capillary melting point apparatus in sealed capillaries and are corrected.

(7) N. J. Leonard and K. L. Carraway, *J. Heterocycl. Chem.*, **3**, 485 (1966).

(8) E. Linnemann and V. Zotta, *Justus Liebigs Ann. Chem.*, **161**, 45 (1872).

(9) E. Linnemann and V. Zotta, *ibid.*, **162**, 4 (1872).

(10) W. H. C. Rueggenberg and M. M. Falkof, *J. Amer. Chem. Soc.*, **67**, 2052 (1945).

(11) M. Konowalow, *Ber.*, **28**, 1861 (1895).

(12) C. A. Bischoff and P. Walden, *Justus Liebigs Ann. Chem.*, **279**, 130 (1894).

Metal–Amine Reactions.[1a,b] Selective 1,2'-Reductive Dimerization of Naphthalene

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The reduction of naphthalene with sodium and amines yields numerous products, including 1,2-dihydronaphthalene (1), 1,4-dihydronaphthalene (2), 1,2,3,-4-tetrahydronaphthalene (3), reductive amination prod-

(1) (a) E. J. Eisenbraun, R. C. Bansal, D. V. Hertzler, W. P. Duncan, P. W. K. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **35**, 1265 (1970); (b) R. C. Bansal, E. J. Eisenbraun, and P. W. K. Flanagan, *J. Amer. Chem. Soc.*, **88**, 1837 (1966); (c) L. Reggel, H. W. Sternberg, and I. Wender, *Nature (London)*, **190**, 81 (1961).

(2) Continental Oil Company Fellowship, 1970–1971, and National Aeronautical and Space Administration Trainee, 1969–1970.

ucts, C$_{20}$ dimers, and decreasing amounts of C$_{30}$ and C$_{40}$ products.[1a-c] The product distribution varies considerably depending on reaction conditions and the selection of the amine.[1a,b] If steric effects are present in the amine, reductive amination diminishes and reductive dimerization may increase; *e.g.*, piperidine gave 46% reductive amination of naphthalene and 11% of a mixture of C$_{20}$ dimers, whereas dipropylamine caused formation of 6% of **4** and 55% of a mixture of reductive dimerization products[1a] now known to be **5**, **6**, and **7**. In our current work with sodium and dipropylamine using a specialized apparatus,[3a] the yield of **4** is 12% and the combined yield of **5**, **6**, and **7** is 62%. In the earlier work, two C$_{20}$ dimers, 1,1',2,2',3,3',4,4'-octahydro-2,2'-binaphthyl and 5,6,6a,6b,11,12,12a,-12b-octahydrodibenzo[*a,g*]biphenylene, were frequently observed, particularly with primary diamines.[1b] We now know there are, however, systems in which they are minor products or may not appear. One of these, sodium and dipropylamine, was chosen for detailed study because the resulting C$_{20}$ dimer mixture was less complex. Indeed, we have learned that in this system a remarkably selective formation of 1,2'-coupled C$_{20}$ dimers results. The major component of the dimer fraction,[3b] a colorless crystalline hydrocarbon, is shown to be 1',2',3',4'-tetrahydro-1,2'-binaphthyl (5). It gives a molecular ion m/e 258.1408 and both analytical and spectral data are consistent with structure **5**. Hydrocarbon **5** shows uv absorption characteristic of an aliphatic-substituted naphthalene and forms a picrate that can be decomposed by stirring with petroleum ether and eluting through a column of basic alumina. The hydrocarbons **6** and **7** did not form picrates.
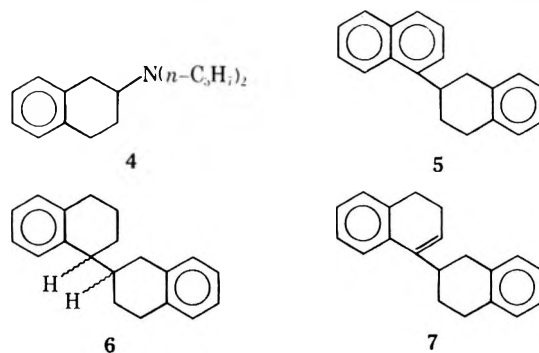
At room temperature, dimers **5**, **6**, and **7** were formed in the ratio 73:11:16, respectively. At higher temperatures (40–80°) dimer **5** was the C$_{20}$ hydrocarbon formed almost exclusively.

To obtain pure **6**, a mixture of **5**, **6**, and **7** was treated with Pd/C in refluxing toluene[3c] and the resulting mixture of **5** and **6** was separated by column chromatography. The ir spectrum of **6** thus prepared from **7** is very similar[4a] to that of **6** obtained by hydrogenation
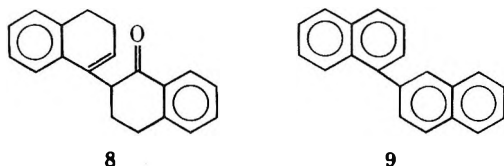
(3) (a) E. J. Eisenbraun and H. Hall, *Chem. Ind. (London)*, 1158 (1971). (b) Correspondence regarding this reference hydrocarbon and other samples should be addressed to Mr. A. J. Streiff, American Petroleum Institute, Carnegie-Mellon University, Pittsburgh, Pa. 15213. (c) L. E. Harris, W. P. Duncan, M. J. Hall, and E. J. Eisenbraun, *Chem. Ind. (London)*, 403 (1971).

(4) (a) Dimer **6** from both sources is a liquid. It should be recognized that **6** may possibly be a mixture of racemates and hence minor differences in the infrared spectra of samples from independent sources are to be expected. (b) J. M. Springer, C. W. Hinman, E. J. Eisenbraun, P. W. K. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **35**, 1260 (1970). (c) H. L. Retcofsky, L. Reggel, and R. A. Friedel, *Chem. Ind. (London)*, 617 (1969). (d) We thank Mr. J. W. Burnham for a sample of **8** prepared by acid-catalyzed dimerization of 1-tetralone.

of 8[4b-d] with Pd/C and its nmr spectrum is consistent with structure 6. Dimer 7 was identified by its nmr and uv spectra and its facile disproportionation with Pd/C catalyst in boiling toluene to 5 and 6.[3c]

8   9

Evidence for the absence of any dimers with a 1,1' or 2,2' ring system among the reaction products was obtained by total aromatization. Treatment of the reaction mixture of 5, 6, and 7 with Pd/C at 350° gave a 92% yield of 1,2'-binaphthyl (9). Analysis of this dehydrogenation product by glc showed that 1,1- and 2,2'-binaphthyl were absent. A sample of the 1,2'-binaphthyl prepared by Pd/C dehydrogenation of 6 from 8 was compared with 9 from the dehydrogenation of 5, 6, and 7 and these were found through melting point of a mixture and spectral comparison to be identical.

Additional evidence that 5 could not be represented by structure 12 was obtained by reducing 5 with Pd/C to 6:10 (62:38) and by reduction of 5 with sodium and diethylamine, and then treating with Pd/C in refluxing toluene[3c] to give 5:6:10 (62:1:37). Since glc studies of these mixtures showed that 11[5] was not present, it is unlikely that 12 or 13 are formed. The presence of the latter would be revealed by its ready disproportionation to 6 and 12 in the presence of Pd/C in boiling toluene.[3c]

10   11

12   13
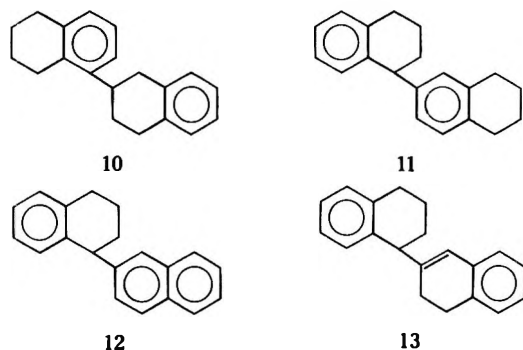
Experimental Section[6]

The amines, obtained from Union Carbide Co., were dried by stirring (24 hr) with KOH, decanting, and distilling from fresh KOH. The high-purity naphthalene was a gift from Sun Oil Co. The sodium (Matheson Coleman and Bell) was reagent grade, 1/16 to 1/4 in. spheres, and was washed with sulfuric acid treated petroleum ether[6a] before use. The 10% Pd/C catalyst was purchased as a stock item from Engelhard Industries, Newark, N. J.

(5) An authentic sample of hydrocarbon 11 was kindly supplied by W. D. Vanderwerff, Sun Oil Co.

(6) (a) The petroleum ether, bp 60–68°, was distilled before use. (b) Glc analyses for the hydrocarbons were obtained on a Hewlett–Packard Model 5750 glc apparatus fitted with thermal conductivity and hydrogen flame detectors using helium as the carrier gas. For the dimer hydrocarbons, a 0.25 in. × 11 ft column of 5% UC W-98 methyl vinyl silicone rubber coated on acid-washed and DMCS-treated Chromosorb G (80–100 mesh) at 265° was used. For the steam-volatile hydrocarbons, a 0.25 in. × 10 ft column of 25% Carbowax 20M coated on Chromosorb W (30–60 mesh) at 190° was used. (c) This yield was calculated from the amount of unrecovered naphthalene and was based on the mixture of 5, 6, and 7.

Melting points were determined with a Hoover–Thomas capillary tube melting point apparatus and are corrected. The uv and ir spectra were obtained with a Cary Model 14 and a Beckman Model IR-5A spectrophotometer, respectively. The nmr spectra (CCl₄) were obtained with Varian HR-60 and HA-100 instruments (TMS standard) and mass spectra with a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer. The elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reduction of Naphthalene with Sodium and Dipropylamine.— To 12.8 g (0.1 mol) of naphthalene and 250 ml of di-n-propylamine (bp 109°) in the reaction flask[3a] was added 9.2 g (0.4 g-atom) of sodium over a period of several hours. A dark brown color developed within 20 min. The mixture was stirred at room temperature for 24 hr and then withdrawn from the unreacted sodium. The reaction mixture was poured cautiously over 400 ml of crushed ice and an orange emulsion resulted. This was extracted with 500 ml of ether (three portions) and the ether layer, which contained the hydrocarbons, was washed with water, twice with 10% aqueous HCl, and then with water until neutral. The acidic extracts and water washings were combined, made basic with NaOH, and extracted with ether. The ether layer was washed with water, dried (Na₂SO₄), and concentrated to yield 1.7 g of amine fraction.

The ether layer containing the amine-free hydrocarbons was dried (Na₂SO₄) and concentrated. The solution was steam distilled and both the pot residue and steam distillate were extracted with ether and dried (Na₂SO₄). Distillation of the extract of the steam distillate yielded 6.3 g of steam-volatile hydrocarbons. These were shown by glc analysis to be a mixture of unreacted naphthalene and 3 in a 93:7 ratio.

The ether extract of the steam-distillation pot residue was concentrated (rotary evaporator) to yield 6.4 g of a dark, viscous oil. This material was distilled [175–180° (0.2 mm)] to give 4.3 g (62%)[6c] of a light yellow oil which was shown by glc analysis to be a mixture of 5:6:7 (73:11:16).

Isolation and Identification of 1',2',3',4'-Tetrahydro-1,2'-binaphthyl (5).—A portion (1 g) of the distilled dimer mixture was dissolved in absolute ethanol, and picric acid (1 g) was added. This mixture was heated until solution was complete, then allowed to cool slowly. The crystalline picrate was filtered out and washed with absolute ethanol. After recrystallization from the same solvent, the yellow needles melted at 101–104°. The hydrocarbon was regenerated by stirring the picrate with petroleum ether (bp 60–68°) and eluting through basic alumina. The clear oil obtained upon concentration of the solution was triturated with petroleum ether until crystals formed. Recrystallization from methanol gave 5 as white needles: mp 64–65°; ir (melt) 3030, 2820, 1600, 1580, 1515, 1498, 1458, 1439, 1402, 1255, 951, 799, 779, 760, and 743 cm⁻¹; mass spectrum (70 eV) m/e (rel intensity) 258 (73), 154 (31), 153 (43), 130 (47), 128 (34), 104 (100); nmr (CCl₄) δ 8.08–6.72 (broad m, 11, Ar H, sharp s at 6.92), 3.91–2.44 (overlapping m, 5, Ar CH and Ar CH₂), and 2.28–1.61 (m, 2, CH₂); uv max (95% C₂H₅OH) 226 mμ (ε 83,600), 274 (7345), and 283 (8240).

Anal. Calcd for C₂₀H₁₈: C, 92.98; H, 7.02. Found: C, 93.15; H, 7.08.

Isolation and Identification of 1,1',2,2',3,3',4,4'-Octahydro-1,2'-binaphthyl (6) and 1',2',3,3',4,4'-Hexahydro-1,2'-binaphthyl (7).—The mother liquor recovered from the picrate preparation in the previous scheme was concentrated, petroleum ether was added, and the slurry was poured onto a column containing basic alumina. Elution with petroleum ether yielded a mixture of the three dimers 5, 6, and 7 in which the latter two were shown by glc studies to be the major constituents.

This dimer fraction (1.5 g) was mixed with 10% Pd/C (0.15 g) and 100 ml of toluene in a 200-ml, one-neck flask equipped with condenser and magnetic stirring bar. After being refluxed for 2 hr, the suspension was filtered to remove catalyst and concentrated to give 1.4 g of viscous oil containing 5 and 6 and none of 7.

This oil was chromatographed (1.25 × 18 in. column) over silica gel (30–200 mesh) and basic and acidic alumina. Dimer 6 was eluted in the first fraction with petroleum ether.[6a] After distillation, 6 was obtained: bp 175–180° (0.2 mm); ir (film) 3010, 2925, 1700, 1670, 1490, 1450, 1435, 1040, 948, 762, 739 cm⁻¹; mass spectrum (70 eV) m/e (rel intensity) 262 (8), 132 (21, 131 (100), 130 (30), 129 (17), 115 (15), and 91 (22); nmr δ 7.32–6.72 (m, 14, Ar H) and 3.08–1.12 (overlapping m, 14,

Ar CH, Ar CH$_2$ and CH$_2$); uv max (95% C$_2$H$_5$OH) 256 mμ (ϵ 2280), 267 (1935), and 274 (1950).

Anal. Calcd for C$_{20}$H$_{22}$: C, 91.55; H, 8.45. Found: C, 91.32; H, 8.67.

Dimer **7**, isolated from the mixture by preparative gas chromatography (UC W-98 on acid-washed Gas-Pack W), was a viscous liquid: bp 180^c (0.2 mm); ir (film) 3000, 2900, 2820, 1480, 1450, 1430, 1040, 1020, 806, 767, 737 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 260 (51), 131 (63), 130 (62), 129 (100), 128 (74), 115 (43), and 104 (69); nmr (CCl$_4$) δ 6.97 (m, 8, Ar H), 5.83 (t, 1, vinyl), 3.2–2.45 (m, 6, Ar CH$_2$), 2.4–1.4 (overlapping m, 5, Ar CH$_2$CH$_2$ and >C=CHCH); uv max (95% C$_2$H$_5$OH) 202 mμ (ϵ 10,100) and 268 (5500).

Anal. Calcd for C$_{20}$H$_{20}$: C, 92.26; H, 7.74. Found: C, 92.10; H, 7.90.

Synthesis of 1,2'-Binaphthyl (9) by Dehydrogenation of C$_{20}$ Dimers.—The dimer fraction (4.3 g of **5**, **6**, and **7**) was mixed with 10% Pd/C (0.5 g) in a 50-ml one-neck flask equipped with reflux condenser and gas outlet tube. As the flask was lowered into a preheated (350°) Woods metal bath, vigorous evolution of gas occurred. After 10 min, gas evolution had subsided, but heating was continued for 1 hr. After cooling, the residue was dissolved in petroleum ether,^{6a} filtered, and concentrated to give 4.0 g of viscous yellow oil. The latter was distilled [153–158° (0.02 mm)] to give 3.9 g (92%) of light yellow solid. This constitutes a 57% yield of **9** based on the amount of reacted naphthalene. After elution through alumina and silica gel with petroleum ether,^{6a} followed by concentration of the solution, a white solid was obtained: mp 73.5–77.5° (lit.^{7} mp 76°); mmp with **9** prepared from **8**,^{3c} 76–77°; mass spectrum (70 eV) *m/e* (rel intensity) 254 (100), 253 (72), 252 (53), 250 (13), 127 (10), 126 (27); nmr (CDCl$_3$) δ 7.18–8.05 (m).

Reduction of 5 with Sodium and Diethylamine.—To 6.5 g (0.025 mol) of **5** in 250 ml of diethylamine was added 2.3 g (0.1 g-atom) of Na over a period of several hours. A dark brown color developed in less than 1 min and persisted throughout the reaction time of 22 hr. The reaction mixture was quenched in ice and extracted with ether, and the ether solution was extracted with 10% HCl.

The ether remaining after washing with water was dried (Na$_2$SO$_4$) and concentrated to give 5.8 g of hydrocarbons. The acidic and aqueous extracts were combined, made basic with NaOH and extracted with ether, dried (Na$_2$SO$_4$), and concentrated to give 0.7 g of nonvolatile amines.

The hydrocarbon fraction showed a trace of **6** and **7**, 10% of **5**, and 89% of an undetermined mixture. When the latter (2.5 g) was treated as before with Pd/C (0.25 g) in 100 ml of refluxing toluene for 5 hr,^{3c} a viscous oil (2.1 g) was obtained which showed the ratio **5:6:10** (62:1:37) by glc.^{6b}

Isolation and Identification of 1',2',3',4',5,6,7,8-Octahydro-1,2'-binaphthyl (10).—The mixture from the preceding reduction was eluted with petroleum ether^{6a} through a column of silica gel and basic, acidic, and neutral alumina. From the first fraction which eluted from the column, pure **10** was obtained: bp 175–180° (0.2 mm); ir (film) 2990, 2800, 2690, 1580, 1488, 1455, 1433, 772, 743, 716 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 262 (50), 131 (27), 130 (100), 129 (23), 115 (21), 104 (100); nmr (CCl$_4$) δ 6.96 (m, 7, Ar H), 3.30–2.45 (m, 9, Ar CH and Ar CH$_2$), 2.12–1.45 (m, 6, CH$_2$); uv max (95% C$_2$H$_5$OH) 258 mμ (ϵ 1208), 267 (1085), 274 (888).

Anal. Calcd for C$_{20}$H$_{22}$: C, 91.55; H, 8.45. Found: C, 91.83; H, 8.40.

Catalytic Reduction of 5, 6, and 7.—A mixture (3.6 g) of **5:6:7** (32:9:9) was stirred (Teflon-covered magnet) at 25° in a 500-ml fluted flask with 0.4 g of 10% Pd/C and 150 ml of 95% ethanol. Hydrogen (1 atm) was introduced and after 5 days, **5** and **7** had disappeared. After filtration (Dicalite Filter-aid) and concentration, a viscous oil remained (3.2 g) which proved to be a mixture of **6:10** (62:38) by glc analysis.

(7) H. A. Weidlich, *Ber.*, **71B**, 1201 (1938).

On the Preparation of 1,4-Dicarboxycubane[1]

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The synthesis of cubane and several important derivatives including the 1,4-diacid was reported in a communication in 1964.[2] Recently, Chapman and his associates[3] have reported a closely related alternative route, chosen because of difficulties encountered in their attempts to follow the preparative method outlined by Eaton and Cole[2] for the synthesis of 1,4-disubstituted cubanes. We wish to report that we have employed the original approach without difficulty. The procedures derive from those employed by Cole[4] and are described fully in the Experimental Section. We note in particular that the conversion of the caged dimer
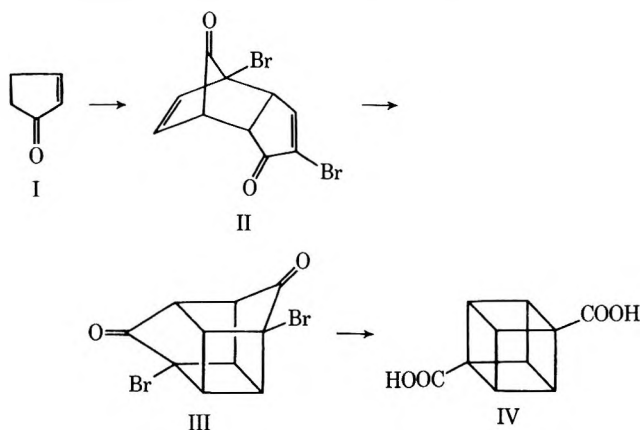
III to 1,4-dicarboxycubane (IV) was accomplished with potassium hydroxide in 55% yield and with sodium hydroxide in 44 (first experiment), 70, 75, 78, and 72% yield, respectively.

Experimental Section

2-Cyclopentenone (I).—A mixture of cyclopentendiols (100 g, 1.0 mol) was converted to 2-cyclopentenone by the method of Depuy and Eilers.[5] A second fractionation of the initial product provided colorless 2-cyclopentenone (47 g, 57%, bp 151–154°).

2,4-Dibromo-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione (II).—2-Cyclopentenone (50 g, 0.61 mol) was added to a slurry of *N*-bromosuccinimide (240 g, 1.45 mol) in carbon tetrachloride (700 ml). The reaction mixture was heated to reflux, stirred vigorously, and illuminated with a General Electric sun lamp to start the reaction. After the initial exothermic reaction had subsided, additional 2-cyclopentenone (50 g) was added. The solution was refluxed for 3 hr. The cooled reaction mixture was filtered and the filtrate was concentrated *in vacuo* at room temperature. The residue was dissolved in anhydrous ether (1 l.) previously saturated with lithium bromide (dried overnight at 100° *in vacuo*). The solution was cooled to −30°. Bromine (1.17 mol) was then added dropwise at a rate approximately equal to the reaction rate. The bath temperature was maintained at −30 to −35°. After the bromination reaction was complete,

(1) This research was supported by a grant from the National Science Foundation.

(2) P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 962, 3157 (1964).

(3) N. B. Chapman, J. M. Key, and K. J. Toyne, *J. Org. Chem.*, **35**, 3860 (1970).

(4) T. W. Cole, Jr., Dissertation, University of Chicago, 1966.

(5) C. H. Depuy and K. L. Eilers, *Org. Syn.*, **42**, 38 (1962).

methylene chloride (750 ml) was added slowly while the temperature was maintained at −25 to −30°. Triethylamine (228 g, 2.26 mol) was then added dropwise in 2.5 hr. During this additior the temperature was maintained at −20 to −30° for the first 90 min. The temperature was allowed to rise to −10° cver the last hour. Further methylene chloride (about 250 ml) was added to aid stirring. When the addition was complete, water (1 l.) was added. The mixture was then filtered to collect the solids, and the organic and the aqueous layers of the filtrate were separated. The aqueous layer was extracted with methylene chloride. The filter cake was washed with hot methylene chloride six times. The combined organic layers were washed with hydrochloric acid (6 *M*, 300 ml) twice followed by brine (300 ml) twice. The organic phase was dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded crude II (42 g). Recrystallization from ethyl acetate provided colorless needles of the product, mp 155–155.5°. The mother liquor (which contained a skin irritant) was refrigerated and a second batch of solid was obtained. This material was worked up to yield additional II (21 g). The overall yield was 33%. The spectroscopic properties of the product were identical with those reported by Eaton and Cole.[2]

6,10-Dibromopentacyclo[5.3.0.0²,⁶.0³,¹⁰.0⁴,⁸]deca-5,9-dione (III). —Dimer II (5 g, 15.7 mol) was dissolved in hot methanol (60 ml) and then cooled to room temperature. Methanolic hydrogen chloride (2 ml) was added. The mixture was transferred to a Pyrex irradiation cell with additional methanol (20 ml). The solution was irradiated with an Hanovia 450-W mercury lamp for 90 min. The solvent was removed *in vacuo*. The orange waxy solid was dissolved in benzene (300 ml) and the mixture was boiled to remove methanol. The hot benzene solution was passed through basic alumina (10 g) and the column was flushed with hot benzene. The solution was evaporated to dryness. The solid was dissolved in benzene (10 ml). *n*-Hexane was added dropwise to precipitate the product. Recrystallization from benzene yielded III (4.2 g, 84%, mp 228–230°). The product exhibited the spectroscopic properties reported by Eaton and Cole.[2]

1,4-Dicarboxycubane (IV).—In a typical experiment, compound III (5.0 g, 15.7 mmol) was added to sodium hydroxide solution (25%, 50 ml). The mixture was refluxed (110°) for 2 hr, then cooled to 0°. The solution was neutralized by the dropwise addition of cold concentrated hydrochloric acid. The temperature of the solution was kept near 0°. As the pH was reduced the solution changed from dark brown to light tan. The precipitation of the product appeared to be complete between pH 4 and 1 and 3. Filtration yielded the desired product as a very light tan powder (2.3 g, 75%). Pure 1,4-dicarboxycubane, mp 226° dec, was obtained by recrystallization from acetic acid. The crude diacid (2.3 g, 11.9 mmol) was dissolved in methanol (50 ml) containing the hydrogen form of methanol washed Bio-Rad cation exchange resin AG 50w.-X8 (300 mg). The mixture was refluxed for 12 hr. The warm solution was filtered to collect the resin and 1,4-dicarbomethoxycubane (2.35 g, 90%, mp 16.–162° after recrystallization from methanol) precipitated as the solution cooled.

Formation of an Unusual Dihydropyrazine Di-*N*-oxide during Hydrolysis of an α-Oximino Acetal

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In connection with the synthesis and structural elucidation of *Cypridina* etioluciferamine,[1] certain model

(1) T. P. Karpetsky and E. H. White, *J. Amer. Chem. Soc.*, **93**, 2333 (1971).

compounds were needed for the spectrographic information they would yield. The most important of these was 2-amino-3-methyl-6-phenylpyrazine 1-oxide (3) which was to be synthesized *via* the pathway shown in eq 1. It was therefore necessary to prepare the un-

known phenylglyoxal 2-oxime 2. The conversion of the known[2,3] phenylglyoxal acetal to a mixture of the *Z* and *E* isomers of 1 was accomplished in 93% yield by the conditions shown in eq 1.[4] The next step, the acid hydrolysis of an α-oximino acetal to the corresponding α-oximinoaldehyde (eq 2), is at face value a simple
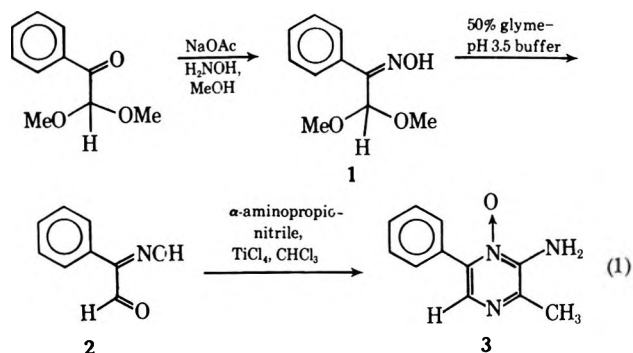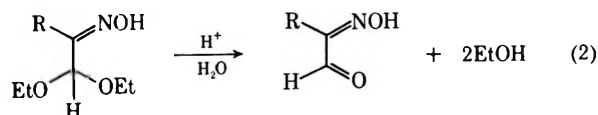
reaction. The yields in this type of conversion are reported to be good, and the desired product is easily isolable (R, yield: isobutyl, 63%;[5] *sec*-butyl, 64%;[6] methyl, 82%[6]). We therefore anticipated no difficulties in the conversion of 1 to 2. Reaction conditions similar to those stated in the literature[5,6] were used for the hydrolysis of 1. After the isolation and recrystallization procedure described in the Experimental Section, physical data on the colorless crystals obtained (71% yield) clearly indicated that this material was not the expected phenylglyoxal 2-oxime. The 100-MHz nmr spectrum (DMSO-d_6) of the compound isolated (Figure 1) shed considerable light on its structure. The singlet at τ 2.73 corresponds to the protons of a phenyl ring which is not directly attached to an electron-withdrawing center. The two multiplets at τ 1.60–1.85 and 2.42–2.64 represent phenyl ring protons which are separated due to a powerful electron-withdrawing element attached directly to that aromatic ring.[7] Furthermore, the two doublets at τ 2.21 and 3.84 and the doublet of doublets at τ 3.68 indicate an ABX spin

(2) W. Madelung and M. E. Oberwegner, *Justus Liebigs Ann. Chem.*, **490**, 232 (1931); *Chem. Abstr.*, **26**, 474 (1932).

(3) W. Madelung and M. E. Oberwegner, *Chem. Ber.*, **65B**, 936 (1932); *Chem. Abstr.*, **26**, 4584 (1932).

(4) The preparation of 1 was modeled after a method originally applied to isobutyrophenone: H. M. Kissman and J. Williams, *J. Amer. Chem. Soc.*, **72**, 5323 (1950).

(5) J. J. Gallagher, G. T. Newbold, W. Sharp, and F. S. Spring, *J. Chem. Soc.*, 4870 (1952).

(6) G. T. Newbold, W. Sharp, and F. S. Spring, *ibid.*, 2679 (1951).

(7) For example, we have found that the phenyl ring protons in 2-amino-3-methyl-6-phenylpyrazine 1-oxide (3) are separated into two multiplets at τ 2.10–2.28 and 2.45–2.63.
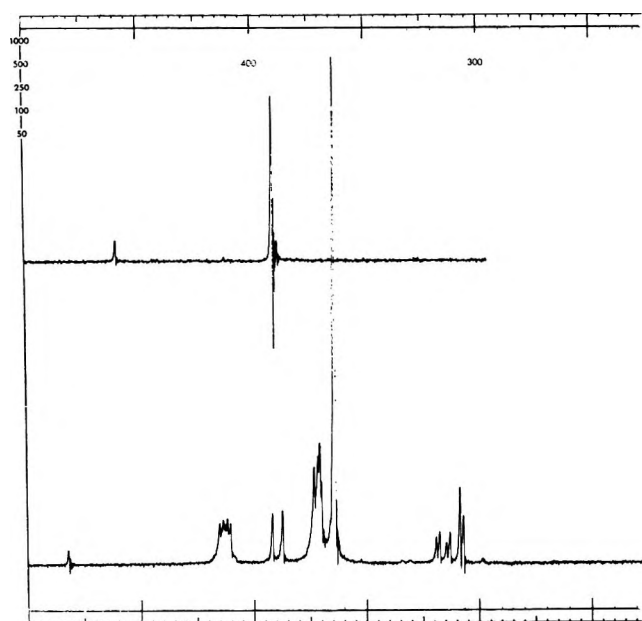
Figure 1.—100-MHz nmr spectrum (τ 0–5.5, DMSO-d_6) of 2,5-dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-dioxide (4). Upper curve offset, 400 Hz.

system under the influence of some powerful electron-withdrawing substituent. The infrared spectrum of this material shows a medium-intensity band at 1595 cm^{-1} interpretable as the imine N-oxide stretch (C=N$^+$—O$^-$).[8-10] Finally, the elemental analysis indicates that this unknown compound has a molecular formula that is consistent with that of phenylglyoxal 2-oxime (C$_8$H$_7$NO$_2$) or some multiple thereof.

Our interpretation of these facts is that the unknown material is 2,5-dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-dioxide (4). This material probably arises from the dimerization of two molecules of 2 with concomitant bond shifts as shown in eq 3. Reactions of

(3)
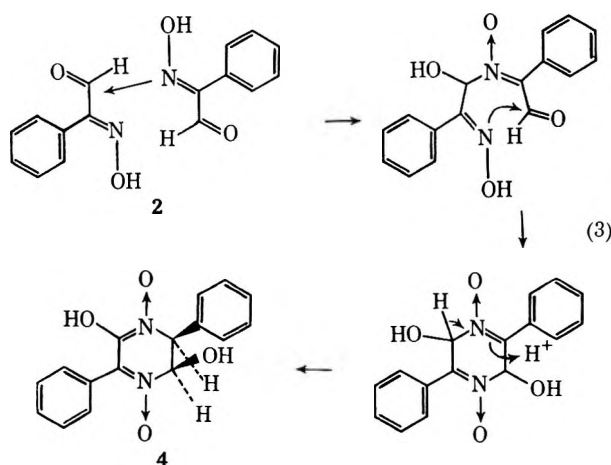
this sort, involving nucleophilic attack of the nitrogen of an oxime on an aldehydic carbonyl, are known. For example, this type of condensation has been used to

prepare benzimidazole 3-oxides[11,12] and is the basis for a synthetic route to purine 1-oxides.[12,13]

The stereochemistry of the substituents about the 5 and 6 carbons of the dihydropyrazine 1,4-dioxide ring is believed to be as shown in structure 4. These assignments are supported by the coupling constant (3 Hz) between the protons on the 5 and 6 carbons indicating that they are cis axial equatorial. This structure is also consistent with the proposed reaction mechanism.[14]

The formation of 4 from 1 appeared to be a major stumbling block in our synthesis of 2. However, upon examining the change in the 100-MHz nmr spectrum (DMSO-d_6) of 4 with time, it was seen that the complex pattern characteristic of the protons of 4 slowly disappeared, to be replaced by the three-line spectra one would expect for 2. The half-life of this conversion, as measured by nmr integration, was found to be 110 min at 40°. After removal of the DMSO at reduced pressure, the infrared spectrum (KBr) of the remaining oil had a strong band at 1698 cm^{-1} indicative of an unsaturated aldehyde, and the absorption at 1595 cm^{-1} characteristic of 4 had completely disappeared. Thus, although 4 is the thermodynamically stable form in certain solvents, 2 is the thermodynamically stable form in DMSO. We were thus able to use 4 as a direct source of 2, which was not characterized but which was directly converted to the desired model compound 3 in moderate yield.[15] In addition, we found that the conversion of 4 to 2 is reversible, 4 being produced when 2 is subjected to the conditions given in the Experimental Section for the synthesis of 4 from 1.[16] This fact indicates that the acetal 1 probably goes through the aldehyde 2 during the production of the heterocycle 4.

It is interesting to note that structures related to 4 have never been reported as products of hydrolysis of α-oximino acetals. Whether the hydrolysis of 1 represents a special case or whether the dihydropyrazine di-N-oxides have been previously overlooked is a matter for speculation at this time. Only recently have papers appeared on the preparation and properties of such 2,3-dihydropyrazine 1,4-dioxides as 5.[17,18] Fi-

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(8) R. F. C. Brown, V. M. Clark, and A. Todd *J. Chem. Soc.*, 2105 (1959).

(9) R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *ibid.*, 2109 (1959).

(10) J. Thesing and W. Sirrenberg, *Chem. Ber.*, 92, 1748 (1959); *Chem. Abstr.*, 54, 4537 (1960).
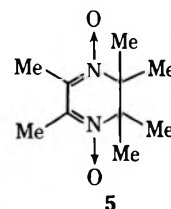
(11) A. J. Boulton, A. C. G. Gray, and A. R. Katritzky, *Chem. Commun.*, 741 (1966).

(12) R. N. Castle, Ed., "Topics in Heterocyclic Chemistry," Wiley, New York, N. Y., 1969, pp 22, 23.

(13) E. C. Taylor and E. E. Garcia, *J. Amer. Chem. Soc.*, 86, 4721 (1964).

(14) The possibility of 4 being a substituted 5,6-dihydropyridazine 1,2-dioxide was ruled out by the nmr and infrared spectra of 4.

(15) The preparation of 3 and other substituted 2-aminopyrazine 1-oxides using titanium tetrachloride as a condensing agent will be the subject of a future publication (see also ref 1).

(16) The ease of reversiblility of the dimerization reaction might explain the somewhat anamolous ultraviolet spectrum of 4. On the basis of model compounds, one would expect an absorption above 280 nm for 4: T. Thesing and W. Sirrenberg, *Chem. Ber.*, 91, 1978 (1958). However, if 4 dissociates in ethanol to give 2, the spectrum of an acetophenone oxime derivative would be expected, as found.

(17) M. Lamchen and T. W. Mittag, *J. Chem. Soc. C*, 2300 (1966).

(18) M. Lamchen and T. W. Mittag, *ibid.*, 1917 (1968).

nally, substituted 2,3-dihydropyrazine 1,4-dioxides offer intriguing possibilities for biologic investigation, since it is know that different N-oxides such as nicotinamide N-oxide, various purine N-oxides, 4-nitroquinoline N-oxide, and chlordiazepoxide function variously as biological oxidants, antimetabolites, oncogenic agents, and tranquilizers.[19]

Experimental Section[20]

2,5-Dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-Dioxide (4).—To a solution of 4.57 g (23.4 mmol) of phenylglyoxal dimethyl acetal oxime[4] (4) in 22.5 ml of glyme was added 22.5 ml of a pH 5.5 buffer (1 N acetic acid, 0.1 N sodium acetate; the oxime was insoluble in this buffer alone or in aqueous methanol). This homogeneous solution was stirred and refluxed. Tlc (Eastman alumina sheets no. 6063, acetone as eluent) indicated a slow reaction rate and 24 hr was required for 1 (R_f 0.49) to disappear and to be replaced by a new compound (R_f 0.22). The solution was then cooled to room temperature, and the solvents were partially removed under reduced pressure (water aspirator). The resulting orange oil and pale yellow liquid was treated with 10 ml of water and extracted with ethyl acetate (three 50-ml portions). These extracts were combined and dried over sodium sulfate; the solvent was then removed to give 3.5 g of an orange oil that crystallized into colorless prisms (perhaps the dimerization occurs at this stage). Recrystallization of this material from ethyl acetate–benzene gave 1.98 g (13.3 mmol, 57%) of colorless prisms. A second crop of 0.50 g (3.4 mmol, 14%) was obtained by concentrating the mother liquor. Infrared spectra run on these two crops of crystals were identical with one another and with that of the analytical sample. This latter sample was prepared by recrystallizing the material twice from ethyl acetate–benzene to give colorless prisms: mp 114.5–117.5°; uv max (MeOH) 221.0 nm (log ϵ 4.31) and 249.0 (4.00, shoulder); ir (KBr) 3225, 3050, 2935, 2875, 2815, and 1595 cm⁻¹; 100-MHz nmr (DMSO-d_6) τ −1.82 (singlet, 0.83 H),* 1.60–1.85 (multiplet, 1.84 H), 2.21(doublet, 1.01 H, J = 9.0 Hz),* 2.42–2.64 (multiplet, 2.73 (singlet, 8.66 H together with previous multiplet), 3.68 (doublet of doublets, 0.84 H, J = 9.0 and 3.0† Hz), and 3.84 (doublet, 0.78 H, J = 3.0 Hz).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73. Found: C, 64.49; H, 4.85.

Phenylglyoxal 2-Oxime (2).—After 745 mg (2.50 mmol) of of 2,5-dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-dioxide (4) was dissolved in 1.5 ml of dimethyl sulfoxide (which previously sat over 5 A molecular sieves for 12 hr), dry nitrogen was blown over the clear solution before it was capped. The stirred reaction solution was then heated to 44–46° for 25 hr. The solvent was then removed by freeze-drying. The resultant oil had ir (KBr) 3125 and 1698 cm⁻¹. As ample of 4 decomposed in a similar manner in DMSO-d_6 had 100-MHz nmr τ −3.20 (singlet, 0.98 H),* 0.35 (singlet, 1.01 H), and 2.58 (singlet, 5.02 H). The material obtained was at least 95% pure by nmr and was not purified further but used immediately in the preparation of 3.

Peaks indicated by an asterisk disappear on addition of D₂O; that indicated by dagger collapses to a doublet (J = 3.0 Hz).

Registry No.—2, 32538-02-6; 4, 32538-03-7.

(19) The role of N-oxides in metabolism and the biologic properties of various types of N-oxides have been reviewed: M. H. Bickel, *Pharm. Rev.*, **21** (4), 325 (1969).

(20) The infrared spectra were taken on a Perkin-Elmer Model 337 spectrophotometer Ultraviolet spectra were recorded using a Cary Model 14 spectrophotometer using matched 1-cm quartz cells. Nmr spectra were run by Mr. Joseph Ahnell using a Varian HA-100 spectrometer. Melting points were taken using a Kofler hot-stage microscope and are uncorrected.

A New Synthesis of *cis*-Jasmone

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The synthesis of *cis*-jasmone (1) has received considerable attention in recent years.[1-10] This contribution stems from our recent discovery of the thermal rearrangement of 3-cyclopropyl-3-oxopropanoates (2) to 2-cyclopentenones (3).[11] *cis*-Jasmone (29–32% over-
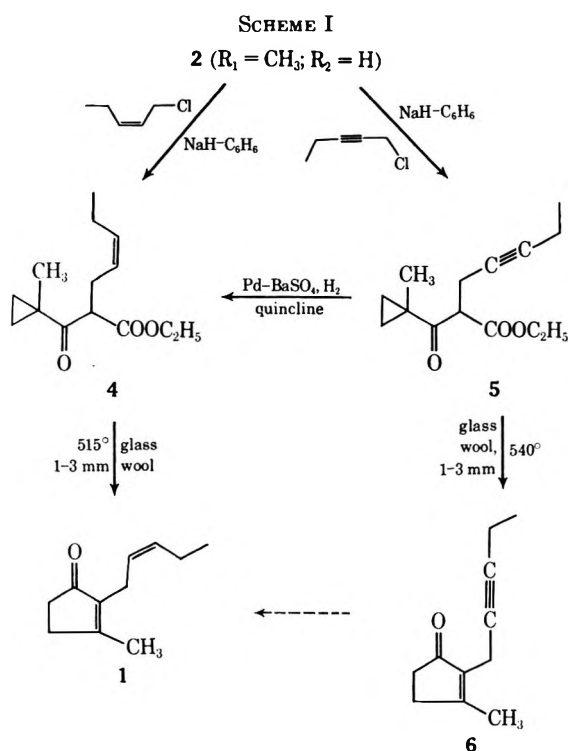

all) and the acetylenic analog 6 (39% overall) were prepared as shown in Scheme I.[12]
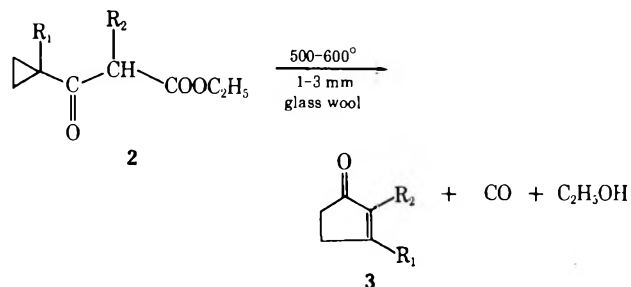
Experimental Section

Melting points were determined on a Mel-Temp apparatus, and neither melting points nor boiling points were corrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Preparative gas–liquid chromatography (glpc) was done on a Varian-Aerograph Model A90-P3 thermal conductivity machine, and retention times were compared on a Varian Aerograph Model 1200 flame ionization machine; individual conditions are noted below. Infrared data were obtained with a Perkin-Elmer Model 237B grating spectrophotometer, and nmr spectra were recorded on a Varian Model A-60 A nmr spectrometer. Mass spectra were done on a Varian-Atlas Model CH-7 (modified) mass spectrometer by Professor R. R. Engel (Queens). Pyrolyses were done with a Hevi-Duty Electric Company Type 77-T (600 W, "Multi-Unit") tube oven.

Ethyl 2-(1′-Methylcyclopropanecarbonyl)-4-heptynoate (5).—Keto ester 5 was prepared by a standard alkylation sequence[11] using 5.02 g (0.105 mol) of 50% sodium hydride dispersion in mineral oil, 17.02 g (0.100 mol) of 2,[13] and 10.25 g (0.100 mol)

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(8) T. Yoshida, A. Yamaguchi, and A. Komatsu, *Agr. Biol. Chem.*, **30**, 370 (1966).

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(10) P. Bedoukian, *Perfum. Essent. Oil Rec.*, **57**, 495 (1966); this is a review article with 20 references.

(11) W. F. Berkowitz and A. A. Ozorio, *J. Org. Chem.*, **36**, 3787 (1971).

(12) The Alkyne 6 has previously been partially hydrogenated to 1 in 72.6% yield.[7]

(13) Ketone 2 was prepared by carbethoxylation of methyl methylcyclopropyl ketone in 80% yield.[11] The starting ketone was obtained either from Aldrich Chemical Co., Cedar Knolls, N. J., or by the procedure of N. L. Goldman, *Chem. Ind. (London)*, 1024 (1963), which starts with α-acetyl-α-methyl-γ-butyrolactone.

SCHEME I

2 (R₁ = CH₃; R₂ = H)

1

and room temperature.[16] Hydrogen uptake (745 ml, 101%) ceased abruptly after 33 min. The reaction mixture was filtered through Celite which was washed thoroughly with ethanol. The filtrate and ethanol washes were combined and concentrated under reduced pressure to give 7.19 g of green oil. The oil was dissolved in 75 ml of benzene, washed twice with cold dilute hydrochloric acid and once with saturated aqueous sodium bicarbonate, then dried over magnesium sulfate and concentrated under reduced pressure to give 6.74 g of green oil. This was fractionated as before, giving 5.811 g (83%) of 4, bp 67–75° (0.005 mm), also pure by thin layer chromatography.

The materials prepared by methods A and B were shown to be identical by comparison of thin layer chromatography R_f values and infrared spectra. Keto ester 4 exhibited ir (CCl_4) 5.71 (ester CO) and 5.89 μ (ketone CO) (no peak was observed in the region 4.5–5.0 μ); nmr (CCl_4) δ 5.21 (symmetrical m, 2, consistent with $CH_{2a}CH_x=CH_yCH_{2b}$ with Δν = 10.5 Hz, J_{xy} = 10 Hz, $J_{ax.by}$ = 6.5 Hz, $J_{ay.bx}$ = 1 Hz), 4.07 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 3.50 (t, 1, J = 7.5 Hz, –$COCHRCOO$–), 2.46 (broadened triplet, 2, J = 6.5 Hz, –$CHCH_2C$=), 2.05 (broadened pentuplet, 2, J = 7 Hz, =CCH_2CH_3), 1.35 (s, 3, >CCH_3), 1.23 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 0.95 (t, 3, J = 7.5 Hz, =CCH_2CH_3), 0.5–1.0 (m, 4, cyclopropyl CH_2); mass spectrum (70 eV) m/e 238 (molecular ion).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.73; H, 9.44.

cis-Jasmone (1).—Pyrolysis[11] of 1.297 g (0.00545 mol) of 4 at 515° and 1–5 mm (glass wool packing) gave 1.067 g of mobile yellow oil which was fractionated on an 8-in. stainless steel spinning band column and gave 0.512 g (57%) of 1, bp 52.5° (0.05 mm). A repeat with 4.863 g (0.0204 mol) of 4 at 535° and 1–5 mm (glass wool packing) gave 3.416 g of crude 1 which, after distillation as before, gave 1.785 g (53%) of 1. Further purification by preparative glpc[17] gave material which was identical by glpc,[18] ir, nmr, and mass spectrum analyses with authentic material (kindly provided by Professor Stork).

3-Methyl-2-(2'-pentynyl)-2-cyclopentenone (6).—Pyrolysis[11] of 3.516 g (0.0149 mol) of 5 at 540° and 0.5–2 mm (glass wool packing) gave 2.725 g of crude 6 which was distilled on an 8-in. stainless steel spinning band column and gave 1.260 g (53%) of 6, bp 79° (1.5 mm). A portion of this material was further purified by preparative glpc,[17] giving pure 6: ir (CCl_4) 5.86 (conjugated CO) and 6.04 μ (C=C) (no peak was observed in the region 4.5–5.0 μ); nmr (CCl_4) δ 2.99 (br s, 2, =CCH_2C=), 2.83–1.83 (m, 9), 2.21 (br s, 3, ring CH_3), 1.12 (t, t, 3, J = 7, 0.5 Hz, =CCH_2CH_3); mass spectrum (70 eV) m/e 162 (molecular ion). The 2,4-dinitrophenylhydrazone derivative had mp 164–165° (lit.[7] mp 166°).

of 1-chloro-2-pentyne[14] (freshly distilled, bp 122.5°) in 400 ml of dry benzene. Work-up gave 25.75 g of amber oil which was fractionated on an 18-in. Teflon annular spinning band column and gave 3.67 g of 2 and 12.68 g of keto ester 5 (68.5% based on unrecovered 2).

A portion of the product was redistilled for analysis: bp 86.5° (0.005 mm); ir (CCl_4) 5.71 (ester CO) and 5.89 μ (ketone CO) (no peak was observed in the region 4.5–5.0 μ); nmr ($CDCl_3$) δ 4.18 (q, 2, J = 7.2 Hz, –$COOCH_2CH_3$), 3.82 (t, 1, J = 7.5 Hz, –$COCHRCOO$–), 2.65 (d, t, 2, J = 7.5, 2.2 Hz, –$CHCH_2C$≡C–), 1.85–2.4 (m, 2, –C≡CCH_2CH_3), 1.40 (s, 3, >CCH_3), 1.25 (t, 3, J = 7.2 Hz, –$COOCH_2CH_3$), 1.07 (t, 3, J = 7.5 Hz, C≡CCH_2CH_3), 0.6–1.1 (m, 4, cyclopropyl CH_2); mass spectrum (70 eV) m/e 236 (molecular ion).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.02; H, 8.59.

Ethyl 2-(1'-Methylcyclopropanecarbonyl)-*cis*-4-heptenoate (4). **Method A.**—Keto ester 4 was prepared by a standard alkylation sequence[11] using 0.80 g (0.0165 mol) of a 50% dispersion of sodium hydride in mineral oil, 2.549 g (0.0150 mol) of 2,[13] and 2.406 g (0.023 mol) of *cis*-1-chloro-2-pentene[15] in 55 ml of dry benzene. Work-up gave 3.5 g of pale yellow oil which was fractionated on an 8-in. stainless steel spinning band column and gave 1.796 g (50%) of 4, bp 68.5–72° (0.005 mm), which was substantially pure by thin layer chromatography (benzene, silica gel G).

Method B.—Keto ester 4 was also prepared by partial hydrogenation of 7.09 g (0.030 mol) of 5 in a mixture of 75 ml of absolute ethanol, 150 mg of synthetic quinoline, and 150 mg of 5% palladium on barium sulfate (Engelhard Industries) at 765 mm

(14) Kindly provided by Dr. W. I. Taylor of International Flavors and Fragrances, Union Beach, N. J.

(15) The alkenyl halide was the gracious gift of Professor G. Stork, Chemistry Department, Columbia University, New York, N. Y.

(16) The procedure of D. J. Cram and N. L. Allinger, *J. Amer. Chem. Soc.*, **78**, 2518 (1956).

(17) A 20 ft × ³/₈ in. column packed with 30% SE-30 silicone gum rubber on Chromosorb P at 175° was used.
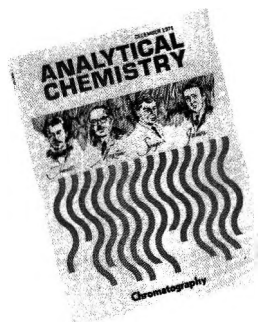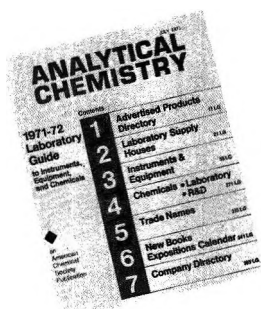
(18) A 5 ft × ¹/₈ in. column packed with 20% SE-30 silicone gum rubber on Chromosorb P at 180° was used.