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AUTHOR INDEX

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Nucleophilic Substitution Reactions on Haloazobenzenes

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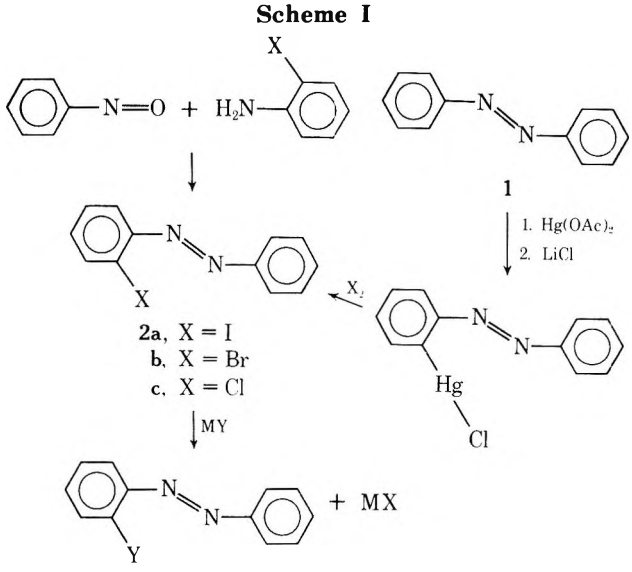
Cuprous cyanide and cuprous alkoxides (methoxide, ethoxide, isopropoxide, and *tert*-butoxide) readily underwent substitution reactions with 2-iodoazobenzene to yield 2-cyanoazobenzene and the 2-alkoxyazobenzenes, respectively. Similar reactions with the corresponding sodium salts gave either no reaction or reduction of 2-iodoazobenzene to azobenzene with one exception, sodium methoxide, which gave 2-methoxyazobenzene. The reactivities of 2-bromo-, 2-chloro-, 3-iodo-, and 4-iodoazobenzene are contrasted to that of 2-iodoazobenzene. Substitution reactions of 2,6-diiodo- and 2,2′-diiodoazobenzene are discussed.

Very few electrophilic substitution reactions of azobenzene give 2-substituted azobenzenes and when they do the yields are very low.[1] Thus to obtain 2-substituted azobenzenes the most convenient method is the condensation of an aromatic nitroso compound with an aniline.[2] The limitations of such reactions are the availability of the necessary two starting materials. In this paper there are described nucleophilic substitution reactions of 2-iodoazobenzene (**2a**) that lead to a number of 2-substituted azobenzenes (Scheme I). The 2-iodoazobenzene (**2a**) can be synthesized by a condensation reaction[3] (Scheme I) or through direct[4] (Scheme I) mercuration of azobenzene (1) or through indirect[5] formation of the same mercurial and subsequent iodination of this mercurial. Such reaction sequences can be extended to other azobenzenes where an R group (or groups) is present on the azobenzene. This has been done for two examples in this paper.

Scheme I



2a, X = I
b, X = Br
c, X = Cl

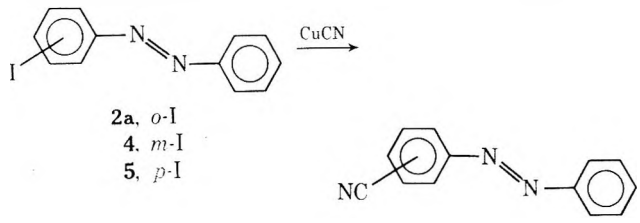
3a, Y = CN
b, Y = OMe
c, Y = OEt
d, Y = O-*i*-Pr
e, Y = O-*t*-Bu
f, Y = OH

Examples of aromatic nucleophilic substitution reactions are numerous in the literature. Substitution is easiest when the ring is activated with an electron-withdrawing group or groups in the ortho and/or para position(s) to the leaving group.[6] For unactivated aromatics the use of the copper salts either as catalysts or in themselves leads to substitution; however, the conditions of reaction are usually rather severe.[7-9] A few cases of nucleophilic substitution of chlorohydroxyazobenzenes are reported in which alkoxides, with cupric salts as catalysts, replace the chlorine.[10]

Results and Discussion

The results of the substitution reactions on monohaloazobenzenes are listed in Table I. The ratio of nucleophilic reagent to haloazobenzene was always kept large to drive the reaction to completion where possible. No difficulty was experienced in isolating the monocyano compounds from the reaction mixtures as other workers have found.[9]

The cyanide ion is a good nucleophile, but with the sodium ion in methanol, it did not substitute for the iodine of 2-iodoazobenzene (**2a**). When dimethylformamide was used as the solvent and the temperature of the reaction was 100°, then a very small yield of 2-cyanoazobenzene (**3a**) was obtained. At reflux no product was obtained. However, with the cuprous ion, in methanol, the substitution of **2a** with cyanide proceeded smoothly and essentially quantitatively to yield **3a**. The reaction of cuprous cyanide with 3-



2a, *o*-I
4, *m*-I
5, *p*-I

3a, *o*-CN
4a, *m*-CN
5a, *p*-CN

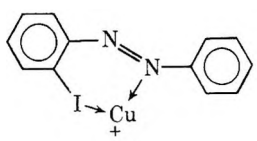
Table I
Nucleophilic Substitution Reactions on Haloazobenzenes

Nucleophilic reagent (MY)	Haloazobenzene	Molar[a] ratio	Solvent	Method	SM	% Yield[b] products
NaCN	2a	3	Methanol	A	100	0
NaCN	2a	3	DMF, 100°[c]	A	50	1
NaCN	2a	3	DMF, 152°	A	0	0, 10 (1)
CuCN	2a	3	Methanol	A	1	94
CuCN	4	3	Methanol	A	95	1
CuCN	4	3	None	C	6	52
CuCN	5	3	Methanol	A	91	1
CuCN	5	3	None	C	33	34
CuCN	2b	4	Methanol	A	15	81
CuCN	2c	4	Methanol	A	95	0
NaOMe	2a	3	Methanol	B	3	95
NaOMe	2b	13	Methanol	B	94	0
CuOMe	2b	13	Methanol	B	32	49
NaOEt	2a	10	Ethanol	B	0	0, 90 (1)
NaO-*i*-Pr	2a	13	2-Propanol	B	0	0, 100 (1)
NaO-*t*-Bu	2a	13	*tert*-Butyl alcohol	B	70	0
CuOEt	2a	7	Ethanol	B	1	89, 1 (3f)
CuO-*i*-Pr	2a	13	2-Propanol	B	0	62, 10 (1), 16 (3f)
CuO-*i*-Pr[d]	2a	13	2-Propanol	B	0	62, 13 (1), 20 (3f)
CuO-*t*-Bu	2a	13	*tert*-Butyl alcohol	B	21	18, 42 (3f)
CuCl	2a	3	Methanol	A	0	100
NaOH	2a	12	Methanol	A	90	0
CuOH	2a	3	Methanol	B	0	0, 93 (3b)
CuOH	2a	16	*tert*-Butyl alcohol	B	64	11
Cu_2O	2a	2	Methanol	A	70	29 (3b)
Cu_2O	2a	2	2-Propanol	A	74	3 (3d)

[a] Ratio of moles of nucleophilic reagent to moles of haloazobenzenes. [b] The percent recovery of starting material (SM) is given. Under products is listed the percent yield of the expected product and then additional products with identification numbers in parentheses. [c] Heated for only 1.5 hr. [d] Reagent made with a 10% molar excess of cuprous chloride.

iodo- (4) and 4-iodoazobenzene (5) in methanol gave only slight yields of the corresponding cyano compounds (**4a** and **5a**). However, with no solvent and a much higher temperature 4 and 5 reacted partially with cuprous cyanide to give **4a** and **5a**, respectively, along with some apparent decomposition. The substitution of 2-bromoazobenzene (**2b**) was slower than that of 2-iodoazobenzene (**2a**) and 2-chloroazobenzene (**2c**) did not react at all under these conditions.

The above results suggest that the essential part of the reaction is the chelation of the cuprous ion by an azo nitrogen and by the iodo group as illustrated (6 and 7). The cop-



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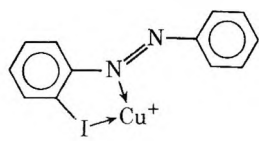

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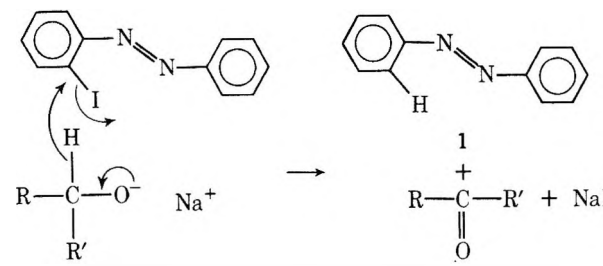
per would then assist in removing the iodine, thus allowing for easy substitution of the cyano group. The sodium ion does not chelate and the 3-iodo- and 4-iodoazobenzenes (**4** and **5**) cannot form such chelates. If chelation were not favored then the 2-iodo- and 4-iodoazobenzenes should be expected to react at about the same rates.[6]

The methoxide ion is generally a better nucleophile[11] than the cyanide ion and this is seen in the case of the reaction of sodium methoxide with 2a to give a high yield of 2-methoxyazobenzene (**3b**). Reaction between sodium methoxide and 2-bromoazobenzene (**2b**) did not take place, indicating that possibly this is on the borderline of reactivity. Reaction of sodium ethoxide and sodium isopropoxide gave exclusively reduction of **2a** to azobenzene (1). Possible reaction mechanisms are a hydride transfer of the α hydro-



gen of the alkoxide or hydrogen abstraction by aryl radicals or, in copper reactions, copper-associated radicals generated through an electron transfer mechanism to give reduction of **2a** and to give a carbonyl compound. The carbonyl compounds, acetaldehyde and acetone, in these reactions were not searched for. Under these mild conditions, the sodium *tert*-butoxide did not undergo the reduction reaction, having no α hydrogen atom, and did not undergo substitution. Bacon and Rennison[13] similarly found that sodium alkoxides, with cuprous oxide as catalyst, gave reduction of 1-bromonaphthalene to naphthalene. In their case, sodium methoxide gave between 5 and 50% substitution and about 10% reduction. Sodium ethoxide gave 5 to 10% substitution and the rest reduction while sodium isopropoxide gave reduction and no substitution. They also found that sodium *tert*-butoxide gave some reduction and no substitution. They surmised that, at their conditions of over 100°, copper-associated radicals possibly were involved and these can remove β hydrogens from a *tert*-butyl group for the reduction. They did show that when the sodium salt of benzyl alcohol was used in the reaction that benzaldehyde resulted.

Two cuprous alkoxides have recently been described. Cuprous methoxide[14] was made by the reaction between methylcopper and methanol and the cuprous *tert*-butox-

Table II
Nucleophilic Substitution Reactions on Dihaloazobenzenes

Nucleophilic reagent (MY)	Dihaloazobenzene	Molar[a] ratio	Solvent	Method	SM	% Yield[b] Mono-	% Yield[b] Di-
CuCN	8	1	Methanol	A	11	75 (9a)	12 (10a)
CuCN	8	7	Methanol	A	0	0	94 (10a)
CuCN	11	7	Methanol	A	3	20 (12a)	45 (13a)
NaOMe	8	1	Methanol	B	20	51 (9b)	20 (10b)
NaOMe	8	9	Methanol	B	0	1 (9b)	81 (10b)
NaOMe	11	15	Methanol	B	100	0	0
CuOMe	11	9	Methanol	B	36	15 (12b)	47 (13b)

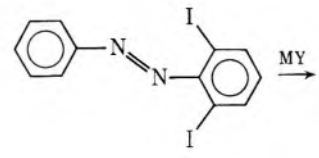
[a] Ratio of moles of nucleophilic reagent to moles of dihaloazobenzene. [b] The percent recovery of starting material (SM) is given. Under mono- and di- are listed the percent yields of the expected products and in parentheses are the identification numbers.

ide[15] was obtained by reaction of lithium *tert*-butoxide and cuprous chloride. For this work the cuprous alkoxides were made in situ and used immediately. The method of making the cuprous alkoxides was to react equal molar amounts of sodium alkoxide with cuprous chloride under reflux for 30 min. The 30-min reflux period was found to be essential since without it no expected products resulted. The reaction of cuprous isopropoxide with **2a** seemed to show no difference in the ratio of products whether the cuprous isopropoxide was made with a slight excess of cuprous chloride or a slight excess of sodium alkoxide. Thus it appears that both sodium and cuprous isopropoxide can give reduction.

Since the sodium methoxide reacted completely with **2a**, cuprous methoxide was not treated with **2a** but was treated with 2-bromoazobenzene (**2b**) to give a fair yield of 2-methoxyazobenzene (**3b**). Cuprous ethoxide reacted with **2a** to give a good yield of 2-ethoxyazobenzene (**3c**) and no detectable reduction product, azobenzene (**1**). Reaction between cuprous isopropoxide and **2a** gave a fair yield of 2-isopropoxyazobenzene (**3d**) in addition to the reduction product, azobenzene (**1**), and some 2-hydroxyazobenzene (**3f**). Cuprous *tert*-butoxide and **2a** gave a low yield of 2-*tert*-butoxyazobenzene (**3e**) along with recovered **2a** and a fair yield of **3f**.

The 2-hydroxyazobenzene (**3f**) that was observed in the case of the reaction between cuprous isopropoxide (or *tert*-butoxide) and **2a** could be due to the decomposition of **3d** (or **3e**) or formation directly by substitution with cuprous hydroxide. 2-Isopropoxyazobenzene (**3d**) was refluxed for 22 hr with cuprous isopropoxide. On work-up, no 2-hydroxyazobenzene (**3f**) was detected, thus suggesting that decomposition of the alkoxyazobenzene is not the path to **3f**. Sodium hydroxide and **2a** were refluxed in methanol but no reaction was observed after 22 hr. This is not surprising, since the hydroxide ion generally is less nucleophilic than cyanide.[12] However, when 1 equiv of cuprous chloride was added to the sodium hydroxide and this refluxed for 30 min, to make cuprous hydroxide, there was obtained on reaction with **2a** an excellent yield of 2-methoxyazobenzene (**3b**) but no **3f**. The reaction of cuprous hydroxide and **2a** in *tert*-butyl alcohol did yield **3f**. This suggests that in methanol there is an equilibrium between the hydroxide and methoxide ions and that the methoxide reacts faster to form **3b**. In *tert*-butyl alcohol the hydroxide ion apparently reacts faster than the *tert*-butoxide ion, giving **3f** and no **3e**. The formation of cuprous hydroxide in the cuprous alkoxide reactions could be generated by decomposition of the cuprous isopropoxide or *tert*-butoxide into cuprous hydroxide and alkene. Commercial cuprous oxide when treated with **2a** in methanol gave a small yield of **3b**, and in isopropyl alcohol a slight amount of **3d**.

In Table II are listed the results of substitution reactions on diiodoazobenzenes. 2,6-Diiodoazobenzene (**8**) with 1 mol of cuprous cyanide gave predominantly the product of monosubstitution, 2-cyano-6-iodoazobenzene (**9a**). When a



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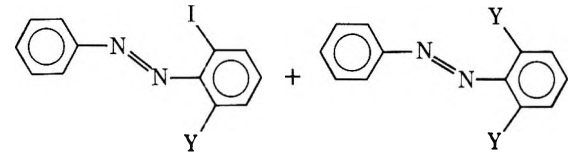
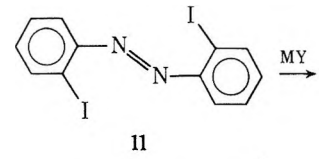


9a, Y = CN
b, Y = OMe

10a, Y = CN
b, Y = OMe

large excess of cyanide was used, then the only product was the disubstituted compound, 2,6-dicyanoazobenzene (**10a**). 2,2′-Diiodoazobenzene (**11**) is not as reactive as **8** and even with an excess of cuprous cyanide reaction did not proceed completely to the dicyano compound, 2,2′-dicyanoazobenzene (**13a**), and some 2-cyano-2′-iodoazobenzene (**12a**) was left. A fair amount of what appeared to be decomposition



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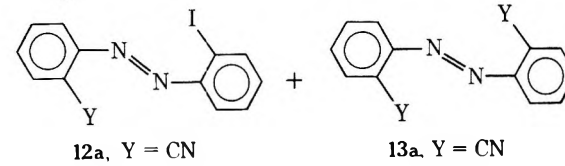

12a, Y = CN
b, Y = OMe

13a, Y = CN
b, Y = OMe

material was observed on working up this reaction. In the reactions of diiodo compounds some loss of cyano compounds resulted if the reaction mixtures were not worked up with the ammonia solution. This is unlike the cases noted earlier in Table I but similar to what others have noted.[9]

Reaction between **8** and sodium methoxide proceeded as with cuprous cyanide. In the equal molar case there was, however, obtained more disubstituted product, 2,6-dimethoxyazobenzene (**10b**), than in the cyanide case, and less monosubstituted product, 2-iodo-6-methoxyazobenzene (**9b**). The 2,6-dimethoxyazobenzene (**10b**) obtained in

Table III
Properties of the Compounds[a]

Compd	Mp °C Found	Mp °C Lit.	Ir $\nu_{C\equiv N}$, cm^{-1}	Nmr, δ values[b] Aromatic region[c]	Nmr, δ values[b] Aliphatic region
1	65–67	68[d]		8.1–7.3	
2a	60–61.5	62[e]		8.1–7.0[f]	
2b	39–40	36[e]		8.1–7.3	
2c	27–28	33[g]		8.1–7.3	
3a	61.5–63		2210	8.1–7.3	
3b	34–36	40[h]		8.1–6.8	s 4.0[i]
3c	130–135[j]			8.1–6.8	q 4.2 ($J \cong 6$) t 1.5 ($J \cong 6$)
3d	130–135[j]			8.2–6.7	sep 4.5 ($J \cong 6$) d 1.3 ($J \cong 6$)
3e	62–64			8.1–6.9	s 1.4
3f	79–80	81[h]		8.3–6.7	s 12.8[i,k]
4	69–70	71[e]		8.0–7.3 d 8.2 ($J \cong 2$) t 7.2 ($J \cong 8$)	
4a	90.5–91		2210	8.3–7.3	
5	105–106	106[e]		8.1–7.3	
5a	120–121	120.5–121.5[d]	2207	8.2–7.3	
8	118–119	118–119[f]		8.2–7.3[f] t 6.6 ($J \cong 8$)	
9a	73–74		2206	8.3–7.5 t 7.2 ($J \cong 8$)	
9b	63.5–64.5			8.2–7.3 7.0–6.9	s 3.8
10a	178–179		2210, 2208[m]	8.3–7.4	
10b	113–115	96–97[n]		8.0–7.0 6.8–6.5	s 3.8[i]
11	158–159	158–158.5[p]		8.1–7.0[f]	
12a	141.5–143		2207	8.2–7.2	
12b	99–100			8.1–6.9	s 4.0
13a	235.5–237		2208	8.2–7.5	
13b	154–155	155[h]		7.9–6.9	s 4.0[i]

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Integrations were correct for all compounds. [c] Multiplets unless otherwise specified. [d] Reference 21. [e] Reference 3. [f] For further elucidation of the NMR spectra see ref 4. [g] Reference 20. [h] Reference 17. [i] These values compare favorably with the values in ref 17. [j] Boiling points at 0.75 mm. [k] Hydroxyl proton. [l] Reference 4. [m] Shoulder peak. [n] References 16 and 17. [p] Reference 22.

this study was found to have a melting point 20° higher than that previously reported.[16,17] An elemental analysis shows a formulation consistent with that of **10b.** In an effort to prove conclusively the structure, **10b** was made by an independent route. 2-Nitroresorcinol was dimethylated,[18] the nitro group reduced,[19] and the resulting aniline condensed with nitrosobenzene to give **10b.** The melting point of this **10b** was identical with that of the **10b** above and a mixture melting point was undepressed. Repeated crystallizations from different solvents failed to change the melting point. The NMR spectrum is also consistent with **10b.**

2,2′-Diiodoazobenzene (**11**) gave no methoxy compounds when treated with sodium methoxide. Moreover, reduction of one of the iodo groups was sometimes observed although this was erratic. Reaction did take place when cuprous methoxide was used, but not all of the starting material was used up in the reaction even though a large excess of cuprous methoxide was used. These results are consistent with those of reaction with cuprous cyanide. Also a very small amount of reduction was noted in the form of 2-methoxyazobenzene (**3b**) contaminating the mono product, 2-iodo-2′-methoxyazobenzene (**12b**).

In conclusion, a number of cuprous salts can be used to effect substitution of ortho iodoazobenzenes in good yield under mild conditions.

Experimental Section

NMR spectra were recorded on a Varian T-60 spectrometer in 5–10% $CDCl_3$ solutions with Me_4Si as the internal standard. Ir spectra were taken in chloroform solution on a Perkin-Elmer IR-257.

The alumina used throughout this work was of activity grade of about 3 and was made by shaking 1000 g of neutral, Fisher alumina (Alcoa F-20) with 75 ml of water. All solvents used in this work were reagent grade and were used without further purification. The ligroin used was of boiling range 63–75°. The cuprous chloride used was Fisher C-457.

Melting points were taken on a Mel-Temp apparatus and are uncorrected. All microanalyses were carried out by the Galbraith Laboratories, Inc., Knoxville, Tenn.

Chromatography of all compounds was as follows. Azobenzene and all monohaloazobenzenes were eluted with a 9:1 mixture of ligroin–benzene. Monoalkoxyazobenzenes were eluted with a 1:1 mixture of ligroin–benzene, diiodoazobenzenes with a 4:1 mixture of ligroin–benzene, monosubstituted diiodoazobenzenes with a 1:1 mixture of ligroin–benzene, and the dicyano- and dimethoxyazobenzenes with benzene.

All monosubstituted azobenzenes were crystallized from ligroin and all disubstituted azobenzenes from benzene.

The concentrations of the reactions were between 0.10 and 0.06 *M* in haloazobenzene.

Method A. 2-Iodoazobenzene (**2a,** 1.00 g, 3.3 mmol), 1.0 g (11 mmol) of cuprous cyanide, and 40 ml of methanol were refluxed for 20 hr. The reaction mixture was then poured into 400 ml of water and extracted with ether. The ether was evaporated and the residue was taken up in ligroin and chromatographed on 100 g of alu-

mina. Elution with a 9:1 mixture of ligroin–benzene gave 0.01 g (1%) of 2-iodoazobenzene. Further elution with a 1:1 mixture of ligroin–benzene gave 0.63 g (94%) of 2-cyanoazobenzene (**3a**). Crystallization from ligroin yielded 0.58 g (87%) of **3a**.

Further reactions of this type are listed in Tables I and II. The properties of all compounds used and made are listed in Table III.

In experiments on compounds 8 and **11**, the reaction mixture was poured into 400 ml of 1 *N* ammonium hydroxide solution instead of 400 ml of water.

Method B. Sodium metal (1.0 g, 43 mmol) was treated with 50 ml of refluxing *tert*-butyl alcohol. When all of the sodium was reacted 4.0 g (40 mmol) of cuprous chloride was added and refluxing was continued for 0.5 hr. Then 1.00 g (3.3 mmol) of 2-iodoazobenzene (**2a**) was added and the reaction mixture was refluxed for an additional 20 hr. At the end of the reflux period, the reaction mixture was poured into 300 ml of water and 200 ml of ether. The mixture was made slightly acidic, stirred for 5 min, and filtered to remove the black residue. The filtrate was separated and the ether was extracted three times with 150-ml portions of 1 *N* sodium hydroxide. The aqueous extracts were combined, acidified, extracted with ether, dried over anhydrous sodium sulfate, evaporated, and crystallized from ligroin to yield 0.27 g (42%) of 2-hydroxyazobenzene (**3f**). The ether layer, after base extractions, was evaporated to yield an oil which was dissolved in ligroin and chromatographed on 75 g of alumina. The first band was eluted with a 9:1 mixture of ligroin–benzene to yield 0.21 g (21%) of recovered 2-iodoazobenzene (**2a**). Elution with a 1:1 mixture of ligroin–benzene gave 0.15 g (18%) of 2-*tert*-butoxyazobenzene (**3e**). Crystallization from ligroin by means of a Dry Ice–acetone bath gave red crystals of **3e**.

Further reactions of this type are listed in Tables I and II. The properties of all compounds used and made are listed in Table III.

A similar reaction, but without the cuprous chloride, gave only recovered **2a**.

Method C. 3-Iodoazobenzene (**4**, 1.00 g, 3.3 mmol) and 1.0 g (11 mmol) of cuprous cyanide were placed in a Schlenk tube and heated in an oil bath to 188° for 18 hr. Sublimation occurred. At the end of the reaction time the reaction mixture was extracted with hot chloroform until the extracts were colorless, leaving a black residue. The solvent was evaporated and the work-up of the reaction then proceeded as in method A.

2,6-Dimethoxyazobenzene (10b). At room temperature were mixed 6.1 g (40 mmol) of 2,6-dimethoxyaniline[19] in 50 ml of 95% ethanol and 5.3 g (50 mmol) of nitrosobenzene in a mixture of 95% ethanol and 50 ml of glacial acetic acid. This mixture was allowed to stand for 20 hr. It was then poured into 1 l. of water and extracted three times with 200-ml portions of ether which was washed three times with 250-ml portions of 2 *N* hydrochloric acid and three times with 150-ml portions of water. The ether layer was dried over anhydrous sodium sulfate and evaporated and the residue was taken up in a 3:2 mixture of ligroin–benzene. This was placed on a column of 150 g of alumina and elution with a 3:2 mixture of ligroin–benzene gave a light yellow colored fraction which was discarded. Elution with a 1:4 mixture of ligroin–benzene gave 2.5 g (26%) of an orange compound which after crystallization from benzene–ligroin gave 2.3 g (24%) of **10b**, mp 113–115°. A mixture melting point with the 2,6-dimethoxyazobenzene made by methoxylation of 8 was 113.5–115.5°.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.06; H, 5.92; N, 11.34.

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Registry No.—**1**, 103-33-3; **2a**, 51343-11-4; **2b**, 4103-29-1; **2c**, 18264-99-8; **3a**, 38302-59-9; **3b**, 6319-21-7; **3c**, 55669-54-0; **3d**, 55669-55-1; **3e**, 55669-56-2; **3f**, 2362-57-4; **4**, 23377-17-5; **4a**, 55669-57-3; **5**, 6639-27-6; **5a**, 1837-93-0; 8, 52221-99-5; **9a**, 55669-49-3; **9b**, 55669-50-6; **10a**, 55669-51-7; **10b**, 29418-48-2; **11**, 5486-04-4; **12a**, 55669-52-8; **12b**, 613-55-8; **13a**, 16288-72-5; **13b**, 613-55-8; sodium cyanide, 143-33-9; copper cyanide, 544-92-3; sodium methoxide, 124-41-4; copper methoxide, 18213-24-6; sodium ethoxide, 141-52-6; sodium isopropoxide, 683-60-3; sodium *tert*-butoxide; copper ethoxide, 55669-53-9; copper isopropoxide, 53165-38-1; copper *tert*-butoxide, 35342-67-7; cuprous chloride, 7758-89-6; sodium hydroxide, 1310-73-2; cuprous hydroxide, 12125-21-2; cuprous oxide, 1317-39-1; *tert*-butyl alcohol, 75-65-0; 2,6-dimethoxyaniline, 2734-70-5; nitrosobenzene, 586-96-9.

References and Notes

(1) K. H. Schündehütte in "Methoden der Organischen Chemie", Vol. X, Part 3, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1965, pp 382–390, and references cited therein.
(2) Reference 1, pp 332–338.
(3) G. M. Badger, R. J. Drewer, and G. E. Lewis, *Aust. J. Chem.*, **17**, 1036 (1964).
(4) P. V. Roling, J. L. Dill, and M. D. Rausch, *J. Organomet. Chem.*, **69**, C33 (1974).
(5) R. J. Cross and N. H. Tennent, *J. Organomet. Chem.*, **61**, 33 (1973).
(6) J. DeBoer and I. P. Dirxx in "The Chemistry of the Nitro and Nitroso Groups", Part 1, H. Feuer, Ed., Interscience, New York, N.Y., 1969, Chapter 8.
(7) M. J. S. Dewar and A. P. Marchand, *J. Am. Chem. Soc.*, **88**, 3318 (1966).
(8) J. Cason and D. D. Phillips, *J. Org. Chem.*, **17**, 298 (1952).
(9) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).
(10) Reference 1, pp 419–423.
(11) W. Reeve and P. F. Aluotto, *Tetrahedron Lett.*, 2557 (1968). These authors have found that hydroxide ion is less nucleophilic than methoxide ion and ref 12 shows cyanide ion to be slightly more nucleophilic than hydroxide ion.
(12) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).
(13) R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc. C*, 312 (1969).
(14) G. Costa, A. Camus, and N. Marsich, *J. Inorg. Nucl. Chem.*, **27**, 281 (1965).
(15) T. Tsuda, T. Hashimoto, and T. Saegusa, *J. Am. Chem. Soc.*, **94**, 658 (1972).
(16) J. Bechhold, *Ber.*, **22**, 2374 (1889).
(17) E. Haselbach, *Helv. Chim. Acta*, **53**, 1526 (1970).
(18) B. B. Dey, T. R. Govindachari, and S. C. Rajagopalan, *J. Sci. Ind. Res.*, **3**, 338 (1945).
(19) N. M. Löfgren and B. Takmen, *Acta Chem. Scand.*, **6**, 1006 (1952).
(20) R. Belcher, A. J. Nutten, and W. I. Stephen, *J. Chem. Soc.*, 2336 (1958).
(21) H. H. Jaffee and R. W. Gardner, *J. Am. Chem. Soc.*, **80**, 319 (1958).
(22) B. T. Newbold, *J. Chem. Soc.*, 6972 (1965).

Arylsulfonoxylation of Aromatic Compounds. VII. The *p*-Nitrophenylsulfonoxylation of Benzyl Alcohol, Benzaldehyde, and Acetophenone[1a-c]

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p-Nitrobenzenesulfonyl peroxide (I) oxidized benzaldehyde in ethyl acetate solution at 0° in the presence of *N,N*-diphenylpicrylhydrazyl to give benzoic acid (85%) with a $\Delta H^{\ddagger}$ of 22 ± 4 kcal mol^{-1}. No nuclear substitution in the aromatic aldehyde was detected. I (1.00) reacts with a mixture of benzene (113) and benzyl alcohol (20) in ethyl acetate to give *p*-nitrobenzenesulfonic acid (1.19), benzoic acid (0.187), phenyl *p*-nitrobenzenesulfonate (0.206), and isomeric hydroxymethylphenyl *p*-nitrobenzenesulfonates (0.378). The orientations of nuclear substitution (partial rate factors based upon the competitive nuclear reactivity of 10.5 for benzyl alcohol) are: ortho, 29.3% (9.2); meta, 9.9 (3.1); para, 60.8 (37.8). The overall kinetics give a $\Delta H^{\ddagger}$ of 15.4 kcal mol^{-1} and $\Delta S^{\ddagger}$ of −23 cal deg^{-1} mol^{-1}. I (1.00) reacts with a mixture of acetophenone (200) and benzene (12) to give isomeric *p*-nitrobenzenesulfonoxy acetophenones (0.16), phenyl *p*-nitrobenzenesulfonate (0.056), *p*-nitrobenzenesulfonic acid (1.16), phenacyl *p*-nitrobenzenesulfonate (0.10), benzoic acid (0.592), and traces of 1,3,5-triphenylbenzene and dypnone together with tars which yield methyl iodide (0.15) when treated with hydrogen iodide. The orientations of nuclear substitution [partial rate factors based upon the relative reactivity (0.15) for acetophenone] are: ortho, 35.9% (0.15); meta, 50.3 (0.22); para, 13.8 (0.12). The overall pseudo-first-order rate constants for the disappearance of the peroxide gave $\Delta H^{\ddagger}$ of 16.7 kcal mol^{-1} and $\Delta S^{\ddagger}$ of 21.8 cal deg^{-1} mol^{-1}. These results are all consistent with electrophilic ionic reactions.

In the preceding papers of this series it has been found that nitrobenzenesulfonyl peroxides are sufficiently stable for routine laboratory use[2] and that they react with both activated and deactivated aromatic nuclei[3] by a typical electrophilic aromatic substitution to yield aryl sulfonate esters.

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

Treatment of either styrene or stilbene with sulfonyl peroxides results in oxidative addition to the double bonds to yield disulfonates.[4] However, the side chains of alkylbenzenes are completely unaffected by sulfonyl peroxides while the nuclei are undergoing arylsulfonoxylation.[1,5] Even the nucleus of anisole undergoes *m*-nitrobenzenesulfonoxylation without formation of any other type of oxidation product.[3] Although the arylsulfonyl peroxides are very reactive reagents for electrophilic substitution, they apparently have very limited power as general oxidizing agents.

In the present work it was planned to investigate the reactions of *p*-nitrobenzenesulfonyl peroxide (I) with benzyl alcohol, benzaldehyde, and acetophenone to determine whether nuclear substitution or oxidation of the reactive side chains would occur. The para peroxide was selected in preference to its isomers because preliminary experiments disclosed that some needed reference compounds derived from o- and *m*-nitrobenzenesulfonyl peroxides were oils, but the *p*-nitrobenzenesulfonyl analogs were easily purified crystalline solids.

Results and Discussion

Reaction of I with Benzyl Alcohol. Although the competitive reaction of I with a mixture of benzyl alcohol and benzene in ethyl acetate (eq 2) gave some oxidation of the

$$\underset{(1.00)}{I} + \underset{(20.0)}{C_6H_5CH_2OH} + \underset{(113.0)}{C_6H_6} \xrightarrow[\text{acetate}]{\text{ethyl}} \underset{(0.187)}{C_6H_5COOH} + \underset{(1.19)}{p\text{-}O_2NC_6H_4SO_3H} + \underset{(0.206)}{p\text{-}O_2NC_6H_4SO_3C_6H_5} + \underset{(0.378)}{p\text{-}O_2NC_6H_4SO_3C_6H_4CH_2OH} \quad (2)$$

Table I
Relative Reactivities (from Competitive Determinations), Orientations, and Partial Rate Factors for the *p*-Nitrophenylsulfonoxylation of Benzyl Alcohol and Acetophenone in Ethyl Acetate at 25°

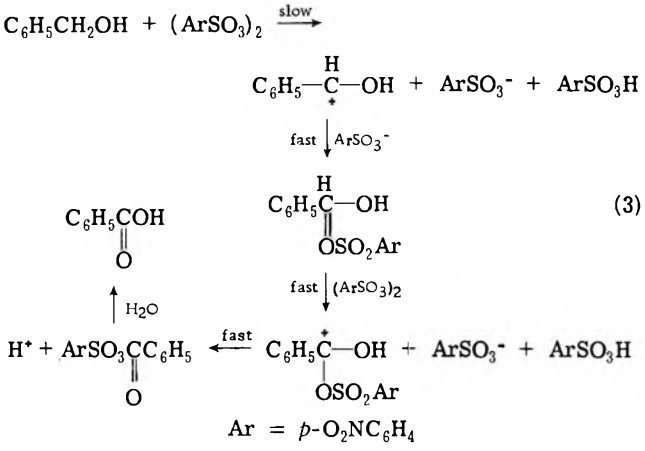
Quantity measured	Benzyl alcohol	Acetophenone
k_{Ar}/k_B	10.5	0.15
% ortho (partial rate factor)	29.3 (9.2)	35.9 (0.15)
% meta (partial rate factor)	9.9 (3.1)	50.3 (0.22)
% para (partial rate factor)	60.8 (37.8)	13.8 (0.12)

alcohol substituent (0.187 mol of benzoic acid per mole of peroxide), an overall 59% yield of nuclear substitution of the two aromatics included a 38% yield of arylsulfonoxylation of the alcohol. This is apparently the first reported successful nuclear substitution of benzyl alcohol and emphasizes the low oxidizing power but high electrophilic reactivity of the sulfonyl peroxides. The orientations of substitution and the partial rate factors (Table I) based upon the competitive relative reactivity to benzene (10.5) bear reasonable resemblance to the relative reactivity (6.48) and the orientations (partial rate factors) for the typically electrophilic nitration of benzyl methyl ether—ortho, 28.6 (9.97); meta, 18.1 (1.32); para, 53.3 (16.3)—even though the nitration apparently proceeds via the protonated ether.[6] The methylene group of benzyl alcohol is obviously activating and ortho–para directing toward arylsulfonoxylation but the inductive effect of the hydroxyl group modifies these effects.

The oxidation of the alcohol group, as expected, stoichiometrically consumed 2 mol of the sulfonyl peroxide per mole of benzoic acid produced (95.7% of the oxidizing power of the peroxide accounted for, but only an 88.7% recovery of the peroxide fragments). An ionic mechanism for the oxidation is probable because the addition of *N,N*-diphenylpicrylhydrazyl to the reaction mixture does not change the yield of benzoic acid.

Kinetic measurements of the disappearance of the peroxide in the reaction mixture (Table II) proved the overall reaction with benzyl alcohol to be clean first order with respect to the peroxide and first order (1.07) with respect to

the alcohol. The rate of reaction with the alcohol is more rapid than with benzaldehyde and yet no aldehyde can be detected in the benzyl alcohol sulfonoxylation products. Therefore benzaldehyde cannot be an intermediate in the oxidation of the alcohol because it should accumulate in measurable quantities. A possible mechanism consistent with these data involves hydride abstraction (eq 3) as a

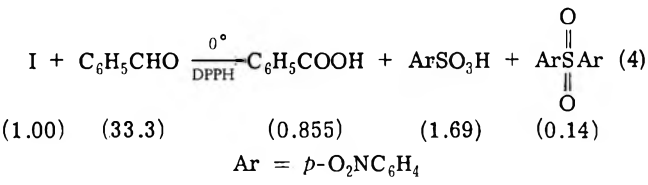


(3)

Ar = *p*-$O_2NC_6H_4$

rate-determining step. The intermediate hydroxy sulfonate could be formed instead by a concerted reaction or a free-radical cage process involving a benzyl alcohol–sulfonyl peroxide coordinated species. From the pseudo-first-order rate constants at various temperatures (Table II), $\Delta H^{\ddagger}$ for the overall reactions was found to be 15.5 ± 0.5 kcal mol^{-1} and $\Delta S^{\ddagger}$ to be − 23 ± 1 cal deg^{-1} mol^{-1}. The $\Delta S^{\ddagger}$ is certainly characteristic of an ionic process, but, as it is calculated from an overall rate, it does not exclude a homolytic process for the side reaction of oxidation.

Reaction of I with Benzaldehyde. The decomposition of I in an ethyl acetate solution of a large excess of benzaldehyde with *N,N*-diphenylpicrylhydrazyl (DPPH) present (eq 4) gave no detectable amount of substitution in the ring

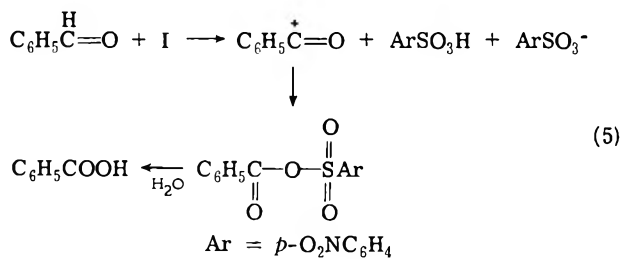


(4)

(1.00) (33.3) (0.855) (1.69) (0.14)

Ar = *p*-$O_2NC_6H_4$

of the aldehyde. In the absence of DPPH or at higher temperatures the yield of benzoic acid decreases to about 60% while the yields of tars and usually the sulfone increase. Degassing the solvent also increases the yield of benzoic acid. The oxidation of the aldehyde to benzoic acid thus appears to be an ionic process, probably proceeding via a



(5)

Ar = *p*-$O_2NC_6H_4$

hydride abstraction (eq 5). There is a competing homolytic induced decomposition involving the peroxide which produces tars and the sulfone.

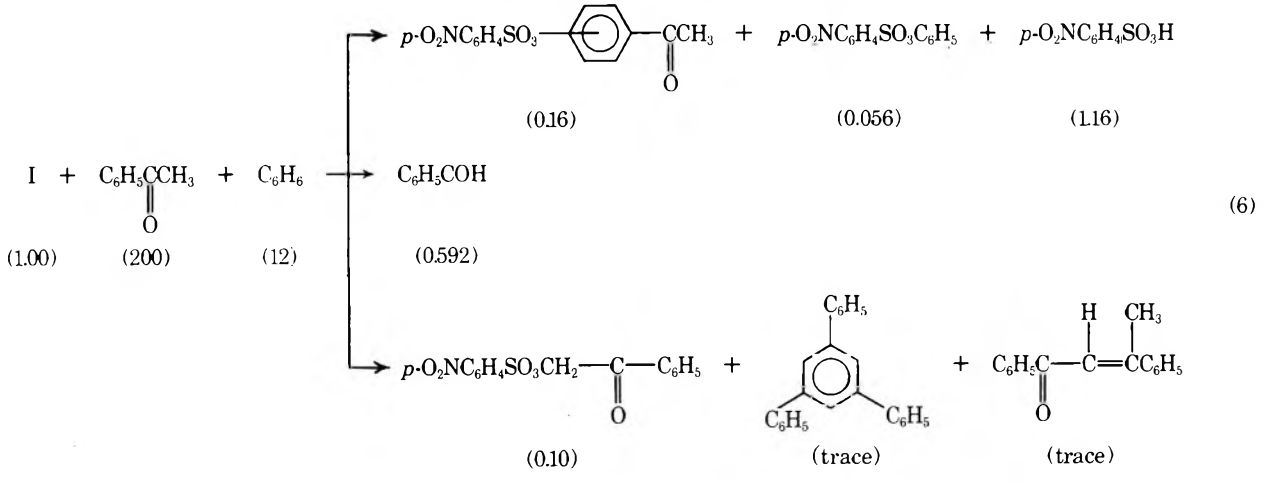
Kinetic studies were complicated by the inability to completely exclude oxygen from the system with its consequent formation of stable peroxides via the free-radical oxidation of the aldehyde. However, by taking duplicate aliquots of the reaction mixture and quenching the sulfonyl peroxide in one sample with anisole before titration, it was possible to correct for the stable carbon peroxides present. Anisole reacts very rapidly with sulfonyl peroxides at room temperature[3] but does not react with the carbon peroxides under these conditions. The difference in titration between the quenched and unquenched samples therefore corresponds to the residual sulfonyl peroxide. The sulfonyl peroxide was found to decompose by first-order kinetics with a $\Delta H^{\ddagger}$ of 22 ± 4 kcal/mol. The inaccuracy of this value precludes a calculation of $\Delta S^{\ddagger}$ of reasonable precision.

Reaction of I with Acetophenone. The competitive reaction of I with a mixture of acetophenone and benzene in ethyl acetate solution (eq 6) obviously proceeds via three separate pathways: substitution of the aromatic nuclei (22%), substitution in the aceto group (10%), and oxidation of the aceto group to benzoic acid (59%).

From the relative yields of substitution in the nuclei of acetophenone and benzene and the orientations of substitution in acetophenone, the partial rate factors for the arylsulfonoxylation of the ketone were calculated (Table I). These partial rate factors are all less than unity with the meta value the largest of the three as expected for an electrophilic substitution.

The small yields of triphenylbenzene and dypnone are undoubtedly produced from acetophenone by condensations catalyzed by *p*-nitrobenzenesulfonic acid. These are typical aldol products and the competing addition of the sulfonyl peroxide to the olefinic bond of the aldol leads to phenacyl *p*-nitrobenzenesulfonate. Similar additions to the sulfonyl peroxides to olefins have been reported by Kergomard.[4,7]

The stoichiometry of the products provides enough oxidizing power by the peroxide to produce the benzoic acid only if the methyl group of the acetophenone persists as



(6)

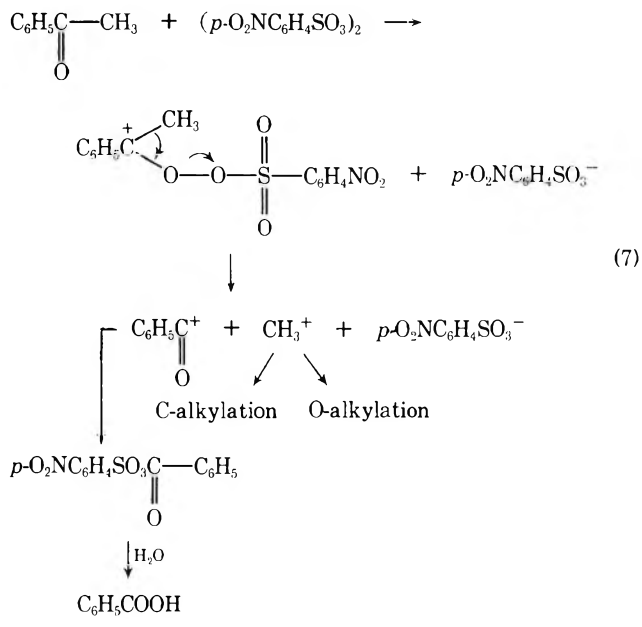
(1.00) (200) (12) (0.592) (0.16) (0.056) (1.16) (0.10) (trace) (trace)

Table II
Temperature and Aromatic Substrate Concentration Dependence of the Pseudo-First-Order Rate Constants for the Disappearance of *p*-Nitrobenzenesulfonyl Peroxide (0.01 *M*) in Ethyl Acetate Solutions of Aromatic Substrates

Aromatic	Concn aromatic, *M*	Temp, °C	$10^4 k$, sec^{-1}
Benzyl alcohol[a]	0.75	9.95	2.86
Benzyl alcohol	0.75	3.95	1.625
Benzyl alcohol	0.565	−2.20	0.588
Benzyl alcohol	0.75	−2.20	0.759
Benzyl alcohol	1.00	−2.20	1.13
Benzyl alcohol	0.75	−7.35	0.476
Benzaldehyde[b]	0.75	20.0	1.98
Benzaldehyde	0.75	15.0	0.865
Benzaldehyde	0.75	10.0	0.502
Acetophenone[c]	0.75	35.15	1.71
Acetophenone	0.75	30.35	1.00
Acetophenone	0.75	25.40	0.681
Acetophenone	0.75	19.65	0.384

[a] Registry no., 100-51-6. [b] Registry no., 100-52-7. [c] Registry no., 98-86-2.

methyl in the products. No methyl *p*-nitrobenzenesulfonate is formed. Partial proof of the fate of the methyl group was obtained by treating the reaction mixture with hydrogen iodide, resulting in a recovery of 25% of the lost methyl group as methyl iodide. These data are consistent with the loss of the methyl groups as carbonium ions (eq 7) which by



(7)

direct transfer either alkylate oxygen atoms to yield ether systems (which can be cleaved by hydrogen iodide) or alkylate unsaturated carbon atoms to produce structures inert to hydrogen iodide. The methyl carbonium ion may, of course, never have a discrete existence but be transferred directly to the species it alkylates. The pseudo-first-order rate constants (Table II) for the overall disappearance of the peroxide correspond to $\Delta H^{\ddagger}$ of 16.7 ± 0.5 kcal/mol^{-1} and $\Delta S^{\ddagger}$ of −21.8 ± 0.7 cal deg^{-1} mol^{-1}.

Hammett Plot. Most of the previous arylsulfonoxylation studies primarily have involved *m*-nitrobenzenesulfonyl peroxide. However, when isomeric nitrobenzenesulfonyl peroxides have been reacted with the same aromatic substrate, only very small differences in orientations and partial rate factors were observed with variation of the peroxide.[3,5] In a Hammett plot, the use of logarithmic values reduces these differences numerically even more. Previously unreported σ^+ parameters for the hydroxymethyl (*m*-, +0.11; *p*-, −0.12) and acetyl (*m*-, +0.36; *p*-, +0.41) substituents were obtained by extrapolation from the Hammett plot previously published[3] for the *m*-nitrophenylsulfonoxylation of benzene derivatives. The *m*-acyl σ^+ value (+0.36) is similar to the corresponding Hammett σ value (+0.376) as expected for a similar inductive influence.

Table III
Melting Points and Yields of Aryl *p*-Nitrobenzenesulfonates ($O_2NC_6H_4SO_3C_6H_4X$)

X	Registry no.	Mp, °C	Yield, %
o-Hydroxymethyl[a]	55660-61-2	84–86	31
m-Hydroxymethyl[a]	55937-77-4	90–91.5	58
p-Hydroxymethyl[a]	55937-77-4	120–122	53
o-Trimethylsiloxymethyl[a]	55660-63-4	75–76	79
m-Trimethylsiloxymethyl[a]	55660-64-5	42–43.5	81
p-Trimethylsiloxymethyl[a]	55660-65-6	52–53.5	84
o-Acetyl[a,b]	55660-66-7	117–119	37
m-Acetyl[a,b]	55660-67-8	100–101	39
p-Acetyl[a,b]	55660-68-9	105–105.5	81
p-Formyl[a]	55660-69-0	142–144	50

Analyses for the elements gave maximum deviations from the theoretical values as follows: all C values ±0.34; [a] all H values ±0.26;[a] all N values ±0.21.[b]

Experimental Section

Materials. Ethyl acetate, benzene, and *p*-nitrobenzenesulfonyl peroxide were prepared[2] or purified[5] by methods previously described. *Caution, p-nitrobenzenesulfonyl peroxide in high states of purity can flash fire if rubbed with a spatula.* Benzyl alcohol, acetophenone, and benzaldehyde were fractionally distilled before use. Recrystallization of the following materials from the given solvents gave *o*-hydroxybenzyl alcohol, mp 83–85° (lit.[8] mp 86°), from benzene–heptane; *m*-hydroxybenzyl alcohol, mp 70–72° (lit.[9] mp 72–73°), from benzene; *p*-hydroxybenzyl alcohol, mp 113–114° (lit.[10] mp 113–114°), from chloroform; *m*-hydroxyacetophenone, mp 95–97° (lit.[11] mp 95–96°), from benzene–heptane; and *p*-hydroxyacetophenone, mp 108–110° (lit.[12] mp 107°), from benzene–heptane. *o*-Hydroxyacetophenone was purified by the literature[13] method. Hexamethyldisilazane, *p*-nitrobenzenesulfonyl chloride, and *p*-hydroxybenzaldehyde were used as received.

Isomeric Aryl *p*-Nitrobenzenesulfonates (Table III) were prepared by the literature[14] method. The hydroxymethyl derivatives were heated with hexamethyldisilazane to convert them to the trimethylsilyl ethers (Table III).

Arylsulfonoxylation of Benzene–Benzyl Alcohol. A solution of *p*-nitrobenzenesulfonyl peroxide[5] (0.203 g, 0.5 mmol) in benzyl alcohol (1.080 g, 10.0 mmol) and benzene (4.401 g, 56.4 mmol) was diluted to 75 ml with ethyl acetate and kept at −2.1° for 92 hr. The ethyl acetate solution was washed with ice water (100 ml), the water extract was neutralized to pH 5 with 1.0 *M* potassium hydroxide, reduced in volume to 20 ml in vacuo, and chilled to 0°, and *S*-benzylthiouronium chloride (0.19 g, 18 mmol) in water (20 ml) was added. The *S*-benzylthiouronium *p*-nitrobenzenesulfonate (0.1802 g) which precipitated, after collection and drying, melted at 200–202° (lit.[5] mp 203–204°). The ethyl acetate raffinate after washing with water was dried with magnesium sulfate and evaporated in vacuo at 0°. The residue was refluxed with hexamethyldisilazane (5 ml, 31 mmol) for 2 hr and *m*-tolyl *m*-nitrobenzenesulfonate was added as an internal standard. The mixture was analyzed (Table IV) by GLC for the isomeric *p*-nitrobenzenesulfonoxybenzyl trimethylsilyl ethers and phenyl *p*-nitrobenzenesulfonate using a column of 5% SE-30 on Chromosorb W (DMCS treated, acid washed). The mixture was also analyzed for trimethylsilyl benzoate by GLC on a similar 20% SE-30 column using naphthalene as an internal standard. When the sulfonoxylation was carried out at room temperature some transesterification with ethyl acetate occurred and some *p*-nitrobenzenesulfonoxybenzyl acetate (mp 89–91°) could be isolated by chromatography of the reaction mixture on silica using benzene to elute.

Table IV
Reaction of p-Nitrobenzenesulfonyl Peroxide with Benzyl Alcohol and Acetophenone

Compd or quantity	Benzyl alcohol[a]		Acetophenone[b]	
	Run 1	Run 2	Run 1	Run 2
Peroxide, mmol	0.5	0.5	0.5	0.5
Benzene, mmol	56.4	56.4	5.0	5.0
Benzene derivative, mmol	10.0	10.0	100	100
Ethyl acetate	to 75 ml	to 75 ml	to 75 ml	to 75 ml
Sulfonate esters, % yield	60.4	56.2	21.4	19.4
k_{ar}/k_B	10.9	10.0	0.141	0.151
p-Nitrobenzenesulfonic acid, mmol	0.575	0.610	0.725	0.714
Benzoic acid, mmol	0.093	0.094	0.300	0.292
Aryl sulfonates, mmol				
Phenyl	0.104	0.1015	0.028	0.027
o-Aryl	0.0575	0.0525	0.028	0.029
m-Aryl	0.0209	0.0167	0.0414	0.0386
p-Aryl	0.120	0.110	0.010	0.012
Isomer distribution, %				
Ortho	29.4	29.3	35.4	36.4
Meta	10.6	9.3	52.3	48.4
Para	60.0	61.6	12.4	15.2

[a] Temperature, −2.1°. [b] Temperature, 25°. Millimoles of phenacyl p-nitrobenzenesulfonate: 0.05, 0.05.

Arylsulfonoxylation of Benzene–Acetophenone. A solution of p-nitrobenzenesulfonyl peroxide (0.203 g, 0.5 mmol) in benzene (0.390 g, 6 mmol) and acetophenone (12.00 g, 100 mmol) diluted to 75 ml with ethyl acetate was kept at room temperature for 91 hr. The solution was then washed with water (70 ml), the raffinate was dried with magnesium sulfate, and the ethyl acetate was removed in vacuo at 0°. The volume was further reduced to about 7 ml by warming to 30° in vacuo to remove residual acetophenone. m-Tolyl m-nitrobenzenesulfonate was added to an aliquot as an internal standard and the isomeric acetylphenyl p-nitrobenzenesulfonates and phenyl p-nitrobenzenesulfonate were analyzed by GLC on the 5% SE-30 column previously described. To a second aliquot was added hexamethyldisilazane and after refluxing (1.5 hr) naphthalene was added as an internal standard and trimethylsilyl benzoate analyzed for by GLC as previously described. The water extract of the original reaction mixture was analyzed for p-nitrobenzene sulfonic acid via the thiouronium salt.

Isolation of the reaction products was accomplished from a large-scale (1.006 g of I) reaction mixture. After water extraction and removal of solvent and remaining acetophenone, the dark residue was chromatographed on silica gel using benzene for elution. The first fraction to elute yielded a white solid (94 mg, mp 129–130°) identified as phenacyl p-nitrobenzenesulfonate by its NMR spectrum: a methylene absorption at τ 5.12 (2 H) and two aromatic absorptions centered at τ 7.10 and 7.61 (9 H total). Anal. Calcd for $C_{14}H_{11}NO_6S$: C, 52.33; H, 3.39. Found: C, 52.33; H, 3.45. The second fraction to elute was a mixture of *cis*- and *trans*-dypnone identified by the mass spectrum (*m/e* 222) and the NMR and ir spectra. Subsequent fractions yielded phenyl p-nitrobenzenesulfonate [180 mg, mp 113–114° (lit.[16] mp 114°)] and a mixture of the isomeric acetylphenyl p-nitrobenzenesulfonates (0.268 mg) which gave three peaks via GLC with retention times identical with those of authentic isomers as well as an ir spectrum identical with that of a mixture of authentic samples.

Zeisel Cleavage of the Products of I with Acetophenone. A mixture of I (1.00 g, 2.5 mmol) and acetophenone (4.0 g, 33 mmol) was stirred at room temperature for 4 days under a nitrogen atmosphere. Hydrogen iodide (60 ml) was then added and the mixture was refluxed for 1 hr while the nitrogen stream was bubbled through toluene (3 ml) in a trap at −80°. The trap contents were analyzed for methyl iodide by GLC on a 150-ft SE-30 capillary column. A 2-ml sample of the toluene solution was treated with tri-n-propylamine to yield methyl tri-n-propylammonium iodide, mp 207–208° (lit.[17] mp 207–208°).

Reaction of I with Benzaldehyde. Freshly distilled benzaldehyde (2.65 g, 25 mmol) and DPPH (3 mmol) diluted to 75 ml total with ethyl acetate was added to I (0.203 g, 0.5 mmol) and the mixture was stirred at room temperature for 24 hr. The reaction mixture was extracted twice with 0.1 *M* potassium hydroxide (20 ml) and the alkaline extract, after acidification to pH 5 with hydrochloric acid, was extracted with three 30-ml portions of ether. These ether extracts were combined, dried, evaporated, and analyzed for benzoic acid by the procedure previously described. The acidified aqueous solution was analyzed for p-nitrobenzenesulfonic acid via the *S*-benzylthiouronium salt. The ethyl acetate raffinate was dried with magnesium sulfate and evaporated to dryness in vacuo, the gummy residue was triturated with heptane (three 30-ml portions), and benzene (30 ml) was added to the combined heptane extracts. Cooling produced a solid (22 mg) which after recrystallization from 1:2:2 acetone–benzene–heptane had mp 248–250° dec and an ir spectrum identical with that of an authentic sample[18] of bis(p-nitrophenyl) sulfone. It was then found that the sulfone could be quantitatively measured (14%) by GLC on a 5% SE-30 on Chromosorb W column using p-formylphenyl p-nitrobenzenesulfonate as a standard.

Under identical conditions, but either at 25° or in the absence of DPPH, the yield of benzoic acid decreases to ca. 60% and the tars increase.

Registry No.—I, 6209-72-9; hexamethyldisilazane, 999-97-3; *S*-benzylthiouronium chloride, 55660-70-3; p-nitrobenzenesulfonoxybenzylacetate, 55660-71-4; phenacyl p-nitrobenzenesulfonate, 55660-72-5; *cis*-dypnone, 54435-79-9; *trans*-dypnone, 22573-24-6; bis(p-nitrophenyl) sulfone, 1156-50-9.

References and Notes

(1) (a) Presented in part at the International Conference on the Mechanisms of Reactions in Solution, University of Kent at Canterbury, England, July 1970. (b) Taken in part from the Ph.D. Thesis of R.V.H., 1970. (b) For the previous paper in this series see R. L. Dannley and P. K. Tornstrom, *J. Org. Chem.*, **40**, 2278 (1975). (c) Supported in part by NSF Grant G.P.-19018.
(2) R. L. Dannley and G. E. Corbett, *J. Org. Chem.*, **31**, 153 (1966).
(3) R. L. Dannley and W. R. Knipple, *J. Org. Chem.*, **38**, 6 (1973).
(4) J. Bolte, A. Kergomard, and M. S. Vincent, *Tetrahedron Lett.*, 1529 (1965).
(5) R. L. Dannley, J. E. Gagen, and O. J. Stewart, *J. Org. Chem.*, **35**, 3076 (1970).
(6) J. R. Knowles and R. O. C. Norman, *J. Chem. Soc.*, 2938 (1961).
(7) J. Bolte, A. Kergomard, and S. Vincent, *Bull. Soc. Chim. Fr.*, 301 (1972).
(8) M. C. Hart and A. D. Hirschfelder, *J. Am. Chem. Soc.*, **42**, 2678 (1920).
(9) C. Mettler, *Ber.*, **38**, 1752 (1905).
(10) F. E. Mumford, H. M. Stark, and D. H. Smith, *Phytochemistry*, **2**, 215 (1963).
(11) P. Pfeiffer, *Justus Liebigs Ann. Chem.*, **383**, 141 (1911).
(12) J. Klingel, *Ber.*, **18**, 2691 (1385).
(13) J. F. Eijkman, F. Bergema, and I. T. Henrard, *Chem. Zentralbl.*, 816 (1905).
(14) M. C. Hart and A. D. Hirschfelder, *J. Am. Chem. Soc.*, **43**, 1961 (1921).
(15) F. N. Keeney, Ph.D. Thesis, Case Western Reserve University, 1969.
(16) F. Bell, *J. Chem. Soc.*, 2777 (1928).
(17) E. Wadekind, *Ber.*, **35**, 776 (1902).
(18) An authentic sample provided by Dr. F. N. Keeney, Dow Chemical Co., Midland, Mich.

Peroxide-Induced Condensation of Olefins and Polychloroethylenes[1]

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Because a chlorine atom adds to a doubly bonded carbon of an olefin much more readily than it abstracts a hydrogen atom attached to an allylic carbon atom, the peroxide-induced reaction of propene with trichloroethylene yields 1,1,4-trichloro-3-methyl-1-butene (**3**) as the chief primary product rather than 1,1-dichloro-1,4-pentadiene (**6**), the product which would form if the allylic hydrogen atom were involved in a reaction analogous to the formation of (3,3-dichloroallyl)benzene by the peroxide-induced condensation of toluene and trichloroethylene, a reaction which involves chlorine abstraction of a benzylic hydrogen atom. Similarly, the primary products of the condensation of propene with *cis*-dichloroethylene and with tetrachloroethylene are 1,4-dichloro-3-methyl-1-butene (**7**) and 1,1,2,4-tetrachloro-3-methyl-1-butene (**9**), respectively. By-products consist chiefly of the products of the reaction of more than 1 mol of one of the reactants with 1 or more mol of the other. Corresponding products are obtained with other alkenes, for example, 2-pentene or 1-octene, and with cyclohexene. The mechanism of the reaction is discussed.

The di-*tert*-butyl peroxide induced reaction of propene with trichloroethylene yields 1,1,4-trichloro-3-methyl-1-butene (**3**) as the chief primary product. Its formation apparently occurs by the following pathway.

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow[130\text{-}140^\circ]{} 2(CH_3)_3CO\cdot$$

$$(CH_3)_3CO\cdot \longrightarrow (CH_3)_2C{=}O + CH_3\cdot$$

$$R\cdot + ClCH{=}CCl_2 \longrightarrow RCHClC\dot{C}l_2$$

$$[R = (CH_3)_3CO\cdot \text{ or } CH_3\cdot]$$

$$RCHClC\dot{C}l_2 \longrightarrow Cl\cdot + RCH{=}CCl_2$$

$$Cl\cdot + CH_2{=}CHCH_3 \longrightarrow ClCH_2\dot{C}HCH_3$$

1

$$\mathbf{1} + ClCH{=}CCl_2 \longrightarrow ClCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCHClC\dot{C}l_2$$

2

$$\mathbf{2} \longrightarrow Cl\cdot + ClCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH{=}CCl_2$$

3

The chlorine atom formed in the final step adds to propene to start a new cycle.

It may be concluded that the chain reaction is propagated by a chlorine atom which adds to the double bonds of the olefins and which is eliminated from the product of the condensation of the resulting radical with the trichloroethylene. In the related reaction of toluene with trichloroethylene, the reaction chain is propagated by hydrogen abstraction of a benzylic hydrogen atom from the toluene and subsequent addition of the so-formed benzyl radical to the trichloroethylene, followed by the elimination of a chlorine atom, resulting in the formation of (3,3-dichloroallyl)benzene.[2] Abstraction of an allylic hydrogen atom from propene by a chlorine atom does not occur under the reaction conditions because addition of a chlorine to the doubly bonded carbon atoms of an olefin is a more rapid reaction than is abstraction of hydrogen from an allylic carbon atom. Thus, the relative rates[3] of addition of a chlorine atom at −9° to the double bonds of 1-butene, *cis*-2-butene, and *trans*-2-butene are 11.7, 12.0, and 11.4, respectively (compared to 1.0 for abstraction of a cyclohexane hydrogen). On the same basis, the relative rates of abstraction of allylic hydrogen of atoms at −9° from the butenes are 0.76, 0.60, and 0.69, respectively. Hence, the rates of addition are respectively 15.4, 20.0, and 26.5 times the rates of abstraction. Therefore, the mechanism shown above occurs rather than the following.

$$Cl\cdot + CH_2{=}CHCH_3 \longrightarrow HCl + CH_2{=}C\dot{H}CH_2$$

$$CH_2{=}C\dot{H}CH_2 + ClCH{=}CCl_2 \longrightarrow CH_2{=}CHCH_2CHClC\dot{C}l_2$$

4

$$\mathbf{4} \xrightarrow{CH_2=CHCH_3} CH_2{=}CHCH_2CHClCHCl_2 + CH_2{=}C\dot{H}CH_2$$

5

$$\mathbf{4} \longrightarrow CH_2{=}CHCH_2CH{=}CCl_2 + Cl\cdot$$

6

Abstraction of allylic hydrogen from propene does occur during the high-temperature (above 200°) chlorination of propene to produce allyl chloride as major product.[5]

In the toluene reaction, the chlorine atom abstracts a benzylic hydrogen[2] more readily than it adds to the aromatic double bond with subsequent loss of a hydrogen atom, an addition which would result in nuclear chlorination.

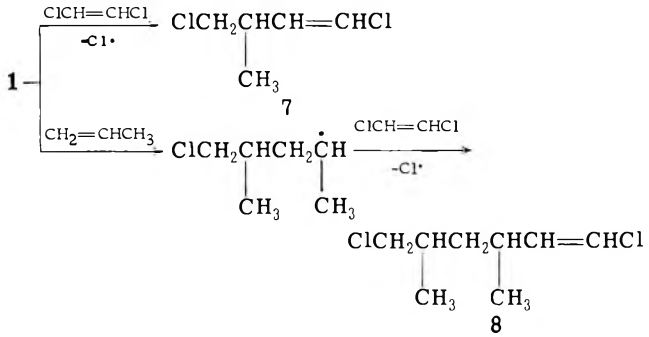
Loss of a chlorine atom from a carbon atom adjacent to the electron-deficient carbon atom of a free radical with resultant formation of a double bond has been observed in many reactions.[4]

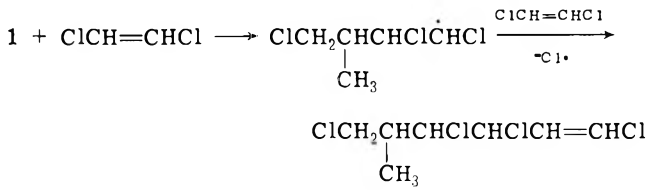
That the primary product of the reaction of propene and trichloroethylene was **3** rather than **5** or **6** was suggested by carbon–hydrogen analysis and by the MS, ir, and NMR data. Mass spectrometric analysis of the compound (calcd mol wt 173.5) showed molecular ion peaks at *m/e* 172, 174, 176, and 178 in the correct ratios for three chlorine atoms in the molecule. The major fragmentation was loss of $-CH_2Cl$. The ir spectrum indicated the presence of a methyl group and of a double bond. More definite information was obtained by NMR analysis, utilizing spin decoupling, which was in agreement with the structure **3**.

A complex mixture of higher molecular weight products was also formed by the propene–trichloroethylene reaction; about 35–40% of the reaction product was too high boiling to be distilled by conventional means. It apparently consisted of polycondensation (telomeric) compounds.

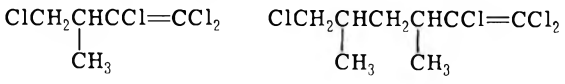
When propene and *cis*-dichloroethylene were heated with di-*tert*-butyl peroxide at 130–140°, the major product was **8**, the product of the reaction of two molecules of the alkene with one of the dichloroethylene; the primary, 1:1, reaction product **7** was formed in minor amount.

Mass spectrographic analysis of material separated from a higher boiling fraction (a complex mixture) suggested that the product of the reaction of two molecular proportions of *cis*-dichloroethylene with one of propene was also formed.



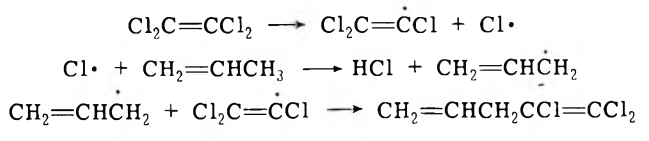


The reaction of propene with tetrachloroethylene in the presence of decomposing di-*tert*-butyl peroxide similarly yielded 1,1,2,4-tetrachloro-3-methyl-1-butene (**9**) and 1,1,2,6-tetrachloro-3,5-dimethyl-1-hexene (**10**), the now-

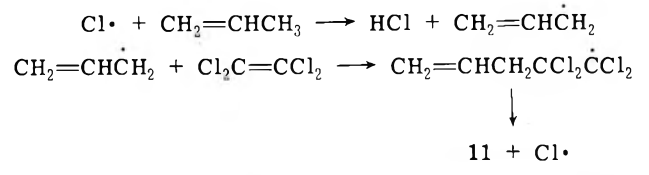


to-be-expected products of the condensation of tetrachloroethylene with one and two molar proportions of propene, respectively. A high-boiling fraction was shown by MS analysis to consist chiefly of $C_{11}H_{18}Cl_4$, the product of the condensation of 3 mol of propene with 1 mol of tetrachloroethylene.

The thermal reaction of propene with tetrachloroethylene at 590° [6] involved allylic hydrogen abstraction and resulted in the formation of 1,1,2-trichloro-1,4-pentadiene (**11**), formed, it was believed, by the following mechanism.[6]

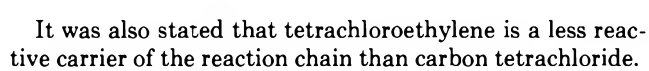


The following chain reaction is probably a more plausible mechanism for the formation of **11**.



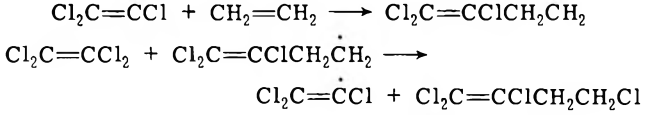
Other olefins reacted in analogous manner with the polychloroethylenes. Thus, the reaction of trichloroethylene with ethylene in the presence of decomposing di-*tert*-butyl peroxide resulted in the formation of 1,1,4-trichloro-1-butene (**12**) and 1,1,6-trichloro-1-hexene (**13**) together with very much of the higher molecular weight telomers.

The peroxide-induced condensation of ethylene with tetrachloroethylene was reported previously.[7] The investigators state, "Chloroolefins which cannot polymerize can take part in a telomerization reaction with olefins. In this process the chloroolefins function as carrier of the chain reaction and supply end groups to the molecules of the telomers. Among reactions of this type, the telomerization of ethylene with tetrachloroethylene is of considerable interest as a method of synthesizing reactive tetrachloroalkenes containing an even number of carbon atoms in the molecule.



It was also stated that tetrachloroethylene is a less reactive carrier of the reaction chain than carbon tetrachloride.

It was obviously believed that, of the polychloroethylenes, only tetrachloroethylene could undergo telomeric condensation with ethylene because the others (unlike tetrachloroethylene) readily polymerizes when treated with decomposing peroxide.[8] It was suggested that the reaction chain involved a sequence analogous to that involved in the peroxide-induced reaction of carbon tetrachloride or chloroform with ethylene.



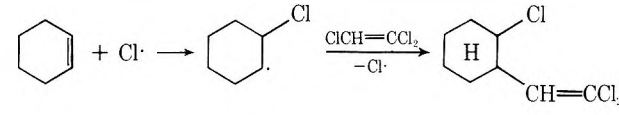
In view of the facts that such a mechanism involves abstraction of chlorine attached to a vinylic carbon atom and that the other polychloroethylenes and other olefins also undergo condensation with each other, it may be concluded that the reaction chain suggested in this paper is more plausible.

Some peroxide-induced reactions, for example the addition of carbon tetrachloride to olefins, occur much more readily with 1-alkenes than with alkenes which have internal double bonds. In the present reaction, trichloroethylene underwent condensation with 2-pentene under the standard conditions to give a 12 mol % yield of 1,1,4-trichloro-3-ethyl-1-pentene and 1,1,4-trichloro-3-methyl-1-hexene (**14**, see Table I), produced via addition of chlorine atoms to 2-pentene to yield two isomeric radicals which reacted to form the isomeric trichloroheptenes, the structures of which were suggested by the MS and NMR spectra.

The reaction of 1-octene with trichloroethylene under the same conditions resulted in a 10 mol % yield of the 1:1 condensation product believed to be 1,1-dichloro-3-(chloromethyl)-1-nonene (**15**), on the basis of the probable mechanism of formation. Compounds formed by condensation of 2 and 3 mol of octene per mole of trichloroethylene were also formed.

1-Octene is sufficiently high boiling to permit carrying out its condensation with trichloroethylene under atmospheric pressure. Heating the reactants with benzoyl peroxide (Table II, expt 8) under reflux (93–100°) for 1.5 hr gave a liquid product shown by GC to contain **15** in about 8 mol % yield. Further heating with two intermittent additions of benzoyl peroxide resulted in increase of the yield to 20 mol % and finally to 32 mol %.

Condensation of cyclohexene with trichloroethylene in the presence of di-*tert*-butyl peroxide at 130–140° yielded 17 mol % of 1-(2,2-dichlorovinyl)-2-chlorocyclohexene (**16**)



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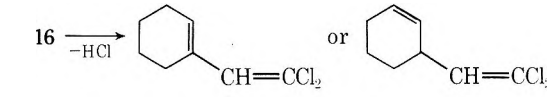


17 **18**

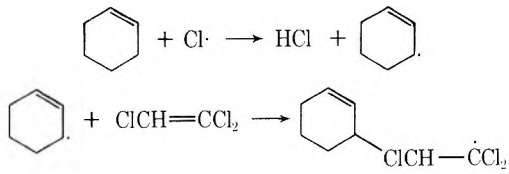
Table I
Properties of the Polychloroalkenes

Compd	Formula	Bp, °C	mm	Bp at 760 mm, °C[a]	Anal., %[b] Calcd C	Calcd H	Found C	Found H
3	$ClCH_2CHMeCH{=}CCl_2$	59	9.4	178	34.62	4.07	35.01	4.03
7	$ClCH_2CHMeCH{=}CHCl$[c]	37–91	41	110–180	43.20	5.80	45.47	6.34
8	$ClCH_2CHMeCH_2CHMeCH{=}CHCl$	110–111	41	201–202	53.06	7.79	52.74	7.52
9	$ClCH_2CHMeCCl{=}CCl_2$	79	9.8	202	28.88	2.91	29.52	3.06
10	$ClCH_2CHMeCH_2CHMeCCl{=}CCl_2$	66	0.5	244	38.43	4.84	38.85	4.85
12	$ClCH_2CH_2CH{=}CCl_2$	60–68	14.0	170–179	30.13	3.16	30.80	3.30
13	$ClCH_2(CH_2)_3CH{=}CCl_2$	89–116	12.5	207–238	38.43	4.84	38.26	4.66
14	$CH_3CHClCHEtCH{=}CCl_2$[d]	81	9.8	207	42.70	5.66	41.71	5.50
15	$ClCH_2CHHexCH{=}CCl_2$	77	0.4	263	49.30	6.98	49.87	7.00
16	$ClC_6H_{10}CH{=}CCl_2$	103	9.3	232	45.00	5.19	46.23	5.20
17 + 18	$C_6H_9CH{=}CCl_2$	76	9.8	199	54.26	5.69	54.27	5.78

[a] Calculated from boiling point under reduced pressure using nomograph prepared for hydrocarbon boiling point conversions: S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, 38, 320 (1946). [b] The analysis of several of the compounds does not agree with the calculated values because the compounds (as shown by GC) are contaminated with impurities which could not readily be separated. [c] Structure of small sample isolated by preparative GLC from fraction shown was determined by MS, NMR, and/or ir. [d] Mixed with $CH_3CH_2CHClCHMeCH{=}CCl_2$.

and its dehydrochlorination product, a mixture of 1-(2,2-dichlorovinyl)cyclohexene (**17**) and 3-(2,2-dichlorovinyl)cyclohexene (**18**).

The dichlorovinylcyclohexene mixture consisted (according to NMR analysis) of about 15% of **17** and 85% of **18**. It might have been expected that it would contain more **17** than **18**, since the hydrogen atom attached to the tertiary allylic carbon atom in **16** would be expected to be more readily eliminated to form hydrogen chloride than would a hydrogen attached to a secondary carbon atom. Formation of more **18** than **17** indicates that abstraction of an allylic hydrogen by a chlorine atom competed with the above chlorine-addition reaction.



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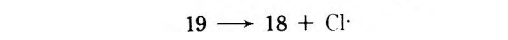

Such allylic hydrogen abstraction occurs with cyclohexene (but not with alkenes) because the relative rate (at 77.8°) for abstraction of an allylic hydrogen by a trichloromethyl radical as compared to addition of the radical to a doubly bonded carbon is 0.83 for cyclohexene and only 0.029 for *cis*-2-butene.[9]

As with the 1-octene, heating cyclohexene and trichloroethylene under reflux with benzoyl peroxide added in small batches resulted in a continuously increasing yield of **16** to about 19 mol % after five additions of the peroxide and 13 hr of reflux.

While 1,2-dichloroethylene reacts with toluene in the presence of decomposing peroxides to yield (3-chloroallyl)benzene,[2] the analogous reaction with 1,2-dibromoethylene does not occur, apparently because the intermediate bromine atoms (or bromine-containing intermediate radicals) do not abstract hydrogen from the toluene side chain to maintain the reaction chain. In the present reaction the intermediate chlorine atoms add to double bonds, and it therefore seemed possible that bromine atoms formed during the reaction of polybromoethylenes might maintain the chain and yield brominated condensation compounds. However, very little reaction occurred when either 1,2-dibromoethylene or tribromoethylene was heated with propene and di-*tert*-butyl peroxide at 130–140°. Most of each of the polybromoethylenes was recovered unchanged. It seems necessary to conclude that steric factors are involved which prevent the addition of bromoalkyl radicals to the polybromoethylenes.

Experimental Section

The di-*tert*-butyl peroxide experiments were carried out in glass liners in an Ipatieff-type rotating autoclave of 850 ml capacity. The normally liquid olefin, the polychloroethylene, and the peroxide (amounts shown in Table II) were weighed into the glass liner which was then sealed into the autoclave and nitrogen was added to a pressure of 30 atm. Condensible gaseous olefins were added by volume from a calibrated Jerguson gage before adding the nitrogen. The autoclave was rotated and heated at 130–140° for 4 hr. It was allowed to cool to room temperature overnight, the pressure was released, and the autoclave was opened. The product was worked up by distillation and characterized by preparative gas chromatography (GC) as discussed below. While it was often not possible to isolate pure products for ultimate (C and H) analysis by distillation, pure samples for characterization were obtained by preparative GC.

When benzoyl peroxide was used, the reactants were heated under reflux in a mercury-sealed stirred glass flask, the peroxide being added intermittently (with intermediate cooling to permit GC analysis of the product) as indicated in Table II.

While the identity of one of the products (**15** formed from 1-octene and trichloroethylene) was suggested on the basis of the mechanism, the structures of the remainder were confirmed by ir (Beckman IR-9), NMR (Varian A-60), and/or MS (CEC, Model 103C) analysis of material separated by preparative GC (Varian Aerograph Autoprep).[10] The specimen was passed through 5- or 10-ft columns containing 20% Carbowax 20M on Chromosorb A; the initial temperature was 70° and was programmed to 220° at 10°/min, using a helium flow rate of 75 ml/min. In many cases quite pure samples for characterization were isolated by fractional distillation (see below).

Trichloroethylene and Propene. Product boiling at 59° (4.4 mm) was examined by ir, MS, and NMR. Ir showed the presence of a methyl group and of a double bond. MS showed molecular ion peaks at *m/e* 172, 174, 176, and 178 in the correct ratios for three chlorine atoms in the molecule; the major fragmentation included *m/e* 123, 125, and 127 due to loss of CH_2Cl, and *m/e* 85 and 87 due to loss of CH_2Cl and HCl. The presence of traces of a higher homolog (M + 42) was apparent. More conclusive information was obtained by NMR analysis utilizing spin decoupling. It was found that the doublets at δ 3.49 and 1.13, even though they exhibited the same coupling constant, were not interacting with each other. The spin-decoupling experiments revealed that the doublets at δ

Table II
Condensation of Polychloroethylenes with Olefins

Expt	Reactants: Chloroethylene	Mol	Olefin	Mol	t-Bu_2O_2, mol	Chief Products: Kind	g	Mol	%
1	$C_2H_2Cl_2$[b]	0.97	C_3H_6	1.2	0.05	7	2[a]	0.01	1
						8	8	0.04	7
						Higher bp	10		
2	C_2HCl_3	1.17	C_3H_6	1.2	0.06	3	32	0.18	16
						Higher bp	75		
3	C_2Cl_4	0.90	C_3H_6	1.2	0.06	9	12	0.058	6
						10	18	0.072	12
						Higher bp	16		
4	C_2HCl_3	1.15	C_2H_4	1.5	0.06	12	6	0.04	4
						13	4	0.02	3
						Higher bp	30		
5	C_2HCl_3	0.71	2-C_5H_{12}	0.82	0.06	14	17	0.085	12
						Higher bp	16		
6	C_2HCl_3	0.68	1-C_8H_{16}	0.88	0.10	15	17	0.070	10
						Higher bp	48[c]		
7	C_2HCl_3	0.38	1-C_8H_{16}	0.22	0.03[d]	15	17[a]	0.070	32
8	C_2HCl_3	1.03	c-C_6H_{10}	0.77	0.04	17 + 18	12	0.068	9
						16	14	0.060	8
						Higher bp	10		
9	C_2HCl_3	0.49	c-C_6H_{10}	0.37	0.05[e]	16	16[a]	0.07	19

[a] Estimated by GLC; separated and characterized by preparative GLC plus MS, NMR, and/or ir. [b] *cis*-Dichloroethylene. [c] Includes fractions boiling at 139–141° (1.1 mm) [326–327° (760 mm)] and 147–151° (1.2 mm) (333–337°), elemental analysis of which suggested that they consisted of $C_{18}H_{33}Cl_3$ and $C_{26}H_{49}Cl_3$, respectively, mixed with minor amounts of other compounds. [d] Benzoyl peroxide added in three portions: 1 g at beginning of experiment; 2 g more after 1.5 hr refluxing; 3 g more after 2.5 hr more refluxing; reflux continued for 3 hr. [e] Benzoyl peroxide added in five portions: 2 g at beginning; 2 g after 12 hr; 2 g after 2 hr; 3 g after 4 hr; and 3 g after 2 hr followed by an additional 3 hr heating.

5.80, 3.49, and 1.13 were all coupling with a multiplet centered between δ 2.99 and 2.93. The nature of the multiplet was difficult to determine from the spectrum, but knowing the number of protons of each type which were coupling and the coupling constants from first-order rules, it was concluded that the multiplet was a sextet of doublets. The number of protons found were one attached to a doubly bonded carbon atom, two attached to a carbon atom holding a chlorine atom, one attached to a saturated tertiary carbon atom, and three constituting a methyl group. It was concluded that **3** was 1,1,4-trichloro-3-methyl-1-butene.

***cis*-Dichloroethylene and Propene.** A fraction boiling at 108–110° (41 mm) showed a major GC peak and two minor peaks. The MS of the major peak had molecular ions at *m/e* 180 and 182. Major fragmentation was M − Cl (*m/e* 145), M − CH_3 (*m/e* 165), and M − 2Cl (*m/e* 109). These data agree with the structure, 1,6-dichloro-3,5-dimethyl-1-hexene, proposed for **8**.

One of the minor GC peaks had molecular ion peaks at *m/e* 138 and 140 in the ratio for two chlorine atoms per molecule. Major fragments were M − Cl (*m/e* 103, 105), M − CH_3 (*m/e* 123, 125), M − HCl (*m/e* 102, 104), and M − CH_3Cl (*m/e* 89, 91). A possible structure is 1,4-dichloro-3-methyl-1-butene (**7**).

The other minor peak (*m/e* 256) contained oxygen but no chlorine. It was not identified.

Tetrachloroethylene and Propene. The MS of a fraction boiling at 79° (9.8 mm) had molecular ion peaks at *m/e* 206, 208, 210, 212, and 214 in the proper ratio for four chlorine atoms per molecule. Major fragment ions were at *m/e* 157, 159, 161, and 163 (M − CH_2Cl) in the ratio for three chlorine atoms per molecule at *m/e* 191, 193, 195, 197, 199 (M − CH_3) and at *m/e* 171, 173, 175, 177 (M − Cl). These data suggest that **9** is 1,1,2,4-tetrachloro-3-methyl-1-butene.

The spectrum of the fraction boiling at 66° (0.5 mm) had molecular ion peaks at *m/e* 248, 250, 252, 254, and 256, indicating four chlorine atoms per molecules. Fragment ion peaks were at *m/e* 213, 215, 217, and 219 (M − Cl); they were also seen at M − CH_3, M − CH_2Cl, and M − ClC_4H_8. It may be concluded that **10** is 1,1,2,6-tetrachloro-3,5-dimethyl-1-hexene.

Trichloroethylene and Ethylene. The product was an unusually complex mixture. One GC peak showed molecular ion peaks at *m/e* 158, 160, 162, and 164, the ratio of the peaks indicating three chlorine atoms per molecule. The major fragment ion peaks were *m/e* 109, 111, and 113 (M − CH_2Cl). Other fragment and rearrangement ion peaks were at *m/e* 121, 122, 123, 124 (M − Cl and M − HCl) and at *m/e* 96 and 98 (M − CH_2CH_2Cl). The most probable structure suggested by these data is 1,1,4-trichloro-1-butene (**12**).

Another GC peak had molecular ion peaks at *m/e* 186, 188, 190, and 192 in the proper ratio for three chlorine atoms per molecule. The most intense fragment ion peak was *m/e* 109 (M − CH_2CHCH_2Cl). Rearrangement ion peaks were seen at *m/e* 122, 124 (M − CH_2CH_2Cl) and 96, 98 ($CH_2CH_2CH_2CH_2Cl$) and fragment ion peaks at *m/e* 35 and 36 (Cl and HCl). A compound which fits these data is 1,1,6-trichloro-1-hexene (**13**).

Trichloroethylene and 2-Pentene. The mass spectrum of material boiling at 79–81° (9.8 mm) showed three groups of ion peaks: (1) *m/e* 164, 166, 168; (2) *m/e* 200, 202, 204, 206; and (3) *m/e* 224, 226, 228, 230, 232. Each compound lost chlorine to give M − 35.

The compound of *m/e* 200–206 (**14**) also lost CH_3CH_2. It apparently was 1,1,4-trichloro-3-ethyl-1-pentene mixed with 1,1,4-trichloro-3-methyl-1-hexene. It underwent dehydrochlorination to produce the compounds of *m/e* 164–168, presumably 1,1-dichloro-3-ethyl-1,3-pentadiene and the methylhexadiene isomer; it is possible that the dehydrochlorination occurred during the MS analysis because of the presence of a hydrogen atom attached to an allylic tertiary carbon atom which was adjacent to a secondary carbon atom holding a chlorine atom.

The NMR spectrum of the fraction showed the presence of an internal olefinic proton, two different methine protons, two methyl groups, and a methylene group. These features are common to $CH_3CHClCH(C_2H_5)CH{=}CCl_2$ and to $C_2H_5CHClCH(CH_3)CH{=}CCl_2$, the structures suggested by MS. No evidence for the chloroalkadienes suggested by MS was seen by NMR; they may have been present in low concentration beyond the detection limit of the NMR method, or they may have been formed during the MS analysis.

Trichloroethylene and Cyclohexene. The NMR spectrum of **16** was consistent with the structure of 2-chloro-1-(2,2-dichlorovinyl)cyclohexane. A doublet at δ 5.75 confirmed the presence of vinylic hydrogen (HC–CH=CCl_2) and a multiplet at a chemical shift of δ 3.65 showed a hydrogen atom in HCCl while a multiplet at δ 3.0–1.0 showed nine hydrogen atoms in the cyclohexane ring. The ir spectrum confirmed a cyclohexylalkenyl chloride. Absorptions at 700–950 cm^{-1} indicated a double bond and C–Cl; at 1450 cm^{-1}, a cyclohexane ring; and at 1625 cm^{-1}, a double bond. The

absence of a band at 1375 cm^{-1} showed absence of a methyl radical.

The MS of a lower boiling fraction [76° (9.8 mm)] showed molecular tions at *m/e* 176, 178, and 180 in the ratios corresponding to two chlorine atoms. The data correspond to $C_8H_{10}Cl_2$. The ir spectrum showed strong bands at 650–750 cm^{-1} for C–Cl stretch and strong bands at 800–1000 cm^{-1} for C–Cl stretch and olefin. Two bands were observed in the C=C stretch region. No methyl was indicated at 1380 cm^{-1} while CH_2 bonding was observed at 1450 cm^{-1}. On the assumption that the product consisted of two isomers (17 and 18), the NMR integrals were consistent with 18 as the major component. NMR spin decoupling revealed that the doublet δ 5.75 was coupling with the proton at δ 3.18. The integral was then found to be consistent with 85% 18 and 15% 17.

Registry No.—3, 22118-81-6; 7, 52890-15-0; 8, 55681-91-9; 9, 55681-92-0; 10, 55681-93-1; 12, 17219-57-7; 13, 55681-94-2; 14, 52026-52-5; 15, 51951-45-2; 16, 55681-95-3; 17, 52026-53-6; 18, 22024-03-9; *cis*-dichoroethylene, 156-59-2; trichloroethylene, 79-01-6; tetrachloroethylene, 127-18-4; propene, 115-07-1; ethylene, 74-85-1; 2-pentene, 109-68-2; 1-octene, 111-66-0; cyclohexene, 110-83-8.

Supplementary Material Available. Additional ir, MS, and NMR data for compounds 3, 9, 10, 14, 16, 17, and 18 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2430.

References and Notes

(1) Presented before the Division of Organic Chemistry at the 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept 1971. The reaction is described in L. Schmerling, U.S. Patent 3,406,210 (Oct 15, 1968). The structures of the products presented in the patent have since been found to be erroneous; the correct structures are presented in this paper.
(2) L. Schmerling and J. P. West, *J. Am. Chem. Soc.*, **75**, 6216 (1953).
(3) M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2181 (1965).
(4) C. Walling, "Free Radicals in Solution", Wiley, New York, N.Y., 1957, pp 268–271.
(5) H. P. A. Groll and G. Nearne, *Ind. Eng. Chem.*, **31**, 1530 (1939).
(6) A. D. Petrov, G. I. Nikishin, and G. V. Somov, *Dokl. Akad. Nauk SSSR*, **131**, 1095 (1960); *Proc. Acad. Sci. USSR*, 379 (1960).
(7) A. N. Nesmeyanov, R. Kh. Freidlina, and A. B. Bielavskii, *Dokl. Akad. Naul SSSR*, **22**, 821 (1958); *Proc. Acad. Sci. USSR*, 753 (1958).
(8) L. Schmerling and J. P. West, *J. Am. Chem. Soc.*, **71**, 2015 (1949).
(9) E. S. Huyser, *J. Org. Chem.*, **26**, 3261 (1961).
(10) See paragraph at end of paper regarding supplementary material.

Photochemistry of Alkenes. IV. Vicinally Unsymmetrical Olefins in Hydroxylic Media[1]

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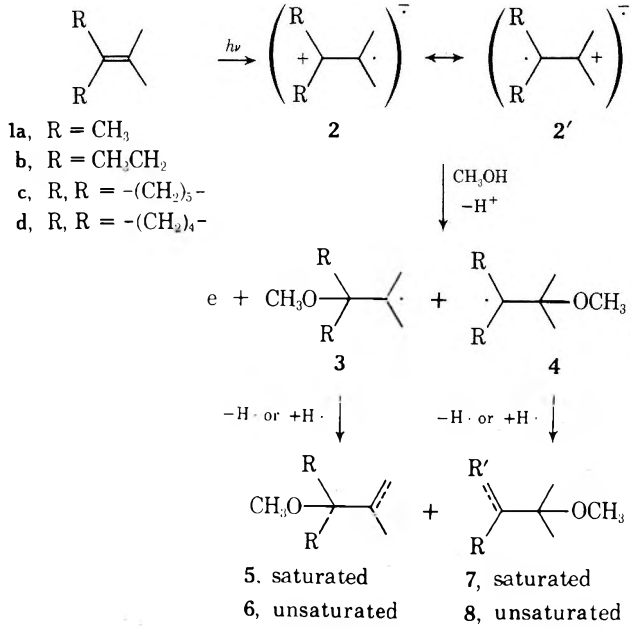
The photochemical behavior of the vicinally unsymmetrical tetrasubstituted olefins **1b–d** in methanol was studied. Each olefin afforded a mixture of saturated and unsaturated ethers **5–8** and hydrocarbons **11–13.** There was no strong dominance in the direction of nucleophilic attack on the excited states from olefins **1b–d.** Isopropylidenenorbornane (14) afforded a complex mixture, with the ether **15** and 2-*endo*-isopropylnorbornane (**16**) as the major products. Evidence for the presence of ejected electrons was obtained using sulfur hexafluoride as an electron trap.

In contrast to the triplet manifold of simple alkenes, in which just one excited state (π,π^*) is clearly low lying, there are two, and possibly three, excited states in the singlet manifold which are low lying and close in energy. Assignment of two of these as π,π^* and π,R(3s) is now widely accepted,[3] and the presence of a π,σ^* state of similar energy has also been proposed.[3b] Studies in these laboratories have been directed toward elucidating the *chemical* properties of these excited states and the effects of structure and environment on their reactivities.

It has recently been reported from these laboratories that tri- and, particularly, tetrasubstituted alkenes exhibit novel photochemical behavior which appears to involve the π,R(3s) Rydberg excited state.[1,4] This state arises from promotion of one of the π electrons to a large molecular orbital similar in size and shape to a 3s atomic orbital. As depicted by **2** and **2′**, this process generates radical cation character in the π core of the molecule. In the case of 2,3-dimethyl-2-butene (**1a**) the excited state **2a** is trapped nucleophilically in hydroxylic media to afford a mixture of saturated and unsaturated ethers, as exemplified in Scheme I.[4] This reaction is of mechanistic interest, as it represents one of the first observations of the chemical behavior of the π,R(3s) excited state in solution. Little is known about the π,R(3s) state, including the important question of whether in vicinally unsymmetrical systems there are differences in electron density and, hence, reactivity at the two termini of the radical cation core. The ex-

Scheme I

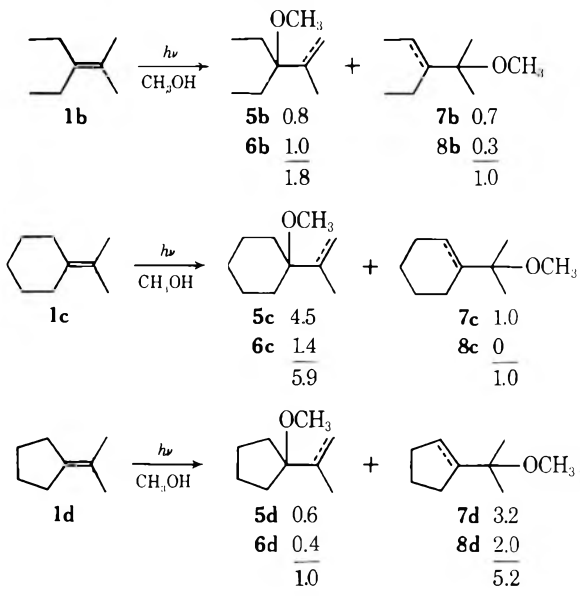


amples initially reported involved olefins having vicinal symmetry about the double bond;[4] in these systems nucleophilic attack at either end of the bond would afford the same radical intermediate (i.e., 3 = 4). We wish now to describe additional insight into the chemical behavior of the π,R(3s) excited state gained by a study of the series of vicinally unsymmetrical olefins **1b–d.** Previous studies have shown that decreasing the ring size in this series on going from acyclic to six-membered to five-membered strongly affects the photochemical behavior in nonnucleophilic media.[5]

Results

The results from irradiation of these olefins in methanol are summarized in Table I and Scheme II. Each olefin afforded a mixture of saturated and unsaturated ethers **5–8.** Ethers **5** and **7** in each series were obtained independently by acid-catalyzed addition of methanol to the corresponding olefin **1.** Ethers **5b** and **7c** were also prepared independently by methylation of the corresponding alcohol. The remaining ethers were characterized by means of their spectral data, as outlined in the Experimental Section. Each olefin also afforded a mixture of saturated (**12**) and unsaturated hydrocarbons (**11** and **13**), which were identified by spectral data and comparison with authentic specimens. It is assumed that **5–8** and **11–13** are all primary products, since there was no significant change in their relative amounts during the course of reaction, except for a slow loss of the unsaturated products on extended irradiation.

Scheme II



Scheme III

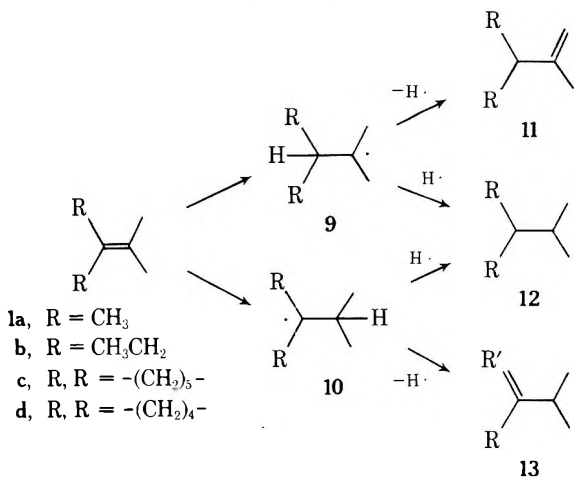


Table I
Irradiation of Alkenes 1 in Methanol[a]

Alkene 1	Time, hr	Yield, %[b] 1	5	6	7	8	11	12	13
1a[c]	4	6	37	30				16	4
1b	6	31	13	16	11	5	1	10	*d*
1c	16	25	25	7.5	5.5	*e*	4	11	
1d	8	10	4	2.5	21	13	1	17	5

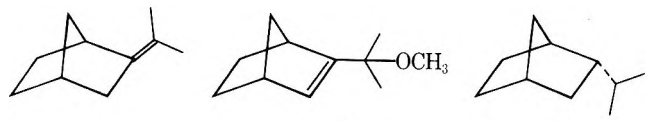
[a] Irradiations were conducted as described in the Experimental Section. [b] Determined by gas chromatographic analysis relative to an internal standard on aliquots removed from the reaction mixture. [c] See ref 4. [d] Trace. [e] None detectable.

Table II
Irradiation of 2,3-Dimethyl-2-butene (1a) in Methanol in the Presence of Sulfur Hexafluoride[a]

[1a], mol/l	Time, hr	[F^-], mol/l
2.0×10^{-1}	3	2.4×10^{-3}
2.0×10^{-1}	5	2.9×10^{-3}
None	3	5.4×10^{-4}
None	5	7.0×10^{-4}

[a] Irradiations were conducted as described in the Experimental Section.

In connection with these and other studies the photochemical behavior of isopropylidenenorbornane (**14**) was also examined. On irradiation in methanol **14** afforded a complex mixture of hydrocarbon and ether products, of which the ether **15** and 2-*endo*-isopropylnorbornane (**16**) were identified as principal components.



14 **15** **16**

An important contribution from the present study was the observation of the presence of free electrons during the irradiation of olefin 1a in methanol obtained using sulfur hexafluoride, a highly efficient specific electron scavanger which has been widely used in radiochemical and photochemical studies.[6] Sulfur hexafluoride undergoes decomposition to fluoride ions on electron capture in methanolic solution, making it a convenient probe for free electrons.[7] As detailed in Table II, irradiation of **1a** in methanol saturated with sulfur hexafluoride resulted in the generation of fluoride ions at concentrations substantially greater than those generated by the slow light-induced decomposition of sulfur hexafluoride under these conditions, in support of the presence of free electrons in the irradiation mixture.

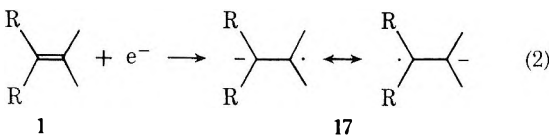
Discussion

Ether Products. As can be seen from Scheme II, the excited states of olefins **1b–d** did not undergo nucleophilic attack at either end with equal facility. Moreover, there was a change from predominant attack at the ring end for **1c,** to more nearly equal degrees of attack at both ends for **1b,** to dominant attack at the *gem*-dimethyl end for **1d.** This pattern does not correlate with the observed regioselectivity of acid-catalyzed addition of methanol to these olefins, which shifts from a 17:1 predominance of **7b** over **5b** to a lesser 4.4:1 predominance of **7c** over **5c** to a 1.1:1 reversed pre-

dominance of **5d** over **7d**. Likewise it is contrary to the increasingly preferred photoreaction in nonnucleophilic media at the ring end of the double bond in going from **1b** to **1c** to **1d**.[5] However, since the photoproduct ratios are not large, the transition state energies for attack at either end apparently differ by less than 1 kcal/mol. The direction of attack will be controlled by several factors, including the relative contributions from resonance forms **2** and **2′**, differences in steric hindrance, and differences in stability of the resulting radicals **3** and **4**. The low selectivities observed suggest that these differences are either small or offsetting.

Hydrocarbon Products. Nucleophilic trapping of the π,R(3s) state should be accompanied by ejection of the excited electron, which no longer has a place in the π system to which to return. The present observation of electron trapping by sulfur hexafluoride confirms the presence of free electrons. In the absence of trapping by sulfur hexafluoride the resulting free electron might be trapped by either the solvent or unreacted starting olefin. The rate for electron capture is generally greater for olefins[8] than methanol,[9] but this advantage is offset by differences in concentration, leaving comparable probabilities for either mode of capture. Electron trapping by methanol results in the generation of hydrogen atoms (eq 1)[9] which, on capture by unreacted starting olefin **1**, would lead to the hydrocarbon photoproducts **11–13** as outlined in Scheme III. Alternatively, electron capture by olefin **1** (eq 2) would afford the radical anion **17**, which on protonation by methanol would give rise to the same radical intermediates **9** and **10** and thence to the hydrocarbon products **11–13**. Both of these routes are consistent with the observed incorporation of deuterium in products **11a** and **12a** on irradiation of 2,3-dimethyl-2-butene (**1a**) in methanol-*O*-*d*.[4,10]

$$e^- + CH_3OH \longrightarrow CH_3O^- + H\cdot \qquad (1)$$



(2)

1 **17**

Work continues in elucidating further the chemical properties of the π,R(3s) excited states of alkenes.

Experimental Section

Infrared spectra were obtained on carbon tetrachloride solutions with a Perkin-Elmer 421 grating spectrophotometer. Gas chromatographic analyses were performed on an Aerograph 90-P or a Hewlett-Packard 5750 instrument using 10 ft × 0.25 in. columns packed with (A) 20% Carbowax 20M, or (B) 20% SE-30 on 60–80 mesh Chromosorb W, or a 20 ft × 0.25 in. column packed with (C) 20% β,β'-oxydipropionitrile on 60–80 mesh Chromosorb P. Nuclear magnetic resonance spectra were determined on carbon tetrachloride solutions with a Jeolco C-60HL or Varian XL-100 spectrometer, using 0.3% tetramethylsilane as an internal standard. NMR data are reported in the following manner: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = unresolved multiplet); integration; coupling constant (given in hertz); and assignment. Mass spectra were obtained using an AEI MS-902 spectrometer; *m/e* values reported include the parent ion peak, if detectable, and other significantly large peaks appearing above *m/e* 55. Unless otherwise indicated, all irradiations were conducted using a Hanovia 450-W medium-pressure mercury arc and a water-cooled quartz immersion well. The solution was purged with nitrogen 5–10 min before irradiation. Vigorous stirring during irradiation was effected by a magnetic stirring bar. For product isolation the solution was added to water semisaturated with sodium chloride and continuously extracted with pentane. After removal of the pentane by distillation, the products were isolated gas chromatographically.

3-Ethyl-2-methyl-2-pentene (1b). A. Irradiation. A 100-ml methanolic solution containing 2.24 g of olefin was irradiated as described above for 6 hr. Gas chromatographic analysis (A and C) revealed partial recovery of olefin **1b** and formation of several hydrocarbon and four ether products. Isolation by gas chromatographic preparative methods afforded **3-ethyl-2-methyl-1-pentene (11b)** and **3-ethyl-2-methylpentane (12b)**, which each had spectral properties and gas chromatographic retention times identical with those of commercial samples. The remaining hydrocarbon products were not isolated.

3-Methoxy-3-ethyl-2-methylpentane (5b) was obtained as a colorless liquid: ν_{max} 2962, 2938, 2880, 2825, 1459, 1379, 1170, 1142, 1070, and 900 cm^{-1}; NMR spectrum τ 6.85 (s, 3, CH_3O–); MS *m/e* 129.1282 (calcd for $C_8H_{17}O$, 129.1280), 115 (83), 101 (100), 83 (25), and 59 (58). This material was identical with a specimen prepared independently as described below.

Isolation of the major ether product afforded **3-methoxy-3-ethyl-2-methyl-1-pentene (6b)** as a colorless liquid: ν_{max} 3092, 2971, 2882, 2827, 1640, 1450, 1379, 1161, 1149, 1123, 1082, 1058, 1029, 936, 919, and 901 cm^{-1}; NMR spectrum τ 4.95 and 5.05 (2 m, 2, CH_2=), 6.97 (s, 3, CH_3O–), and 9.27 [t, 6, $(CH_3CH_2)_2C$–]; MS *m/e* 142.1356 (calcd for $C_9H_{18}O$, 142.1358), 113 (100), 101 (18), 81 (22), and 55 (23).

2-Methoxy-3-ethyl-2-methylpentane (7b) was obtained as a colorless liquid: ν_{max} 2934, 2875, 2825, 1458, 1377, 1361, 1187, 1155, 1139, 1080, 1061, and 830 cm^{-1}; NMR spectrum τ 6.85 (s, 3, CH_3O–), and 8.93 [s, $(CH_3)_2C$–]; MS *m/e* 129.1277 (calcd for $C_8H_{17}O$, 129.1280), 83 (5), 73 (100), 59 (4), and 55 (8). This material was identical in retention time and spectral properties with a sample prepared as described below.

A mixture of (*E*)- and (*Z*)-**4-methoxy-3-ethyl-4-methyl-2-pentene (8b)** was obtained as a colorless liquid: ν_{max} 3057, 2978, 2934, 2880, 2824, 1459, 1376, 1361, 1168, 1145, 1069, and 894 cm^{-1}; NMR spectrum τ 4.53 (q, 1, J = 6.5 Hz, CH-3), 7.07 (s, 3, CH_3O–), 7.88 (q, 2, J = 7.5 Hz, CH_3CH_2–), 8.32 (d, 3, J = 6.5, CH_3-4), 8.79 [s, 6, $(CH_3)_2C$–], and 8.98 (t, 3, J = 7.5 Hz, CH_3CH_2–); MS *m/e* 142.1356 (calcd for $C_9H_{18}O$, 142.1358), 127 (93), 113 (37), 95 (34), 73 (100), 69 (26), and 67 (35).

B. Acid-Catalyzed Methanolysis. A solution containing 1 g of olefin **1b** and 10 drops of concentrated sulfuric acid in 30 ml of methanol was allowed to stand at room temperature for 18 days. The resulting solution was neutralized with sodium bicarbonate, diluted with water, and continuously extracted with pentane. The pentane solution was concentrated by distillation. Gas chromatographic analysis revealed the formation of two ether products in a 17:1.0 ratio. Isolation of the major component afforded ether **7b**. The second component had a retention time identical with that of ether **5b**.

Independent Synthesis of 3-Methoxy-3-ethyl-2-methylpentane (5b). A solution containing 3.5 g (20 mmol) of 2-methyl-3-ethyl-3-pentanol[11] in 25 ml of freshly distilled 1,2-dimethoxyethane was added dropwise to 1.33 g (20 mmol) of a 50% suspension of sodium hydride in oil, which had been washed with pentane, under nitrogen with stirring. After 6 hr 4.12 g (29 mmol) of methyl iodide was added dropwise to the solution in an ice bath. After addition, the mixture was stirred at 30° overnight. After cooling, the solution was diluted with 10 ml of water. The organic layer was collected and concentrated by distillation to afford 1.53 g (10.3 mmol, 53%) of ether **5b**, bp 75–76° (63 mm). This material was identical in every respect with that obtained photochemically as described above.

Isopropylidenecyclohexane (1c). A. Irradiation. A 100-ml methanolic solution containing 2.48 g (20 mmol) of olefin **1c**[12] was irradiated as described above for 16 hr. Gas chromatographic analysis (A and C) revealed a partial recovery of olefin **1c** and the formation of three hydrocarbon products and three ether products. Isolation by preparative gas chromatographic techniques (A and C) afforded **isopropylcyclohexane (12c)** which had spectral properties and a retention time identical with those of a commercial specimen. Isolation of the second component afforded **2-cyclohexylpropene (11c)** as a colorless liquid: ν_{max} 3091, 2935, 2860, 1645, 1453, 1375, 1108, and 891 cm^{-1} (lit.[13] ν_{max} 1650 and 883 cm^{-1}). The third hydrocarbon was not isolated.

1-Methoxy-1-isopropylcyclohexane (5c) was obtained as a colorless liquid: ν_{max} 2940, 2865, 2829, 1463, 1384, 1367, 1156, 1144, 1075, 940, 923, 912, and 804 cm^{-1}; NMR spectrum τ 6.88 (s, 3, CH_3O–) and 9.15 [d, 6, J = 7 Hz, $(CH_3)_2C$–]; MS *m/e* 156.1516 (calcd for $C_{10}H_{20}O$, 156.1514), 113 (100), and 81 (47). This material was identical in retention time and spectral properties with a sample prepared independently as described below.

1-Methoxy-1-(2'-propenyl)cyclohexane (6c) was obtained as a colorless liquid: ν_{max} 3090, 2938, 2861, 2825, 1638, 1447, 1148, 1079, 927, and 901 cm^{-1}; NMR spectrum τ 7.08 (s, CH_3O–), 5.10 (d, J = 10 Hz, vinyl); MS m/e 154.1359 (calcd for $C_{10}H_{18}O$, 154.1357), 139 (15), 113 (91), 111 (100), 81 (63), 79 (42), and 67 (22).

2-Methoxy-2-cyclohexylpropane (7c) was obtained as a colorless liquid: ν_{max} 2980, 2938, 2859, 2830, 1450, 1379, 1363, 1230, 1201, 1169, 1146, 1112, 1074, 889, and 854 cm^{-1}; NMR spectrum τ 6.87 (s, 3, CH_3O–) and 8.95 [s, $(CH_3)_2C$–]; MS m/e 141.1282 (calcd for $C_9H_{17}O$, 141.1279), 81 (27), 74 (27), 73 (100), 72 (34), and 59 (31). This material was identical in retention time and spectral properties with specimens prepared independently as described below.

B. Acid-Catalyzed Methanolysis. A solution containing 1 g of olefin **1c** and 10 drops of concentrated sulfuric acid in 20 ml of methanol was allowed to stand at room temperature for 11 days. The resulting solution was neutralized with sodium bicarbonate and continuously extracted with pentane. The pentane solution was concentrated by distillation. Preparative gas chromatographic techniques (C) afforded the two ether products **7c** and **5c** in a 4.4:1.0 ratio, each having retention times and spectral properties identical with those given above.

Independent Synthesis of 2-Methoxy-2-cyclohexylpropane (7c). 2-Cyclohexyl-2-propanol was prepared by the addition of methyllithium (60 ml of 2.2 M solution) dropwise to an ice-cold solution of cyclohexyl methyl ketone in 25 ml of anhydrous ether under nitrogen. After 1 hr of stirring at room temperature, 50 ml of water was added dropwise and the solution was stirred for an additional 1 hr. The reaction mixture was then extracted with ether and the combined ether extracts were dried over saturated sodium chloride solution followed by anhydrous sodium sulfate. Distillation afforded 7.98 g (56%) of 2-cyclohexyl-2-propanol, bp 42° (4 mm).

A solution containing 2.15 g (15 mmol) of 2-cyclohexyl-2-propanol in 50 ml of anhydrous ether was added dropwise with stirring to 0.81 g of a 50% suspension of sodium hydride in oil, which had been washed with pentane, under nitrogen. After 4 hr of stirring the solution was cooled in an ice bath and 2.41 g (17 mmol) of methyl iodide was added dropwise. After addition, the mixture was stirred at room temperature for 24 hr. The mixture was treated with 5 ml of water and extracted with three 25-ml portions of ether. The combined ether fractions were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated by distillation. Isolation by preparative gas chromatography (C) afforded a specimen of **7c** which had spectral properties identical with those described above.

Isopropylidenecyclopentane (1d). A. Irradiation. A 100-ml methanolic solution containing 2.2 g of olefin **1d** was irradiated as described above for 8 hr. Gas chromatographic analysis (B and C) revealed a partial recovery of olefin **1d** and the formation of three hydrocarbon and four ether products. Isolation by preparative gas chromatographic techniques afforded **isopropylcyclopentane (12d)** which had a retention time and spectral properties identical with those of a commercial sample. **1-Isopropyl-1-cyclopentene (13d)** was obtained as a colorless liquid which had spectral properties identical with those of an authentic sample prepared by treatment of 2-cyclopentyl-2-propanol with p-toluenesulfonic acid.[14] **2-Cyclopentylpropene (11d)** was obtained as a colorless liquid, ν_{max} 3088, 2962, 2875, 1644, 1453, 1377, and 892 cm^{-1} (lit.[13] ν_{max} 1650 and 881 cm^{-1}).

1-Methoxy-1-isopropylcyclopentane (5d) and **2-methoxy-2-cyclopentylpropane (7d)** were obtained as colorless liquids which had the same retention times and spectral properties as the specimens prepared independently as described below. **1-Methoxy-1-(2'-propenyl)cyclopentane (6d)** was observed as one component of a mixture of the four ethers in an NMR spectrum (τ 5.10), but attempts to isolate the material were unsuccessful. **2-Methoxy-2-(1'-cyclopentenyl)propane (8d)** was obtained as a colorless liquid: ν_{max} 3058, 2981, 2934, 2850, 2823, 1462, 1442, 1372, 1359, 1258, 1167, 1143, 1072, 950, and 911 cm^{-1}; NMR spectrum τ 4.41 (m, –CH=), 6.90 (s, CH_3O–), and 8.70 [s, $(CH_3)_2C$–]; MS m/e 140.1203 (calcd for $C_9H_{16}O$, 140.1201), 125 (100), 109 (18), 95 (15), 93 (40), and 67 (20).

B. Acid-Catalyzed Methanolysis. A solution containing 1 ml of olefin **1d** and 6 drops of concentrated sulfuric acid in 10 ml of methanol was allowed to stand for 1 day. The solution was neutralized with sodium bicarbonate and extracted with pentane. The combined pentane extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated by distillation. Preparative gas chromatographic techniques (A) afforded the ethers **5d** and **7d** in a 1.1:1.0 ratio.

1-Methoxy-1-isopropylcyclopentane (5d) was obtained as a colorless liquid: ν_{max} 2960, 2876, 2826, 1467, 1386, 1368, 1190, and 1080 cm^{-1}; NMR spectrum τ 6.94 (s, 3, CH_3O–), 8.39 [m, 9, $(CH_2)_4CH$–], and 9.12 [d, 6, J = 6.75 Hz, $(CH_3)_2C$–]; MS m/e 142.1355 (calcd for $C_9H_{18}O$, 142.1358), 113 (13), 99 (100), 81 (12), 69 (16), and 67 (78).

2-Methoxy-2-cyclopentylpropane (7d) was obtained as a colorless liquid: ν_{max} 2957, 2873, 2830, 1466, 1381, 1363, 1186, 1124, 1079, and 909 cm^{-1}; NMR spectrum τ 6.87 (s, 3, CH_3O–), 8.55 [m, 9, $(CH_2)_4CH$–], and 8.93 [s, 6, $(CH_3)_2C$–]; MS m/e 127.1120 (calcd for $C_8H_{15}O$, 127.1124), 95 (72), 69 (50), 67 (100), and 59 (33). The infrared spectrum was similar to that previously reported.[15]

2-Isopropylidenenorbornane (14). A. Irradiation. A 100-ml methanolic solution containing 2.72 g of olefin **14**, prepared by the general method of Kornblum et al.,[12,14] was irradiated as described above for 7 hr. Gas chromatographic analysis (B) revealed the formation of seven ether and several hydrocarbon products. The following two principal products were isolated by preparative techniques.

2-(2'-Methoxy-2'-propyl)-2-norbornene (15) was obtained as a colorless liquid: ν_{max} 3055, 2971, 2873, 2822, 1442, 1370, 1368, 1273, 1161, and 1069 cm^{-1}; NMR spectrum τ 4.19 (d, J = 3 Hz, olefinic), 6.88 (s, CH_3O–), 7.09 (m, bridgehead), 8.73 (s, CH_3–), and 8.75 (s, CH_3–); MS m/e 166.1354 (calcd for $C_{11}H_{18}O$, 166.1357), 151 (40), 123 (100), 108 (15), 107 (20), and 91 (42).

2-*endo*-Isopropylnorbornane (16) was obtained as a colorless liquid: ν_{max} 2950, 2869, 1462, 1450, 1381, 1362, and 1310 cm^{-1}; NMR spectrum τ 7.78 (m, bridgehead). This material was identical in retention time and spectral properties with an authentic sample obtained as described previously.[16]

Irradiation of 2,3-Dimethyl-2-butene (1a) in the Presence of Sulfur Hexafluoride. Through a solution containing 1.68 g (20 mmol) of 2,3-dimethyl-2-butene (**1a**) in 100 ml of methanol was bubbled nitrogen (15 min) followed by sulfur hexafluoride (10 min). Sulfur hexafluoride was slowly bubbled through the solution during the irradiation, which was carried out by the general procedure described above. After irradiation, 80 ml of the solution was diluted to 100 ml with distilled water. Fluoride concentrations were then determined from the potential of an Orion fluoride ion activity electrode (94-09) vs. a Fischer standard saturated calomel electrode with cracked glass junction as measured by a Beckman Century SS pH meter on expanded scale. A calibration curve was obtained using sodium fluoride in 80:20 methanol–water standard solutions. The results are summarized in Table II.

Acknowledgment. Support of this research by the Army Research Office is gratefully acknowledged. The authors are indebted to R. P. Buck and S. Riffle for invaluable assistance with the fluoride ion concentration measurements.

Registry No.—**1a**, 563-79-1; **1b**, 19780-67-7; **1c**, 5749-72-4; **1d**, 765-83-3; **5b**, 55660-92-9; **5c**, 55660-93-0; **5d**, 55660-94-1; **6b**, 55660-95-2; **6c**, 55660-96-3; **7b**, 55660-97-4; **7c**, 55660-98-5; **7d**, 3275-02-3; (*E*)-**8b**, 55660-99-6; (*Z*)-**8b**, 55661-00-2; **8d**, 55661-01-3; **11c**, 2157-18-8; **11d**, 55661-02-4; **14**, 4696-14-4; **15**, 55661-03-5; **16**, 55661-04-6; 2-methyl-3-ethyl-3-pentanol, 55661-05-7; methyl iodide, 74-88-4; 2-cyclohexyl-2-propanol, 16664-07-6; methyllithium, 917-54-4; cyclohexyl methyl ketone, 823-76-7; sulfur hexafluoride, 2551-62-4.

References and Notes

(1) Part III: P. J. Kropp and T. R. Fields, *J. Am. Chem. Soc.*, **96**, 7559 (1974).
(2) Alfred P. Sloan Research Fellow.
(3) (a) A. J. Merer and R. S. Mulliken, *Chem. Rev.*, **69**, 639 (1969); (b) F. H. Watson, Jr., A. T. Armstrong, and S. P. McGlynn, *Theor. Chim. Acta*, **16**, 75 (1970); F. H. Watson, Jr., and S. P. McGlynn, *ibid.*, **21**, 309 (1971).
(4) P. J. Kropp, E. J. Reardon, Jr., Z. L. F. Gaibel, K. F. Williard, and J. H. Hattaway, Jr., *J. Am. Chem. Soc.*, **95**, 7058 (1973).
(5) P. J. Kropp, H. G. Fravel, Jr., and T. R. Fields, in preparation.
(6) S. J. Rzad and J. H. Fendler, *J. Chem. Phys.*, **52**, 5395 (1970), and references cited therein.
(7) Although sulfur hexafluoride normally yields six fluoride ions for each electron captured in methanolic solution, this ratio may not hold in the presence of olefinic material in view of the known reaction of the initially

formed intermediate, the sulfur pentafluoride radical, with alkenes; see H. W. Sidebotton, J. M. Tedder, and J. C. Walton, *Trans. Faraday Soc.*, **65**, 2103 (1969).
(8) See, for example, C. F. Cullis, J. M. Francis, and A. J. Swallow, *Proc. R. Soc. London Ser. A*, **287**, 15 (1965).
(9) See, for example, A. Habersbergerová, Lj. Josimović, and J. Teplý, *Trans. Faraday Soc.*, **66**, 656, 669 (1970).
(10) In addition to the routes proposed here for the formation of photoproducts **11** and **13** there is an alternative, competing pathway involving simple migration of the double bond in the starting olefin. This process is ubiquitous in olefin photochemistry and is the subject of a separate report (ref 5). Its occurrence in competition with the other two routes accounts for the fact that irradiation of **1a** in methanol-*O-d* results in the formation of **11a** with a significantly lower level of deuterium incorporation than for **12a** (ref 4).
(11) D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76**, 4446 (1954).
(12) N. Kornblum, S. D. Boyd, H. W. Pinnick, and R. G. Smith, *ibid.*, **93**, 4316 (1971).
(13) G. Chiurdoglu and S. Van Walle, *Bull. Soc. Chim. Belg.*, **66**, 612 (1957).
(14) T. R. Fields, unpublished.
(15) W. Hueckel and S. K. Guptè, *Justus Liebigs Ann. Chem.*, **685**, 105, 118 (1965).
(16) K. Alder and H.-J. Ache, *Chem. Ber.*, **95**, 503 (1962).

Transannular Photochemical Ring Closure of 1,2,5,6-Tetramethylenecyclooctane as a Synthetic Route to Small-Ring Propellanes

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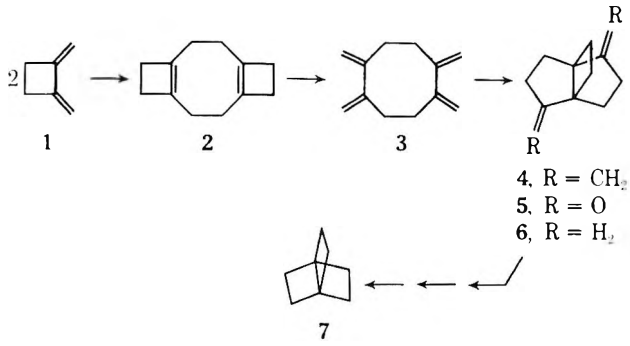
The synthesis of 2,6-dimethylene[3.3.2]propellane (**4**) in three steps and 12% overall yield from allene dimer **1** is reported. The key reaction is the formation of **4** by transannular photochemical ring closure of 1,2,5,6-tetramethylenecyclooctane (**3**). A chemical separation of **4** from isomers that are carried through the synthesis is described, which makes the purification of the intermediates (**1**–**3**) unnecessary. Compound **4** has been converted to the parent [3.3.2]propellane (**6**), which undergoes free-radical addition of bromine across the central bond to give **13**.

The synthesis of small-ring propellanes has been an area of considerable activity in recent years.[2] Theoretical interest in [2.2.2]propellane (**7**)[3] has given special stimulus to the preparation of this molecule. A derivative of **7** has been synthesized by Eaton and his coworkers through two successive ring contractions of [4.2.2]propellane-2-one.[4a] This key intermediate was prepared from the enol acetate of 1,3-cyclohexanedione by photoaddition of ethylene, base-catalyzed elimination of the elements of acetic acid, and photoaddition of a second molecule of ethylene.[4b] Evidence for the intermediacy of the parent compound (**7**) in the electrochemical reduction of 1,4-dibromobicyclo[2.2.2]octane[5] and in the mercury-sensitized photolysis of 1,4-dimethylenecyclohexane[6] has also been reported.

Our route[7] to the [2.2.2]propellane ring system took cognizance of the fact that photochemical ring closure in 1,4-dimethylenecyclohexane provided a formally attractive synthesis of **7**. However, since the ring in this diene prefers a chair conformation,[8] we anticipated that ring closure to **7** might be a rather inefficient process. Moreover, because short-wavelength light or a high-energy sensitizer would be required to excite the isolated double bonds in 1,4-dimethylenecyclohexane, it seemed possible that **7**, if formed, might undergo photoinitiated opening back to the starting material. Finally, were only small amounts of **7** to be formed, for either or both of the above reasons, its separation from unreacted starting material would be problematical. Therefore, we explored the route, outlined in Scheme I, which circumvented these difficulties by effecting photochemical ring closure in 1,2,5,6-tetramethylenecyclooctane (**3**).[9] Cyclooctane rings readily undergo 1,5-transannular reactions;[10] and excitation of **3**, either direct or sensitized, was expected to be easy because of the conjugated diene systems present in the molecule. Moreover, the methylene groups in the anticipated photocyclization product (**4**) could be ozonized to give **5**, a precursor of the parent [3.3.2]propellane (**6**) and, more important, a promising intermediate for the synthesis of **7**.[11] As indicated in Scheme I, a synthesis of **3** can be constructed by noting that **3** is the product of cyclobutene ring opening in **2**, which is in turn a dimer of 1,2 dimethylenecyclobutane (**1**). Thus our synthesis began with attempts to prepare **2** from **1**.

Scheme I



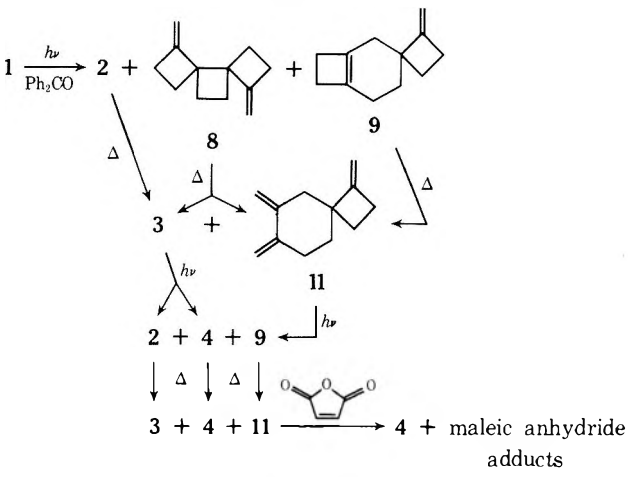
Results and Discussion

The simplest route to **1** is through the thermal dimerization of allene, which also produces about 20% of 1,3-dimethylenecyclobutane.[12] Since we required large amounts of **1**, our first task was to improve the literature method for its preparation. Allene gas was passed through a tube packed with glass balls and heated to 500°. The pyrolysate was collected in a flask cooled with Dry Ice. The flask, containing unreacted allene, allene dimers, and higher oligomers, was then connected to the inlet of the heated tube and allowed to warm to room temperature. Only the allene distilled through the tube, and the pyrolysate was trapped in a second flask. The two flasks were then interchanged and the allene was cycled through the tube again.[13] Allene, recycled thus ten times, gave yields of dimers on the order of 25%. With further recycling even higher yields could be realized.

Although dimerization of butadiene, catalyzed by complexes of Ni^0, gives high yields of 1,5-cyclooctadiene,[14] experiments on the dimerization of **1** to **2** in the presence of $Ni(PPh_3)_4$ were not at all promising. Mixtures of dimers of **1** were obtained, and substantial amounts of starting material remained unreacted. We were discouraged from pursuing further experiments with different ligands on the Ni^0 catalyst by the finding of Heimbach[15] that tris(2-biphenyl phosphite)nickel(0), which gives a 97% yield of 1,5-cyclooctadiene from butadiene,[14] with 2,3-disubstituted butadienes produces the corresponding derivatives of 1,5-cyclooctadiene in only 3–6% yield.

Photosensitized dimerization[16] of **1** proved to be a more promising method for the preparation of synthetically useful quantities of **2**. Initial experiments were performed on samples of **1** purified by preparative GLC. However, as expected, the presence of 1,3-dimethylenecyclobutane did not alter the course of the reaction; so the mixture of allene dimers was used for preparative runs. When **1** was irradiated in solution in the presence of benzophenone, three photodimers were isolated by GLC. They were easily identified by NMR as **2**, **8**, and **9** (Scheme II). Inspection of the NMR

Scheme II



spectrum of the crude photolysate showed, however, the two singlets at δ 2.15 and 2.27, belonging to **2**, to be absent. Several resonances belonging to neither **8** nor **9** were observed; and on refluxing a benzene solution of the photodimers of **1**, these resonances were found to decrease as those belonging to **2** increased in intensity. In analogy with the formation of 1,5-cyclooctadiene by Cope rearrangement of *cis*-1,2-divinylcyclobutane in the sensitized photodimerization of butadiene,[17] the precursor of **2** is almost certainly the syn isomer of **8**.

The desired dimer (**2**) could be separated on a preparative scale from its isomers by spinning band distillation, as well as by GLC. On pyrolysis in a flow system at 330°, it was converted cleanly to **3**. At lower temperatures the product (**10**) of opening just one of the cyclobutene rings in **2** could be isolated. Dimer **9** on pyrolysis at 330° also underwent cyclobutene ring opening to give **11**. At temperatures above 200° **8** gave a mixture of **2**, **3**, **9**, **10**, and **11**. As the pyrolysis temperature was raised, **3** and **11** were isolated in increasing amounts until they became the sole products. At 330° **8** gave **3** and **11** in a ratio of 11:9. Presumably, at temperatures above 200° the most substituted bond in the central cyclobutane ring of **8** is broken, forming a highly stabilized biradical that is partitioned between **2** and **9**. At higher pyrolysis temperatures these compounds undergo cyclobutene ring opening, as discussed above, until at 330° only **3** and **11** are detected.

Because **8** constitutes 58% of the original photodimer mixture, while **2** comprises only 29%, the amount of **3** produced from the mixture of photodimers can be maximized by employing the former, as well as the latter, as a source of **3**. Although **8** can be separated from **9** by spinning band distillation, **11**, the pyrolysis product of **9**, is also formed from **8**. Therefore, for experiments in which pure samples of **3** were not required the mixture of all three photodimers was pyrolyzed at 330° to give a product consisting of 60% **3** and 40% **11**. It was hoped that at higher temperatures **3** and **11** might be equilibrated (via bond cleavage, reclosure, and the intermediacy of **10**, or **10**, **2**, and **9**) and that the equilibrium would favor **3**. In the event the former expectation was realized, but the latter was not. At 500° **2**, **3**, **8**, **9**, and **11** all gave a 50:50 mixture of **3** and **11**. Since even at 360° there was some equilibration between **3** and **11**, pyrolysis of the crude photolysate was carried out at 330° in order to maximize the amount of **3** present in the pyrolysate.

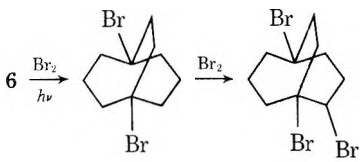
Samples of pure **3** could be obtained either by pyrolysis of pure **2** or by preparative GLC separation of **3** from **11**. On direct photolysis **3** was converted to a 1:1 mixture of **2** and **4**. When the photolysis was monitored by GLC, **10** could be identified as the precursor of **2**. Sensitized photolysis of **3** was briefly investigated; but while no **2** was formed, the **4** that was obtained was contaminated with several unidentified photoproducts, and GLC analysis indicated a larger loss of volatile material than in the direct photolysis. Since it was found that on direct photolysis **11** only underwent cyclobutene ring closure to **9** and that the presence of **9** and **11** did not affect the photochemistry of **3**, for preparative purposes the crude pyrolysate, containing both **3** and **11**, was photolyzed. The products then consisted of **2**, **4**, and **9** with smaller amounts of **10** and **11** present when, in order to minimize polymer formation, the irradiation was not prolonged. From this mixture the desired product of transannular bond formation (**4**) could be isolated by careful preparative GLC.

The three-step synthesis of **4** described above had the virtue of not requiring purification of any of the intermediates, since the mixture of allene dimers could be photolyzed, the photolysate pyrolyzed, and the pyrolysate photolyzed. However, a tedious GLC separation was required to isolate **4**; and we sought a way to circumvent it. Crucial to the solution of this problem was the discovery that **4** proved to be quite stable thermally. When it was pyrolyzed in our flow system at 330°, GLC analysis indicated no new products formed and no appreciable loss of **4**. Although the central bond in the [3.3.2]propellane skeleton of **4** is adjacent to two vinyl groups, effective conjugation of them with the bridgehead radicals that would result from cleavage of this bond is geometrically impeded. This fact is probably the origin of the thermal stability of **4**, which allowed it to remain intact under conditions which led to cyclobutene ring opening in **2**, **9**, and **10**. Thus, pyrolysis of the crude photolysate, containing **2**, **4**, **9**, **10**, and **11**, gave a mixture of **3**, **4**, and **11**. Since **3** and **11** are both conjugated dienes, while **4** is not, only the former two compounds underwent Diels–Alder reactions. Consequently, treatment of the crude pyrolysate, containing **3**, **4**, and **11**, with maleic anhydride, followed by chromatography, yielded **4**, which was found to be 97% pure by GLC. This chemical separation of **4** from its isomers allowed its preparation by the route shown in Scheme II, without purification of any of the intermediates, in 12% overall yield, based on the weight of allene dimer. Since the crude allene dimer mixture contains only 80% of **1** and since the maximum yield of **4** possible from it by the sequence sensitized photolysis, pyrolysis, direct photolysis is 30%, the maximum theoretical yield of

the synthesis shown in Scheme II is 24%, based on the weight of crude dimer. It is somewhat amusing to note that all the steps in this synthesis, starting with the dimerization of allene, require only heat or light; the final purification step alone requires an additional reagent.

Ozonolysis of **4** in 95% ethanol to the diketone **5** proceeded in 80% yield. When the ozonolysis was done in methanol, in addition to **5**, 20% of another compound (**12**) was also isolated. The mass spectrum and NMR of this second compound were consistent with its formulation as the monodimethyl ketal of **5**, to which **12** was hydrolyzed in dilute aqueous acid. The structure (**5**) for the ozonolysis product of **4** was supported by analytical and spectral data. In particular, the ir showed a sharp absorption at 1740 cm^{-1}, indicating that both carbonyl groups were contained in five-membered rings. The rather complex NMR spectrum could be greatly simplified by stirring a CCl_4 solution of the diketone with D_2O containing K_2CO_3. This resulted in the exchange of four protons and caused the NMR spectrum to collapse to an AA'BB' pattern for the protons on the two-carbon bridge and a broad singlet for the two nonexchangeable protons on each of the three-carbon bridges. When the exchangeable protons were replaced with bromine by adding Br_2 to a CCl_4 solution of the diketone, not only was the AA'BB' pattern revealed, but the broad singlet observed in the deuterated ketone was also resolved into an AB quartet.

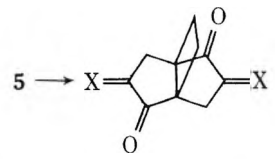
The structure (**5**) for the diketone was confirmed by its Wolff–Kishner reduction to the parent hydrocarbon (**6**), whose NMR spectrum displayed a sharp singlet for the four equivalent protons on the two-carbon bridge. Subsequently, we learned[18] that [3.3.2]propellane (**6**) had been prepared by a very different route than ours;[19] and comparison of our NMR and ir spectra of **6** with those kindly provided by Professor Cargill showed the compounds prepared by the two different routes to be identical. We briefly investigated the chemistry of **6** and found that, although it was unreactive toward trifluoroacetic acid at 100° for 12 hr and toward bromine at room temperature in the dark, when a solution of **6** in CCl_4 containing Br_2 was exposed to a fluorescent lamp for 3 days, no starting material remained. Two compounds, **13** and **14**, were isolated by fractional crystallization. Following the reaction by NMR



13 14

showed that **14** was a secondary product, formed from **13**, presumably by the mechanism proposed by Russell and Brown for the reaction of tertiary bromides with molecular bromine.[20] Addition of bromine radicals across the central bond of [*n.m.*2]propellanes has been previously observed in systems where $n \leq 4$ and $m = 2$.[4,21] Although this reaction is much faster when the propellane contains two four-membered rings, our finding that bromine adds to **6** shows that in [*m.n.*2]propellanes, addition of bromine atoms to the central bond occurs for $m + n \leq 6$.

Whereas Eaton's synthesis of a derivative of [2.2.2]propellane involved two successive contractions of a cyclohexanone ring,[4] our route from **5** required the simultaneous contraction of two cyclopentanone rings. In keeping with the spirit of our synthesis of **5**, we first tried to convert it directly to **7** by gas-phase photodecarbonylation.[22] However, from either direct or mercury-sensitized irradiation of **5**, no material was isolated that could be unequivocally identified as even a decomposition product of **7**. An obvious route from **5** to a derivative of **7** was through a double Wolff rearrangement of the bis(diazo) diketone (**17**).[23] Attempts to prepare the bis(hydroxymethylene) diketone (**15**) for reaction with tosyl azide[23] were not fruitful. Synthesis of the bis(oximino) diketone (**16**) by reaction of **5** with 2 equiv of butyl nitrite[24] was successful, but the conversion of **16** to **17** by reaction with chloroamine, generated in situ,[24] proceeded in yields so low as to be synthetically useless. Further studies of ring contraction in **5** were abandoned when we learned[25] of Eaton's synthesis of [3.2.2]propellan-2-one,[4b] a precursor of a derivative of **7**, one carbonyl less distant than **5**.



15, X = CHOH
16, X = NOH
17, X = N_2

Although our synthesis of **7** or a derivative thereof was abandoned short of the final goal, a number of the compounds prepared are of interest as potential intermediates in the synthesis of other molecules of theoretical import. For instance, **2** undergoes ozonolysis of both double bonds to give cyclododecanetetr-1,4,7,10-one in essentially quantitative yield. This tetraketone has been used in the preparation of a [2.2]pyrrolophane,[26] a nitrogen-bridged [12] annulene,[27] and a derivative of tricyclo[6.4.0.$0^{4,9}$]dodecane.[28] We are currently exploring the use of **2**, as well as **3** and **13**, in the synthesis of other interesting molecules.

Experimental Section

Dimerization of Allene. Allene gas (61.3 g) from a lecture bottle was passed into a vertical column, 14 in. long and 1 in. in diameter, packed with glass beads and heated to 500 ± 10°. The allene was passed in at a rate of about 1 g/min. The effluent gases were trapped in a 125-ml erlenmeyer flask cooled in Dry Ice–acetone. When all the allene had been passed through the column once, the collection flask was removed and attached to the inlet of the pyrolysis column while a second erlenmeyer flask served as a collector. The allene in the filled erlenmeyer flask was allowed to distil into the heated column at room temperature. Repeated switching of the two flasks[13] allowed the accumulation of allene dimers by recycling the unpyrolyzed allene. After recycling ten times, the unreacted allene was allowed to distil off at room temperature. The residue was transferred to a round-bottomed flask and distilled at room temperature under aspirator vacuum, the distillate being collected in a flask cooled in a Dry Ice–acetone bath. The yield of dimer (pale yellow in color) was 15.0 g (24%). The allene dimers formed a polymer slowly at room temperature and were stored at −20° under nitrogen. The allene dimers could be separated by preparative GLC at 45° on a 0.375 in. × 20 ft column of 20% γ-methyl-γ-nitropimelonitrile on Chromosorb P.

Benzophenone-Sensitized Photolysis of Allene Dimers. The allene dimers (6.1 g) were dissolved in 150 ml of pentane. Benzophenone (0.1 g) was added to the solution and the solution was placed in an immersion well and degassed by bubbling nitrogen through it for 0.5 hr. The solution was photolyzed with a Hanovia high-pressure mercury lamp, using a Pyrex filter. Throughout the photolysis the solution was kept under a positive pressure of nitrogen. After 7 hr the photolysis was stopped and the solvent was removed under reduced pressure. The yield was 4.6 g of a pale yellow liquid. The crude product was chromatographed on 120 g of neutral alumina to remove the benzophenone and polymeric material. Fractions (100 ml) were taken and the column was eluted with pentane. The dienes were eluted in fractions 2–4. The solvent was removed, yielding 4.4 g of product (72%). The diene mixture was stored under nitrogen at −20°. The three compounds in this mixture were easily separable by preparative GLC on a 0.375 in. × 10

ft column of 20% SE-30 on Chromosorb W at 150°. The proportions[29] and retention times (He flow rate 180 ml/min) of the three compounds were as follows: **8**, 58%, 16.6 min; **9**, 13%, 25.4 min; **2**, 29%, 39.9 min. Dimer **1** could also be separated from **8** and **9** by spinning band distillation of the crude dimer mixture with benzophenone added as a chaser solvent. A fraction collected at 75–79° (30 mm) was found to be pure **8**. Fractions collected between 79 and 104° proved to be mixtures of **8**, **9**, and **2**. A fraction collected at 104–108° (30 mm) consisted of 93% **2**, 6% **9**, and 1% **8**. This fraction crystallized, and recrystallization from ethanol afforded pure **2**, mp 41–41.5°. The NMR spectra of these compounds have previously been reported.[9]

Pyrolysis of the Photolysis Mixture (2, 8, 9). The mixture (6.6 g) from benzophenone-sensitized photolysis of the allene dimers was dissolved in 60 ml of hexane and slowly added from a dropping funnel (1 drop every 5 sec) to the top of a pyrolysis column 12 in. long and 0.5 in. in diameter, packed with glass helices, heated to 330°, and with nitrogen passing through it at a rate of 5 ml/sec. The outlet tube from the pyrolysis column reached to the bottom of a volumetric flask that was used as a trap. Several pieces of glass wool were packed into the bottom of the trap and a piece was wrapped around the outside of the outlet from the pyrolysis column so that the glass wool was also in contact with the inner wall of the trap. The glass wool was wetted with hexane before the trap was attached to the column. After all the solution had been added to the pyrolysis column, the column was washed with 20 ml more hexane. The solution collected in the trap was evaporated to yield 5.5 g (83%) of a 60:40 mixture of **3** and **11**, which could be separated by preparative GLC on a 0.375 in. × 10 ft column of 20% Carbowax 20M on Chromosorb W at 130° with a helium flow of 180 ml/min. The retention times under these conditions follow: **11**, 20.1 min; **3**, 23.3 min. The NMR of **11** ($CDCl_3$) showed δ 1.6–1.9 (m, 4 H), 2.1–2.8 (m, 6 H), 4.6–5.0 (m, 6 H); uv λ_{max} (hexane) 230 nm (log ϵ 3.7). The NMR of **3** ($CDCl_3$) showed δ 2.40 (s, 8 H), 4.80 (d, 4 H, J = 2 Hz), 4.90 (d, 4 H, J = 2 Hz); uv λ_{max} 228 nm (log ϵ 4.0); mass spectrum M^+ m/e 160.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 90.14; H, 10.33.

Isolation of 4,5-Dimethylenebicyclo[6.2.0]dec-9-ene (10) from Low-Temperature Pyrolysis of 2. When **2** was pyrolyzed at 220°, GLC analysis on the SE-30 column showed another product of longer retention time than **3**. This product, which itself gave **3** on pyrolysis at 250°, was isolated by preparative GLC and identified as **10** on the basis of NMR, ($CDCl_3$) δ 2.0–2.5 (m, 12 H), 4.73 (d, 2 H, J = 2 Hz), 5.05 (d, 2 H, J = 2 Hz), and uv, λ_{max} 232 nm (log ϵ 3.7).

Unsensitized Photolysis of Pyrolysate (3 and 11). The pyrolysate was photolyzed 2 g at a time in 150 ml of pentane with a Hanovia high-pressure mercury lamp. The solution was degassed thoroughly by bubbling nitrogen through it for 0.5 hr, and the photolysis was done under a positive pressure of nitrogen. The solution was photolyzed for 7 hr and analyzed by GLC on the Carbowax column under the conditions described above. The photolysate consisted of (in order of elution) **4**, 30%; **11**, 10%; **9**, 33%; **10**, 2%; and **2**, 25%. After longer periods of photolysis **11** was converted to **9** and **10** to **2**, so that only three components (**4**, **9**, and **2**) were present in the mixture. However, photolysis for longer times also caused the formation of more polymeric material, which coated the outside of the lamp casing. The NMR ($CDCl_3$) of a sample of **4**, collected from GLC, showed δ 1.4–1.9 (m, 4 H), 1.98 (s, 4 H), 2.3–2.7 (m, 2 H), 2.7–3.2 (m, 2 H), 4.67 (m, 2 H), and 4.82 (m, 2 H).

Chemical Separation of 4. The crude photolysate was dissolved in 60 ml of hexane and pyrolyzed as described before. The hexane was evaporated; the pyrolysate was dissolved in 30 ml of chloroform, which had been filtered through basic alumina; and 7 g of maleic anhydride was added. The mixture was refluxed for 1 hr under nitrogen. The chloroform was removed and pentane was added to the residue. All of the residue, including the solid maleic anhydride adducts, were placed on a column of 100 g of silica gel. The column was eluted with pentane, 100-ml fractions being taken. Fractions 3–7 contained the olefin **4**. These fractions were combined and the solvent was removed. The yield of **4** from 5.5 g of the 60:40 mixture of **3** and **11** was 1.1 g, which was found to be 97% pure by GLC.

Ozonolysis of 2,6-Dimethylene[3.3.2]propellane (4). To 10 ml of 95% ethanol was added 0.4 g of **4**. The solution was cooled to −78° in a Dry Ice–acetone bath, and oxygen rich in ozone was bubbled into the solution at a rate of 0.05 ft^3/min for 12 min until the solution turned blue. The solution was allowed to stand for 4 min and was then purged of ozone by bubbling nitrogen through it for 15 min. To the solution, still at −78°, was added 0.8 ml of dimethyl sulfide. The solution was then kept for 1 hr at −20° in the freezer and for an additional 1 hr at room temperature. GLC analysis showed only one product. The solvent was then removed under reduced pressure and the residue was chromatographed on 15 g of silica gel to remove the dimethyl sulfoxide. The column was eluted with ether, taking 40-ml fractions. The diketone was eluted in fractions 2–5. The chromatographed material was crystallized from ether–pentane, yielding 0.33 g of material (80%), mp 65–73°. Recrystallization yielded pure **5**, mp 75–76°. The mass spectrum showed the parent peak at m/e 164; the NMR exhibited a complex pattern between δ 1.8 and 3.0.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.97; H, 7.35.

Deuteration of the Diketone 5. The diketone **5** (20 mg) in 0.2 ml of carbon tetrachloride was stirred with 0.1 ml of D_2O containing 15 mg of potassium carbonate. After 1 hr NMR showed that deuteration was nearly complete. The water layer was removed, and a fresh 0.1 ml of D_2O containing 15 mg of potassium carbonate was added. The mixture was stirred for 1 more hr. The NMR spectrum (CCl_4) was considerably simplified from that of the undeuterated material, showing a broad singlet at δ 2.0 and a symmetrical AA′BB′ pattern of equal intensity centered at δ 2.27. The mass spectrum confirmed that four deuterium atoms had been introduced.

Bromination of the Diketone 5. The diketone **5** (5 mg) was placed in an NMR tube and 0.1 ml of CCl_4 containing 0.004 ml of Br_2 was added. The color of the Br_2 solution began to get lighter immediately and hydrogen bromide was evolved. The NMR showed a symmetrical AA′BB′ multiplet centered at δ 2.73 and an AB quartet centered at δ 3.52 (J = 17 Hz).

Reduction of the Diketone 5 to [3.3.2]Propellane (6). The diketone (0.16 g) was placed in a flask, and 10 ml of ethylene glycol, 0.60 g of potassium hydroxide, and 0.60 ml of 95% hydrazine were added. The solution was refluxed for 24 hr under nitrogen. At the end of this time a thick layer of white solid had collected near the bottom of the condenser. The solid was washed out of the condenser with $CDCl_3$ and an NMR spectrum was recorded. The NMR spectrum showed a sharp singlet at δ 1.64 (4 H) and multiplets centered at δ 1.3 (4 H), 1.6 (4 H), and 2.0 (4 H). GLC analysis of this material showed only one peak. Work-up of the ethylene glycol reaction mixture showed a negligible amount (<2%) of product present in it. To obtain the parent [3.3.2]propellane (**6**) as a solid, it was washed out of the condenser with Freon-114 (bp 3°) in a 0° cold room. The solution was filtered through sodium sulfate into a Pyrex tube. The Freon-114 was allowed to evaporate at room temperature, leaving behind a white solid. A few milligrams of potassium carbonate were added to the tube, which was sealed under pump vacuum. The propellane was allowed to sublime to the tip of the tube by immersing the tube in a water bath at 60°. Because of the ease with which **6** sublimed, it was not possible to determine its melting point accurately.

Bromination of [3.3.2]Propellane (6). To an NMR tube containing 0.2 ml of carbon tetrachloride, 0.05 ml of methylene chloride (as a standard), and 40 mg of [3.3.2]propellane was added 0.05 ml of bromine. The NMR tube was allowed to stand at room temperature under a fluorescent light. After 1.5 hr a new peak could be seen at δ 2.58. After 3 days the NMR spectrum showed that no starting material remained, and the solvent was evaporated. TLC of the residue on silica gel using 5% ether–pentane gave two well-separated spots. The residue was dissolved in pentane and allowed to crystallize in the freezer at −20°; 44 mg of crystals were collected. The NMR of the crystals and the mother liquor showed that the compound with the singlet at δ 2.58 was in the mother liquor and that the crystals were another compound. The crystals were dissolved in pentane and allowed to crystallize again. The compound in the mother liquor was also crystallized from pentane. From each crystallization 15 mg was obtained. NMR and TLC indicated that complete separation of the two compounds had been achieved. The faster moving compound on TLC is the one obtained from the mother liquor, containing the singlet at δ 2.58. The NMR (CCl_4) of the crystals (**13**) from the mother liquor exhibited a sharp singlet at δ 2.58 and multiplets centered at δ 1.8 and 2.6. The ratio of the integration of the low-field to the high-field resonances was 12:4. The mass spectrum of **13** showed no molecular ion; the peaks of highest m/e at 215 and 217 corresponded to $M^+ - Br$.

Anal. Calcd for $C_{10}H_{16}Br_2$: C, 40.57; H, 5.45. Found: C, 40.80; H, 5.66.

The NMR ($CDCl_3$) of the less soluble, slower moving compound

(14) exhibited δ 2.0 (m, 4 H), 2.7 (m, 10 H) and a poorly resolved quartet at δ 4.86 (1 H, J = 5 and 9 Hz). The mass spectrum of **14** showed no molecular ion; the peaks with highest m/e at 280, 282, and 284 correspond to $M^+ - Br$. Even after three recrystallizations the tribromide melted over a broad range (93–99°), suggesting that it may be a mixture of stereoisomers.

Anal. Calcd for $C_{10}H_{15}Br_3$: C, 32.03; H, 4.03. Found: C, 31.67; H, 4.01.

Preparation of Bis(oximino) Diketone (16). The diketone **5** (0.118 g) was dissolved in 20 ml of dry *tert*-butyl alcohol and the solution was degassed with nitrogen for 15 min. This solution was then added to a flask (under nitrogen) containing 2.02 g of potassium *tert*-butoxide monoalcoholate with stirring. After 10 min 0.4 ml of *n*-butyl nitrite was added through a serum cap and the solution was stirred under nitrogen overnight. The mixture was then diluted with water, extracted four times with ether, acidified with acetic acid, and extracted two times with methylene chloride. The aqueous layer was then saturated with sodium chloride and extracted eight times with ethyl acetate. The ethyl acetate extracts were combined, shaken with saturated sodium chloride solution, and dried over sodium sulfate. The solvent was removed under reduced pressure, and the yellow solid residue was evacuated at 0.2 mm for 2 hr; the yield was 76 mg (48%). The crude **16** did not crystallize readily, and it was purified by washing two times with a 1:4 methanol–ether solution, which removed almost all of the yellow color. The ir of this material showed characteristic absorptions at 1630, 1735, and 3560 cm^{-1}. The NMR (acetone-d_6) showed an AA′BB′ multiplet centered at δ 2.42 (4 H), an AB quartet centered at δ 3.04 (4 H, J = 20 Hz), and a broad peak at δ 3.2 (2 H) which disappeared upon shaking with D_2O.

Preparation of Bis(diazo) Diketone (17). Bis(oximino) diketone (**16**, 48 mg) was added to a flask containing 3 ml of water and cooled in an ice–water bath. Sodium hydroxide solution (0.5 ml, 1 N) was added, and the solution turned bright yellow in color. 0.070 ml of 15 N ammonium hydroxide was then added, followed by 1.7 ml of 5% sodium hypochlorite solution, added dropwise over a period of 15 min. After 1 hr the ice bath was removed. The mixture was allowed to stir at room temperature for 6 hr and then was extracted with five portions of methylene chloride (passed through basic alumina). The methylene chloride extracts were combined and the solvent was evaporated. The residue was a yellow solid, 2.5 mg (5% yield). The ir showed characteristic diazo, 2080 cm^{-1}, and carbonyl, 1660 cm^{-1}, absorptions. The NMR ($CDCl_3$) exhibited (inter alia) an AA′BB′ pattern centered at δ 2.48 and an AB quartet centered at δ 3.20 (J = 14 Hz).

Preparation of Cyclododecanetetr-1,4,7,10-one by Ozonolysis of 2. The ozonolysis was carried out as described above for **4**, except that sufficient CH_2Cl_2 was added to keep **2** in solution. An essentially quantitative yield of the product was obtained. After recrystallization from acetone it had mp 131–132° (lit.[26] mp 129–130), and its NMR and ir matched those described.[26]

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Registry No.—**1**, 14296-80-1; **2**, 6788-95-0; **3**, 27567-69-7; **4**, 28547-76-4; **5**, 28547-75-3; **6**, 27613-46-3; **8**, 27567-70-0; **9**, 27567-71-1; **10**, 55702-10-8; **11**, 55702-12-0; **13**, 55702-11-9; **14**, 55702-13-1; **16**, 55702-14-2; **17**, 55702-15-3; allene, 463-49-0; *n*-butyl nitrite, 544-16-1.

References and Notes

(1) (a) Address correspondence to this author at the Department of Chemistry, University of Washington, Seattle, Wash. 98195. (b) National Institutes of Health Postdoctoral Fellow, 1969–1970. (c) Summer Undergraduate Research Participant.
(2) Reviews: D. Ginsburg, *Acc. Chem. Res.*, **2**, 121 (1969); **5**, 249 (1972).
(3) W.-D. Stohrer and R. Hoffmann, *J. Am. Chem. Soc.*, **94**, 779 (1972); M. D. Newton and J. M. Schulman, *ibid.*, **94**, 4392 (1972); J. J. Dannenberg and T. M. Prociv, *J. Chem. Soc., Chem. Commun.*, 291 (1973).
(4) (a) P. E. Eaton and G. H. Temme, III, *J. Am. Chem. Soc.*, **95**, 7508 (1973); (b) P. E. Eaton and K. Nyi, *ibid.*, **93**, 2786 (1971).
(5) K. B. Wiberg, G. A. Epling, and M. Jason, *J. Am. Chem. Soc.*, **96**, 912 (1974).
(6) J. J. Dannenberg, T. M. Prociv, and C. Hutt, *J. Am. Chem. Soc.*, **96**, 913 (1974).
(7) Preliminary communication: W. T. Borden, I. L. Reich, L. A. Sharpe, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 3808 (1970).
(8) M. St. Jacques and M. Bernard, *Can. J. Chem.*, **47**, 2911 (1969).
(9) W. T. Borden, L. A. Sharpe, and I. L. Reich, *Chem. Commun.*, 461 (1970).
(10) A. C. Cope, *Q. Rev., Chem. Soc.*, **20**, 119 (1966).
(11) Subsequent to the appearance of our preliminary communication, Eaton and Nyi[4b] reported the preparation of this compound by photoaddition of ethylene to derivatives of bicyclo[3.3.0]oct-1(5)-ene-2,6-dione.
(12) A. T. Bloomquist and J. A. Verdol, *J. Am. Chem. Soc.*, **78**, 109 (1956).
(13) This procedure is similar to one described by J. Heller, "Catch 22", Dell Publishing Co., New York, N.Y., 1974, p 10.
(14) G. Wilke, *Angew. Chem., Int. Ed. Engl.*, **2**, 105 (1963)
(15) P. Heimbach, private communication, July 17, 1970.
(16) Review: N. J. Turro, "Molecular Photochemistry", W. A. Benjamin, New York, N.Y., 1965, pp 212–216.
(17) G. S. Hammond, N. J. Turro, and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961).
(18) R. L. Cargill, private communication, March 20, 1970.
(19) R. L. Cargill, J. R. Damewood, and M. M. Cooper, *J. Am. Chem. Soc.*, **88**, 1330 (1966).
(20) G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 4025 (1955).
(21) D. E. Applequist and R. Searle, *J. Am. Chem. Soc.*, **86**, 1389 (1964).
(22) See, for example, ref 16, pp 224–227.
(23) For relevant examples of and leading references to this method of ring contraction see ref 4.
(24) M. P. Cava, R. L. Little, and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2257 (1958).
(25) We thank Professor Eaton for sending us a preprint prior to publication.
(26) H. H. Wasserman and D. T. Bailey, *Chem. Commun.*, 107 (1970).
(27) W. W. Paudler and E. A. Stephan, *J. Am. Chem. Soc.*, **92**, 4468 (1970).
(28) H.-G. Fritz, H. Henke, and H. Musso, *Chem. Ber.*, **107**, 3164 (1974).
(29) Relative amounts of products, as measured by GLC, were not corrected for differences in response of the thermal conductivity detector used.

7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dione and Its Radical Anion. An Experimental and Theoretical Study

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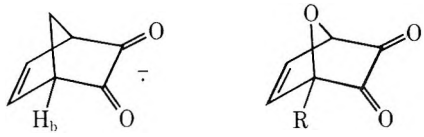
The synthesis of 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dione (**2a**) and its 1-methyl derivative is described. Electrolytic reduction of **2a** gives its radical anion which has a large bridgehead hydrogen coupling of 2.48 G. Using the INDO method with a MINDO/2′ optimized geometry, spin densities for **2a**·⁻ are calculated and partitioned into their spin polarization and spin delocalization components. Mechanisms for the interaction of the vinyl and bridgehead hydrogens in **2a**·⁻ with the unpaired electron are discussed based on the spin partitioning calculation.

There has been considerable interest in studying the delocalization of the unpaired electron in rigid, strained systems using semidione,[2] semifuraquinone,[3] and semiquinone[4] radical anions as spin labels. Recently, we reported long-range coupling in the radical anion of bicyclo[2.2.1]hept-5-ene-2,3-dione (**1**) and two of its derivatives.[5] Since the hyperfine splitting constants (hfsc's) of the bridgehead (H_b) and vinyl hydrogens of these radical anions appeared to be somewhat sensitive to changes in geometry, we decided to examine what effect the introduction of a heteroatom at the 7 position would have on these couplings. We now report the synthesis of 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dione (**2a**) and its radical anion.

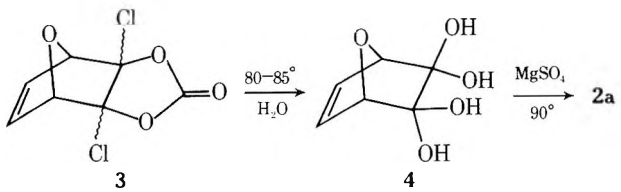


1 **2**

a, R = H
b. R = CH_3

Results and Discussion

Synthesis of 2a·⁻ and 2b·⁻. Our method of preparing **2a** was based on a recent report that hydrolysis of dichlorovinylene carbonate adducts produces α-diketones.[6] Thus, a 4:1 mole ratio of dichlorovinylene carbonate to furan was heated at 120° in a sealed glass tube for 20 hr to give a 57% yield of the endo and exo furan adducts (**3**). Hydrolysis of these adducts in 50% aqueous *p*-dioxane gave the dihydrate **4**, which is surprisingly stable at room temperature. Upon heating **4** in *p*-dioxane at 90° in the presence of $MgSO_4$, the diketone **2a** was obtained. When exposed to moist air, **2a** immediately formed a mixture of its monohydrate with a small amount of **4**. An attempt to prepare the

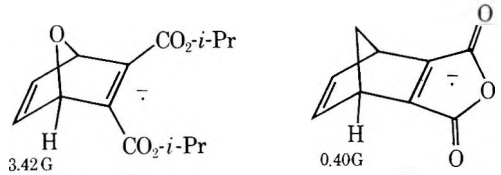


3 **4**

sulfur and nitrogen analogs of **2a** by the same route was unsuccessful. Both thiophene and pyrrole failed to give Diels–Alder adducts with dichlorovinylene carbonate.

Electrolytic reduction of **2a** or **3** (in DMSO with *n*-Bu_4NClO_4 as supporting electrolyte) produced an ESR spectrum consisting of a triplet of triplets with a^H = 2.48 (2 H) and 0.81 G (2 H). No signal could be detected 30 sec after the current was terminated. Treatment of **2a** with a DMSO solution of the enolate anion of propiophenone[7a] under flow conditions[7b] or with a hexamethylphosphoramide solution of sodium failed to give an ESR spectrum of **2a**·⁻. Methyl labeling was used to assign the splittings in **2a**·⁻. Electrolytic reduction of **2b** produced an ESR spectrum with a^H = 2.43 (1 H), 0.75 (2 H), and 0.16 G (3 H), which is consistent with the 2.48-G splitting in **2a**·⁻ arising from the bridgehead hydrogens.

The bridgehead coupling of 2.48 G in **2a**·⁻ is considerably larger than the 1.04-G coupling observed for the bridgehead hydrogen in **1**.[5] A similar trend has also been reported by Nelsen and coworkers for the bridgehead hydrogens in **5** and **6** where splittings of 3.42 and 0.40 G were found, re-



5 **6**

spectively.[3] These authors suggested that the enhanced bridgehead splitting in **5** is not simply the result of geometrical changes but that significant spin density is present at the oxygen.

The Optimized Geometry of 2a·⁻. Since there is no experimental structural data available for **2a**·⁻, the choice of geometry for this radical anion is significant in the evaluation of the sign and magnitude of the spin polarization (SP) and spin delocalization (SD) contributions to the resultant spin density. MINDO/2′ [8] (half-electron method[9]) has been quite reliable in predicting the heat of formation and equilibrium geometry of hydrocarbons. We performed the Simplex[10] optimization to locate the energy-minimized equilibrium geometry with respect to the heat of formation (see Experimental Section for details). The optimized geometry of **2a**·⁻ is shown in Figure 1.

Owing to the high cost of computer time, we did not optimize the geometry of the neutral diketone **2a**. It is reasonable to assume that the major geometrical differences between **2a** and **2a**·⁻ are in the C_2–O_{12} (C_3–O_{13}) and C_2–C_3 bond lengths.[11] A comparison between the HOMO Ψ_2 of **2a** with the HOMO Ψ_3 of **2a**·⁻ leads one to conclude that in **2a**·⁻ the C_2–O_{12}(C_3–O_{13}) bond length would be longer and the C_2–C_3 bond length would be shorter.

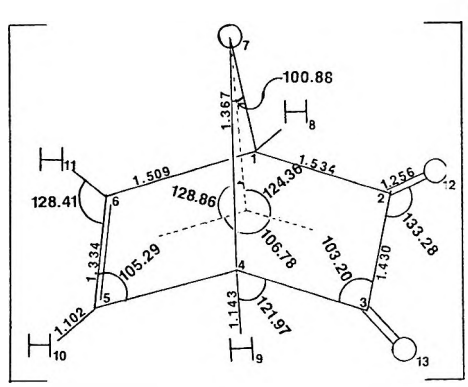
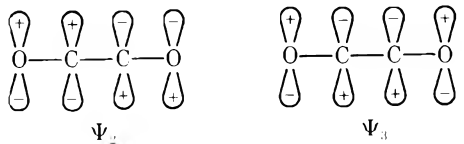


Figure 1. MINDO/2′ optimized geometry of **2a**·⁻. Nonbonded distance 1–4 = 2.130 Å. Dihedral angle (8,1,2,12) is 18.46°.



Although MINDO/2′ (half-electron method) tends to underestimate the C_1–O_7 (C_4–O_7) bond length by ~0.05 Å and the C_2–O_{12} (C_3–O_{13}) bond length by ~0.02 Å,[13] it does indicate that the interaction between the ethylenic and semidione π systems in **2a**·⁻ is slightly greater than the interaction between the two ethylenic π systems in norbornadiene (the bond angle θ^{12} in the optimized geometry of **2a**·⁻ is 106.78° compared to 115.00° for the same angle in norbornadiene[14]). The C_1–C_4 nonbonded distance in **2a**·⁻ (Table I) is ~0.1 Å shorter than its hydrocarbon analog **1**.[15]

Table I
Bond Lengths (Å) of 2a·⁻ and Norbornadiene

Bond	2a·⁻ Standard	2a·⁻ Optimized	Norbornadiene[b]
C_2–C_3	1.460	1.430	
C_2–C_{12}(C_3–O_{13})	1.220	1.256	
C_1–C_2(C_3–C_4)	1.515	1.534	1.538
C_1–C_6(C_4–C_5)	1.515	1.509	1.538
C_1–O_7(C_4–O_7)	1.430	1.367	
C_5–C_6	1.340	1.334	1.339
C_1–C_4[c]		2.130	
C_4–H_9(C_1–H_8)	1.090	1.143	1.100
C_6–H_{11}(C_5–H_{10})	1.080	1.102	1.098

[a] Reference 16. [b] Reference 14. [c] Nonbonded distance.

INDO Calculation of Spin Densities for 2a·⁻. The INDO (UHF)[17] s-orbital spin density was partitioned into spin polarization[18] and spin delocalization[19] components to elucidate the mechanism of hyperfine interaction in the open shell system. Previous work in UHF spin partitioning has been published by Kato and coworkers.[20] The isotropic hfsc's were calculated using the equation

$$a^n \cong A^n\rho_n \qquad (1)$$

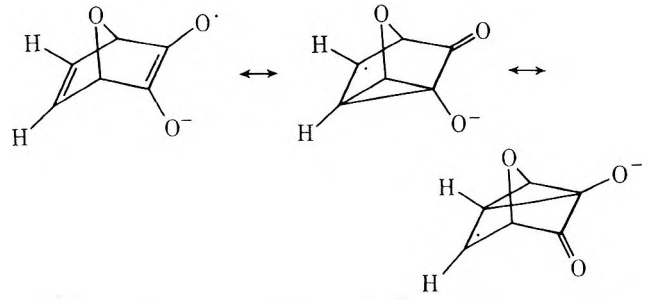
where A^n was evaluated by the direct parametization scheme, proposed recently,[21] and ρ_n is the INDO s-orbital spin density. Based on the MINDO/2′ optimized geometry (with a slight modification of the C–O and C=O bond lengths[13]), we obtained the values given in Table II.

It is apparent that spin density is transferred to C_5 and C_6 by overlap of the semidione and ethylenic π systems. This 1,3-π orbital overlap (homohyperconjugation) has been previously postulated in unsaturated bicyclic systems.[5b,22] The interaction places spin density on C_5 and C_6

Table II
INDO Calculation of Hfsc's for 2a·⁻

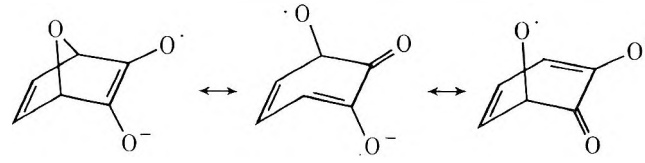
Atom no.	Element	Spin density	SP, G	SD, G	Hfsc, G[a]
1, 4	^{13}C	−0.0021	−2.346	+0.005	−2.341
2, 3	^{13}C	−0.0011	−1.417	+0.218	−1.199
12,13	^{17}O	+0.0094	−15.537	−0.002	−15.539[b]
7	^{17}O	+0.0026	−0.818	−3.415	−4.233
5, 6	^{13}C	+0.0026	−4.024	+6.895	+2.871
8, 9	^{1}H	+0.0034	−0.767	+3.781	+3.014
10, 11	^{1}H	−0.0016	−1.558	+0.126	−1.432

[a] SP + SD. [b] Note that A^n for ^{17}O in eq 1 is negative.

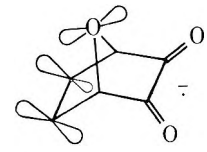


which can then be transmitted to H_{10} and H_{11} by spin polarization. Our spin partitioning calculation fully supports this mechanism (+6.895 G contribution); however, spin polarization to C_5 and C_6 from C_3 and C_2, respectively, cannot be neglected (−4.024 G contribution).

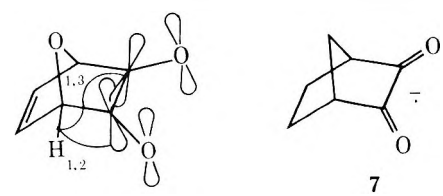
Although positive spin density is transmitted to O_7 by *both* spin polarization and spin delocalization, the latter predominates through a homohyperconjugation interaction.[22a,23] One cannot exclude the possibility of overlap of the back lobe of an oxygen sp^3 orbital with the ethylenic π



system which would be facilitated by the size of the oxygen and its proximity to the ethylenic π orbitals as is found in **2a**·⁻.



Two mechanisms also appear to be operative in the hfs of H_8 and H_9. Spin polarization induced by the negative spin densities at C_1 and C_4 seems to be less important than 1,2-hyperconjugation and 1,3-homohyperconjugation[5b] of the spin label with the C–H bond. A comparison of our spin-partitioning calculation for **2a**·⁻ with an equivalent calcula-



7

tion for **1** and **7**[5b,24] reveals that the spin polarization contribution to the hfs's of the bridgehead hydrogens in these radical anions varies little. Since negative spin polarization contributions indicate a direct through space interaction

mechanism, it is apparent that the spin polarization contribution from O_7 to H_8 and H_9 is not very significant. Interestingly, the hfs's of the bridgehead hydrogens of **1** and **7** are 1.04 and 2.49 G, respectively, which shows that an enhancement of coupling at this position is possible with a change in geometry alone. We conclude, therefore, that the large hfs of the bridgehead hydrogens in **2a**$\cdot^-$ relative to **1** results primarily from changes in geometry rather than an electronic effect of O_7. It seems likely that this is also true for **5**, although the symmetry plane which bisects the HOMO of the spin label is different in **5** than in **2a**$\cdot^-$.[2]

Experimental Section

ESR Spectra. The spectra were recorded in dimethyl sulfoxide (distilled from CaH_2) using a Varian Associates V-4502 spectrometer.

Computational Method. The MO calculation is based on the following steps. (A) After inputting the initial geometrical parameters, the MINDO/2'[25] wave function is built from monoelectronic MO's obtained by linear combination of a basis set of AO's (LCAO). (B) For n geometrical parameters to be optimized, $n - 1$ vertices are constructed and wave functions at each of the $n + 1$ vertices are solved for self-consistency (i.e., for the best possible LCAO with respect to the total energy). (C) Inherent in the standard direct search Simplex[10] method[26] is the procedure of reflection, expansion, and contraction (REC) of the initial vertices with respect to the centroid (center of gravity) of the remaining vertices. (D) The procedure of REC is repeated iteratively until tests (mean square deviation of geometrical parameters and the heat of atomization) show that the calculation converges to the point which represents the true equilibrium geometry. (E) From the set of optimized geometrical parameters, spin properties of the molecule in question are computed by the INDO method.

Preparation of 3. A sealed tube containing a solution of 35 g of dichlorovinylene carbonate[6] and 4.0 g of freshly distilled furan was heated at 120° for 20 hr. The resulting solution was cooled and the excess carbonate was removed by distillation [60–61° (30 mm)] giving a thick paste. Chromatography of this material on silica gel followed by elution with benzene–ethyl acetate (95:5) gave a light yellow solution of the endo and exo isomers which was decolorized with Norit. Removal of solvent in a rotatory evaporator gave 5.72 g of a white solid (57% yield of the combined isomers).

Separation of the endo and exo adducts could be achieved by recrystallization from ether. The adduct formed in smaller amounts (38%) recrystallized first: mp 177–179°; ir (KBr) 1870 cm^{-1} (C=O); NMR (acetone-d_6) δ 5.53 (t, 1, J = 2.3 Hz) and 6.87 (t, 1, J = 2.3 Hz); mass spectrum (70 eV) m/e 222 (parent), 154, 68 (base).

Anal. Calcd for $C_7H_4Cl_2O_4$: C, 37.70; H, 1.81. Found: C, 37.81; H, 1.73.

The adduct formed in larger amounts (62%) recrystallized next: mp 112–114°; ir (KBr) 1874 cm^{-1} (C=O); NMR (acetone-d_6) δ 5.47 (t, 1, J = 2.3 Hz) and 6.70 (t, 1, J = 2.3 Hz); mass spectrum (70 eV) m/e 222 (parent), 154, 68 (base).

Anal. Calcd for $C_7H_4Cl_2O_4$: C, 37.70; H, 1.81. Found: C, 37.78; H, 1.84.

Hydrolysis of 3. A mixture of the endo and exo adducts (2.5 g) was added to a solution of 50 ml of H_2O and 50 ml of p-dioxane. The mixture was heated to 80–85° for 1 hr, during which time the solid completely dissolved, giving a light yellow solution. Upon cooling in ice–water, the solution became colorless and the pH of the solution was then adjusted to ~4.5 with the careful addition of $NaHCO_3$. Removal of the solvent under reduced pressure in a rotatory evaporator gave a white solid consisting of **4** and NaCl which was used directly to prepare **2a**. Small amounts of pure **4**, however, could be obtained by adding the mixture of **4** and NaCl to boiling acetone, filtering, and cooling to −10°. Colorless crystals of **4** were formed: mp 94–95° (crystals turned yellow at ~90°); ir (KBr) 3235 (OH) and 1084 cm^{-1} (C–O); NMR (DMSO-d_6) δ 6.30 (t, 1, J = 2.0 Hz), 4.42 (t, 1, J = 2.0 Hz), and 4.6–5.9 (broad s, 2); mass spectrum (20 eV) m/e 142 (P − H_2O), 141, 124 (P − $2H_2O$), 123 (base), 68.

Anal. Calcd for $C_6H_8O_5$: C, 45.00; H, 5.04. Found: C, 45.25; H, 5.10.

Preparation of 7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dione (2a). The above mixture of NaCl and **4** was introduced into a Schlenck tube containing 50 ml of p-dioxane (distilled from CaH_2) and 3 g of $MgSO_4$. While stirring the mixture was heated at 80–90° for 1 hr, resulting in the formation of a deeply orange solution. The mixture was transferred to a second Schlenk tube (fitted with a filter) attached to a simple distillation apparatus which had been evacuated and filled with nitrogen several times. The orange solution was then filtered into the distillation apparatus and the p-dioxane was removed under reduced pressure, giving a red liquid. The pressure was further reduced to ~1 mm and **2a** distilled at ~70°, giving 1.15 g of red crystals (82% yield from **3**); mp 64–66°; ir ($CDCl_3$) 1780 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.94 (t, 2, J = 1.0 Hz) and 6.83 (t, 2, J = 1.0 Hz).

Anal. Calcd for $C_6H_4O_3$: C, 58.07; H, 3.25. Found: C, 58.36; H, 3.68.

It was necessary to keep **2a** under a dry atmosphere since exposure to moist air resulted in the rapid formation of a white solid consisting of its monohydrate and **4**.

1-Methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dione (2b) was prepared by the method described for **2a**. Reaction of 2-methylfuran with dichlorovinylene carbonate gave a 58% yield of endo and exo adducts. Only one of these adducts, the one that recrystallized first from ether, could be obtained pure: mp 94–96°; ir 1845 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.72 (s, 3), 5.14 (d, 1, J = 2.0 Hz), 6.36 (d, 1, J = 6.0 Hz), and 6.53 (q, 1, J = 2.0 and 6.0 Hz).

Anal. Calcd for $C_8H_6Cl_2O_4$: C, 40.54; H, 2.55. Found: C, 40.66; H, 2.80.

Hydrolysis of 3.0 g of a mixture of these adducts in aqueous p-dioxane followed by dehydration in p-dioxane and $MgSO_4$ gave **2b** as red crystals: mp 30–33°; ir ($CDCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 3), 4.93 (d, 1, J = 2.0 Hz), 6.57 (d, 1, J = 5.5 Hz), and 6.87 (q, 1, J = 2.0 and 5.5 Hz).

Anal. Calcd for $C_7H_6O_3$: C, 60.87; H, 4.38. Found: C, 61.32; H, 4.70.

Acknowledgment. Computer time was generously provided by the University of Wisconsin—Oshkosh. We wish to thank Drs. M. F. Chiu, D. H. Lo, C. A. Ramsden, and M. J. S. Dewar for assistance on the MO calculation. The authors would also like to thank Professor Glen A. Russell for communicating some of his unpublished results, and Mr. Gregory Kulibert for his assistance in the synthesis of **3**.

Registry No.—**2a**, 55058-68-9; **2a** radical ion, 55058-69-0; **2b**, 55058-70-3; **2b** radical ion, 55058-71-4; **2b** endo adduct, 55058-72-5; **2b** exo adduct, 55102-63-1; *endo*-**3**, 55058-73-6; exo-**3**, 55102-64-2; **4**, 55058-74-7; dichlorovinylene carbonate, 17994-23-9; furan, 110-00-9; 2-methylfuran, 534-22-5.

References and Notes

(1) Supported in part by grants from the Research Corporation while at Wake Forest University and the Duncan Research Fund while at the University of Wisconsin—Oshkosh.
(2) G. A. Russell, K. D. Schmitt, and J. Mattox, *J. Am. Chem. Soc.*, **97**, 1882 (1975), and references cited therein.
(3) S. F. Nelsen and E. T. Travecedo, *Tetrahedron Lett.*, 2685 (1969); S. F. Nelsen, E. F. Travecedo, and E. D. Seppanen, *J. Am. Chem. Soc.*, **93**, 2913 (1971).
(4) D. Kosman and L. M. Stock, *J. Am. Chem. Soc.*, **91**, 2011 (1969), and references cited therein.
(5) (a) R. L. Blankespoor, *J. Am. Chem. Soc.*, **96**, 6196 (1974); (b) G. A. Russell, G. W. Holland, K.-Y. Chang, R. G. Keske, J. Mattox, C. S. C. Chung, K. Stanley, K. Schmitt, R. L. Blankespoor, and Y. Kosugi, *ibid.*, **96**, 7237 (1974).
(6) H.-D. Scharf, W. Droste, and R. Liebig, *Angew. Chem., Int. Ed. Engl.*, **7**, 215 (1968).
(7) (a) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 1807 (1964); (b) G. A. Russell and R. L. Blankespoor, *Tetrahedron Lett.*, 4573 (1971).
(8) QCPE No. 228, Indiana University, Bloomington, Ind.
(9) M. J. S. Dewar, J. A. Hashmall, and C. G. Venier, *J. Am. Chem. Soc.*, **90**, 1953 (1968).
(10) A simplex is an n-dimensional analog of a triangle or of a tetrahedron. The only properties of simplices required for this optimization procedure are that any n-dimensional simplex has $n + 1$ vertices and $n + 1$ ($n - 1$)-dimensional hyperfaces, and that any m-dimensional hyperface is itself a m-dimensional simplex. In addition, there are two other properties of simplex. First, every simplex has $\frac{1}{2}n(n + 1)$ edges (There are $n + 1$ vertices, each of which can pair up with one of n others. This counts each edge twice, hence the factor of $\frac{1}{2}$). Second, given any vertex as origin, the set of vectors, $\mathbf{Q}_i - \mathbf{Q}_o$ (where $\mathbf{Q}_i$ and $\mathbf{Q}_o$ (where $\mathbf{Q}_i$ and $\mathbf{Q}_o$ are vectors corresponding to the vertix i and the origin, respectively) form a basis for the n-dimensional space in which the simplex lies.
(11) A change in the C_2–C_3 bond length from **2a** to **2a**$\cdot^-$ would likely affect the amount of strain present and result in a change of the angle θ.[12] The hfs's of the vinyl and bridgehead hydrogens are sensitive to changes in θ.
(12) Angle between planes C_1–C_2–C_3–C_4 and C_1–C_4–C_5–C_6.

(13) This is one of the artifacts of MINDO/2′: unpublished result of G. A. Russell and C. S. C. Chung, 1974, after thorough testing and comparison with both experimental structural data and ab initio MO calculations [with extended basis set (e.g., 4-31G)]. The optimized geometry of **2a**·⁻ was modified accordingly.
(14) G. Dallinga and L. H. Toneman, *Recl. Trav. Chim. Pays-Bas*, **87**, 805 (1968), and references cited therein.
(15) Based on the MINDO/2′ optimized geometry of **1**, unpublished results of G. A. Russell, C. S. C. Chung, and R. L. Blankespoor, 1974.
(16) J. A. Pople and D. L. Beveridge, "Approximate MO Theory", McGraw-Hill, New York, N.Y., 1970.
(17) (a) J. A. Pople and R. K. Nesbet, *J. Chem. Phys.*, **22**, 571 (1954); (b) J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Am. Chem. Soc.*, **90**, 4201 (1968); QCPE No. 141, Indiana University, Bloomington, Ind.
(18) The definition of spin polarization is the same as suggested by J. P. Copla, E. de Boer, D. Lazdins, and M. Karplus, *J. Chem. Phys.*, **47**, 3098 (1967).
(19) G. A. Russell and C. S. C. Chung, *Mol. Phys.*, in preparation.
(20) H. Nakatsuji, H. Kato, and T. Yonezawa, *J. Chem. Phys.*, **51**, 3175 (1969), and references cited therein.
(21) M. F. Chiu, B. C. Gilbert, and B. T. Sutcliffe, *J. Phys. Chem.*, **76**, 553 (1972).
(22) (a) G. A. Russell, G. W. Holland, and K.-Y. Chang, *J. Am. Chem. Soc.*, **89**, 6629 (1967); (b) S. F. Nelsen and E. D. Seppanen, *ibid.*, **89**, 5740 (1967); (c) D. Kosman and L. M. Stock, *Chem. Commun.*, 551 (1968).
(23) G. A. Russell, G. W. Holland, K.-Y. Chang, and L. H. Zalkow, *Tetrahedron Lett.*, 1955 (1967).
(24) G. A. Russell and C. S. C. Chung, to be published.
(25) A. Brown, M. J. S. Dewar, H. Metiu, P. Student, and J. Wasson, *Proc. R. Soc., London*, to be published.
(26) (a) J. A. Nelder and R. Mead, *Comput. J.*, **7**, 308 (1964); (b) R. O'Neill, *Appl. Stat.*, **20**, 338 (1971); (c) private communication with P. W. Dillon and G. R. Underwood; (d) W. Boekelheide, J. N. Murrell, and W. Schmidt, *Tetrahedron Lett.*, 575 (1972).

The Chemistry of Polyunsaturated Bicyclo[4.2.2]decyl Systems

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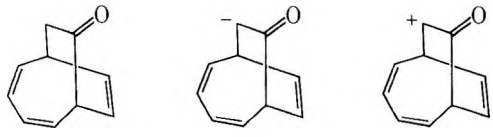
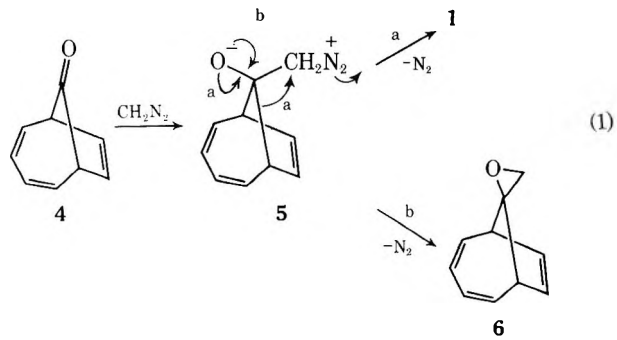
Bicyclo[4.2.2]deca-2,4,9-trien-7-one (**1**, 50–85%) and spiro[bicyclo[4.2.1]nona-2,4,7-trien-9,2′-oxirane] (**6**, 15–50%) result from reaction of bicyclo[4.2.1]nona-2,4,7-trien-9-one (**1**) and diazomethane. Bicyclo[4.2.2]deca-2,4,9-trien-7-one tosylhydrazone (**7**) is converted by methyllithium to bicyclo[4.2.2]deca-2,4,7,9-tetraene (**8**, 78%), *cis*-9,10-dihydronaphthalene (**9**, <1%), and naphthalene (5%). 7-Acetoxy- (**10**) and 7-pyrrolidinobicyclo[4.2.2]deca-2,4,7,9-tetraenes (**11**) are formed in excellent yields from acid-catalyzed reactions of **1** with isopropenyl acetate and pyrrolidine, respectively. Bases convert **1** to bicyclo[4.2.2]deca-2,4,9-trien-7-one enolate (**2**); **2** reacts with deuterium oxide to give *anti*-8-deuteriobicyclo[4.2.2]deca-2,4,9-trien-7-one (**13**), which is then converted to 8,8-dideuteriobicyclo[4.2.2]deca-2,4,9-trien-7-one (**15**) upon much longer exposure to the basic deuterating medium. Enolate **2** reacts with acetyl chloride to yield **10** (85%) and with trimethylsilyl chloride to form 7-trimethylsiloxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**12**, 72%). Methylation of **2** in hexamethylphosphoramide or dimethylformamide at 0° produces 7-methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**16**, 92%); in glyme **16** (43%) and 8,8-dimethylbicyclo[4.2.2]deca-2,4,9-trien-7-one (**18**, 26%) are formed. Enolate **2** rearranges slowly to the β-tetralone anion and probably the anion of *cis*-9,10-dihydro-2-naphthol; secondary methylation products are 2-methoxy-3,4-dihydronaphthalene (**22**) and 2-methoxynaphthalene (**23**). Thermolysis of **16** gives naphthalene (66%) and **23** (33%). Enolate **2** reacts with isoamyl nitrite to produce bicyclo[4.2.2]deca-2,4,9-triene-7,8-dione monooxime (**32**, 63%) and with methyl formate to yield 8-formylbicyclo[4.2.2]deca-2,4,9-trien-7-one (**35**, 95%). Oxime **32** is converted to bicyclo[4.2.2]deca-2,4,9-triene-7,8-dionequinoxaline (**33**) by o-phenylenediamine; **35** and hydrazine give 3,4-diazatricyclo[5.4.2.$0^{2,6}$]trideca-2,5,8,10,12-pentaene (**36**). 8-Diazobicyclo[4.2.2]deca-2,4,9-trien-7-one (**37**, 55%) forms from **35**, tosyl azide, and triethylamine. Diazo ketone **37** photolyzes in dioxane–water to bicyclo[4.2.1]nona-2,4,7-triene-*syn*-9-carboxylic acid (**39**, 61%). Decomposition of **37** by acetic acid and by hydrogen chloride occurs with rearrangement to *exo*- and *endo*-2-acetoxybicyclo[5.2.1]deca-3,5,8-trien-10-ones (**43** and **44**), and *exo*-2-chlorobicyclo[5.2.1]deca-3,5,8-trien-10-one (**54**, 94%), respectively. Chloride **54** reacts with silver acetate yielding **43** (53%); hydrogenolysis of **54** produces bicyclo[5.2.1]decan-10-one (**56**, 61%). Hydrogenation of **43** gives *exo*-2-acetoxybicyclo[5.2.1]decan-10-one (**50**, 73%) which upon saponification and oxidation results in bicyclo[5.2.1]deca-2,10-dione (**52**, ~100%). Acetate **43** and chloride **54** rearrange to *endo*-6-(*cis*-2′-acetoxyvinyl)-*cis*-bicyclo[3.3.0]octa-3,7-dien-2-one (**58**, 93%) and *endo*-6-(*cis*-2′-chlorovinyl)-*cis*-bicyclo[3.3.0]octa-3,7-dien-2-one (**60**, 100%), respectively. Lead tetraacetate oxidizes **1** to *anti*-8-acetoxybicyclo[4.2.2]deca-2,4,9-trien-7-one (**64**, 100%). Attempted Wolff–Kishner reductions of bicyclo[4.2.2]deca-2,4,9-trien-7-one hydrazone (**66**) or the semicarbazone produce 2,3-diazatricyclo[6.3.1.$0^{4,11}$]dodeca-1,5,9-triene (**70**, 47–54%). 3-Methyl-2,3-diazatricyclo[6.3.1.$0^{4,11}$]dodeca-1,5,9-triene (**73**, 75%) is formed from **1** and methylhydrazine. Photolysis of **1** leads to tricyclo[3.3.2.$0^{2,8}$]deca-3,6-dien-9(10)-one (**78**, 68%), which reverts to **1** upon treatment with acid.

The properties and interconversions of C_{10} bicyclopolyunsaturated systems are subjects of intense interest.[2] We now describe the chemistry of bicyclo[4.2.2]deca-2,4,9-trien-7-one (**1**) and its derivatives, and the 8-ketobicyclo[4.2.2]deca-2,4,9-trien-7-yl carbanion (**2**) and carbonium ion (**3**).



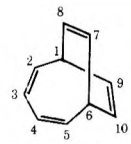
1 **2** **3**

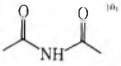
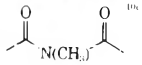
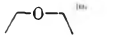
Ketone **1** (50–85%) along with spiro[bicyclo[4.2.1]nona-2,4,7-trien-9,2′-oxirane] (**6**, 15–50%) are obtained from reactions of bicyclo[4.2.1]nona-2,4,7-trien-9-one (**4**)[3a–c] with diazomethane and lithium chloride[3d] in methanol–chloroform–ether at 0°. Ketone **1** and epoxide **6** are presumably formed by nucleophilic approach of diazomethane



4 **5** **6** (1)

Table I
^{1}H NMR For Substituted Bicyclo[4.2.2]deca-2,4,7,9-tetraenes

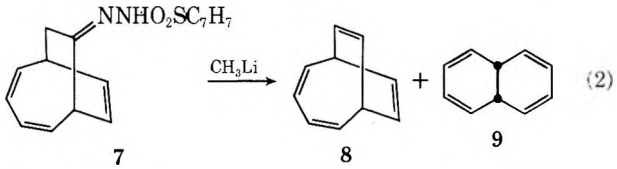


Substituent	^{1}H NMR, δ						
	$H_{2,5}$	$H_{3,4}$	H_7	H_8	$H_{9,10}$	$H_{1,6}$	H_5[a]
7-H (8)[b]	6.12	5.74		5.50	5.50	3.15	5.50
7-OAc (10)[b]	6.10	5.69		5.35	5.49	3.23	2.03
7-OSi$(CH_3)_3$ (12)	6.15	5.75		4.78	5.50	3.18	0.11
7-OCH_3 (16)[b]	6.10	5.65		4.50	5.48	3.20	3.40
7-$N(CH_2)_4$ (11)	6.15	5.80		4.15	5.55	3.40	3.00, 185
7-CH_3[11c]	6.4–5.7	6.4–5.7		5.28	5.5	3.07	1.74
7-Br[11b]	5.9	5.9		5.4	5.9	3.4, 3.1	
7-CO_2CH_3[11b]	5.8	5.8		6.7	5.8	3.8, 3.3	3.67
7,8-$(CO_2CH_3)_2$[10a]	6.18	5.86			5.67	3.70	
3,4- 	7.55		5.78	5.78	5.78	3.55–3.8	
3,4- 	6.50		4.75	4.75	4.75	2.3–2.7	
3,4- 	7.39		5.79	5.79	5.79	3.5–3.7	
3,4- 	6.10		5.69	5.69	5.69	3.1–3.3	

[a] Proton resonance of the substituent at C-7. [b] Proton assignments were based on double-irradiation experiments.

from the less hindered anti side of **4**, forming the zwitterionic intermediate **5**, which collapses to products (eq 1). Ketone **1** was obtained preparatively from the reaction mixture by (1) formation and separation of its semicarbazone and regeneration of **1** in pyruvic acid under argon at 25°, or, more advantageously, by (2) formation of the Girard's reagent T adduct and hydrolysis of the water-soluble intermediate. The structure of **1** was proven by its hydrogenation to bicyclo[4.2.2.]decan-7 one, which was prepared independently by ring expansion of bicyclo[4.2.1]nonan-9-one with diazomethane.[3b]

Ketone **1** is converted readily to bicyclo[4.2.2]deca-2,4,9-trien-7-one tosylhydrazone (**7**). Tosylhydrazone **7** is decomposed (eq 2) by methyllithium (4 equiv)[4] in hexane

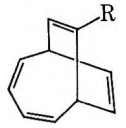


(2)

7 8 9

at 25° to bicyclo[4.2.2]deca-2,4,7,9-tetraene (**8**, 78%); *cis*-9,10-dihydronaphthalene (**9**, <1%), and naphthalene (5%) are also produced. This preparation of **8** is a more advantageous and rapid route than those previously reported.[2] Tetraenes **8** and **9** were identified by comparison to authentic samples.[5]

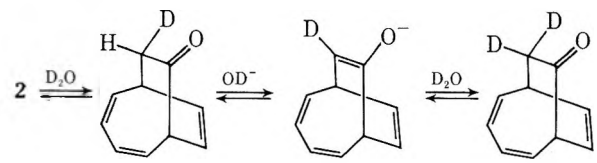
Ketone **1** provides a useful entry to 7-substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes via acid-catalyzed processes. Isopropenyl acetate reacts with **1** as accelerated by *p*-toluenesulfonic acid to give 7-acetoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**10**). Supportive data for the structure assigned as **10** include its ^{1}H NMR properties (Table I); double irradiation of the bridgehead multiplet at δ 3.23 causes simplification of the absorbances at δ 6.10, 5.49 (to s), and 5.35 (to s). The structure of **10** is confirmed by its acid-catalyzed hydrolysis to **1** (~100%).



10, R = OCCH$_3$
11, R = N
12, R = OSi$(CH_3)_3$

Acid-catalyzed condensation of **1** with pyrrolidine yields 7-pyrrolidinobicyclo[4.2.2]deca-2,4,7,9-tetraene (**11**), an extremely hygroscopic enamine. The structure of **11** is revealed by its ^{1}H NMR absorptions (Table I) and by its hydrolysis to **1** (100%).

Various bases convert **1** to its enolate ion (**2**). Enolate **2** undergoes facile monodeuteration. Thus treatment of **1** at 25–30° in carbon tetrachloride for 12 hr with deuterium oxide containing sodium deuteroxide yields *anti*-8-deuteriobicyclo[4.2.2]deca-2,4,9-trien-7-one (**13**, eq 3). The



(3)

13 14 15

stereochemical assignment of **13** is based upon deuteration from the less hindered anti side of **2**. Steric factors allow rapid monodeuteration as compared to slow dideuteration of **1**. Proton removal from **13** and thus deuteration of **13** via **14** to **15** are hindered processes. However, at relatively long exposure times (12 days) and using higher concentrations of sodium deuterioxide, **13** undergoes effective dideuteration to 8,8-dideuteriobicyclo[4.2.2]deca-2,4,9-trien-7-one

Table II
Product Distribution from Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Potassium *tert*-Butoxide and Methyl Fluorosulfonate in Polar Solvents

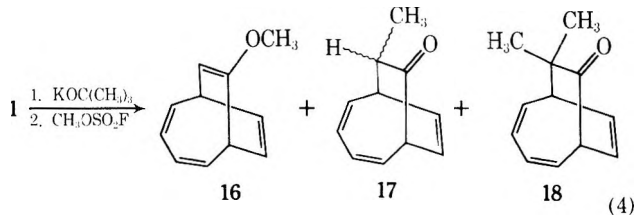
Potassium *tert*-butoxide, contact time,[a] 0-10°	Solvent	Product percentage 16	1	18	22	23
4 min[b]	Hexamethylphosphoramide	92.2	2.5	3.0	0.6	1.5
4 min	Dimethylformamide	93.0	3.1	2.8	0.2	0.9
14 min	Hexamethylphosphoramide	91.0	0.8	5.5	1.2	1.0
30 min	Dimethylformamide	82.0	7.1	1.0	5.5	2.6
12 hr	Dimethylformamide	72.0	1.0	1.0	7.4	16.0
24.5 hr	Dimethylformamide	60.0	3.5	1.5	10.0	12.0

[a] Typical reaction used 3 equiv of potassium *tert*-butoxide. [b] Average of seven reactions; see Table III.

(**15**). Dideuterio ketone **15** is prepared much more advantageously under more forcing conditions involving reaction of **2** with excess potassium *tert*-butoxide (≫2 equiv) in hexamethylphosphoramide, quenching with deuterium oxide, and neutralization with boron trifluoride etherate.

Enolization of **1** in basic media to **2** also allows synthesis of 7-substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes. Thus reaction of **1** with potassium *tert*-butoxide (2 equiv) in glyme (5 min) at 25° and then acetyl chloride gives acetoxytetraene **10** in 83% yield, recovered **1** (8%), and unidentified products (9%). 7-Trimethylsiloxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**12**, 72%) is obtained upon addition of trimethylsilyl chloride to **1** and potassium *tert*-butoxide in glyme. Silyl ether **12** is very sensitive to atmospheric moisture and its structure is assigned from its ir and ^{1}H NMR absorptions (Table I) and its hydrolysis to **1** (~100%).

A study has been made of methylation of **2**. Reaction of **1** with excess potassium *tert*-butoxide (~3 equiv) in glyme for 4 min at 25° and then rapid addition of methyl fluorosulfonate (3 equiv) gives the following products (eq 4) in the indicated yields: 7-methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**16**, 43%), recovered **1** (9.5%), 8-methylbicyclo-[4.2.2]deca-2,4,9-trien-7-one (**17**, ~1%),[6a] and 8,8-dimethylbicyclo[4.2.2]deca-2,4,9-trien-7-one (**18**, 26%)[6b] along with unidentified components (~20%) of higher retention times. All products were separated by preparative GLC.[7]

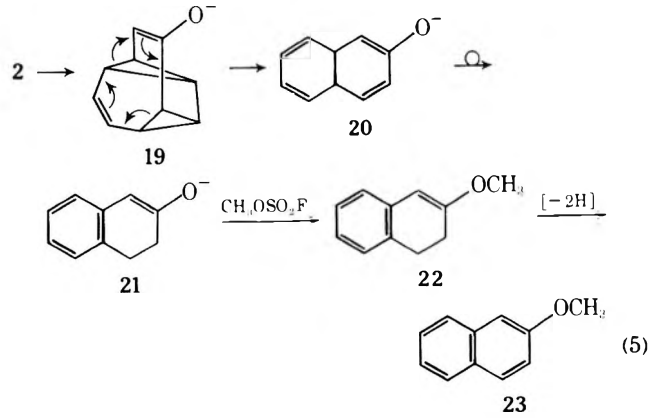


(4)

Purified methoxytetraene **16** is homogeneous upon GLC analysis; it does not rearrange or decompose during GLC treatment. The structure of **16** is partly assigned on the basis of its ^{1}H NMR absorptions (Table I) along with double-irradiation experiments; decoupling of bridgehead proton (C-1, -6) absorptions at δ 3.20 simplifies the resonances at δ 6.10, 5.48 (to s), and 4.50 (to s). The structure and the homogeneity of **16** are confirmed by hydrolysis of the sample to **1** (100%).

Methyl ketone **17** is difficult to separate from **1** and its presence in **1** is established by mass spectral analysis (*m/e* 160). Dimethyl ketone **18** exhibits carbonyl (1700 cm^{-1}) and *gem*-dimethyl (1380 and 1370 cm^{-1}) ir absorptions along with ^{1}H NMR and mass spectral properties consistent with the structural assignment.

Polar solvents enhance the efficiency of O-methylation of **2** to **16**. Thus when **1** is treated with potassium *tert*-butoxide (3 equiv) in hexamethylphosphoramide at 0–5° for 4 min followed by excess methyl fluorosulfonate (Table II), methoxytetraene **16** is formed in 92.2% average yield along with recovered **1** (2.5%), methyl ketone **17** (trace), dimethyl ketone **18** (3.0%), 2-methoxy-3,4-dihydronaphthalene[8] (**22**, 0.6%), and 2-methoxynaphthalene[8] (**23**, 1.5%). Similar results are obtained when methylation of **1** is effected in dimethylformamide at 0–5° (Table II). Methoxydihydronaphthalene (**22**) presumably results upon conversion of **1** to **19**, rearrangement to **20**, and then isomerization and methylation (eq 5, or/and methylation and isomerization). Oxidation, after rearrangement of **19**, in combination with methylation and isomerization accounts for formation of **23**.



(5)

After it had been communicated by us[1b] that **1** (a) undergoes efficient base-catalyzed deuterium exchange to **13** and **15**, (b) reacts with potassium *tert*-butoxide (3 equiv) in hexamethylphosphoramide at 5° for 4 min and then excess methyl fluorosulfonate to give **16** as isolated in 93–95% yield, and (c) is converted by potassium *tert*-butoxide (3 equiv, 3 min) in glyme at 20° and then acetyl chloride to **10** in 83% yield (>90% efficiency), Goldstein and Klein[9] reported that reaction of **1** with potassium *tert*-butoxide in dimethyl sulfoxide or dimethylformamide at 0–10° and then dimethyl sulfate gives **16** seriously contaminated with **22** as derived by rapid isomerization of **2** to **20** and its subsequent methylation. These authors state[9] that (1) methylation of **1** was effected under "closely similar conditions" to those communicated by us; (2) no evidence was provided concerning the homogeneity or the proof of structure of the **16** in our prior report;[1b] (3) if **1** is exposed to potassium *tert*-butoxide at 0–10° for as long as 20 min and then dimethyl sulfate is added, only **22** is obtained (and thus, presumably, during the basic treatment, **2** is isomerized completely to **20**), and (4) their most efficient preparative procedure for methylation of **1** gives **22** in only 40% efficiency even "under conditions of deliberately incomplete deprotonation of **1**".

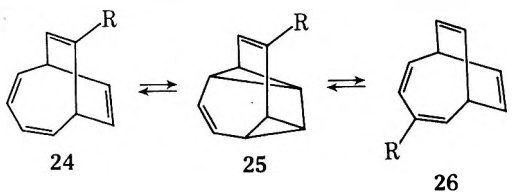
We should like to emphasize presently that **16** is pro-

Table III
Product Distribution from Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Potassium *tert*-Butoxide and Methyl Fluorosulfonate in Hexamethylphosphoramide

	Product percentage				
Trial	16	1	18	22	23
1	95.0	4.0	1.0		
2	92.0	5.0	1.5		1.5
3	91.0	3.0	2.9		3.1
4	90.0	1.5	6.1	1.7	1.0
5	93.0	1.0	3.0	1.0	2.0
6	92.0	1.0	5.1	0.7	1.2
7	93.0	2.3	1.8	1.1	1.8
Average	92.2	2.5	3.0	0.6	1.5

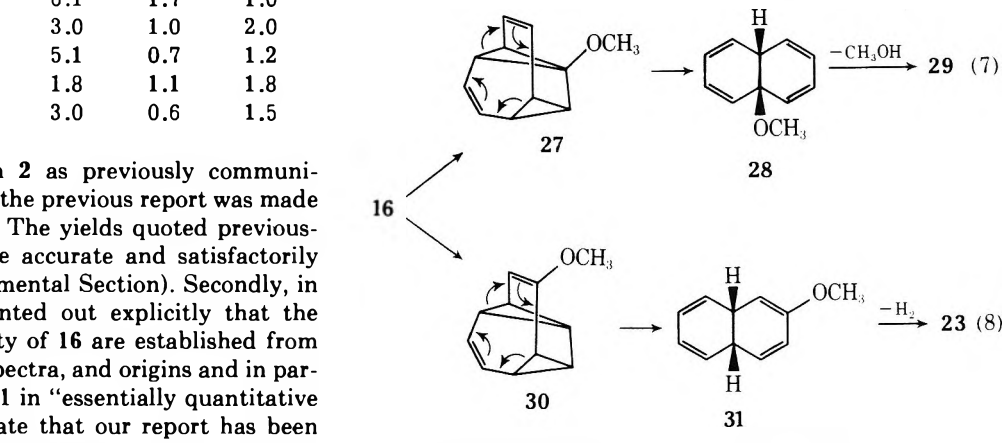
duced in 93–95% yield from **2** as previously communicated.[1b] The data from which the previous report was made are summarized in Table III. The yields quoted previously[1b] and as now repeated are accurate and satisfactorily reproducible (also see Experimental Section). Secondly, in our publication[1b] it was pointed out explicitly that the structure and the homogeneity of **16** are established from its analysis, ir and ^{1}H NMR spectra, and origins and in particular from its hydrolysis to **1** in "essentially quantitative yield". It is indeed unfortunate that our report has been misrepresented. Thirdly, enolate **2**, though generated essentially quantitatively, rearranges slowly. When the methylations with methyl fluorosulfonate are run after increased contact times of **1** with potassium *tert*-butoxide, there is a decrease in the yield of methoxytetraene **16** and a concomitant increase in the by-products obtained (Table II). After contact of **2** with potassium *tert*-butoxide for 24.5 hr at 0° and then methylation, the major product is still tetraene **16** (60%) but now significant amounts of methyl ether **22** (10%) and methoxynaphthalene **23** (12%) are formed. During our study of the methylation of enolate **1**, **22** and **23** were never formed as major reaction products. Further, enolate **1**, as generated using a twofold excess of potassium *tert*-butoxide in dimethylformamide at 0° for 0.5 hr, gives ketone **1** (92%) upon quenching with water; no β-tetralone is obtained under conditions where >2% could be detected. Under the conditions of the preparative experiments presently described, rapid rearrangement of **2** to **20** is not observed.

A subject of particular interest in the present research is that the 7-substituted tetraenes **10**, **11**, **12**, and **16** (represented as **24**), as prepared initially or upon gas chromatography at elevated temperatures, might isomerize (rapidly) to 3-substituted bicyclo[4.2.2]decatetraenes (**26**) via internal addition (internal Diels–Alder reaction) to **25** and opening (retro Diels–Alder reaction) as do analogous tetraenes[10] (eq 6). Tetraenes **10**, **11**, **12**, and **16** upon preparation (as previously described) and **10**, **12**, and **16** after gas chromatography at temperatures up to 200° hydrolyze quantitatively to **1**, and thus, under the indicated conditions, they do not rearrange to their corresponding 3-substituted bicyclo[4.2.2]decatetraenes (eq 6).[11]

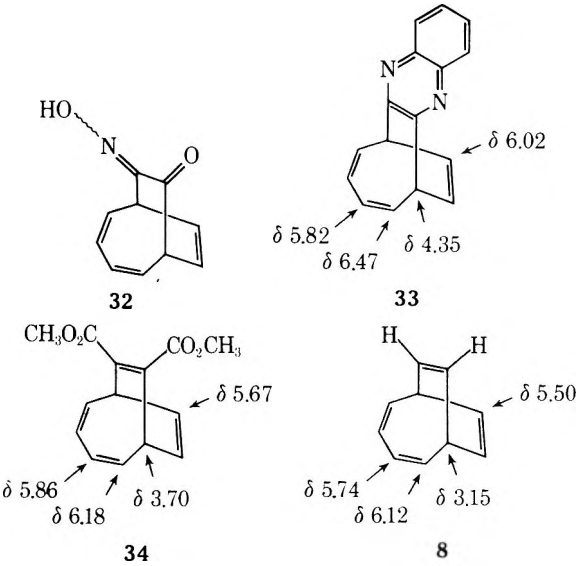


24 25 26 (6)

Methoxytetraene **16** displays expected thermal behavior, however, after extended exposure to elevated temperatures. Thus when **16** is heated for 0.5 hr at 200° in hexamethylphosphoramide, naphthalene (**29**, 17%) and 2-methoxynaphthalene (**23**, 10%) are obtained along with unrearranged **16** (73%). Heating **16** neat in a sealed evacuated tube for 21 hr at 200° gives methanol, **29** (59%), **23** (30%), and recovered **16** (11%). Thermolysis of **16** probably occurs via allowed internal Diels–Alder reactions (**27** and **30**, eq 7 and 8) and subsequent disallowed openings to *cis*-9,10-dihydronaphthalene derivatives (**28** and **31**) which then aromatize. The sequence in eq 7 is favored over that in eq 8 by about 2:1; the reasons for this difference are not clear.



Base-catalyzed enolization of **1** provides for further functionalization at C-8. Reaction of potassium *tert*-butoxide and isoamyl nitrite[12] with **1** in *tert*-butyl alcohol gives bicyclo[4.2.2]deca-2,4,9-triene-7,8-dione monoxime (**32**, 63%), which is converted by o-phenylenediamine in acetic acid to bicyclo[4.2.2]deca-2,4,9-triene-7,8-dionequinoxaline (**33**).

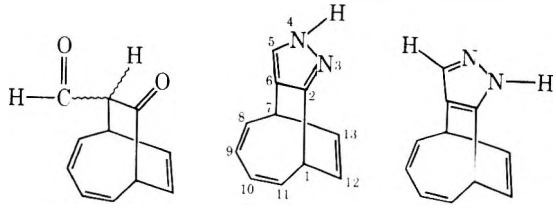


Quinoxaline **33** is identified by its ir and mass spectral properties, proper combustion analysis, and ^{1}H NMR absorptions typical of bicyclo[4.2.2]deca-2,4,7,9-tetraenyl systems.

Comparison of the ^{1}H NMR absorptions of quinoxaline **33**, 7,8-dicarbomethoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**34**), and bicyclo[4.2.2]deca-2,4,7,9-tetraene (**8**) reveals a large effect of the quinoxaline moiety. As expected from their similarities in symmetry, **33**, **34**, and **8** display identical line shape patterns in the ^{1}H NMR of the vinylic region. Diester **34**, a relatively electron-deficient tetraene, shows sizable downfield ^{1}H NMR shifts for protons at C-1, -6, -2, -5, -9, and -10 (Table I) relative to parent **8** ($\Delta\delta$ 0.55, 0.06, and 0.17, respectively). Quinoxaline **33** reveals even greater

downfield shifts for such protons ($\Delta\delta$ 1.20, 0.35, and 0.52, respectively). These shifts probably stem from inductive effects, since they fall off with distance from the substituent; neither **33** nor **34** shows any noticeable ^{1}H NMR shifts for their protons at C-3 and -4.

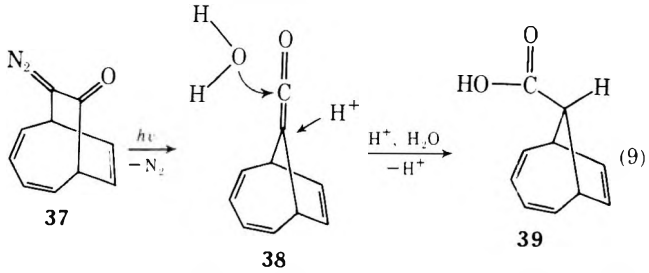
Ketone **1** is also functionalized at C-8 by base-catalyzed condensation with excess methyl formate and sodium methoxide (4 equiv) in ether to give 8-formylbicyclo[4.2.2]deca-2,4,9-trien-7-one (**35**), mp 56–57°, in 95% yield. Formyl ketone **35** is characterized by spectral means and by reaction with hydrazine[13] to form 3,4-diazatricyclo[5.4.2.0^{2,6}]trideca-2,5,8,10,12-pentaene (**36a,b**). The



35 **36a** **36b**

product, a pyrazole derivative, probably exists as a mixture of tautomers **36a** and **36b**.

Formyl ketone **35** is converted by tosyl azide and triethylamine[14] to 8-diazobicyclo[4.2.2]deca-2,4,9-trien-7-one (**37**, 55%). Diazo ketone **37** is a yellow solid exhibiting intense ir absorptions for a diazo group (2150 cm^{-1}) and carbonyl group stretching (1650 cm^{-1}), a mass spectral ion at *m/e* 144 (P − N_2), and ^{1}H NMR absorptions typical for trienyl systems. Photolysis of **37** in dioxane–water results in ring contraction (**38**) and hydration to give bicyclo[4.2.1]nona-2,4,7-triene-*syn*-9-carboxylic acid (**39**, 61%, eq 9). The syn carboxylic acid (**39**) is identical (ir, melting



37 **38** **39** (9)

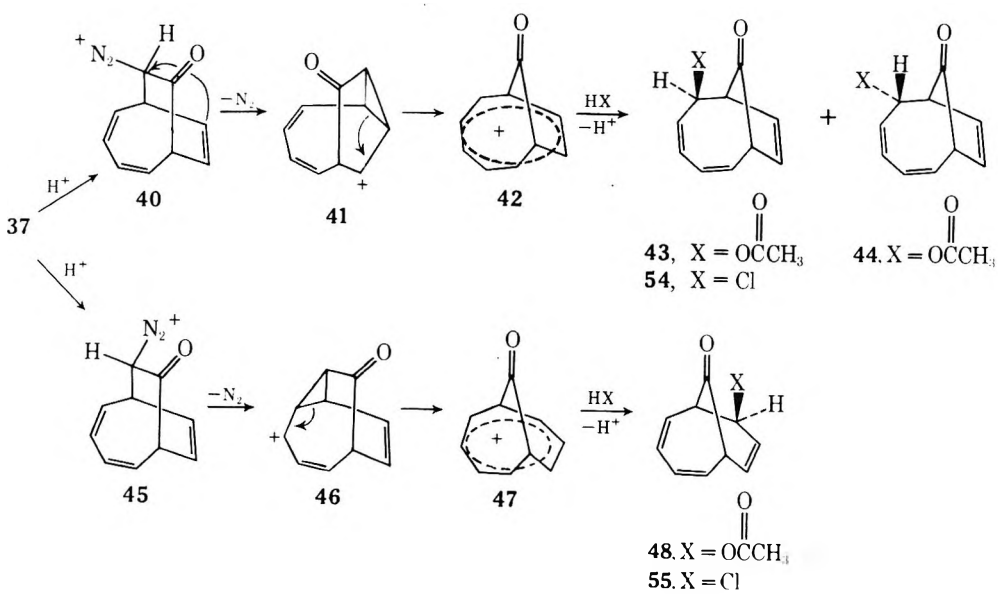
point, and ^{1}H NMR) with that prepared by chromic acid oxidation of bicyclo[4.2.1]nona-2,4,7-triene-*syn*-9-carboxaldehyde[15] and is shown to be homogeneous by reaction with diazomethane to give methyl bicyclo[4.2.1]nona-2,4,7-triene-*syn*-9-carboxylate (93%). The mechanistic aspect of interest in the conversion of **37** to **39** (eq 9) is that ketene **38** hydrates by a process in which a proton is delivered to C-9 from the anti direction.

Protic decomposition of **37** results in profound structural rearrangement, presumably via a cationic process involving isomeric derivatives of **3**. Thus **37** reacts with glacial acetic acid at 25° to yield a mixture of *exo*- and *endo*-2-acetoxybicyclo[5.2.1]deca-3,5,8-trien-10-one (**43** and **44**, eq 10). Precision rectification effects removal of the minor endo acetate **44** from **43**. The ^{1}H NMR of the reaction products (**43** and **44**) reveals immediately that they are not 8-acetoxybicyclo[4.2.2]deca-2,4,9-trien-7-ones [*anti*-8-acetoxybicyclo[4.2.2]deca-2,4,9-trien-7-one (**64**) has been independently prepared in this research and will be discussed later].

Acid-catalyzed decomposition of **37** with rearrangement might be expected to occur by one of the following sequences (eq 10 and 11) to give products of different bicyclic structural types. One sequence (eq 10) involves proton delivery to **37** from the less hindered anti side, loss of nitrogen with back-side interaction of the monoene (C-9, -10) bridge to **41** with collapse to bishomotropylium ion **42**, and exchange with acetic acid to produce exo,endo acetoxy ketones **43** and **44** as major and minor products, respectively. An alternative sequence (eq 11, as analogous to electrophilic additions to bicyclo[4.2.2]deca-2,4,7,9-tetraenes[16]) could arise from migration of the diene bridge to C-8 of **37**, reorganization of **46** to bishomotropylium ion **47**, and conversion to *exo*- and *endo*-7-acetoxybicyclo[4.3.1]deca-2,4,8-trien-10-one (**48** and **49**) by reaction with acetic acid.

As part of the evidence that acetoxy ketone **43** forms instead of **48** as the major product of acetolysis of **37**, the acetate was hydrogenated (eq 12) in ethanol with palladium on carbon as catalyst to *exo*-2-acetoxybicyclo[5.2.1]decan-2-one (**50**, 73%). Saponification of **50** by sodium hydroxide in methanol gave *exo*-2-hydroxybicyclo[5.2.1]decan-2-one (**51**), which is oxidized quantitatively by chromium trioxide in acetone to bicyclo[5.2.1]decane-2,10-dione (**52**, eq 12). Diketone **52** is dissimilar in ^{1}H NMR, ir, and physical properties to bicyclo[4.3.1]decane-7,10-dione (**53**, the product expected from **48** by hydrogenation, saponification, and then oxidation with chromium trioxide) as prepared previously via reaction of 1-morpholinocycloheptene and acryloyl chloride.[17]

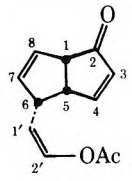
To obtain additional information concerning the acid-catalyzed decomposition process of **37** and as possible further corroboration that **43** is the major product of its reac-



40 **41** **42** **43**, X = OCCH$_3$ **44**. X = OCCH$_3$ (10)
54, X = Cl

45 **46** **47** **48**. X = OCCH$_3$ (11)
55. X = Cl

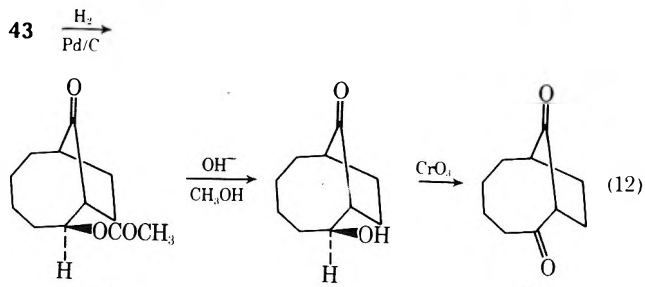
Table IV
Double Irradiation of 58[a,b]



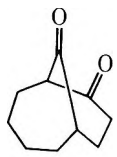
58

Irradiation of H at C	^{1}H NMR, δ								
	7.50	7.14	6.08	5.80	5.50 H at C	4.69	4.14	3.80	3.46
	-4	-2'	-3	-7	-8	-1'	-6	-5	-1
-4		−	+	−	−	−	−	+	−
-2'	−		−	−	−	+	+	−	−
-3	+	−		−	−	−	−	+	−
-7	−	−	−		+	−	+	−	+
-8	−	−	−	+		−	+	−	+
-1'	−	+	−	−	−		+	−	−
-6	−	+	−	+	+	+		+	+
-5	+	−	+	−	−	−	+		+
-1	−	−	−	+	+	−	+	+	

[a] −, no effect; +, pattern simplification upon double irradiation. [b] Shift of $CH_3C(=O)O-$ at δ 2.10.



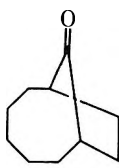
50 51 52



53

tion with acetic acid, a study was made of the behavior of **37** with hydrogen chloride. Diazo ketone **37** is decomposed rapidly in hydrogen chloride to *exo*-2-chlorobicyclo-[5.2.1]deca-3,5,8-trien-10-one (**54**) in 94% yield. The structure and stereochemistry assigned to **54** are based on its spectral properties, transformations, and by extension of the mechanistic principles used to account for the formation of **43** from **37**.

For proof of its bicyclic ring system, **54** was hydrogenolyzed in ethanol over palladium on carbon to bicyclo-[5.2.1]decan-10-one (**56**, 61%). The product exhibits car-

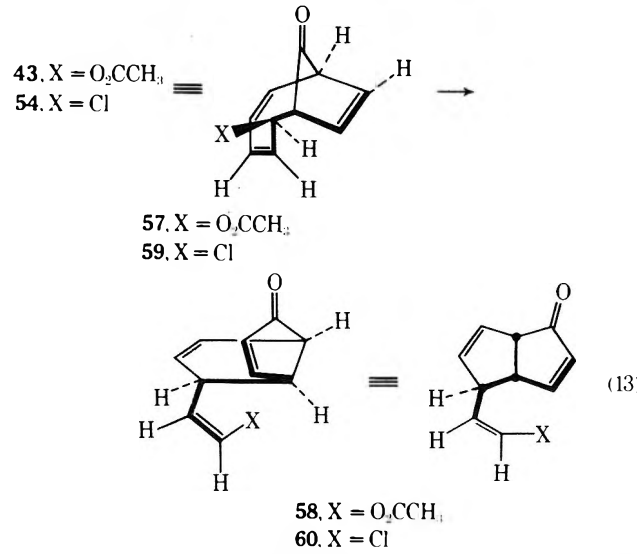


56

bonyl absorption at 1730 cm^{-1} (lit. 1731 cm^{-1})[18a] and its structure was conclusively established by its conversion to bicyclo[5.2.1]decan-10-one 2,4-dinitrophenylhydrazone, which melts at 175–176° (lit.[18a] 176–177.5°) and shows no melting point depression upon admixture with an authentic sample.[18b,c]

It is also pertinent that chloro ketone **54** reacts with silver acetate in acetic acid to give acetoxy ketones **43** and **44** in 53% conversion. The spectral properties (ir, ^{1}H NMR, and GLC) of the product show that the ratio of **43** and **44** from the silver acetate reaction is essentially the same as that from decomposition of diazo ketone **37** by acetic acid. It is thus apparent that the cationic intermediates (**42**) in reactions of **54** with silver acetate–acetic acid and of **37** with acetic acid are essentially identical.

Attempts to purify acetoxy ketone **43** and chloro ketone **54** by preparative GLC lead to Cope rearrangements. Thus **43** rearranges to *endo*-6-(*cis*-2'-acetoxyvinyl)-*cis*-bicyclo[3.3.0]octa-3,7-dien-2-one (**58**, 93%) at a column temperature of 225° (eq 13) and **54** isomerizes to *endo*-6-(*cis*-2'-chlorovinyl)-*cis*-bicyclo[3.3.0]octa-3,7-dien-2-one (**60**, 100%) at column temperatures above 160° (eq 13). The re-



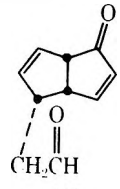
57, X = O_2CCH_3
59, X = Cl

58, X = O_2CCH_3
60, X = Cl

active conformations **57** and **59** (eq 13) for Cope rearrangements of **43** and **54** thus lead, in keeping with mechanism requirements, to products (**58** and **60**) containing the more stable cis ring junctures and cis stereochemistry for the exocyclic olefinic moieties.

The structure of **58** is assigned in part on the basis of infrared absorptions for ester carbonyl (1760 cm^{-1}) and α,β-unsaturated carbonyl (1695 cm^{-1}), by complete analysis of its ^{1}H NMR spectrum, and by double-irradiation experiments (Table IV). Comparison of the ^{1}H NMR of **58** to that of bicyclo[3.3.0]oct-3-en-2-one (**61**)[19] supports the assignment that **58** contains the bicyclo[3.3.0] system. Assignment of the cis stereochemistry of the C-1'–C-2' olefin of **58** is supported by the ^{1}H NMR coupling constant (J = 6 Hz) for the proton absorption of δ 7.14 and 4.69. The J value is well within accepted values for cis olefinic protons[20] (J = 6–12 Hz) and is too small for trans olefinic protons (J = 12–18 Hz).

The structure of **58** is further elucidated upon its hydrolysis by aqueous trifluoroacetic acid to *endo*-6-(1'-oxoethyl)-*cis*-bicyclo[3.3.0]octa-3,7-dien-2-one (**62**) in 75% yield. The structure of **62** is consistent with its exact mass measure-

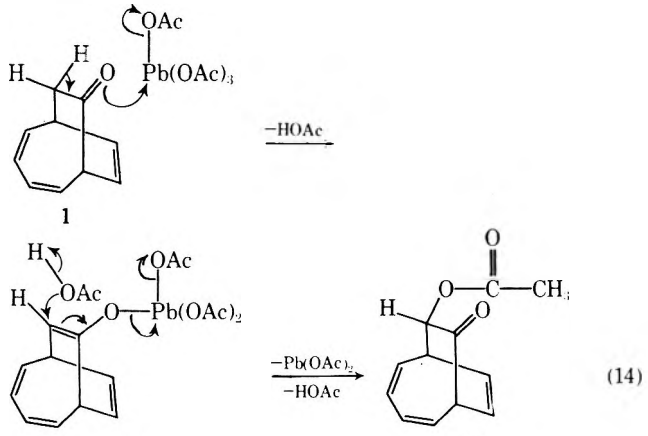


62

ment (*m/e* 162), infrared absorptions at 1715 and 1700 cm^{-1} for aldehyde and α,β-unsaturated ketone stretching, and ^1H NMR absorptions with coupling constants and shifts of C-3 and C-4 protons similar to those of **61**.

Chloro ketone **60** is assigned from its infrared carbonyl stretching absorption at 1700 cm^{-1}, mass spectrum (*m/e* 180), and ^1H NMR absorptions similar to those of **58**, **62**, and **67**. Partial double-irradiation experiments are also consistent with the assigned structure of **60**.

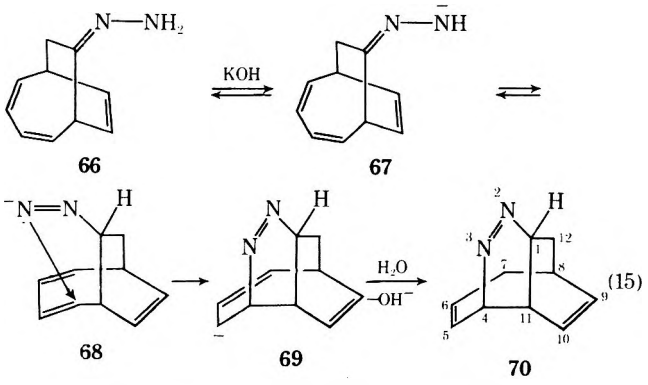
Ketone **1** has also been functionalized in its C-8 position by oxidation with lead tetraacetate (1 equiv) in refluxing acetic acid to give *anti*-8-acetoxybicyclo[4.2.2]deca-2,4,9-trien-7-one (**64**, 100%, eq 14). The stereochemistry of **64** is



(14)

tentatively assigned on the basis of probable reaction mechanisms involving carbonyl oxygen coordination with lead tetraacetate to produce enol lead(IV) complex **63** and acetic acid (eq 14); attack of **63** by acetic acid and/or acetate ion from the less hindered side (anti to the diene bridge) or/and collapse of **63** via a cyclic process occurring favorably from the anti direction will give **64**. Acetoxy ketone **64** shows no evidence of thermal rearrangement.

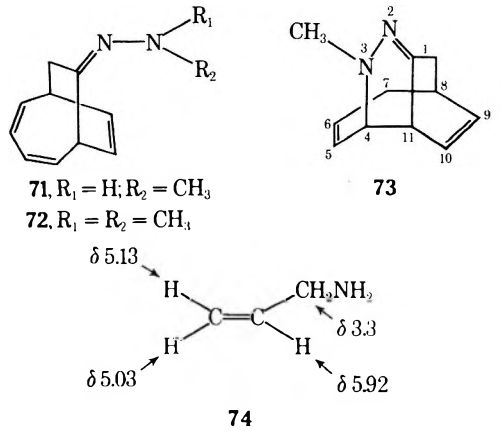
Attempts to reduce **1** by Wolff–Kishner sequences fail to produce bicyclo[4.2.2]deca-2,4,7-triene (**65**), a hydrocarbon of interest in these laboratories. Rather ketone **1** reacts with hydrazine and potassium hydroxide in ethylene glycol at 170–200° to give 2,3-diazatricyclo[6.3.1.$0^{4,11}$]dodeca-2,5,9-triene (**70**, 47%). Similarly **70** is formed (48–54%) from (1) bicyclo[4.2.2]deca-2,4,9-trien-7-one semicarbazone and potassium hydroxide at 200°, and (2) bicyclo[4.2.2]deca-2,4,9-trien-7-one hydrazone (**66**)[21] and potassium *tert*-butoxide in dimethyl sulfoxide at 25–30°. Pyrazoline **70** may be produced from **66** via a sequence as in eq 15.



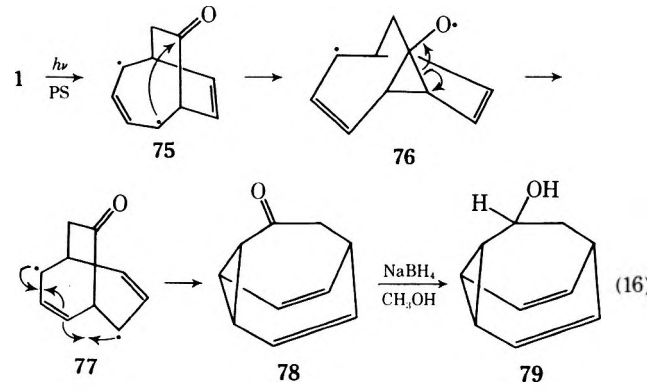
(15)

Pyrazoline **70** displays ir azo absorption at 1650 cm^{-1}; its uv spectrum shows end absorption (λ_{max} 220 nm, ϵ_{max} 3700) and that consistent with a pyrazoline (λ_{max} 333 nm, ϵ_{max} 330).[22] Its ^1H NMR reveals resonances consistent with the assigned structure. The structure of **70** is delineated by ^1H NMR double irradiation and europium shift reagent effects. Double irradiation at δ 2.80 (H at C-7) simplifies only the absorption at δ 6.03 (H at C-9, -10); decoupling the triplet at δ 4.84 (H at C-1) simplifies the septuplet at δ 1.73 (H at C-12). Assignments of the protons at C-1, -4, and -11 are based on the magnitude of the shifts caused by europium complexation; protons closest to the azo group complexed by europium should have the largest shift. The olefinic protons on C-9 and -10 and the exo proton on C-12 are the farthest removed from the azo linkage and show the least effect in their chemical shifts.

To learn more about its hydrazones, **1** was converted by methylhydrazine and 1,1-dimethylhydrazine to bicyclo-[4.2.2]deca-2,4,9-trien-7-one methylhydrazone (**71**, 100%) and bicyclo[4.2.2]deca-2,4,9-trien-7-one dimethylhydrazone (**72**, 75%), respectively. Reaction of **71** and potassium hydroxide at 200° or of **1**, methylhydrazine, and potassium hydroxide in ethylene glycol at 200° yields 3-methyl-2,3-diazatricyclo[6.3.1.$0^{4,11}$]dodeca-1,5,9-triene (**73**, 75%). Dimethylhydrazone **72** is not changed by potassium hydroxide at these elevated temperatures. Heterocycle **73** exhibits proper ir and mass spectra (*m/e* 174) and appropriate ^1H NMR absorptions. The ^1H NMR assignments of **73** are consistent with those of **74**.

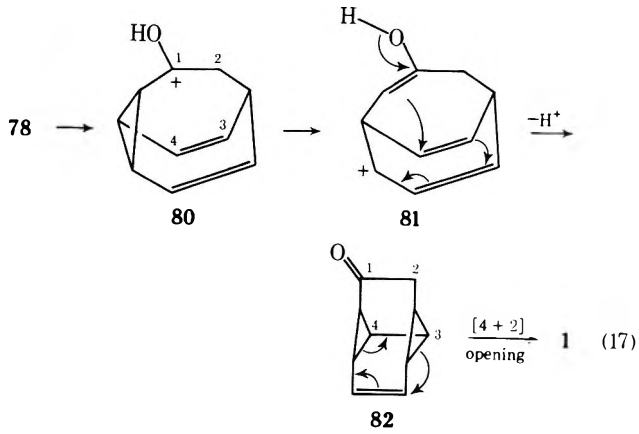


Ketone **1** responds photochemically; irradiation of **1** in acetone through Vycor yields tricyclo[3.3.2.$0^{2,8}$]deca-3,6-dien-9(10)-one (**78**, 68%), along with **1** (10%) and an unidentified isomer.[23] Photoisomerization of **1** using Michler's ketone as sensitizer and Pyrex optics also produces **78** (44%). Ketone **78** is identical with an authentic sample[24] and it is reduced by sodium borohydride to tricyclo[3.3.2.$0^{2,8}$]deca-3,6-dien-9-ol (**79**, 88%), a fluctional molecule. Photosensitized conversion of **1** to **78** is rationalizable by a diradical sequence as in eq 16.



(16)

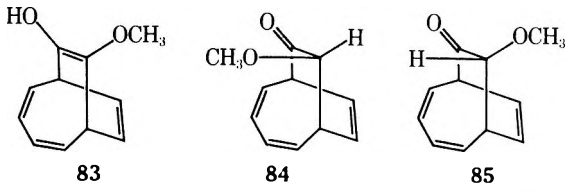
Ketone **78** reacts with dilute trifluoroacetic acid to produce **1** quantitatively. Further, **78** is converted by *p*-tosylhydrazide in ethanol containing hydrochloric acid to tosylhydrazone **7**. A possible sequence for acid-catalyzed



(17)

rearrangement of 78 to 1 is indicated in eq 17. A related cationic rearrangement of bullvalene to bicyclo[4.2.2]deca-2,4,7,9-tetraene (8) is known.[11b]

Refluxing acetoxy ketone **64** in methanol containing *p*-toluenesulfonic acid as catalyst quantitatively produces *syn*- and *anti*-8-methoxybicyclo[4.2.2]deca-2,4,9-trien-7-one (**84** and **85**, respectively) as a 93:7 mixture. The gross structures of **84** and **85** are assignable on the basis of their spectral properties. The conversion of **64** to **84** and **85** may arise via 7-hydroxy-8-methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**83**, as generated by any of a number of sequences). Tautomerization of enol **83** by proton transfer from the less hindered anti side yields **84** as the major product; reaction from the syn side gives **85**.



Investigations of the synthesis and chemistry of *syn*- and *anti*-8-hydroxybicyclo[4.2.2]deca-2,4,9-trien-7-ones as well as bicyclo[4.2.2]deca-2,4,9-triene-7,8-dione are presently under way in these laboratories. Further, synthesis of triene **65** and determination of the properties of the bicyclo[4.2.2]deca-2,4,9-trien-7-yl radical, carbanion, carbonium ion, and carbene, respectively, are being studied.

Experimental Section

General. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. and Microanalysis, Inc., Wilmington, Del. Melting points (uncorrected) were determined using a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained on Perkin-Elmer Model 137 or 457 recording spectrophotometers. Proton magnetic resonance spectra were determined on Varian Associates NMR spectrophotometers, Models A-60, A-60A, and HA-100. Unless noted otherwise, all spectra were measured in chloroform-*d* or carbon tetrachloride solutions using tetramethylsilane as an internal standard. Ultraviolet spectra were determined using a Cary Model 14 recording spectrophotometer. Mass spectra were obtained using an AEI Model MS9 spectrometer. GLC analyses and separations were performed on an Aerograph instrument, Model A-90-C. GLC column A was prepared from 20% SE-30 on Chromosorb W (0.25 in. × 12 ft); column B consisted of 15% Carbowax 20M on Chromosorb W (0.25 in. × 10 ft); and column C was made of 12% Apiezon J on Chromosorb P (0.125 in. × 10 ft). In the Experimental Section, compounds are always listed in their order of elution.

Bicyclo[4.2.1]nona-2,4,7-trien-9-one (4). Ketone **4** was prepared by the method of Antkowiak[3a,b] in 49–65% yield from cyclooctatetraene in 99+% purity (GLC, column A).

Reaction of Bicyclo[4.2.1]nona-2,4,7-trien-9-one (4) and Diazomethane. Ketone **4** was treated with diazomethane as previously reported[3b] to produce bicyclo[4.2.2]deca-2,4,9-trien-7-one (**1**) and spiro[bicyclo[4.2.1]nona-2,4,7-trien-9,2′-oxirane] (**6**). Separation, analysis, and isolation of the products by GLC (column A) gave epoxide **6** (15–50%) and ketone **1** (85–50%).

The spectral properties of **6** follow: ir (neat) 980 (m), 860 (s), and 745 cm^{-1} (s); exact mass, calcd, 146.0732; found, 146.0734.

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.99; H, 6.88.

Ketone **1** has the following properties: ir (neat) 1710 cm^{-1} (s); uv λ_{max} (EtOH) 202, 258, 265, and 300 nm (ϵ_{max} 4250, 3070, 2920, and 373); exact mass, calcd, 146.0732; found, 146.0734.

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.20; H, 6.83.

Bicyclo[4.2.2]deca-2,4,9-trien-7-one Semicarbazone. The crude mixture from ring expansion of **4** containing ketone **1** (85%) and epoxide **6** (15%, 3.15 g, 0.0185 mol) was dissolved in ethanol (250 ml)–water (20 ml) and semicarbazide hydrochloride (5 g) and sodium acetate (7.5 g) were added. The mixture was warmed for 1 hr at 75°, concentrated under reduced pressure to half volume, and cooled in ice. The crude semicarbazone (3.29 g, 88% based on **1**) was filtered and air dried. Bicyclo[4.2.2]deca-2,4,9-trien-7-one semicarbazone was obtained as white crystals, mp 199.5–200.5°, from 50% aqueous ethanol: exact mass, calcd, 203.1059; found, 203.1061.

Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45. Found: C, 64.68; H, 6.43.

Preparative Isolation of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1). The previously reported[3b] separation of ketone **1** from the ring-expansion mixture via the Girard's reagent T adduct was used extensively for isolation of ketone **1**.

Alternatively, if ketone **1** is stored as its semicarbazone, regeneration may be effected as follows. Semicarbazone (3.00 g, 0.015 mol) was dissolved in pyruvic acid (16 g) and stirred for 30 hr under argon. The mixture was diluted with water, neutralized with aqueous sodium bicarbonate, and extracted with ether. The ether layer was washed with brine, dried, and concentrated under reduced pressure. Pure **1** was obtained by distillation, bp 83–86° (0.2 mm) (0.50 g, 23%). (The efficiency of recovery of **1** by this method is expected to be much greater in larger scale experiments.)

Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one Tosylhydrazone (7)[3b] with Methyllithium.[4] A suspension of tosylhydrazone **7** (0.200 g, 0.00064 mol) in hexane (5 ml) was flushed with argon at 0°. Methyllithium (2.0 ml, 1.45 *M*, 2.9 mmol) was added slowly, the system was warmed to 25°, and the mixture was stirred for 3 hr. After addition of water and separation, the water layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The residue (72 mg, 84%) consisted of five components (GLC analysis, column A); the three major components (98% of the mixture) were *cis*-9,10-dihydronaphthalene (**9**, 1%), bicyclo[4.2.2]deca-2,4,7,9-tetraene (**8**, 94%), and naphthalene (5%). Preparative GLC (column A) provided pure samples of **9**, **8**, and naphthalene; the retention times and spectral properties of each product matched those of authentic samples. The ^1H NMR of **8** is in Table I.

7-Acetoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (10). Ketone **1** (0.50 g, 0.0034 mol), isopropenyl acetate (15 ml), and a trace of *p*-toluenesulfonic acid were refluxed for 60 hr. Potassium carbonate was added, the solvent was removed under reduced pressure, and the residue was distilled, bp 78–79° (0.05 mm). The distillate (0.55 g, 86%) gave only one GLC peak (column A). Preparative GLC yielded pure **10**: ir (neat) 1760 (s) and 1210 cm^{-1} (s); ^1H NMR, see Table I.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.62; H, 6.35.

Hydrolysis of 7-Acetoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (10). Hydrochloric acid (3 *N*, 0.25 ml) was added to acetoxytetraene **10** (0.20 g, 0.0011 mol) in hexamethylphosphoramide (3 ml) and stirred overnight at 25°. The mixture was poured into water and the resultant suspension was extracted with ether. After standard work-up of the organic layer, the resultant oil (0.16 g) was a 19:1 mixture of ketone **1** and acetate **10** by GLC (column A) and ^1H NMR analysis.

7-Pyrrolidinobicyclo[4.2.2]deca-2,4,7,9-tetraene (11). A mixture of **1** (0.16 g, 0.0011 mol) and pyrrolidine (0.16 g, 0.0022 mol) in benzene (10 ml) containing several grains of *p*-toluenesulfonic acid was refluxed for 12 hr making use of a Dean-Stark water separator. The red-brown solution, after concentration in vacuo, produced a dark brown residue (0.22 g). After storage under reduced pressure for several hours, the highly water sensitive product was transferred in carbon tetrachloride to a NMR tube under argon. ^1H NMR analysis showed that **11** (ca. 90%) had formed; **1** and benzene were slight impurities; ^1H NMR, see Table I. The sensitivity of **11**

precluded ir or combustion analysis; upon standing in carbon tetrachloride for 1 day, complete hydrolysis of 11 to 1 and pyrrolidine had occurred; exact mass, calcd, 199.1361; found, 199.1359.

Hydrolysis of 7-Pyrrolidinobicyclo[4.2.2]deca-2,4,7,9-tetraene (11). Enamine 11 in carbon tetrachloride containing 1% Me_4Si was swirled with hydrochloric acid (3 *N*, 3 drops) for 15 min at 25°. The aqueous layer was removed and the organic layer was dried over anhydrous potassium carbonate. The solution, on analysis by ^1H NMR and GLC (column A), contained ketone 1 exclusively.

Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Potassium *tert*-Butoxide and Acetyl Chloride in Glyme. Potassium *tert*-butoxide (0.22 g, 0.002 mol) was added all at once to ketone 1 (0.10 g, 0.0007 mol) in dry glyme (5 ml) at 25°, and the resulting brown slurry was stirred rapidly for 4–5 min. Acetyl chloride (0.16 ml, 0.002 mol) was added and the mixture was stirred for 5 min. After addition of potassium carbonate (0.2 g) the solvent was aspirated, and the residue was dissolved in ether (15 ml), filtered, and concentrated. GLC analysis (column A) of the oily residue (0.12 g) revealed a three-component mixture: unidentified impurity (9%), 1 (8%), and 7-acetoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**10**, 83%). Preparative GLC provided pure 1 and **10**.

7-Trimethylsiloxybicyclo[4.2.2]deca-2,4,7,9-tetraene (12). Ketone 1 (0.292 g, 0.002 mol) was dissolved in dried glyme (15 ml) and potassium *tert*-butoxide (0.9 g, 0.008 mol) was added. After the solution was stirred for 3 min, trimethylsilyl chloride (1.1 g, 0.010 mol) was added and the mixture was stirred for 5 min. The solution was concentrated and the residue was distilled to provide a pale yellow oil (0.33 g, 76%), bp 65–67° (0.05 mm). GLC analysis (column A) showed the distillate to be a mixture of **12** (overall yield 72%) and 1 (7%). Silyl ether **12** has the following properties: ir (neat) 1660 (m), 1200 (s), 940 (s), and 840 cm^{-1} (s); ^1H NMR, see Table I; exact mass, calcd, 218.1127; found, 218.1123. Ether **12** hydrolyzes on standing for only a few hours in the atmosphere.

Base-Catalyzed Mono- and Dideuteration of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1). Deuterium oxide (3 drops) containing sodium hydride (57% suspension in mineral oil, 5 grains) was added to 1 (50 mg) in carbon tetrachloride (0.5 ml) containing 1% TMS. The reaction was run in a NMR tube continually tumbled at 25°; reaction progress was monitored by examining the absorption at δ 2.55 for peak and integration disappearance. After 12 hr, half of the organic phase was removed, dried (potassium carbonate), and concentrated to *anti*-8-deuteriobicyclo[4.2.2]deca-2,4,9-trien-7-one (**13**, 25 mg): ^1H NMR δ 5.9 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 3.5 (m, 1 H, H at C-6), 3.0 (m, 1 H, H at C-1), and 2.55 (m, 1 H, H at C-8); exact mass, calcd, 147.0794; found, 147.0791.

The remaining organic layer was tumbled continually (an additional 8.5 days) at 25° until the methylene absorption disappeared. The aqueous layer was removed. The organic layer was worked up as above to yield 8,8-dideuteriobicyclo[4.2.2]deca-2,4,9-trien-7-one (**15**, 25 mg): ^1H NMR δ 5.9 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 3.5 (m, 1 H, H at C-6), and 3.0 (m, 1 H, H at C-1); exact mass, calcd, 148.0857; found, 148.0854.

Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Potassium *tert*-Butoxide and Deuterium Oxide. Ketone 1 (1.0 g, 0.00685 mol) was added to potassium *tert*-butoxide (2.50 g, 0.022 mol) in dry hexamethylphosphoramide (50 ml) at 0–5° and stirred for 4 min. Deuterium oxide (5 ml) was added and stirring was continued for 4 min. Boron trifluoride etherate was then slowly added until the mixture was slightly acidic. After water had been added the mixture was extracted with ether. Standard work-up with subsequent distillation yielded 8,8-dideuteriobicyclo-[4.2.2]deca-2,4,9-trien-7-one (**15**, 0.75 g, 75%), bp 72–76° (0.1 mm).

Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Potassium *tert*-Butoxide and Water in Dimethylformamide. Ketone 1 (0.15 g, 0.001 mol) containing naphthalene (0.13 g, 0.001 mol) as an internal standard was dissolved in dry dimethylformamide (5 ml) and added to potassium *tert*-butoxide (0.22 g, 0.002 mol) in dimethylformamide (5 ml) at 0°. The mixture was stirred for 0.5 hr, poured into water, neutralized with 3 *N* hydrochloric acid, and extracted with ether. Standard work-up and concentration gave 0.25 g (92%) of a residue containing 1 and naphthalene (GLC analysis, column A). NMR analysis of the product showed the ratio of naphthalene to 1 to be 1.0:0.92.

Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Potassium *tert*-Butoxide and Methyl Fluorosulfonate in Glyme. Ketone 1 (0.10 g, 0.00069 mol) was dissolved in dry glyme (5 ml) and potassium *tert*-butoxide (0.25 g, 0.0022 mol) was added at 25°. After the solution was stirred for 4 min, methyl fluorosulfonate (0.25 g, 0.0022 mol) was added all at once and the mixture was stirred for an additional 1 min. The solvent was removed under reduced pressure and the residue was dissolved in chloroform and analyzed by GLC (column A).

The product mixture contained 7-methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**16**, 43%), 1 (9.5%), 8-methylbicyclo[4.2.2]deca-2,4,9-trien-7-one (**17**, trace), and 8,8-dimethylbicyclo[4.2.2]deca-2,4,9-trien-7-one (**18**, 26%), as well as several very minor unidentified components of longer retention times.

Pure dimethyl ketone **18** was obtained by preparative GLC. **18** is unstable upon storage in air: ^1H NMR δ 5.9 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 3.5 (m, 1 H, H at C-6), 2.6 (m, 1 H, H at C-1), and 1.2 (d, 6 H, methyl C-H); exact mass, calcd, 174.1044; found, 174.1041.

Mass spectral analysis of ketone 1 as collected by GLC from the reaction mixture indicated the presence of methyl ketone **17**, *m/e* 160. The amount of **17** present was estimated by comparing the mass spectral peaks of 1 and **17**.

Reaction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Potassium *tert*-Butoxide and Methyl Fluorosulfonate in Hexamethylphosphoramide. Ketone 1 (0.50 g, 0.0034 mol) was added to potassium *tert*-butoxide (1.25 g, 0.011 mol) in dried hexamethylphosphoramide (30 ml) at 0–5° under argon and the solution was stirred for 4 min. Methyl fluorosulfonate (1.2 ml, 1.85 g, 0.016 mol) was added all at once and stirring of the mixture was continued for 4 min. The reaction mixture was quenched with aqueous sodium bicarbonate and the aqueous layer was washed with ether. Standard work-up and concentration yielded a yellow oil (0.54 g, 99%) which contained five components by GLC analysis (columns A and C). The major product was 7-methoxybicyclo-[4.2.2]deca-2,4,9-trien-7-one (**16**) in the percentage shown in Tables II and III. Similar results were obtained using dimethylformamide as solvent (see Table II).

Methoxytetraene **16** was collected by preparative GLC: ir (neat) 1670 (m), 1620 (w), 1210 (s), and 830 cm^{-1} (s); ^1H NMR, see Table I; exact mass, calcd, 160.0888; found, 160.0886.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.29; H, 7.74.

Reactions were run varying the contact time of 1 with potassium *tert*-butoxide before quenching with methyl fluorosulfonate; the product distribution for base times of 14 min, 30 min, 8 hr, and 24.5 hr are summarized in Table II.

Reaction of β-Tetralone with Potassium *tert*-Butoxide and Dimethyl Sulfate in Dimethylformamide. β-Tetralone (0.58 g, 0.004 mol) in dry dimethylformamide (10 ml) was treated with potassium *tert*-butoxide (0.55 g, 0.005 mol) in dimethylformamide (5 ml) for 15 min at 0° and then dimethyl sulfate (0.58 g, 0.005 mol) was added. The mixture was stirred for 10 min and poured into aqueous sodium bicarbonate. Product work-up in the usual manner and distillation of the residue produced a clear liquid (0.44 g), bp 144° (11 mm). GLC analysis (column A) showed the product to contain β-tetralone (5.0%), **22** (94%, overall yield 65%), and an unidentified component (1%) of mass *m/e* 172 representing a dimethylation product.

Pure **22** was collected by preparative GLC: ir (neat) 1640 cm^{-1} (m); ^1H NMR δ 6.9 (m, 4 H, aromatic C–H), 5.5 (s, 1 H, H at C-1), 3.68 (s, 3 H, methyl C–H), 2.9 (m, 2 H, H at C-4), and 2.40 (m, 2 H, H at C-3); exact mass, calcd, 160.0888; found, 160.0890.

Hydrolysis of 7-Methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (16). Methoxytetraene **16** (0.07 g, 0.00043 mol) was dissolved in chloroform-*d* (0.5 ml) containing 1% Me_4Si and naphthalene (ca. 0.11 g) as internal standards. Initial NMR analysis showed an aromatic:olefinic proton ratio of 1.0:0.82. The solution was treated with hydrochloric acid (3 *N*, 0.25 ml) and mixed for 1 hr at 25°. The aqueous layer was removed and the organic layer was dried over anhydrous potassium carbonate. The product was found to be exclusively naphthalene and ketone 1 by ^1H NMR and GLC (column A) methods; ^1H NMR analysis showed the aromatic:olefinic proton ratio to be 1.0:0.83, indicating essentially quantitative formation of **1**.

Thermal Rearrangement of 7-Methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (16). Method A. 7-Methoxybicyclo[4.2.2]deca-2,4-,7,9-tetraene (**16**, 0.25 g, 0.0014 mol) in dry hexamethylphosphoramide (3 ml) was heated for 0.5 hr at 200°. After cooling to 25°, the mixture was poured into aqueous sodium bicarbonate and extracted with ether. The ethereal extracts were worked up in the usual way and concentrated to a mixture (0.24 g) (GLC, column A) containing three components corresponding in retention times to naphthalene (**29**, 18%), 7-methoxytetraene (**16**, 72%), and 2-methoxynaphthalene (**23**, 10%).

Method B. 7-Methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (**16**, 0.15 g, 0.0009 mol) was placed in a tube, evacuated to 0.05 mm, and sealed at 25°. Ether **16** was then heated to 200° for 21 hr, the tube was opened, and the product was analyzed by GLC (column A) and preparative GLC followed by ^{1}H NMR and ir spectral methods. The mixture consisted of three major and one minor products: methanol, naphthalene (**29**, 59%), 7-methoxytetraene (**16**, 11%), and 2-methoxynaphthalene (**23**, 30%).

2-Methoxynaphthalene (23). 2-Naphthol (3.4 g, 0.0237 mol) was dissolved in hexamethylphosphoramide (20 ml) and sodium hydride (1.05 g, 57% suspension, 0.025 mol) was added at 25° all at once. The mixture was stirred for 0.25 hr and methyl iodide (1.55 ml, 0.025 mol) was added. After 5 min the mixture was worked up and concentrated. Crystallization of the residue from ethanol yielded **23** (3.32 g, 89%): mp 70–71.5° (reported mp 72°);[25] ir (KBr) 1480 (m), 1030 (m), 840 (m), 820 (m), and 745 cm^{-1} (m); ^{1}H NMR δ 7.75–6.9 (m, 7 H, H at C-1, -3, -4, -5, -6, -7, -8) and 3.75 (s, 3 H, methyl C–H).

Bicyclo[4.2.2]deca-2,4,9-triene-7,8-dione Monooxime (32). Ketone **1** (1.02 g, 0.007 mol) and potassium *tert*-butoxide (7.5 g, 0.07 mol) were stirred in *tert*-butyl alcohol (75 ml) for 0.75 hr under argon. Isoamyl nitrite (3.0 ml) was added and stirring was continued for 1 hr; isoamyl nitrite (2.5 ml) was again added and the mixture was stirred for 0.5 hr. The solution was poured into ether–ice water and the aqueous layer was extracted with ether. The aqueous layer was acidified with acetic acid and reextracted with ether. The latter ethereal layers were worked up in the usual manner and concentrated in vacuo. Solution of the crude product (0.75 g, 63%) in methylene chloride and recrystallization from 1:2 methylene chloride–cyclohexane produced **32**, a yellow powder: mp 178–178.5°; ir (KBr) 3300 (s), 1710 (s), and 1690 cm^{-1} (s); ^{1}H NMR δ 5.9 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 4.3 (dd, 1 H, H at C-6), and 3.7 (m, 1 H, H at C-1); exact mass, calcd, 175.0633; found, 175.0636.

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.30; H, 5.30.

Bicyclo[4.2.2]deca-2,4,9-triene-7,8-dionequinoxaline (33). Oximino ketone **32** (0.5 g, 0.0029 mol) and o-phenylenediamine (0.31 g, 0.0029 mol) were refluxed in ethanol (10 ml)–acetic acid (10 ml) for 1 hr. The mixture was cooled and poured into water; the product was filtered and air dried (0.30 g, 46%). Recrystallization from methanol produced **33**: mp 194.5–195°; ir (KBr pellet) 1500 (m), 950 (s), 760 (s), and 730 cm^{-1} (s); ^{1}H NMR δ 8.02 and 7.67 (two m, 4 H, H on aromatic nucleus), 6.47 (m, 2 H, H at C-2, -5), 6.02 (m, 2 H, H at C-9, -10), 5.82 (m, 2 H, H at C-3, -4), and 4.35 (m, 2 H, H at C-1, -6). Proton assignments for **33** are based on double irradiation; irradiation of the multiplet at δ 4.35 (H at C-1, -6) causes simplification of the multiplet at δ 6.47 and collapse of the absorption at δ 6.02 to a singlet; exact mass, calcd, 232.1000; found, 252.1004.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.48; H, 5.19; N, 12.10.

8-Formylbicyclo[4.2.2]deca-2,4,9-trien-7-one (35). Ketone **1** (0.88 g, 0.006 mol) was added to freshly prepared sodium methoxide (1.30 g, 0.024 mol) in dry ether (100 ml). After introduction of methyl formate (1.45 g, 0.024 mol), the mixture was stirred for 22 hr. Cold hydrochloric acid (3 *N*, 50 ml) was added and the mixture was extracted with ether. The combined ethereal washes were worked up; concentration of the solution yielded a brown oil (1.00 g, 95%) which precipitated from pentane as a tan solid. Pure **35** was prepared by elution through a silica gel column (25% ether–75% cyclohexane solvent) and crystallization from pentane at −78°: mp 56–57°; ir (KBr pellet) 1660 (s), 1580 (s), and 1120 cm^{-1} (m); ^{1}H NMR δ 8.1 (s, 1 H, aldehydic C–H), 5.9 (m, 7 H, H at C-2, -3, -4, -5, -8, -9, -10), and 3.5 (m, 2 H, H at C-1, -6); exact mass, calcd, 174.0681; found, 174.0683.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.55; H, 5.75.

3,4-Diazatricyclo[5.4.2.0^{2,6}]trideca-2,5,8,10,12-pentaene (36). Formyl ketone **35** (0.52 g, 0.003 mol) was dissolved in ethanol (1 ml). Anhydrous hydrazine (0.13 g, 0.004 mol) in ethanol (3 ml) was added (precipitation occurred immediately) and the stirred mixture was refluxed for 18 hr. The dark solution was cooled, poured into water, and extracted with ether. The dark oil (0.52 g) obtained from concentration of the organic phase, on elution through a silica gel column (ethyl acetate solvent), yielded a difficultly crystallizable oil (0.44 g, 86%). Pure **36** was prepared by crystallization from benzene–cyclohexane: mp 106–107°; ir (KBr) 3250 cm^{-1} (s); ^{1}H NMR δ 9.25 (br s, 1 H, N–H, shift is concentration dependent, disappears upon addition of D_2O), 7.15 (s, 1 H, H at C-5), 5.9 (m, 6 H, H at C-8, -9, -10, -11, -12, -13), and 4.0 (m, 2 H, H at C-1, -7); exact mass, calcd, 170.0844; found, 170.0847.

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92. Found: C, 77.35; H, 6.09.

7-Diazobicyclo[4.2.2]deca-2,4,9-trien-8-one (37). Formyl ketone **35** (1.0 g, 0.0575 mol) was dissolved in methylene chloride (30 ml) and triethylamine (1.22 g, 0.12 mol) and tosyl azide (1.1 g, 0.0575 mol) were added at 25°. The mixture was stirred for 4 hr. Potassium hydroxide (5 g) in water (60 ml) was added and the mixture was then stirred for 15 min. After layer separation and extraction of the aqueous portion with methylene chloride, the combined organic phases were washed with water and dried over anhydrous potassium carbonate. Concentration yielded a dark brown oil (0.92 g) which contained **37** and tosyl azide as indicated by micro TLC analysis on silica gel G with 1:1 ether–hexane solvent. Separation on a silica gel column (1:3 ether–cyclohexane) yielded **37** as a bright yellow liquid which crystallized at −20° and remained solid upon rewarming (0.52 g, 55%): mass spectrum (P − N_2) *m/e* 144; ^{1}H NMR δ 5.9 (m, 6 H, H at C-2, -3, -4, -5, -9, -10) and 3.65 (m, 2 H, H at C-1, -6).

Photolysis of 7-Diazobicyclo[4.2.2]deca-2,4,9-trien-8-one (37) in Water–Dioxane. Diazo ketone **37** (0.75 g, 0.0044 mol) was dissolved in *p*-dioxane (50 ml) and water (25 ml) and the solution was degassed with argon for 0.5 hr. The solution was then irradiated with a 450-W medium-pressure Hanovia lamp in all-quartz equipment for 6 hr. Upon completion of the experiment, **37** was absent as evidenced by the lack of evolution of nitrogen upon addition of a drop of concentrated hydrochloric acid to an aliquot of the reaction mixture. The solution was concentrated and then the residue was triturated with aqueous potassium carbonate and extracted with ether. The aqueous layer was acidified with hydrochloric acid and extracted with ether. After standard work-up and concentration of the organic phase, a single product (0.43 g, 61%) as evidenced by micro TLC analysis (1:1 ether–petroleum ether solvent) was obtained.

The product was filtered through silica gel and recrystallized from ether–petroleum ether at −78° to provide pure bicyclo[4.2.1]nona-2,4,7-triene-*syn*-9-carboxylic acid (**39**), mp 173–174.5° (lit.[15] mp 173–174°), as white crystals: ir (KBr) 3150 (br, s), 1730 (s), and 1680 cm^{-1} (s); ^{1}H NMR δ 11.2 (s, 1 H, –COOH, shift is concentration dependent), 6.1 (m, 4 H, H at C-2, -3, -4, -5), 5.25 (d, 2 H, H at C-7, -8), and 3.3 (m, 3 H, H at C-1, -6, -9); exact mass, calcd, 162.0681; found, 162.0683.

Methyl Bicyclo[4.2.1]nona-2,4,7-triene-*syn*-9-carboxylate. Crude acid **39** (0.35 g, 0.0022 mol) from the preceding photolysis was dissolved in ether (50 ml), treated with diazomethane (0.3 *M*, 30 ml, excess) at 25°, and stirred for 0.5 hr. Formic acid was added to destroy excess diazomethane. The ether layer was extracted with aqueous sodium bicarbonate and saturated brine, dried, and concentrated to a yellow oil (0.41 g) which was ca. 99% pure by GLC analysis (column A). Distillation afforded methyl bicyclo[4.2.1]nona-2,4,7-triene-*syn*-9-carboxylate as a white solid: bp 66.5° (0.05 mm); mp 27–29° (0.37 g, 93%); ir (neat) 1720 (s), 1220 (s), and 1205 cm^{-1} (s); ^{1}H NMR δ 5.9 (m, 4 H, H at C-2, -3, -4, -5), 5.15 (d, 2 H, H at C-7, -8), 3.5 (s, methyl C–H) superimposed on 3.3 (m, H at C-1, -6, -9. total 6 H); exact mass, calcd, 176.0837; found, 176.0840.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.19; H, 6.90.

***exo*-2-Acetoxybicyclo[5.2.1]deca-3,5,8-trien-10-one (43).** Diazo ketone **37** (0.88 g, 0.0051 mol) was dissolved in acetic acid (12 ml) and stirred at 25° for 4 hr. The mixture was concentrated and distilled to give **43** (0.87 g, 84%): bp 102–103° (0.1 mm); ir (neat) 1760 (s), 1740 (s), 1370 (m), and 1230 cm^{-1} (s); ^{1}H NMR δ 5.9 (m, 6 H, H at C-3, -4, -5, -6, -8, -9), 5.00 (t, 1 H, H at C-2), 3.24 (m, 1 H, H at C-7), 3.05 (dd, 1 H, H at C-1), and 2.11 (s, 3 H, methyl C–H). Double irradiation at δ 3.05 simplifies the triplet at δ 5.00; irradiation of the triplet causes simplification of the absorption at δ 3.05. This decoupling indicates that the proton bound to carbon substituted by acetoxyl is adjacent to a bridgehead proton. Additional properties of **43** follow: uv λ_{max} (EtOH) 200, 225, and 285 nm (ϵ_{max} 6080, 4000, and 600); exact mass, calcd, 204.0786; found, 204.0788.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.60; H, 5.88. Found: C, 70.80; H, 5.83.

Attempts to purify **43** by GLC (column A, injector 250°, column 225°) produced *endo*-6-(*cis*-2′-acetoxyvinyl)-*cis*-bicyclo[3.3.0]-octa-3,7-dien-2-one (**58**) as the major product (93%) as a pale yellow solid, mp 69–71°. Rearrangement of **43** was temperature dependent. Only 70% of the rearranged product was formed at

150° (injector 200°) while 85% conversion was observed at 180° (injector 230°): ir (KBr) 1760 (s), 1695 (s), 1220 (s), and 1040 cm^{-1} (s); ^1H NMR coupling constants δ 7.50 (dd, J = 6, 3 Hz), 7.14 (dd, J = 6, 1 Hz), 6.08 (dd, J = 6, 1.5 Hz), 4.69 (dd, J = 10, 6 Hz), and 4.14 (t, J = 10 Hz); uv λ_{max} (ether) 208 nm (ϵ_{max} 31,500); exact mass, calcd, 204.0786; found, 204.0788.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.60; H, 5.88. Found: C, 70.68; H, 5.90.

***endo*-6-(1′-Oxoethyl)-*cis*-bicyclo[3.3.0]octa-3,7-dien-2-one (62).** Acetoxy ketone **58** (53.1 mg, 0.00026 mol) in chloroform-*d* (0.5 ml) was treated with water (3 drops) containing trifluoroacetic anhydride (1 drop) for 6 days with continuous swirling; the reaction was monitored by ^1H NMR. The aqueous layer was removed; the organic layer was dried (K_2CO_3) and concentrated to a clear oil (39.0 mg) which contained two major components by GLC analysis (column A). The products, **62** (80%, overall yield 75%) and **58** (15%), were collected by preparative GLC.

Keto aldehyde **62** was purified with large loss to yield 8 mg of pure compound: ^1H NMR δ 9.80 (s, 1 H, H at C-1′), 7.32 (dd, J = 6, 2.5 Hz, 1 H, H at C-4), 6.02 (dd, J = 6.2 Hz, 1 H, H at C-3), 5.6 (m, 2 H, H at C-7, -8), 3.55 (m, 3 H, H at C-1, -5, -6), and 2.6 (br d, 2 H, H at C-2′); exact mass, calcd, 162.0681; found, 162.0683.

Catalytic Hydrogenation of exo-2-Acetoxybicyclo[5.2.1]deca-3,5,8-trien-10-one (43). Ketone **43** (1.06 g, 0.0052 mol) was dissolved in absolute ethanol (100 ml), 10% palladium on carbon (0.1 g) was added, and the mixture was placed in a Parr apparatus (50 lb) for 6 hr. After the mixture had been filtered and concentrated, the residue was taken up in ether and concentrated (1.07 g). The material was eluted through silica gel, first with ether–cyclohexane (1:3) and then with ether, to a clear liquid (0.80 g, 73%) which crystallized. *exo*-2-Acetoxybicyclo[5.2.1]decan-10-one (**50**) was collected by preparative GLC (column A) as a white solid: mp 47–49°; ir (KBr) 1730 (s), 1370 (m), 1240 (s), and 1230 cm^{-1} (s); ^1H NMR δ 2.05 (s, acetoxy methyl C–H) superimposed on 1.85 (m, aliphatic C–H); exact mass, calcd, 210.1256, found, 210.1260.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.28; H, 8.57.

Reaction of exo-2-Acetoxybicyclo[5.2.1]decan-10-one (50) with Sodium Hydroxide in Methanol–Water. Acetoxy ketone **50** (0.70 g, 0.0033 mol) was dissolved in hot methanol (10 ml) and sodium hydroxide (1 pellet, ca. 0.004 mol) dissolved in water (1 ml) was added. The mixture was stirred at 25° for 1 day and poured into water. The aqueous layer was extracted with ether. The ether extract was processed in the usual manner to yield an oil (0.52 g) which was greater than 99% pure (GLC, column A). The material was eluted through silica gel (gradient elution 20% ether–cyclohexane, 50% ether–cyclohexane, ether) to produce an oil which crystallized from pentane at −78° to white *exo*-2-hydroxybicyclo-[5.2.1]decan-10-one (**51**): mp 47–48.5° (0.27 g, 50%); ir (KBr) 3450 (s) and 1730 cm^{-1} (s); exact mass, calcd, 168.1150; found, 168.1153.

Bicyclo[5.2.1]decane-2,10-dione (52). Hydroxy ketone **51** (0.20 g, 0.0012 mol) was dissolved in acetone (10 ml). Chromium trioxide in 25% sulfuric acid (2.6 *M*, 1 ml, 0.0026 mol) was added dropwise and the mixture was stirred for 0.5 hr. Methanol (0.15 ml) and then water were added, and the mixture was extracted with ether. The aqueous layer was acidified and extracted with ether; the aqueous layer was then made alkaline and reextracted with ether. The ether extracts were processed and concentrated to a liquid (0.21 g, 100%) which contained one component based on GLC analysis (column A). The material was purified by preparative GLC to yield **52** as a clear liquid: ir (neat) 1730 (s) and 1700 cm^{-1} (s); exact mass, calcd. 166.0994; found, 166.0996. The product was dissimilar in all respects to bicyclo[4.3.1]decane-7,10-dione (**53**) prepared from 1-morpholinocycloheptene and acryloyl chloride.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.13; H, 8.53.

***exo*-2-Chlorobicyclo[5.2.1]deca-3,5,8-trien-10-one (54).** Diazo ketone **37** (0.69 g, 0.004 mol) was dissolved in dry ether (10 ml) and hydrogen chloride was bubbled through the solution for 15 min. The mixture was kept for 15 min, then diluted with ether and extracted with water, aqueous sodium bicarbonate, and saturated brine. The organic layer was dried and concentrated to **54**, a yellow liquid (0.68 g, 94%). The compound was extremely labile. Its purification was unsuccessful: ir (neat) 1740 cm^{-1} (s); ^1H NMR δ 5.9 (m, 7 H, H at C-2, -3, -4, -5, -6, -8, -9) and 3.2 (m, 2 H, H at C-1, -7); exact mass, calcd, 180.0342; found, 180.0344.

Attempts to distil or preparatively GLC **54** led to quantitative rearrangement to *endo*-6-(2′-*cis*-chlorovinyl)-*cis*-bicyclo[3.3.0]octa-3,7-dien-2-one (**60**) as a yellow liquid: ir (neat) 1700 cm^{-1} (s); ^1H NMR δ 7.5 (dd, 1 H, H at C-4), 5.9 (m, 5 H, H at C-3, -7, -8, -1′, -2′), 2.75 (m, 2 H, H at C-5, -6), and 2.5 (m, 1 H, H at C-1); uv λ_{max} (ether) 208 nm (ϵ_{max} 31.3 × 10^3); exact mass, calcd, 180.0342; found, 180.0342.

Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02, Found: C, 66.14; H, 4.87.

Bicyclo[5.2.1]decan-10-one (56). Chloro ketone **54** (0.48 g, 0.0027 mol) in absolute ethanol containing 10% palladium on carbon (0.06 g) was placed in a Parr apparatus (hydrogen pressure 50 lb) for 6 hr. The mixture was filtered and the residue was washed with ether. The filtrate was concentrated and the residue was taken up in ether and processed to a yellow oil (0.40 g). Micro TLC analysis (1:9 ethyl acetate–petroleum ether) of the oil showed two components, R_f values of 0.8 and 0.5.

The crude product was eluted through a silica gel column (5% ethyl acetate–petroleum ether solvent); the first material off the column (0.28 g) was a mixture of a saturated and unsaturated ketone by GLC (column A), ir, and mass spectral measurements (*m/e* 150, 152).

The ketones were dissolved in absolute ethanol (35 ml) containing 10% palladium on carbon (0.05 g) and rehydrogenated at atmospheric pressure. Hydrogen uptake ceased after 2 hr and the product was worked up as before to an oil (0.25 g, 61%) which was greater than 98% pure by GLC analysis. Pure **56** was collected by preparative GLC and has spectral properties identical with those previously reported:[13a] mass spectrum *m/e* 152; ^1H NMR δ 2.1 (s) superimposed on 1.9 (m); exact mass, calcd, 152.1201; found, 152.1204. The ir differed from that reported for bicyclo[4.3.1]decan-10-one (Sadtler No. 28389).

Bicyclo[5.2.1]decan-10-one 2,4-Dinitrophenylhydrazone. Ketone **56** (0.076 g, 0.0005 mol) was treated with 2,4-dinitrophenylhydrazone (0.2 g) in concentrated sulfuric acid (2 ml), water (3 ml), and methanol (5 ml) to yield a crude derivative (0.14 g, 82%). Bicyclo[5.2.1]decan-10-one dinitrophenylhydrazone recrystallized from ethanol as bright orange plates, mp 175–176° (lit.[18a] mp 176–177.5°), *m/e* 332. Admixture with an authentic sample[18b] showed no melting point depression. Both samples possess identical ir spectral properties: ir (KBr) 3300 (w), 3100 (w), 1610 (s), and 1330 cm^{-1} (s); exact mass, calcd, 332.1484; found, 332.1488.

***exo*-2-Acetoxybicyclo[5.2.1]deca-3,5,8-trien-10-one (43).** Chloro ketone **54** (0.24 g, 0.0013 mol) was dissolved in acetic acid (5 ml) containing silver acetate (0.43 g, 0.0026 mol) in a flask wrapped with aluminum foil. The mixture was stirred at 25° for 3 days, diluted with ether (40 ml), and filtered. The light tan precipitate was washed with ether. The combined filtrate was worked up and concentrated. Evaporative distillation (0.075 mm) of the yellow liquid (0.19 g) provided a liquid (0.16 g) containing 10% **54** by GLC analysis. The major component of the mixture (80%) was **43** (overall yield 47%) identical with previously prepared **43** which also rearranges to **58** upon preparative GLC as previously described.

Attempted Wolff–Kishner Reduction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1). Ketone **1** (0.25 g, 0.0017 mol), potassium hydroxide (0.75 g), and hydrazine hydrate (1.5 ml) were refluxed in ethylene glycol (4 ml) for 2 hr. The mixture was cooled, poured into water, and extracted with pentane. The pentane solution was concentrated to an off-white solid (0.13 g) which contained two highly volatile materials (5%) of short retention time and a material (95%) of long retention time by GLC analysis (column A).

2,3-Diazatricyclo[6.3.1.$0^{4,11}$]dodeca-2,5,9-triene (**70**, overall yield 47%) was collected as a white solid by preparative GLC, mp 170–172°. A fresh SE-30 GLC column was necessary for consistent GLC results: ir (mull) 1650 (w), 1560 (w), and 940 cm^{-1} (m); ^1H NMR δ 6.03 (m, 2 H, H at C-9, -10), 5.53 (m, 2 H, H at C-4, -5), 5.03 (m, 1 H, H at C-6), 4.84 (t, 1 H, H at C-1), 2.80 (m, 2 H, H at C-7, -8), 2.40 (m, 1 H, H at C-11), 2.40 (m, 1 H, H at C-11), 2.20 (dt, 1 H, H at C-12), and 1.73 (septet, 1 H, H at C-12); exact mass, calcd, 160.1000; found, 160.1003.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.79; H, 7.72; N, 17.57.

Bicyclo[4.2.2]deca-2,4,9-trien-7-one Hydrazone (66). Ketone **1** (0.22 g, 0.0015 mol) and hydrazine hydrate (10 ml) were warmed for 2 hr at 75°. The mixture was extracted with chloroform. The chloroform layers were filtered through potassium carbonate and concentrated to give **66** as a yellow oil (0.23 g, 96%): ir (neat) 3330 (m), 3200 (m), and 1650 cm^{-1} (m); ^1H NMR δ 5.8 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 4.75 (broad s, 2 H, NH, disappears with D_2O), 3.5 (m, 1 H, H at C-6), 2.9 (m, 1 H, H at C-1), and 2.4 (m, 2 H, H at C-8); exact mass, calcd, 160.1000; found, 160.1003.

Attempted Wolff–Kishner Reduction of Bicyclo[4.2.2]deca-2,4,9-trien-7-one Hydrazone (66). Potassium *tert*-butoxide (0.15

g, 0.0014 mol) was dissolved in dry dimethyl sulfoxide (1.5 ml). Hydrazone **66** (0.15 g, 0.0009 mol) dissolved in dry dimethyl sulfoxide (3.0 ml) was added in 5 min. After stirring for 2 hr, the mixture was quenched with pentane and water. The aqueous layer was then washed with ether and the combined organic layer was concentrated to a tan solid (0.08 g) which was 92% pyrazoline **70** by GLC analysis (overall yield 50%). Two volatile products (combined yield 8%) were not identified.

2,3-Diazatricyclo[6.3.1.0^{4,11}]dodeca-2,5,9-triene (70). Bicyclo[4.2.2]deca-2,4,9-trien-7-one semicarbazone (1.54 g, 0.0076 mol) and potassium hydroxide (3.5 g) were refluxed in ethylene glycol (20 ml) for 2.5 hr. The mixture was cooled and worked up as before to yield a tan solid (0.68 g) which was 94% **70** by GLC analysis (column A) (overall yield 54%). Two volatile minor components were not identified.

Bicyclo[4.2.2]deca-2,4,9-trien-7-one Methylhydrazone (71). Ketone **1** (0.12 g, 0.0008 mol) was warmed to 75° with methylhydrazine (5 ml) for 18 hr. Water was added and the mixture was extracted with chloroform. The organic layer was dried through potassium carbonate and concentrated to **71** (0.14 g, 100%): ir (neat) 3350 (m), 1620 (m), and 1100 cm^{-1} (s); ^{1}H NMR δ 5.75 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 3.9 (m, 1 H, NH, disappears with D_2O), 3.35 (quintet, 1 H, H at C-6), 2.8 (d imposed on m, 4 H, H at C-1, methyl CH), and 2.4 (m, 2 H, H at C-8); exact mass, calcd, 174.1157; found, 174.1159.

3-Methyl-2,3-diazatricyclo[6.3.1.0^{4,11}]dodeca-1,5,9-triene (73). Ketone **1** (0.28 g, 0.0019 mol), potassium hydroxide (0.75 g), and methylhydrazine (1.5 ml) were refluxed in ethylene glycol (4 ml) for 2.5 hr. The reaction mixture was worked up as before to yield a yellow oil (0.24 g, 74%) which was homogeneous by GLC analysis (column A).

Pure **73** was collected by preparative GLC. A fresh SE-30 column was necessary for consistent GLC results: ir (neat) 1640 (w), 1610 (w), 1600 (w), and 1420 cm^{-1} (m); ^{1}H NMR δ 6.00 (m, 2 H, H at C-9, -10), 5.80 (m, 1 H, H at C-5), 5.36 (m, 1 H, H at C-5), 3.82 (m, 1 H, H at C-4), 3.49 (m, 2 H, H at C-8, -11), 2.75 (s, 3 H, methyl C-H), 2.48 (dd, 1 H, H at C-12), 2.1 (m, 2 H, H at C-7, -12), and 1.64 (dd, 1 H, H at C-7); exact mass, calcd, 174.1157; found, 174.1159.

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 17.08. Found: C, 75.68; H, 8.01; N, 16.77.

Bicyclo[4.2.2]deca-2,4,9-trien-7-one Dimethylhydrazone (72). Ketone **1** (0.10 g, 0.00063 mol) and dimazine (5 ml) were refluxed for 36 hr. The mixture was diluted with water and extracted with methylene chloride. The organic layer was concentrated to **72**, a yellow oil (0.09 g, 75%): ir (neat) 1610 cm^{-1} (m); ^{1}H NMR δ 5.7 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 3.4 (m, 1 H, H at C-6), 2.7 (m, 3 H, H at C-1, -8), and 2.3 (d, 6 H, methyl CH); exact mass, calcd, 188.1313; found, 188.1315.

Irradiation of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) in Acetone. Ketone **1** (0.50 g, 0.0034 mol) in acetone (150 ml) was degassed with argon for 0.5 hr and irradiated with a 450-W Hanovia medium-pressure lamp through a Vycor filter for 9 hr in an all-quartz apparatus fitted with a reflux condenser and a stirrer. The solvent was removed under reduced pressure. The residue (0.6 g) was loaded on a silica gel column (90 g), gradient eluted with 5% ethyl acetate–petroleum ether (500 ml) and 35% ethyl acetate–petroleum ether (1 l.), and collected in 12-ml fractions.

Fractions 28–35 contained ketone **1** (0.05 g, 10%). Fractions 38–41 contained a clear oil, isomeric with the starting ketone, and homogeneous by GLC (column A) (0.06 g, 12%) of unidentified structure: exact mass, calcd, 146.0732; found, 146.0734.

Upon concentrating cuts 43–50, tricyclo[3.3.2.0^{2,8}]deca-3,6-dien-9(10)-one (**78**) remained as a clear oil (0.34 g, 68%) homogeneous by GLC analysis. Pure **78** was obtained by preparative GLC, mp 40–41° (lit.[25] mp 36–37°), and is identical with an authentic sample: ir (neat) 1665 cm^{-1} (s); ir (CCl_4) 1685 cm^{-1} (lit. 1685 cm^{-1}); ^{1}H NMR δ 5.8 (m, 4 H, H at C-3, -4, -6, -7) and 2.5 [m, 6 H, H at C-1, -2, -5, -8, -10 (-9)]; uv λ_{max} (heptane) 200, 290, 300, 312, and 322 nm (ϵ_{max} 7400, 130, 105, 85, and 61); exact mass, calcd, 146.0732; found, 146.0734. The NMR of **74** is temperature dependent as reported.

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.93; H, 7.19.

Irradiation of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) in Ether. Ketone **1** (0.50 g, 0.0034 mol) in anhydrous ether (100 ml) was purged with argon for 0.5 hr and irradiated with a 450-W Hanovia medium-pressure lamp for 9 hr with Pyrex optics. Concentration under reduced pressure yielded a yellow oil (0.50 g, 100%) which contained (GLC, column A) ketone **1** (25%), unidentified isomer (27%), and tricyclo[3.3.2.0^{2,8}]deca-3,6-dien-9(10)-one (**78**, 48%).

Irradiation of Bicyclo[4.2.2]deca-2,4,9-trien-7-one (1) with Michler's Ketone as Sensitizer. Ketone **1** (0.25 g, 0.0017 mol) and Michler's ketone (0.50 g) in benzene (100 ml) were degassed with argon for 0.5 hr and irradiated with a 450-W Hanovia medium-pressure lamp through Pyrex optics for 2.5 hr. The solution was filtered, concentrated, and eluted through a silica gel column with ether. The residue was sublimed at 50–60° (0.1 mm) to yield **78** as a white solid (0.11 g, 44%).

Reaction of Barbaralone with Diazomethane.[24] Barbaralone was prepared[3a,b] in 64% yield from bicyclo[4.2.1]nona-2,4,7-trien-9-one by Michler's ketone sensitized irradiation: mp 49–51°; ^{1}H NMR δ 5.7 (complex t, 2 H, H at C-3, -7), 4.3 (complex t, 4 H, H at C-2, -4, -6, -8), and 2.7 (t, 2 H, H at C-1, -5).

Alcoholic ethereal diazomethane (125 ml, 0.33 *M*, 0.041 mol) was added at −5° to barbaralone (0.81 g, 0.0061 mol) in methanol (15 ml). After 28.5 hr, solvent and excess diazomethane were removed under reduced pressure to yield a yellow oil (0.91 g, 100%) consisting of 9-aldehydotricyclo[3.3.1.0^{2,8}]nona-3,6-diene (54%) and tricyclo[3.3.2.O^{2,8}]deca-3,6-dien-9(10)-one (**78**, 46%). The aldehyde and ketone **78** were purified by preparative GLC (column A); 9-aldehydotricyclo[3.3.1.0^{2,8}]nona-3,6-diene exhibits ^{1}H NMR absorptions at δ 9.5 (d, 1 H, aldehydic CH), 5.7 (t, 2 H, H at C-3, -7), 4.1 (m, 4 H, H at C-2, -4, -6, -8), 2.8 (m, 2 H, H at C-1, -5), and 2.0 (m, 1 H, H at C-9). Ketone **78** is identical with that previously prepared.

Reaction of Tricyclo[3.3.2.0^{2,8}]deca-3,6-dien-9-one (78) with Tosyl Hydrazide. Ketone **78** (0.20 g, 0.00135 mol), tosyl hydrazide (0.25 g, 0.00135 mol), and concentrated hydrochloric acid (1 drop) in absolute ethanol (6 ml) were stored for 2 hr at 25° and 10 hr at −5°. The mixture was concentrated to ca. 2 ml under reduced pressure and stored at −25° and the resulting precipitate was filtered (0.28 g, 68%). The white crystalline product is identical with **7** previously prepared, mp 155–157°. The residue after filtration also is exclusively **7** (by ^{1}H NMR analysis).

Reaction of Tricyclo[3.3.2.0^{2,8}]deca-3,6-dien-9-one (78) with Dilute Trifluoroacetic Acid. Ketone **78** (ca. 25 mg) in chloroform-*d* (0.5 ml) was treated with water (3 drops) and trifluoroacetic anhydride (1 drop) and swirled overnight at 25°. After the aqueous layer had been separated, the organic layer was removed, dried over anhydrous potassium carbonate, and filtered. ^{1}H NMR and GLC analysis of the resultant solution revealed the exclusive presence of **1**.

Tricyclo[3.3.2.0^{2,8}]deca-3,6-dien-9-ol (79). Ketone **78** (0.16 g, 0.0011 mol) was dissolved in methanol (5 ml) and cooled to 0°. Sodium borohydride (0.20 g, excess) in water (2 ml) and sodium hydroxide (2 *N*, 0.4 ml) was added to the ketone solution. The mixture was stored at 0° for 15 hr. After vacuum evaporation of the methanol, the residue was taken up in ether, worked up in the usual fashion, and concentrated to an oil (0.14 g, 88%) which contained only one component (GLC, column A).

Alcohol **79** was collected by preparative GLC: ir (neat) 3350 (s), 1645 (w), and 1620 cm^{-1} (w); ^{1}H NMR δ 5.8 (m, 2 H, H at C-3, -7), 5.1 (br t, 2 H, H at C-4, -6), 3.8 (m, 1 H, H at C-9), 2.3 (br m, 6 H, H at C-1, -2, -5, -8, -10), and 2.0 (s, 1 H, hydroxylic OH, shift is concentration dependent, disappears upon addition of D_2O); uv λ_{max} (ethanol) 198 and 225 nm (ϵ_{max} 12,100 and 3670); exact mass, calcd, 148.0888; found, 148.0891.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.14; H, 8.39.

The infrared data previously reported[24] match the observed spectrum of **79**. The ^{1}H NMR of **79** is temperature dependent.

***anti*-8-Acetoxybicyclo[4.2.2]deca-2,4,9-trien-7-one (64).** Ketone **1** (0.50 g, 0.0034 mol) and lead tetraacetate (1.5 g, 0.0034 mol) were refluxed in acetic acid (20 ml) for 5 hr. The mixture was poured into water and extracted with ether and methylene chloride, and the combined organic extracts were treated in the usual manner and concentrated. Upon storage at −20°, the crude product crystallized (0.70 g, 100%); GLC analysis (column A) showed the material to be 99% pure. Distillation afforded **64**, pale yellow crystals: bp 94–96° (0.04 mm); mp 81–82°; ir (KBr pellet) 1740 (s) and 1220 cm^{-1} (s); ^{1}H NMR δ 5.9 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 5.35 (m, 1 H, H at C-8), 3.6 (m, 2 H, H at C-1, -6), and 2.0 (s, 3 H, methyl CH); exact mass, calcd, 204.0786; found, 204.0783.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.60; H, 5.88. Found: C, 70.71; H, 5.67.

Acid-Catalyzed Reaction of *anti*-8-Acetoxybicyclo[4.2.2]deca-2,4,9-trien-7-one (64) with Methanol. Ketone **64** (0.20 g, 0.0001 mol) in methanol (10 ml) containing 25 grains of *p*-toluenesulfonic acid was refluxed for 7 hr. The mixture was worked

up as usual and concentrated to a yellow oil (0.18 g, 100%) which was a 93:7 mixture of syn and anti isomers (column A). *syn*-8-Methoxybicyclo[4.2.2]deca-2,4,9-trien-7-one (**84**) was obtained by preparative GLC: ir (neat) 1720 cm^{-1}; ^1H NMR δ 5.8 (m, 6 H, H at C-2, -3, -4, -5, -9, -10), 4.05 (dd, 1 H, H at C-8), 3.7 (m, 2 H, H at C-1, -6), and 3.35 (s, 3 H, methoxy CH); exact mass, calcd, 176.0837; found, 176.0835.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.15; H, 6.89.

Registry No.—**1**, 36628-97-4; 1 semicarbazone, 54549-46-1; **4**, 34733-74-9; **6**, 36628-98-5; **7**, 36629-01-3; **8**, 15677-13-1; **10**, 36629-05-7; **11**, 36629-06-8; **12**, 36629-04-6; **13**, 54594-41-1; **15**, 36629-00-2; **16**, 36629-02-4; **18**, 36661-61-7; **22**, 40815-23-4; **23**, 93-04-9; **32**, 54549-47-2; **33**, 54549-48-3; **35**, 54549-49-4; **36**, 54549-50-7; **37**, 54549-51-8; **39**, 54549-59-6; **39** Me ester, 54549-60-9; **43**, 54549-61-0; **50**, 54549-62-1; **51**, 54549-63-2; **52**, 54549-52-9; **54**, 54549-64-3; **56**, 4696-15-5; **56** 2,4-DNP, 54549-53-0; **58**, 54549-65-4; **60**, 54549-66-5; **62**, 54549-67-6; **64**, 54549-68-7; **66**, 54549-54-1; **70**, 54618-47-2; **71**, 54657-23-7; **72**, 54549-55-2; **73**, 54549-56-3; **78**, 15719-09-2; **79**, 54549-57-4; **84**, 54549-69-8; 84 2,4-DNP, 54549-70-1; diazomethane, 334-88-3; semicarbazide hydrochloride, 563-41-0; isopropenyl acetate, 108-22-5; pyrrolidine, 123-75-1; potassium *tert*-butoxide, 865-47-4; acetyl chloride, 75-36-5; trimethylsilyl chloride, 75-77-4; deuterium oxide, 7789-20-0; methyl fluorosulfonate, 421-20-5; β-tetralone, 530-93-8; dimethyl sulfate, 77-78-1; 2-naphthol, 135-19-3; isoamyl nitrite, 110-46-3; *o*-phenylenediamine, 95-54-5; methyl formate, 107-31-3; tosyl azide, 938-10-3; methylhydrazine, 60-34-4; dimazine, 57-14-7; barbaralone, 6006-24-2; 9-aldehydotricyclo[3.3.1.$0^{2,8}$]nona-3,6-diene, 54549-58-5; tosyl hydrazide, 1576-35-8; trifluoroacetic acid, 76-05-1; methanol, 67-56-1.

References and Notes

(1) (a) Abstracted from the Ph.D. Dissertation of J. B. Press, The Ohio State University, Columbus, Ohio, 1973. (b) This research has also been described in part by J. B. Press and H. Shechter, *Tetrahedron Lett.*, 2677 (1972).

(2) This work has been reviewed by (a) T. L. Burkoth and E. E. van Tamelen, "Nonbenzenoid Aromatics", Vol. 1, J. R. Snyder, Ed., Academic Press, New York, N.Y., 1969, Chapter 3; (b) L. T. Scott and M. Jones, Jr., *Chem. Rev.*, **72**, 181 (1972).

(3) (a) T. A. Antkowiak, Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1968; (b) T. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press, and H. Shechter, *J. Am. Chem. Soc.*, **94**, 5366 (1972); (c) see also L. A. Paquette, R. H. Meisinger, and R. E. Wingard, *ibid.*, **94**, 2155 (1972); E. Vedejs, R. A. Gabel, and P. D. Weeks, *ibid.*, **94**, 5842 (1972); (d) a modification of the method of M. Stoll and W. Scherrer, *Helv. Chim. Acta*, **23**, 941 (1940).

(4) An extension of the methods of R. Shapiro and M. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967), and G. Kaufman, F. Cook, H. Shechter, J. Bayless, and L. Friedman, *ibid.*, **89**, 5736 (1967).

(5) We should like to acknowledge the gift by Dr. M. J. Broadhurst.

(6) (a) The stereochemistry of **17** is not known. (b) 7-Methoxy-8-methylbicyclo[4.2.2]deca-2,4,7,9-tetraene, a product possibly expected from dimethylation of **2**, has not been found.

(7) Treatment of **1** with less potassium *tert*-butoxide (~1.25 equiv) in glyme at 25° and subsequent quenching with methyl fluorosulfonate results in enhanced recovery of **1**, lower conversion to **16**, and no **18**.

(8) These products were identified by comparison with authentic samples.

(9) M. J. Goldstein and S. A. Klein, *Tetrahedron Lett.*, 1085 (1973).

(10) (a) W. Grimme, H. J. Riebel, and E. Vogel, *Angew. Chem., Int. Ed. Engl.*, **7**, 823 (1968); (b) J. S. McConaghy, Jr., and J. J. Bloomfield, *Tetrahedron Lett.*, 1121 (1969); (c) J. Altman, E. Babad, M. B. Rubin, and D. Ginsburg, *ibid.*, 1125 (1969); (d) J. Altman, E. Babad, D. Ginsburg, and M. B. Rubin, *Israel J. Chem.*, **7**, 435 (1969); (e) W. von Philipsborn, J. Altman, E. Babad, J. J. Bloomfield, D. Ginsburg, and M. B. Rubin, *Helv. Chim. Acta*, **53**, 725 (1970).

(11) (a) Comparison of the ^1H NMR of **10**, **11**, **12**, and **16** and that for previously reported tetraenes (Table I) indicates that there are strong electronic effects by the 7 substituent on the proton resonance at C-8. With respect to unsubstituted tetraene **8** with C-8 proton absorption at δ 5.5, electron-withdrawing groups at C-7 cause significant shifts downfield whereas electron donors produce large upfield shifts. Thus the 7-bromo[11b] and 7-acetyl derivatives[11b] show resonance for their C-8 protons at δ 5.9 and 6.7, respectively, whereas the 7-acetoxy (**10**), 7-methyl,[11c] 7-trimethylsiloxy (**12**), 7-methoxy (**16**), and 7-pyrrolidino (**11**) derivatives display absorptions at δ 5.35, 5.28, 4.78, 4.50, and 4.15, respectively. (b) H. P. Löffler and G. Schröder, *Angew. Chem., Int. Ed. Engl.*, **7**, 736 (1968). (c) G. Schröder, U. Prange, and J. F. M. Oth, *Chem. Ber.*, **105**, 1854 (1972).

(12) A modification of the method of F. Litvan and R. Robinson, *J. Chem. Soc.*, 1997 (1938).

(13) The synthetic method is that of W. E. Parham and J. F. Dooley, *J. Am. Chem. Soc.*, **89**, 985 (1967).

(14) The experimental method is a modification of that described by M. Regitz and J. Rüter, *Chem. Ber.*, **101**, 1263 (1968).

(15) D. C. Sanders, Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1972.

(16) (a) M. Roberts, H. Hamberger, and S. Winstein, *J. Am. Chem. Soc.*, **92**, 6346 (1970); (b) G. Schröder, U. Prange, B. Putze, J. Thio, and J. F. M. Oth, *Chem. Ber.*, **104**, 3406 (1971); (c) L. A. Paquette and M. J. Broadhurst, *J. Org. Chem.*, **38**, 1886 (1973).

(17) J. R. Hargreaves, P. W. Hickmott, and B. J. Hopkins, *J. Chem. Soc. C*, 592 (1969).

(18) (a) C. D. Gutsche and T. D. Smith, *J. Am. Chem. Soc.*, **82**, 4067 (1960). (b) We wish to thank Dr. C. D. Gutsche for supplying the authentic sample in a personal communication, May 9, 1973. (c) Both samples possess identical ir properties.

(19) S. Moon and C. R. Ganz, *J. Org. Chem.*, **35**, 1241 (1970).

(20) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", 2nd ed, Wiley, New York, N.Y., 1967.

(21) Hydrazone **66**, prepared (96%) from **1** and hydrazine, shows expected spectral properties and reacts with tosyl chloride in pyridine to give **7**.

(22) S. G. Cohen and R. Zand, *J. Am. Chem. Soc.*, **84**, 586 (1962); (b) M. Schwarz, A. Besold, and E. R. Nelson, *J. Org. Chem.*, **30**, 2425 (1965); (c) R. M. Moriarty, *ibid.*, **28**, 2385 (1963).

(23) The minor product may be tricyclo[5.3.0.$0^{2,10}$]deca-3,5-dien-8-one. The properties and the possible structure of this product are discussed in ref 1a.

(24) W. von E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967).

(25) W. Staedel, *Justus Liebigs Ann. Chem.*, **217**, 24 (1883).

The Importance of Nonbonded Interactions in the Bicyclo[4.2.1]nona-2,4,7-trienyl System[1]

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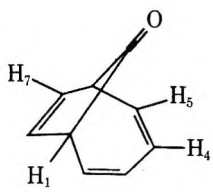
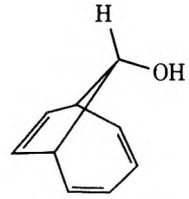
Spectral evidence is presented showing the importance of nonbonded interactions in the 9-bicyclo[4.2.1]nonatrienyl system when charge is induced at C_9. CNDO/2 calculations were made for the corresponding cation in a variety of geometries. The geometric variations were designed such that they are in line with the rearrangement process observed in the reactions of these compounds. The implications of the combined results from the spectral measurements and the calculations on the solvolytic reactions of these compounds are significant and in general emphasize the strong involvement of the four-carbon bridge containing the butadiene moiety.

Recent work by Schweig shows the importance of through-space interactions between adjacent chromophores in the bicyclo[4.2.1]nona-2,4,7-trienyl system.[2] The photoelectron spectra of bicyclo[4.2.1]nona-2,4,7-trienone (I) shows that the compound is not bicycloconjugated[3] but instead is homoconjugated where the *n* molecular orbital of the ketone group interacts directly with the butadiene moiety. These results have a bearing on the nature of the cation formed in solvolyses of *endo*-II-OTs[4] and *exo*-II-OTs,[5,6] protonation of 9-*exo*-methylenehicyclo[4.2.1]nona-2,4,7-triene,[7] and photolysis of bicyclo[4.2.1]nona-2,4,7-trien-9-one tosylhydrazone in CH_3OH–CH_3ONa,[5] or by the ionization of *endo*-II-OSOCl.[8] In order to gain a further understanding of the delocalization which occurs when charge is induced at or near the 9 carbon of these bicyclic structures, we approached the problem using spectroscopic measurements and CNDO/2 calculations.



I



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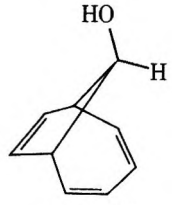

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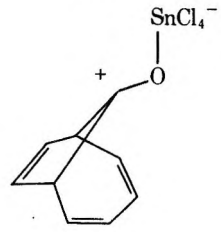


III

Spectroscopic Measurements. NMR measurements were made on the ketone I under a variety of conditions in order to determine the effect of positive charge formally introduced into the carbonyl carbon. Table I lists chemical shifts for the various hydrogens in I as measured on a Varian HR220. Assignment of the signals is based on the coupling constants, which do not vary greatly with the changes in conditions. The coupling constants (hertz), $J_{1,2}$ and $J_{1,8}$, are 7.5 and 1 in CCl_4, and are ~7 and 1.4 in SO_2, respectively. These values vary by ca. 0.1 Hz with the addition of metal salts to the sample solutions.

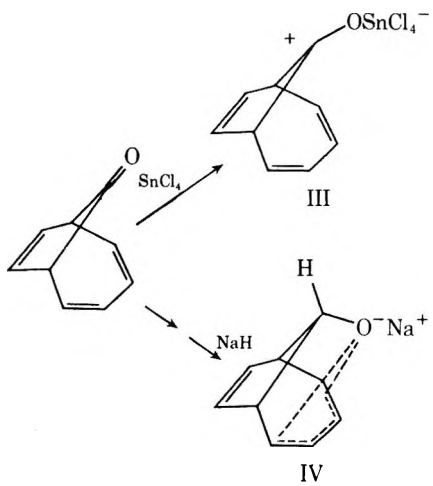
The spectra of I in CCl_4 containing 2 equiv of Eu(fod)$_3$ show all the signals deshielded where the bridgehead hydrogens feel the greatest effect. The effect on all the olefinic hydrogens is approximately comparable and considerably less than on the bridgehead hydrogens. The signal for $H_{2(5)}$ is shifted more than the signal for $H_{3(4)}$ which in turn is shifted only slightly more than that for $H_{7(8)}$.

The addition of 4 equiv of $SnCl_4$ to a solution of I in liquid SO_2 at −40° produces a burgundy-colored solution owing to complex formation (III). The ketone is recovered in good yield on quenching of this solution in methanol containing K_2CO_3. The recovered material contained 5% of another product whose structure was not identified. The NMR spectra of the ketone–$SnCl_4$ complex shows all the signals deshielded as a result of the induced positive charge, and the shifts are similar to those previously observed for other ketone–$SnCl_4$ complexes.[9]

The bridgehead hydrogens again experience the largest shift. The monoene hydrogens show little effect, while the butadiene hydrogens are shifted more significantly. Clearly very little charge is delocalized into the olefinic region, but to the extent that it occurs, it involves the butadiene π system primarily. Thus, polarization of the carbonyl group by a Lewis acid enhances homoconjugation between the carbonyl group and the butadiene π system.

Homoconjugation still prevails in the salts (IV) (Scheme I) of the endo carbinol II-OH, formed by reduction of I. The addition of 2 equiv of NaH to *endo*-II-OH in DME produces a bright red solution. The visible spectrum of the solution shows a broad band with λ_{max} at 538 nm and ϵ equal to 114. However, the NMR spectra of a 1 *M* solution of this alkoxide revealed that none of the olefinic protons

Scheme I



had shifted relative to those for *endo*-II-OH. The carbinol is recovered quantitatively on quenching with water. In contrast, no color was observed on treatment of a 1 *M* solution of *exo*-II-OH in DME with NaH. Thus, delocalization of the charge on the alkoxide oxygen into the π system in IV occurs preferentially through the butadiene moiety.

The experimental results indicate that homoconjugation between the one-carbon bridge and the butadiene moiety is important with little or no involvement of the other double bond. This is the case when the compound is neutral,[2] when the carbonyl has an induced positive charge, and when the oxygen of the reduced carbinol is negatively charged. While the noninvolvement of the simple double bond may be due to electronic considerations, it might also be attributed to its remoteness and its orientation as a result of the near-planar arrangement of the five-membered ring.

CNDO/2 Calculations. The electronic structure of the 9-bicyclo[4.2.1]nona-2,4,7-trienyl cation was analyzed using the CNDO/2 method.[10,11] The program contained the BINDEX subroutine for calculating bond indices as previously described by Wiberg.[12] The initial geometric parameters were measured directly from a model constructed with Drieding models and submitted to the GEOM subroutine which calculated the Cartesian coordinates. The calculations of the energy, electron density, and bond indices (Table II) were then based on this conformation and its corresponding coordinates (Figure 1).

In the initial calculations for the cation, the C_2 to C_8 distance was maintained at 2.47 Å and the C_9 bridge was tipped relative to the other two bridges. There is always a small residual bond index between C_2 and C_5 (0.09). In the undistorted cation the C_2–C_1–C_9 bond angle is 109.30°. First, aside from the olefinic sites, the C_1–C_2 bond is significantly delocalized resulting in a corresponding increase in bond indices between $C_1(C_6)$–C_9 and $C_2(C_5)$–C_9. The interactions between $C_2(C_5)$–$C_8(C_7)$ and $C_8(C_7)$–C_9 are only slight. Movement of the one-carbon bridge toward the two-carbon bridge reduces the degree of delocalization and destabilizes the system. Movement toward the butadiene moiety stabilizes the system in a smooth way to a minimum value when the C_2–C_1–C_9 bond angle is 100.00°. The total stabilization gained by this 10° change is 7.2 kcal.

This stabilization is accompanied by a further weakening of the $C_1(C_6)$–$C_2(C_5)$ bond and an increase in the $C_2(C_5)$–C_9 interaction. The charges at most of the atoms are hardly affected by this change and are equal to C_1 (+0.024), C_2 (+0.036), and C_3 (+0.008). The observed changes are from +0.002 to −0.001 at $C_8(C_7)$ and from +0.307 to +0.282 at C_9 when the bond angle decreases from 110° to 100.0°, respectively.

The description of the cation which emerges from these calculations indicates that the charge at C_9 is slightly dispersed into carbons $C_1(C_6)$ and $C_2(C_5)$ primarily. This results from the delocalization of the σ bonds $C_1(C_6)$–$C_2(C_5)$, and occurs with little change in the electronic character of the monoene and butadiene moieties. Structure VI (Scheme II) shows these interactions.

One other variation was attempted in order to further define the nature of the cation. Guided by the molecular rearrangements observed under solvolytic conditions,[4,6] the tipped cation VI was further distorted in order to reduce the interatomic distance between $C_2(C_5)$ and $C_8(C_7)$. This was accomplished by rotating the cyclopentenyl substructure (C_1, C_9, C_6, C_7, C_8) about an axis defined by the bridgehead carbons. The general symmetry of the molecule is maintained where the only changes are the decrease in the bond angle C_8–C_1–C_2 and the corresponding increase in the bond angle C_9–C_1–C_2.

Table I
Chemical Shifts of Bicyclo[4.2.1]nona-2,4,7-trien-9-one at 220 MHz

H	Chemical shifts, Hz from Me_4Si		Δδ	
	CCl_4[a]	CCl_4 with $Eu(fod)_3$[a]	Hz	δ
1(6)	655	1068	413	1.88
2(5)	1270	1419	149	0.68
3(4)	1270	1402	132	0.60
7(8)	1258	1382	124	0.56
H	SO_2[b]	SO_2 with $SnCl_4$[b]	Hz	δ
1(6)	703	831	128	0.58
2(5)	1292	1303	11	0.05
3(4)	1292	1328	25	0.11
7(8)	1269	1273	4	0.02

[a] 25°. [b] −40°.

Table II
Results of Calculations of the Bicyclo[4.2.1]nona-2,4,7-trienyl Cation

Bond angle for C_2–C_1–C_9	Energy, kcal	Bond indices									Interatomic distances	
		C_1–C_2	C_1–C_9	C_1–C_8	C_2–C_3	C_3–C_4	C_2–C_9	C_2–C_8	C_8–C_9	C_8–C_7	C_2–C_9	C_8–C_9
120.0	−44,148.5	0.95	1.07	0.94	1.88	1.09	0.05	0.02	0.07	1.88	2.62	2.21
109.3	−44,173.3	0.90	1.11	0.97	1.88	1.09	0.09	0.02	0.03	1.89	2.44	2.26
106.9	−44,176.5	0.89	1.11	0.98	1.88	1.09	0.09	0.02	0.03	1.89	2.40	2.28
106.0	−44,177.6	0.89	1.11	0.98	1.88	1.09	0.10	0.02	0.03	1.89	2.39	2.28
103.5	−44,179.8	0.88	1.11	0.99	1.88	1.08	0.11	0.02	0.03	1.89	2.35	2.30
102.0	−44,180.8	0.88	1.11	0.99	1.88	1.08	0.11	0.02	0.02	1.89	2.33	2.31
100.0	−44,181.5	0.88	1.10	1.00	1.87	1.08	0.11	0.02	0.02	1.88	2.30	2.33
98.0	−44,181.3	0.88	1.10	1.00	1.87	1.08	0.12	0.02	0.02	1.88	2.27	2.35

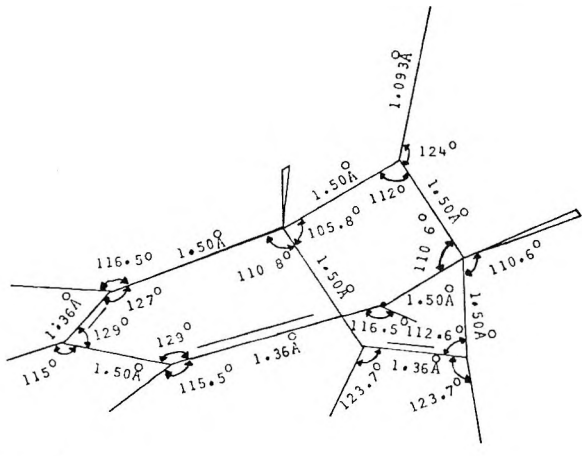


Figure 1.

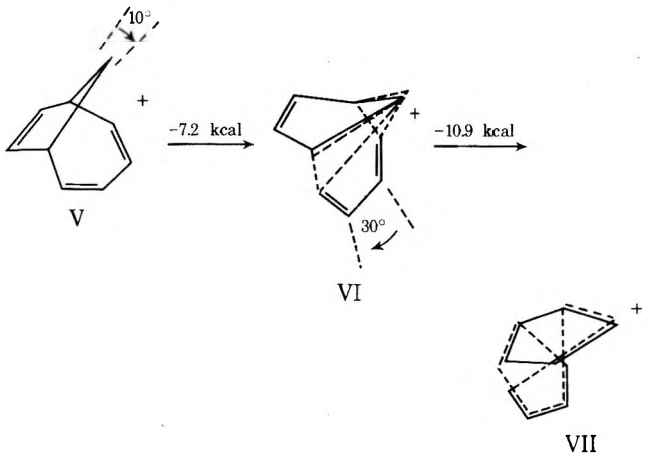
Table III
Calculations on Cation VI

Bond angle $C_2-C_1-C_8$	Energy, kcal	Bond indices								
		C_1-C_2	C_1-C_9	C_1-C_8	C_2-C_3	C_3-C_4	C_2-C_9	C_2-C_8	C_8-C_9	C_7-C_8
110.6	−44,181.5	0.88	1.10	1.00	1.87	1.08	0.11	0.02	0.02	1.88
107.1	−44,182.7	0.88	1.11	0.99	1.87	1.09	0.11	0.03	0.03	1.87
104.6	−44,183.3	0.87	1.12	0.98	1.86	1.09	0.10	0.04	0.03	1.86
103.7	−44,184.1	0.87	1.13	0.98	1.86	1.10	0.10	0.05	0.03	1.86
101.3	−44,183.8	0.87	1.13	0.97	1.85	1.10	0.10	0.06	0.03	1.84
95.6	−44,183.9	0.86	1.15	0.95	1.83	1.12	0.08	0.10	0.04	1.80
90.6	−44,187.1	0.85	1.17	0.93	1.79	1.14	0.08	0.15	0.05	1.74
86.6	−44,189.1	0.84	1.19	0.91	1.76	1.15	0.07	0.20	0.06	1.67
85.6	−44,189.9	0.84	1.20	0.91	1.75	1.16	0.07	0.21	0.06	1.65
84.6	−44,190.5	0.83	1.20	0.90	1.74	1.16	0.06	0.22	0.06	1.64
82.6	−44,191.6	0.83	1.21	0.89	1.71	1.17	0.06	0.26	0.07	1.59
80.6	−44,192.4	0.82	1.22	0.88	1.69	1.17	0.05	0.29	0.07	1.55
78.6	−44,187.5	0.81	1.23	0.86	1.67	1.18	0.05	0.33	0.08	1.51
75.6	−44,186.2	0.80	1.23	0.85	1.64	1.18	0.04	0.38	0.08	1.43
67.4	−44,175.4	0.80	1.05	0.93	1.62	1.04	0.01	0.46	0.09	1.09

Table IV
Calculations on Cation VI

Bond angle $C_2-C_1-C_8$	Charge densities					Interatomic distance C_2-C_8, Å
	$C_1(C_6)$	$C_2(C_5)$	$C_3(C_4)$	$C_7(C_8)$	C_9	
110.6	3.976	3.964	3.992	4.001	3.718	2.47
107.1	3.976	3.959	3.995	4.000	3.718	2.41
104.6	3.976	3.995	3.997	3.999	3.720	2.37
103.7	3.977	3.953	3.998	3.998	3.721	2.36
101.3	3.977	3.949	4.000	3.997	3.725	2.32
95.6	3.979	3.937	4.004	3.992	3.740	2.22
90.6	3.983	3.923	4.008	3.987	3.757	2.13
86.6	3.985	3.911	4.010	3.984	3.779	2.06
85.6	3.985	3.908	4.010	3.983	3.785	2.04
84.6	3.986	3.905	4.010	3.981	3.792	2.02
82.6	3.985	3.898	4.008	3.980	3.809	1.98
80.6	3.987	3.892	4.007	3.976	3.826	1.94
78.6	3.989	3.886	4.005	3.974	3.840	1.90
75.6	3.987	3.878	3.999	3.959	3.884	1.84
67.4	3.960	3.905	3.912	3.874	4.202	1.66

Scheme II



As can be seen by the results listed in Table III, this motion further stabilizes the system in a smooth way to a minimum value when the $C_8-C_1-C_2$ bond angle is 80.6° and the $C_2-C_1-C_9$ bond angle is 130.0°. That is, closing the angle 30° stabilizes the cation by 10.9 kcal. The resulting structure has minimal through-space interactions of the olefinic moieties with the cation center at C_9. On the other hand, the closer proximity of $C_2(C_5)$ and $C_8(C_7)$, 1.94 Å, increases the interaction between the monoene and diene where the final bond index is 0.29. The bond indices for the monoene and butadiene moieties are significantly reduced, but the π character of the butadiene structure is preserved with the central bond (C_3-C_4) maintaining a lower bond index.

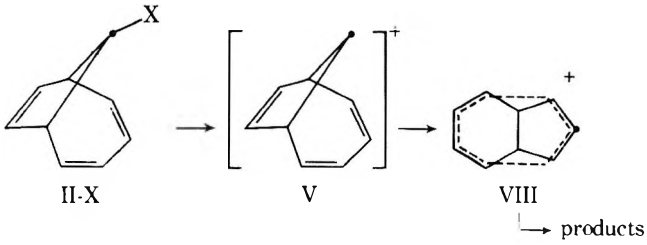
The other changes occur in the formal σ structure, where $\sigma_{1,2}$ and $\sigma_{6,5}$ are further delocalized, the bonds $\sigma_{1,8}$ and $\sigma_{6,7}$ are also delocalized and the double bond character between $C_1(C_6)$ and C_9 increases. Accompanying these electronic changes is a shift of the partial positive charge from $C_1(C_6)$ and C_9 to $C_2(C_5)$ (Table IV). The centers $C_3(C_4)$ and $C_7(C_8)$ continue to feel very little charge.

One final operation which was performed, but the results are not tabulated, involved elongation of the $C_1(C_6)-C_2(C_5)$ bonds at various points down Table III. The effect of bond elongation was to destabilize the system in every case.[13]

Discussion

Treatment of ketone I with $SnCl_4$ in liquid SO_2 at low temperatures successfully induced sufficient charge at C_9 to permit observation of the shifts of the hydrogen signals in the NMR spectra, but not enough to permit the rear-

Scheme III



rangement process to occur (Scheme III). Delocalization of charge away from C_9 into the olefinic moieties is probably minimal, since it is a tertiary center with an oxygen substituent. However, some charge is delocalized and primarily into the butadiene. In line with these observations, calculations on the unsubsituted cation (V) reveal that C_9 interacts to a slight extent with the butadiene moiety, and that the cation is substantially stabilized by slight tipping of C_9 toward the four-carbon bridge.

Regarding the character of the "tipped" cation (VI), it is not simply a 1,2-bishomocyclopentadienyl cation, which is antihomoaromatic, since there is a significant delocalization of the C_1–C_2 and C_6–C_5 σ bonds plus an accompanying increased interaction between C_2 and C_5. Furthermore, some level of interaction, although slight, is always maintained with the monoene.

The unrearranged cation (V) (Scheme IV) described here has some interesting implications on the solvolytic behavior of *endo*-II-OTs[4] and *exo*-II-OTs.[5,6] First of all, the rearrangement of cation V to form VIII competes very efficiently with chemical capture. However, to the extent that V can be captured, both steric and electronic considerations would predict chemical capture at C_9 to form exo product.

Contrary to this expectation, chemical capture of the cation produced in the photolysis of bicyclo[4.2.1]nona-2,4,7-trien-9-one tosylhydrazone in methanol is reported to yield only *endo*-II-OMe plus the rearranged products and no *exo*-II product.[5] Thus, in this reaction either the protonation step to produce *exo*-II-N_2^+ is stereospecific where the approach of the methanol is endo, generating a tight ion pair[14,15] which subsequently produces *endo*-II-OMe, or there is no specificity in the steps leading to the generation of cation V but the approach of the methoxide anion is guided endo by the stabilizing interaction with the butadiene moiety or a combination of these effects. The latter view is supported by the observed interaction between the negative oxygen atom and the butadiene moiety in IV.

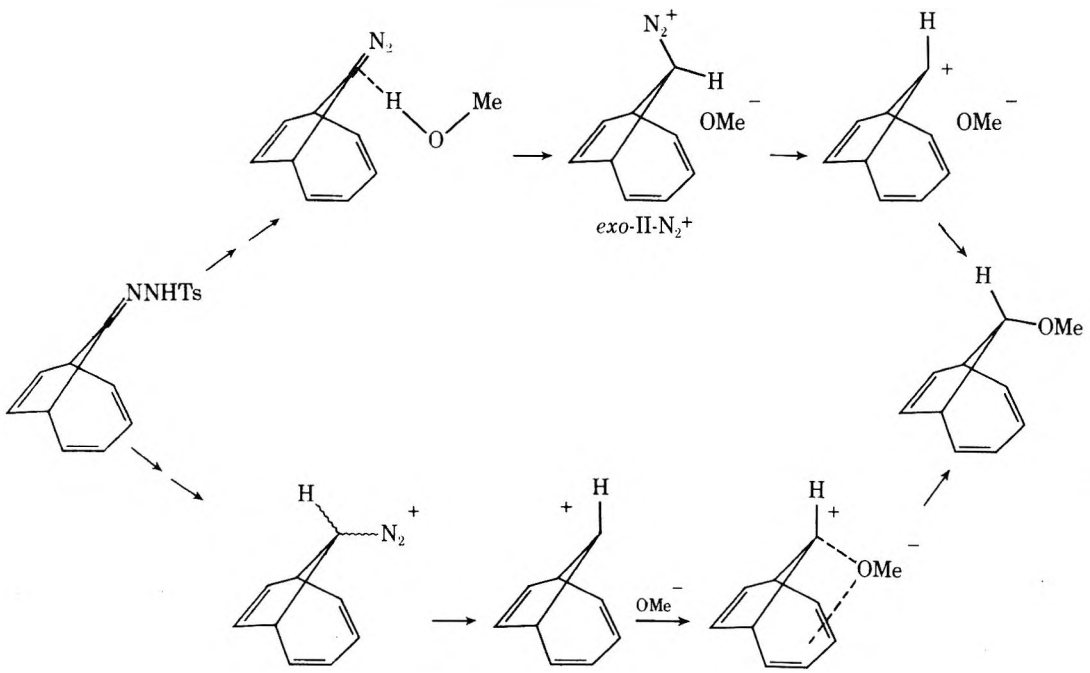
In line with this view, the ionization of *endo*-II-OTs may proceed with considerable interaction between the forming toluenesulfonate anion and the butadiene moiety. With this interaction present, the solvolytic rates of *endo*-II-OTs will have a relatively low solvent sensitivity.[6]

The stability of cation V was calculated for a variety of conformations produced by tipping the one-carbon and the four-carbon bridge. Tipping of the one-carbon bridge toward the four-carbon bridge and subsequent tipping of the four bridge toward the two-carbon bridge produces a smooth exothermic change which results in a cation which is further stabilized by as much as 18 kcal.

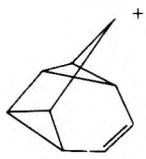
While we do not pretend to know the exact mechanism for the ionic rearrangement reaction which results in the formation of the bishomotropylium ion (Scheme III), the simple operations performed here on cation V prove to be energetically very favorable and could possibly resemble the initial stages of the rearrangement reaction. It is realized that the geometries used in these calculations are at best good approximations of the real system, since neither vibrations of the cationic system away from the equilibrium geometry nor solvation were taken into account. However, the implications of this work are that the initial stages of the rearrangement reaction must proceed via an efficient exothermic pathway with no significant minimums. Secondly, regarding the character of the cation when $C_2(C_5)$ migrates from $C_1(C_6)$ to $C_8(C_7)$, the results in Table III show that the process which continues to close the distance between $C_2(C_5)$ and $C_8(C_7)$ with a possible resultant formation of a biscyclopropylcarbinyl cation, X, is energetically very costly. That is, reduction of this distance to 1.66 Å destabilizes the cation by 17 kcal.

It may well be that all pathways leading from VII to VIII will include some endothermic steps, where those involving structures like IX will prove less favorable because of the

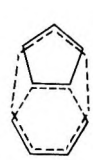
Scheme IV



steric strain considerations than those involving more delocalized structures like X.



IX



X

Experimental Section

exo-Bicyclo[4.2.1]nona-2,4,7-trien-9-ol. A solution containing 10 g of ketone I,[4] 50 g of aluminum isopropoxide, freshly distilled (131–134°, 4–5 mm), 0.5 ml of acetone, and 500 ml of xylene, dried over sodium, was refluxed for 12 hr. To the cooled mass was added 100 ml of 10% aqueous NaOH and the mixture was extracted with ether. After the ethereal extract was washed with water and dried, the ether and xylene were removed by distillation at 1 atm. The remaining residue was chromatographed on 100 g of activity III alumina. The pentane fractions contained 6.17 g of *endo*-II-OH while the 50% ether–pentane fractions contained 1.66 g of *exo*-II-OH.

Analysis of the ethereal extract before distillation by VPC on a 2-m column containing 2.5% KOH–Carbowax 20M on Chromosorb W 80/100 mesh at 120° revealed a mixture of 80% *endo*-II-OH (4.5 min) and 20% *exo*-II-OH (11.0 min). Only 0.1% of another product was detected. This endo/exo ROH ratio of 4:1 did not change when the reaction mixture was heated for up to 4 days.[5]

Epimerization of *exo*-II-OH under the same conditions for 16 hr gave a 1:4 endo/exo ROH mixture.

The carbinol, *exo*-II-OH, was recrystallized from hexanes: mp 84–85°; ir (KBr) 3250, 3160, 3140, 2960, 2920, 1580 cm^{-1}; δ_{Me_4Si} (CS_2) 5.84 (m, 2.04, H_2), 5.69 (m, 2.04, H_3), 5.13 (d, J = 1.5 Hz, 2.04, H_7), 3.77 (s, 0.95, H_9), 2.78 (d, J = 7.2 Hz, 2.00, H_1), and ca. 2.8 (broad, 0.94, OH). The exo stereochemistry is indicated by the lack of coupling between H_1 and H_9.

Preparation of Ketone–$SnCl_4$ Complex. Sulfur dioxide (0.4 ml) was distilled into a NMR tube containing 34 mg of ketone I under nitrogen at −78°. Excess $SnCl_4$, 2–5 equiv, was added and the tube was stoppered. Spectral measurements were made at −40°.

After 0.5 hr, 1 ml of saturated Na_2CO_3 in methanol was added and the mixture was extracted with ether in the usual manner. The ketone I was recovered in 25% yield, and was >95% pure. Long reaction times produced ca. 10% of another ketonic product, not identified ($\nu_{C=O}$ 1720 cm^{-1}).

While the recovery from liquid SO_2 was poor (25%), the recovery from a nitromethane solution was good. The ketone was recovered in 93% yield along with 5% of an aromatic product.

Preparation of Sodium Alcoholates. To 1 mmol of the carbinol in 1 ml of anhydrous DME was added 2 equiv of pentane-washed sodium hydride with stirring. Color developed after a few minutes with the *endo*-II-OH. After NMR measurements were made at 0°, the solutions were diluted with DME and the uv–visible spectra were measured. *endo*-II-OH had λ_{max} 538 nm (ϵ 114) while *exo*-II-OH had no spectra. The solutions were quenched with wet ether and worked up in the usual way. The recovered yield of *endo*-II-OH was 91%.

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Registry No.—I, 34733-74-9; *endo*-II-OH, 34712-67-9; *exo*-II-OH, 55606-59-2; III, 55606-56-9; *endo*-IV, 55606-60-5; *exo*-IV, 55606-61-6; 9-bicyclo[4.2.1]nona-2,4,7-trienyl cation, 50613-69-9; aluminum isopropoxide, 555-31-7; $SnCl_4$, 7646-78-8; sodium hydride, 7646-69-7.

References and Notes

(1) This research was supported by the Cottrell Research Foundation and USPHS Grant 2-T01-GM-01045.
(2) W. Shafer, H. Schmidt, A. Schweig, R. W. Hoffman, and H. Kurz, *Tetrahedron Lett.*, 1953 (1974).
(3) M. J. Goldstein and R. Hoffman, *J. Am. Chem. Soc.*, **93**, 6193 (1971).
(4) (a) A. F. Diaz, J. Fulcher, M. Sakai, and S. Winstein, *J. Am. Chem. Soc.*, **96**, 1264 (1974); (b) A. F. Diaz and J. Fulcher, *ibid.*, **96**, 7954 (1974).
(5) W. Kirmse and G. Voigt, *J. Am. Chem. Soc.*, **96**, 7598 (1974).
(6) A. F. Diaz and J. Fulcher, *J. Am. Chem. Soc.*, submitted for publication.
(7) D. C. Sanders and H. Shechter, *J. Am. Chem. Soc.*, **95**, 6858 (1973).
(8) A. S. Kende and T. L. Bogard, *Tetrahedron Lett.*, 3383 (1967).
(9) D. G. Farnum, M. A. T. Heybey, and B. Webster, *J. Am. Chem. Soc.*, **86**, 673 (1964).
(10) J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.*, **43**, S129 (1965).
(11) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **43**, S136 (1965); **44**, 3289 (1966).
(12) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).
(13) R. Cetina, M. Rubio, and A. Sigrist, *Rev. Latinoam. Quim.*, in press.
(14) A. Diaz and S. Winstein, *J. Am. Chem. Soc.*, **88**, 1318 (1966).
(15) E. H. White and C. A. Elliger, *J. Am. Chem. Soc.*, **89**, 165 (1967).

Synthesis and Chemistry of 2,4-Dehydro-5-homoadamantanone[1]

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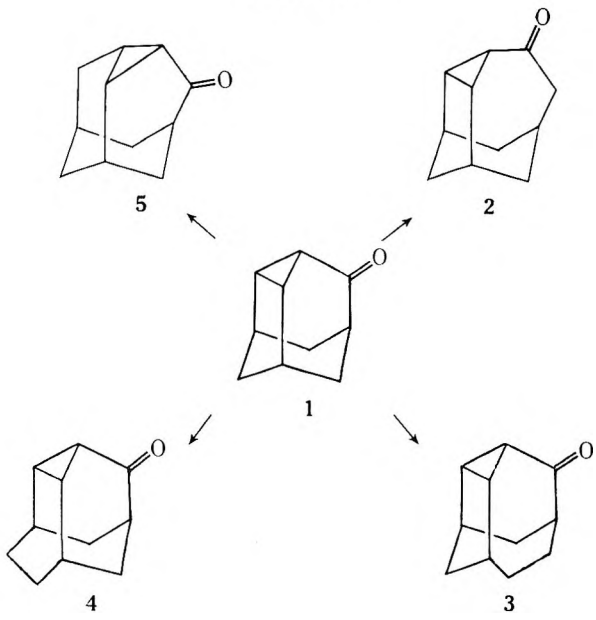
Received March 19, 1975

2,4-Dehydro-5-homoadamantanone (**5**) is readily prepared by a four-step reaction sequence from bicyclo[3.3.1]non-6-ene-3-carboxylic acid. Treatment of **5** with lithium in liquid ammonia proceeds by regiospecific cleavage of the C-3 to C-4 bond in **5** to give tricyclo[5.3.1.$0^{4,9}$]undecan-2-one (**27**). In contrast, perchloric acid catalyzed acetolysis of **5** leads to regiospecific cleavage of the C-2 to C-4 bond in **5** and formation of 2-*exo*-acetoxy-5-homoadamantanone. Sodium borohydride reduction of **5** occurs stereospecifically to afford 2,4-dehydro-5-*endo*-homoadamantanol (**9**). Acid-catalyzed isomerization of **9** provides 2-*exo*-homoadamant-4-enol exclusively which, in turn, gives homoadamant-4-en-2-one (**14**) upon Jones oxidation. Sodium borohydride reductions of enone **14** and ketone **27** both proceed by stereospecific attack at the exo face of the carbonyl carbon. The stereospecific synthesis of both 2-exo- and 2-endo-substituted homoadamantanes is presented. It is also shown that the stereochemistry of a 2-monosubstituted homoadamantane can be directly assigned from its characteristic ^1H NMR spectrum.

Homologation of 8,9-dehydro-2-adamantanone (**1**), without disruption of the conjugated cyclopropyl ketone moiety, allows for four "dehydrohomoadamantanones", **2–5** (Scheme I). As **1** has been shown to be a useful precursor for the synthesis of adamantyl,[3–6] protoadamantyl,[5–8] and isotwistyl[8,9] derivatives, cyclopropyl ketones **2–5** offer the potential for the synthesis of a variety of variously substituted polycyclic compounds. Recently, we have prepared

Scheme I

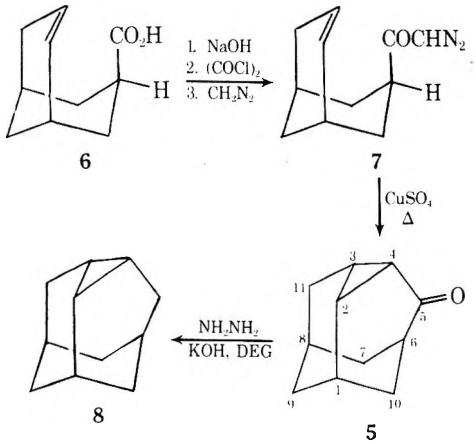


9,10-dehydro-2-homoadamantanone (**3**).[10] We now wish to report the synthesis of 2,4-dehydro-5-homoadamantanone (**5**) and some of the aspects of its chemistry.[11]

Results and Discussion

Cyclopropyl ketone **5** is readily obtained from bicyclo[3.3.1]non-6-ene-3-*endo*-carboxylic acid (**6**).[12] Sequential treatment of the sodium salt of **6** with oxalyl chloride and then diazomethane gives α-diazomethyl ketone **7** which, when decomposed in the presence of cupric sulfate in refluxing tetrahydrofuran, provides **5** (Scheme II). By this route, **5** was obtained in isolated yields of 50–70% from **6**. The skeletal framework of **5** was established by Wolff–Kishner reduction of **5** to give the known hydrocarbon 2,4-dehydrohomoadamantane (**8**).[13] The carbonyl absorption at 1688 cm^{-1} in **5** is indicative of a conjugated carbonyl.

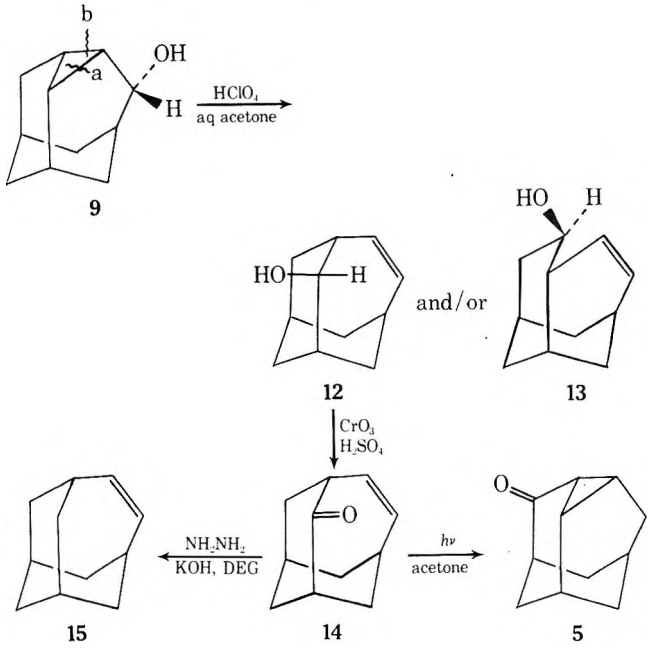
Scheme II

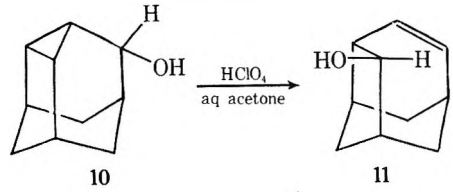


Sodium borohydride reduction of **5** affords a single alcohol to which we have assigned the structure of 2,4-dehydro-5-*endo*-homoadamantanol (**9**)[14] (Scheme III). An examination of molecular models shows that attack at the carbonyl carbon in **5** across the face of the seven-membered ring (i.e., endo attack) should be significantly impeded by the endo hydrogen at C-11. By contrast, there is no apparent steric hindrance to attack at the carbonyl carbon in **5** across the face of the six-membered ring (i.e., exo attack).

We have shown previously that treatment of 8,9-dehydro-2-adamantanol (**10**) with dilute perchloric acid in refluxing 80% aqueous acetone affords 2-*exo*-protoadamantenol (**11**).[5] An analogous cyclopropylcarbinyl–homoallyl

Scheme III

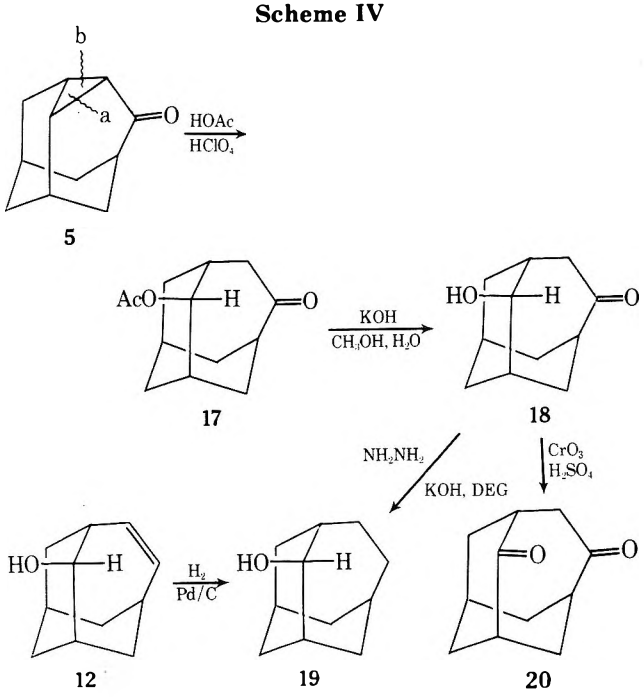




rearrangement in **9** might lead to 2-*exo*-homoadamant-4-enol (**12**) by cleavage of bond a in **9** and/or to 2-*exo*-tricyclo[5.3.1.$0^{4,9}$]undec-5-enol (**13**) by cleavage of bond b in **9**. Reaction of **9** with 0.005 *M* perchloric acid in refluxing aqueous acetone gives **12** exclusively. The skeletal framework of **12** follows from the conversion of **12** to the known hydrocarbon 4-homoadamantene (**15**).[13,15] Jones oxidation of **12** gives homoadamant-4-en-2-one (**14**) and Wolff–Kishner reduction of **14** provides **15**. Furthermore, irradiation of an acetone solution of **14** through a Pyrex filter regenerates ketone **5** by an oxadi-π-methane photorearrangement,[16] a reaction characteristic of β,γ-unsaturated ketones.

We have also shown that acid-catalyzed conjugate additions to **1** provide a general route to 2-exo-substituted 5-protoadamantanones (**16**).[8] Cyclopropyl ketone **5** undergoes an analogous reaction. Perchloric acid catalyzed acetolysis of **5** affords 2-*exo*-acetoxy-5-homoadamantanone (**17**) in ca. 90% yield (Scheme IV). Thus, conjugate addition to **5** also proceeds by the preferential cleavage of bond a. The skeletal framework of **17** and the skeletal position and stereochemistry of the acetoxy substituent in **17** follow from the conversion of **17** to 2-*exo*-homoadamantanol (**19**). Hydrolysis of **17** gives 2-*exo*-hydroxy-5-homoadamantanone (**18**) and Wolff–Kishner reduction of **18** provides **19**. Catalytic hydrogenation of enol **12** affords an independent

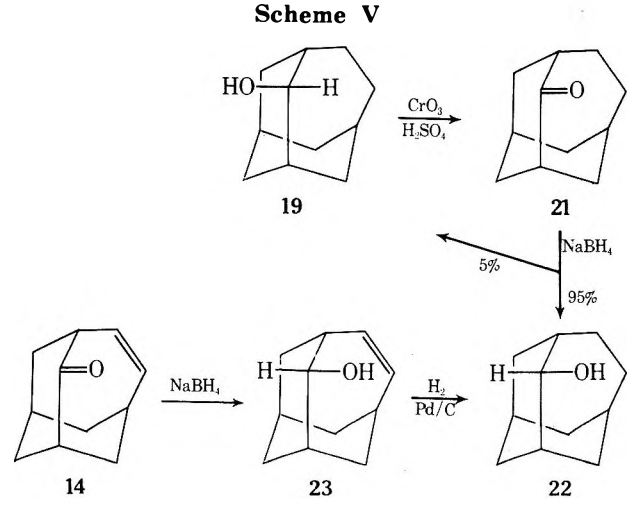
Scheme IV



route to **19**. It might also be noted that Jones oxidation of keto alcohol **18** gives 2,5-homoadamantanedione (**20**).

As expected, Jones oxidation of alcohol **19** gives 2-homoadamantanone (**21**) (Scheme V). Although 4-homoadamantanone (**26**) has been known for some time,[15,17] ketone **21** and 9-homoadamantanone, the other possible "homoadamantanones", have not been reported previously. Sodium borohydride reduction of **21** provides a 95:5 mixture of 2-*endo*-homoadamantanol (**22**) and **19**, respectively. An examination of molecular models shows that whereas there is no apparent steric hindrance to attack at the exo face of the carbonyl carbon in **21**, the endo hydrogen at C-5 in **21** appears to create some difficulty for attack at the endo face of the carbonyl carbon.

Scheme V

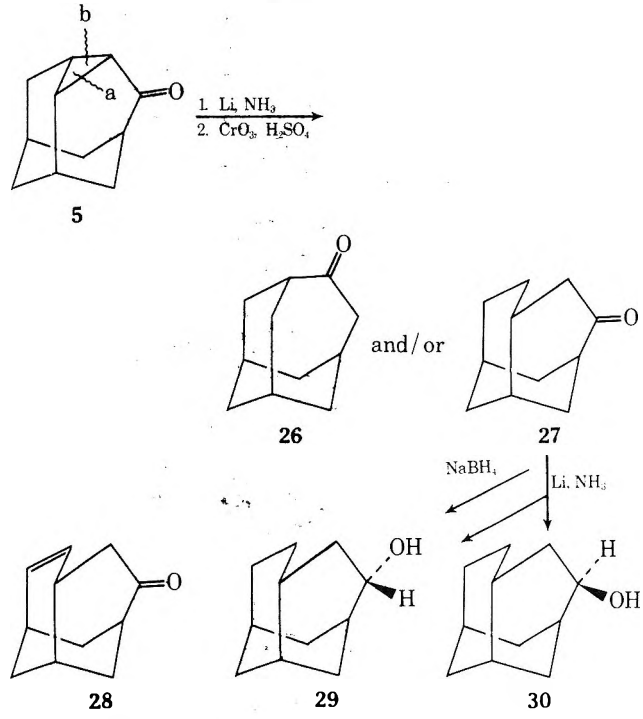


Alcohol **22** has also been independently synthesized. Sodium borohydride reduction of enone **14** gives 2-*endo*-homoadamant-4-enol (**23**) exclusively and catalytic hydrogenation of **23** provides **22**. An examination of molecular models shows that attack at the carbonyl carbon of **14** proceeds exclusively at its exo face because the orbitals of the π bond in **14** effectively prevent attack at the endo face. It is to be emphasized that the reactions summarized in Schemes III–V permit the stereospecific synthesis of both 2-exo- and 2-endo-substituted homoadamantanes.

The ^{1}H NMR spectra of the compounds generated in this study suggest that the stereochemistry of a 2-monosubstituted homoadamantane can be directly assigned from the characteristic splitting pattern of the C-2 hydrogen signal. Thus, whereas the ^{1}H NMR signals of the endo hydrogens at C-2 in **12** and **17–19** all appear as broad singlets, the ^{1}H NMR signals of the exo hydrogens at C-2 in **22** and **23** both appear as doublets of doublets. This is also the case for 2-*exo*-acetoxyhomoadamantane (**24**) and 2-*endo*-acetoxyhomoadamantane (**25**) (see Experimental Section).

Reductive cleavage of the cyclopropane ring in conjugated cyclopropyl ketones with lithium in liquid ammonia usually proceeds regiospecifically.[18] Such a reaction with cyclopropyl ketone **5** might lead to 4-homoadamantanone (**26**) by cleavage of bond a in **5** and/or to tricyclo[5.3.1.0^{4,9}]undecan-2-one (**27**) by cleavage of bond b in **5** (Scheme VI). Treatment of **5** with lithium in refluxing ammonia, followed by Jones oxidation of the reaction mixture, gives ketone **27** exclusively. As ketone **27** is identical with the ketone resulting from the catalytic hydrogenation of enone **28**,[19] the skeletal structure and the skeletal position of the carbonyl substituent in **27** are established. *Thus, it is possible to achieve selective regiospecific cleavage of the C-2 to C-4 bond* (i.e., **5** → **17**) *or the C-3 to C-4 bond* (i.e., **5** → **27**) *in 2,4-dehydro-5-homoadamantanone.*

Scheme VI



Sodium borohydride reduction of ketone **27** also proceeds stereospecifically to give 2-*endo*-tricyclo[5.3.1.0^{4,9}]-undecanol (**29**). An examination of molecular models clearly shows that attack at the endo face of the carbonyl carbon in **27** is prevented by the endo hydrogen at C-6. In contrast, reduction of **27** with lithium in liquid ammonia provides a ca. 1:1 mixture of **29** and 2-*exo*-tricyclo[5.3.1.0^{4,9}]undecanol (**30**). Jones oxidation of **29** or **30** regenerates **27**.

Aspects of the chemistry of 2-homoadamantanone and its derivatives are currently under active investigation.[21]

Experimental Section

All melting points were obtained in sealed capillary tubes using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or

337 spectrophotometers and proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers. Apparent splittings are given in all cases. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^1H NMR spectrum of the product(s) vs. the signal of a predetermined amount of added standard (generally trichloroethylene) and are regarded as being accurate to ca. ±10%. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

2,4-Dehydro-5-homoadamantanone (5). A slurry of 4.61 g (27.7 mmol) of 3-*endo*-carboxybicyclo[3.3.1]non-6-ene (**6**)[12] in 50 ml of water was titrated to a phenolphthalein end point with 1 *N* sodium hydroxide. The solvent was evaporated at reduced pressure and the residue was heated at 70° (0.1 mm) for 12 hr. The resulting dry sodium salt of **6** was treated with 50 ml of anhydrous benzene and 4 ml of anhydrous pyridine, cooled to 0°, and stirred as 7 ml (82.6 mmol) of oxalyl chloride was added dropwise. After addition was complete, the reaction mixture was stirred at 0° for 15 min and at room temperature for 15 min. The mixture was then filtered and the residue was washed several times with benzene. Evaporation of the solvent and excess oxalyl chloride provided a residue of 3-*endo*-bicyclo[3.3.1]non-6-enoyl chloride. The crude acid chloride was dissolved in 100 ml of anhydrous ether, cooled to 0°, and a solution of ca. 4.5 g (107.1 mmol) of diazomethane in 400 ml of anhydrous ether was added rapidly with stirring. The reaction mixture was stirred at 0° for 1 hr and at room temperature for 19 hr. Evaporation of the solvent at reduced pressure gave 3-*endo*-bicyclo[3.3.1]non-6-enyl diazomethyl ketone (**7**) as a viscous oil.

The unpurified α-diazo ketone **7**, dissolved in 100 ml of tetrahydrofuran, and 4.5 g of cupric sulfate were stirred at reflux for 12 hr, then cooled and filtered. The solvent was evaporated at reduced pressure and the residue was dissolved in 30 ml of water and 50 ml of ether. The aqueous and ethereal layers were separated and the aqueous layer was extracted with ether (3 × 25 ml). The ether extracts were combined and dried over anhydrous magnesium sulfate, and the solvent was evaporated at reduced pressure. The residue was dissolved in a solution of 50 ml of methanol and 50 ml of water, 4.5 g of potassium hydroxide was added, and the mixture was refluxed for 4 hr. Evaporation at reduced pressure removed the methanol from the reaction mixture and the residue was extracted with ether (3 × 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. The residue was sublimed (100°, 0.1 mm), then column chromatographed on silica gel with benzene as eluent, and finally resublimed to give 2.29 g (51% yield) of pure **5**: mp 253–254°; δ_{Me_4Si} ($CDCl_3$) 2.7–1.1 (br m); ν (CCl_4) 3030, 2935, 2860, 1688, 1460, 1450, 1440, 1350, 1340, 1300, 1250, 1160, 1125, 1095, 1015, and 1000 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.29; H, 8.49.

2,4-Dehydrohomoadamantane (8). A solution of 209 mg (1.29 mmol) of **5**, 1.0 g of potassium hydroxide, and 1.0 g of 95% hydrazine in 8 ml of diethylene glycol was heated with stirring at 110° for 30 min, and then for 24 hr at 180°. During this time, a white solid appeared on the water-cooled condenser. The system was cooled and the material on the condenser was dissolved in cyclohexane. The pot residue was diluted with water (50 ml) and extracted with cyclohexane (3 × 30 ml). The cyclohexane extracts from condenser and pot were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a solid which GLC analysis (5 ft × 0.25 in. Carbowax column, 175°) showed contained a major component of short retention time and a minor component of much longer retention time (which was not investigated further). Isolation of the major product by GLC (above conditions) gave pure **8** which was identified by comparison of its ir spectrum with that of an authentic sample prepared by an alternative route.[13] GLC analysis of the product mixture showed that **8** was obtained from **5** in ca. 35% yield.

5-*endo*-2,4-Dehydrohomoadamantanol (9). A solution of 500 mg (3.09 mmol) of **5** in 5 ml of methanol was added dropwise to a stirred solution of 380 mg (10.0 mmol) of sodium borohydride in 10 ml of methanol at 0°. The reaction mixture was stirred for 45 min at 0° and then for 45 min at room temperature, at which point 10 ml of water was added. The resulting solution was saturated with sodium chloride and then extracted with ether (3 × 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. Analysis of the residue by ^1H NMR indicated that **9** was obtained in ca. 75% yield. GLC analysis (5 ft × 0.25 in. FFAP column, 170°) showed a single component to be present and purification of **9** by GLC (above conditions) gave a white solid: mp 269–272°; δ_{Me_4Si} ($CDCl_3$) 4.28 (apparent t, J = 5.5 Hz, 1 H, CHOH) and 2.6–0.6 (br m, 15 H); ν (CCl_4) 3675, 3450 (br), 3050, 2935, 2875, 1440, 1380, 1345, 1080, 1060 and 1040 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.66; H, 9.53.

2-*exo*-Homoadamant-4-enol (12). A solution of 128 mg (0.78 mmol) of **9** in 15 ml of 80% aqueous acetone which was 0.005 *M* in perchloric acid was stirred at reflux for 15 hr. The solution was then saturated with sodium chloride and extracted with ether (3 × 30 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. Analysis of the residue by ^1H NMR indicated that **12** was obtained in approximately quantitative yield. GLC analysis (10 ft × 0.25 in. FFAP column, 200°) showed a single component to be present and purification of **12** by GLC (above conditions) gave a white solid: mp 265–266°; δ_{Me_4Si} ($CDCl_3$) 6.24–5.58 (m, 2 H, CH=CH), 3.84 (br s, 1 H, CHOH), and 2.8–0.8 (br m, 13 H); ν (CCl_4) 3630, 3420 (br), 3025, 2920, 2845, 1440, 1060, and 1020 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.54; H, 9.76.

Homoadamant-4-en-2-one (14). To a stirred solution of 129 mg (0.78 mmol) of **12** in 15 ml of acetone at 0° was added 600 μl of a freshly prepared solution of Jones reagent (2.8 g of chromic anhydride, 4.5 ml of sulfuric acid, and 12 ml of water). The reaction mixture was stirred at 0° for 20 min, then 20 ml of water was added, and the mixture was stirred at room temperature for an additional 30 min. The resulting solution was saturated with sodium chloride and extracted with ether (3 × 40 ml). The combined ether extracts were washed with saturated aqueous sodium bicarbonate (3 × 50 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated at reduced pressure and the residue was column chromatographed on silica gel with benzene as eluent and then sublimed at 100° (0.5 mm) to afford 114 mg (89% yield) of **14** as a white solid: mp 252–253°; δ_{Me_4Si} ($CDCl_3$) 6.34–5.64 (m, 2 H, CH=CH) and 3.1–1.2 (br m, 12 H); ν (CCl_4) 3065, 2950, 2875, 1712, 1435, 1300, 1255, and 1100 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.31; H, 8.74.

Homoadamantene (15). By a procedure analogous to that employed for **5** → **8**, Wolff-Kishner reduction of **14** provided **15** as the only reaction product (GLC analysis) in ca. 40% yield. Olefin **15** was isolated by GLC (5 ft × 0.25 in. FFAP column, 130°) and was identified by comparison of its ir spectrum with that of an authentic sample prepared by an alternative route.[15]

Acetone-Sensitized Photoisomerization of 14. A solution of 55 mg of **14** in 3 ml of acetone was irradiated through a Pyrex filter with a Hanovia L 450-W high-pressure mercury lamp. Monitoring the photolysis by GLC (5 ft × 0.25 in. FFAP column, 200°) showed a gradual disappearance of **14** and the appearance of a single photoproduct of longer retention time. After irradiation for 2.5 hr, no starting material remained and only the photoisomer was present. The solvent was evaporated at reduced pressure and the residue was sublimed to give 26 mg (47% yield) of **5**.

2-*exo*-Acetoxy-5-homoadamantanone (17). A solution containing 1.01 g (6.23 mmol) of **5** and 300 μl of 70% perchloric acid in 30 ml of acetic acid was stirred for 14 hr at 100°, then diluted with water (100 ml) and neutralized with solid sodium bicarbonate. The resulting mixture was extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided an oil which by ^1H NMR analysis contained a ca. 90% yield of **17**. GLC analysis (5 ft × 0.25 in. FFAP column, 190°) showed a single component to be present and isolation by GLC (above conditions) gave **17** as a clear oil: δ_{Me_4Si} ($CDCl_3$) 4.74 (br s, $W_{1/2}$ = 5.4 Hz, 1 H, $CHOCOCH_3$) and 2.9–1.2 (br m, 17 H, containing $CHOCOCH_3$ singlet at δ 2.07); ν (CCl_4) 2930, 2865, 1736, 1701, 1445, 1370, 1085, and 1025 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.14; H, 8.04.

2-*exo*-Hydroxy-5-homoadamantanone (18). A reaction mixture containing 1.095 g (4.93 mmol) of **17**, 1 g of potassium hydroxide, 25 ml of methanol, and 25 ml of water was refluxed for 4 hr. At this point the methanol was evaporated at reduced pressure and the residue was saturated with sodium chloride and extracted with ether (4 × 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. GLC analysis (5 ft × 0.25 in. Carbowax column, 220°) of the residue showed a major component of long retention

time and several very minor components of short retention time (which were not investigated further). Analysis of the residue by ^{1}H NMR indicated that **18** was obtained in ca. 85% yield. Purification by GLC (above conditions) gave **18** as a white solid: mp 310.5–312°; δ_{Me_4Si} ($CDCl_3$) 3.73 (br s, $W_{1/2}$ = 5 Hz, 1 H, CHOH) and 2.8–1.1 (br m, 15 H); ν (CCl_4) 3610, 3460, 2910, 2850, 1698, 1440, 1350, 1080, and 1030 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.33; H, 8.71.

2-*exo*-Homoadamantanol (19). A. A solution of 95 mg of **12** in 50 ml of ethanol was stirred with 400 mg of 5% palladium on charcoal under an atmosphere of hydrogen for 24 hr. The reaction mixture was then filtered to remove the catalyst. The catalyst was washed several times with methanol and the filtrate and washings were combined. Evaporation of the solvent at reduced pressure gave a solid residue which by ^{1}H NMR analysis contained a ca. 85% yield of **19**. Isolation of the product by GLC (5 ft × 0.25 in. Carbowax column, 190°) provided **19** as a white solid: mp 282.5–284°; δ_{Me_4Si} ($CDCl_3$) 3.62 (br s, $W_{1/2}$ = 5 Hz, 1 H, CHOH) and 2.5–1.0 (br m, 17 H); ν ($CHCl_3$) 3625, 3015, 2910, 1450, 1440, 1055, 1020, 980, and 945 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.32; H, 10.76.

B. By a procedure analogous to that employed for **5** → **8**, Wolff–Kishner reduction of **18** afforded **19** in an isolated yield of ca. 70%.

2,5-Homoadamantanedione (20). Oxidation of 77 mg of **18** with Jones reagent by the procedure described for **12** → **14** provided 62 mg of material which was purified by GLC (5 ft × 0.25 in. Carbowax column, 235°) to give **20** as a white solid: mp 306.5–307°; δ_{Me_4Si} ($CDCl_3$) 3.2–1.5 (br m); ν (CCl_4) 2920, 2850, 1702 (br), 1450, 1285, 1165, and 1045 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.21; H, 7.66.

2-Homoadamantanone (21). Oxidation of 258 mg of **19** with Jones reagent by the procedure described for **12** → **14** gave 224 mg (88% yield) of **21**. Isolation by GLC (5 ft × 0.25 in. Carbowax column, 190°) afforded **21** as a white solid: mp 278–279°; δ_{Me_4Si} ($CDCl_3$) 3.0–1.0 (br m); ν (CCl_4) 2915, 2860, 1700, 1440, 1220, 1115, 1070, 1000, and 960 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.50; H, 9.76.

2-*endo*-Homoadamant-4-enol (23). Sodium borohydride reduction of **14** by the procedure described for **5** → **9** provided **23**. Isolation by GLC (5 ft × 0.25 in. Carbowax column, 190°) gave **23** as a white solid: mp 291.5–292.5°; δ_{Me_4Si} ($CDCl_3$) 6.19 (dd, J = 10 and 8 Hz, 1 H, CH=CH at C-5), 5.67 (dd, J = 10.5 and 8 Hz, 1 H, CH=CH at C-4),[20] 3.73 (dd, J = 6 and 5 Hz, 1 H, CHOH), and 2.8–1.1 (br m, 13 H); ν ($CHCl_3$) 3580, 3450, 3020, 2915, 2860, 1460, 1450, 1400, 1390, 1090, 1050, and 1040 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.68; H, 9.53.

Oxidation of **23** with Jones reagent by the procedure described for **12** → **14** regenerated **14**.

2-*endo*-Homoadamantanol (22). Catalytic hydrogenation of **23** by the procedure described for **12** → **19** gave **22**. Isolation by GLC (5 ft × 0.25 in. Carbowax column, 190°) provided **22** as a white solid: mp 283.5–285.5°; δ_{Me_4Si} ($CDCl_3$) 3.85 (dd, J = 5.5 and 4 Hz, 1 H, CHOH) and 2.5–0.9 (br m, 17 H); ν ($CHCl_3$) 3625, 3450, 3010, 2915, 1445, 1060, and 1025 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.52; H, 10.78.

Jones oxidation of **22** by the procedure described for **12** → **14** gave **21**.

2-*exo*-Acetoxyhomoadamantane (24). To a solution of 262 mg (1.58 mmol) of **19** in 6 ml of acetic anhydride was added 0.5 g of sodium acetate. The mixture was stirred at 95° for 2 hr, then cooled and diluted with water (75 ml). The resulting mixture was neutralized with solid sodium bicarbonate and extracted with ether (3 × 30 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. Analysis of the residue by ^{1}H NMR indicated that **24** was obtained in ca. 90% yield. Isolation by GLC (5 ft × 0.25 in. Carbowax column, 220°) gave **24** as an oil: δ_{Me_4Si} ($CDCl_3$) 4.62 (br s, $W_{1/2}$ = 5 Hz, 1 H, $CHOCOCH_3$) and 2.4–1.0 (br m, 19 H, containing $CHOCOCH_3$ singlet at δ 2.00); ν (CCl_4) 2900, 2850, 1730, 1440, 1360, 1240, 1035, and 985 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.07; H, 9.77.

2-*endo*-Acetoxyhomoadamantane (25). Treatment of **22** according to the conditions employed for **19** → **24** provided **25** which was isolated by GLC (5 ft × 0.25 in. QF-1 column, 175°) as an oil: δ_{Me_4Si} ($CDCl_3$) 4.92 (dd, J = 6 and 4 Hz, 1 H, $CHOCOCH_3$) and 2.7–0.9 (br m, 19 H, containing $CHOCOCH_3$ singlet at δ 2.02); ν (CCl_4) 2910, 2850, 1730, 1445, 1360, 1240, 1040, and 1025 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.21; H, 9.72.

Tricyclo[5.3.1.0^{4,9}]undecan-2-one (27). To a mechanically stirred slurry of 3.15 g (0.45 mol) of lithium in ca. 250 ml of refluxing ammonia was added dropwise a solution of 1.75 g (10.8 mmol) of **5** in 15 ml of anhydrous ether. The reaction mixture was stirred at reflux for 4 hr and then 35 g of solid ammonium chloride was slowly added. The ammonia was allowed to evaporate, and the resulting residue was diluted with water (250 ml) and extracted with ether (4 × 200 ml). The combined ether extracts were washed successively with 5% hydrochloric acid (2 × 100 ml), 5% aqueous sodium bicarbonate (100 ml), and saturated sodium chloride, and then dried over anhydrous magnesium sulfate. The solvent was evaporated at reduced pressure and the residue was oxidized with Jones reagent by the procedure described for **12** → **14**. Column chromatography of the oxidation product on silica gel with benzene as eluent, followed by sublimation (90°, 0.3 mm), provided 880 mg (50% yield) of **27**. Final purification by GLC (5 ft × 0.25 in. QF-1 column, 175°) gave **27** as a white solid: mp 297–298°; δ_{Me_4Si} ($CDCl_3$) 3.0–0.5 (br m); ν (CCl_4) 2925, 2865, 1705, 1450, 1440, 1405, 1260, 1220, 1145, 1090, 1080, 1050, and 1030 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.29; H, 9.61.

2-*endo*-Tricyclo[5.3.1.0^{4,9}]undecanol (29). Sodium borohydride reduction of 81 mg of **27** by the procedure described for **5** → **9** afforded 93 mg of material which by ^{1}H NMR analysis contained a ca. 85% yield of **29**. Isolation by GLC (5 ft × 0.25 in. Carbowax column, 190°) gave **29** as a white solid: mp >300°; δ_{Me_4Si} ($CDCl_3$) 4.23 (apparent t, J = 8.6 Hz, 1 H, CHOH) and 2.5–0.6 (br m, 17 H); ν (CCl_4) 3630, 3335, 2910, 2855, 1460, 1445, 1100, and 1020 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.63; H, 10.85.

Jones oxidation of **29** by the procedure described for **12** → **14** gave **27**.

Lithium–Ammonia Reduction of 27. Reduction of 120 mg of **27** with lithium in liquid ammonia was carried out by the procedure described for **5** → **27**. GLC (5 ft × 0.25 in. Carbowax column, 190°) and ^{1}H NMR analysis of the crude reaction mixture suggested the presence of two alcohol products. The residue from the reaction was chromatographed on silica gel. Elution with 50:50 benzene–heptane provided 25 mg of **29** (shorter retention time by GLC). Further elution with 75:25 benzene–heptane afforded 25 mg of **2-*exo*-tricyclo[5.3.1.0^{4,9}]undecanol (30)** which was isolated by GLC (above conditions) as a white solid: mp 240–241°; δ_{Me_4Si} ($CDCl_3$) 4.08 (apparent t, J = 8.5 Hz, 1 H, CHOH); ν (CCl_4) 3625, 3350, 2915, 2875, 1465, 1450, 1040, and 985 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.34; H, 10.74.

Jones oxidation of **30** by the procedure described for **12** → **14** gave **27**.

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Registry No.—**5**, 55638-01-2; **6**, 21932-98-9; **8**, 55638-02-3; **9**, 55638-03-4; **12**, 55638-04-5; **14**, 55638-05-6; **15**, 24669-57-6; **17**, 55638-06-7; **18**, 55638-07-8; **19**, 55638-08-9; **20**, 55638-09-0; **21**, 55638-10-3; **22**, 55659-65-9; **23**, 55659-66-0; **24**, 55638-11-4; **25**, 55659-67-1; **27**, 55638-12-5; **29**, 55638-13-6; **30**, 55659-68-2.

References and Notes

(1) A preliminary report of this work was presented at the 9th Middle Atlantic Regional Meeting of the American Chemical Society, Wilkes-Barre, Pa., April 25, 1974.
(2) NDEA Graduate Fellow, 1973–1974, and Unidel Fellow, 1972.
(3) J. E. Baldwin and W. D. Foglesong, *J. Am. Chem. Soc.*, **90**, 4303 (1968).
(4) R. K. Murray, Jr., and K. A. Babiak, *J. Org. Chem.*, **38**, 2556 (1973).
(5) R. K. Murray, Jr., and K. A. Babiak, *Tetrahedron Lett.*, 311 (1974).
(6) R. K. Murray, Jr., T. K. Morgan, Jr., and K. A. Babiak, *J. Org. Chem.*, **40**, 1079 (1975).
(7) H. W. Whitlock, Jr., and M. W. Siefken, *J. Am. Chem. Soc.*, **90**, 4929 (1968).
(8) R. K. Murray, Jr., and T. K. Morgan, Jr., *J. Org. Chem.*, in press.
(9) R. K. Murray, Jr., and T. K. Morgan, Jr., *Tetrahedron Lett.*, 3299 (1973).

(10) R. K. Murray, Jr., D. L. Goff, and R. E. Ratych, *Tetrahedron Lett.*, 763 (1975).
(11) For a study concerning the generation and behavior of 2,4-dehydro-5-homoadamantyl cations see G. A. Olah, G. Liang, K. A. Babiak, and R. K. Murray, Jr., *J. Am. Chem. Soc.*, in press.
(12) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970).
(13) Z. Majersk, S. H. Liggero, and P. v. R. Schleyer, *Chem. Commun.*, 949 (1970); R. Yamaguchi, T. Katsushima, T. Imagawa, and M. Kawanisi, *Synth. Commun.*, **4**, 83 (1974). We are grateful to Professor Kawanisi of Kyoto University for providing us with a copy of the ir spectrum of **8**.
(14) We have adoped the convention that a substituent is designated as endo if it is oriented toward the *larger* ring of a polycyclic skeleton, and exo if it faces the *smaller* ring.
(15) J. E. Nordlander, F. Wu, S. P. Jindal, and J. B. Hamilton, *J. Am. Chem. Soc.*, **91**, 3962 (1969); P. v. R. Schleyer, E. Funke, and S. H. Liggero, *ibid.*, **91**, 3965 (1969); R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 671 (1970). We are grateful to Professor Nordlander of Case Western Reserve University for providing us with a copy of the ir spectrum of **15**.
(16) For a review see S. S. Hixson, P. S. Mariano, and H. E. Zimmerman, *Chem. Rev.*, **73**, 531 (1973).
(17) J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970).
(18) E. Piers and P. M. Worster, *J. Am. Chem. Soc.*, **94**, 2895 (1972); W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966), and references cited therein.
(19) D. P. G. Hamon and G. F. Taylor, *Tetrahedron Lett.*, 155 (1975). We are grateful to Professor Hamon of the University of Adelaide for providing us with copies of the ir and ^{1}H NMR spectra of **27**.
(20) This assignment follows from our earlier observation[6] that the upfield and downfield olefinic "triplets" in the ^{1}H NMR spectrum of 2-protoadamantenone may be assigned to the hydrogens at C-4 and C-5, respectively.
(21) Note Added in Proof. An independent synthesis of ketone **5** has recently been reported: D. P. G. Hamon and G. F. Taylor, *Tetrahedron Lett.*, 155 (1975).

Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. VI. Methyl 4-Amino-4,6-dideoxy-α-D-idopyranoside[1,2]

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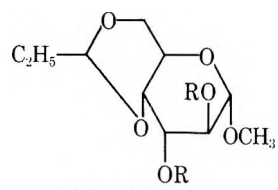
The synthesis of methyl 4-amino-4,6-dideoxy-α-D-idopyranoside (**11**) starting from methyl 4,6-*O*-benzylidene-α-D-altropyranoside (**1**) is presented. The structure of **11** was confirmed by mass spectral analysis and also by degradation of its *N*-acetate **12** to L-threoninol. Methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-idopyranoside (**12**) is shown to exist in the *C1* conformation (**15**) in solution by NMR. The preparation of methyl 4,6-dideoxy-4-*N*,*N*-dimethylamino-α-D-idopyranoside is also discussed.

The synthesis of several 4-amino-4,6-dideoxy hexoses and their derivatives of potential biological activity were reported previously.[1,4] The preparation of the derivatives of all the eight members of this class of carbohydrates was undertaken in our laboratory with two major objectives in mind: (1) to establish the structures of those 4-amino-4,6-dideoxy hexoses such as glucose,[5] galactose,[6] and mannose,[7] which were isolated from natural sources and to provide samples for the identification of other members of these amino sugars and their derivatives which may subsequently be found to occur in nature and (2) to investigate their immunochemical and other biological properties. This paper describes the synthesis of the derivatives of 4-amino-4,6-dideoxy-D-idose.

Conversion of methyl 4,6-*O*-benzylidene-α-D-altropyranoside (**1**) to its dibenzyl ether, **2**, followed by mild acid hydrolysis provided methyl 2,3-di-*O*-benzyl-α-D-altropyranoside (**3**). Treatment of **3** with excess of methanesulfonyl chloride in pyridine gave the di-*O*-methylsulfonate **4**. Selective displacement of the primary methylsulfonyl group with iodide to give **5** and subsequent reduction with Raney nickel yielded the 6-deoxy derivative, **6**. Treatment of **6** with lithium azide in dimethylformamide at 150° provided the 4-azido sugar, **7**, with inversion of configuration at C-4. Reduction of **7** with lithium aluminum hydride gave methyl 4-amino-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-idopyranoside (**8**), which was characterized as its *N*-acetate, **9**. Reductive debenzylation of **9** in the presence of 10% Pd/C as a catalyst under neutral conditions gave 70% of methyl 4-acetamido-4,6-dideoxy-α-D-idopyranoside (**10**). Hydrolysis of **10** with barium hydroxide provided methyl 4-amino-4,6-dideoxy-α-D-idopyranoside (**11**) in 84% yield. Hydrogenation of **8** in the presence of 10% Pd/C and hydrogen chloride as catalysts also yielded amino sugar **11**, which was further characterized by acetylation with acetic anhydride in pyridine to obtain the triacetate **12**.



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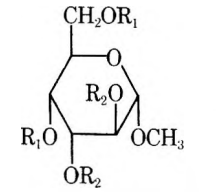

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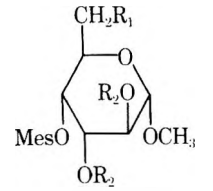

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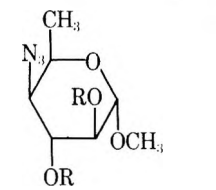
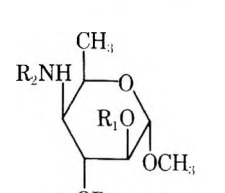
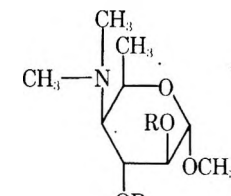
6, R_1 = H; R_2 = $CH_2C_6H_5$



7, R = $CH_2C_6H_5$



8. R_1 = $CH_2C_6H_5$; R_2 = H
9. R_1 = $CH_2C_6H_5$; R_2 = Ac
10. R_1 = H; R_2 = Ac
11. R_1 = R_2 = H
12. R_1 = R_2 = Ac



13, R = $CH_2C_6H_5$
14, R = H

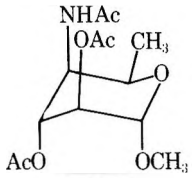
Since 4-*N*,*N*-dimethylamino-4,6-dideoxy-D-glucose oc-

curs in nature as a component of the antibiotic amicetin,[5b,10] the dimethylamino analog of **11** was prepared as follows. Treatment of **8** with formaldehyde in the presence of formic acid gave the dimethylamino derivative, **13**, as an oil which on hydrogenolysis in the presence of 10% Pd/C and HCl as catalysts provided methyl 4-*N*,*N*-dimethylamino-4,6-dideoxy-α-D-idopyranoside (**14**).

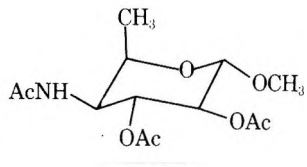
The structural assignment for the amino sugars described above is based on previous experience[4a,b] that azide displacement of the methanesulfonyl group usually occurs with inversion of configuration and without carbon skeleton rearrangement. However, formation of a 5-azido furanose by the azide displacement of a pyranose-4-methylsulfonate has also been reported.[11] The structure of **10** was therefore confirmed by the following methods.

Comparison of the mass spectra of several methyl 4-acetamido-4,6-dideoxy hexopyranosides showed that they exhibit nearly identical fragmentation patterns with only slight variations in relative intensities.[12,13] On the other hand, similar 5-acetamido sugar derivatives produce a significantly different fragmentation pattern in their mass spectra.[11,14] A mass spectrum of **10** clearly showed that it belonged to the 4-amino-4,6-dideoxy hexose series as it had an intense *m/e* peak at 74 $[CH_3CH(OH)CH(NH_2)]^+$, characteristic of a 4-acetamido-4,6-dideoxy sugar derivative.[12] In addition, degradation of **10** to L-threoninol by a previously described procedure[4d,15] confirmed the D-threo stereochemistry at C-4 and C-5 as required for a D-idose derivative.

An NMR spectrum of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-idopyranoside (**12**) in $CDCl_3$ indicates that this idose derivative exists as the *C1* (D) conformer, **15**



15 (*C1*)



16 (*1C*)

(*CA* in the Isbell–Tipson system of conformational nomenclature[16] and $^4C_1$, according to the new British–U.S. rules[17]). Although this requires four of the five substituents to exist in the axial orientation and only the methyl (6-deoxy) group in the equatorial position, similar behavior was also observed by Horton and coworkers in the case of α-D-iodpyranose pentaacetate.[18] The NMR spectrum of **12** in $CDCl_3$ exhibited a singlet at τ 5.4 for the anomeric proton resonance, ruling out a *1C* conformation[16] **16** which would require a 1,2-diaxial coupling.[19] The other peaks in the NMR spectrum of **12** are also consistent with the above interpretation. The anomeric proton resonance in the NMR spectrum of **10** in CD_3OD also appeared at τ 5.4.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography was carried out using silica gel H from Brinkmann Instruments on 5 × 20 glass plates. A solvent system consisting of diethyl ketone, diisopropyl ketone, and ligroin (6:3:1) was used unless otherwise mentioned. The NMR spectra were taken on a Varian A-60 or T-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on either a Beckman IR-4 or a Perkin-Elmer Infracord instrument. Specific rotations were measured using a Perkin-Elmer 141 polarimeter. The pK_a's were determined in 50% aqueous methanol. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-altropyranoside (2). A mechanically stirred mixture of 26.6 g (0.095 mol) of methyl 4,6-*O*-benzylidene-α-D-altropyranoside[9] (**1**), 110 g (2.76 mol) of powdered sodium hydroxide, and 250 ml of toluene was heated to reflux. Benzyl chloride (104 ml) was added to this refluxing mixture in four 26-ml portions at 1-hr intervals. An additional 27 g of NaOH was then added and the mixture was allowed to reflux for 1 more hr. The toluene and benzyl chloride were removed by steam distillation. The remaining mixture was cooled, and the yellow solid was filtered, washed with water, and recrystallized twice from ethanol to give 34.0 g (78%) of **2** as white needles, mp 90–91°, $[\alpha]^{26}D$ +38.1° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.70; H, 6.53. Found: C, 72.56; H, 6.56.

Methyl 2,3-Di-*O*-benzyl-α-D-altropyranoside (3). Concentrated hydrochloric acid (3.0 ml) was added dropwise to a stirred solution of 11.93 g (0.024 mol) of **2** in 250 ml of CH_3OH at room temperature. Hydrolysis was complete in 1 hr as indicated by TLC. The mixture was neutralized with Na_2CO_3, and steam distilled. The residue was extracted with $CHCl_3$, dried (K_2CO_3), concentrated in vacuo, and then dried at 50° (0.5 mm presence) for 5 hr to give 9.0 g (95%) of **3** as a thick, colorless syrup, homogeneous by TLC. A portion of this material was chromatographed twice over Woelm grade III alumina using 50% ether–pentane as eluent to obtain an analytical sample, $[\alpha]^{26}D$ +71.5° (*c* 1.1, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.33; H, 7.00. Found: C, 67.36; H, 7.14.

Methyl 2,3-Di-*O*-benzyl-4,6-di-*O*-methylsulfonyl-α-D-altropyranoside (4). A solution of 8.63 g (0.02 mol) of **3** and 25.0 g (0.2 mol) of methanesulfonyl chloride in 100 ml of dry pyridine was allowed to stand at 25° for 24 hr. The mixture was poured onto water, extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated in vacuo to a yellow syrup. Column chromatography over alumina gave a gum on elution with ether. Drying to constant weight under vacuum gave 8.7 g (70%) of **4** which was homogeneous by TLC. A small sample was rechromatographed over alumina for analysis.

Anal. Calcd for $C_{23}H_{30}O_{10}S_2$: C, 52.06; H, 5.70; S, 12.09. Found: C, 52.29; H, 5.75; S, 11.97.

Methyl 6-Deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-altropyranoside (6). A solution of 4.0 g (7.0 mmol) of **4** and 1.8 g (12.0 mmol) of sodium iodide in 40 ml of 2-butanone was heated under reflux with stirring for 11 hr. The mixture was cooled and the precipitated sodium methanesulfonate was removed by filtration. The filtrate was evaporated to dryness, and the residue was dissolved in $CHCl_3$, washed with 5% sodium thiosulfate solution, dried (Na_2SO_4), and concentrated in vacuo to yield 4.01 g (95%) of **5** as a thick syrup, which did not give satisfactory elemental analysis even after a column chromatography over alumina. To a solution of 3.81 g of this material (**5**) in 150 ml of warm ethanol was added an excess (9 teaspoons) of Raney nickel[20] with mechanical stirring. The mixture was then stirred at room temperature for 1 hr. Filtration of the catalyst followed by removal of the solvent gave a gum which crystallized on addition of cold water. It was recrystallized from 2-propanol to give 1.54 g (50%) of **6**, mp 85–86°, $[\alpha]^{25}D$ +53.9° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{22}H_{28}O_7S$: C, 60.53; H, 6.62; S, 7.35. Found: C, 60.73; H, 6.63; S, 7.54.

Methyl 4-Azido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-idopyranoside (7). A solution of 3.0 g (23 mmol) of **6** and 1.2 g (25 mmol) of lithium azide was heated under reflux for 5 hr, at which point a TLC analysis indicated the reaction to be complete. After cooling, the mixture was poured onto water, extracted with petroleum ether, and dried (Na_2SO_4) and the solvent was removed under vacuum. The chromatography of the residue over alumina using ether–pentane (2:8) as eluent gave 2.51 g (91%) of **7** as a clear liquid which was homogeneous by TLC. A small portion of this material was rechromatographed for analysis, $n^{26.5}D$ 1.5370, $[\alpha]^{26}D$ +17.4° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.77; H, 6.57; N, 10.96. Found: C, 65.79; H, 6.63; N, 11.01.

Methyl 4-Acetamido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-idopyranoside (9). A solution of 2.55 g (7.1 mmol) of **7** in 15 ml of dry dioxane was added with stirring to a suspension of 0.9 g (24 mmol) of $LiAlH_4$ in 40 ml of dioxane. The reaction mixture was heated to 80° and maintained at that temperature for 1 hr. The mixture was cooled and ethyl acetate was added to decompose the excess $LiAlH_4$. The solvents were removed under vacuum, the residue was suspended in ether, and water was added dropwise with stirring until the aluminum salts were converted into a white paste. The mixture was then repeatedly extracted with ether, dried (Na_2SO_4), and evaporated to dryness to give 2.2 g (93%) of **8** as a gum, pK_a = 7.65. This material was dissolved in 15 ml of pyridine, 5 ml of acetic anhydride was added, and the mixture was allowed to stand at

26° for 3 hr. Addition of ice water to the mixture provided a solid which was recrystallized twice from ethanol–water to give 1.45 g (59%) of **9**, mp 102–103°, $[\alpha]^{26}D$ +20.8° (*c* 1.18, EtOH).

Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.18; H, 7.32; N, 3.51. Found: C, 69.03; H, 7.34; N, 3.57.

Methyl 4-Acetamido-4,6-dideoxy-α-D-idopyranoside (10). A solution of 550 mg (1.4 mmol) of **9** in 50 ml of CH_3OH was hydrogenated in the presence of 200 mg of 10% Pd/C for 17 hr at 25°. Filtration of the catalyst followed by evaporation of the solvent under vacuum gave a solid which was recrystallized from $CHCl_3$–pentane to give 160 mg (70%) of **10**: mp 131–133°; $[\alpha]^{26}D$ +155.8° (c 1.0, EtOH); NMR (CD_3OD) τ 8.9 (d, $J_{5,6}$ = 8 Hz, 3, CCH_3), 8.0 (s, 3, $COCH_3$), 6.7 (s, 3, OCH_3), 5.4 (s, 1, C-1 H).

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.54; H, 7.86; N, 6.52.

Degradation of 100 mg (0.455 mmol) of **10** according to a previously described procedure[4d,15] gave 18 mg (20% for four steps) of L-threoninol hydrogen oxalate, mp 188–189° dec. A mixture melting point with an authentic sample was unchanged.

Methyl 4-Amino-4,6-dideoxy-α-D-idopyranoside (11). A solution of 250 mg (1.15 mmol) of **10** and 250 mg of $Ba(OH)_2 \cdot H_2O$ in 10 ml of water was heated at 100° for 40 hr. The solution was cooled and acidified to pH 3 with H_2SO_4. The inorganic salts were filtered off and the filtrate was evaporated to dryness at 26° under vacuum. The residue was dissolved in CH_3OH and passed over a 5-ml column of Dowex-1 ($^-$OH form). The solvent was removed in vacuo and the residue was triturated with ether to give 170 mg (84%) of **11**, mp 114–116°. It was recrystallized from ethanol–ether–pentane for analysis, mp 118–119°, $[\alpha]^{24}D$ +82.2° (*c* 0.6, CH_3OH), pK_a = 7.90.

Anal. Calcd for $C_7H_{15}NO_4$: C, 47.44; H, 8.53; N, 7.82. Found: C, 47.43; H, 8.54; N, 8.06.

Compound **11** was also obtained as follows: a solution of 219 mg (0.6 mmol) of **8** in 50 ml of methanol was mixed with 4 drops of HCl and 75 mg of 10% Pd/C and hydrogenated at 25° for 12 hr. The catalyst was filtered and the filtrate was passed over Dowex-1 ($^-$OH form) to remove the acid. The solution was then passed through a 4-ml Dowex-50 (H^+) column and washed with 50 ml of methanol and the basic material was eluted with 100 ml of 6% NH_4OH in methanol. This solution was evaporated to dryness under vacuum and the residue was recrystallized from ethanol–ether–pentane to give 28 mg (30%) of **11**, mp 118–119°. a mixture melting point with the analyzed sample was unchanged.

Methyl 4-Acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-idopyranoside (12). A solution of 102 mg (0.46 mmol) of **10** in 1.0 ml of pyridine was acetylated with 0.5 ml of acetic anhydride at room temperature for 15 hr. The solvents were removed in vacuo and the residue was dissolved in $CHCl_3$ and passed over 10 g of Merck acid-washed alumina. Removal of the solvent gave a gum which solidified on trituration with petroleum ether. It was recrystallized from acetone–pentane to give 119 mg (85%) of **12**: mp 97–98°; $[\alpha]^{26}D$ +65.2° (*c* 0.90, CH_3OH); NMR τ 8.9 (d, $J_{5,6}$ = 8 Hz, 3, CCH_3), 7.9 (3 s, 9, acetates), 6.65 (s, 3, OCH_3), 5.45–6.0 (m, 2, C-4 H and C-5 H), 5.4 (s, 1, C-1 H), 5.2 (broad s, 2, C-2 H and C-3 H).

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.70; H, 7.03; N, 4.29.

Methyl 4,6-Dideoxy-4-*N,N*-dimethylamino-α-D-idopyranoside (14). A solution of 732 mg (4.1 mmol) of **11** in 4 ml of formic acid and 2 ml of 36% formalin was heated on a steam bath for 14 hr. The solution was evaporated to dryness, redissolved in ether, and extracted with 10 ml of 6 *N* hydrochloric acid. The acid layer was made basic with KOH and the liberated amine was extracted with ether, dried (K_2CO_3), and concentrated under vacuum to give 700 mg of impure **13** as a yellow oil, pK_a = 6.96. This material was dissolved in 100 ml of methanol and hydrogenated in the presence of 8 drops of HCl and 300 mg of 10% Pd/C for 29 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in ether and neutralized over Dowex-1 ($^-$OH). The solvent was removed under vacuum to give a gum which solidified on addition of petroleum ether. It was recrystallized from acetone–pentane to give 183 mg (50%) of **14**, mp 86–87°, $[\alpha]^{29}D$ +88.1° (*c* 1.2, $CHCl_3$), pK_a = 7.19.

Anal. Calcd for $C_9H_{19}NO_4$: C, 52.58; H, 9.46; N, 7.06. Found: C, 52.47; H, 9.57; N, 7.23.

Acknowledgment. Financial support from the National Institutes of Health through Grant GM11520 is gratefully acknowledged.

Registry No.—**1**, 5328-47-2; **2**, 33164-02-2; **3**, 33164-03-3; **4**, 55570-13-3; **5**, 55570-14-4; **6**, 53951-08-9; **7**, 55570-15-5; **8**, 55570-16-6; **9**, 55570-17-7; **10**, 55570-18-8; **11**, 55637-42-8; **12**, 55570-19-9; **13**, 55570-20-2; **14**, 55570-21-3; benzyl chloride, 25168-05-2; methanesulfonyl chloride, 124-63-0; lithium azide, 19597-69-4.

References and Notes

(1) Part V: C. L. Stevens, K. K. Balasubramanian, C. P. Bryant, J. B. Filippi, and P. M. Pillai, *J. Org. Chem.*, **38**, 4311 (1973).
(2) A preliminary account on part of this work has been reported: C. L. Stevens, P. Blumbergs, J. P. Dickerson, and D. Chitharanjan, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 4–9, 1965, p 5C.
(3) Taken in part from the Ph.D. Dissertation of J. P. Dickerson, Wayne State University, 1966.
(4) (a) C. L. Stevens, P. Blumbergs, and D. H. Otterbach, *J. Org. Chem.*, **31**, 2817 (1966); (b) C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. G. Taylor, *ibid.*, **31**, 2822 (1966); (c) C. L. Stevens, R. P. Glinski, and K. G. Taylor, *ibid.*, **33**, 1586 (1968); (d) C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and S. K. Gupta, *J. Am. Chem. Soc.*, **92**, 3160 (1970); (e) J. S. Brimecombe, O. A. Ching, and M. Stacey, *Carbohydr. Res.*, **8**, 498 (1968); (f) J. Jary, P. Novak, Z. Ksandr, and Z. Samek, *Chem. Ind. (London)*, 1490 (1967); (g) J. Jary and P. Novak, *Collect. Czech. Chem. Commun.*, **33**, 1744 (1968); (h) S. W. Gunner, W. G. Overend, and N. R. Williams, *Carbohydr. Res.*, **4**, 498 (1967).
(5) (a) C. L. Stevens, K. Nagarajan, and T. H. Haskell, *J. Org. Chem.*, **27**, 2991 (1962); (b) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Am. Chem. Soc.*, **85**, 1552 (1963); (c) R. W. Wheat, E. L. Rollins, and J. M. Leatherwood, *Biochem. Biophys. Res. Commun.*, **9**, 120 (1962); (d) C. L. Stevens, P. Blumbergs, F. A. Daniher, R. W. Wheat, A. Kiyomoto, and E. L. Rollins, *J. Am. Chem. Soc.*, **85**, 3061 (1963); C. L. Stevens, P. Blumbergs, F. A. Daniher, J. L. Strominger, M. Matsuhashi, D. N. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, *ibid.*, **86**, 2939 (1964).
(6) (a) C. L. Stevens, P. Blumbergs, D. H. Otterbach, J. L. Strominger, M. Matsuhashi, and D. N. Dietzler, *J. Am. Chem. Soc.*, **88**, 2937 (1964); (b) B. Jann and K. Jann, *Eur. J. Biochem.*, **2**, 26 (1967).
(7) (a) C. H. Lee and C. P. Schaffner, *Tetrahedron Lett.*, 5837 (1966); (b) C. L. Stevens, S. K. Gupta, R. P. Glinski, K. G. Taylor, P. Blumbergs, C. P. Schaffner, and C. H. Lee, *Carbohydr. Res.*, **7**, 502 (1968).
(8) It may be recalled here that when the isolation of 4-amino-4,6-dideoxy-D-mannose (perosamine) was reported,[7a] its synthesis had almost been completed.[7b]
(9) G. J. Robertson and W. Whitehead, *J. Chem. Soc.*, 319 (1940); N. K. Richtmeyer, *Methods Carbohydr. Chem.*, **1**, 107 (1962).
(10) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, p 203.
(11) C. L. Stevens, R. P. Glinski, and K. G. Taylor, *J. Am. Chem. Soc.*, **88**, 2073 (1966); C. L. Stevens, R. P. Glinski, K. G. Taylor, and F. Sirokman, *J. Org. Chem.*, **35**, 592 (1970).
(12) For a table of the relative intensities of various fragments in the mass spectra of several methyl 4-acetamido-4,6-dideoxy-α-D-hexopyranosides, including compound **10**, see C. L. Stevens, D. Chitharanjan, K. G. Taylor, and P. M. Pillai, *J. Org. Chem.*, following paper in this issue.
(13) For a detailed interpretation of the mass spectra of these sugars, see E. B. Hills, Ph.D. Dissertation, Wayne State University, 1973.
(14) D. C. DeJongh and S. Hanessian, *J. Am. Chem. Soc.*, **87**, 3744 (1965).
(15) C. L. Stevens, S. K. Gupta, R. P. Glinski, G. E. Gutowski, and C. P. Bryant, *Tetrahedron Lett.*, 1817 (1968).
(16) H. S. Isbell, *J. Res. Natl. Bur. Stand.*, **57**, 171 (1956); H. S. Isbell and R. S. Tipson, *J. Res. Natl. Bur. Stand., Sect. A*, **64**, 171 (1960); *Science*, **130**, 793 (1959).
(17) According to the rules recently approved by the British and U.S. Carbohydrate Nomenclature Committees, Reeves's *C1* and *1C* conformations have been designated as $^4C_1$ and $^1C_4$, respectively: *J. Chem. Soc., Chem. Commun.*, 505 (1973).
(18) N. S. Bhacca, D. Horton, and H. Paulsen, *J. Org. Chem.*, **33**, 2484 (1968).
(19) For a recent review on NMR in carbohydrate chemistry, see G. Kotowycz and R. U. Lemieux, *Chem. Rev.*, **73**, 669 (1973).
(20) R. Mozingo, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 181.

Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. VII. 4-Amino-4,6-dideoxy-D-altrose Derivatives[1,2]

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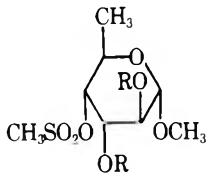
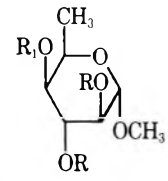
Methyl 4-amino-4,6-dideoxy-α-D-altropyranoside (**8**) was synthesized starting from methyl 6-deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-altropyranoside (**1**) employing a double inversion sequence at C-4. Preparations of several derivatives of **8**, including *N*-acetate **9**, triacetate **10**, and the dimethylamino derivative, **12** are discussed. Hydrolysis of **12** with 1 *N* hydrochloric acid provided the crystalline free sugar hydrochloride, **13**. The structure of **9** was confirmed by mass spectral analysis and also by its degradation to D-allothreoninol. Methyl 4,6-dideoxy-4-dimethylamino-α-D-altropyranoside (**12**) is shown to exist in the *C1* conformation in solution by NMR.

In view of the potential physiological activity of 4-amino-4,6-dideoxy hexoses,[1,4] the synthesis of several members of this class of carbohydrates was necessary both for their identification from natural sources and a complete evaluation of their biological activity. Here we describe the stereospecific synthesis of the derivatives of 4-amino-4,6-dideoxy-D-altrose. The amine function was introduced by utilizing a double inversion sequence[5] at carbon 4 of a 6-deoxy-D-altrose derivative.

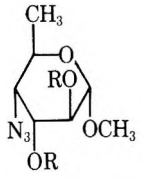
A displacement reaction of methyl 6-deoxy-2,3-di-*O*-benzyl 4-*O*-methylsulfonyl-α-D-altropyranoside[1] (**1**) with sodium benzoate in dimethylformamide to give **2** and subsequent hydrolysis of **2** with sodium hydroxide solution provided methyl 6-deoxy-2,3-di-*O*-benzyl-α-D-idopyranoside (**3**). Treatment of **3** with methanesulfonyl chloride in pyridine gave the inverted mesylate, **4**. In order to establish that no carbon skeleton rearrangement had taken place during the benzoate displacement of **1**, the methylsulfonyl group in **4** was displaced with sodium benzoate, the intermediate benzoyl derivative was hydrolyzed, and the resulting alcohol was treated with methanesulfonyl chloride in pyridine. The isolation of the original mesylate, **1**, in 60% yield for the three steps provided evidence that the benzoate displacement reactions took place with inversion of configuration and without any structural rearrangement.



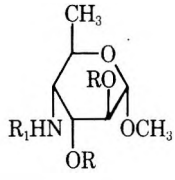
1, R = $CH_2C_6H_5$



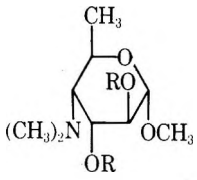
2, R = $CH_2C_6H_5$; R_1 = COC_6H_5
3, R = $CH_2C_6H_5$; R_1 = H
4, R = $CH_2C_6H_5$; R_1 = SO_2CH_3



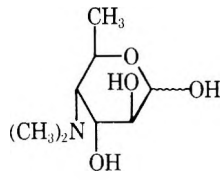
5, R = $CH_2C_6H_5$



6, R = $CH_2C_6H_5$; R_1 = H
7, R = $CH_2C_6H_5$; R_1 = Ac
8, R = R_1 = H
9, R = H; R_1 = Ac
10, R = R_1 = Ac



11, R = $CH_2C_6H_5$
12, R = H



13

Treatment of **4** with sodium azide in dimethylformamide gave the azido derivative **5**, which was hydrogenated in the presence of 10% Pd/C under neutral conditions to give the 4-amino sugar, **6**. Compound **6** was also characterized as its *N*-acetate, **7**. Hydrogenolysis of **6** in the presence of 10% Pd/C and hydrochloric acid as catalysts provided methyl 4-amino-4,6-dideoxy-α-D-altropyranoside (**8**). The *N*-acetate **9** was obtained both by the reductive debenzylation of **7** and by the selective N-acetylation of **8**. Aminoglycoside **8** was further characterized as the triacetate **10** by acetylation with excess of acetic anhydride in pyridine. Attempted hydrolysis of **8** to obtain the corresponding free sugar under a variety of acid conditions was unsuccessful.

Treatment of **6** with formaldehyde and formic acid (Clark–Eschweiler conditions) provided the dimethylamino derivative, **11**, which was characterized both as its crystalline hydrochloride and the quaternary salt with methyl iodide. Debenzylation of **11** by hydrogenation in the presence of 10% Pd/C and HCl as catalysts gave methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-altropyranoside (**12**). Hydrolysis of **12** with 1 *N* hydrochloric acid at 100° for 8 hr gave the free sugar **13**, which was characterized as its crystalline hydrochloride. The synthesis of the dimethylamino sugar, **13**, is significant, as an analogous compound, 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-D-glucose, has been isolated from the antitumor antibiotic, amicetin.[6,7]

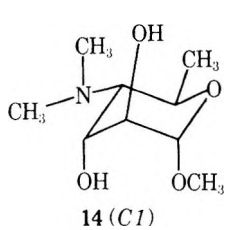
Although the displacement of a methylsulfonyl group with azide anion at position 4 of hexopyranosides has been known to proceed with inversion of configuration and without carbon skeleton rearrangement,[5,6] formation of a 5-azido furanose in the displacement of a pyranose-4-mesylate has also been reported.[9] It was, therefore, necessary to confirm the structure of the amino sugar derivatives discussed above by additional means. Degradation of **9** by a previously reported procedure[10] gave D-allothreoninol, confirming the D-erythro stereochemistry at C-4 and C-5, as required for a D-altrose derivative. Also, a comparison of the mass spectrum of **9** with seven other methyl 4-acetamido-4,6-dideoxy-D-hexopyranosides (see Table I) showed that the fragmentation pattern was nearly identical for all the eight isomeric 4-amino sugar derivatives.[11] On the other hand, similar 5-acetamido furanose derivatives produced a significantly different fragmentation pattern[12] in their mass spectra, thus showing that **9** is indeed a 4-amino-4,6-dideoxyhexopyranosyl derivative.

Table I
Mass Spectra of Methyl 4-Acetamido-4,6-dideoxy-α-D-hexopyranosides

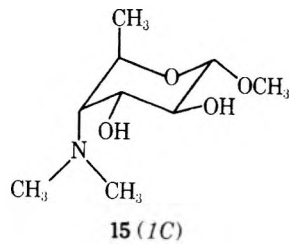
m/e	Rel abundance							
	Gluco[a]	Galacto[b]	Manno[c]	Talo[d]	Allo[e]	Gulo[f]	Altro	Ido[g]
41	10	13	12	15	9	8	12	6
42	10	16	12	17	6	10	10	6
43	73	80	100	100	55	94	80	65
44	16	11	44	12	22	10	17	5
45	10	11	13	19	8	15	21	8
56	19	21	23	28	17	23	23	23
57	64	47	71	50	100	67	78	60
58	29	24	25	27	42	28	33	25
59	93	70	99	80	78	88	88	47
60	100	80	95	80	82	100	100	100
61	7	6	6	11	6	8	8	6
70	5	6	4	10	4	4	4	4
71	9	9	6	10	6	9	9	8
72	9	7	7	9	16	9	18	6
73	9	7	8	15	6	14	9	4
74	75	78	72	60	34	49	60	51
75	5	6	5	12	3	8	4	3
82	9	11	7	10	12	8	7	9
84	6	18	7	10	8	4	6	12
85	4	6	2	5	3	6	4	5
86	14	22	11	21	7	11	12	9
87	27	14	20	20	11	19	17	15
98	7	9	7	9	8	8	7	8
99	61	37	66	45	96	98	76	56
100	22	19	19	18	33	32	40	40
101	60	43	46	45	38	43	66	20
102	83	76	60	58	40	52	75	21
114	14	7	7	7	16	13	20	15
115	26	13	13	16	33	28	29	28
128	10	15	11	11	2	7	12	11
142	22	5	11	5	25	11	29	1
146	17	100	16	70	2	9	6	1
159	6	1	1	4	15	2	14	4
170	1	6	6	4	1	3	7	8
188	18	7	4	13	1	2	9	1

[a] Reference 5b. [b] Reference 8. [c] Reference 10a. [d] C. L. Stevens, R. P. Glinski, and K. G. Taylor, *J. Org. Chem.*, 33, 1586 (1968). [e] β-methyl glycoside, ref 4. [f] J. P. Dickerson, Ph.D. Dissertation, Wayne State University, 1966. [g] Reference 1.

A NMR analysis of the dimethylamino sugar, **12**, in $CDCl_3$ showed that the anomeric proton appeared as a doublet ($J_{1,2}$ = 3 Hz) at τ 5.4, indicating a diequatorial coupling. This means that **12** exists in solution as the *C1*(D) conformer, **14** (*CA* in the Isbell–Tipson system of conformational nomenclature[13] and $^4C_1$ according to the new British–U.S. rules[14]) and not as the *1C*(D) conformer, **15** ($^1C_4$),[14] which would require diaxial coupling between C-1 H and C-2 H. This finding is in total agreement with previ-



14 (*C1*)



15 (*1C*)

ous reports that both α-D-altropyranose pentaacetate[15] and α-D-idopyranose pentaacetate[16] exist in the *C1*(D) conformation in solution. Further, methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-idopyranoside has also been found to exist in solution as the *C1*(D) conformer.[1]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography was carried out using silica gel H from Brinkmann Instruments on 5 × 20 glass plates. A solvent system consisting of diethyl ketone, diisopropyl ketone, and ligroin (6:3:1) was used unless otherwise mentioned. The NMR spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Infracord instrument. Specific rotations were measured using a Perkin-Elmer 141 polarimeter. The pK_a's were determined in 50% aqueous methanol. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Methyl 4-*O*-Benzoyl-6-deoxy-2,3-di-*O*-benzyl-α-D-idopyranoside (2). A mixture of 34.0 g (0.08 mol) of methyl 6-deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-altropyranoside[1] (**1**) and 34.0 g of sodium benzoate in 500 ml of DMF was heated under reflux with vigorous stirring for 50 hr. A TLC analysis indicated that the reaction was complete. The mixture was poured into 2.5 l. of water and extracted with ether (3 × 200 ml), and the ether layer was dried (Na_2SO_4) and evaporated under vacuum to give 32.8 g (91.3%) of **2** as a pale yellow oil. A small portion was evaporatively distilled (110°, 10^{-3} mmHg) for analysis, $[\alpha]^{24}D$ +78.3° (*c* 1.6, MeOH).

Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.70; H, 6.53. Found: C, 72.88; H, 6.83.

Methyl 6-Deoxy-2,3-di-*O*-benzyl-α-D-idopyranoside (3). A

solution of 7.9 g (17 mmol) of **2** in 200 ml of ethanol and 100 ml of water containing 16 g (0.4 mol) of NaOH was heated under reflux on a steam bath for 8 hr. A TLC analysis showed that the hydrolysis was complete. Most of the solvents were removed under vacuum and the residue was diluted with 80 ml of water. The mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness to yield 4.6 g (75.2%) of **3** as an oil. Evaporative distillation (100°, 10^{-3} mmHg) of a small sample gave a colorless liquid for analysis, $[\alpha]^{24}D$ +33.6° (*c* 1.43, MeOH).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 69.37; H, 7.31. Found: C, 69.45; H, 7.22.

Methyl 6-Deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-idopyranoside (4). Methanesulfonyl chloride (5.8 g, 15 mmol) was added dropwise to a solution of 4.6 g (12.8 mmol) of **3** in 200 ml of pyridine cooled in a Dry Ice bath. After the addition was complete, the mixture was allowed to warm up to 0° and then left at that temperature for 3 days. The mixture was poured into 1 l. of ice–water. An oily layer was formed which crystallized on standing, 4.58 g (82%), mp 82–85°. It was recrystallized from 2-propanol to give 4.1 g (74%) of **4**: mp 85–86°; NMR ($CDCl_3$) τ 8.75 (d, $J_{5,6}$ = 7 Hz, 3, CCH_3), 7.20 (s, 3, SO_2CH_3), 6.55 (s, 3, OCH_3), 2.65 (d, 10, aromatic); $[\alpha]^{26}D$ +34.5° ($CHCl_3$). A mixture melting point with **1** was depressed to 67–68°.

Anal. Calcd for $C_{22}H_{28}O_7S$: C, 60.53; H, 6.62; S, 7.35. Found: C, 60.73; H, 6.66; S, 7.15.

Treatment of 1.3 g (3 mmol) of **4** with sodium benzoate in DMF and subsequent hydrolysis of the benzoyl derivative with NaOH and mesylation of the alcohol provided 780 mg (60%) of **1**, mp 85–86°, $[\alpha]^{25}D$ +53.9° (*c* 1.0, $CHCl_3$).[1]

Methyl 4-Azido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-altropyranoside (5). A solution of 4.0 g (9.2 mmol) of **4** and 3.0 g (47 mmol) of NaN_3 in 75 ml of DMF was heated under reflux for 2 hr. After cooling, the reaction mixture was poured into 375 ml of water, extracted with petroleum ether, dried (Na_2SO_4), and concentrated in vacuo to yield 3.2 g (91.5%) of a slightly yellow oil. Column chromatography over Woelm grade I neutral alumina using ether–petroleum ether (1:4) as eluent gave 2.5 g (71.4%) of **5**, homogeneous by TLC, $[\alpha]^{26}D$ +39.8° (*c* 1.0, $CHCl_3$), $n^{27}D$ 1.5358.

Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.77; H, 6.57; N, 10.96. Found: C, 65.90; H, 6.69; N, 10.69.

Methyl 4-Amino-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-altropyranoside (6). A solution of 2.45 g (6.4 mmol) of **5** in 50 ml of methanol was hydrogenated in the presence of 100 mg of 10% Pd/C for 18 hr at slightly above atmospheric pressure. Filtration of the catalyst followed by removal of the solvent under vacuum gave 1.6 g (70%) of **6** as a gum, one spot on TLC. A small portion was evaporatively distilled (100–105°, 10^{-3} mmHg) for analysis: NMR ($CDCl_3$) τ 8.75 (d, $J_{5,6}$ = 7 Hz, 3, CCH_3), 6.65 (s, 3, OCH_3), 2.7 (s, 10, aromatic); $[\alpha]^{25}D$ +64.5° (*c* 1.4, CH_3OH); pK_a = 7.65.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.30; H, 7.84; N, 3.94.

Methyl 4-Acetamido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-altropyranoside (7). A solution of 500 mg (1.4 mmol) of **6** in 5 ml of pyridine was treated with 5 ml of acetic anhydride overnight. The solvents were removed in vacuo, and the residue was partitioned between water and $CHCl_3$. The chloroform solution was dried (Na_2SO_4) and evaporated to dryness. The residue which crystallized on standing was recrystallized from ethanol–ether to give 338 mg (60%) of **7**, mp 99–100°.

Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.50. Found: C, 69.03; H, 7.45; N, 3.52.

Methyl 4-Amino-4,6-dideoxy-α-D-altropyranoside (8). A solution of 500 mg (1.4 mmol) of **6** in 50 ml of methanol was hydrogenated in the presence of 100 mg of 10% Pd/C and 5 drops of concentrated HCl at slightly above atmospheric pressure for 10 hr. The catalyst was filtered and the filtrate was passed over a column of 4 ml of Dowex-I (^-OH). The solution was then passed over a column of 4 ml of Dowex-50 (H^+). The free amine was liberated with 200 ml of ethanol containing 3% ammonium hydroxide. The solvents were removed under vacuum and the residue was triturated with ether. The white solid obtained was recrystallized from 1-propanol–ether to give 161 mg (61%) of **8**, mp 116–117°, $[\alpha]^{24}D$ +128.5° (c 0.85, MeOH).

Anal. Calcd for $C_7H_{15}NO_4$; C, 47.42; H, 8.54; N, 7.91. Found: C, 47.17; H, 8.46; N, 8.13.

Methyl 4-Acetamido-4,6-dideoxy-α-D-altropyranoside (9). A. By Hydrogenation of Compound 7. A solution of 330 mg (0.8 mmol) of **7** in 50 ml of methanol containing 3 drops of concentrated HCl was hydrogenated at slightly above atmospheric pressure with 75 mg of 10% Pd/C as catalyst for 8 hr. The catalyst was removed by filtration, the acid was neutralized by passing over Dowex-I (OH^-), and the solution was evaporated to dryness. The residue which solidified on trituration was recrystallized from 2-propanol–ether to give 102 mg (67%) of **9**, mp 151–153°, $[\alpha]^{22}D$ +198.3° (*c* 1.0, MeOH).

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.50; H, 7.67; N, 6.13.

B. By Selective Acetylation of 8. A solution of 160 mg (0.74 mmol) of **8** in 50 ml of MeOH was cooled to 0° and 16 drops of acetic anhydride was added 2 drops at a time at 10-min intervals. Evaporation of the solvent in vacuo followed by trituration of the residue with ether gave a crystalline material which was recrystallized from 2-propanol–ether to give 128 mg (7) of **9**, mp 151–153°. A mixture melting point of this sample with the previously analyzed sample was undepressed.

Degradation of 100 mg (0.45 mmol) of **8** according to a previously reported procedure[10] gave 23 mg (26% for four steps) of D-allothreoninol hydrogen oxalate, mp 172–173° dec. A mixture melting point with an authentic sample was unchanged.

Methyl 4-Acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-altropyranoside (10). A solution of 120 mg (0.33 mmol) of **6** in 5 ml of pyridine was treated with 5 ml of acetic anhydride at room temperature for 24 hr. The solvents were removed in vacuo and the residue was diluted with 10 ml of ice–water. The mixture was extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from 2-propanol–pentane to give 152 mg (87%) of **30**, mp 168–169°, $[\alpha]^{24}D$ +129.2° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.49; H, 7.12; N, 4.64.

Methyl 2,3-Di-*O*-benzyl-4,6-dideoxy-4-dimethylamino-α-D-altropyranoside (11). A solution of 4.0 g (13.2 mmol) of **6** in 15 ml of 88% formic acid and 2.5 ml of 37% formalin was heated on a steam bath for 10 hr. The solvents were removed under vacuum, and the residue dissolved in 50 ml of methanol was passed over a column of Dowex-I (^-OH). The solution was then passed over a column of Dowex-50X_2(H^+) and the free amine was liberated by elution with 100 ml of methanol containing 5 ml of ammonium hydroxide. The solution was concentrated and the oily residue was evaporatively distilled (110–115°, 10^{-3} mmHg) to give 3.6 g (67%) of **11** as a colorless oil, $[\alpha]^{26}D$ +76.1° (*c* 1.3, CH_3OH), pK_a = 7.25.

Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.42; H, 7.97; N, 3.69.

Treatment of 200 mg of **10** with HCl in 2-propanol and recrystallization from 2-propanol–ether gave 201 mg (88%) of the hydrochloride salt of **11**, mp 154–155°, $[\alpha]^{26}D$ 0.6° (*c* 1.0, CH_3OH).

Anal. Calcd for $C_{23}H_{32}ClNO_4$: C, 65.44; H, 7.65; Cl, 8.41; N, 3.32. Found: C, 65.37; H, 7.65; Cl, 8.35; N, 3.17.

A small portion of **10** was also converted to the quaternary salt by treatment with methyl iodide in methanol. The salt was recrystallized from absolute ethanol, mp 159–161°, $[\alpha]^{26}D$ +63.1° (*c* 1.0, CH_3OH).

Anal. Calcd for $C_{24}H_{34}INO_4$: C, 54.65; H, 6.49; I, 24.07; N, 2.66. Found: C, 54.39; H, 6.69; I, 24.14; N, 2.86.

Methyl 4,6-Dideoxy-4-dimethylamino-α-D-altropyranoside (12). A solution of 550 mg (1.4 mmol) of **11** in 150 ml of methanol containing 10 drops of concentrated HCl was hydrogenated at slightly above atmospheric pressure in the presence of 150 mg of 10% Pd/C. The hydrogenation was complete in 20 hr. The catalyst was filtered and the filtrate was passed over Dowex-I (^-OH). The solution was evaporated to dryness and the residue which solidified on trituration with petroleum ether was recrystallized from ether–petroleum ether to give 188 mg (83%) of **12**: mp 110–112°; NMR ($CDCl_3$) 7.65 (d, $J_{5,6}$ = 7 Hz, 3, CCH_3), 7.50 [s, 6, $N(CH_3)_2$], 6.55 (s, 3, OCH_3), 5.4 (d, $J_{1,2}$ = 3 Hz, 1, C-1 H); pK_a = 7.52.

Anal. Calcd for $C_9H_{19}NO_4$: C, 52.67; H, 9.33; N, 6.82. Found: C, 52.74; H, 9.43; N, 6.67.

A small portion of **12** was converted to its hydrochloride salt and recrystallized from ethanol–ether, mp 156–158°, $[\alpha]^{26}D$ +132.9° (*c* 1.0, CH_3OH).

Anal. Calcd for $C_9H_{20}ClNO_4$: C, 44.70; H, 8.34; Cl, 14.67; N, 5.79. Found: C, 44.47; H, 8.29; Cl, 14.88; N, 5.77.

4,6-Dideoxy-4-dimethylamino-D-altrose Hydrochloride (13). A solution of 50 mg of the hydrochloride of **12** in 7.5 ml of 1 *N* HCl was heated on an oil bath at 95–98° for 8 hr. The solution was evaporated to dryness and then repeatedly azeotroped with absolute ethanol. The residue was triturated with ether to give 28 mg (61%) of **13**, mp 174–177°. Recrystallization from 2-propanol–ether gave 24 mg of **13**, mp 176–177°, $[\alpha]^{25}D$ +86.8° (initial −43.9°)

(final, 2.5 hr) (c 1.0, H_2O). The material also traveled as a single spot on paper chromatography using 2-propanol–water–ammonia (7:2:1) and 1-butanol–water–ammonia (7:2:1) systems.

Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.19; H, 7.97; N, 6.15. Found: C, 42.18; H, 8.03; N, 6.40.

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Registry No.—**1**, 53951-08-9; **2**, 55570-34-8; **3**, 55570-35-9; **4**, 53928-92-0; **5**, 55570-36-0; **6**, 55570-37-1; **7**, 55570-38-2; **8**, 55637-43-9; **9**, 51255-06-2; **10**, 51209-16-0; **11**, 55570-39-3; **11** HCl, 55605-89-5; **11** methiodide, 55605-90-8; **12**, 55570-40-6; **12** HCl, 55570-41-7; **13**, 55570-42-8; sodium benzoate, 532-32-1; methanesulfonyl chloride, 124-63-0; acetic acid, 64-19-7.

References and Notes

(1) Part VI: C. L. Stevens, J. P. Dickerson, K. G. Taylor, P. Blumbergs, and P. M. Pillai, *J. Org. Chem.*, preceding paper in this issue.
(2) For a preliminary account of this work see C. L. Stevens, P. Blumbergs, J. P. Dickerson, and D. Chitharanjan, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 4–9, 1965, p 5C.
(3) Taken in part from the Ph.D. Dissertation of D. Chitharanjan. Wayne State University, 1969.
(4) C. L. Stevens, K. K. Balasubramanian, C. P. Bryant, J. B. Filippi, and P. M. Pillai, *J. Org. Chem.*, **38**, 4311 (1973), and references cited therein.
(5) (a) C. L. Stevens, P. Blumbergs, F. A. Daniher, J. L. Strominger, M. Matsuhashi, D. N. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, *J. Am. Chem. Soc.*, **86**, 2939 (1964); (b) C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. G. Taylor, *J. Org. Chem.*, **31**, 2822 (1966).
(6) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Am. Chem. Soc.*, **85**, 1552 (1963).
(7) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, p 203.
(8) C. L. Stevens, P. Blumbergs, and D. H. Otterbach, *J. Org. Chem.*, **31**, 2817 (1966).
(9) C. L. Stevens, R. P. Glinski, and K. G. Taylor, *J. Am. Chem. Soc.*, **88**, 2073 (1966); C. L. Stevens, R. P. Glinski, K. G. Taylor, and F. Sirokman, *J. Org. Chem.*, **35**, 592 (1970).
(10) (a) C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and S. K. Gupta, *J. Am. Chem. Soc.*, **92**, 3160 (1970); (b) C. L. Stevens, S. K. Gupta, R. P. Glinski, G. E. Gutowski and C. P. Bryant, *Tetrahedron Lett.*, 1817 (1968).
(11) For a detailed interpretation of the mass spectra of these sugars, see E. B. Hills, Ph.D. Dissertation, Wayne State University, 1973.
(12) D. C. DeJongh and S. Hanessian, *J. Am. Chem. Soc.*, **87**, 3744 (1965).
(13) H. S. Isbell, *J. Res. Natl. Bur. Stand.*, **57**, 171 (1956); H. S. Isbell and R. S. Tipson, *J. Res. Natl. Bur. Stand., Sect. A*, **64**, 171 (1960); *Science*, **130**, 793 (1959).
(14) According to the rules recently approved by the British and U.S. Carbohydrate Nomenclature Committees, Reeves's *Cl* and *IC* conformations have been designated as $^4C_1$ and $^1C_4$, respectively: *J. Chem. Soc., Chem. Commun.*, 505 (1973).
(15) B. Coxon, *Carbohydr. Res.*, **1**, 357 (1966).
(16) N. S. Bhacca, D. Horton, and H. Paulsen, *J. Org. Chem.*, **33**, 2484 (1968).

Synthesis and Reactions of Methyl 2,3-Di-*O*-benzyl-4,6-dideoxy-α-D-*threo*-hex-4-enopyranoside[1]

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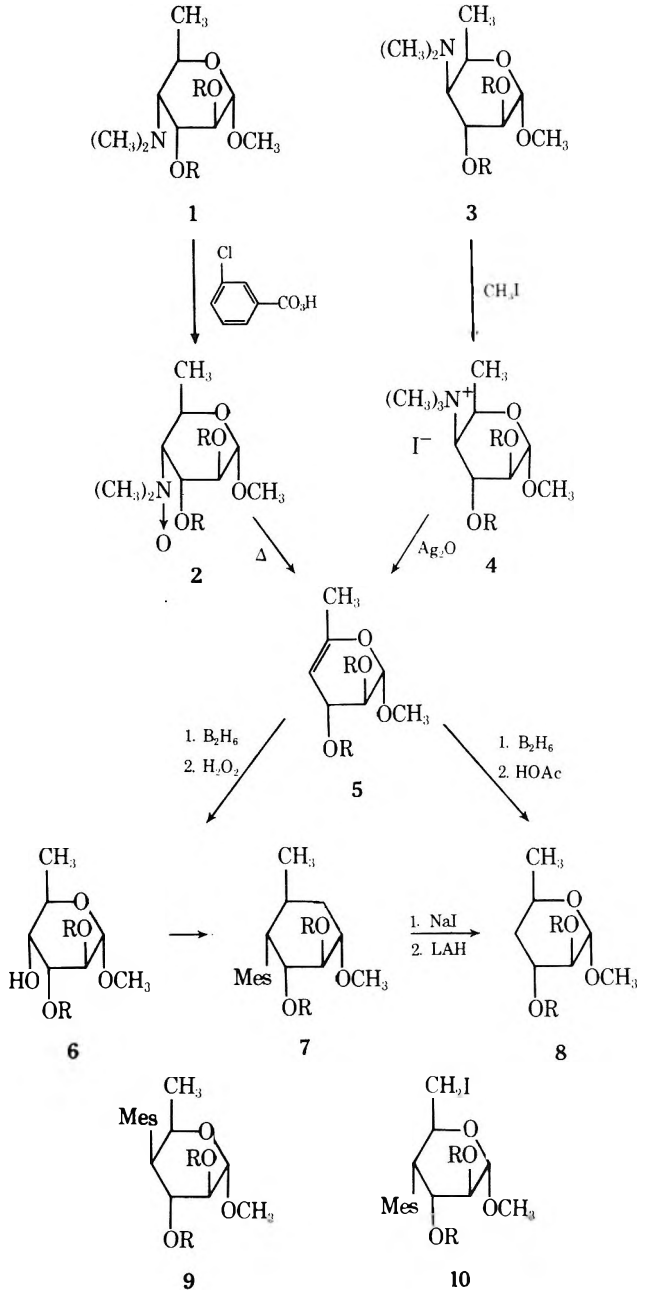
The syntheses of a 4,6-unsaturated sugar derivative, methyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-*threo*-hex-4-enopyranoside (**5**), by a Cope elimination of methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-*N*-oxo-α-D-altropyranoside (**2**) and by a Hofmann elimination of methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-idopyranoside methiodide (**4**) are described. Hydroboration of **5** and subsequent oxidation with hydrogen peroxide yielded methyl 6-deoxy-2,3-di-*O*-benzyl-α-D-altropyranoside (**7**), whereas hydroboration of **5** followed by hydrolysis with acetic acid provided methyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-*arabino*-hexopyranoside (**8**).

Unsaturated sugars, although neglected for a long time, are gaining importance recently because of their potential value in synthetic carbohydrate chemistry.[3] In addition, it has been suggested that some unsaturated sugars play significant biological roles in metabolic pathways.[4,5] Unsaturated sugars also occur naturally, for example, ascorbic acid and the nucleoside antibiotic, blasticidin S.[6] We now describe the synthesis of a 4,5-unsaturated hexose derivative and its hydroboration reactions under oxidative and nonoxidative conditions.

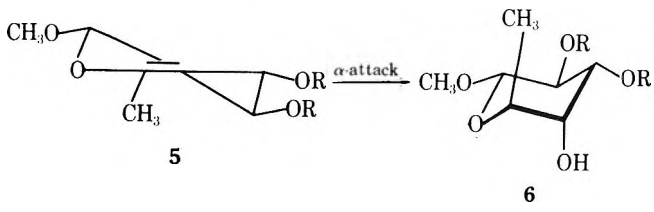
Treatment of methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-altropyranoside[7] (**1**) with freshly purified *m*-chloroperbenzoic acid[8] afforded the *N*-oxide **2**, which was characterized as its crystalline hydrochloride. Pyrolysis of **2** at 98–100° under reduced pressure (Cope elimination) gave the unsaturated sugar, 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-*threo*-hex-4-enopyranoside (**5**), in 72% yield. Compound **5** was also prepared by a Hofmann elimination reaction as follows. Conversion of methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-idopyranoside[9] (**3**) to the quaternary ammonium iodide (**4**) followed by treatment of **4** with silver oxide in methanol provided **5** in 52% yield. The structure of **5** was established by its analysis and spectral data.

Attempted synthesis of **5** by base-catalyzed elimination of methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-methylsulfonyl-α-D-idopyranoside[7,9] (**9**) and from methyl 2,3-di-*O*-benzyl-6-deoxy-6-iodo-4-*O*-methylsulfonyl-α-D-altropyranoside[7] (**10**) according to the procedure of Helferich and Himmen[10] were unsuccessful.

Hydroboration of **5** with a mixture of sodium borohydride and boron trifluoride etherate and subsequent treatment with hydrogen peroxide provided methyl 6-deoxy-2,3-di-*O*-benzyl-α-D-altropyranoside (**6**) in 72% yield. The structure of **6** was confirmed by its conversion to the crystalline methylsulfonate **7** and its identification with an authentic sample.[7] The formation of **6** as the major product in this reaction suggests that the addition of diborane takes



place almost exclusively from the bottom side of the molecule (α-attack) as shown below. No other product was detected in the reaction mixture.



Hydroboration of **5** followed by hydrolysis with acetic acid gave methyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-*arabino*-hexopyranoside (**8**). The structure of **8** was established as follows. Treatment of **7** with sodium iodide to form a mixture of epimeric 4-iodo derivatives[11] and subsequent reduction of this mixture with lithium aluminum hydride provided **8** which was shown to be identical with the hydroboration product of **5** by ir, GC, and optical rotation.

Attempted hydrogenation of **5** under a variety of conditions was unsuccessful. Thus, **5** appeared to decompose (by TLC) during hydrogenation using methanol, ethanol, dioxane, and acetic acid as solvents and platinum and Pd/C as catalysts.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography was carried out using silica gel H from Brinkmann Instruments on 5 × 20 glass plates. A solvent system consisting of diethyl ketone, diisopropyl ketone, and ligroin (6:3:1) was used unless otherwise mentioned. The NMR spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Infracord instrument. Specific rotations were measured using a Perkin-Elmer 141 polarimeter. Gas chromatographic analyses were performed on a F & M Model 810 instrument fitted with a dual ionization detector. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Methyl 2,3-Di-*O*-benzyl-4,6-dideoxy-4-(*N,N*-dimethylamino)-*N*-oxo-α-D-altropyranoside (2). A solution of 128 mg (0.33 mmol) of the dimethylamino sugar[7] **1** in 50 ml of ether and 64 mg (0.36 mmol) of 99.9% pure *m*-chloroperbenzoic acid[8] was stirred at room temperature for 24 hr. An additional 10 mg of the peracid was added and stirring was continued for 1 more hr. The acid was neutralized by stirring with 60 mg of $NaHCO_3$ for 1 hr. The inorganics were filtered and the filtrate was washed with water. The ether extract was dried ($MgSO_4$) and evaporated to dryness to give 104.3 mg (76.8%) of **2** as a colorless gum. A solution of this material was treated with HCl in 2-propanol and the hydrochloride was recrystallized from 2-propanol–ether, 92 mg (81%), mp 171–172°, $[\alpha]^{25}D$ +81.8° (*c* 0.9, MeOH).

Anal. Calcd for $C_{22}H_{32}ClNO_5$: C, 63.07; H, 7.36; Cl, 8.09; N, 3.20. Found: C, 63.04; H, 7.49; Cl, 8.10; N, 3.22.

Methyl 2,3-Di-*O*-benzyl-4,6-dideoxy-4-(*N,N*-dimethylamino)-α-D-idopyranoside Methiodide (4). A solution of 148 mg (0.38 mmol) of methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-(*N,N*-dimethylamino)-α-D-idopyranoside[9] (**3**) in 10 ml of CH_3OH and 5 ml of CH_3I was heated under reflux on a steam bath for 2.5 hr. Evaporation of the solvents in vacuo followed by trituration with ether yielded 147 mg (73%) of **4**, mp 159–162°. Recrystallization from methanol–ether gave pure **4**, mp 162–163°, $[\alpha]^{25}D$ +12.6° (c 0.8, CH_3OH).

Anal. Calcd for $C_{24}H_{34}INO_4$: C, 54.65; H, 6.49; I, 24.07; N, 2.66. Found: C, 54.45; H, 6.47; I, 24.16; N, 2.73.

Methyl 2,3-Di-*O*-benzyl-4,6-dideoxy-α-D-*threo*-hex-4-enopyranoside (5). A. By Cope Elimination of 2. A solution of 100 mg (0.24 mmol) of the hydrochloride salt of **2** was passed over a column of Dowex-1 (HCO_3^- form) and eluted with methanol. Evaporation of the solution in vacuo yielded 83.4 mg (91%) of **2** as a gum. This material was taken up in a sublimation apparatus, degassed with N_2, and pyrolyzed at 100° (0.1 mmHg). The product was recrystallized from methanol–water to give 50 mg (71%) of **5**: mp 62–62.5°; ir ($CHCl_3$) 1675 cm^{-1} (double bond); NMR ($CDCl_3$) τ 2.61 (s, 10, aromatic), 5.15–5.43 (complex m, 6, CH_2, H-2, H-3), 5.95 (broad s, 1, H-4), 6.27 (d, $J_{1,2}$ = 3 Hz, 1, H-1), 6.49 (s, 3, OCH_3), 8.21 (s, 3, C-CH_3); $[\alpha]^{23}D$ −20.1° (*c* 1.0, CH_3OH).

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.04; H, 7.25.

B. By Hofmann Elimination of 4. A mixture of 96 mg (0.18 mmol) of **3** in 25 ml of CH_3OH and 10 ml of water and silver oxide (freshly prepared from 52.3 mg of $AgNO_3$) was heated on an oil bath at 60–65° for 20 min. The solvents were removed under vacuum and the residue was diluted with 10 ml of water and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to dryness to give 32.2 mg (52.5%) of **5**, mp 59–61°. It was recrystallized from methanol–water, mp 62–62.5°, $[\alpha]^{24}D$ −20° (c 1.0, CH_3OH). A mixture melting point with the analyzed sample from A above was unchanged.

Methyl 6-Deoxy-2,3-di-*O*-benzyl-α-D-altropyranoside (6). A solution of 340 mg (1 mmol) of **5** and 17 mg (0.5 mmol) of $NaBH_4$ in 1 ml of diglyme (distilled over $LiAlH_4$ under reduced pressure) was stirred at 20° in a cold water bath. A solution of 140 mg (1 mmol) of boron trifluoride etherate in 0.5 ml of diglyme was added dropwise to the stirred mixture in about 20 min. After stirring for an additional 1 hr, the reaction mixture was cooled in an ice bath and 1 ml of water was added followed by 0.5 ml of 2 *N* NaOH solution and 0.5 ml of 30% H_2O_2. Care was taken to maintain the solution slightly basic, around pH 8. After stirring for 1 hr, the solution was poured onto water and extracted thoroughly with ether. The combined ether extracts were washed with $NaHCO_3$ solution,

dried ($MgSO_4$), and concentrated under vacuum to give 274 mg (77%) of 6 as an oil. Column chromatography over Woelm grade I neutral alumina gave 241 mg (67.3%) of 6, homogeneous in several TLC systems, $[\alpha]^{26}D$ +44.7° (c 1.1, CH_3OH).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.48; H, 7.31. Found: C, 70.71; H, 7.19.

Methyl 6-Deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-altropyranoside (7). A solution of 72 mg (0.2 mmol) of 6 in pyridine was treated with 460 mg of methanesulfonyl chloride at 0° for 2 days. The mixture was poured onto ice–water, and the solid was filtered and recrystallized from 2-propanol to give 72 mg (82%) of 7, mp 85–86°, $[\alpha]^{24}D$ +54.0° (c 0.9, $CHCl_3$) [lit.[9] mp 85–86°, $[\alpha]^{25}D$ +53.9° (c 1.0, $CHCl_3$)].

Methyl 2,3-Di-*O*-benzyl-4,6-dideoxy-α-D-*arabino*-hexopyranoside (8). A. By Hydroboration of 5. Compound 5 (170 mg, 0.5 mmol) was subjected to hydroboration as described under the preparation of 6 using $NaBH_4$ and boron trifluoride etherate in diglyme. The reaction mixture was decomposed with 45 mg (0.75 mmol) of glacial acetic acid and the solution was boiled for 2 hr. The solvents were evaporated in vacuo and the product was extracted with ether, washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated under vacuum to give 131 mg (76.6%) of an oil. This material was purified by column chromatography on Florisil to yield 112 mg of 8 as an oil, $n^{24}D$ 1.5325, $[\alpha]^{23}D$ +74.3° (c 0.9, $CHCl_3$), homogeneous on TLC.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.78; H, 7.79.

B. From Compound 7. A solution of 150 mg (0.34 mmol) of 7 in 30 ml of acetonylacetone and 240 mg (1.6 mmol) of sodium iodide was heated at 125° for 3.5 hr with mechanical stirring. The mixture was cooled, diluted with 5 ml of water, and extracted thoroughly with petroleum ether (bp 50–70°). The petroleum ether extract was washed with sodium thiosulfate solution followed by water, dried ($MgSO_4$), and evaporated to dryness to give 123 mg of a pale yellow oil showing two major spots on TLC, probably corresponding to methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-iodo-α-D-altropyranoside and methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-iodo-α-D-idopyranoside. This material was further purified by column chromatography over Woelm grade I alumina to yield 87 mg of a mixture of the two iodo derivatives. A solution of 85 mg (0.18 mmol) of this mixture in 20 ml of anhydrous ether was treated with 130 mg of lithium aluminum hydride. The excess hydride was destroyed by the careful addition of water. The inorganic salts were removed by filtration, the filtrate was washed with water, dried ($MgSO_4$), and concentrated under vacuum, and the residue (48 mg, 76%) was evaporatively distilled to yield 31 mg of 8, $n^{24}D$ 1.5316, $[\alpha]^{24}D$ +76.4° (c 1.4, CH_3OH). This material was identical with the sample prepared by the hydroboration of 5 as shown by its ir spectrum, TLC, and GC using a 5-ft 6% ethylene glycol succinate column.

Acknowledgments. The authors thank Dr. K. Grant Taylor for useful discussions. Financial assistance from the National Institutes of Health (Grant GM 11520) is gratefully acknowledged.

Registry No.—1, 55570-39-3; 2 HCl, 55570-70-2; 3, 55570-20-2; 4, 55570-71-3; 5, 55570-72-4; 6, 33159-49-8; 7, 55570-73-5; 8, 55570-74-6; iodomethane, 74-88-4; methanesulfonyl chloride, 124-63-0.

References and Notes

(1) For a preliminary account of this work, see C. L. Stevens and D. Chitharanjan, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p 12C.
(2) Taken from the Ph.D. Dissertation of D. Chitharanjan, Wayne State University, 1969.
(3) For reviews on unsaturated sugars, see R. J. Ferrier, *Adv. Carbohydr. Chem.*, **20**, 67 (1965); **24**, 199 (1969).
(4) R. U. Lemieux, E. Fraga, and K. A. Watnabe, *Can J. Chem.*, **46**, 61 (1968).
(5) A. Melo, W. H. Elliott, and L. Glaser, *J. Biol. Chem.*, **243**, 1467 (1968); O. Gabriel and L. Lindquist, *ibid.*, **243**, 1469 (1968).
(6) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, p 189.
(7) Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. VII: C. L. Stevens, D. Chitharanjan, K. G. Taylor and P. M. Pillai, *J. Org. Chem.*, preceding paper in this issue.
(8) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).
(9) Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. VI: C. L. Stevens, J. P. Dickerson, K. G. Taylor, P. Blumbergs, and P. M. Pillai, *J. Org. Chem.*, in this issue.
(10) B. Helferich and E. Himmen, *Chem. Ber.*, **61**, 1825 (1929).
(11) For the mechanism and product ratio of a similar reaction, see C. L. Stevens, K. G. Taylor, and J. A. Valicenti, *J. Am. Chem. Soc.*, **87**, 4759 (1965).

Bicyclic Nucleosides Related to Pyrimidine Nucleosides. IV. Synthesis of 4- and 6-Ribofuranosylthiazolo[5,4-*d*]pyrimidines and 4-Arabinofuranosylthiazolo[5,4-*d*]pyrimidines[1]

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Ribosylation of the bis(trimethylsilyl) derivative of thiazolo[5,4-*d*]pyrimidine-5,7-dione has afforded a mixture of α- and β-4-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione. Thiation of the β anomer was followed by methylation to afford 7-methylthio-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one, which on treatment with methanolic ammonia was converted to 7-amino-4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one, a cytidine analog. An alternate ribosylation using a Friedel–Crafts catalyst afforded the 6-ribosyl derivative. Thiation of thiazolo[5,4-*d*]pyrimidine-5,7-dione afforded thiazolo[5,4-*d*]pyrimidin-5-one-7-thione, which was condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose to afford the 4,6-diribosyl derivative.

In recent years there has been an increasing interest in the synthesis of bicyclic nucleosides with a ribofuranosyl moiety residing in the pyrimidine ring. This interest has been generated to a large extent by the isolation and identification of 3-ribosyluric acid from beef blood.[2] This interest has been directed to a large extent toward 3-ribosyl purines[3–5] but other ring systems have also been investigated.[6,7] These systems have generally afforded, in addition to the desired isomer, substantial amounts of other products. This has been found to be especially true in the case of the purines.[5] In an effort to improve the selectivity of the ribosylation reaction we have investigated and reported on the use of a bulky 8 substituent in the purine series to direct the site of ribosylation to the 3 position.[8–10] This prompted us to investigate an alternate approach to the synthesis of this type of pyrimidine analog. We have now investigated the use of the thiazolo[5,4-*d*]pyrimidine ring system in which ribosylation of the thiazole ring would result in the loss of aromaticity in that ring and should, therefore, be inhibited.[11] Using this approach, the uridine

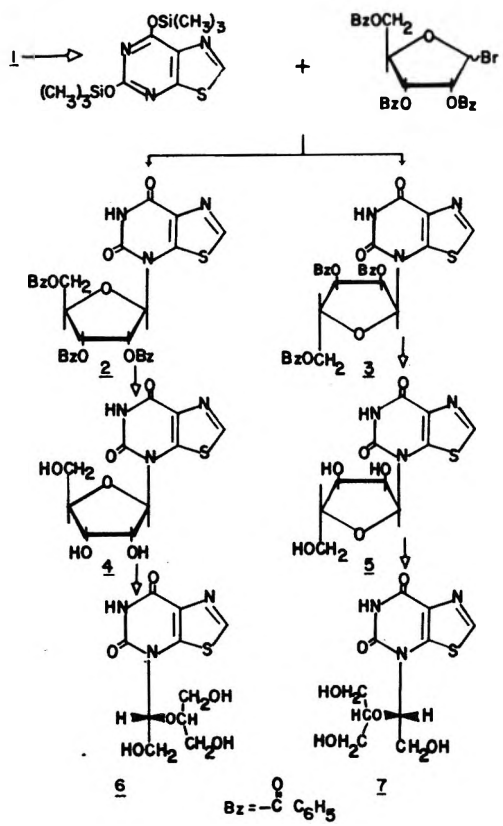
Table I
Ultraviolet Spectral Data for Certain Thiazolo[5,4-*d*]pyrimidine Nucleosides and Model Methyl Derivatives

No.	Compd	pH 1		pH 11	
		λ_{max}, nm	$\epsilon_{max} \times 10^{-3}$	λ_{max}, nm	$\epsilon_{max} \times 10^{-3}$
4	4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]-pyrimidine-5,7-dione	257	9.04	264	10.05
5	4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]-pyrimidine-5,7-dione	256.5	8.28	265	10.23
9	4-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione	261	9.80	266	10.40
11	6-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione	257	9.15	282	10.94
18	6-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]-pyrimidine-5,7-dione	257	9.60	282.5	8.0

and cytidine analogs of thiazolo[5,4-*d*]pyrimidine have now been prepared. In addition, we found that the use of stannic chloride furnished the 6-ribosyl derivative.

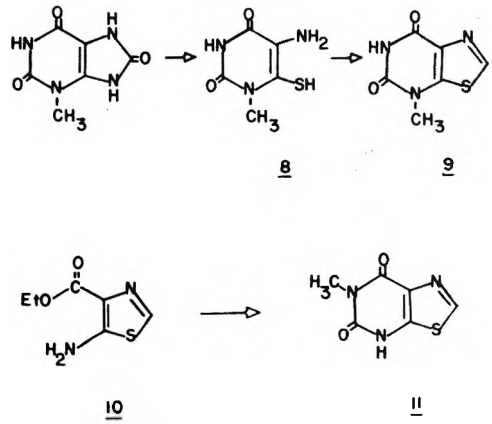
The silylation of thiazolo[5,4-*d*]pyrimidine-5,7-dione[12] (1) was accomplished with hexamethyldisilizane (HMDS) and a catalytic amount of ammonium sulfate. The silyl derivative of 1 was condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dimethylformamide at room temperature for 3 days to yield a mixture of two nucleosides which we assigned the structures 2 and 3 (vide infra) (Scheme I). The nucleoside mixture was separated by column chromatography to furnish 2 (46%) and 3 (19%) (based on unrecovered 1), which were found to have essentially identical ultraviolet spectra. We also obtained very similar R_f values for 2 and 3 [0.61 and 0.51, respectively, in chloroform–acetone (4:1)], which suggested that we had in hand a pair of anomers rather than a pair of isomers. This conclusion was also supported by the ^{1}H NMR spectra for 2 and 3, which were found to be essentially identical except for the different chemical shift values observed for the peaks assigned to the anomeric protons.[13] A removal of the protecting groups from 2 (methanolic ammonia) and 3 (methanolic sodium methoxide) afforded the nucleosides 4 and 5, respectively, which once again exhibited essentially identical ultraviolet spectra. Treatment of 4 and 5 with sodium periodate was followed by a reduction of the resultant dialdehydes with sodium borohydride to yield compounds 6 and 7, respectively. If the original nucleosides were indeed anomers (diastereoisomers), then 6 and 7 should be enantiomers with equal but opposite optical rotations.[14] The optical rotations of 6 and 7 were determined and found to be +73.3 and −75.0, respectively, which confirmed the anomeric nature of the two compounds.

Scheme I



The actual site of glycosylation for the two nucleosides was still undetermined (although we had assumed N-4) and prompted us to synthesize the two model methyl compounds, 4-methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (9) and 6-methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (11). The synthesis of 9 was achieved by treatment of 3-methyluric acid[15] with ammonium sulfide to give 1-methyl-6-thiouramil[16] (8). Ring closure of 8 with formic acid afforded the desired 4-methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (9) (Scheme II). The synthesis of 11 was accomplished by treatment of ethyl 5-aminothiazolo-4-carboxylate[17] (10) with methyl isocyanate.[18] A comparison of the ultraviolet spectra for the deblocked nucleosides 4 and 5 with those of the methyl derivatives (Table I) established unequivocally that the nucleosides 2 and 3 were both 4-substituted derivatives as we had presumed (Scheme I).

Scheme II

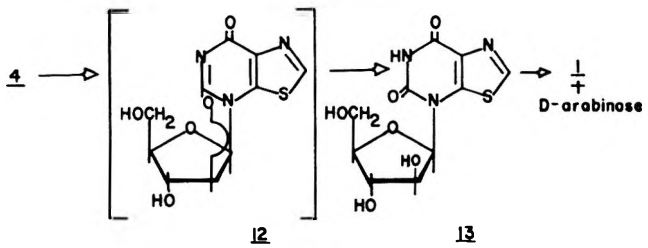


The assignment of anomeric configuration for the individual nucleosides could not be made unequivocally on the basis of ^{1}H NMR spectra, since the coupling constants for

both **4** and **5** ($J_{1',2'}$ = 6.0 and 2.8 Hz, respectively) were greater than 1 Hz.[13,19] However, a *tentative* assignment was made using ^{1}H NMR spectroscopy on the basis of the relative chemical shifts[13] observed for the anomeric protons of **4** and **5**. The nucleoside with the downfield chemical shift for the anomeric proton was assigned the cis nucleoside (α) structure, i.e., **5**.

This prompted us to initiate a synthesis of the 2,2′-anhydronucleoside in order to make an unequivocal anomeric assignment. Treatment of **4** with diphenyl carbonate and sodium bicarbonate in dimethylformamide at 150° for 15 min[20] gave a material which was not isolated, but was presumably the desired anhydronucleoside (**12**) (Scheme III).

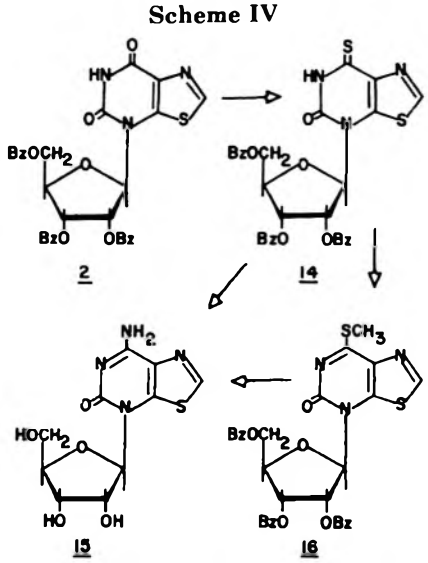
Scheme III



Treatment of **12** with 1.0 *N* sodium hydroxide furnished a nucleoside with the same ultraviolet spectra as that observed for **4** (Table I) but with a different R_f value. Hydrolysis of this nucleoside with 2 *N* hydrochloric acid and a paper chromatographic comparison of the hydrolysate with D-ribose, D-arabinose, and D-xylose showed that the sugar moiety of this nucleoside was D-arabinose. This established the structure as 4-(β-D-arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**13**), which also established that **4** must be the β anomer, since the intermediate anhydronucleoside derivative (**12**) can only be formed by a β-D-ribonucleoside.

It was necessary to functionalize the 7 position so that nucleophilic substitution by ammonia could be used in order to prepare the cytidine analog. The reaction of **2** with phosphorus pentasulfide proceeded smoothly to yield **14** (Scheme IV). The direct displacement of a thio group by

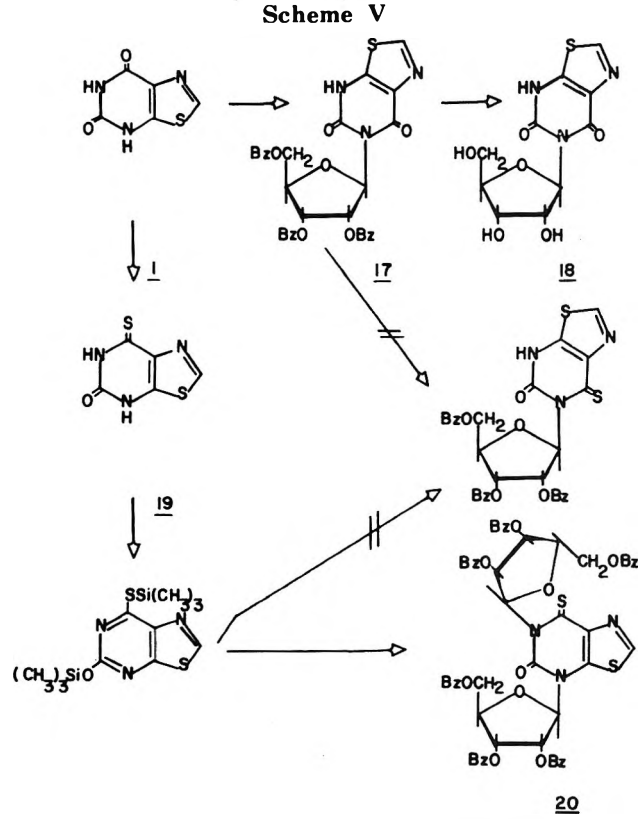
Scheme IV



ammonia has been reported for pyrimidine nucleosides[21] and 6-azapyrimidine nucleosides;[22] however, treatment of **14** with liquid ammonia at room temperature for 5 days resulted in the isolation of only a very low yield of the desired 7-amino-4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (**15**). This prompted us to convert **14** into 7-methylthio-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (**16**). The site of methylation was established by ^{1}H NMR spectroscopy[13] and was further corroborated by the reaction of **16** with methanolic ammonia, which not only removed the protecting benzoyl groups but also displaced the methylthio group to give the desired cytidine analog **15**.

We then initiated an alternate route using a different condensation method[23] for the preparation of the nucleoside **2** in an effort to eliminate the formation of the α anomer. Silylation of thiazolo[5,4-*d*]pyrimidine-5,7-dione (**7**) with hexamethyldisilizane followed by a reaction with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in 1,2-dichloroethane in the presence of 1 equiv of stannic chloride gave a nucleoside (**17**), which was different from either **2** or **3**. Debenzoylation of this nucleoside with sodium methoxide afforded a deblocked nucleoside which we assigned the structure **18** (Scheme V). A comparison of the ultraviolet

Scheme V



spectral data obtained for **18** with the spectral data for the model methyl compounds (**9** and **11**) established the site of ribosylation as N-6 for **17** and **18**, with a tentative assignment of β being assigned on the basis of the $J_{1',2'}$ for **18**. Although this product was unexpected, it is not without precedent, since although the reaction between bis(trimethylsilyl)lumazine and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide gave primarily 1-(β-D-ribofuranosyl)lumazine (analogous to **4**), the same reaction in the presence of stannic chloride gave[6] an appreciable quantity of the 3-ribosyllumazine derivative (analogous to **17**).

In an effort to prepare 7-amino-6-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one, we attempted to thiate **17** with phosphorus pentasulfide. However, regardless of the temperature or solvent used for this reaction, only starting material was isolated. This was very surprising, since a facile thiation of **2** was observed under these same conditions. The most apparent explanation is that the presence of the 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl group on the nitrogen adjacent to the site of reaction may sterically hinder the approach of phosphorus pentasulfide at the 7 position.

In order to circumvent this difficulty, thiazolo[5,4-*d*]py-

rimidine-5,7-dione (**1**) was thiated to afford thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (**19**). Silylation of **19** with bis(trimethylsilyl)acetamide followed by ribosylation in the presence of stannic chloride yielded a product which, on the basis of elemental analysis and proton magnetic resonance spectra, was assigned the diriboside structure **20**. The possibility that the sugar residues were attached to N-4 and the exocyclic sulfur was eliminated by a comparison of the ultraviolet spectral data for **20** with the uv spectral data observed for **16**, since **16** can be viewed as the methyl model of the *N*-4,7-*S*-diriboside. The other possibility in which a sugar could be attached to the exocyclic sulfur (N-6–7-S) seemed highly unlikely because of the presence of an absorption maxima at 350 nm (both pH 1 and 11) in the ultraviolet spectra of **20**. Exclusion of these two possibilities leaves the *N*-4,*N*-6-diriboside as the most likely structure for **20**.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a Varian A56/60 spectrophotometer and chemical shifts are reported as δ (parts per million) relative to an internal standard (tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate). Ultraviolet spectra were measured with a Beckman DK-2 spectrophotometer. Thin layer chromatography was run on SilicAR 7GF (Mallinckrodt) spread to a thickness of 0.25 mm on glass plates and column chromatography was run in glass columns with sintered glass bottoms dry packed with SilicAR CC-7, 200–325 mesh (Mallinckrodt). All solvent proportions are given by volume.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (2) and 4-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (3). Thiazolo[5,4-*d*]pyrimidine-5,7-dione (**1**, 10.0 g) was silylated with hexamethyldisilizane (HMDS, 50 ml) by heating the solution at reflux temperature for 15 hr. The excess HMDS was removed by vacuum distillation and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[8] (prepared from 29.8 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) which had been dissolved in dimethylformamide (100 ml) was added to the residue. The solution was stirred at room temperature for 3 days and then poured into methanol (1 l.) containing NH_4OH (8 ml, 28% aqueous). This mixture, on standing at room temperature for 24 hr, yielded a solid which was collected by filtration. Heating this solid in a mixture of chloroform–ethanol (1:1, 1 l.) left an insoluble material which was collected by filtration and shown to be unreacted **1** (2.4 g). The filtrate was cooled to room temperature and the resulting crystals were collected by filtration to provide pure **2** [10.6 g, R_f 0.61 in chloroform–acetone (4:1)]. The methanol filtrate (from the previous filtration) was evaporated to dryness, dissolved in $CHCl_3$ (25 ml), and applied to a dry packed column (7 × 21 cm) of SilicAR CC-7. The column was eluted with chloroform–acetone (9:1, 1 l.) and fractions containing **2** (15-ml fractions, no. 36–50) were evaporated to dryness, dissolved in a mixture of chloroform–ethanol (1:1), and allowed to cool, and the solid was collected by filtration to yield an additional amount of **2**. Fractions containing pure **3** [51–75, R_f 0.51 in chloroform–acetone (4:1)] were evaporated to dryness to yield a hard foam. The filtrate from the work-up of fractions 36–50 was evaporated to dryness, dissolved in $CHCl_3$ (15 ml), and applied to a second dry packed column of SilicAR CC-7 (4.8 × 20 cm) and eluted as above to yield some additional pure **2** and **3**. Total yield of **2**, 13.0 g; mp 230–231°; ^{1}H NMR (DMSO-d_6) δ 11.9 (s, 1, NH), 6.42 (d, 1, $J_{1',2'}$ = 3.0 Hz, H-1′).

Anal. Calcd for $C_{31}H_{23}N_3O_9S$: C, 60.67; H, 3.78; N, 6.85. Found: C, 60.87; H, 3.92; N, 7.02.

Total yield of **3**, 5.95 g; hard foam; ^{1}H NMR (DMSO-d_6) as above except δ 6.89 (d, 1, $J_{1',2'}$ = 4.0 Hz, H-1′).

Anal. Calcd for $C_{31}H_{23}N_3O_9S$: C, 60.67; H, 3.78; N, 6.85. Found: C, 60.89; H, 4.01; N, 6.68.

4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (4). The nucleoside **2** (6.2 g) was mixed with methanolic ammonia (75 ml, saturated at −5°) in a pressure bottle and allowed to stand at room temperature for 4 days. The solution was then evaporated to dryness and the residue was extracted with ethyl acetate (100 ml in four portions), leaving a solid. Recrystallization of the solid from MeOH (60 ml) yielded 2.87 g of **4**: mp 203–205° (cloudy melt); ^{1}H NMR (DMSO-d_6) δ 8.95 (s, 1, H-2) 6.11 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1′).

Anal. Calcd for $C_{10}H_{11}N_3O_6S$: C, 39.86; H, 3.60; N, 13.94. Found: C, 39.72; H, 3.75; N, 13.92.

4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (5). To a suspension of **3** (1.0 g) in anhydrous MeOH (20 ml) was added sodium methoxide (ca. 50 mg). This suspension was protected from moisture and stirred at room temperature for 15 hr. The crystals which had formed were collected by filtration to yield 0.36 g of a solid which was recrystallized from 95% MeOH to yield 0.3 g of **5**: mp 170° slow dec; ^{1}H NMR (DMSO-d_6) δ 8.76 (s, 1, H-2), 6.17 (d, 1, $J_{1',2'}$ = 2.8 Hz, H-1′).

Anal. Calcd for $C_{10}H_{11}N_3O_6S$: C, 39.86; H, 3.60; N, 13.94. Found: C, 39.67; H, 3.61; N, 14.25.

Periodate Oxidation and Sodium Borohydride Reduction of 4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (4) and 4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (5). 4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**4**, 40 mg) was suspended in 0.1 *M* sodium periodate solution (3.2 ml) in a 5-ml volumetric flask. The suspension was gently heated to dissolve the solid material and the solution was then stirred for 15 min at room temperature. Sodium borohydride (120 mg) was added to the solution in small portions and the mixture was stirred at room temperature for 30 min. The excess sodium borohydride was destroyed by the addition of 10% acetic acid (added dropwise until gas evolution ceased, ~1.4 ml). The solution was diluted to 5.0 ml, and the optical rotation of this solution was measured and found to be $[\alpha]^{27}$D +73.3°.

4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**5**, 40 mg) was treated in an identical fashion; the optical rotation was measured and found to be $[\alpha]^{27}$D −75.0°.

4-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (9). Ammonium hydroxide (28%, 75 ml) cooled in an ice bath with stirring was saturated with hydrogen sulfide gas to afford a solution of ammonium sulfide. The solution was added to a mixture of 3-methyluric acid[15] (5.2 g) and 2% NH_4OH (30 ml). The resulting suspension was stirred and then heated in a sealed container at 160° for 6 hr. The resulting solution was evaporated to dryness to yield a solid residue[16] (**8**, 4.0 g) which could be recrystallized from water. The crude solid was suspended in formic acid (85%, 70 ml) and heated at reflux temperature for 12 hr to yield 3.6 g of crude product. This solid was reprecipitated twice from dilute NH_4OH with 1 *N* HCl to yield an analytical sample of **9**, mp 350°.

Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.33; H, 2.75; N, 22.95. Found: C, 39.41; H, 2.95; N, 23.20.

6-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (11). Ethyl 5-aminothiazole-4-carboxylate (**10**, 2.0 g) and methyl isocyanate (1.5 ml) were added to pyridine (4 ml) and the suspension was heated at reflux temperature for 1 hr and then cooled to room temperature. A mixture of EtOH (5 ml) and diethyl ether (150 ml) was added to yield a solid which was collected by filtration (2.5 g). The solid (2.5 g) was added to 5% aqueous NH_4OH (40 ml) at reflux temperature and the solution was heated for 5 min. This solution was acidified with acetic acid to furnish a solid. The suspension was cooled to room temperature, and the solid was collected by filtration and recrystallized from water to yield **11**, 0.55 g, mp 348–350°.

Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.35; H, 2.75; N, 22.95. Found: C, 39.00; H, 2.81; N, 22.72.

4-(β-D-Arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (13). A mixture of **4** (1.0 g), diphenyl carbonate (0.88 g), and $NaHCO_3$ (0.016 g) in DMF (5 ml) was heated for 30 min in an oil bath at 150°. The suspension was poured into ether (100 ml) with stirring, and the resulting solid was collected by filtration and washed with an additional quantity of ether (50 ml). This solid [5,2′-*O*-anhydro-4-(β-D-arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**12**, 0.95 g)] was air dried, suspended in 1 *N* NH_4OH (10 ml), and stirred at room temperature for 2 hr. The solution was adjusted to pH 7.0 with 1 *N* HCl to yield crystals which were collected by filtration and washed with water (5 ml). The solid was recrystallized from water to yield 0.67 of **13**: mp over 245° slow dec; ^{1}H NMR (DMSO-d_6) δ 8.81 (s, 1, H-2), 6.15 (d, 1, $J_{1',2'}$ = 3.0 Hz, H-1′); uv λ_{max} ($\epsilon \times 10^{-3}$), pH 1, sh 275 nm (7.1), 258.5 (8.2); pH 11, 265 (8.6).

Anal. Calcd for $C_{10}H_{11}N_3O_6S \cdot 0.5H_2O$: C, 38.70; H, 3.89; N, 13.59. Found: C, 38.89; H, 4.07; N, 13.36.

Hydrolysis of 4-(β-D-arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione. 4-(β-D-Arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**13**, 10 mg) was heated in a 2 *N* HCl solution (2 ml) on a steam bath for 3 hr and the solution was then filtered.

The filtrate was adjusted to pH 7.0 with 1 *N* NaOH and then concentrated to 1 ml. Solutions of D-arabinose, D-ribose, and D-xylose were similarly treated. The concentrated filtrates were spotted on Whatman No. 1 chromatography paper and chromatographed with 1-butanol–acetic acid–water (3:1:1). The chromatograms were sprayed with aniline–phthalic acid reagent.[24] The hydrolysis solution gave a spot at R_f 0.33, which corresponded to the R_f value for D-arabinose (R_f values for ribose and xylose were 0.43 and 0.39, respectively), thus establishing that the carbohydrate moiety of **13** was indeed D-arabinose.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (14). The nucleoside **2** (10.0 g) was dissolved in pyridine (125 ml) and P_2S_5 (3.6 g, 1 equiv) was then added. The solution was heated at reflux temperature for 6 hr, at which time an additional 1 equiv of P_2S_5 (3.6 g) was added. Heating was continued for an additional 6 hr, at which time the solution was evaporated to near dryness and water (200 ml) was added. This mixture was heated on a steam bath for 30 min with stirring, and the solid material was collected by filtration, washed with water (100 ml), and air dried. This solid was dissolved in chloroform (200 ml) and the chloroform solution was extracted with 0.1 *N* HCl (4 × 100 ml), saturated aqueous $NaHCO_3$ (4 × 100 ml), and water (2 × 100 ml). The $CHCl_3$ solution was then dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and washed with $CHCl_3$ and the filtrate and wash were evaporated to dryness. The residue was dissolved in $CHCl_3$ (20 ml), applied to a dry packed column of SilicAR CC-7 (7 × 25 cm), and eluted with chloroform–acetone (19:1, 1 l.) to remove the impurities which remained on the column. The eluent was evaporated to dryness, and the residue was dissolved in $CHCl_3$ (20 ml), applied to a second column of SilicAR CC-7 (7 × 20 cm), and eluted with chloroform–acetone (19:1). Fractions of 20 ml were collected, and fractions 24–75 contained pure **14**, which was crystallized from chloroform–ethanol (1:9) to yield 5.8 g of product. All other fractions containing **14** were combined, evaporated to dryness, dissolved in $CHCl_3$ (10 ml), and applied to a third column of SilicAR CC-7 (4.5 × 23 cm). Eluted as above, fractions 12–24 contained pure **14** (1.5 g) for a total yield of 7.3 g: mp 188.5–189.5°; ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1, 2); uv λ_{max} (ε × 10^{-3}), pH 1, 362 nm (18.9), sh 277 (19.5), 244 (33.7); pH 11, 326 (24.5), 275 (19.8).

Anal. Calcd for $C_{31}H_{23}N_3O_8S_2$: C, 59.12; H, 3.68; N, 6.67. Found: C, 59.25; H, 3.69; N, 6.56.

7-Methylthio-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (16). The nucleoside **14** (0.63 g) was added to sodium hydride (0.024 g) in DMF (5 ml) and the suspension was stirred at room temperature until bubbling had ceased (ca. 15 min). Methyl iodide (0.23 g, 0.1 ml) was added and the solution was stirred for an additional 1 hr. This solution was evaporated to dryness, then xylene (5 ml) was added and the suspension was again evaporated to dryness. The residue was dissolved in $CHCl_3$ (30 ml), and the $CHCl_3$ solution was extracted with water (4 × 15 ml) and then dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and washed with $CHCl_3$ (20 ml), and the combined filtrate and wash were evaporated to dryness, dissolved in $CHCl_3$ (2 ml), and applied to a dry packed column of SilicAR CC-7 (2.5 × 25 cm) and eluted with chloroform–acetone (19:1). Fractions of 20 ml were collected and fractions 6–8 contained pure **16.** These fractions were evaporated to dryness to yield a hard foam which on trituration with ether gave a solid: yield 0.60 g; ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1, H-2), 2.65 (s, 3, $-SCH_3$); uv λ_{max} (ε × 10^{-3}) pH 1, 327 nm (16.8), sh 285 (23.8), 274 (24.5), 244 (35.0); pH 11, 324 (17.1), sh 285 (25.4), 270 (26.4), 244 (40.6).

Anal. Calcd for $C_{32}H_{25}N_3O_8S_2$: C, 59.72; H, 3.92; N, 6.53. Found: C, 59.90; H, 4.20; N, 6.24.

7-Amino-4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (15). Method A. The nucleoside **14** (1.0 g) was suspended in liquid ammonia (5 ml) and the reaction mixture was allowed to stand at room temperature in a sealed pressure vessel for 5 days. The excess ammonia was allowed to evaporate and the residue was extracted with ether (4 × 10 ml). Crystallization of the solid residue from water (20 ml) yielded ca. 50 mg of **15**: mp 201° slow dec; ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1, H-2), 7.90 (br m, 2, NH_2), 6.08 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1'); uv λ_{max} (ε × 10^{-3}) pH 1, 294 nm (10.1), 259 (7.6); pH 11, sh 281 (8.2), 266 (9.9), 229 (17.2).

Anal. Calcd for $C_{10}H_{12}N_4O_5S\cdot H_2O$: C, 37.74; H, 4.42; N, 17.61. Found: C, 37.91; H, 4.45; N, 17.40.

Method B. The nucleoside **16** (1.5 g) was suspended in MeOH saturated with ammonia (50 ml, saturated at 0°) and the mixture was allowed to stand in a pressure bottle at room temperature for 96 hr. The crystals which had formed were collected by filtration and washed with MeOH (20 ml) to yield **15** (0.55 g). The filtrate was evaporated to dryness and the residue was extracted with carbon tetrachloride (4 × 20 ml), then recrystallized from water to yield some additional **15** for a total yield of 0.60 g; this material was shown to be identical with that obtained by method A by thin layer chromatography in chloroform–methanol (7:3) and by a comparison of ultraviolet spectra.

6-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (17). Thiazolo[5,4-*d*]pyrimidine-5,7-dione (**1**, 1.0 g) was silylated with hexamethyldisilazane (15 ml), as before, and the bis(trimethylsilyl) derivative was dissolved in 1,2-dichloroethane (100 ml). To this solution was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (2.7 g) followed by stannic chloride (1.5 g, 0.69 ml) and the mixture was stirred for 4 hr at room temperature. Pyridine (1 ml) was then added and the precipitate which formed was collected by filtration and washed with $CHCl_3$ (50 ml). The filtrate and wash were combined and extracted with 0.1 *N* HCl (3 × 35 ml), saturated aqueous $NaHCO_3$ (3 × 35 ml), and water (2 × 50 ml). The $CHCl_3$ solution was dried over Na_2SO_4 and filtered, the Na_2SO_4 was washed with $CHCl_3$ (50 ml), and the filtrate and wash were evaporated to dryness. The resulting syrup was dissolved in a minimum volume of $CHCl_3$ (2 ml), applied to a dry packed SilicAR CC-7 column (3.5 × 20 cm), and eluted with chloroform–acetone (4:1). The fractions containing **17** [R_f 0.53, chloroform–acetone (4:1)] were combined and evaporated to dryness, and the residue was recrystallized from ethanol–chloroform (15:1) to yield 2.0 g of product: mp 234–235°; mmp with **2** 205–215°; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1, H-2); uv λ_{max} (ε × 10^{-3}) pH 1, sh 277 nm (17.5), 236 (32.5); pH 11, sh 295 (13.2), 277 (15.9), 230 (47.5).

Anal. Calcd for $C_{31}H_{23}N_3O_9S$: C, 60.67; H, 3.78; N, 6.85. Found C, 60.61; H, 3.77; N, 6.91.

6-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (18). Sodium methoxide (125 mg) was added to **17** (1.0 g) suspended in MeOH (20 ml). The mixture was stirred at room temperature for 15 hr, and the precipitate was collected by filtration, washed with MeOH (5 ml), and air dried (0.47 g). The filtrate and wash were neutralized with Amberlite CG-50 ion exchange resin (H^+ form), the suspension was filtered, and the resin was washed with hot MeOH (10 ml). The filtrate and wash were combined and evaporated to dryness and the residue was extracted with ether (4 × 10 ml). The solid which remained was dissolved in hot water (5 ml) by the addition of a minimum volume of concentrated NH_4OH and reprecipitated by adjusting the pH of the solution to 6.0 with 1 *N* HCl to yield some additional **18** for a total yield of 0.14 g: mp 294–296° dec; ^{1}H NMR (DMSO-d_6) δ 7.95 (s, 1, H-2), 6.23 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1').

Anal. Calcd for $C_{10}H_{11}N_3O_6S\cdot 0.5H_2O$: C, 38.70; H, 3.90; N, 13.54. Found: C, 38.74; H, 3.89; N, 13.40.

Thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (19). Thiazolo[5,4-*d*]pyrimidine-5,7-dione (**1**, 10.0 g) and P_2S_5 (13.2 g) were added to pyridine (80 ml) and the mixture was heated at reflux temperature for 6 hr. An additional 1 equiv of P_2S_5 (13.2 g) was then added and the heating was continued for an additional 6 hr. The resulting solution was evaporated to dryness, water (150 ml) was added, and the suspension was heated on a steam bath with stirring for 1 hr. The resulting solid was collected by filtration and reprecipitated from hot 0.5 *N* NaOH (400 ml) with 1 *N* HCl. After cooling, the precipitate was collected by filtration, washed with water (50 ml), and dissolved in 0.1 *N* NaOH (400 ml). This solution was applied to a 2.0-cm column (diameter) containing 50 ml (wet volume) of Amberlite IRA-400 CP ion exchange resin (strong base, Cl^- form). The column was washed with 0.1 *N* NaOH (100 ml) and then **19** was eluted with 1.5 *N* NaCl which was 0.01 *N* in NaOH (1.5 l.). Acidification (pH 2) of the eluent with 1 *N* HCl yielded 5.75 g of product: mp 360°; uv λ_{max} (ε × 10^{-3}) pH 1, 342 nm (18.4), 333 (19.2), 270 (7.5); pH 11, 351 (18.5), 291 (7.8), 267 (8.2).

Anal. Calcd for $C_5H_3N_3OS_2$: C, 32.42; H, 1.63; N, 22.69. Found: C, 32.42; H, 1.62; N, 22.61.

Ribosylation of Thiazolo[5,4-*d*]pyrimidin-5-one-7-thione. Thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (**19**, 2.5 g) was silylated with bis(trimethylsilyl)acetamide (9.5 ml) in 1,2-dichloroethane (25 ml) at 50° for 15 min. The solvent and excess BSA were removed by distillation and the resulting solid residue was combined with 1-*O*-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (6.8 g) in 1,2-dichloroethane (30 ml). Stannic chloride (4.5 g, 2.0 ml) was added and the solution was stirred at room temperature for 15 hr. Pyridine (2.2 ml, 2 equiv) was added to the solution, and the resulting precipitate was removed by filtration and washed with $CHCl_3$ (100 ml). The combined filtrate and wash were extracted

with 0.1 *N* HCl (4 × 50 ml), saturated aqueous $NaHCO_3$ (4 × 50 ml), and water (2 × 50 ml). The organic phase was dried over Na_2SO_4, the Na_2SO_4 was removed by filtration and washed with $CHCl_3$ (30 ml) and the combined filtrate and wash were evaporated to dryness. The resulting syrup was dissolved in $CHCl_3$, applied to a dry packed column of SilicAR CC-7 (7 × 18 cm), and eluted with chloroform–acetone (19:1). Fractions containing the major band [R_f 0.73, chloroform–acetone (19:1), fraction no. 7–23, 20-ml fractions] were concentrated and applied to another SilicAR CC-7 (4.6 × 20 cm) column. Fractions 3–10 (20-ml fractions) from the second column contained pure **20**. These fractions were combined and evaporated to a hard foam and then triturated with ether (100 ml) to give 3.9 g of solid: mp 119–122°; ^1H NMR ($CDCl_3$) δ 8.46 (s, 1, H-2), 8.33–7.33 (m, ca. 30, $-COC_6H_5$); uv λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 350 nm (14.4), sh 275 (19.5), 238 (45.3); pH 11, 350 (15.7), sh 275 (26.1), 237 (91.0).

Anal. Calcd for $C_{57}H_{43}N_3O_{15}S_2 \cdot 2H_2O$: C, 61.68; H, 4.26; N, 3.78. Found: C, 61.59; H, 4.45; N, 3.68.

Registry No.—**1**, 5082-82-6; **2**, 35867-92-6; **3**, 55520-41-7; **4**, 35867-91-5; **5**, 35867-90-4; **8**, 55520-42-8; **9**, 55520-43-9; **10**, 18903-18-9; **11**, 55520-44-0; **12**, 55520-45-1; **13**, 35867-89-1; **14**, 55520-46-2; **15**, 55520-47-3; **16**, 55520-48-4; **17**, 55520-49-5; **18**, 55520-50-8; **19**, 55520-51-9; **20**, 55520-52-0; 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide 22860-91-9; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9.

References and Notes

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(2) R. Falconer and J. M. Gulland, *J. Chem. Soc.*, 1369 (1939); H. S. Forrest, D. Hatfield, and J. M. Lagowski, *J. Chem. Soc.*, 963 (1961).
(3) D. Lipkin, C. T. Cori, and J. A. Rabi, *J. Heterocycl. Chem.*, **6**, 995 (1969).
(4) R. Lohrmann, J. M. Lagowski, and H. S. Forrest, *J. Chem. Soc.*, 451 (1964).
(5) N. J. Leonard and R. A. Laursen, *Biochemistry*, **4**, 354 (1965).
(6) G. Ritzmann, K. Harzer, and W. Pfleiderer, *Angew. Chem., Int. Ed. Engl.*, **10**, 932 (1971).
(7) B. H. Rizkalla, A. D. Broom, M. G. Stout, and R. K. Robins, *J. Org. Chem.*, **37**, 3975 (1972).
(8) C. L. Schmidt and L. B. Townsend, *J. Org. Chem.*, **37**, 2300 (1972).
(9) C. L. Schmidt and L. B. Townsend, *J. Heterocycl. Chem.*, **10**, 687 (1973).
(10) C. L. Schmidt and L. B. Townsend, *J. Chem. Soc., Perkin Trans. 1*, in press.
(11) C. L. Schmidt, W. J. Rusho, and L. B. Townsend, *Chem. Commun.*, 1515 (1971).
(12) S. J. Childress and K. L. McKee, *J. Am. Chem. Soc.*, **73**, 3862 (1951).
(13) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. II, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N.Y., 1973, pp 267–398.
(14) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **7**, 1329 (1970), and references cited therein.
(15) W. Traube, *Ber.*, **33**, 3035 (1900).
(16) G. P. Hager and C. Kaiser, *J. Am. Pharm. Assoc.*, **44**, 193 (1955).
(17) A. H. Cook, I. Heilbron, and A. L. Levy, *J. Chem. Soc.*, 1598 (1947).
(18) A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1069 (1949).
(19) R. U. Lemieux and D. R. Lineback, *Annu. Rev. Biochem.*, **32**, 155 (1963).
(20) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).
(21) I. L. Doerr, J. F. Codington, and J. J. Fox, *J. Med. Chem.*, **10**, 247 (1967).
(22) V. P. Chernetskii and I. V. Alekseeva, *Chem. Heterocycl. Compd.*, **3**, 861 (1967).
(23) U. Niedballa and H. Vorbruggen, *Angew. Chem., Int. Ed., Engl.*, **9**, 461 (1970).
(24) S. M. Partridge, *Nature (London)*, **164**, 443 (1949).

C-Glycosyl Nucleosides. VII.[1] Synthesis of Some 3-β-D-Ribofuranosyl-1,2,4-oxadiazoles and 3-β-D-Ribofuranosylpyrazoles

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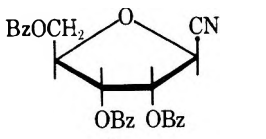
Two syntheses of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonamidoxime (**2a**) are described via either addition of hydroxylamine to 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide or chlorination and amination of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose oxime. Reactions of **2a** with acetic anhydride and ethyl acetoacetate give rise to 5-substituted 3-β-D-ribofuranosyl-1,2,4-oxadiazoles, while acetaldehyde gives the related Δ^2-1,2,4-oxadiazoline. The condensation of both *O*-benzoyl and *O*-benzyl derivatives of 2,5-anhydro-D-allose with 1-chloroacetonylidenetriphenylphosphorane gives unsaturated chloro ketones that can be cyclized with hydrazine to 5-methyl-3-β-D-ribofuranosylpyrazoles. A potential route for the synthesis of pyrazoles is explored via addition of ethyl glyoxylate hydrazone to nitroolefins followed by chlorination and base-catalyzed cyclization. This has required the synthesis of a *C*-glycosyl nitroolefin via addition of nitromethane to 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose followed by dehydration. While pyrazole synthesis was achieved in a model system, the carbohydrate derivative failed to cyclize.

The natural occurrence of a number of *C*-glycosyl nucleosides, many of which possess antibacterial or antitumor activity,[2] has prompted considerable activity directed toward the synthesis of this type of compound.[3] Our general approach has been based upon the development of a facile synthetic route for the preparation of variously protected derivatives of 2,5-anhydro-D-allose.[4] The latter compounds, which already include the critical *C*-glycosyl carbon–carbon bond, contain a reactive aldehyde function that can be elaborated into a variety of heterocyclic systems. We have, for example, described the use of these key intermediates in syntheses of 2-β-D-ribofuranosylmaleimide (showdomycin),[5] of variously substituted 4-β-D-ribofuranosylpyrazoles,[6] and of both 3- and 5-β-D-ribofuranosylisoxazoles.[1] In the present paper we further extend those studies and describe routes for the synthesis of several 3-β-D-ribofuranosyl-1,2,4-oxadiazoles and 3-β-D-ribofuranosylpyrazoles.

The most frequently encountered route for the synthesis of substituted 1,2,4-oxadiazoles involves the acylation and subsequent cyclization of amidoximes. This procedure was originally developed by Tiemann[7] some 90 years ago and has recently been reexamined by Moussebois et al.[8] The chemistry of amidoximes has been reviewed[9] and it can be seen that the most common route for their synthesis involves the condensation of nitriles with hydroxylamine.[10] For our purposes the key intermediate would be 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonamidoxime (**2a**), and this compound could be obtained by the reaction of the readily available 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**1**)[11,4] with hydroxylamine in methanol at 50°. Under these conditions **2a** was obtained in only 34% yield and it was necessary to effect purification by chromatography on silicic acid in order to remove several more polar by-products arising, presumably, from partial debenzoylation. While amidoximes have been prepared as substituents upon the

heterocyclic rings of several nucleosides,[12] **2a** is, to the best of our knowledge, the first example of a carbohydrate amidoxime. Debenzoylation of **2a** by treatment with methanolic ammonia gave free 2,5-anhydro-D-allonamidoxime (**2b**) in high yield. The rather low yield of **2a** obtained directly from the nitrile 1 could be much improved by use of an alternate synthetic route.[13] We have previously described the synthesis of the chloro oxime **4**, or its nitroso tautomer, via low-temperature chlorination of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose oxime (**3**).[1] Without purification **4** was treated with ammonia in ether at 0° to give pure **2a** in almost quantitative yield. The entire process is extremely efficient and the overall yield of **2a** from the diphenylimidazolidine derivative of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose[4] is 89% without the necessity of any chromatography.



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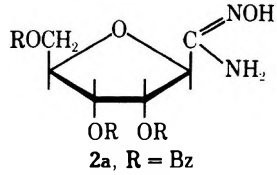
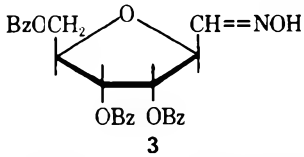


2a, R = Bz
b, R = H



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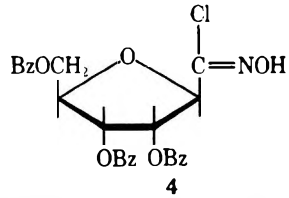
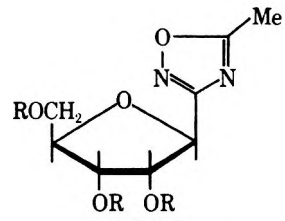


4

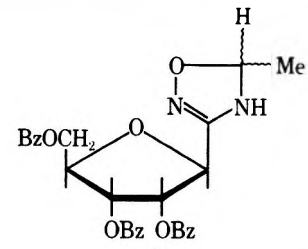
The amidoxime **2a** was then subjected to several types of ring closure reactions. First of all, it was treated with acetic anhydride under reflux, giving, presumably via the *O*-acetyl intermediate, 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methyl-1,2,4-oxadiazole (**5a**) in 48% yield. Typical of most of the compounds in the present work, **5a** was obtained as a homogeneous foam following chromatography on silicic acid. While **5a**, and many other compounds in this series, have eluded crystallization, its purity was assured by elemental analysis and NMR spectroscopy. Debenzoylation of **5a** was readily achieved using methanolic ammonia giving 5-methyl-3-(β-D-ribofuranosyl)-1,2,4-oxadiazole (**5b**) in 70% yield. As has been seen quite frequently in other perbenzoylated *C*-glycosides that we have examined,[1,6] the NMR spectrum of **5a** shows overlapping signals for C_2'H and C_3'H and also for C_4'H and C_5'H_2. The purity of the samples is nevertheless apparent from other sharp signals due to C_1'H, heterocyclic protons, and ring substituents. Following debenzoylation, however, there is excellent resolution of all the sugar protons, especially in spectra run in pyridine-d_5. The spectrum of **5b**, for example, is readily amenable to first-order analysis.

Amidoximes are also known to react with aldehydes giving Δ^2-1,2,4-oxadiazolines.[14] Thus a solution of **2a** and acetaldehyde in aqueous ethanol reacted slowly at room temperature over 3 days, giving a 47% yield of 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methyl-Δ^2-1,2,4-oxadiazoline (**6**). While **6** was analytically pure, its NMR spectrum clearly showed it to be the expected mixture of diastereoisomers. Brief treatment of **6** with chlorine in carbon tetrachloride led to rapid and complete dehydrogenation giving **5a** identical with that from the acetic anhydride reaction. We have previously found chlorine to be a particularly effective reagent for the dehydrogenation of pyrazolines to pyrazoles.[6]

While amidoximes do not readily react with simple esters, they are known to condense with β-keto esters.[14a,15] In our case **2a** underwent a fairly clean condensation with ethyl acetoacetate in toluene under reflux giving 5-acetonyl-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-oxadiazole (**7**) in 61% yield. This structure is quite in accord



5a, R = Bz
b, R = H



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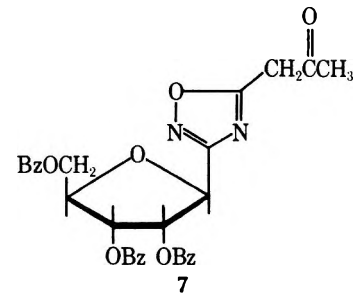

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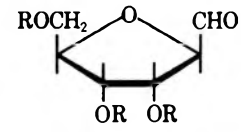
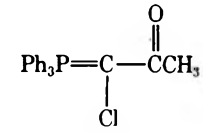
with the proposals of the early German workers[14a,15] and is confirmed by NMR spectroscopy, which shows the presence of an acetonyl function and the absence of heterocyclic protons. It should be noted that the reactions described above are basically prototypes of ones that could be used to introduce more highly functionalized substituents onto the heterocyclic ring of 1,2,4-oxadiazole-*C*-glycosides. This must, however, await further study.

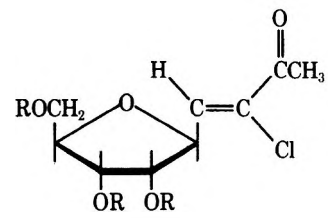
In an earlier paper we have described several methods for the preparation of functionally substituted 4-(β-D-ribofuranosyl)pyrazoles.[6] It was also of interest to explore routes to 3-(β-D-ribofuranosyl)pyrazoles, especially since the antibiotic pyrazomycin fits into this class.[2] While our approaches to the synthesis of pyazomycin itself will mainly be described elsewhere,[17] we now describe some simple routes to the basic heterocyclic system. Of the various methods for the synthesis of 3,5-disubstituted pyrazoles,[18] the one best suited to the starting materials at hand appeared to be the condensation of an α-chlorovinyl ketone with hydrazine.[19] To this end 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose (**8a**) was freshly regenerated as previously described from its diphenylimidazolidine derivative[4] and treated with 1-chloroacetonylidenetriphenylphosphorane (**9**)[20] in methylene chloride. Following chromatography on silicic acid 5,8-anhydro-6,7,9-tri-*O*-benzoyl-3-chloro-1,3,4-



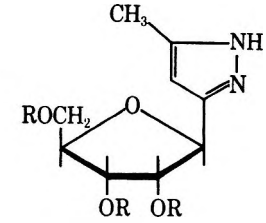
8a, R = benzoyl
b, R = benzyl



9



10a, R = benzoyl
b, R = benzyl



11a, R = benzoyl
b, R = H
c, R = benzyl

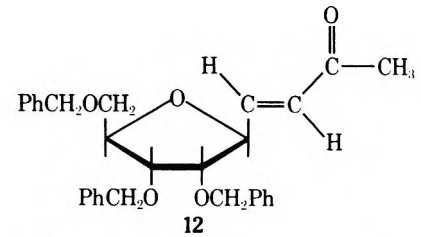
trideoxy-D-*allo*-non-3-eneulose (**10a**) was obtained as a homogeneous foam in 78% yield. The NMR spectrum of **10a** was well resolved and clearly indicated the presence of only a single geometrical isomer. In the absence of the other isomer it is difficult to make a direct assignment of configuration. As will be seen below, however, we have isolated both the *Z* and *E* isomers of the closely related benzyl ethers (**10b** and *E* isomer), which show chemical shifts for C_4H of 6.80 and 6.30 ppm, respectively. The chemical shift of C_4H (6.86 ppm) in **10a** strongly suggests that this compound has the *Z* configuration.

Treatment of **10a** with hydrazine hydrate in acetic acid under reflux led, presumably via initial hydrazone formation followed by intramolecular cyclization and dehydrohalogenation,[18] to 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methylpyrazole (**11a**), which was isolated in 69% yield by chromatography on silicic acid. Under these conditions loss of benzoyl groups did not appear to be a serious side reaction. Attempted debenzoylation of **11a** using methanolic sodium methoxide at room temperature led to the formation of the desired triol (**11b**) as a major product accompanied by several by-products that were difficult to remove. Debenzoylation using methanolic ammonia was considerably cleaner, but even here it was necessary to use ion exchange chromatography on a column of AG-1-X2 resin with a gradient of methanol in water[21] in order to fully purify the product. In this way 5-methyl-3-(β-D-ribofuranosyl-)pyrazole (**11b**) was isolated as a spectroscopically and analytically pure amorphous solid in 30% yield.

In an effort to improve the yield of **11b** we have also examined the use of benzyl ethers as the triol protecting group. Thus 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (**8b**) was liberated from its diphenylimidazolidine derivative[4] and directly treated with the chloro ylide **9** at room temperature, giving a 4:1 mixture of the *Z* (**10b**) and *E* isomers of the desired unsaturated chloro ketone in a combined yield of 87%. While the mixture was entirely satisfactory for the next step, a portion of the mixture was separated by preparative TLC and the pure isomers were characterized by their NMR spectra. These assignments of configuration were based upon the expected deshielding of C_4H in the *Z* isomer (**10b**) by the C_2 carbonyl group and are supported, to a lesser degree, by a deshielding of C_5H in the *E* isomer.

Treatment of the mixture of **10b** and its *E* isomer with hydrazine in acetic acid as above for **10a** gave the desired pyrazole **11c** in 56% yield following preparative TLC. Attempted debenzylation of **11c** by catalytic hydrogenolysis in the presence of palladium catalysts seemed capricious and usually gave a mixture of products even after several changes of catalyst. The use of sodium in liquid ammonia, however, led to rapid debenzylation and gave **11b**, identical with that from the benzoate, in 83% yield. In this case only desalting with Dowex 50(H^+) resin and preparative TLC were necessary for purification of the product. Our subsequent experience with debenzylations using boron trichloride[5] suggest that this might provide a convenient alternate route.

A slightly different approach to the synthesis of **11b** was also attempted without ultimate success. Thus the condensation of **8b** with acetonylidenetriphenylphosphorane[20] led to the isolation of 5,8-anhydro-6,7,9-tri-*O*-benzyl-1,3,4-trideoxy-D-*allo*-non-3-eneulose (**12**) as a syrup in 85% yield. The formation of only a single geometrical isomer was apparent from the NMR spectrum, and the large vicinal vinyl coupling ($J_{3,4}$ = 16 Hz) allowed assignment of the *E* configuration (**12**).[22] The reaction of **12** with hydrazine hydrate in acetic acid proceeded quite rapidly and led to the isolation of a crystalline, roughly equal mixture of two diastereomeric pyrazolines in 74% yield. The NMR spectrum of this material, however, showed the presence of an extraneous three-proton singlet at 1.86 ppm. In addition, its infrared spectra showed a strong absorption at 1645 cm^{-1}, typical of a tertiary amide, and the absence of any NH stretching bands near 3300 cm^{-1}. The elemental analysis also confirmed the presence of an acetyl group and we consider this product to be *N*-acetyl-3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-5-methyl-Δ^5-pyrazoline (**13**). We can offer no convincing argument as to the mechanistic origin of the *N*-acetyl function, and the formation of this type of product does not appear to have been previously observed.[18] We have been unsuccessful in our attempts to cleave the *N*-acetyl group by treatment with methanolic ammonia, sodium methoxide, and hydrogen chloride and equally unsuccessful in various attempts to dehydrogenate **13** with chlorine, bromine, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. In view of the successful syntheses of **11b** via the chloro ketones (**10a,b**), this route has not been explored further.



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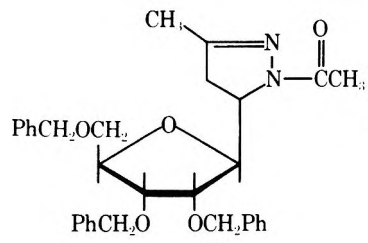

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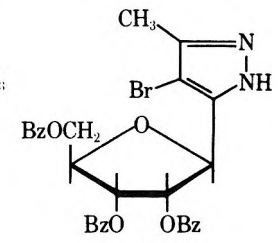
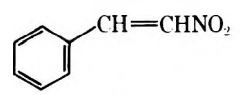


14

In an effort to introduce some reactive functionality into the pyrazole ring several approaches have been briefly explored. The reaction of **11a** with a small excess of bromine in chloroform readily gave the 4-bromo derivative **14** in 87% yield,[23] as shown by the disappearance of the resonance due to C_4H in the NMR spectrum. The nitration of **11a** under several conditions, however, led only to unreacted starting material or to the formation of nitrobenzoyl derivatives.

We have also considered an alternative route for the preparation of nitropyrazoles via cyclization of an appropriate nitroolefin. To test the concept we initially examined a model system based upon commercially available β-nitrostyrene (**15**). This nitroolefin underwent facile reaction with (*E*)-ethylglyoxylate hydrazone (**16**),[24] giving crystalline ethyl N^2-(2-nitro-1-phenylethyl)glyoxylate hydrazone (**17a**) in 39% yield. The chlorination of hydrazones has



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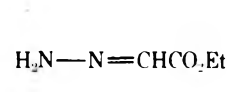

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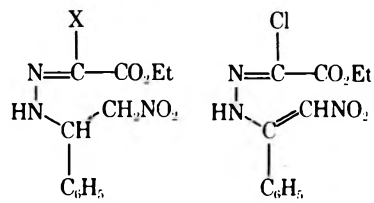
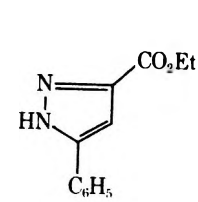


17a, X = H
b, X = Cl

18

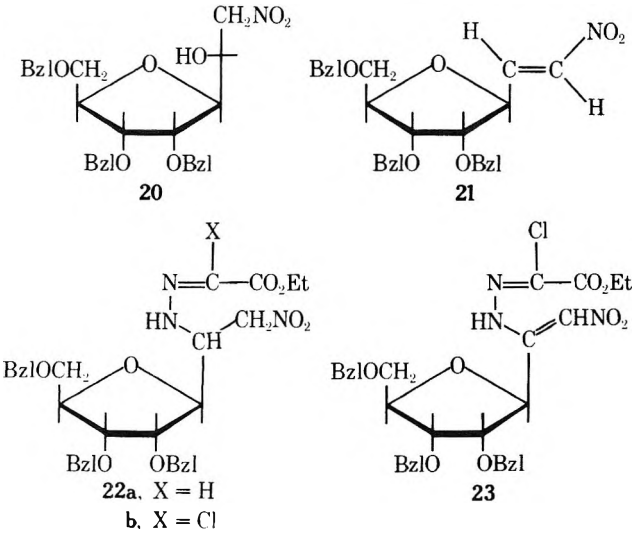


19

been known for many years[25] and reaction of **17a** with about 5 molar equiv of chlorine at −70° gave the crystalline chlorohydrazone **17b** in 70% yield. Care had to be taken to remove the excess chlorine at a low temperature, however, and an attempted chlorination using a large excess of chlorine and allowing the reaction to warm to room temperature led to the gradual formation of a second yellow product with a TLC mobility just greater than that of **17b**. The two substances could be separated by preparative TLC and the new product, which was obtained as yellow crystals in 22% yield, was shown by NMR and mass spectra to be ethyl N^2-(2-nitro-1-phenylvinyl)-2-chloroglyoxylate hydrazone (**18**), which presumably arose by benzylic chlorination and dehydrohalogenation of **17b**.

It was hoped that generation of a nitro-stabilized carbanion from **17b** would lead to intramolecular displacement of chlorine by either a direct SN2 process or, more likely, via an intermediate nitrilimine.[26] Treatment of **17b** with triethylamine in tetrahydrofuran led to complete disappearance of the starting material and formation of several new products which were separated by preparative TLC. From the major band a crystalline product was isolated in 14% yield and shown to be the known 3-ethoxycarbonyl-5-phenylpyrazole (**19**).[27] The formation of **19** shows that the desired cyclization of **17b** to a nitropyrazoline did occur but was followed by loss of nitrous acid giving the pyrazole. Other examples of the loss of nitrous acid from nitropyrazolines are to be found in the literature.[28]

In the hope that the spontaneous loss of nitrous acid might be avoided under appropriate conditions, we reacted the sugar aldehyde **11b** with nitromethane in the presence of sodium methoxide and obtained a crystalline nitro alcohol in 74% yield. This compound gave an ORD spectrum with a positive Cotton effect centered about 284 nm and on the basis of the empirical rules developed by Satoh et al.[29] is considered to be 3,6-anhydro-4,5,7-tri-*O*-benzyl-1-deoxy-1-nitro-D-*glycero*-D-*altro*-heptitol (**20**). Dehydration of **20** was readily accomplished by treatment with acetic anhydride and pyridine in benzene, giving (*E*)-3,6-anhydro-4,5,7-tri-*O*-benzyl-1,2-dideoxy-1-nitro-D-*allo*-hept-1-enitol (**21**) in 84% yield. While both vinyl protons in **21** were



masked by the aromatic resonances, the absence of any vinyl signal near 6.0 ppm strongly suggests that the product has the *E* configuration.[30]

The nitroolefin **21** reacted readily with **16** to form a mixture of diastereomeric nitro esters (**22a**) in 59% yield. While both diastereomers are suitable for subsequent steps, the major, more polar one could be isolated in crystalline form. We are not able to assign specific stereochemistry to the crystalline isomer at this time. As was the case with the model compound **17a**, careful low-temperature chlorination of **22a** led to the chlorohydrazone **22b**, which was isolated as an analytically pure syrup by preparative TLC in 84% yield. If, however, the chlorination reaction mixture was allowed to warm up before excess chlorine was removed, the crystalline nitroolefin **23** was isolated as a major product. Unfortunately, we have been unable to effect cyclization of **22b** by treatment with triethylamine or with other tertiary bases such diisopropylethylamine and 1,5-diazabicyclo[4.3.0]non-5-ene. Using these bases in different solvents and at various temperatures **22b** either remained unchanged or underwent extensive decomposition. It would thus appear that this route is not well suited for the preparation of the desired nitropyrazole *C*-glycosides.

Forthcoming papers in this series will describe our work on totally different routes toward the synthesis of pyrazomycin[17] and of purine-related C-glycosides.

Experimental Section

The general analytical methods used are similar to those described previously.[5] We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their continuous help with NMR spectroscopy.

2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allonamidoxime (2a). A. A solution of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylcyanide (**1**, 500 mg, 1.06 mmol)[11,4] and free base hydroxylamine [from 100 mg (1.4 mmol) of the hydrochloride][31] in methanol (40 ml) was heated at 50° for 12 hr. The solvent was then evaporated and the residue was purified by preparative TLC using benzene–acetone (9:1), which separated one principal product from several more polar by-products. Elution of the major band gave 180 mg (34%) of **2a** as a TLC-homogeneous syrup: λ_{max} (MeOH) 229 nm (ε 39,600), 274 (2900), 281 (2400); $[\alpha]^{23}D$ −17.9° (*c* 0.6, $CHCl_3$); NMR (acetone-d_6) 4.70 ppm (m, 3, C_5H, C_6H_2), 4.77 (d, 1, $J_{2,3}$ = 5 Hz, C_2H), 5.20 (br s, 2, NH_2), 5.87 (dd, 1, $J_{3,4}$ = 5, $J_{4,5}$ = 10 Hz, C_4H), 6.00 (dd, 1, C_3H), 7.5 (m, 9, Ar), 8.0 (m, 6, Ar).

Anal. Calcd for $C_{27}H_{24}N_2O_8$ (504.48): C, 64.28; H, 4.80; N, 5.55. Found: C, 64.52; H, 4.89; N, 5.44.

B. A solution of **8a** [regenerated from 10.0 g (15 mmol) of the diphenylimidazolidine derivative as previously described[4]] and hydroxylamine hydrochloride (5.0 g, 75 mmol) in ethanol (125 ml) and pyridine (125 ml) was heated under reflux for 2 hr and then evaporated to dryness. The residue was dissolved in chloroform (600 ml), washed with 5% aqueous sodium bisulfate, aqueous sodium bicarbonate, and water, dried ($MgSO_4$), and evaporated, leaving 7.0 g (97%) of oxime **3** that was identical by TLC (ether–hexane, 2:1) with an authentic sample.[1] This material was dissolved in ether (100 ml), cooled to −70°, and treated with a stream of chlorine gas for 10 min. After a further 10 min at −70° the solvent was evaporated in vacuo and the residue was coevaporated with benzene. The resulting chloro oxime (**4**)[1] was dissolved in ether (200 ml) and added to a saturated solution of ammonia in ether (1 l.) at 0°. After 12 hr at 0° the solvent was evaporated and the residue was dissolved in ether, washed twice with water, dried ($MgSO_4$), and evaporated, leaving 6.74 g (92% from **3**) of **2a** that was homogeneous by TLC and NMR analysis.

2,5-Anhydro-D-allonamidoxime (2b). A solution of **2a** (1.0 g, 1.98 mmol) is saturated methanolic ammonia was stored overnight at room temperature and then evaporated to dryness. The residue was purified by chromatography on a column of silicic acid (100 g) using chloroform–methanol (7:3), giving 350 mg (92%) of homogeneous **2b** as a clear syrup. Attempted crystallization from 2-propanol gave **2b** only as an amorphous, very hygroscopic solid: $[\alpha]^{23}D$ −30.8° (*c* 0.3, MeOH); NMR (pyridine-d_5–D_2O) 4.00 (dd, 1, J_{gem} = 13, $J_{5,6a}$ = 2.5 Hz, $C_{6a}H$), 4.15 (dd, 1, $J_{5,6b}$ = 3 Hz, $C_{6b}H$), 4.43 (m, 1, C_5H), 4.74 (m, 2, C_3H and C_4H), 4.94 ppm (d, 1, $J_{2,3}$ = 3 Hz, C_2H).

Anal. Calcd for $C_6H_{12}N_2O_5$ (192.18): C, 37.50; H, 6.30; N, 14.58. Found: C, 37.78; H, 6.31; N, 13.94.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methyl-1,2,4-oxadiazole (5a). A solution of **2a** (3.0 g, 5.9 mmol) in acetic anhydride (70 ml) was heated under reflux and in the dark for 12 hr in a nitrogen atmosphere. Evaporation of the solvent left a dark syrup that was coevaporated several times with dioxane and then chromatographed on a column of silicic acid using benzene–acetone

(98:2). The major product was 1.5 g (48%) of **5a**, which was obtained as a homogeneous foam: λ_{max} (MeOH) 229 nm (ε 37,500), 274 (2900), 281 (2300); $[\alpha]^{23}D$ −22.8° (*c* 0.6, $CHCl_3$); NMR ($CDCl_3$) 2.48 (s, 3, C_5Me), 4.7 (m, 3, $C_4'H$, $C_5'H_2$), 5.42 (d, 1, $J_{1',2'}$ = 3 Hz, $C_1'H$), 5.98 (narrow m, 2, $C_2'H$, $C_3'H$), 7.4 (m, 9, Ar), 8.0 ppm (m, 6, Ar).

Anal. Calcd for $C_{29}H_{24}N_2O_8$ (528.50); C, 65.90; H, 4.58; N, 5.30. Found: C, 65.79; H, 4.71; N, 5.29.

5-Methyl-3-(β-D-ribofuranosyl)-1,2,4-oxadiazole (5b). A solution of **5a** (280 mg, 0.53 mmol) in methanol (10 ml) was mixed with saturated methanolic ammonia (5 ml) and stored at room temperature for 48 hr. Following evaporation of the solvent the residue was chromatographed on a column of Merck silica gel G (50 g) using chloroform–methanol (19:1), giving 80 mg (70%) of **5b** as a homogeneous, clear syrup: uv (MeOH) only end absorption; $[\alpha]^{23}D$ −30.9° (c 0.2, MeOH); NMR (pyridine-d_5) 2.29 (s, 3, C_5Me), 4.09 (dd, 1, J_{gem} = 14, $J_{4',5'a}$ = 4 Hz, $C_{5'a}H$), 4.20 (dd, 1, $J_{4',5'b}$ = 4 Hz, $C_{5'b}H$), 4.66 (ddd, 1, $J_{3',4'}$ = 4 Hz, $C_4'H$), 4.81 (dd, $J_{2',3'}$ = 4 Hz, $C_3'H$), 4.97 (dd, 1, $J_{1',2'}$ = 5 Hz, $C_2'H$), 5.52 ppm (d, 1, $C_1'H$).

Anal. Calcd for $C_8H_{12}N_2O_5$ (216.19): C, 44.44; H, 5.60; N, 12.96. Found: C, 44.18; H, 5.63; N, 12.98.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methyl-Δ²-1,2,4-oxadiazoline (6). A solution of **2a** (150 mg, 0.3 mmol) and acetaldehyde (2.5 ml) in ethanol (5 ml) and water (2.5 ml) was stored at room temperature for 3 days. The mixture was then evaporated to dryness and the residue, which still contained **2a**, was purified by preparative TLC using benzene–acetone (9:1), giving 75 mg (47%) of **6** as a syrupy, diastereomeric mixture: λ_{max} (MeOH) 230 nm (ε 31,400), 273 (3200), 281 (2500); $[\alpha]^{23}D$ −79.2° (*c* 0.4, $CHCl_3$); the NMR spectrum ($CDCl_3$) was complex owing to the presence of two diastereomers.

Anal. Calcd for $C_{29}H_{26}N_2O_8$ (530.51): C, 65.65; H, 4.94; N, 5.28. Found: C, 65.29; H, 4.92; N, 5.28.

Treatment of 6 (10 mg) with ~1 *M* chlorine in carbon tetrachloride (1 ml) in the dark for 10 min led to complete dehydrogenation, giving **5a**. Following isolation by TLC the ir and NMR spectra of the latter were identical with those of **5a** prepared using acetic anhydride as above.

5-Acetonyl-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-oxadiazole (7). A solution of **2a** (100 mg, 0.2 mmol) and ethyl acetoacetate (400 mg, 3.1 mmol) in toluene (50 ml) was heated under reflux for 48 hr. The solvent was then evaporated and the residue was purified by preparative TLC using benzene–acetone (9:1), giving 70 mg (61%) of **7** as a homogeneous syrup: λ_{max} (MeOH) 230 nm (ε 38,900), 274 (5400); $[\alpha]^{23}D$ −41.6° (*c* 0.3, $CHCl_3$); NMR ($CDCl_3$) 2.22 (s, 3. $COCH_3$), 3.91 (s, 2, CH_2CO), 4.75 (m, 3, $C_4'H$, $C_5'H_2$), 5.46 (d, 1, $J_{1',2'}$ = 3 Hz, $C_1'H$), 6.00 (m, 2, $C_2'H$, $C_3'H$), 7.4 (m, 9, Ar), 8.0 ppm (m, 6, Ar).

Anal. Calcd for $C_{31}H_{26}N_2O_9$ (570.54): C, 65.26; H, 4.59; N, 4.91. Found: C, 65.06; H, 4.45; N, 4.83.

(*Z*)-5,8-Anhydro-6,7,9-tri-*O*-benzoyl-3-chloro-1,3,4-trideoxy-D-*allo*-non-3-eneulose (10a). 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allose (**8a**) was regenerated from its diphenylimidazolidine derivative (8.25 g, 12.35 mmol) as previously described.[4] The directly obtained aldehyde was dissolved together with 1-chloroacetonylidenetriphenylphosphorane (12.0 g, 34 mmol)[20] in methylene chloride (500 ml) and stirred at room temperature for 18 hr. The solution was then washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a column of silicic acid using ether–hexane (2:1), giving 5.30 g (78%) of **10a** as a foam that contained a single geometric isomer: λ_{max} (MeOH) 230 nm (ε 49,100), 274 (3300), 281 (2600); $[\alpha]^{23}D$ −36.9° (*c* 0.3, $CHCl_3$); NMR ($CDCl_3$) 2.33 (s, 3, $COCH_3$), 4.54 (dd, 1, J_{gem} = 13, $J_{8,9a}$ = 3.5 Hz, $C_{9a}H$), 4.6–4.8 (m, 2, C_8H, $C_{9b}H$), 5.30 (dd, 1, $J_{4,5}$ = 7.5, $J_{5,6}$ = 6 Hz, C_5H), 5.59 (dd, 1, $J_{6,7}$ = 6 Hz, C_6H), 5.73 (dd, 1, $J_{7,8}$ = 9 Hz, C_7H), 6.86 (d, 1, C_4H), 7.4 (m, 9, Ar), 8.0 (m, 6, Ar).

Anal. Calcd for $C_{30}H_{25}O_8Cl$ (548.96): C, 65.63; H, 4.59; Cl, 6.46. Found: C, 65.79; H, 4.74; Cl, 6.05.

5,8-Anhydro-6,7,9-tri-*O*-benzyl-3-chloro-1,3,4-trideoxy-D-*allo*-non-3-eneulose (10b). 2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-allose (**8b**) was regenerated from its diphenylimidazolidine derivative (1.30 g, 2.07 mmol) as previously described.[4] The crude aldehyde was then treated with 1.5 g (4.2 mmol) of **9** in methylene chloride (100 ml) at room temperature for 14 hr. The mixture was washed with water, evaporated, and purified by chromatography on a column of silicic acid using ether–hexane (2:1), giving 910 mg (87%) of **10b** as a roughly 4:1 mixture of geometrical isomers, λ_{max} (MeOH) 244 nm (ε 10,300).

Anal. Calcd for $C_{30}H_{31}O_5Cl$ (507.01): C, 71.06; H, 6.16. Found: C, 70.96; H, 6.08.

In a separate experiment a sample of this mixture was separated into its geometric isomers by preparative TLC using ether–hexane (9:1). The NMR spectrum of the major, more polar *Z* isomer (**10b**) in $CDCl_3$ showed 2.06 (s, 3, $COCH_3$), 3.51 (dd, 1, J_{gem} = 11, $J_{8,9a}$ = 3 Hz, $C_{9a}H$), 3.70 (dd, 1, $J_{8,9b}$ = 2.5 Hz, $C_{9b}H$), 3.88 (dd, 1, $J_{5,6}$ = 3, $J_{6,7}$ = 4.5 Hz, C_6H), 4.04 (dd, 1, $J_{7,8}$ = 7 Hz, C_7H), 4.28 (m, 1, C_8H), 4.45–4.7 (m, 6, OCH_2Ar), 5.07 (dd, 1, $J_{4,5}$ = 7 Hz, C_5H), 6.80 (d, 1, C_4H), 7.3 ppm (m, 15, Ar).

The NMR spectrum of the less polar *E* isomer ($CDCl_3$) showed 3.50 (dd, 1, J_{gem} = 11, $J_{8,9a}$ = 3 Hz, $C_{9a}H$), 3.70 (dd, 1, $J_{8,9b}$ = 2.5 Hz, $C_{9b}H$, 3.81 (dd, 1, $J_{5,6}$ = 2, $J_{6,7}$ = 4.5 Hz, C_6H), 4.00 (dd, 1, $J_{7,8}$ = 8 Hz, C_7H), 4.24 (m, 1, C_8H), 4.30, 4.42, 4.49, 4.58, 4.74, and 4.91 (d, 1, J_{gem} = 12–13 Hz, CH_2Ar), 5.20 (dd, 1, $J_{4,5}$ = 8 Hz, C_5H), 6.30 (d, 1, C_4H), 7.30 ppm (m, 15, Ar).

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methylpyrazole (11a). A solution of **10a** (5.30 g, 9.65 mmol) and 85% hydrazine hydrate (5.0 ml, ~100 mmol) in glacial acetic acid (250 ml) was heated under reflux for 18 hr. The cooled solution was evaporated to dryness and the residue was triturated with ethyl acetate (500 ml) and filtered. The filtrate was washed with aqueous sodium bicarbonate, dried, and evaporated, leaving a residue that was purified by chromatography on a column of silicic acid using benzene–ether (2:3). Evaporation of the major product left 3.50 g (69%) of **11a** as a syrup: λ_{max} (MeOH) 229 nm (ε 41,400), 274 (3900), 279 (sh, 3100); $[\alpha]^{23}D$ −3.2° (*c* 0.2, $CHCl_3$); NMR ($CDCl_3$) 2.21 (s, 3, CH_3), 4.69 (m, 3, $C_4'H$, $C_5'H_2$), 5.36 (m, 1, virtually coupled to $C_3'H$, $C_1'H$), 5.80 (m, 2, $C_2'H$, $C_3'H$), 6.05 (s, 1, C_4H), 7.3 (m, 9, Ar), 7.9 (m, 6, Ar), 8.90 ppm (br s, 1, NH).

Anal. Calcd for $C_{30}H_{26}N_2O_7$ (526.53): C, 68.48; H, 4.98; N, 5.32. Found: C, 68.10; H, 4.96; N, 5.15.

5-Methyl-3-(β-D-ribofuranosyl)pyrazole. (11b). A. A solution of **11a** (1.0 g, 1.9 mmol) in saturated methanolic ammonia (100 ml) was kept at room temperature for 12 hr and then evaporated to dryness. The residue was partitioned between ethyl acetate and water and the aqueous phase was evaporated to a syrup. The latter was dissolved in water (3 ml) and applied to a 1 × 15 cm column of freshly regenerated Bio-Rad AG-1-X2 resin. After a water wash the column was eluted with a gradient of 10–50% methanol in water, the elution being followed by TLC using chloroform–methanol (7:3). Evaporation of the pooled major peak gave 120 mg (30%) of **11b** as an amorphous solid that was homogeneous by NMR: λ_{max} (MeOH) 216 nm (ε 5100); $[\alpha]^{23}D$ −37.7° (*c* 0.3, H_2O); ORD (MeOH) $[\Phi]_{226}$ (tr) −1300°, $[\Phi]_{200}$ 0°; NMR (pyridine-d_5) 2.22 (s, 3, CH_3), 4.12 (dd, 1, J_{gem} = 12, $J_{4',5'a}$ = 3.5 Hz, $C_{5'a}H$), 4.28 (dd, 1, $J_{4',5'b}$ = 3.5 Hz, $C_{5'b}H$), 4.63 (m, 1, $C_4'H$), 4.81 (m, 2, $C_2'H$, $C_3'H$), 5.55 (d, 1, $J_{1',2'}$ = 4.5 Hz, $C_1'H$), 6.26 ppm (s, 1, C_4H).

Anal. Calcd for $C_9H_{14}N_2O_4$ (214.22): C, 50.46; H, 6.59; N, 13.08. Found: C, 50.54; H, 6.78; N, 12.99.

B. A solution of **11c** (100 mg, 0.20 mmol) in tetrahydrofuran (3 ml) was added to liquid ammonia (50 ml) and then small pieces of freshly cut sodium were added until a blue color persisted. The mixture was kept for an additional 10 min and then solid ammonium chloride (1 g) was added. The solvent was evaporated with a stream of argon and a solution of the resulting white residue in water was passed through a column (30 ml) of Dowex 50 (H^+) resin. The resin was washed with water and then eluted with dilute ammonia, giving a material that still retained some salt. This was purified by preparative TLC using chloroform–methanol (7:3) giving 35 mg (83%) of **11b** that was homogeneous by TLC and identical with that from A above.

C. Attempted debenzoylation of **11a** using methanolic sodium methoxide at room temperature overnight led to **11b** that was contaminated with some very close-moving impurities that were difficult to remove by preparative TLC.

3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-methylpyrazole (11c). A solution of **10b** (800 mg, 1.6 mmol) and 85% hydrazine hydrate (1 ml) in glacial acetic acid (50 ml) was heated under reflux for 12 hr and then worked up as above for **11a**. Preparative TLC using two developments with benzene–ether (3:2) gave 430 mg (56%) of **11c** as a syrup: λ_{max} (MeOH) 252 nm (ε 700), 259 (800), 264 (600), 268 (500); $[\alpha]^{23}D$ 9.9° (*c* 0.08, $CHCl_3$); NMR ($CDCl_3$) 2.22 (s, 3, CH_3), 3.52 (dd, 1, J_{gem} = 11, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 3.75 (dd, 1, $J_{4',5'b}$ = 3.5 Hz, $C_{5'b}H$), 3.96 (dd, 1, $J_{1',2'}$ = 3.5, $J_{2',3'}$ = 4.5 Hz, $C_2'H$), 4.08 (dd, 1, $J_{3',4'}$ = 6.5 Hz, $C_3'H$), 4.26 (m, 1, $C_4'H$), 4.38, 4.42, 4.47, 4.63 (d, 1, J_{gem} = 12 Hz, OCH_2Ar), 4.61 (s, 2, $C_5'O-CH_2Ar$), 5.15 (d, 1, $C_1'H$), 5.86 (s, 1, C_4H), 7.25 ppm (m, 15, Ar).

Anal. Calcd for $C_{30}H_{32}N_2O_4$ (484.57): C, 74.35; H, 6.66; N, 5.78. Found: C, 74.37; H, 6.60; N, 5.89.

(*E*)-5,8-Anhydro-6,7,9-tri-*O*-benzyl-1,3,4-trideoxy-D-*allo*-non-3-eneulose (12). A solution of **8b** [regenerated, as above, from

4.05 g (6.5 mmol) of the diphenylimidazolidine derivative][4] and acetonylidenetriphenylphosphorane (4.2 g, 13 mmol) were allowed to react in methylene chloride (500 ml) at room temperature for 16 hr. The solution was washed with water, evaporated to dryness, and chromatographed on a column of silicic acid using ether–hexane (2:1), giving 2.6 g (85%) of a single geometrical isomer (**12**) as a syrup: λ_{max} (MeOH) 225 nm (sh, ϵ 9400); $[\alpha]^{23}D$ −14.6° (c 0.2, $CHCl_3$); NMR ($CDCl_3$) 2.10 (s, 3, $COCH_3$), 3.51 (d, 1, $J_{3,9}$ = 4 Hz, C_9H_2), 3.70 (dd, 1, $J_{5,6}$ = 6.5, $J_{6,7}$ = 5 Hz, C_6H), 3.91 (dd, 1, $J_{7,8}$ = 4 Hz, C_7H), 4.24 (dt, 1, C_8H), 4.45–4.6 (m, 6, CH_2Ar), 4.6 (under CH_2Ar, 1, C_5H), 6.27 (dd, 1, $J_{3,4}$ = 16, $J_{3,5}$ = 1 Hz, C_3H), 6.62 (dd, 1, $J_{4,5}$ = 5 Hz, C_4H), 7.3 ppm (m, 15, Ar).

Anal. Calcd for $C_{30}H_{32}O_5$ (472.56); C, 76.24; H, 6.83. Found: C, 75.87; H, 6.86.

***N*-Acetyl-3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-5-methylpyrazoline (13).** A solution of **12** (2.6 g, 5.5 mmol) and 90% hydrazine hydrate (2.5 g, ~50 mmol) in glacial acetic acid (200 ml) was heated at 100° for 1.5 hr. After evaporation of the cooled solution the residue was dissolved in chloroform, washed with aqueous sodium bicarbonate and water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (200 g) using chloroform–ethyl acetate (10:3). Crystallization of the major product from ethyl acetate–hexane gave 2.15 g (74%) of a roughly equal mixture of diastereomers of **13** with mp 114–116°: λ_{max} (MeOH) 238 nm (ϵ 11,700); $[\alpha]^{23}D$ 129.9° (c 1.0, $CHCl_3$); ir (KBr) 1645 cm^{-1} (NAc), no NH or amide II: NMR ($CDCl_3$) 1.86 (s, 3, $COCH_3$), 2.13 and 2.19 (s, total 3, CH_3), 2.70 ppm (m, 2, C_4H_2), other sugar protons appearing as doubled signals in the expected regions.

Anal. Calcd for $C_{32}H_{36}N_2O_5$ (528.62): C, 72.70; H, 6.86; N, 5.30. Found: C, 72.38; H, 6.79; N, 5.30.

4-Bromo-5-methyl-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazole (14). Bromine (0.25 ml) was added to a solution of **11a** (100 mg, 0.19 mmol) in chloroform (20 ml) and the mixture was heated under reflux for 1.5 hr. The mixture was diluted with chloroform, washed with aqueous bicarbonate and water, dried ($MgSO_4$), and evaporated, leaving a solid residue. The latter was purified by preparative TLC using benzene–ether (3:2), giving 100 mg (87%) of **14** as a homogeneous foam: λ_{max} (MeOH) 230 nm (ϵ 42,300), 275 (3100), 282 (2500); $[\alpha]^{23}D$ −27.1° (c 0.2, $CHCl_3$); NMR ($CDCl_3$) 2.21 (s, 3, CH_3), 4.70 (apparent s, 3, C_4H, C_5H_2), 5.42 (d, 1, $J_{1',2'}$ = 4.5 Hz, C_1H), 5.98 (m, 2, C_2H, C_3H), 7.35 (m, 9, Ar). 7.95 ppm (m, 6, Ar).

Anal. Calcd for $C_{30}H_{25}N_2O_7Br$ (605.44): C, 59.51; H, 4.16; N, 4.63. Found: C, 59.45; H, 4.27; N, 4.79.

Ethyl N^2-(2-Nitro-1-phenylethyl)glyoxylate Hydrazone (17a). A solution of β-nitrostyrene (7.7 g, 52 mmol) and (*E*)-ethyl glyoxylate hydrazone (**16**, 6.0 g, 52 mmol)[32] in tetrahydrofuran (200 ml) was heated under reflux for 48 hr. Following evaporation of the solvent the residue was chromatographed on a column of silicic acid using ether–hexane (2:1) and the major product was crystallized from chloroform–hexane, giving 5.0 g (36%) of **17a** with mp 93–94°: λ_{max} (MeOH) 280 nm (ϵ 16,600); NMR ($CDCl_3$) 1.28 (t, 3, CH_3), 4.21 (q, 2, OCH_2), 4.67 (dd, 1, J_{gem} = 13, J_{vic} = 5 Hz, NO_2CH), 5.01 (dd, 1, J_{vic} = 7.5 Hz, NO_2CH), 5.23 (m, 1, ArC**H**), 6.84 (s, 1, N=C**H**), 7.04 (d, 1, NH), 7.30 ppm (s, 5, Ar).

Anal. Calcd for $C_{12}H_{15}N_3O_4$ (265.26): C, 54.33; H, 5.70; N, 15.84. Found: C, 53.94; H, 5.67; N, 15.58.

Ethyl N^2-(2-Nitro-1-phenylethyl)-2-chloroglyoxylate Hydrazone (17b). A solution of chlorine in carbon tetrachloride (13.2 ml of 1.36 *M*, 18.5 mmol) was added dropwise over 30 min to a stirred solution of **17a** (1.0 g, 3.8 mmol) in methylene chloride (30 ml) at −70°. The solvent was then evaporated in vacuo (below 0°) and the residue was crystallized from chloroform–hexane, giving 790 mg (70%) of **17b** with mp 77–78°: λ_{max} (MeOH) 276 nm (λ 17,300); ir (KBr) 1710 (CO), 1550 cm^{-1} (NO_2); mass spectrum (70 eV) *m/e* 299, 301 (M^+), 252, 254, (M − HNO_2), 239, 241 (M − CH_2NO_2), 104 (ArCH=CH_2); NMR ($CDCl_3$) 1.32 (t, 3, CH_3), 4.28 (q, 2, OCH_2), 4.67 (dd, 1, J_{gem} = 12.5, J_{vic} = 5 Hz, $CHNO_2$), 5.08 (dd, 1, J_{vic} = 8 Hz, $CHNO_2$), 5.33 (ddd, 1, $J_{H,NH}$ = 4 Hz, ArC**H**), 6.91 (d, 1, NH), 7.32 ppm (s, 5, Ar).

Anal. Calcd for $C_{12}H_{14}N_3O_4Cl$ (299.75): C, 48.09; H, 4.71; N, 14.02. Found: C, 47.95; H, 4.58; N, 13.87.

Ethyl N^2-(2-Nitro-1-phenylvinyl)-2-chloroglyoxylate Hydrazone (18). A reaction similar to that for preparation of **17b** was conducted on 320 mg (1.2 mmol) of **17a** but using a large excess of chlorine and allowing the mixture to gradually warm to room temperature during the addition. Under these conditions a new yellow spot with an R_f just greater than that of **17b** was gradually formed. Following evaporation of the solvent the residue was purified by preparative TLC using two developments with ether–hexane (1:1). Elution of the slower of the resulting two bands gave 100 mg (30%) of **17b** identical with that above while the faster band gave 80 mg (22%) of **18** with mp 124–125° from chloroform–hexane: λ_{max} (MeOH) 220 nm (ϵ 8600), 273 (10,600), 370 (18,400); ir (KBr) 1725 (CO), 1615 (Ar), 1565 (NO_2), 1500 cm^{-1} (Ar); mass spectrum (70 eV) *m/e* 297, 299 (M^+), 251, 253, (M − EtOH), 216 (*m/e* 251 − Cl), 103, 77 (C_6H_5); NMR ($CDCl_3$) 1.26 (t, 3, CH_3), 4.28 (q, 2, OCH_2), 6.80 (s, 1, C=$CHNO_2$), 7.50 ppm (s, 5, Ar).

Anal. Calcd for $C_{12}H_{123}O_4Cl$ (297.75): C, 48.41; H, 4.06; N, 14.11. Found: C, 48.26; H, 4.18; N, 13.71.

3-Ethoxycarbonyl-5-phenylpyrazole (19). A solution of **17b** (100 mg) in triethylamine (1 ml) and tetrahydrofuran (10 ml) was heated under reflux overnight. The solvent was evaporated and the residue was partitioned between chloroform and water. The dried organic phase was purified by preparative TLC using ether–hexane (2:1). Elution of the major band and crystallization from ether–hexane gave 10 mg (14%) of **19** with mp 139–141° (reported[27] mp 140°): mass spectrum (70 eV) *m/e* 216 (M^+), 170 (M − EtOH), 142 (*m/e* 170 − CO); NMR ($CDCl_3$) 1.25 (t, 3, CH_3), 4.23 (q, 2, OCH_2), 7.00 (s, 1, C_4H), 7.35 (m, 3, Ar), 7.70 ppm (m, 2, Ar).

3,6-Anhydro-4,5,7-tri-*O*-benzyl-1-deoxy-1-nitro-D-*glycero*-D-*altro*-heptitol (20). A solution of **8b** [regenerated from 4.0 g (6.40 mmol) of the diphenylimidazolidine derivative[4]] in a mixture of methanol (200 ml) and nitromethane (20 ml) was stirred at 0° while methanolic sodium methoxide (10 ml of 0.48 *M*) was added dropwise. After an additional 1 hr at 0° the mixture was neutralized with Dowex 50 (H^+) resin, filtered, and evaporated. The residue was partitioned between chloroform and water, the dried organic phase was evaporated and the residue was crystallized from ether–hexane, giving 2.35 g (74%) of **20** with mp 42–44°: λ_{max} (MeOH) 207 nm (ϵ 31,500), 247 (500), 252 (600), 258 (750), 264 (600), 267 (400); $[\alpha]^{23}D$ −12.4° (c 0.18, $CHCl_3$); ORD (MeOH) $[\Phi]_{320}$ (pk) 1100°, $[\Phi]_{284}$ 0°, $[\Phi]_{229}$ (tr) −3000°, $[\Phi]_{220}$ 0°; ν_{max} (KBr) 1555 cm^{-1} (NO_2); NMR ($CDCl_3$) 3.19 (br s, 1, C_2OH), 3.38 (dd, 1, J_{gem} = 10.5, $J_{6,7a}$ = 3 Hz, $C_{7a}H$), 3.58 (dd, 1, $J_{6,7b}$ = 3 Hz, $C_{7b}H$), 4.00 (s, 2, C_4H, C_5H), 4.17 (m, 1, C_6H), 4.3–4.6 (m, 10, C_1H_2, C_2H, C_3H, and CH_2Ar), 7.27 ppm (m, 15, Ar).

Anal. Calcd for $C_{28}H_{31}NO_7$ (493.54): C, 68.14; H, 6.33; N, 2.84. Found: C, 68.00; H, 6.54; N, 2.98.

(*E*)-3,6-Anhydro-4,5,7-tri-*O*-benzyl-1,2-dideoxy-1-nitro-D-*allo*-hept-1-eneitol (21). A solution of acetic anhydride (1 ml) and pyridine (2 ml) in benzene (5 ml) was added to a stirred solution of **20** (1.5 g, 3.0 mmol) in benzene at 0°. After storage overnight at 4° the solvent was evaporated and the residue was dissolved in chloroform and washed with aqueous sodium bicarbonate and water. The dried organic phase was evaporated and purified by preparative TLC using ether–hexane (2:1). Elution of the major band gave 1.20 g (84%) of **21** as a syrup: λ_{max} (MeOH) 245 nm (sh, ϵ 4100), 250 (sh, 4050), 257 (sh, 3800); $[\alpha]^{23}D$ −17.6° (c 0.3, $CHCl_3$); NMR ($CDCl_3$) 3.44 (dd, 1, J_{gem} = 11, $J_{6,7a}$ = 3.5 Hz, $C_{7a}H$), 3.56 (dd, 1, $J_{6,7b}$ = 3.5 Hz, $C_{7b}H$), 3.76 (dd, 1, $J_{3,4}$ = 6.5 Hz, C_4H), 3.95 (dd, 1, $J_{4,5}$ = 4.5 Hz, C_5H), 4.23 (dt, 1, $J_{5,6}$ = 3.5 Hz, C_6H), 4.35–4.7 (m, 7, C_3H and CH_2Ar), 7.1–7.35 ppm (m, 17, C_1H, C_2H, and Ar).

Anal. Calcd for $C_{28}H_{29}NO_6$ (475.52): C, 70.20; H, 6.15; N, 2.95. Found: C, 70.42; H, 6.31; N, 2.69.

2-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-2-(2-carboethoxymethylenehydrazino)-1-nitroethane (22a). A solution of **21** (3.0 g, 6.3 mmol) and **16** (4 g, 34 mmol)[32] in tetrahydrofuran (100 ml) was stored at room temperature for 48 hr. Following evaporation of the solvent the residue was purified by preparative TLC using CCl_4–ethyl acetate (4:1), giving 2.2 g (59%) of **22a** as a mixture of isomers suitable for direct use in the next step. A portion of this material was separated into its diastereomers by further preparative TLC using two developments with chloroform–ethyl acetate (10:1). The major, more polar isomer was then crystallized from ethyl acetate–hexane with mp 83–87°: λ_{max} (MeOH) 283 nm (ϵ 12,400); $[\alpha]^{23}D$ 36.7° (c 0.1, $CHCl_3$); NMR ($CDCl_3$) 1.28 (t, 3, CH_3), 3.37 (dd, 1, J_{gem} = 10.5, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 3.54 (dd, 1, $J_{4',5'b}$ = 3.5 Hz, $C_{5'b}H$), 3.93 (m, 1, C_2H), 4.22 (q, 2, OCH_2CH_3), 4.1–4.8 (m, 12, CH_2CH, C_1H, C_3H, C_4H, OCH_2Ar), 6.68 (s, 1, N=CH), 7.25 ppm (m, 15, Ar).

Anal. Calcd for $C_{32}H_{37}N_3O_8$ (590.63): C, 65.07; H, 6.14; N, 7.11. Found: C, 65.27; H, 6.28; N, 6.93.

Chlorination of the Hydrazone 22a. A. A 7.3% solution of chlorine in carbon tetrachloride (3 ml) was added dropwise to a stirred solution of **22a** (250 mg, 0.42 mmol) in tetrahydrofuran at −65°. After 15 min TLC using carbon tetrachloride–ethyl acetate (4:1) showed complete conversion of **22a** to a faster spot and excess chlorine was removed with a stream of nitrogen at −60°. The sol-

vent was then evaporated in vacuo below 0° and the resulting syrup was purified by preparative TLC using CCl_4–ethyl acetate (4:1). Elution of the major band gave 220 mg (84%) of the chlorohydrazone **22b** as a very pale yellow oil: λ_{max} (MeOH) 274 nm (ε 13,700); $[\alpha]^{23}D$ −0.7° (*c* 0.7, $CHCl_3$); NMR ($CDCl_3$) 1.31 (t, 3, CH_3), 3.37 (dd, 1, J_{gem} = 12, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 3.52 (dd, 1, $J_{4',5'b}$ = 3.5 Hz, $C_{5'b}H$), 3.8–4.7 (m, 13), 4.30 (q, 2, OCH_2), 7.3 ppm (m, 15, Ar); mass spectrum (70 eV) *m/e* 626, 628 (M^+).

Anal. Calcd for $C_{32}H_{36}N_3O_8Cl$ (626.12): C, 61.39; H, 5.80; N, 6.71. Found: C, 61.17; H, 5.69; N, 6.43.

Elution of the faster yellow band gave 10 mg (4%) of crystalline **23** (see below).

B. The hydrazone **22a** (100 mg) was treated with chlorine in carbon tetrachloride (2 ml of 7.3%) at −60° as above in A, giving essentially a single spot of **22b**. The solvent was directly evaporated at room temperature and the residue was purified by preparative TLC using CCl_4–ethyl acetate (4:1), giving two well-resolved bands. Elution of the slower band gave 60 mg (57%) of **22b** identical with that above. Elution of the faster band gave 50 mg (46%) of the nitroolefin **23** that crystallized spontaneously. Recrystallization from ethyl acetate–hexane at −15° gave **23** as fine white needles with mp 107–108°: λ_{max} (MeOH) 263 nm (ε 9400), 366 (21,600); $[\alpha]^{23}D$ 69.6° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) 1.24 (t, 3, CH_3), 3.60 (dd, 1, J_{gem} = 11, $J_{4',5'a}$ = 2.5 HZ, $C_{5'a}H$), 3.88 (dd, 1, $J_{4',5'b}$ = 1.5 Hz, $C_{5'b}H$), 4.05–5.05 (m, 11, $C_{2'}H$, $C_{3'}H$, $C_{4'}H$, OCH_2), 5.47 (s, $J_{allylic} \simeq 1$ Hz, $C_{1'}H$), 7.3 (m, 15, Ar), 7.55 (d, 1, $J_{allylic} \simeq 1$ Hz, $NO_2CH{=}C$), 12.1 ppm (s, 1, NH).

Anal. Calcd for $C_{32}H_{34}N_3O_8Cl$ (624.10): C, 61.58; H, 5.49; N, 6.73. Found: C, 61.46; H, 5.65; N, 6.58.

Registry No.—**1**, 23316-67-8; **2a**, 55428-60-9; **2b**, 55428-61-0; **3**, 50720-88-2; **4**, 50720-94-0; **5a**, 55428-62-1; **5b**, 55428-63-2; (*S*)-**6**, 55428-64-3; (*R*)-**6**, 55515-13-4; **7**, 55428-65-4; **8a**, 39037-99-5; **8b**, 37699-02-8; **9**, 6161-37-1; **10a**, 55428-66-5; **10b**, 55428-67-6; (*E*)-**10b**, 55428-68-7; **11a**, 55428-69-8; **11b**, 55428-70-1; **11c**, 55428-71-2; **12**, 55428-72-3; (*S*)-**13**, 55428-73-4; (*R*)-**13**, 55428-74-5; **14**, 55428-75-6; **16**, 55428-76-7; **17a**, 55428-77-8; **17b**, 55428-78-9; **18**, 55428-79-0; **19**, 5932-30-9; **20**, 55428-80-3; **21**, 55428-81-4; (*S*)-**22a**, 55428-82-5; (*R*)-**22a**, 55515-14-5; (*S*)-**22b**, 55428-83-6; (*R*)-**22b**, 55428-84-7; **23**, 55428-85-8; hydroxylamine, 7803-49-8; bromine, 7726-95-6; β-nitrostyrene, 102-96-5; chlorine, 7782-50-5.

References and Notes

(1) For Part VI, see H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, in press.
(2) For a survey, see R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970.
(3) For a review, see L. Goodman in "Basic Principles in Nucleic Acid Chemistry", P.O.P. Ts'O, Ed., Academic Press, New York, N.Y., 1974, p 117.
(4) H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **38**, 1836 (1973).
(5) G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, **38**, 1841 (1973).
(6) H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **39**, 2176 (1974).
(7) (a) F. Tiemann, *Ber.*, **17**, 126 (1884); (b) F. Tiemann and P. Krüger, *ibid.*, **17**, 1685 (1884).
(8) (a) C. Moussebois and F. Eloy, *Helv. Chim. Acta*, **47**, 838 (1964); (b) R. Lenaers, C. Moussebois, and F. Eloy, *ibid.*, **45**, 441 (1962).
(9) F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962).
(10) (a) E. Normann, *Ber.*, **17**, 2746 (1884); (b) F. Tiemann and P. Krüger, *ibid.*, **18**, 727 (1885).
(11) M. Bobek and J. Farkas, *Collect. Czech. Chem. Commun.*, **34**, 247 (1968).
(12) See, e.g., (a) B. C. Hinshaw, J. F. Gerster, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, **35**, 236 (1970); (b) J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 182 (1972).
(13) (a) A. Werner and C. Bloch, *Ber.*, **32**, 1975 (1899); (b) A. Werner and H. Buss, *ibid.*, **27**, 2193 (1894).
(14) (a) F. Tiemann, *Ber.*, **22**, 2412 (1889); (b) H. Zimmer, *ibid.*, **22**, 3140 (1889); (c) J. Barrans, *Ann. Fac. Sci. Univ. Toulouse Sci. Math. Sci. Phys.*, **25**, 7 (1961); *Chem. Abstr.*, **60**, 12005 (1964).
(15) (a) E. Richter, *Ber.*, **22**, 2449 (1889); (b) L. H. Shubart, *ibid.*, **22**, 2433 (1889).
(16) K. Gerzon, D. C. de Long, and J. C. Cline, *Pure Appl. Chem.*, **28**, 489 (1971).
(17) Unpublished work by H. Takei, H. P. Albrecht, D. B. Repke, and J. G. Moffatt.
(18) For a review, see T. L. Jacobs in "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, p 45.
(19) See, e.g., (a) K. v. Auwers and H. Broche, *Ber.*, **55**, 3880 (1922); (b) G. V. Deshmukh and T. S. Wheeler, *J. Chem. Soc.*, 96 (1939).
(20) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).
(21) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).
(22) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Elmsford, N.Y., 1969, p 301.
(23) E. Buchner, *Justus Liebigs Ann. Chem.*, **273**, 214 (1893).
(24) H. Staudinger, L. Hammet, and J. Siegwart, *Helv. Chim. Acta*, **4**, 228 (1921).
(25) For a brief review, see E. Enders in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 10, Part 2, George Thieme Verlag, Stuttgart, 1967, p 379.
(26) The reactions of chlorohydrazones are summarized in ref 25, p 511.
(27) J. Elguero, G. Guiraud, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 619 (1966).
(28) (a) W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.*, **72**, 3843 (1950); (b) *ibid.*, **73**, 4664 (1951).
(29) (a) C. Satoh, A. Kiyamoto, and T. Okuda, *Chem. Pharm. Bull.*, **12**, 518 (1964); (b) C. Satoh and A. Kiyomoto, *Carbohydr. Res.*, **17**, 138 (1968).
(30) G. Descotes, Y. Bahurel, M. Bourillot, G. Pingeon, and R. Rostaing, *Bull. Soc. Chim. Fr.*, 282 (1970).
(31) I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, *J. Med. Chem.*, **11**, 144 (1968).
(32) Prepared by the method of Staudinger et al.[24] and purified by chromatography on silicic acid using ether–hexane (2:1): NMR ($CDCl_3$) 1.28 (t, 3, CH_3), 4.25 (q, 2, OCH_2), 6.80 (br s, 2, NH_2), 7.05 ppm (s, 1, HC=N).

Pseudonucleoside Analogs. Synthesis and Spectral Properties of 5-(*cis*-3-Hydroxymethylcyclopentane)uracil, a Carbocyclic Analog of 2′,3′-Dideoxypseudouridine[1]

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In our search for the specific structural features necessary for the observed differences in certain physicochemical properties of α- and β-pseudouridines, we have synthesized the title compound, **1**. Two alternative syntheses of the key *cis*-3-hydroxymethylcyclopentaneacetic acid lactone (**16**) from norbornylene were investigated. In each instance the cis stereochemistry of **16** and thus that of 5-(*cis*-3-hydroxymethylcyclopentane)uracil (**1**) was assured by the cyclic nature of the intermediates. The lactone **16** was obtained by Baeyer–Villiger oxidation of the bicyclo[3.2.1]octan-3-one **15**, and it could be formylated to the sodium enolate derivative **19**. Base-catalyzed condensation with thiourea yielded 5-(*cis*-3-hydroxymethylcyclopentane)-2-thiouracil (**20**), which was converted to **1** by treatment with aqueous chloroacetic acid. From ir and uv spectral studies of **1**, it can be inferred that there is an interaction between the hydroxy group on the side chain and the pyrimidine ring, but it appears that such an interaction cannot alone be the cause of the differences in the uv spectral properties and equilibrium between the tautomeric monoanionic species in the anomeric pseudouridines. A specific role for the "glycosyl" ring oxygen in the pseudouridines is proposed.

Certain physicochemical properties of pseudouridine, a nucleoside from transfer RNA's, have been the subject of studies in a number of laboratories during the past several years. Since the early reports[2,3] on the different ratio of the two tautomers A and B (Figure 1) in the α- and β-pseudouridine monoanion, reflected in the uv spectral shifts of these compounds at pH ~11–12, several explanations have been offered, and promptly challenged, in an attempt to correlate this phenomenon with specific structural features and intramolecular interactions.

Chambers[2] originally suggested that an intramolecular H bond from the C-5′ hydroxyl to the C-4 carbonyl group (D, Figure 1) was stabilizing the N-1 over the N-3 anion (A and B respectively, Figure 1) in the β isomer. Implicitly this proposal postulates the predominance of the syn conformer in aqueous solution.

In earlier reports on the synthesis[4,5] and ir spectra[5] of various 5-(hydroxycyclopentane)pyrimidines that bear structural similarities to pseudonucleosides, we suggested that a weak intramolecular hydrogen bond to the π-electron orbitals of the pyrimidine ring could explain the difference in the equilibrium of monoanionic species observed in α- and β-pseudouridines. Corollary to these interpretations is the predominance of the anti rotamer population of β-pseudouridine, since the C-5′ hydroxy group is stereochemically the most likely intramolecular H-bonding donor to the ring π system (C, Figure 1).

More recently the uv absorption properties of β-pseudouridine were carefully reexamined by Dugaiczyk.[6] The only observed difference between the spectra of the respective ionic species of β-pseudouridine and its 2′,3′-isopropylidene and 5′-*O*-acetyl-2′,3′-*O*-isopropylidene derivatives was a small (1 and 0.5 nm respectively) hypsochromic shift in the latter two. The spectrum of the uracil monoanion represents the combined contribution of the two tautomeric species each of which is characterized by a different pK_a. Paradoxically the $\epsilon_{280/260}$ ratio at pH 11.2–12.2, which is taken as a quantitative measure of the relative proportions of the two monoanionic forms, varied from 2.22 for the parent compound to 2.40 for the 2′,3′-*O*-isopropylidene and 2.58 for the 5′-*O*-acetyl-2′,3′-isopropylidene derivatives, but the pK_a's of all three compounds were reported to be the same, i.e., 9.10.[6] Of course, the possibility cannot be excluded that with each progressive substitution on the "sugar" ring, the individual pK_a's at N-1 and N-3 of the pyrimidine are proportionally modified so that there is no net change in the observed pK_a. Also the conformational change(s) affecting the interrelationship(s) of the various structural entities of the pseudonucleoside, induced by the additional substitution, have not been considered. It has been experimentally confirmed, for example, that in uridine derivatives a 2′,3′-*O*-isopropylidene group facilitates interaction between the 5′ position and the aglycon.[7] In addition, a 5′-acetoxy group should be expected to have an effect upon the conformation of the exocyclic CH_2OH group and upon the sugar–base torsion angle. Extrapolation of these effects to the pseudouridine series is reasonable because it has been shown (NMR) that the ribose conformations of pseudouridine and uridine are very similar.[8]

Elaborate discussions of ^1H NMR (proton magnetic resonance), NOE (nuclear Overhauser effect) data,[8–10] and molecular orbital calculations[10] of pseudouridine led to the contradicting conclusions that in the β isomer an intramolecular bond between C-5′ hydroxyl and C-4 carbonyl is unlikely because even though the gauche–gauche rotamer of the 5′-hydroxymethyl group is favored a substantial fraction of the molecules exist in the anti conformation,[9] that both syn and anti conformations coexist in rapid equilibrium in roughly equal populations, and that the syn conformation is stabilized by the existence of a hydrogen bond between the C-5′ hydroxyl and C-4 carbonyl groups.[10] Whatever conclusions are made, however, are dependent upon the somewhat arbitrary selection of the factors employed in the theoretical calculations. For example, the assumption that the 2′ and 3′ hydroxyl groups do not come in proximity to either the base or the 5′-hydroxymethyl group led to calculations in which the 2′ and 3′ hydroxyl groups were replaced by hydrogen atoms. That assumption and the corollary calculations may not be valid. By analogy to the molecule of uridine, intramolecular interaction between C-2′ hydroxyl and the C-4 carbonyl group in the β-pseudouridine is to be considered.[11a] Also the range of concentration (0.1 *M*) at which the NOE measurements were conducted are not unequivocally regarded as precluding intermolecular associations.[12] Indeed, ir studies indicate that 5′-*O*-acetyl-2′-3′-*O*-isopropylidene β-pseudouridine at concentrations 10^{-2} *M* or below ($CDCl_3$) self-associates to a considerable extent.[13] It should be noted that different types of self-associations are probably involved, depending upon the nature of the solvent; i.e., in water the mode of as-

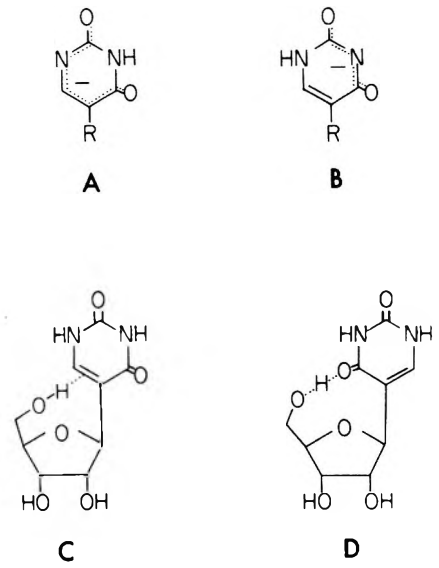


Figure 1.

sociation would be by vertical stacking of the bases while in apolar solvents it would be by horizontal hydrogen bonding.[11b]

Clearly the factors involved in the equilibrium of the monoanionic species of the "anomeric" pseudouridines merit further study. An inspection shows that various uracils carrying a substituent at position 5 fall into two distinct spectral groups based on the relative predominance of the N-1 over the N-3 monoanion (Figure 2). While the balance between the mesomeric and inductive effects among the side groups may vary,[22] those derivatives in which the C-5 substituents are joined to C-5 by carbon–carbon linkages are directly comparable. Among these, it is apparent that the presence of an allylic oxygen on the side–side chain favors the formation of the N-1 monoanion.

Intramolecular hydrogen bonding potentials, inductive, mesomeric, and electrostatic through-space effects, as well as interactions with the solvent, are all pertinent factors. It is recognized that more than one of these factors may be operative at any one time on the total molecule and may contribute to the apparent net effect.

In the α- and β-pseudouridines the C-2′, C-3′, and C-5′ hydroxyl groups are potential donors to an intramolecular hydrogen bond linking the substituent on C-5 to the pyrimidine. In addition, the inductive, mesomeric, and electrostatic effects of the tetrahydrofuran ring of the furanose must be taken into account. Substitution of the cyclopentane ring for the furanose ring of pseudouridines retains the stereochemical arrangement of the individual groups, essentially unchanged, with the exception of the allylic ether oxygen. In both ring systems (tetrahydrofuran and cyclopentane) the angle of maximum puckering rotates without substantial change in potential energy, but the presence of one or more endocyclic or exocyclic substituents gives rise to induced potential energy barriers opposing pseudorotation.[23] It is reasonable to assume that particular substituents impose analogous restrictions upon either the cyclopentane pseudonucleoside analogs or the parent tetrahydrofuran compounds. Thus they allow the formation of analogous conformational species for either of the ring systems in the C-5 substituent.

In our systematic attempt to develop model systems which would help to elucidate this problem, we have synthesized some additional appropriately substituted cyclopentane analogs of pseudouridine that will hopefully provide additional insight into the character and influence of the intramolecular hydrogen bonding. Moreover, the comparison of their physicochemical properties to those of analogous tetrahydrofuran derivatives, such as the ones depicted in Figure 2, should also allow definitive conclusions regarding the chemical reactivity and its effect on these properties of the "allylic" ether oxygen of the "sugar" ring in the pseudonucleosides. One illustration of the importance of the ether function is its reversible cleavage on either acid or base solutions,[2] leading in either case to intermediates susceptible to the addition of nucleophiles.

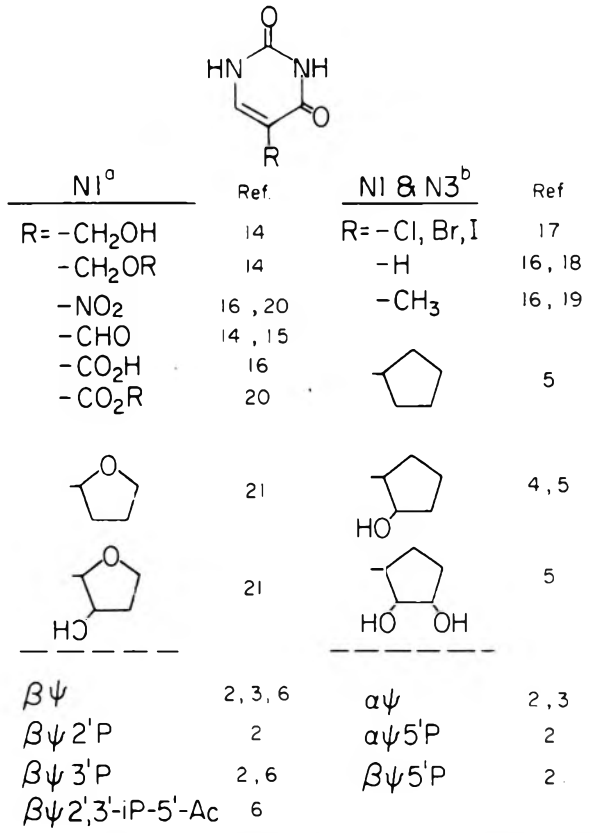


Figure 2. (a) The N-1 monoanion predominates in this series. (b) The N-1 and N-3 monoanions exist in approximately equal concentrations.

In this report we discuss the synthesis of 5-(*cis*-3-hydroxymethylcyclopentane)uracil (**1**, Figure 3) and its uv and ir spectral properties. Some conclusions are reached regarding the possible role of the C-5′ hydroxyl group and the "glycosyl" ring oxygen in effecting the equilibrium of the tautomeric monoanions of the pseudouridines. This model compound, **1**, incorporates the aglycon moiety and the stereochemical features at the C-5′ of β-pseudouridine (**3**), but it lacks the allylic cyclic ether oxygen and hydroxyls at the C-2′ and C-3′ positions. Molecules of **1** should possess greater freedom of rotation around the C-5 and C-1′ bond. This reduced restriction upon the range of the torsion angle should enhance the intramolecular hydrogen bonding potential of the C-5′ hydroxyl group, and any effect that this may have upon the spectral and ionization properties of the pyrimidine moiety.

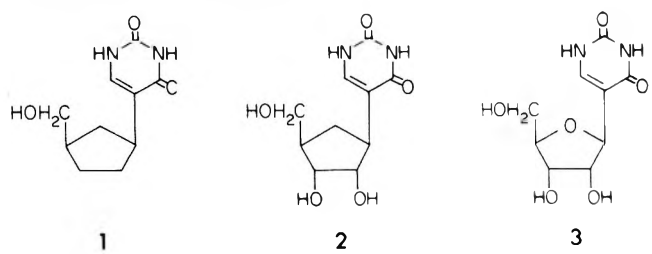
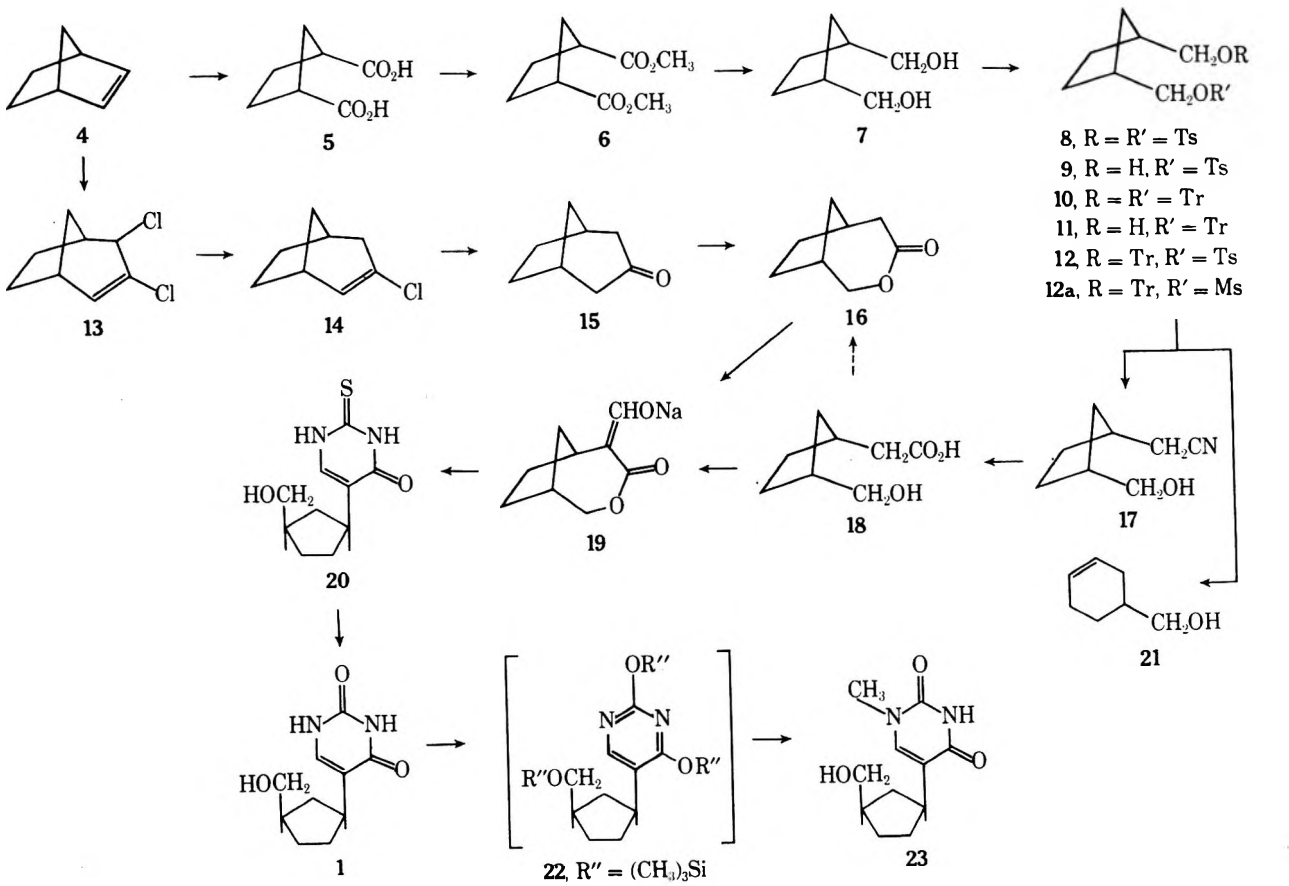


Figure 3.

Scheme I



The pathways investigated for the synthesis of the cyclopentane analog, **1**, are shown in Scheme I. Two alternative syntheses of the key lactone, **16**, from norbornylene were investigated. In each instance the cis stereochemistry of **16**, and thus that of **1**, was assured by the cyclic nature of the intermediates.

The preparation of the *cis*-1,3-cyclopentanedicarboxylic acid (**5**) by oxidation of bicyclo[2.2.1]heptene-2 (norbornylene) with sodium permanganate,[25] and more recently with $NaIO_4$ in the presence of RuO_2,[26] has been reported. In our hands the oxidation of norbornylene in 100-g quantity with $NaMnO_4$, as described,[25] gave inconsistent results. When heptane and $KMnO_4$ were substituted for 2,2,4-trimethylpentane and $NaMnO_4$,[27] the yield of the crude dicarboxylic acid, **5**, was 59%. The modified method of Shealy and Clayton[28] for the oxidation of *exo-cis*-norbornylene-2,3-diol consistently gave high yields, 90%. The published method[29] for the preparation of the diethyl ester of **5** was considered too cumbersome. The simpler general method of Clinton and Laskowski[30] also gave comparable yields, 78%, but the procedure of choice that gave high average yields, 96%, was based on that of Radin et al., employing 2,2-dimethoxypropane (DNP).[31]

Reaction of the diol, **7**, with 1 equiv of *p*-toluenesulfonyl chloride in pyridine produced a mixture of the di- and monotosylates, **8** and **9**, in a ratio of ~1:4. These tosylated derivatives were readily resolved on a silica gel column.

Substitution of the sulfonyloxy group of **9** by CN^- led to the *cis*-3-hydroxymethylcyclopentaneacetonitrile (**17**), which was hydrolyzed to *cis*-3-hydroxymethylcyclopentaneacetic acid (**18**). In order to improve the overall yield of **17** from the diol **7**, the latter was tritylated. It was hoped that the first trityl group to be introduced would sterically inhibit further reaction at that stage. Yet a mixture of the di- and monotrityl derivatives, **10** and **11**, was obtained. The combined yield of these products was somewhat higher than that of the tosyl derivatives, **8** and **9**, but the ratio between the mono- and disubstituted trityl derivatives was 1:1.75. Although the sulfonates, **12** and **12a**, were obtained in almost quantitative yield, 95%, from **11**, the use of the trityl derivatives does not offer any particular advantage over the direct tosylation of **7**. The *cis*-3-hydroxymethylcyclopentaneacetonitrile (**17**) was obtained from the monotosylate **9** with KCN in DMF.[32] Hydrolysis of that nitrile gave the corresponding carboxylic acid, **18**. A small analytical sample was obtained by high vacuum distillation in a molecular still, but that operation was accompanied by extensive polymerization. A product was isolated from the residue of that distillation in crystalline form. Its NMR spectrum was very similar to that of the acid **18**, except for the absence of the OH signal. Also, in its ir spectrum the OH band was greatly attenuated and the carbonyl band was broadened and shifted (25 cm^{-1}) to higher frequency. Unfortunately, an accurate molecular formula could not be derived from elemental analysis for C and H only. It was presumed to be an oligomer of **18**.

Various attempts to effect the cyclization of the hydroxy acid **18** to the lactone **16** resulted in only traces of the desired product. Recent investigations on the kinetics of cyclization of ω-halogenocarboxylic acids to medium-ring (8–11 membered) lactones and on the stability of these products offer an explanation for the failure of the acid **18** to cyclize. Cyclization to **16** would involve the formation of a bicyclic ring structure with a newly formed eight-membered lactone ring, but measurements of the tendency for lactone formation compared with ring size reveal a reactivity minimum lying at the eight- and nine-membered rings.[33] Another factor is the stability of the lactone structure. It was found, for example, that eight-membered rings with a cis ester function hydrolyze 10^3–10^5 times as fast as the

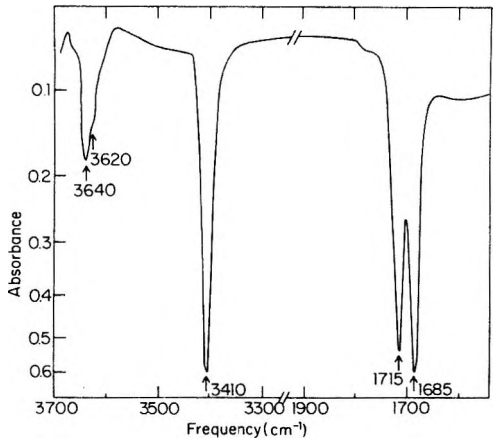


Figure 4. The bands of the O–H and N–H are depicted at 5 × and those of the C=O at 1 × scale.

higher homologs.[34] This property has been related to the transition state intermediate involved in lactone formation, which has been presumed to be ring shaped and to possess the same less stable cis conformation of the ester function.[33,35]

The desired lactone, **16**, was prepared satisfactorily by Baeyer–Villiger oxidation of the bicyclo[3.2.1]octan-3-one **15**, which in turn was obtained by known methods from norbornylene (**4**) as illustrated in Scheme I.[36] The ketone **15** was oxidized to *cis*-3-hydroxymethylcyclopentaneacetic acid lactone (**16**). As anticipated,[37] that lactone proved to be unstable in both acid and basic media, and when heated was converted to polymeric products.

The formylation of the lactone **16** with methyl formate in the presence of CH_3ONa gave a preparation of the sodium derivative, **19**. From the condensation of that material with thiourea in sodium ethoxide–ethanol, 5-(*cis*-3-hydroxymethylcyclopentane)-2-thiouracil (**20**) was obtained and was converted quantitatively to the corresponding uracil, **1**.

Spectral Studies. Intramolecular interaction between an OH group and the π electrons in aromatic or olefinic systems has been extensively investigated by ir spectroscopy. Such studies have shown clearly that the frequency separation between the free and the bonded OH bands ($\Delta\nu$) is a measure of the enthalpy of the interaction.[38,39] In the neutral species of the 5-(*cis*-3-hydroxymethylcyclopentane)uracil **1**, there are two potential acceptor sites for a hydrogen bond, i.e., the region of the C-4 carbonyl group, including both the n and π orbitals, and the C-5–C-6 double bond. Of these, the double bond is the weaker base. Because of the extremely low solubility of the pyrimidine **1** in carbon tetrachloride, it was necessary to carry out the present hydrogen-bonding spectral study with the corresponding N-1 methyl derivative, **23**. That methylation does not impair the extrapolation of the results obtained to the parent compound. A comparison of the frequencies of some principal ir bands in the anion of N-1 and N-3 monomethyl thymines with the corresponding bands in the equilibrium mixture of the two tautomeric anions of thymine itself has shown that the introduction of a methyl group at either N-1 or N-3 causes only a small ~5-cm^{-1} shift.[20] The methyl group exerts both a mesomeric and an inductive effect,[40] but the $\Delta\nu$ values attributable to its electronic effects should be of the order of only ~10 cm^{-1} based on the increased hydrogen bond basicity upon alkylation of aromatic hydrocarbons.[41]

Part of the ir spectrum of **23** is illustrated in Figure 4. The band at ~3640 cm^{-1} can be assigned to the ν_{OH} of the free hydroxyl group. However, it appears to be unsymmetrical with a shoulder at ~3620 cm^{-1}. This second unresolved band at the lower frequency must be derived from the hydroxyl group interacting with the pyrimidine ring. Thus it seems that in solution in an inert solvent and sufficiently dilute ($<5 \times 10^{-4}$ *M*) to prevent intermolecular associations, **1** displays two partially unresolved, concentration-independent bands in the O–H stretching region. The data indicate that, in carbon tetrachloride at least, a significant proportion of the population of **1** exists as an intramolecularly associated species. The small $\Delta\nu$ (~20 cm^{-1}) value between the band of the nonbonded OH group at 3640 cm^{-1} and that at 3620 cm^{-1} must be attributed to a weak interaction analogous to an ordinary hydrogen bond, but one that depends on the overlap between the occupied π orbitals in the electron donor (i.e., C-5–C-6 double bond of the pyrimidine ring) and the vacant O–H antibonding orbital.[42] The band at 3410 cm^{-1} is assigned to the ring N–H. The absence of any other band in this region that theoretically could be attributed to a strong hydrogen bond of the side chain hydroxyl to the C-4 carbonyl group is noteworthy. The lack of an interaction involving a carbonyl group is also substantiated by the high frequency, $\nu_{C=O}$, of the two carbonyl bands (1685 and 1715 cm^{-1}), as well as by the narrowness and symmetry of these bands.[43] These ir spectra in carbon tetrachloride demonstrate that the intramolecular interaction is, at the very least, stereochemically permissible, but direct examination of such interactions in an aqueous environment remains impractical. Some information regarding that problem can be derived from a comparison of the pK_a's and of the uv spectra of the compounds studied.

In the uracil[18] and thymine[19] series, introduction of a methyl group at N-1 raises the pK_a by ~0.2 to 0.4 pK units. In some other uracil derivatives where the C-5 substituent exerts a resonance effect upon the N-1 of the pyrimidine,[44] methylation at that center causes an even greater increase of about 0.7 pK units. The 5-nitrouracil is an extreme case where methylation at N-1 causes an increase in the pK_a from 5.55 ± 0.03[45] to 7.20 ± 0.02.[46] From this and the examples shown in Figure 2 which illustrate the results of the inductive effect of various C-5 substituents on the ionization of N-1, it appears reasonable to assume that the greater the increase in the pK_a upon methylation at N-1 in a particular uracil derivative the lower the proportion of the N-3 monoanion (B, Figure 1) in the equilibrium mixture of the tautomeric species A and B of the unmethylated pyrimidine. As there is virtually no difference between the pK_a's of **1** (10.22 ± 0.05) and its N-1 monomethyl derivative, **23** (10.34 ± 0.05), it is probable that in the equilibrium mixture of the tautomeric monoanions of **1** species B predominates over species A. Certainly the prominent shoulder at 270 nm in the uv absorption curve of the "monoanion(s)" of **1** at pH ~12 is strong support for the relative abundance of the anionic species B.[47] This could be the result of a sup-

Table I
Uv Spectral Properties

Compd	Charge	λmax, nm ($\epsilon \times 10^{-3}$)	λmin, nm ($\epsilon \times 10^{-3}$)	Apparent pK_a's (±)
20	0	279 (18.75)	242 (2.25)	
	−1	310 (8.70)	292 (7.4)	
		262 (13.85)	245 (11.00)	
		237 (12.15)		
1	0	266 (7.65)	236 (2.10)	10.22 (0.05)
	−1	290 (5.6)	245 (2.10)	
		265–270 sh		
23	0	273 (4.5)	239 (0.9)	10.34 (0.06)
	−1	270 (3.25)	246 (1.45)	

pression of the ionization from N-1, as might be expected from the inductive effect of the 5 substituent. There is no obvious reason to support the alternative of an enhancement of the ionization from N-3.

Other evidence on the issue of intramolecular interactions in aqueous solutions of **23** is obtained from a detailed study of its uv spectra in the strongly alkaline pH region. It shows a minor but distinct shift in the spectrum between pH 12.4, at which there must be complete conversion of the pyrimidine to the corresponding monoanion, and pH 15, a pH range over which the ionization of the hydroxy function at the 5 substituent should occur. This evidence of an intramolecular interaction between the hydroxy group in the side chain and a region of the pyrimidine is in analogy to the spectral differences between the ribosyl and the deoxyribosyl nucleosides at high alkaline pH, which are related to the ionization of the 2′-OH group.[48,49] It is confirmatory of the conclusions from the ir studies of **23**.

In summary, with regard to the uv spectral properties and ratio of monoanionic species at equilibrium of the "anomeric" uracil pseudonucleosides and some analogous cyclopentane isosteres, the following points emerge: The hydroxy group at the 5′ terminal of the pseudonucleosides alone does not exert a substantial influence. Similar conclusions can now be drawn for the 2′- and 3′-hydroxyl groups from our previous studies.[5] On the other hand, the allylic oxygen function in the "sugar" moiety of the pseudonucleosides, or in simpler tetrahydrofuran analogs, such as the ones illustrated in Figure 2, is sufficient for the modification of the equilibrium of the monoanionic species. This may be attributed to the field effect of that lone pair of oxygen electrons which possesses π character.[50] Thus the problem related to the differences in spectra and equilibrium of monoanionic tautomeric species in the α- and β-pseudouridines can be now focused on the identification and mode of interaction of the single or the combination of structural features that, particularly in the α anomer, interfere with the effect of the allylic oxygen of the "sugar".

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. The ^{1}H NMR spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Routine uv (H_2O) and infrared spectra were determined with Unicam SP800 and Perkin-Elmer Infracord spectrophotometers. Accurate ϵ values in the uv were measured with a Beckman DU. For the ir studies of hydrogen bonding a long-path (25 mm) cell with NaCl windows and spectrograde CCl_4 freshly distilled from P_2O_5 were used. The concentration of the examined material in solution was less than 5×10^{-3} *M*. A matched cell filled with the same solvent served as a reference, and the spectra were recorded with a Perkin-Elmer 221 spectrophotometer. All solvents were removed in a Buchler flask evaporator under reduced pressure unless otherwise indicated. All solids were dried under reduced pressure over P_2O_5 at suitable temperature. An Eastman chromagram silica gel sheet was used for TLC and developed as indicated. Composition and homogeneity of liquid samples were monitored by a Varian Aerograph 2440 gas chromatograph using a column (5 ft × 1/8 in.) packed with 1.5% OV-101 on 100/120 Chromosorb H/P. Silica gel for column chromatography was grade 923, 100–200 mesh from Grace-Davison Chemical, unless otherwise specified.

***cis*-1,3-Cyclopentanedicarboxylic Acid (5).** A solution of 66.6 g (0.34 mol) of $NaMnO_4 \cdot 3H_2O$ in 500 ml of H_2O was added dropwise and with continuing vigorous stirring over a period of ~3 hr to a mixture of 10.34 g (0.11 mol) of norbornylene in 580 ml of 2,2,4-trimethylpentane and 730 ml of H_2O into which was bubbled a constant stream of CO_2. Throughout the addition of the permanganate solution, the temperature of the mixture was maintained at 10–15° and vigorous CO_2 sparging was continued. Immediately after the addition was completed the resulting mixture was decolorized with SO_2 at <20°, then concentrated to about 400 ml, filtered, and the filtrate was cooled in an ice bath and acidified with 30 ml of concentrated HCl. The resulting salts were removed by filtration, washed well with ether, and the washings were saved. The aqueous filtrate was extracted with ether (3 × 200 ml) and the combined ether extract and washings were dried with Na_2SO_4. Evaporation of the solvent gave a white solid which, without further purification, was used in the next step. The average yield was 90% and the melting point of each batch varied over a 2° range between 116 and 121°. A sample purified by recrystallization from ether melted at 123–124° (lit. mp 119.9–120.6°);[25] NMR ($CDCl_3$) τ 6.8–8.5 (envelope, 2, CH_2), 7.5–8.5 (envelope, 4, CH_2CH_2); ir λ_{max} (KBr) 1680 cm^{-1} (ν_{CO}).

Dimethyl *cis*-Cyclopentane-1,3-dicarboxylate (6). A. The dicarboxylic acid **5** (15.8 g, 0.1 mol) was combined with 60 ml of ethylene dichloride, 25 ml of CH_3OH, and 3 ml of concentrated H_2SO_4, and the solution was heated at reflux overnight. The mixture was then washed successively with 100 ml each of water, a saturated solution of $NaHCO_3$, and water again, and then dried with Na_2SO_4. Concentration of the dry solution and distillation of the residue gave 14.6 g (78%) of the dimethyl ester: bp 78–80° (1–2 Torr); NMR ($CDCl_3$) τ 6.32 (s, 6, 2 OCH_3), 6.9–7.6 (envelope, 2, CH_2), 7.6–8.3 (envelope, 4, CH_2CH_2); ir λ_{max} (neat) 3000, 1740 (ν_{CO}), 1435 (δ_{as} OCH_3), 1365 (δ_s OCH_3), four partially resolved bands at 1265, 1250, 1200, and 1183, and broad bands centered at 1040, 1008, and 920 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.57. Found: C, 58.27; H, 7.60.

B. The same quantity of the acid was dissolved in 117 ml of CH_3OH and to the solution were added 11.76 ml of concentrated HCl and 294 ml of 2,2-dimethoxypropane. The container was stoppered, and the reaction mixture was stirred at room temperature for 1 hr, then concentrated to ~200 ml and added (with the aid of a small volume of benzene for rinsing) to 400 ml of CH_2Cl_2. The resulting solution was washed with saturated $NaHCO_3$ solution twice, then water, and dried over Na_2SO_4. After evaporation of the solvent the residue was distilled, and the product (17.9 g, 96%) was collected at 77–79° (1–2 Torr). Combined preparations were distilled on a spinning band column. The pure product distilled at 79° (1.2 Torr).

***cis*-1,3-Bis(hydroxymethyl)cyclopentane (7)** was prepared by the reduction of the dimethyl ester **6** with $LiAlH_4$, using a modification of the procedure of Birch and Dean.[29] To a suspension of 2.8 g of $LiAlH_4$ in 400 ml of dry ether was added dropwise a solution of 13.7 g (0.074 mol) in 100 ml of ether. The mixture was allowed to stir overnight at room temperature under nitrogen, then was cooled in an ice bath, and the reaction was quenched by the successive addition of 2.8 ml of H_2O, 2.8 ml of NaOH (15%), and 9 ml of H_2O. The salts were removed by filtration and continuously extracted (Soxhlet) with ether. The combined filtrate and extract was dried over Na_2SO_4, then concentrated, and the residue was distilled to give 9.27 g (96.5%) of the product, boiling at 78–79° (0.040 Torr) [lit. bp 118° (0.5 Torr)]:[29] NMR (Me_2SO-d_6) τ 5.62 (t, 2, 2 OH, J = 5.5 Hz), 6.71 (pair of d, 4, $J_1 = J_2$ = 5.5 Hz, 2 CH_2O), 7.65–9.5 (envelope, 8); ir λ_{max} (neat) 3400 (broad, ν_{OH}), 3900, 3800, 1450, 1380, 1060, 1020, 950 cm^{-1}.

***cis*-1,3-Bis(hydroxymethyl)cyclopentane Ditosylate (8) and Monotosylate (9).** *cis*-1,3-Bis(hydroxymethyl)cyclopentane (**7**, 17.20 g, 0.132 mol) was dissolved in 75 ml of dry pyridine, and the solution was cooled in an ice bath. A solution of 27.7 g (0.145 mol) of *p*-toluenesulfonyl chloride in ~100 ml of dry ether was added dropwise with mechanical stirring. Upon completion of the addition, the mixture was allowed to stand at 0–5° for 3 days and then poured with efficient stirring into 150 ml of ice water. Stirring was continued until the ice had melted, and then the mixture was extracted with benzene (6 × 80 ml). The extract was then washed successively with 2 × 100 ml of 3 *N* HCl and 100 ml of saturated $NaHCO_3$ solution, then dried over Na_2SO_4 and concentrated to a viscous oil which was charged directly onto a silica gel column (500 g, 7 × 23 cm). The two tosylated derivatives were eluted with a 4:1 mixture of benzene–ether (ditosylate, **8**, 8.67 g, 0.0198 mol, 15%) followed by ether (monotosylate, **9**, 19.64 g, 0.069 mol, 52.5%). The elution was monitored by TLC (benzene).

Analytically pure material of the monotosylate **9** could be obtained by dissolving the crude product in petroleum ether (bp 40–60°), treating the resulting solution with Norit, filtering, evaporating the solvent, and holding the clear viscous residue under high vacuum for at least 12 hr:[51] NMR (Me_2SO-d_6) τ 5.58 (s, 1, OH), 6.08 (d, 2, J = 6.5 Hz, CH_2OTs), 6.72 (d, 2, J = 6 Hz, CH_2OH), 7.58 (s, 3, CH_3Ph); ir λ_{max} (neat) 3400 (broad, ν_{OH}), 1350 (ν_{as} SO_2), 1170 cm^{-1} (ν_s SO_2).

Anal. Calcd for $C_{14}H_{20}O_4S$ (9): C, 59.13; H, 7.08; S, 11.27. Found: C, 59.09; H, 7.19; S, 11.20.

The crude ditosylate 8 was dissolved in ~200 ml of hot ether by gradually adding a little methanol. Several crops of pure material were collected as white needles, mp 105–107° (lit. mp 108.5–109°),[29] by adding petroleum ether and cooling; NMR (Me_2SO-d_6) τ 6.09 (d, 4, J = 6.5 Hz, 2 CH_2O), 7.57 (s, 3, CH_3Ph); ir λ_{max} (KBr) 3000, 1600, 1350, 1195, 1175, 1100, 1020, 960, 943, 930, 880, 835, 825, 798, 710, 675 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_6S_2$ (8): C, 57.51; H, 5.97; S, 14.62. Found: C, 57.58; H, 6.01; S, 14.68.

***cis*-1,3-Bis(hydroxymethyl)cyclopentane Ditrityl (10) and Monotrityl (11) Derivatives.** A solution of the dimethanol 7 (3.9 g, 0.03 mol) in ~50 ml of dry pyridine was cooled to about 7° and trityl chloride (9.17 g, 0.033 mol) was added in one portion. The reaction mixture was stirred in the cold for 72 hr, then the bulk of the solvent was removed in vacuo at below 30°. The viscous residue was treated with 500 ml of crushed ice, and, when the ice melted, the supernatant solution was discarded and the gummy residue was dissolved in benzene. The resulting solution was washed twice with aqueous saturated NaCl solution, dried over Na_2SO_4, and concentrated to a small volume which was charged on a silica gel column (4 × 50 cm). The products were eluted with benzene–ether (8:2). Homogeneous fractions [TLC, C_6H_6–EtOEt (8:2)] were pooled and evaporated to dryness. The ditrityl derivative 10 was recrystallized from petroleum ether (bp 30–60°) to yield 4.98 g (0.00811 mol) of product: mp 129–131°; NMR ($CDCl_3$) τ 2.32–2.90 (envelope, 30), 7.03 (d, 4, J = 6.5 Hz, 2 CH_2O); ir λ_{max} (KBr) 3040, 2910, 2850, 1590, 1480, 1440, 1205, 1070, 1055, 900, 775, 763, 748, 705 cm^{-1} (broad).

Anal. Calcd for $C_{45}H_{42}O_2$ (10): C, 87.90; H, 6.88. Found: C, 87.95; H, 6.85.

The monotrityl derivative 11 was recrystallized from ether–petroleum ether (bp 30–60°). Three crops were obtained, totaling 5.30 g (0.0142 mol) of product: mp 127–128°; NMR ($CDCl_3$) τ 2.45–3.0 (envelope, 15), 6.63 (d, 2, J = 6 Hz, CH_2OH), 7.03 (d, 2, J = 6 Hz, CH_2OTr); ir λ_{max} (KBr) 3400 (broad), 3050, 2910, 2880, 1590, 1480, 1440, 1210, 1030, 900, 776, 768, 754, 710, 698 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}O_2$ (11): C, 83.83; H, 7.57. Found: C, 83.90; H, 7.63. The combined yield of the two trityl derivatives 10 and 11 was 74%.

***O*-Trityl-*cis*-1,3-bis(hydroxymethyl)cyclopentane *p*-Toluenesulfonate (12) and Methanesulfonate (12a).** The monotrityl derivative 11 (1 g, 0.0027 mol) was dissolved in 5 ml of dry pyridine, and to that solution was added an excess of *p*-toluenesulfonyl or methanesulfonyl chloride. The mixture was stirred at room temperature overnight, then poured into ice water with stirring, and the product was extracted with chloroform. The extracts were washed with aqueous saturated NaCl solution and dried over Na_2SO_4. Evaporation of the solvent gave a gummy or oily residue which was chromatographed on a silica gel column (*l* 25 cm). The product was eluted with benzene–ether (4:1). Removal of the solvent and vacuum drying gave a quantitative yield of a pale yellow oil.

***p*-Toluenesulfonate 12:** NMR ($CDCl_3$) τ 6.22 (d, 2, J = 6.5 Hz, CH_2OTs), 7.13 (d, 2, J = 6.5 Hz, CH_2OTr), 7.69 (1, 3, CH_3Ph).

Anal. Calcd for $C_{33}H_{34}O_4S$: C, 75.25; H, 6.51; S, 6.09. Found: C, 75.41; H, 6.56; S, 6.12.

Methanesulfonate 12a. The oil solidified to a waxy material after several weeks: NMR ($CDCl_3$) τ 6.0 (d, 2, J = 6.5 Hz, CH_2OMs), 7.05 (d, 2, J = 5.0 Hz, CH_2OTr), 7.12 (s, 3, CH_3SO_2); ir λ_{max} (neat) 3030, 2930, 2850, 1590, 1480, 1440, 1350, 1170, 1070, 900 (broad), 825 (broad), 765, 750, 710 cm^{-1}.

Anal. Calcd for $C_{27}H_{30}O_4S$: C, 71.91; H, 6.71; S, 7.11. Found: C, 71.94; H, 6.71; S, 7.00.

***cis*-3-Hydroxymethylcyclopentaneacetonitrile (17).** A stirred solution of 16.90 g (0.0595 mol) of *cis*-1,3-bis(hydroxymethyl)cyclopentane monotosylate (9), 0.18 g (1.43 mmol) of iodine, and 5.65 g (0.087 mol) of potassium cyanide in a mixture of 43.5 ml of dimethylformamide and 25.5 ml of water was kept in a stoppered flask at 60° for 3 days. It was poured with stirring into 120 ml of ice water, and, after the ice had melted, the mixture was extracted with CH_2Cl_2 (5 × 90 ml). The combined extracts were dried with Na_2SO_4 and concentrated, and the viscous residue was first fractionated in vacuo (5 Torr) through a short Vigreux column with an oil bath at 50°. The distillate, collected between 32 and 43°, consisted of the bulk of DMF and a trace of the product. When this distillation ceased, the remaining liquid was transferred into a smaller flask, and the product (5.0 g, 60%) was distilled at 86–90° (0.015–0.017 Torr):[32] NMR ($CDCl_3$) τ 6.46 (s, 1, OH), 6.56 (s, 2, CH_2O), 7.6 (s, 2, CH_2CN); ir λ_{max} (neat) 3400, 2960, 2890, 2250 (ν_{CN}), 1450, 1420, 1050, 1009 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.27; H, 9.47; N, 10.00.

***cis*-3-Hydroxymethylcyclopentaneacetic Acid (18).** A solution of the nitrile 17 (4.70 g, 0.0338 mol) in a mixture of 50 ml of ethanol, 12.5 ml of water, and 6.0 g of KOH was heated to reflux under nitrogen for 6 days. The ethanol was removed by distillation, while the volume of the reaction mixture was maintained at ~50 ml by successive addition of small volumes of water. The resulting mixture of the aqueous solution and a small amount of solid was continuously extracted with ether for 24 hr, then cooled, acidified with 9 ml of concentrated HCl, and again continuously extracted with a fresh volume of ether for an additional 24 hr. The latter extract was dried with Na_2SO_4 and concentrated to a yellowish oil. The bulk of the product was purified (as indicated by GLC) by filtration through a pad (*d* 1 cm, *l* 1 cm) of Norit, yield 4.2 g (78%). An analytical sample was obtained by high vacuum (0.013 Torr) distillation in a molecular still:[52] NMR ($CDCl_3$) τ 3.04 (s, 2, 2 OH), 6.42 (d, 2, J = 6 Hz, CH_2O), 7.6 (s, 2, CH_2CO); ir λ_{max} (neat) 3400 (sh), 2950, 2600 (sh), 1700, 1400, 1020, 1005 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.73, H, 8.92. Found: C, 60.76; H, 8.88.

***cis*-3-Hydroxymethylcyclopentaneacetic Acid Lactone (16).** A mixture of 15 g (0.121 mol) of the ketone 15, 35 g of purified *m*-chloroperbenzoic acid,[53] and 21.0 g (0.25 mol) of sodium bicarbonate in 500 ml of $CHCl_3$ (freed of ethanol by passing over basic alumina) was mechanically stirred in a sealed flask and in the dark for 1 week. During that time, the built-up pressure was periodically released. The mixture was filtered and the solids were washed well with $CHCl_3$. The combined filtrates were washed several times with small volumes of cold 10% sodium sulfite solution until it gave a negative test with starch–iodide paper (~350 ml of the sulfite solution is required), then with cold $NaHCO_3$ solution and dried over Na_2SO_4. After the solvent was removed the remaining oil was chromatographed on a silica gel column (250 g) developed with a mixture of petroleum ether (bp 30–60°)–$CHCl_3$ (4:1). Two components identified (ir and ^1H NMR) as *m*-chlorobenzoic acid [recrystallized from ether–petroleum ether (bp 30–60°), mp 156–157°] and starting material (purified by sublimation) were eluted first. The composition of the eluent was then changed to 1:1, and fractions containing the lactone 16 were pooled and concentrated, leaving an oil that on drying in vacuo became a waxy solid. Recrystallization[54] from petroleum ether (bp 30–60°), including treatment with Norit, gave a total of 10.4 g (61%) of product: mp 125–129°; NMR ($CDCl_3$) τ 5.81 (d, 2, J = 3 Hz, CH_2O), 6.9–7.8 (envelope), 7.8–8.6 (envelope); ir λ_{max} (KBr) 2980, 1725 (ν_{CO}), 1460, 1420, 1390, 1340, 1320, 1260, 1215, 1160, 1090, 1040, 990, 970, 935, 875, 852, 780, 700 cm^{-1}.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.52.

α-Hydroxymethylene-(*cis*-3-hydroxymethyl)cyclopentaneacetic Acid Sodium Salt (19). To a cooled (ice bath) stirred suspension of 1.62 g (0.03 mol) of sodium methylate in 60 ml of dry ether, a mixture of 4.20 g (0.03 mol) of the lactone 16 and 3.6 g (3.85 ml, 0.06 mol) of methyl formate was added dropwise. The ice was allowed to melt and the mixture was stirred for 4 days. The solvent was decanted from the precipitated gum, which was repeatedly triturated with dry ether to give a granular, brownish solid, collected and dried in vacuo, yield 3.150 g. In aqueous solution the solid showed a strong absorption at 277 nm which was eliminated upon acidification.

5-(*cis*-3-Hydroxymethylcyclopentane)-2-thiouracil (20). In a representative experiment, the sodium enolate 19 (3.04 g) was added to a solution of thiourea (2.43 g, 0.032 mol) in 250 ml of dry EtOH containing 736 mg (0.032 mol) of sodium, and the mixture was heated at reflux for 6 hr. It was acidified with an excess of glacial acetic acid and the solvent was removed. The residue was chromatographed on a Dowex 50 (H^+, 200–400 mesh) column (*l* 50 cm) which was washed with water. The fraction containing the product was evaporated to dryness, the residue was dissolved in methanol, and the solution was treated with Norit and filtered. Water (~20 ml) was added to the filtrate, which was then concentrated. Upon removal of the methanol, an aqueous suspension of the product was obtained. After overnight cooling the product was collected, washed once with water, and dried in vacuo at 80° (365 mg, mp 211–212°): NMR (Me_2SO-d_6) τ −0.90 (broad, 2, 2 NH), 2.87 (s, 1, HC=), 5.56 (poorly resolved triplet, OH), 6.69 (t, 2, J =

5 Hz, CH_2O), 7.28 (broad, 1), 6.58–8.65 (envelope, 7); ir λ_{max} (KBr) 3400, 3200, 2980, 2900, 1660, 1560, 1470, 1210 (broad), 1120, 1050, 1000, 915 cm^{-1} (broad).

Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.07; H, 6.23; N, 12.38; S, 14.17. Found: C, 53.05; H, 6.24; N, 12.27; S, 14.11.

5-(*cis*-3-Hydroxymethylcyclopentane)uracil (1). A mixture of 362 mg (0.0016 mol) of the thiouracil **20** and ~15 ml of water containing 198 mg (0.002 ml) of $ClCH_2COOH$ was heated at gentle reflux. Within 30 min a clear yellow solution resulted. After ~18 hr, 0.7 ml of concentrated HCl was added to the solution, and the refluxing was continued for a total of 30 hr. Upon cooling a solid separated and was collected by filtration, washed with a small volume of cold water, and dried. The combined filtrates were chromatographed on a Dowex 50 (H^+, 200–400 mesh) column (*l* 50 cm) and washed with water. After evaporation of the appropriate fraction, an additional small amount of material was recovered. The crude product was dissolved in 40 ml of methanol, the solution was decolorized with Norit and filtered, and the filtrate was concentrated on the steam bath until it became turbid. After cooling (5°) overnight the product was collected, washed once with a small volume of cold methanol and then with ether, and dried in vacuo (280 mg, mp 274–275°). An additional 37 mg was recovered from the mother liquors, total yield 94%: NMR (Me_2SO-d_6) τ −0.96 (s, 1, N-3 H), −0.61 (d, 1, J = 3 Hz, N-1 H), 2.88 (d, 1, J = 3 Hz, HC=), 5.55 (t, 1, J = 5 Hz, OH), 6.70 (t, 2, J = 5 Hz, collapses to a doublet with D_2O, J = 6 Hz, CH_2O), 7.26 (multiplet, 1), 7.69–9.08 (envelope, 7); ir λ_{max} (KBr) 3500 (sh), 3250, 3100, 2950, 1740, 1670, 1460, 1420, 1245, 1208, 1060, 1015, 945, 920, 850 (broad), 780, 775 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.13; H, 6.65; N, 13.29.

5-(*cis*-3-Hydroxymethylcyclopentane)-1-methyluracil (23). A mixture of the uracil derivative **1** (210 mg, 0.001 mol), 7 ml of hexamethyldisilazane, and 0.4 ml of trimethylchlorosilane was heated in a bath at 150–160° for ~20 hr. The solvents were removed by distillation in vacuo by maintaining the temperature of the bath at 50° while gradually reducing the pressure to 0.050 Torr. To the viscous residue, **22**, was added 10 ml of CH_3I and the solution was heated under reflux overnight. The solvent was then evaporated by boiling, the residue was dissolved in ~10 ml of EtOH, and the solution was heated under reflux for 12 hr. After removal of the solvent the residue was chromatographed on a silica gel 60 (E. Merck) column (4 × 16 cm) which was washed with C_6H_6–CH_3OH (8:2). Fractions containing the product (TLC) were pooled, the solvent was removed, and the viscous residue was dried in vacuo and then dissolved in EtOH. The solution was treated with Norit and again the solvent was removed. Upon the addition of a few milliliters of dry ether and standing at room temperature for several hours, the residue solidified. The solvent was then decanted, and the solid was dissolved in 2–3 drops of ethanol. Addition of an excess of dry ether induced crystallization (rosettes). After standing overnight at room temperature the product was collected, washed with dry ether, and recrystallized once more, as above, with Norit treatment. The pure product was collected, washed with ether, and dried under high vacuum at room temperature: yield 150 mg (67%); mp, shrinks at 127° and melts at 147–148°, NMR (Me_2SO-d_6) τ −1.12 (s, 1, N-3 H), 2.59 (s, 1, HC=), 5.54 (t, 1, J = 5 Hz, OH), 6.68 (t, 2, J = 6 Hz, CH_2O), 6.78 (s, 3, CH_3N), 7.25 (broad, 1), 7.77–9.11 (envelope, 7); ir λ_{max} (KBr) 3400 (sh), 3200, 3050, 2920, 2850, 1715, 1685, 1450, 1320, 1180–1210 (three partially resolved bands), 1100, 1045, 1000, 930, 900, 840, 760 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.91; H, 7.15; N, 12.47.

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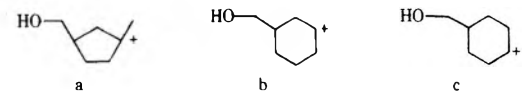
References and Notes

(1) This investigation was supported in part by funds from the National Cancer Institute (Grants CA-08748 and CA-16191).
(2) R. W. Chambers, *Prog. Nucleic Acid Res. Mol. Biol.*, **5**, 349 (1966), and references cited therein.
(3) J. Ofengand and H. Schaefer, *Biochemistry*, **4**, 2832 (1965).
(4) J. D. Fissekis and B. A. Markert, *J. Org. Chem.*, **31**, 2945 (1966).
(5) J. D. Fissekis and B. Markert Creegan, *J. Org. Chem.*, **32**, 3595 (1967).
(6) A. Dugaiczyk, *Biochemistry*, **9**, 1557 (1970).
(7) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 1390 (1969).
(8) F. H. Hruska, A. A. Grey, and I. C. P. Smith, *J. Am. Chem. Soc.*, **92**, 4088 (1970).
(9) R. Deslauriers and I. C. P. Smith, *Can. J. Biochem.*, **50**, 766 (1972).
(10) R. K. Nanda, R. Tewari, G. Govil, and I. C. P. Smith, *Can. J. Biochem.*, **52**, 371 (1974).
(11) (a) P. O. P. Ts'o, "Basic Principles in Nucleic Acid Chemistry", Vol. I, P. O. P. Ts'o, Ed., Academic Press, New York, N.Y., 1974, p 512; (b) p 537.
(12) See discussion of the paper by M. Guéron, C. Chachaty, and T.-D. Son, *Ann. N.Y. Acad. Sci.*, **222**, 307 (1973).
(13) A. Dugaiczyk, J. P. Cruz, and M. Martinez, *Biochemistry*, **11**, 3523 (1972).
(14) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).
(15) A. Dugaiczyk and J. J. Eiler, *J. Biol. Chem.*, **244**, 2750 (1969).
(16) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(17) I. Wempen and J. J. Fox, *J. Am. Chem. Soc.*, **86**, 2474 (1964).
(18) K. Nakamishi, N. Suzuki, and F. Yamazaki, *Bull. Chem. Soc. Jpn.*, **34**, 53 (1961).
(19) E. Wittenburg, *Chem. Ber.*, **99**, 2391 (1966).
(20) K. L. Wierzchowski, E. Litońska, and D. Shugar, *J. Am. Chem. Soc.*, **87**, 4621 (1965).
(21) J. D. Fissekis, unpublished results.
(22) The influence of some C-5 substituents on the electronic state of uracil depending upon the presence of a C-5 heteroatom or C-5 carbon–carbon linkage has been discussed recently: P. D. Ellis, R. B. Dunlap, A. L. Pollard, K. Seidman, and A. D. Cardin, *J. Am. Chem. Soc.*, **95**, 4398 (1973).
(23) For a quantitative treatment of the concept of pseudorotation in the sugar ring of nucleosides, see C. A. Altona and M. Sandaralingam, *J. Am. Chem. Soc.*, **94**, 8205 (1972); also R. L. Lipnick, *ibid.*, **96**, 2941 (1974) for an account of restricted pseudorotation in monosubstituted cyclopentanes.
(24) The discovery that crystals grown from an aqueous solution of β-pseudouridine in the presence of $NiCl_2$ were those of the α anomer created additional interest in the possible role of the β and α isomers of pseudouridine in tRNA: D. C. Rohrer and M. Sandaralingam, *J. Am. Chem. Soc.*, **92**, 4950 (1970).
(25) S. F. Birch, W. J. Oldham, and E. A. Johnson, *J. Chem. Soc.*, 818 (1947).
(26) R. D. Clark, *Org. Prep. Proced.*, **6**, 49 (1974).
(27) J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960).
(28) Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, **91**, 3075 (1969).
(29) S. F. Birch and R. A. Dean, *J. Chem. Soc.*, 2477 (1953).
(30) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).
(31) N. S. Radin, A. K. Hajra, and Y. Akahori, *J. Lipid Res.*, **1**, 250 (1960).
(32) A minor low boiling by-product of that reaction was identified as 3-cyclohexene-1-methanol, **21**, by comparison of its ir and nmr spectra with those of an authentic sample purchased from Aldrich. A most likely route involves the formation (EI) of a from **9**, followed by ring expansion to give b and/or c. Either one of the latter two species could yield **21**.



a b c

(33) C. Galli, G. Illuminati, and L. Mandolini, *J. Am. Chem. Soc.*, **95**, 8374 (1973).
(34) R. Huisgen and H. Ott, *Tetrahedron*, 253 (1959).
(35) In a recent lactonization method involving simultaneous activation of both carboxyl and hydroxyl groups, the lowest reported yield (9%) among the seven-, nine-, and 12- to 16-membered lactones was that of the nine-membered one. No data for the eight-membered lactone were available: E. J. Corey and K. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
(36) W. Kraus, G. Klein, H. Sadlo, and W. Rothenwohrer, *Synthesis*, 485 (1972). In this paper the reported yield (62 g, 74%) for *exo*-3,4-dichlorobicyclo[3.2.1]octene-2 (**13**) is obviously in error. In doubling the scale of that experiment a 77% yield of **13** was obtained.
(37) It has been noted that the eight- and nine-membered lactones are relatively more reactive toward hydrolysis, with the ring-closure and ring-opening reactions being inversely related to each other.[33,34]
(38) M. Ōki, H. Iwamura, T. Onoda, and M. Iwamura, *Tetrahedron*, **24**, 1905 (1968).
(39) Von W. Ditter and W. A. P. Luck, *Ber. Bunsenges. Phys. Chem.*, 73, 526 (1969).
(40) For a detailed discussion of the "Electronic Effect of the Methyl Group", see D. T. Clark and D. J. Fairweather, *Tetrahedron*, **25**, 4083 (1969).
(41) M. Tamres, *J. Am. Chem. Soc.*, **74**, 3375 (1952).
(42) M. Ōki and H. Iwamura, *J. Am. Chem. Soc.*, **89**, 576 (1967).
(43) S. Sriraman and R. Sabesan, *J. Mol. Struct.*, **6**, 225 (1970).
(44) J. D. Fissekis and F. Sweet, *J. Org. Chem.*, **38**, 264 (1973).
(45) D. J. Brown, *J. Chem. Soc.*, 3647 (1959).

(46) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 211 (1955).
(47) See ref 18 and 19 for an interpretation of the "shoulder" in the uv spectra of the monoanions of uracils as a contribution of the N-1 anion.
(48) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).
(49) J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Am. Chem. Soc.*, **75**, 4315 (1953).
(50) For a discussion of the energetic and orientational nonequivalence of lone pairs in organic molecules, see O. Eisenstein, N. T. Anh, Y. Jean, A. Devaquet, J. Cantacuzene, and L. Salem, *Tetrahedron*, **30**, 1717 (1974).
(51) Several attempts to crystallize the monotosylate derivative failed. It decomposes during sublimination in vacuo, and it separates from methanol, petroleum ether, or various solvent mixtures as an oil.
(52) The distillation leaves a waxy residue from which a crystalline material (mp 65–67°) was isolated by recrystallization from ether containing a trace of chloroform. The ir spectrum of this material is similar to that of **18** but shows a greatly attenuated OH band and a small shift of the carbonyl absorption to 1725 cm^{-1}.
(53) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).
(54) The material can also be purified by sublimation in vacuo at <50°.

Side Reactions in Peptide Synthesis. II.[1] Formation of Succinimide Derivatives from Aspartyl Residues

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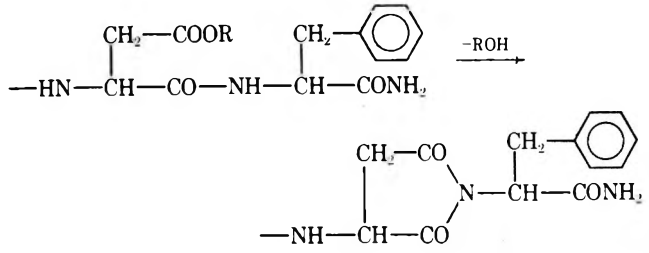
Acylation of peptides in which the side chain of an aspartyl residue is unprotected can result in the formation of succinimide derivatives. The presence of base enhances the formation of such by-products: the carboxylate attacks the carbonyl of active esters and forms a reactive intermediate, probably a mixed anhydride, that in turn acylates the adjacent amide. This is a particularly serious side reaction in acylation with activated derivatives of glycine. The observation that substituted phenols liberated in active ester reactions can combine with tertiary bases and thus liberate the free side-chain carboxyl groups from their salts is also reported.

In our continued effort toward the total synthesis of the gastrointestinal hormone cholecystokinin,[2] synthesis of the N-terminal octapeptide was reported earlier.[3] Preparation of peptides corresponding to C-terminal sequences of this hormone was also undertaken and involved several intermediates that were used in synthesis of gastrin[4,5] and caerulein,[6] peptides which have C-terminal sequences closely related to that of cholecystokinin, and also in the synthesis of a biologically active dodecapeptide portion of cholecystokinin.[7] The initial steps of our synthesis are summarized in Scheme I. The aspartyl residue in the penultimate position was incorporated as the β-benzyl ester, but the side-chain protection was removed from the resulting dipeptide amide. Thus, from there on the synthesis was continued with amino components in which the carboxyl group of the aspartyl residue remained unprotected. This approach, applied also in other laboratories,[4,7] seemed to offer certain advantages. Protection of a side-chain carboxyl in the form of *tert*-butyl ester requires prolonged acidolysis at the deprotection stage; this was undesirable because of the presence of several acid-sensitive residues (tryptophan, tyrosine *O*-sulfate) in cholecystokinin. Benzyl ester protection was also considered but the presence of methionines in the sequence made it questionable whether or not hydrogenolysis can be applied for deblocking.[8] Last, but not least, a free carboxyl was thought to be less likely to lead to aminosuccinimide derivatives[9] (Chart I) than β esters of aspartic acid. Early removal of the benzyl ester protection, prior to the incorporation of the first methionine residue, was expected to circumvent these difficulties.

Scheme I
Synthesis of the Protected Pentapeptide VI

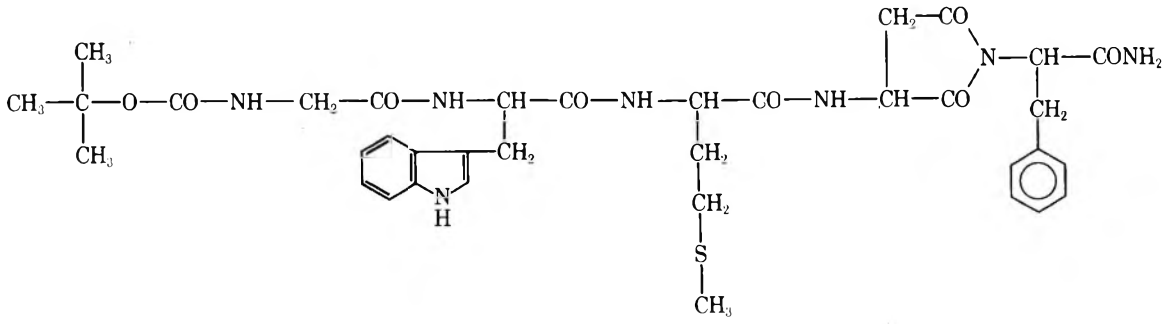
Z-Phe-ONP
↓ NH_3
Z-Phe-NH_2 (I)
↓ 1. H_2/Pd 2. Z-Asp(Bzl)ONP
Z-(Bzl)Asp-Phe-NH_2 (II)
↓ H_2/Pd
Asp-Phe-NH_2 (III)
↓ Boc-Met-ONP
Boc-Met-Asp-Phe-NH_2 (IV)
↓ 1. TFA 2. Boc-Trp-ONP
Boc-Trp-Met-Asp-Phe-NH_2 (V)
↓ 1. TFA 2. Boc-Gly-ONP
Boc-Gly-Trp-Met-Asp-Phe-NH_2 (VI)

Chart I
Formation of Succinimide Derivatives from Aspartyl Peptides



In the synthesis of the protected tetrapeptide amide V and the protected pentapeptide amide VI, the formation of several by-products was observed. Most of these by-products represented only minor impurities. The presence of slow moving, polar materials on thin layer plates was attributed to air oxidation, producing peptides in which the methionine residues were oxidized to sulfoxides or sulfones. These impurities could be readily removed by recrystallization of the crude products. On the other hand, some less readily explained by-products could also be detected in the protected tetra- and pentapeptide derivatives. These products seemed to be less polar, since they moved faster on the chromatograms than the desired intermediates. In the step leading from the tetrapeptide derivatives to the protected

Chart II
Structure of the Succinimide Derivative VII Formed from the Protected Pentapeptide VI



VII

pentapeptide amide VI, a faster moving impurity was present in significant quantity, in some experiments exceeding the amount of the desired product. Therefore, an examination of this by-product (VII) became necessary.

Isolation of the major by-product VII by countercurrent distribution and further purification by chromatography on a silica gel column provided a homogeneous material that had the same amino acid composition as the (protected) pentapeptide amide VI. Their uv and NMR spectra also were quite similar; thus only some subtle difference could exist between the two compounds. In the ir spectrum of VII, a weak but definite carbonyl band at 1790 cm^{-1} suggested that a succinimide derivative[10] was at hand. Indeed, the ring could be opened by the action of ammonia or of alkali in alcohol. The values of elemental analysis and the electrophoretic mobility of the deblocked peptide substantiated the assignment of structure VII (Chart II) to this material.

The unexpected ring closure prompted a series of experiments aimed at the clarification of the reasons for this side reaction. These experiments (Table I) demonstrated that compound VII was present as a minor product if 1 mol of base was added to the tetrapeptide amide trifluoroacetate, an amount enough to liberate the amine from its salt, but not to form a salt with the carboxyl. With 2 mol of base, the formation of VII is enhanced. The effect of *tert*-butyloxycarbonylglycine active esters was similar. An excess of active ester was found to be harmful independently of whether *p*-nitrophenyl,[11] *o*-nitrophenyl,[12] or 2,4,5-trichlorophenyl[13] esters were used. We had to assume that the carboxylate as a nucleophile attacks the electrophilic carbonyl of the active ester and the resulting mixed anhydride intermediate acylates the amide group. A competition between amino groups and carboxylates for the carbonyl of active esters resulting in undesired acylation (e.g., acetylation) products was noted earlier.[14] The presence of base enhances this side reaction by increasing the concentration of carboxylate. Excess active ester has similar influence on the outcome of the two competing reactions. Also, when compound VI was treated with equimolar amounts of diisopropylethylamine and *tert*-butyloxycarbonylglycine *p*-nitrophenyl ester, the formation of significant amounts of the succinimide derivative VII was clearly visible on thin layer chromatograms. The observation that succinimide derivatives formed only to a minor extent in the incorporation of tryptophan, but that the side reaction became a major contributor when active esters of *tert*-butyloxycarbonylglycine were used for acylation, suggests that the side chain of the amino acids hinders the attack of carboxylate on the active ester carbonyl. In glycine, the absence of a side chain allows a more ready approach of the nucleophile, the carboxylate group. In the continuation of the chain lengthening, incorporation of methionine, tyrosine, and aspartic acid β-*tert*-butyl ester was accompanied with the formation of nonpolar by-products, but only to a small extent. In subsequent preparations of the protected pentapeptide VI, only 1 mol of tertiary base was applied and only a slight excess of active ester, the latter being added slowly in several portions. The yield and the quality of the product were superior to those experienced earlier.

Table I
The Effect of the Amount of Tertiary Base and of Excess Active Ester on the Formation of Succinimide Derivative VII

Tube no.	DIEA (0.4 *M*), ml	Boc-Gly-ONP % excess	Yield of crude product, g	Mp, °C	Ratio of VI:VII
1	0.5	20	0.14	163–167	5:1
2	1.0	20	0.13	140–150	5:2
3	1.0	20	0.12	138–145	5:4
4	1.0	100	0.11	128–135	1:5
5	0.5	100	0.14	130–145	5:3

In the synthesis shown in Scheme I, an additional observation was made. After deblocking with trifluoroacetic acid, the trifluoroacetates of the tripeptide and tetrapeptide amides were treated with 2 mol of tertiary base (diisopropylethylamine[15]). One mole was added for the liberation of the free amine from the trifluoroacetate salt, the second for the purpose of converting the free carboxyl group of the aspartyl residue to a carboxylate. After completion of the acylation, the products were isolated by removal of the solvent in vacuo and trituration of the residue with ether, then with ethyl acetate and ether. No acids were applied in the process and yet the products were not the expected diisopropylethylammonium salts of protected peptides, but essentially the free acids. This was shown by melting points, comparisons with authentic samples, and particularly by NMR spectra. We had to assume that the phenols (*p*-nitrophenol, 2,4,5-trichlorophenol) liberated from the active esters are responsible for this "acidification". The acidities of *p*-nitrophenol and of 2,4,5-trichlorophenol are too weak to account for such an effect. A satisfactory explanation was suggested by an earlier observation[16,17] of the formation of a crystalline complex from *p*-nitrophenol and pyridine. Indeed, an examination of washings from the crude products revealed complexes of *p*-nitrophenol with diisopropylethylamine and of 2,4,5-trichlorophenol and diisopropylethylamine. With triethylamine, similar complexes were formed. Treatment with *p*-nitrophenol removed diisopropylethylamine from the salt of compound VI, prepared from the components. The complexes could be identified on thin layer plates by their uv absorption and, in the case of *p*-nitrophenol, by their bright yellow color. From a practical point of view, these

observations raise the question whether or not it was necessary to add tertiary base to the reaction mixture with the intention to convert the carboxyl group to a carboxylate. During the acylation process, the gradually appearing substituted phenol at least partially liberated the free carboxyl group from the carboxylate, and still the reactions proceeded to completion. Thus, the free carboxyl of the aspartyl side chain did not prevent—by protonation—the acylation of the amine. Indeed, in a subsequent experiment, the protected tripeptide amide IV (Scheme I) was successfully prepared from the L-aspartyl-L-phenylalanine amide (III) by acylation with protected methionine active ester, without the addition of any tertiary base. Similarly, when in the preparation of the pentapeptide amide VI only 1 mol of base was used, enough to liberate the amine from its trifluoroacetate salt, but no base was added because of the presence of a free carboxyl in the amino component, the results were quite satisfactory. Thus the addition of tertiary amine for the neutralization of the free side chain carboxyl group of an aspartyl residue is not only unnecessary, but in fact disadvantageous.

The results of these studies necessitate a reconsideration of the use of unprotected side-chain carboxyls in peptide synthesis. They also show that by avoiding an excess on active esters and by using tertiary base only for the liberation of the amine from its salts, the formation of succinimide derivatives can be kept at a minimum.

Experimental Section[18]

Capillary melting points are reported uncorrected. On thin layer chromatograms, the protected peptides were revealed by *tert*-butyl hypochlorite–KI reagents[19] and by charring.[20] Tryptophan-containing peptides were detected by Ehrlich reagent. Peroxide-free ether was used; reagent-grade DMF was dried over a molecular sieve (Linde Type 4A). For amino acid analysis, samples were hydrolyzed with constant boiling HCl in evacuated, sealed ampoules at 110° for 16 hr and analyzed by the Spackman–Stein–Moore method.[21]

Benzyloxycarbonyl-L-phenylalanine Amide (I). Benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester[22] (8.4 g, 20 mmol) was dissolved in tetrahydrofuran (50 ml). Ammonia was passed over the stirred solution for 2 hr. The solvent was removed in vacuo, and the residue was triturated with ether, filtered, and dried in vacuo. The amide weighed 5.5 g (92%), mp 163–164° (lit.[5] mp 161–162°, lit.[4] mp 164–165), $[\alpha]^{25}D$ −6.3° (c 2, DMF).

Benzyloxycarbonyl-(β-benzyl)-L-aspartyl-L-phenylalanine Amide (II). A sample of I (9.0 g, 30 mmol) was dissolved in 95% ethanol (450 ml) by gentle warming. After cooling, 1 *N* HCl (30 ml) was added, and the mixture was hydrogenated in the presence of 10% Pd on charcoal catalyst (1.8 g). The catalyst was removed by filtration and the solvents by evaporation in vacuo. The residue was dissolved in DMF (69 ml) and DIEA (4.8 ml, 30 mmol) was added, followed by benzyloxycarbonyl-β-benzyl-L-aspartic acid *p*-nitrophenyl ester[23] (15.8 g, 33 mmol). Next day the ninhydrin reaction was negative. The solvent was removed in vacuo, and the residue was triturated with ethyl acetate (100 ml) and filtered. The solid was suspended in water (200 ml), stirred for 15 min, filtered, and dried: yield 14.7 g (97%); mp 170–171° (lit.[5] mp 170–171°); $[\alpha]^{25}D$ −22.6° (c 2, DMF) [lit.[5] −25.9° (c 1, DMF)].

In a second experiment, the corresponding *o*-nitrophenyl ester[24] was used with similar results.

***tert*-Butyloxycarbonyl-L-methionyl-L-aspartyl-L-phenylalanine Amide (IV). A.** Compound II (14.5 g, 29 mmol) was dissolved in 95% aqueous acetic acid (240 ml) and hydrogenated in the presence of 10% Pd on charcoal catalyst (3 g) for 6 hr. The solution was filtered through a filter precoated with Celite (3.0 g) and charcoal (1.0 g), evaporated in vacuo, and reevaporated with a small quantity of water (5 ml). This was repeated three more times. The resulting aspartylphenylalanine amide (III) was used without purification. It was suspended in DMF (200 ml), and DIEA (4.8 ml) was added. *tert*-Butyloxycarbonyl-L-methionyl *p*-nitrophenyl ester[25] (12.0 g, 32.4 mmol) was added to the suspension; soon a clear solution formed. After about 16 hr, the ninhydrin reaction became negative. The solvent was evaporated in vacuo, and the residue was thoroughly triturated with ethyl acetate (20 ml) and ether (250 ml), stirred for 20 min with this solvent mixture, filtered, and dried to give 10.75 g (70%), mp 206–208° dec. A sample was recrystallized from EtOH, mp 211–212° dec (lit.[5] mp 209–210° dec), $[\alpha]^{25}D$ −41.9 (c 2.0, DMF) [lit.[5] −39.3° (c 1, DMF)].

B. Compound III (prepared from 375 mg of compound II as described above) was suspended in DMF (6 ml), and Boc-Met-ONP (0.33 g) was added to the stirred suspension. Gradually a clear solution formed. After about 48 hr, the solvent was removed in vacuo and the residue was triturated with ether. The protected tripeptide amide IV (0.32 g, 85%) melted at 206–208° and was homogeneous on TLC.

***N-tert*-Butyloxycarbonyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine Amide (V).** A sample of the protected tripeptide amide IV (8.3 g, 16.3 mmol) was dissolved in distilled TFA containing 5% anisole (30 ml). After 30 min in an ice bath, under N_2, the TFA was evaporated in vacuo, and the residue was triturated with ether, filtered, washed with ether, and dried to yield the tripeptide amide trifluoroacetate (8.3 g). This was dissolved in DMF (90 ml), and DIEA (5 ml) was added, followed by *tert*-butyloxycarbonyl-L-tryptophan *p*-nitrophenyl ester[26] (8.0 g, 18.8 mmol). 1-Hydroxybenzotriazole[27] (2.3 g) was added to the suspension; a further 10 ml of DMF was used for the rinsing. The stirred reaction mixture became clear in about 5 min. After 2 hr, the ninhydrin reaction was negative. (Without the catalyst, the reaction required 72 hr.) The solvents were removed in vacuo, and the residue was triturated with ethyl acetate (20 ml) and ether (250 ml), filtered, washed with ether, and dried, 10.2 g (90.2%), mp 194–195° dec. A sample was crystallized from ethanol, mp 212–213° (lit.[5] mp 209–210° dec, $[\alpha]^{25}D$ −35.0° (c 2.0, DMF) [lit.[5] −35.7° (c 1, DMF)]. Amino acid analysis: Asp, 1.05; Met, 1.0; Phe, 0.98.

Anal. Calcd for $C_{34}H_{44}N_6O_8S$: C, 58.6; H, 6.4; N, 12.1. Found: C, 58.4; H, 6.2; N, 11.8.

With *tert*-butyloxycarbonyl-L-tryphophan 2,4,5-trichlorophenyl ester, similar results were obtained.

***N-tert*-Butyloxycarbonylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine Amide (VI). A.** The *tert*-butyloxycarbonyl group was removed from compound V (0.70 g, 1 mmol) with TFA (2 ml, containing 5% anisole) as described in the previous experiment. The trifluoroacetate salt was dissolved in DMF (8 ml) and DIEA (0.32 ml, 2 mmol) was added, followed by *tert*-butyloxycarbonylglycine *p*-nitrophenyl ester[28] (0.33 g, 1.1 mmol). The solution was kept overnight at room temperature, when the ninhydrin and fluorescamine[29] reactions became negative. The solvents were evaporated in vacuo, the residue was thoroughly triturated with ether (30 ml), and the supernatant was decanted. The residue was triturated with ethyl acetate (5 ml) and then ether (30 ml) was added. The suspension was stirred for 10 min and filtered. The solid was resuspended in ethyl acetate (10 ml), stirred for 10 min, and filtered, yield 0.60 g. Crystallization from ethanol yielded compound VI, which on TLC still showed a few minor spots, mp 187–190° dec. The yield of this reaction was found to be variable, sometimes as low as 40%. The purification of the product was difficult: it formed gels in several solvents.

B. To a sample of the tetrapeptide amide trifluoroacetate (0.71 g, 1 mmol) in DMF (8 ml), DIEA (0.16 ml) was added. The active ester, Boc-Gly-ONP (0.36 g, 1.2 mmol), was added in five portions at 90-min intervals, the first four portions 0.25 mmol each, the final addition 0.20 mmol. Before each addition, a sample (0.1 ml) was removed and diluted with ether, and the precipitate was separated by centrifugation and examined on TLC. After the last addition of active ester, the mixture was allowed to stand overnight and worked up as described in the previous experiments. The product (0.72 g) had mp 178–180° dec. After trituration with ethyl acetate (6 ml), the product (0.67 g, 93% corrected for sample) melted at 185–186° dec. The formation of only slight amounts of VII could be detected both during the reaction and in the crude product.

Preparation of the Diisopropylethylammonium Salt of VI. A crude sample of VI (1.7 g) was dissolved in a 1:1 mixture of chloroform and ethanol (50 ml), and DIEA (0.48 ml) was added. The solution was distinctly alkaline. The solvents were removed by a stream of N_2 and the residue was dried in a dessiccator. It was distributed through 46 transfers in a Craig apparatus with 10 ml upper and 10 ml lower phases of the system chloroform–methanol–water (3:2:1). On examination on TLC, tubes 18–26 showed the presence of the diisopropylethylammonium salt of VI as a single entity. These fractions were pooled, the solvents were removed, and the residue was dried to yield 0.94 g. The NMR spectrum of this compound revealed this to be the DIEA salt of VI, mp 125–

134° dec. Amino acid analysis: Asp, 1.0; Gly, 1.14; Met, 0.97; Phe, 1.0.

Anal. Calcd for $C_{44}H_{66}N_8O_9S$: C, 59.9; H, 7.5; N, 12.7. Calcd for $C_{44}H_{66}N_8O_9S \cdot 2H_2O$: C, 57.5; H, 7.7; N, 12.2. Found: C, 57.3; H, 7.3; N, 12.2.

Conversion of the Diisopropylethylammonium Salt of VI to the Free Acid VI by *p*-Nitrophenol. A sample of the DIEA salt of VI (7 mg) was suspended in ether (2 ml), followed by the addition of *p*-nitrophenol (3 mg). The ether solution was decanted, concentrated, and applied to a thin layer plate of silica gel. Ether was used for elution. The *p*-nitrophenol–DIEA complex was identified by comparison with an authentic sample. The ether-insoluble material melted at 195–197° dec and was similarly identified as VI.

Isolation of the Succinimide Derivative VII. The ethyl acetate soluble portions obtained from the crude reaction products of VI from several experiments (3.45 g) were distributed in a 60-tube Craig apparatus with 10-ml phases in the solvent system chloroform–methanol–water (3:2:1). After 80 transfers, on the basis of TLC chromatograms, fractions 0–3 (1.9 g), 4–6 (0.9 g), 7–10 (0.14 g), and 11–22 (0.35 g) were pooled. Fractions 4–6 contained the succinimide with some impurities. This material was chromatographed on a column of silica gel (20 g). First, chloroform was used for elution; 6-ml fractions were collected. After 25 fractions, the eluent was changed to a mixture of 2% methanol in chloroform. Purified VII was detected in fractions 75–149. These fractions were combined and solvents removed to leave a residue (550 mg) of compound VII in homogeneous (TLC) form, mp 131–136° dec, $[\alpha]^{25}D$ −76.2° (*c* 2, DMF containing 1% AcOH). On TLC in $CHCl_3$–MeOH (9:1) R_f 0.38, in EtOAC–pyridine–HOAC–H_2O (60:20:6:11) R_f 0.8. Amino acid analysis: Asp, 1.01; Gly, 0.96; Met, 1.01; Phe, 1.0.

Anal. Calcd for $C_{36}H_{45}N_7O_8S$: C, 58.8; H, 6.2; N, 13.3. Found C, 58.5; H, 6.1; N, 13.1.

Fractions 11–22 of the countercurrent distribution yielded *t*-Boc pentapeptide amide VI (0.35 g) in homogeneous form; mp 201–202° dec (lit.[4] mp 200–202° dec, lit.[6] mp 196°), $[\alpha]^{25}D$ −32.2° (*c* 2, DMF containing 1% AcOH) [lit.[4] −27.7 (*c* 2, DMF), lit.[6] −27 (*c* 1, DMF)]. Amino acid analysis: Asp, 1.15; Gly, 0.89; Met, 1.0; Phe, 1.0.

Anal. Calcd for $C_{36}H_{47}N_7O_9S$: C, 57.4; H, 6.3; N, 13.0. Found: C, 57.1; H, 6.4; N, 13.3.

Studies on the Formation of VII. A. The Effect of Different Active Esters. In three parallel experiments, the preparation of VI was carried out under identical conditions: 1 mmol of amino component, 2 mmol of DIEA, and 1.1 mmol of active ester in 8 ml of DMF with 2,4,5-trichlorophenyl ester, *o*-nitrophenyl ester, and *p*-nitrophenyl ester of *tert*-butyloxycarbonyl glycine as acylating agents. The crude products were stirred with EtOAC (5 ml), separated by centrifugation, dried, and weighed. The results are shown in Table II.

Table II
The Influence of Different Active Esters on the Formation of Compound VII

	With Boc-Gly-ONO	With Boc-Gly-OCP	With Boc-Gly-ONP
Wt of crude product, g	0.64	0.66	0.60
Mp of crude product, °C	100–125	100–125	140–150
Wt of purified material, g	0.35	0.38	0.39
Mp of purified material, °C	177–180	177–178	181–184

B. The Effect of the Amount of Base and of the Excess of Ester. Five aliquots (1 ml each) of a 0.2 *M* DMF solution of the trifluoroacetate, obtained by deprotection of the protected tetrapeptide amide VI in DMF, were placed in 40-ml centrifuge tubes equipped with a 24/40 standard tapered joint.[30] A 0.4 *M* solution of DIEA in DMF was added in amounts shown in Table I To keep the concentration of the amino component identical in each experiment, DMF (0.5 ml) was added to tubes 1 and 5. The amount of active ester used (Boc-Gly-ONP) is shown in Table I. The reaction was allowed to proceed overnight. The solvent was removed in vacuo, each residue was triturated with ether (15 ml), the semisolid products were separated by centrifugation and decantation and triturated with ethyl acetate (3 ml), and the mixture was diluted with ether (15 ml). The crude products were separated again by centrifugation. Their weights and melting points are shown in Table I, and also their content on compounds VI and VII as estimated from the intensities of the respective spots on TLC.

C. Reaction of Boc-Gly-ONP and Boc-Met-ONP with VI in the Presence of DIEA. Compound VI (38 mg) was added to a 0.025 *M* solution (0.2 ml) of DIEA in DMF. This was divided into two equal portions. To one portion Boc-Gly-ONP (7.5 mg) was added, to the other Boc-Met-ONP (9.5 mg); DMF (0.1 ml) was used in each tube for rinsing. The solutions were kept overnight. The solvent was removed by a stream of nitrogen. The residues were triturated with ether (2 ml) and centrifuged and the ether solution was decanted. The remaining residues were examined on TLC. The formation of VII was observed in both cases, but was more pronounced in the experiment with Boc-Gly-ONP.

D. Opening of the Succinimide Ring. A sample (0.05 mmol) of compound VII was dissolved in 95% ethanol (2 ml). A 0.2 *N* NaOH solution (0.25 ml) was added, and the mixture was kept at room temperature for 90 min and then acidified with 0.2 *N* HCl (0.25 ml). Examination on TLC [silica gel, EtOAc–pyridine–AcOH–H_2O (60:20:6:11)] showed the disappearance of VII (R_f 0.80), the formation of VI (R_f 0.46), and an even larger amount of a new derivative with R_f 0.33, presumably the pentapeptide derivative containing a β-aspartyl residue.

A sample of VII (5 mg) was dissolved in MeOH (3 ml) and NH_3 was passed over the solution for 1 hr. After 2 days at room temperature, examination on TLC in the system described above revealed the disappearance of VII and the formation of two new compounds, with R_f values 0.68 and 0.63.

E. Electrophoresis. Samples of compounds VI and VII (40 mg each) were treated with TFA (0.5 ml) containing 5% anisole for 30 min at ice-bath temperature under a blanket of nitrogen. The TFA was removed in vacuo, the residues were triturated with ether, and trifluoroacetates were isolated by centrifugation. Samples were dissolved in 1 *N* AcOH and applied to Whatman No. 3 MM paper. Electrophoresis was carried out with the Savant flat plate apparatus, in a buffer of pyridine (300 ml), AcOH (11.5 ml), and H_2O (2700 ml) at 30 V/cm for 2.5 hr. After drying, the spots were revealed with ninhydrin; the pentapeptide amide corresponding to VI moved slightly toward the cathode, while the spot of deblocked VII moved further away from the origin, with about 40% of the mobility of lysine.

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Registry No.—I, 4801-80-3; II, 5241-68-9; III, 5241-71-4; IV, 5920-14-9; V, 5235-21-2; V trifluoroacetate, 5908-10-1; VI, 5915-71-9; VI diisopropylethylammonium salt, 55701-83-2; VII, 55701-84-3; benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester, 2578-84-9; DIEA, 7087-68-5; benzyloxycarbonyl-β-benzyl-L-aspartic acid *p*-nitrophenyl ester, 55723-11-0; benzyloxycarbonyl-β-benzyl-L-aspartic acid o-nitrophenyl ester, 55701-85-4; *tert*-butyloxycarbonyl-L-methionyl *p*-nitrophenyl ester, 2488-18-8; Boc-Met-ONP, 41120-66-5; Boc-Trp *p*-nitrophenyl ester, 15160-31-3; Boc-Trp 2,4,5-trichlorophenyl ester, 15160-30-2; Boc-Gly *p*-nitrophenyl ester, 3655-05-8; Boc-Gly-ONP, 38606-09-6; *p*-nitrophenol, 100-02-7; Boc-Gly 2,4,5-trichlorophenyl ester, 7536-61-0.

References and Notes

(1) For the previous paper in this series, cf. M. Bodanszky, Y. S. Klausner, and A. Bodanszky, *J. Org. Chem.*, **40**, 1507 (1975).
(2) V. Mutt and E. Jorpes, *Biochem. J.*, **125**, 57 (1971).
(3) M. Bodanszky, N. Chaturvedi, D. Hudson, and M. Itoh, *J. Org. Chem.*, **37**, 2303 (1972).
(4) J. C. Anderson, G. W. Kenner, J. K. MacLeod, and R. C. Sheppard, *Tetrahedron, Suppl. 8*, Part I, 39 (1966).
(5) J. M. Davey and J. S. Morley, *J. Chem. Soc. C*, 555 (1966).
(6) L. Bernardi, G. Bosisio, R. de Castiglione, and O. Goffredo, *Experientia*, **23**, 700 (1967).
(7) M. A Ondetti, J. Pluscec, E. S. Sabo, J. T. Sheehan, and N. Williams, *J. Am. Chem. Soc.*, **92**, 195 (1970).
(8) Removal of protecting groups by hydrogenolysis from methionine-containing intermediates was reported by H. Medzihradszky-Schweiger and K. Medzihradszky, *Acta Chim. Acad. Sci. Hung.*, **44**, 15 (1965); **50**, 339 (1966). However, according to experience gained in this laboratory (M. Bodanszky and A. Bodanszky, unpublished), while the presence of tertiary base allows hydrogenolysis of benzyloxycarbonyl and benzyl ester

groups, it does not permit deblocking of O-benzyl serine residues.
(9) Formation of succinimide derivatives in peptides containing β esters in an aspartyl residue was reported several times in the literature (cf. footnote 14 in ref 7). Ring closure was generally thought to be less likely when the side chain of aspartyl residues is unprotected. However, succinimide derivatives formed during the attempted purification of the peptide antibiotic amphomycin: M. Bodanszky, G. F. Sigler, and A. Bodanszky, *J. Am. Chem. Soc.*, **95**, 2353 (1973). Yet, since a readiness to accept two acyl residues on its amino group is characteristic for glycine, only Asp-Gly sequences were considered prone to this side reaction.
(10) S. K. Freeman, "Interpretive Spectroscopy", Reinhold, New York, N.Y., 1965, p 104.
(11) M. Bodanszky, *Nature (London)*, **175**, 685 (1955).
(12) M. Bodanszky, M. L. Fink, K. W. Funk, M. Kondo, C. Y. Lin, and A. Bodanszky, *J. Am. Chem. Soc.*, **96**, 2234 (1974).
(13) J. Pless and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1609 (1963).
(14) M. Bodanszky, "Peptides-1968", E. Bricas, Ed., North-Holland Publishing Co., Amsterdam, 1968, p 150.
(15) M. Bodanszky and A. Bodanszky, *Chem. Commun.*, 591 (1967).
(16) J. T. Sheehan, U.S. Patent 3,196,144.
(17) M. Bodanszky and M. A. Ondetti, "Peptide Synthesis", Wiley-Interscience, New York, N.Y., 1966, p 104.
(18) The following abbreviations were used: DMF, dimethylformamide; TFA, trifluoroacetic acid; DIEA, diisopropylethylamine.
(19) D. P. Schwartz and M. J. Pallansch, *Anal. Chem.*, **30**, 219 (1958).
(20) T. Ziminski and E. Borowski, *J. Chromatogr.*, **23**, 480 (1966).
(21) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).
(22) M. Bodanszky and V. duVigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).
(23) S. Guttmann, *Helv. Chim. Acta*, **44**, 721 (1961).
(24) M. Bodanszky, M. Kondo, C. Y. Lin, and G. F. Sigler, *J. Org. Chem.*, **39**, 444 (1974).
(25) E. Scoffone, F. Marchiori, A. M. Tamburro, and R. Rocchi, *Gazz. Chim. Ital.*, **94**, 695 (1974).
(26) Prepared according to the general procedure described in *Biochem. Prep.*, **9**, 110 (1962): mp 114–116°; $[\alpha]^{25}D$ +1.4° (c 2, DMF containing 1% AcOH).
(27) W. König and R. Geiger, *Chem. Ber.*, **106**, 3626 (1973).
(28) E. Sandrin and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1637 (1963).
(29) K. Samejima, W. Dairman, and S. Udenfriend, *Anal. Biochem.*, **42**, 222 (1971); K. Samejima, W. Dairman, J. Stone, and S. Udenfriend, *ibid.*, **42**, 237 (1971).
(30) M. Bodanszky, K. W. Funk, and M. L. Fink, *J. Org. Chem.*, **38**, 3565 (1973); cf. also ref 24.

Carbon-13 Nuclear Magnetic Resonance Spectral Analysis of Quassinoid Bitter Principles[1]

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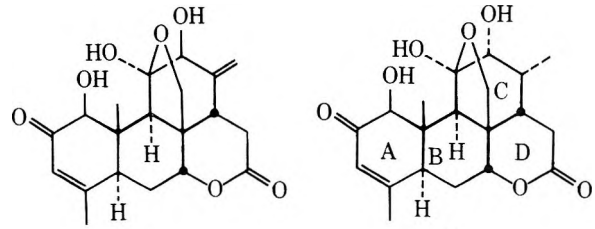
The ^{13}C NMR spectra of several types of quassinoid terpenic substances are presented and all chemical shifts assigned. The data are used for the corroboration of the structure of a new quassinoid principle.

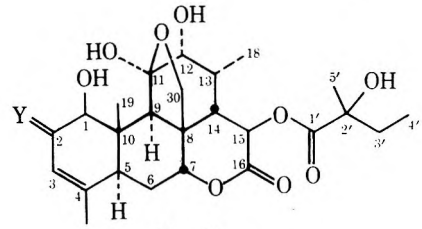
The bitter principles of the plant family Simaroubaceae are a group of structurally complex, highly oxygenated, triterpene degradation products which have attracted attention especially since the advent of ^{1}H NMR spectroscopy.[3] The latter and mass spectroscopy have been the major tools of structure analysis in this field of terpene chemistry in recent times. In view of the diagnostic power of ^{13}C NMR spectroscopy this new analytical method now has been utilized for the analysis of quassinoid compounds of several structure types and the data applied to the confirmation of the structure of a new substance from *Perriera orientalis* Courchet.

The ^{13}C NMR investigation was initiated by an inspection of the proton-decoupled as well as single-frequency, off-resonance decoupled spectra of ailanthone (**1**), chaparrinone (**2**), and glaucarubinone (**3a**), three compounds differing from each other only in rings C and D.

The chemical shifts of the carbonyl carbons of **1**, **2**, and **3a** are deduced from known ^{13}C NMR parameters of 2-cyclohexenones, δ-lactones, and branched esters.[1,4,5] Similarly, the olefinic carbon shifts are derived from those of 2-cyclohexenone and methylenecyclohexane models. The methyl shifts of the three compounds are based on the differentiation of the 4- and 10-methyl groups of **1** by the use of 1-methylcyclohexene as a model, and 13-methyl group of **2** being recognized by default and the two methyl groups of the side chain of **3a** differing from each other by their being the equivalent of neopentyl and homoneopentyl carbons. The 2.3-ppm difference of the chemical shift of C(18) in **2** vs. **3a** is a reflection of the δ effect[6] exerted by the interaction of the peri C(13) and C(15) substituents. As a comparison of the high-field C(19) shifts of compounds **1**–**3** with



1 **2**



3a, Y = O
b, Y = α-OH, β-H

those of substances possessing an 8β-methyl group instead of the oxymethylene bridge (vide infra) indicates, shielding of up to 2 ppm is due to the heterocycle spanning C(8) and C(11).

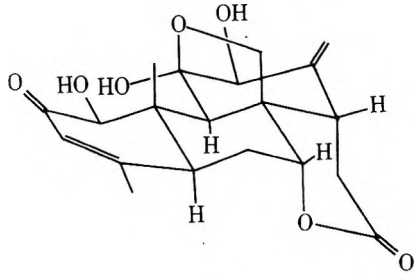
The methylene shifts of ailanthone (**1**) and chaparrinone (**2**) are distinguished easily from each other in view of one being associated with an expectedly low-field oxymethylene, another with a ketomethylene and, finally, one with an unsubstituted, upfield methylene function. In accord with conformations **4** and **5** for ailanthone and chaparrinone, respectively, one of the ketomethylene hydrogens, H(15β), experiences a peri interaction with C(18) in the lat-

Table I
Carbon Chemical Shifts[a]

	1	2	3a	3b
C(1)	82.5	82.5	82.6	82.6
C(2)	197.2	197.1	196.8	71.3
C(3)	125.0	124.7	124.8	125.7
C(4)	162.5	162.3	162.5	133.8
C(5)	43.3	43.1	43.9	40.1
C(6)	25.1	25.0	24.7	24.9
C(7)	77.7	77.6[b]	77.4	77.9
C(8)	44.5	44.9[c]	46.8	46.7
C(9)	46.1	41.1	41.1	40.9
C(10)	44.5	44.3[c]	44.5	44.1[d]
C(11)	108.9	108.9	108.9	109.1
C(12)	79.1	77.9[b]	78.4	78.5
C(13)	146.6	30.4	31.4	31.4
C(14)	41.1	41.1	44.5	44.6[d]
C(15)	34.3	29.4	69.8	69.5
C(16)	169.1	167.6	166.8	167.1
C(18)	119.7	12.5	14.8	14.8
C(19)	9.5	9.4	9.9	10.1
C(30)	71.2	70.1	70.0	70.1
4-Me	22.2	22.1	22.1	20.9
C(1′)			174.4	174.4
C(2′)			73.9	73.9
C(3′)			32.5	32.6
C(4′)			7.6	7.7
C(5′)			24.7	24.9

[a] The δ values are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [b-d] Signals within any vertical column may be reversed.

ter but not in the former. This phenomenon is reflected by a difference of 4.9 ppm of the C(15) shifts, chaparrinone (**5**)



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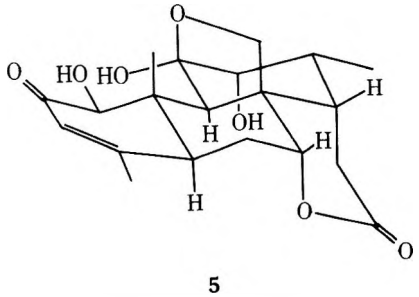
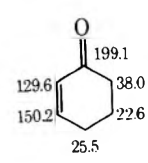


5

being more shielded. The ketomethylene signal is replaced in glaucarubinone (**3a**) by one for its side chain methylene group.

Differentiation of the oxymethines of compounds **1**, **2**, and **3a** is founded on the C(1) and C(7) shifts being constant and C(1) being deshielded by its α-keto group. The assignment of the C(1) shift and its distinction from the C(7) shift is confirmed by the C(1) shift perturbation on acetylation (vide infra). The extra oxymethine signal of **3a** is that of C(15). The designation of the nonoxygenated methine shifts is more difficult. The appearance of an extra methine signal in the spectra of **2** and **3a** in comparison with the spectrum of **1** reveals the C(13) resonance in the former. Since the change of stereochemistry of the 12-hydroxy group from **1** to **2** or **3a** imposes a 1,3-diaxial interaction and hence a γ effect of up to 7 ppm on C(9) in the latter two substances, only the 46.1-ppm shift can be assigned to C(9) of **1** and the 41.1-ppm shift to the same carbon of **2** and **3a**. Furthermore, since C(5) is least affected by the ring C changes, the constant 43–44-ppm shift can be related to it. This leaves the C(14) shift by default. Its identity in **1** and **2** is in conformity with the known minimal difference of the shift of a cyclohexyl methine vicinal to an exo methylene vs. equatorial methyl group[7] and the lower field position of C(14) in **3a** as contrasted to **2** is related to the added β and γ effects of the C(15) substituent of the former. Among the nonprotonated, saturated sites of the three substances the oxy carbon of the side chain of **3a** is unique. Dioxygenated C(11) shows a constant downfield signal. Carbon 10 exhibits similar shift constancy, leaving C(8) by default. All carbon shifts of ailanthone (**1**), chaparrinone (**2**), and glaucarubinone (**3a**) are listed in Table I.

^{13}C NMR analysis of glaucarubin (**3b**), a simaroubaceous substance differing from the aforementioned glaucarubinone (**3a**) only by the replacement of the 2-keto group by an equatorial hydroxy function, had to be based on solely a proton-decoupled spectrum because of the low sample size. This limitation necessitated, inter alia, differentiation of the trigonal carbons 3 and 4 by line width characteristics, i.e., the C(4) signal being considerably slimmer than the C(3) line in view of the slower relaxation of C(4) and the absence of one-bond, carbon–hydrogen residual coupling in its signal. All carbon shifts of glaucarubin (**3b**) are nearly identical with those of glaucarubinone (**3a**) except those of carbons 2, 3, 4, and 5 and the 4-methyl shift. The difference of the olefinic carbon shifts of the ketone and alcohol are reminiscent of the Δδ values of related carbons of 2-cyclohexenone (**6**)[8] and 2-cyclohexenol (**7**).[9] Carbon 5, whose



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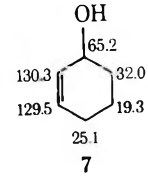

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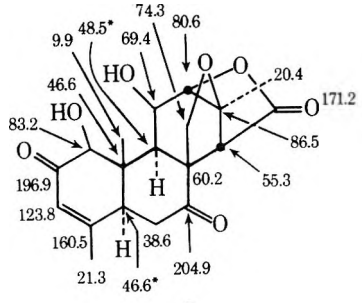
equivalent site in the models is unperturbed, is shielded in the alcohol (**3b**). This shift change affects also the 4-methyl group and may reflect subtle conformational modification of ring A perhaps due to greater ring puckering in the compound of fewer trigonal carbon sites.

Samaderine B (**8**) is a C_{19} quassinoid product whose ring A retains the substitution pattern of compounds **1**, **2**, and **3a**, C(7) has the lactone oxygen terminus replaced by a double-bonded oxygen, and whose remaining skeleton is modified drastically. The ring A identity is reflected in the shift similarity of C(1), C(2), C(3), C(4), and the 4-methyl group. The 10-methyl group is also unaffected, even though the two-atom bridge across ring C now is at a different location. The assignment of the shifts of C(11) and C(12) is based on the shifts of the same oxymethines of the bruceines (vide infra) and the expected deshielding of C(12) when part of a lactone ring. It is worth noting that the C(18) signal is diagnostic for the samaderine B ring system in view of the C(13) attachment of the oxymethylene bridge foisting a β effect upon C(18) and thus strongly deshielding this methyl group. All chemical shifts of samaderine B are denoted on formula **8**.[10]

In contrast to the quassinoid substances described thus



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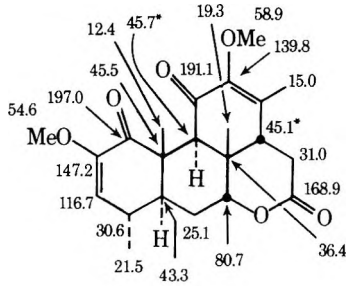

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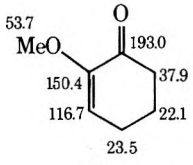
far, quassin (**9**) possesses two 2-methoxy-2-cyclohexenone chromophores. Hence one major task is the differentiation of the trigonal carbon shifts. The lactone carbonyl shift is nearly the same as that of ailanthone (**1**), while the two other carbonyl groups differ from each other and from the carbonyl shift of model **10** by C(1) being deshielded (i.e., a β effect) by the neighboring angular methyl group and C(11) being shielded (i.e., γ effects) by the angular methyl functions. The olefinic oxy carbons, C(2) and C(12), are distinguishable by the former being characterized by the oxy carbon shift of model **10** to which is added a mildly shielding γ effect by C(19) and C(12) experiencing stronger shielding from its vicinal, olefinic methyl group. Carbon 3 is a unique olefinic center and the C(13) signal was obscured. While the shift of the 2-methoxy group is normal, when compared with the methoxy shift of model **10**, the 12-methoxy group is deshielded by ca. 4 ppm, reminiscent of the deshielding effect on the methoxy shift of anisoles by two ortho substituents,[7,11]



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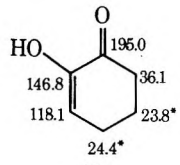

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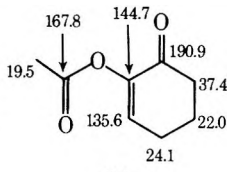
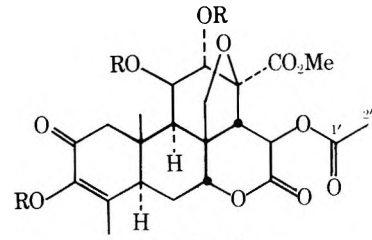


12

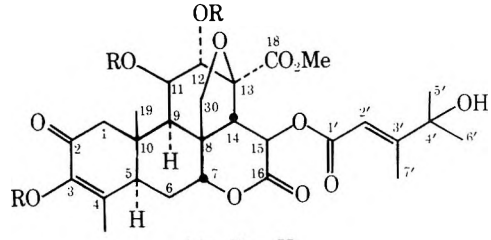
The four *C*-methyl groups of quassin (**9**) can be recognized in the following manner. The 4-methyl unit can be expected to exhibit a shift similar to that of the like carbons in compounds **1–3**. The C(18) shift differs from that of the 4-methyl group by the addition of a strong shielding component due to the neighboring methoxy group. This added shift must be of a magnitude between the ca. 6-ppm difference of the *C*-methyl shifts of toluene and o-cresyl methyl ether and the ca. 9-ppm difference for the 2-methyl group of *o*-xylene and 2,3-dimethylanisole.[4] The added γ effect is predictably closer to the smaller $\Delta\delta$ value, since C(18) experiences less compression from its methoxy neighbor and C(15) in a C/D cis ring system than the methyl group of a 2,6-disubstituted toluene. While no direct evidence can be brought to bear upon the distinction of C(19) and C(30), only a minimal shift change can be expected for C(19) from the δ value of the angular methyl group of compounds **1–3** and 8. Being an olefinic methyl group, C(18) can be differentiated from the other methyl functions by a simple single-frequency, off-resonance decoupling technique. Since the C(18) hydrogens are downfield from those of the remaining methyl groups in the ^1H NMR spectrum, the residual one-bond, carbon–hydrogen coupling of C(18) is distinctly larger than that of the other methyl groups, when the decoupling frequency is placed at the far upfield end of the ^1H NMR spectral range. This simple confirmation of the C(18) shift was applied also to the corroboration of the 4-methyl shifts of compounds **1**, **2**, **3a**, and 8.

The removal of the β effect due to the oxygen bridge on the one-carbon unit attached to C(8) in the previous compounds shields this quaternary carbon in quassin (**9**). The C(5) shift can be selected on the assumption of its invariancy throughout the quassinoid series alongside the constancy of the 4-methyl, C(6), and C(10) shifts and is confirmed by smaller residual coupling in the single frequency off-resonance decoupled (sford) spectrum. The remaining nonoxygenated methine signals of quassin (**9**) consist of one upfield and two nearly identical, downfield peaks. Since the difference between the two allylic methines, C(4) and C(14), lies in the former feeling a γ effect from C(19) and the latter experiencing no such shielding influence but strong deshielding by at least its neighboring methyl groups, C(4) is represented by the upfield signal and C(9) and C(14) by the indistinguishable downfield peaks. All chemical shifts of quassin are delineated on formula **9**.

Brucein B (**13a**) and brucein C (**14a**) are simaroubaceous compounds whose oxymethylene bridge is samaderine-like,



13a, R = H
b, R = Ac



14a, R = H
b, R = Ac

whose ring D is of the glaucarubinone (**3a**) type, and whose C(18) is in the high oxidation state of a carboxylic ester. Their ^{13}C NMR analysis was undertaken with the use of their triacetates, **13b** and **14b**, respectively, and 2-oxy-2-cyclohexenones **11** and **12** acting as models. While brucein B (**13a**) and its triacetate (**13b**) were run in hexadeuteriodimethyl sulfoxide and brucein C (**14a**) and its triacetate (**14b**) in deuteriochloroform solution, respectively, the solvent-induced shift changes were minimal and the sford spectra in both solvents useful for facilitating the interpretation of multiplets under solvent signals. Since the difference between the two bruceins is limited to the C(15) side chain, the ^{13}C NMR analysis of brucein C (**14a**) is a simple extension of the interpretation of the spectra of brucein B (**13a**). All δ values of **13a**, **13b**, **14a**, and **14b** are listed in Table II.

All carbonyl shifts of the bruceins and their acetates are

Table II
Carbon Chemical Shifts

	13a[a]	13b[a]	14a[b]	14b[b,c]
C(1)	48.7	49.9	47.8[i]	49.9
C(2)	192.9	188.6	193.0	188.3
C(3)	144.1	140.7	144.3	141.6
C(4)	128.3	148.3	129.4	146.0
C(5)	39.9[d]	39.5[e]	42.1[j]	42.0[k]
C(6)	28.7	27.6	29.1	28.2
C(7)	82.8	81.4	83.2	82.3
C(8)	44.7	43.9	45.5	44.8
C(9)	40.4[d]	41.4[e]	41.6[j]	40.5[k]
C(10)	40.9	38.4	41.1	40.0
C(11)	71.4	68.2	71.2	69.0
C(12)	74.7	70.9	75.4	71.0
C(13)	81.4	79.0	81.6	79.8
C(14)	48.7	48.8	49.7[i]	51.6
C(15)	67.3	66.4	66.7	65.3
C(16)	167.0	166.5	168.0	168.1
C(18)	169.9	168.8[f]	168.0	168.1
C(19)	15.0	14.8	15.2	15.6
C(30)	72.3	73.1	73.6	73.7
4-Me	13.3	14.0	13.1	14.5
OMe	52.3	52.4	52.7	52.7
C(1′)	168.7	168.6[f]	165.9	164.9
C(2′)	20.4	20.0	111.5	111.0
C(3′)			171.3	166.6[m]
C(4′)			73.6	73.7
C(5′)			27.9	28.2
C(6′)			27.9	28.2
C(7′)			15.2	15.6
3-OAc		167.5, 21.0[h]		167.4, 21.5[l]
11-OAc		168.1,[g] 20.0[h]		168.1, 20.2[l]
12-OAc		168.3,[g] 20.0[h]		168.1, 20.8[l]

[a] The δ values are in parts per million downfield from Me_4Si. In Me_2SO-d_6 solution; $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [b] In $CDCl_3$ solution; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c] Some CD_3OD was added for dissolution of the compound. [d-l] Signals within any vertical column may be reversed. [m] This signal may be interchanged with the signal of one of the acetyl carbonyl groups.

Table III
Carbon Chemical Shifts[a]

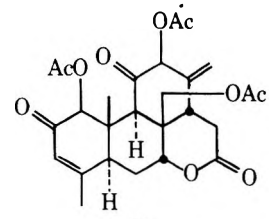
	15	16	17a	17b
C(1)	83.3	83.2	83.2	79.1
C(2)	191.3	191.7	191.2	72.9
C(3)	125.1	124.7	124.7	119.3
C(4)	162.6	162.3	162.3	138.2
C(5)	40.8[b]	40.6	39.2	38.6
C(6)	24.0	24.5	24.1	23.5
C(7)	78.4[c]	76.9	76.5	76.7
C(8)	41.3	43.4	46.7	46.6
C(9)	49.7	46.4	46.4	47.7
C(10)	43.6	43.4	43.7	41.9
C(11)	201.8	204.8	204.6	204.5
C(12)	75.0[c]	81.3	81.8	80.7
C(13)	140.7	33.6[d]	30.4[e]	30.0
C(14)	39.5[b]	34.8[d]	34.1	34.1
C(15)	30.5	27.8	70.1	69.8
C(16)	170.1	170.0	170.5[f]	170.4[f]
C(18)	115.5	12.8	14.6	14.5
C(19)	10.4	11.0	11.5	11.2
C(30)	63.9	60.9	60.5	60.9
4-Me	21.7	21.9	21.8	20.4 ± 0.2[g]
C(1′)			166.2[f]	166.2[f]
C(2′)			80.0	80.0
C(3′)			30.6[e]	30.0
C(4′)			7.0	7.0
C(5′)			20.4 ± 0.2[g]	20.4 ± 0.2[g]

[a] The δ values are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [b-e] Signals within any vertical column may be reversed. [f] Any of these signals may be interchanged with an acetate carbonyl signal. [g] This signal cannot be differentiated from that of an acetate methyl group.

based on comparisons among the four compounds, glaucarubinone (**3a**) and models **11** and **12** and the carbon shifts of the C(15) side chain of **14a** and **14b** rely on calculations from models.[4] As the shift distribution of the enol-one chromophore of **11** and **12** indicates, acetylation of a cyclic α-diketone monoenol shields mildly the olefinic oxy carbon and more strongly the carbonyl group, while exerting a powerful deshielding influence on the nonoxygenated, olefinic site. This phenomenon permits the shift assignment of C(2), C(3), and C(4) in compounds **13** and **14**. The nuclear methyl groups, C(19) and the 4-methyl group, in the bruceins and their acetates are differentiatable by the size of the residual coupling in their sford spectra. Carbon 19 of brucein B (**13a**) is 5.6 ppm downfield of the same carbon of chaparrinone (**2**) in view of the removal of at least a γ effect of the latter's 1-hydroxy group. The 4-methyl group, on the other hand, is shielded by 8.9 ppm when compared with that of chaparrinone (**2**). This influence of the 3-hydroxy function on its neighboring methyl group is reminiscent of and greater than the impact of the 12-methoxy group on its vicinal methyl function in quassin (**9**) (vide supra). The increased size of this shielding effect in brucein B (**13a**) must be due to the greater compression felt by the methyl group from the 3-hydroxy unit and equatorial C(6) (with respect to ring A).

The oxymethines can be characterized as those impervious to acetylation and those experiencing shielding. The former group is composed of C(7) and C(15), whose shifts are similar to those of the same carbons in glaucarubinone (**3a**), while the latter category is made up of C(11) and C(12). The C(11) shift of the bruceins is similar to that of C(11) of samaderine B (**8**), while the C(12) shift can be calculated approximately from the δ value of C(12) in chaparrinone (**2**) by the substitution of an equatorial, oxygen β effect by one of an axial variety. Being under the influence of a large number of β effects and minimal number of γ effects, C(14) can be expected to be downfield of the remaining, undifferentiatable methines, C(5) and C(9). Quaternary centers C(8) and C(10) are shielded relative to glaucarubinone (**3a**), but C(10) more so in view of the lack of a β effect from a 1-hydroxy group.

Acetylation of ailanthone (**1**), chaparrinone (**2**), glaucarubinone (**3a**), and glaucarubin (**3b**) unravels their hemiacetals liberating 11-keto compounds **15**, **16**, **17a**, and **17b**, respectively. Their ^{13}C NMR spectra were analyzed, only



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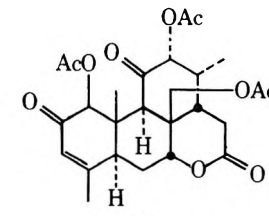

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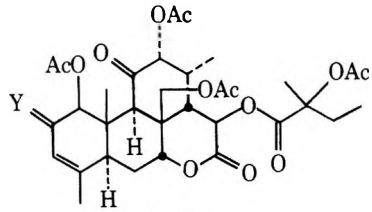
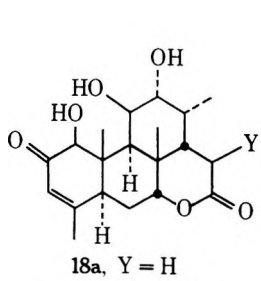
the proton-decoupled spectrum having been inspected in the case of **17a**, and the chemical shifts are listed in Table III. All acetate methyl and carbonyl shifts fall into the range of 20.4 ± 0.2 and 169.4 ± 0.3 ppm, respectively.



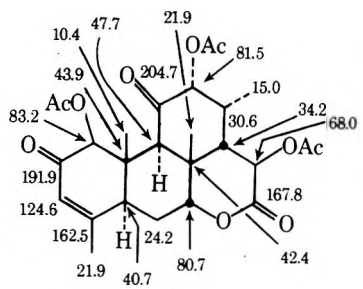
17a, Y = O
b, Y = α-OAc,β-H

Shift assignment of the methyl and methylene groups, olefinic centers, and carbonyl groups, except for the difficult differentiation of C(16) from C(1′), can be made on the basis of all the arguments made thus far. Recognition of the individual quaternary carbon shifts is based on the expectation of the δ values of **15** and **16** reflecting minimal structural change in the C(10) environment and the quaternary carbon shifts of **17a** and **17b** showing the same relationship for C(8). Comparison of the oxymethine shifts of the four compounds reveals the C(7) shift of **16, 17a,** and **17b** to be nearly identical, the C(15) shifts to be associated only with **17a** and **17b** and to be the same as those of the natural products, **3a** and **3b,** respectively, themselves, and the C(2) shift of glaucarubin pentaacetate (**17b**) to be unique. Distinction of the α-keto oxymethines, C(1) and C(12), depends on the expected invariance of the C(1) shift of **15, 16** and **17a** and of the C(12) shift of **16, 17a** and **17b.** The C(7) and C(12) shifts of ailanthone triacetate (**15**) are difficult to distinguish. Among the nonoxygenated methine signals that of the α-ketomethine, i.e., C(9), is recognized readily because of its downfield position and its ca. 3-ppm upfield move on experiencing an added γ effect by the C(12) inversion of an equatorial acetoxy group in **15** to an axial substituent in the other compounds. The next low-field signal is that of C(5), its position being similar to its location in the spectra of the natural products. Finally, a distinction of the C(13) and C(14) shifts is made on the basis of C(14) being expected to undergo a shift change on the introduction of the C(15) side chain into compounds **17a** and **17b.** It is noteworthy that acetylation of glaucarubin (**3b**) produces ring A shift changes previously associated with allyl alcohol to allyl acetate conversions.[12] Thus C(3) and C(4) of glaucarubin pentaacetate (**17b**) are shielded and deshielded strongly, respectively.

Recently there was isolated a new quassinoid substance from the simaroubaceous plant *Perriera orientalis* Courchet whose infrared, ultraviolet, ^{1}H NMR, and mass spectral analyses showed it to be the 15β-hydroxy derivative of klaineanone (**18a**).[3,13] Structure **18b** of the new natural substance was revealed also by comparison of the ^{1}H NMR spectra of its derivative **19** and the 15-deoxy equivalent derived from klaineanone (**18a**).[13] A ^{13}C NMR analysis of



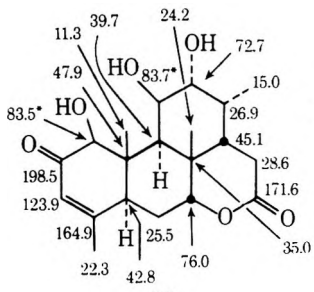
18a, Y = H
b, Y = OH



19

18a, the new quassinoid principle, and compound **19** now was undertaken. While the usual two spectra could be run on 15β-hydroxyklaineanone (**18b**), the investigation was limited solely to proton-decoupled spectra of klaineanone (**18a**) and compound **19** owing to the availability of only small quantities of material.

Comparison of the ^{13}C NMR spectra of **18a** and **18b** reveals all except two signals to be nearly identical. Since the sford spectrum of **18b** exhibits the carbon type of each signal and since the nonidentical signals can be associated with a methine and an oxymethine unit, changes expected for the modification of the C(15) environment, the correlation of the klaineanone (**18a**) signals and its carbon types can be considered established. A spectral comparison of klaineanone (**18a**) with chaparrinone (**2**) shows strong shift alteration, especially in ring C, some of which are readily explicable. Thus C(8) and C(12) of klaineanone (**18a**) are shielded owing to missing β effects, C(14) is deshielded in view of a missing γ effect, the C(13) shift is modified as a consequence of alteration of the groups exerting γ effects, and C(11) and C(30) are shifted dramatically owing to their different substitution pattern. A comparison of the carbon shifts of klaineanone (**18a**) and 15β-hydroxyklaineanone (**18b**) reveals the influence of the new hydroxy group in the form of a 36.8-ppm α effect on C(15) and a 9.8-ppm β effect on C(14). This is in full accord with the previously proposed structure for 15β-hydroxyklaineanone (18b).[3,13] Furthermore, confirmation of the structure is revealed by comparison of the ^{13}C NMR spectra of **19** and glaucarubinone tetraacetate (**17a**). All shifts are nearly the same except those of C(7) and C(30). Both shift changes are due to the removal of the 30-acetoxy group in **19** and suggest a rotamer population preference of this group in **17a** favoring a gauche interaction with H(7). The carbon shifts of the acetyl groups of **19** are within the range cited for **17a** (vide supra). All shifts for compounds **18a, 18b,** and **19** are listed on formulas **20, 21,** and **19,** respectively.[10]



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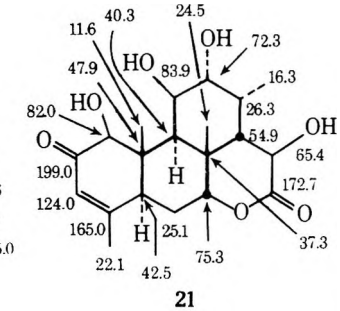

21

In view of the ease of detection of nonprotonated carbon sites in structurally complex organic compounds by application of the noise off-resonance decoupling technique (nord)[14,15] it is possible to obtain directly the C(8) and C(10) shifts and to analyze them in terms of a specific quassinoid structure type. The above shift determinations of the naturally occurring substances reveal three diagnostically distinct shift patterns. All compounds exhibit a signal within the 40–50-ppm range. Those showing the other signal within the same range represent the 7,30-dioxy structure type, those with 5–10-ppm upfield signal the 7-oxy-30-deoxy type, and those with a 10–15-ppm downfield signal the 7-oxo-30-oxy type. In view of there being an oxygen bridge emanating from C(30) in the first and third kinds of natural quassinoid substances, the oxycarbon signal in the nord spectrum differentiates the C(11) from the C(13) terminus of this bridge.

Experimental Section

The carbon shifts denoted on various formulas and in Tables I–III were recorded on a Varian DP-60 spectrometer operating at 15.08 MHz or a Varian XL-100-15 spectrometer functioning at

25.20 MHz. All spectra were obtained with the use of Fourier transform techniques. The δ values portrayed on formulas **8**, **9**, **19**, **20**, and **21** refer to Me_2SO-d_6 solutions, those on formulas **6** and **7** to deuteriochloroform solutions, and those on formulas **10**, **11** and **12** imply chloroform [δ (Me_4Si) = δ($CHCl_3$) + 77.2 ppm] as solvent.

Registry No.—**1**, 981-15-7; **2**, 22611-34-3; **3**, 1259-86-5; **3a**, 1448-23-3; **13a**, 25514-29-8; **13b**, 37746-38-6; **14a**, 25514-30-1; **14b**, 55606-57-0; **15**, 990-35-2; **16**, 990-33-0; **17a**, 55658-68-9; **17b**, 55606-58-1.

References and Notes

(1) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXXI. For Part XXX see S. G. Levine, R. E. Hicks, H. E. Gottlieb, and E. Wenkert, *J. Org. Chem.*, **40**, 2540 (1975).
(2) Address correspondence to Department of Chemistry, Rice University, Houston, Texas 77001.
(3) J. Polonsky, *Prog. Chem. Org. Nat. Prod.*, **30**, 101 (1973).
(4) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(5) The lactone carbonyl carbon and several other sites in the quassinoid skeleta show appreciable shift variability indicative of subtle conformational transmission of the effect of configurational changes through especially rings B, C, and D. Strong bond angle distortions are noted in the X-ray analysis of glaucarubin (**3b**) *p*-bromobenzoate: G. Kartha and D. J. Haas, *J. Am. Chem. Soc.*, **86**, 3630 (1964).
(6) S. H. Grover, J. P. Guthrie, J. B. Stothers, and C. T. Tan, *J. Magn. Reson.*, **10**, 227 (1973).
(7) E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gašić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell and P. M. Wovkulich, in G. C. Levy, "Topics in Carbon-13 NMR Spectroscopy", Vol. II, Wiley, New York, N.Y., in press.
(8) Cited in ref 1.
(9) F. Fringuelli, H. E. Gottlieb, E. W. Hagaman, A. Taticchi, E. Wenkert, and P. M. Wovkulich, *Gazz. Chim. Ital.*, in press.
(10) The starred numbers indicate possible shift reversal.
(11) K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **44**, 2855 (1966).
(12) G. Lukacs, F. Piriou, S. D. Gero, D. A. van Dorp, E. W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, 515 (1973); N. J. Bach, H. E. Boaz, E. C. Kornfeld, C.-J. Chang, H. G. Floss, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, **39**, 1272 (1974); E. Wenkert, M. J. Gašić, E. W. Hagaman, and L. D. Kwart, *Org. Magn. Reson.*, **7**, 51 (1975).
(13) J. Polonsky, Z. Baskévitch-Varon, and M. Debray, *C. R. Acad. Sci., Ser. C*, **280**, 1149 (1975).
(14) E. Wenkert, A. O. Clouse, D. W. Cochran, and D. Doddrell, *J. Am. Chem. Soc.*, **91**, 6879 (1969).
(15) This technique is one of various possible methods of generating low-power noise modulation over the ^1H NMR spectral range. As a consequence it is not surprising that several experimental variations to achieve the goal initially described in ref 14 have been published recently: E. W. Randall, *Chem. Br.*, **7**, 371 (1971); I. H. Sadler, *J. Chem. Soc., Chem. Commun.*, 809 (1973).

Equilibrium in the Behrend Rearrangement of Nitrones

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A group of α-phenyl-*N*-benzylnitrones bearing one of the substituents nitro (*o*-, *m*-, or *p*-), chloro (*o*- or *p*-), methyl (*p*-), methoxy (*o*-, *m*-, *p*-), as well as the *p*-methoxy-*p*-nitro derivative and α,α-diphenyl-*N*-benzylnitrone, were made to undergo Behrend rearrangement to the isomeric nitrone resulting from 1,3-prototropic shift by treatment with sodium methoxide in refluxing ethanol. It was demonstrated that an equilibrium mixture was obtained in each case by approaching the equilibrium from either side. Equilibrium compositions were determined by NMR spectroscopy. All para substituents favored the isomer with substituent on the α-phenyl group. *m*-Methoxy as a substituent was almost without effect on the equilibrium, and a *m*-nitro group slightly favored the isomer with the substituent on the *N*-benzyl group. The ortho substituents strongly favored the isomer with the substituent on the *N*-benzyl group, presumably for steric reasons. α-Phenyl-*N*-benzhydrylnitrone was favored over its isomer, α,α-diphenyl-*N*-benzylnitrone (K = 0.57). The results with the para substituents are consistent with an electronically amphoteric capability of the nitrone group for conjugation.

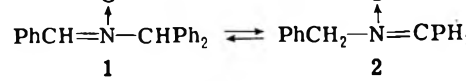
Isomerization of nitrones by a 1,3-prototropic shift has been called the Behrend rearrangement after its discoverer[2] (eq 1). The closely related isomerization of imines has

$$RCH_2\overset{O}{\overset{\uparrow}{N}}{=}CHR' \longrightarrow RCH{=}\overset{O}{\overset{\uparrow}{N}}{-}CH_2R' \qquad (1)$$

been extensively studied, owing to its importance in biological transamination,[3] but the Behrend rearrangement has received only casual attention.

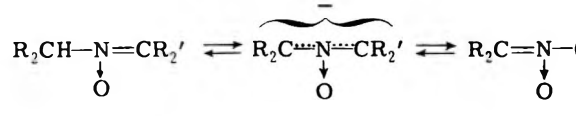
The initial work on the Behrend rearrangement was essentially qualitative,[2,4-6] directed mainly to the question of whether or not a given nitrone would rearrange. Neubauer[4] investigated a number of substituted α-phenyl-*N*-benzylnitrones, examining the products by fractional crystallization. According to his work and that of Behrend, two such systems (*p*-chloro and *p*-nitro) underwent the 1,3-prototropic shift reversibly, one of them (α-*m*-nitrophenyl) underwent irreversible rearrangement, and many (*p*-methoxy, *p*-hydroxy, o-hydroxy, *o*-chloro, *o*-nitro) were inert to attempted rearrangement catalyzed by alcoholic sodium ethoxide. The confusing inconsistency of the observations was noted much later by Lamchen.[7]

The Behrend rearrangement may occur during the preparation or isolation of nitrones, as first noticed by Behrend and König.[2] Cope and Haven prepared[8] α,α-diphenyl-*N*-benzylnitrone (**2**) successfully from benzophenone imine and *N*-benzylhydroxylamine hydrochloride when they used ammonia as the base, but use of sodium ethoxide brought about isomerization to α-phenyl-*N*-benzhydrylnitrone (**1**).



$$\underset{\mathbf{1}}{PhCH{=}\overset{O}{\overset{\uparrow}{N}}{-}CHPh_2} \rightleftharpoons \underset{\mathbf{2}}{PhCH_2{-}\overset{O}{\overset{\uparrow}{N}}{=}CPH_2} \qquad (2)$$

Smith and Robertson[9] encountered rearrangement of certain nitrones during a study of the site of alkylation of oxime anions. The collected reports point to catalysis by strong base, an unelucidated dependence of both the ease and direction of rearrangement on structure, and a susceptibility to rearrangement equal to or greater than that of imines. The mechanism is presumed to involve abstraction of a proton to form a delocalized carbanion (eq 3).[7,9]



$$R_2CH{-}\overset{O}{\overset{\downarrow}{N}}{=}CR_2' \rightleftharpoons R_2C{\cdots}\overset{O}{\overset{\downarrow}{N}}{\cdots}CR_2' \rightleftharpoons R_2C{=}\overset{O}{\overset{\downarrow}{N}}{-}CHR_2' \qquad (3)$$

Table I

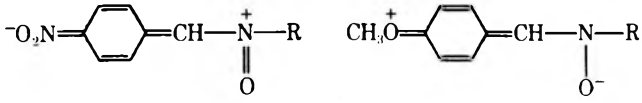
α-Phenyl-N-benzylnitrones

$R-C_6H_4CH_2-\overset{O}{\overset{\uparrow}{N}}=CHC_6H_4-R'$

Nitrone	R	R'	Yield, %	Mp, °C	Ir, cm^{-1} N→O	Ir, cm^{-1} C=N	NMR, ppm N=CH	NMR, ppm NCH_2
5a	p-NO_2	H	71	112–113[a]	1150	1615, 1605, 1590	(~7.5)[b]	5.06
5b	p-Cl	H	86	124–125[c]	1175	1595	(~7.3)[b]	4.91
5c	p-CH_3	H	92	82–83	1160	1580	(~7.3)[b]	4.94
5d	p-CH_3O	H	99	108–109	1150	1615	(~7.3)[b]	4.92
5e	o-NO_2	H	58	104.5–105.5[d]	1140	1615, 1580	>7.1[b]	5.4
5f	o-Cl	H	96.5	73.5–75[e]	1150	1600, 1590	>7.1[b]	5.11
5g	o-CH_3O	H	30	90–92	1145	1605, 1595, 1580	>6.8[b]	5.10
5h	m-NO_2	H	62	116–117[f]		1590	>7.3[b]	5.15
5i	m-CH_3O	H	58	95.5–97	1150	1590	>6.8[b]	5.0
5j	p-CH_3O	p-NO_2	77.5	140–141	1160	1615, 1605	>7.35[b]	5.05
6a	H	p-NO_2	75.5	118–119[g]	1155	1600	7.44	4.97
6b	H	p-Cl	93	121–122[h]	1150	1585	(~7.3)[b]	4.93
6c	H	p-CH_3	90	117–118[i]	1150	1595	(~7.3)[b]	4.92
6d	H	p-CH_3O	89	108–109[j]	1150	1605	(~7.4)[b]	4.94
6e	H	o-NO_2	79	127–128[k]	1175	1615, 1695, 1585	>7.1[b]	5.01
6f	H	o-Cl	81.5	87.5–88.5[l]	1155	1575	>7.1[b]	5.01
6g	H	o-CH_3O	69	83.5–85	1160	1600	>6.7[b]	4.98
6h	H	m-NO_2	89.5	149–150[m]	1160	1590	>7.25[b]	5.08
6i	H	m-CH_3O	70	76–77	1155	1600, 1585	>6.8[b]	5.02
6j	p-NO_2	p-CH_3O	45.5	151.5–152.5		1610, 1585	>7.3[b]	5.11

[a] Lit. mp 113.5–114.5°: R. Behrend and E. König, *Ber.*, **23**, 2751 (1890). [b] Signal incorporated in phenyl multiplet. [c] Lit.[4] mp 125–126°. [d] Lit. mp 104–105°: C. Kjellin and K. G. Kuzlenstjena, *Ber.*, **30**, 1898 (1897). [e] Lit. mp 75–77°: F. Wegener, *Justus Liebigs Ann. Chem.*, **314**, 235 (1900). [f] Lit.[2] mp 114–115°. [g] Lit.[14] mp 118°. [h] Lit.[4] mp 121°. [i] Lit. mp 119°: P. Grammaticakis, *C. R. Acad. Sci.*, **224**, 1568 (1947). [j] Lit. mp 109°: E. Beckmann, *Ber.*, **23**, 1690 (1890). [k] Lit. mp 124°: E. Beckmann, *Justus Liebigs Ann. Chem.*, **367**, 273 (1909). [l] Lit.[4] mp 86°. [m] Lit. mp 148–150°: H. Goldschmidt, *Ber.*, **23**, 2174 (1890).

The present study was undertaken in order to obtain systematic data on the Behrend rearrangement. Apart from the lack of consistency of the previous reports with expectations based on accepted effects of substituents,[7] there is also the interesting aspect that the nitrone function should be electronically amphoteric in its interaction with attached aryl groups (cf. structures **3** and **4**). We also wished

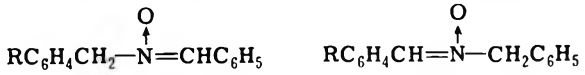


3 **4**

to have information on the position of equilibrium of pairs of nitrones for interpreting the results of oxidation of the corresponding hydroxylamines, which would form the same pairs of isomeric nitrones.[10]

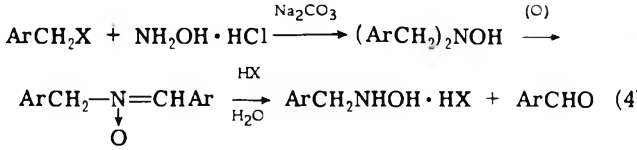
Results and Discussion

This study required a series of α-phenyl-*N*-benzylnitrones (*N*-benzylbenzaldimine *N*-oxides) of unambiguous structures (**5** and **6**). These were prepared by condensation



5 **6**

of benzaldehydes with *N*-benzylhydroxylamines without added base, under which conditions it could be demonstrated spectroscopically that rearrangement did not occur. The required *N*-benzylhydroxylamines were obtained in either of two ways: benzaldoximes were reduced with diborane, or *N,N*-dibenzylhydroxylamines (obtained from benzyl halides and hydroxylamines) were oxidized to the corresponding nitrone and then hydrolyzed (eq 4). The nitrones



$$ArCH_2X + NH_2OH \cdot HCl \xrightarrow{Na_2CO_3} (ArCH_2)_2NOH \xrightarrow{(O)} ArCH_2\underset{\underset{O}{\downarrow}}{N}=CHAr \xrightarrow[H_2O]{HX} ArCH_2NHOH \cdot HX + ArCHO \quad (4)$$

prepared are listed in Table I. α-Phenyl-*N*-benzhydrylnitrone and α,α-diphenyl-*N*-benzylnitrone were prepared as reported by Cope and Haven.[9] Their infrared spectra showed one or more bands in the 1580–1615-cm^{-1} region, attributable to N → O stretching. The NMR signals of the benzylic hydrogens appeared in the range δ 4.91–5.40; the "aldehydic", N=CH signals fell in among the phenyl multiplets, in the region δ 6.8–7.8 ppm, and could not be unambiguously identified. The nitrones were presumed to have been obtained in the configurations with the phenyl and benzyl groups trans, which would be the more stable for steric reasons; in general, this assumption was supported by their spectra (the benzylic methylene group always showed a sharp NMR singlet, which was not altered by subjection to equilibrating conditions). The signals for ortho hydrogens of the α-phenyl groups appeared about 0.8 ppm downfield of the other hydrogens (generally about δ 8.0–8.2).

The composition of the mixtures of isomeric nitrones obtained by the Behrend rearrangement was determined by NMR. The signals of the benzylic protons of the pairs of isomers **1–2**, **5a–6a** through **5h–6h**, and **5j–6j** were sufficiently differentiated to allow independent integration. For **5i–6i** mixtures, in which the benzylic proton signals were not clearly resolved, it was necessary to compare the strength of the total benzylic signal with that of the ortho protons furthest downfield, making use of the fact that **5i** has two ortho protons in the region δ 8.15–8.3 ppm, where-

Table II
Equilibrium Values

$RC_6H_4CH_2NCHC_6H_4R' \rightleftharpoons RC_6H_4CH{=}NCH_2C_6H_4R'$
(5 = O-substituted, 6 = O-substituted)

Substituents R	Substituents R′	Start	6, %	K, 5/6	Time, hr
p-NO_2	H	5a	54.9	0.82	1
			53.3	0.88	2
		6a	49.7	1.01	1
			50.5	0.98	3
p-Cl	H	5b	62.8	0.59	1
			63.3	0.58	6
		6b	62.2	0.61	1
			59.3	0.69	5
p-CH_3	H	5c	60.2	0.66	1
			61.9	0.62	3
		6c	61.4	0.63	1
			63.4	0.58	3
p-CH_3O	H	5d	75.3	0.33	2
			74.8	0.34	3
		6d	75.3	0.33	2
			74.5	0.34	5
o-NO_2	H	6e	8.2	11.2	3
			10.0	9.0	25
o-Cl	H	5f	19.3	4.18	1
			18.5	4.41	3
		6f	17.6	4.68	1
			18.5	4.41	3
o-CH_3O	H	5g	30.7	2.25	5
			32.8	2.04	7.5
		6g	33.6	1.98	1.5
			33.5	1.99	3
m-NO_2	H	5h	46.4	1.16	1
			46.9	1.13	3
		6h	44.8	1.23	1
			44.7	1.24	3
m-CH_3O	H	5i	53.8	0.86	3
		6i	51.5	0.94	1
			49.5	1.01	3
p-CH_3O	p-NO_2	5j	72.8	0.36	1
			72.3	0.37	3
		6j	75.0	0.33	1
			72.1	0.39	3

as 6i has only one (the proton that is ortho to both the methoxy group and the azomethine group has its signal at higher field). For every pair of isomers, the reliability of the method was tested on mixtures of known composition. The percentage of each isomer in the known mixtures differed among separate determinations in most instances by less than one percent unit. Duplicate determinations were made for all unknown mixtures, and in many cases, duplicate experiments were performed.

The analytical spectra were taken in deuteriochloroform solution. We found that unanticipated signals sometimes appeared as a result of disproportionation of the nitrones (eq 5), apparently catalyzed by traces of HCl in the solvent.

$$2RC_6H_4CH{=}N(O){-}CH_2C_6H_4R' \rightleftharpoons RC_6H_4CH{=}N(O){-}CH_2C_6H_4R + R'C_6H_4{=}N(O){-}CH_2C_6H_4R' \quad (5)$$

The addition of a small amount of triethylamine to the solvent before preparing the solutions for analysis completely suppressed disproportionation, even after standing for 24 hr. In untreated deuteriochloroform, mixtures of **5d** and **6d** rapidly developed four distinct peaks in the benzylic proton region, and solutions of Va and VIa developed three benzylic peaks and formed a precipitate of α-p-nitrophenyl-N-p-nitrobenzylnitrone.

Behrend rearrangement was brought about by means of sodium methoxide in refluxing ethanol. In every case, equilibrium was reached within 1 hr; determinations made after 3 hr did not differ significantly from the earlier ones. For every isomeric pair, equilibrium was approached from each side. Use of triethylamine in place of sodium methoxide did not bring about rearrangement. The results are recorded in Table II.

For one pair of nitrones only, equilibrium was not unambiguously achieved. The pair with o-nitro groups (**5e–6e**) formed a precipitate of a sodium salt when treated with alcoholic sodium methoxide; it was identical (spectrum and melting point) regardless of the isomer used. When a molar amount of the base was used instead of the usual catalytic amount, a ca. 60% yield of this product was isolated. The infrared band at 1355 cm^{-1}, characteristic of the nitro group, was absent. Acidification, even when carried out cautiously, produced only an intractable tar. Analysis for sodium gave variable results, but was qualitatively consistent with a monosodium salt; it seems most likely that a benzylic proton was lost, with the formation of a nitronate salt or a heterocyclic system. This substance was not further investigated.

Our results eliminate the inconsistencies in previous reports[2,4,7] and show that a straightforward thermodynamic equilibrium is reached with only a catalytic amount of strong base. Earlier reports that certain of the nitrones included in Table II did not rearrange must have resulted from inability to detect the minor isomer. The conditions required to bring about equilibration were similar to those that have been used for isomerization of the corresponding imines catalyzed by simple bases, although the time required may have been somewhat less.

All para substituents studied favored formation of the para-substituted benzylidene derivative (**6**), although the effect of the p-nitro group was very small. Such a situation may be explained if electron-donating substituents favor this isomer by combined inductive and mesomeric effects, but the effect of electron-withdrawing substituents is more than counterbalanced by enhanced conjugation, as in **3**. This interpretation is supported by the facts that a m-nitro group, in contrast, disfavors the substituted benzylidene isomer, and that the effect of a methoxy group drops sharply in going from the para to the meta position. The two ortho substituents for which results were obtained, chloro and methoxy, both strongly disfavored the substituted benzylidene isomer; presumably this fact is a result of steric interference by the ortho substituent with conjugation.

The system **1–2** had an equilibrium constant of 0.57, consistent with the report of Cope and Haven[8] that **2** easily isomerized to **1** in the presence of strong base. The fact that the α-monophenyl isomer is more stable than the α,α-diphenyl isomer is presumably a steric phenomenon.

Experimental Section

Infrared spectra were determined as Nujol mulls on a Perkin-Elmer Model 237B instrument, and NMR spectra were determined in deuteriochloroform solution with tetramethylsilane as internal reference, on a Varian A-60 instrument, unless otherwise indicated. Melting points are uncorrected. Elemental analyses were made by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Hydroxylamines. Benzylhydroxylamine was prepared from benzyl chloride according to the method of Sneed and Jones,[11] in which *N,N*-dibenzylhydroxylamine is first prepared by reaction with hydroxylamine, and is then oxidized to a nitrone by mercuric oxide and then hydrolyzed. *o*-Nitrobenzylhydroxylamine,[12] *o*-chlorobenzylhydroxylamine,[13] *m*-nitrobenzylhydroxylamine,[2] *m*-methoxybenzylhydroxylamine, and *p*-nitrobenzylhydroxylamine[14] were prepared analogously. *N,N*-Bis(*m*-Methoxybenzyl)hydroxylamine was obtained in 72.5% yield by refluxing a solution of 16.0 g (80 mmol) of *m*-methoxybenzyl bromide, 2.73 g (40 mmol) of hydroxylamine hydrochloride, and 13.3 g (120 mmol) of sodium carbonate in a mixture of 125 ml of 90% ethanol and 50 ml of water for 4 hr, and diluting the cooled reaction mixture with 300 ml of water to induce crystallization; mp 86–88° after recrystallization from cyclohexane; ir 3100–3350 (OH), 3040, 1605, 1600, 1590, 1260, 1170, 1040, 785, 745, and 695 cm^{-1}; NMR δ 3.67 and 3.74 (singlets, total 10 H, CH_3O and CH_2) and 6.64–7.35 ppm (m, 9 H, aryl CH plus OH).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.49; H, 7.04; N, 5.03.

Oxidation with mercuric oxide produced an oil that could not be crystallized or distilled; its NMR spectrum, δ 3.78 (s, 6 H, CH_3O), 5.0 (s, 2 H, CH_2), 6.77–7.62 (m, 8 H, aryl CH plus N=CH), and 8.15–8.25 (m, 1 H, 6-H of α-*m*-methoxyphenyl), was consistent with the expected α-*m*-methoxyphenyl-*N*-*m*-methoxybenzylnitrone. Hydrolysis of the foregoing oil by steam distillation from 10 g of concentrated hydrochloric acid to remove the *m*-anisaldehyde formed, followed by basification of the residual solution with excess sodium carbonate solution and extraction with ether, drying ($MgSO_4$), and concentrating, produced *m*-methoxybenzylhydroxylamine as an oil which resisted attempts at crystallization. The entire amount was allowed to stand for 12 hr at ambient temperature with 0.715 g (6.75 mmol) of benzaldehyde in a small amount of ethanol. Concentration of the mixture gave 0.94 g (39%) of α-phenyl-*N*-*m*-methoxybenzylnitrone: mp 95.5–97°; ir 3040, 1590, 1485, 1295, 1260, 1150, 1045, 950, 875, 765, 755, and 695 cm^{-1}; NMR δ 3.77 (s, 3 H, CH_3O), 5.0 (s, 2 H, CH_2), 6.8–7.7 (m, 8 H, aryl CH plus N=CH), and 8.15–8.3 ppm (m, 2 H, *o*-H of α-phenyl).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.53; H, 6.30; N, 5.65.

Bis(*m*-nitrobenzyl)hydroxylamine, required for preparing previously known *m*-nitrobenzylhydroxylamine,[2] was prepared in 38% yield from *m*-nitrobenzyl bromide in a manner analogous to that used for bis(*m*-methoxybenzyl)hydroxylamine. It had mp 106–108°; NMR δ 4.0 (s, 4 H, CH_2) and 7.3–8.34 ppm (m, 9 H).

Anal. Calcd for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32. Found: C, 55.62; H, 4.40.

p-Nitrobenzylhydroxylamine[14] (35% yield), *p*-chlorobenzylhydroxylamine[4] (29% yield), *p*-methylbenzylhydroxylamine (23% yield), *p*-methoxybenzylhydroxylamine[15] (24% yield), and *o*-methoxybenzylhydroxylamine[16] (38% yield) were prepared by reduction of the corresponding benzaldoxines with diborane in tetrahydrofuran by the method of Feuer, Vincent, and Bartlett.[17] In several instances, a substantial amount of the corresponding benzylamine was also formed; it could be removed by preferential precipitation as the hydrochloride when dry HCl was passed into an ethereal solution of the reduction products, providing that the resulting mixture was filtered forthwith.

Nitrones. The required unsymmetrically substituted nitrones were prepared by dissolving equimolar amounts of a hydroxylamine and an aldehyde in a minimal volume of ethanol and allowing the mixture to stand at ambient temperature for about 12 hr. The precipitated products were then recrystallized from benzene or ethanol. The data are collected in Table I. Nitrones **1** and **2** were prepared as described by Cope and Haven.[8]

Isomerization of Nitrones. The instance of α-phenyl-*N*-*o*-chlorobenzylnitrone (**5f**) provides a representative example. To a solution of 0.3 g (1.22 mmol) of **5f** in 5 ml of absolute ethanol was added 2 drops of a stock solution prepared from 0.64 g (11.8 mmol) of sodium methoxide and 2 g of ethanol. The resulting solution was heated at reflux, and samples were removed after 1 and 3 hr. Each sample was evaporated to dryness in a stream of nitrogen. and the residue was dissolved in 50 ml of ether and washed with water. The ethereal solution was dried ($MgSO_4$), filtered, and then evaporated to dryness under aspirator vacuum; the residue was dissolved in deuteriochloroform to which sufficient triethylamine had been added to give a basic reaction, and the solution was examined by NMR spectroscopy. Comparison of the integrated intensities of the signals of the methylene groups of **5f** and its isomer **6f** gave the following values for the percent of **6f**: after 1 hr, 17.7 and 17.5; after 3 hr, 20.5 and 20.0. In a second experiment, the values were: after 1 hr, 16.4 and 18.7; after 3 hr, 16.7 and 16.9. The average of all values was 18.05% **6f** and 81.95% **5f**, corresponding to an equilibrium constant **5f**/**6f** of 4.54.

The averaged equilibrium data obtained from each of the nitrones are listed in Table II. Agreement of values within each series was similar to the example of **6f**, and in most cases better (the outside limit for variation of determined composition was 3.9 percent units), and not significantly different from the variation of determined compositions of known mixtures.

Reliability of the determinations was established by making up mixtures of pairs of nitrones of known composition by weight, and performing duplicate NMR analyses on them. For each pair, a known composition approximating the equilibrium composition was used; for several pairs, a range of different known compositions was used. The system **5f**–**6f** provides a representative example: mixture 1 (33.4% **5f**, 66.6% **6f**), found 33.0:67.0; mixture 2 (67.2% **5f**, 32.8% **6f**), found 66.6:33.4, 67.6:32.4.

Attempted Equilibration of the o-Nitro System (5f–6f). Treatment of α-phenyl-*N*-*o*-nitrobenzylnitrone (**5e**) in the normal manner resulted in formation of a small precipitate, which was collected after 3 hr of refluxing: ir 3150–3600, 3130, 3060, 1625, 1520, 1505, 1290, 1215, 1175, 1100, 770, 750, 740, 725, and 685 cm^{-1}. The filtrate was examined in the customary manner, and gave no evidence of rearrangement, even after the reaction mixture had been refluxed for 6 hr. Similar treatment of the isomer, **6e**, produced a precipitate with superimposable ir spectrum. Spectroscopic examination of the filtrate after 1 hr of refluxing showed no rearrangement. After 3 hr of refluxing, the following ratios of **5e**:**6e** were found: 6.8:93.2; 8.8:91.2; 9.0:91.0. After 25 hr of refluxing, ratios of 9.95:90.05 and 10.0:90.0 were obtained.

A solution of 1.024 g of **5e** and 0.208 g of sodium methoxide in 12 ml of absolute ethanol was refluxed for 15 min and then filtered while hot. The precipitate was washed with ether and dried: wt 0.70 g; mp 267° dec. It was insoluble in chloroform or ether, but dissolved in water with gas evolution. Contact with concentrated H_2SO_4 caused an explosion with a flash of fire. Extraction of a water solution of the salt with ether produced nothing; addition of tribenzylammonium bromide, in an attempt to liberate any weak acid from its salt, likewise produced nothing extractable. Acidification with sulfuric acid, however, allowed a yellow substance to be extracted into ether, but concentration of the dried ether solution produced only a dark tar with inconclusive ir and NMR spectra.

The initial precipitate had an ir spectrum superimposable on those of previous samples, but it could not be purified. Analysis for sodium by repeated evaporation to dryness with sulfuric acid produced residues of sodium sulfate that corresponded to values for sodium content of 4.0–11.0% among different preparations (calcd for a monosodium salt $C_{14}H_{11}N_2O_3Na$, 8.3%). The material was not further investigated.

Registry No.—**5a,** 22661-28-5; **5b,** 55606-33-2; **5c,** 55606-34-3; **5d,** 55606-35-4; **5e,** 22661-27-4; **5f,** 55606-36-5; **5g,** 55606-37-6; **5h,** 55606-38-7; **5i,** 55606-39-8; **5j,** 55606-40-1; **6a,** 22661-23-0; **6b,** 22687-09-8; **6c,** 55606-41-2; **6d,** 32114-41-3; **6e,** 22661-22-9; **6f,** 22687-07-6; **6g,** 55606-42-3; **6h,** 5367-21-5; **6i,** 55606-43-4; **6j,** 55606-44-5; *p*-nitrobenzylhydroxylamine, 2912-97-2; *p*-chlorobenzylhydroxylamine, 51307-68-7; *p*-methylbenzylhydroxylamine, 16814-17-8; *p*-methoxylbenzylhydroxylamine, 51307-59-6; *o*-nitrobenzylhydroxylamine, 37558-77-3; *o*-chlorobenzylhydroxylamine, 55606-45-6; *o*-methoxybenzylhydroxylamine, 55606-46-7; *m*-nitrobenzylhydroxylamine, 55606-47-8; *m*-methoxybenzylhydroxylamine, 55606-48-9; benzylhydroxylamine, 622-30-0; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-nitrobenzaldehyde, 555-16-8; *p*-chlorobenzaldehyde, 104-88-1; *p*-methylbenzaldehyde, 104-87-0; *m*-methoxybenzaldehyde, 591-31-1; *o*-nitrobenzaldehyde, 552-89-6; *o*-chlorobenzaldehyde, 89-98-5; *o*-methylbenzaldehyde, 135-02-4; *m*-nitrobenzaldehyde, 99-61-6; bis-(*m*-nitrobenzyl)hydroxylamine, 55606-49-0; *m*-nitrobenzyl bromide, 3958-57-4; *N,N*-bis-(*m*-methoxybenzyl)hydroxylamine, 55606-50-3; *m*-methoxybenzyl bromide, 874-98-6; α-*m*-methoxyphenyl-*N*-*m*-methoxybenzylnitrone, 55606-51-4.

References and Notes

(1) From the doctoral dissertation of Stewart E. Gloyer.
(2) R. Behrend and E. König, *Justus Liebigs Ann. Chem.*, **263**, 355 (1891); R. Behrend, *ibid.*, **265**, 238 (1891).
(3) C. W. Shoppee, *J. Chem. Soc.*, 696 (1932); P. Ossorio and E. D. Hughes, *ibid.*, 426 (1952); T. C. Bruice and R. M. Topping, *J. Am. Chem. Soc.*, **83**, 3480 (1963); D. J. Cram and R. D. Guthrie, *ibid.*, **87**, 397 (1965).

(4) C. Neubauer, *Justus Liebigs Ann. Chem.*, **298**, 187 (1897).
(5) M. Martynoff, *Ann. Chim. (Paris)*, **7**, 424 (1937).
(6) M. Remart-Lucas and J. Hoch, *Bull. Soc. Chim., Fr.*, **5**, 987 (1938).
(7) M. Lamchen in "Mechanisms of Molecular Rearrangements", Vol. I, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1968, pp 43–47.
(8) A. C. Cope and A. C. Haven, *J. Am. Chem. Soc.*, **72**, 4896 (1950).
(9) P. A. S. Smith and J. E. Robertson, *J. Am. Chem. Soc.*, **84**, 1197 (1962).
(10) P. A. S. Smith and S. E. Gloyer, *J. Org. Chem.*, following paper in this issue.
(11) L. W. Jones and M. C. Sneed, *J. Am. Chem. Soc.*, **39**, 677 (1917).
(12) C. Kjellin and K. G. Kuzlenstjena, *Ber.*, **30**, 517 (1897).
(13) R. Behrend and D. Nissen, *Justus Liebigs Ann. Chem.*, **269**, 395 (1892).
(14) R. Behrend and E. König, *Justus Liebigs Ann. Chem.*, **263**, 192 (1891).
(15) E. Beckmann, *J. Prakt. Chem.*, **56**, 80 (1897).
(16) O. L. Brady and C. L. Bennett, *J. Chem. Soc.*, 896 (1927).
(17) H. Feuer, B. Vincent, and R. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965).

Oxidation of Dibenzylhydroxylamines to Nitrones. Effects of Structure and Oxidizing Agent on Composition of the Products

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A group of dibenzylhydroxylamines bearing a para substituent (nitro, chloro, methyl, methoxy), a meta substituent (nitro, methoxy), or an ortho substituent (nitro, chloro, methoxy) as well as the *p*-methoxy-*p'*-nitro derivative, and the α-phenyl derivative, was treated with the oxidizing agents *N*-bromosuccinimide, (diacetoxyiodo)benzene, mercuric oxide, iodine, *tert*-butyl hydroperoxide, or ceric ammonium nitrate. The products were pairs of isomeric substituted *N*-benzyl-α-phenylnitrones; the compositions were determined by NMR. The isomer ratios differed from the known equilibrium ratios, in most cases only moderately, but markedly with the *p*-methoxy-*p'*-nitro and the α-phenyl examples; these facts imply kinetic control of product composition. Isomer ratios generally varied with the oxidizing agent used from slightly to moderately, a circumstance not altogether consistent with a common product-determining step, such as disproportionation of an intermediate nitroxide. Oxidations with mercuric oxide differed noticeably from those with the other oxidizing agents, especially in the cases with ortho substituents. Variation among oxidizing agents was marked with the α-phenyl derivative. Alternative product-determining steps, not involving nitroxide disproportionation, appear to be involved.

Oxidation of N,N-disubstituted hydroxylamines to nitrones (eq 1) has long been known, and occurs easily with a variety of oxidizing agents and in good yields. Although no

$$(R_2CH)_2NOH \xrightarrow{(O)} R_2C{=}N(\rightarrow O){-}CHR_2 \qquad (1)$$

general study of this reaction has been reported,[2] it has generally been presumed to proceed by a one-electron oxidation to an intermediate nitroxide radical. Support for this view is to be found in the work of Sheina and Gallai,[3] who observed a one-electron stage in the electrolytic oxidation of *N*-phenyl-*N*-benzylhydroxylamine, and that of Gutch and Waters,[4] who observed ESR signals corresponding to nitroxides during oxidation of several hydroxylamine derivatives with ceric ion or ferricyanide.

Oxidation of dibenzylhydroxylamine by oxygen in basic solution has been studied kinetically by Cowley and Waters,[5] who followed the appearance of the ESR signal of dibenzyl nitroxide. The second stage in the reaction was presumed to be disproportionation of the nitroxide into benzaldehyde *N*-phenylnitrone and dibenzylhydroxylamine (eq 2), but it was not specifically investigated.

$$(PhCH_2)_2NOH \xrightarrow[OH^-]{O_2} (PhCH_2)_2NO\cdot$$

$$2(PhCH_2)_2NO\cdot \longrightarrow PhCH{=}N(\rightarrow O){-}CH_2Ph + (PhCH_2)_2NOH \qquad (2)$$

Oxidation of hydroxylamines bearing two different N substituents appears not to have been studied, except for the work of Johnson, Rodgers, and Trappe[6] on the autoxidation of *N*-methyl-*N*-ethyl- and *N*-methyl-*N*-propylhydroxylamine, and certain cases where only one of the substituents bore an α hydrogen, and was thus oxidizable. If both substituents have α hydrogens, one would expect a pair of isomeric nitrones to be formed. If the ratio of isomers is thermodynamically determined, it would be identical with that determined from experiments on the equilibration of nitrones, modified slightly by any necessary differences in experimental conditions (i.e., temperature and solvent), but if the ratios are kinetically controlled, some differences from the equilibrium ratios might be found. If disproportionation of an intermediate nitroxide is the product-forming stage in the oxidation, the isomer ratios obtained would be the same, regardless of the oxidizing agent, even if kinetically determined. However, if the oxidizing agent is involved in the product-forming step, the isomer ratios might be sensitive to the nature of the oxidizing agent, presuming kinetic control.

We have undertaken a study of the ratios of isomeric nitrones produced from substituted dibenzylhydroxylamines, using a variety of oxidizing agents. We anticipated that the results would clarify some of the features of the mechanism, and would also have some practical value for the prediction of the major product to be expected where two are possible.

Results

A series of *N,N*-dibenzylhydroxylamines was prepared by treatment of monobenzylhydroxylamines[7] with benzyl halides in the presence of sodium carbonate. The yields and properties are reported in Table I. α-Phenyldibenzylhydroxylamine (*N*-benzyl-*N*-benzhydrylhydroxylamine) was prepared by the reaction of phenylmagnesium bromide with benzaldehyde-*N*-phenylnitrone.

Oxidations were carried out with *N*-bromosuccinimide in chloroform in the presence of pyridine or other amine, with (diacetoxyiodo)benzene (phenyliodoso acetate) in methylene chloride in the presence of cyclohexylamine, with

Table I
Dibenzylhydroxylamines[a] $YC_6H_4CH_2N(OH)CH_2C_6H_4Z$ from $YC_6H_4CH_2NHOH$ and $ZC_6H_4CH_2X$

Registry no.	Substituent Y	Source Z	Source X	Yield, %[b]	Mp, °C	NMR, δ
55648-93-6	*p*-NO_2	H	Br	79	127–128[c]	3.79 (s, 4 H)
55648-94-7	*p*-Cl	H	Cl	56	105–106	2.60 (s, 2 H), 2.66 (s, 2 H)
55648-95-8	*p*-CH_3	H	Cl	54	96–99	2.26 (s, 3 H), 3.64 (s, 4 H)
55648-96-9	*p*-CH_3O	H	Br	27	95–96.5	3.66 (s, 3 H), 3.68 (s, 4 H)
55648-97-0	*m*-NO_2	H	Br	30	97.5–100	3.78, 3.80 (singlets, 4 H total)
55648-98-1	*m*-CH_3O	H	Br	47	58–59	3.64, 3.66, 3.72 (singlets, 7 H total)
55648-99-2	*o*-NO_2	H	Br	49	93–95	3.79 (s, 2 H), 4.12 (s, 2 H)
55649-00-8	*o*-Cl	*o*-Cl	Cl	75	91–92.5	3.64 (s, 2 H), 3.76 (s, 2 H)
55649-01-9	*o*-CH_3O	H	Br	39	121–123	3.54, 3.64, 3.68 (singlets, 7 H total)
55649-02-0	*o*-CH_3O	*p*-NO_2	Br	29.5	118–119	3.84 (s, 4 H), 3.76 (s, 3 H)

[a] Satisfactory analyses for C, H, and N (±0.25%) were obtained for all new compounds. [b] After one or more recrystallizations; yields of crude product were in most cases nearly twice as great. [c] Lit.[30] mp 125.5–126.5°.

Table II
Ratios of Isomeric Nitrones Obtained by Oxidation of Dibenzylhydroxylamines $YC_6H_4CH_2N(OH)CH_2C_6H_4Z$

A = $YC_6H_4CH_2N(\rightarrow O)=CHC_6H_4Z$; B = $YC_6H_4CH=N(\rightarrow O)CH_2C_6H_4Z$

Hydroxylamine, substituents		Oxidizing agent[a] NBS		$PhI(OAc)_2$		HgO		I_2		*t*-BuOOH		$Ce(NH_4)_2(NO_3)_6$		Registry no.	
Y	Z	% B	A/B	% B	A/B	% B	A/B	% B	A/B	% B	A/B	% B	A/B	A	B
p-NO_2	H	58.5	0.71	66.5	0.50	68.5	0.46	62.0	0.61	62.5	0.60	*g*		22661-28-5	22661-23-0
p-Cl	H	54.5	0.83	59.0	0.69	62.0	0.61	61.5	0.63	58.5	0.71	57.0	0.75	55606-33-2	22687-09-8
p-CH_3	H	48.0[b]	1.09	49.5[b]	1.02	56.5[b]	0.77							55606-34-3	55606-41-2
p-CH_3O	H	51.5	0.94	50.5	0.98	52.5	0.90	55.5	0.80	54.5	0.83			55606-35-4	32114-41-3
m-NO_2	H	56.0	0.79	61.1	0.64	66.5	0.50	59.5	0.68					55606-38-7	5367-21-5
m-CH_3O	H	48.0	1.09			49.5	1.02	55.5	0.80					55606-39-8	55606-43-4
o-NO_2	H	56.6	0.77	51.5	0.94	45.0	1.22							22661-27-4	22661-22-9
o-Cl	H	55.0	0.82	49.0	1.04	44.0	1.27							55606-36-5	22687-07-6
o-CH_3O	H	28.0	2.56	37.5	1.67	33.5	2.00							55606-37-6	55606-42-3
p-CH_3O	*p'*-NO_2	34.0	1.92	32.5	2.08	27.0	2.70	26.5	2.78					55606-40-1	55606-44-5
Ph_2CHNCH_2Ph[h] | OH		89.0[c]	0.12	71.0	0.41	50.5	0.98	72.0	0.39			*i*		3376-29-2	3376-27-0
		82.5[d]	0.21												
		84.5[e]	0.18												
		86.0[f]	0.16												

[a] The figures in the columns are averages of duplicate determinations made on the results of duplicate experiments. [b] One determination only. [c] In presence of pyridine. [d] In presence of cyclohexylamine. [e] In presence of 2,6-lutidine. [f] In presence of triethylamine. [g] Extensive hydrolysis vitiated the results. [h] A = α,α-diphenyl-*N*-benzylnitrone; B = α-phenyl-*N*-benzhydrylnitrone. [i] Did not react.

mercuric oxide suspended in ether, with iodine in chloroform in the presence of pyridine, with *tert*-butyl hydroperoxide in benzene, and with ceric ammonium nitrate in water overlaid with ether. The progress of the reactions was followed by TLC, and when no more hydroxylamine remained, the unwanted substances were removed and the mixtures of nitrones were analyzed by NMR in the manner previously described. In general, duplicate experiments were carried out for each situation, and duplicate determinations were made for each experiment. The results are reported in Table II in two forms: the percent of the isomer derived from the substituted benzaldehyde, and the ratio of the two isomers. The total yields of nitrones, determined by weighing the isolated products before analysis, were in all cases between 90 and 99%.

With three of the oxidizing agents that required base [NBS, $PhI(OAc)_2$, I_2], the effect of changing from pyridine to cyclohexylamine, involving a difference of five powers of ten in base strength, was examined in the oxidation of *N*-benzyl-*N*-benzhydrylhydroxylamine. There was no significant difference in product ratio with the latter two oxidizing agents, but with NBS, an increase in the proportion of isomer B from 82.5 to 89% was observed, reproducible in three independent experiments. However, 2,6-lutidine did not show this effect, and 1,4-diazabicyclo[2.2.2]octane (triethylenediamine) showed a difference of only 3.5%, close to the limit of reliability of the determinations.

The effect of degree of completion of oxidation on the product ratio was investigated with mercuric oxide oxidation of *p*-nitro- and *p*-chlorodibenzylhydroxylamine and with oxidation of *p*-methoxydibenzylhydroxylamine oxidizing by *tert*-butyl hydroperoxide. The values were constant from 13 to 100% of completion, within the reliability of the determinations. A wider selection of experiments was not feasible for technical reasons. Table III shows the results with mercuric oxide.

The possibility that nitrone, once formed, might be slowly isomerized toward the equilibrium ratio was examined extensively, by conducting oxidations of hydroxylamines to which a known amount of one of the nitrones had been added. With NBS (eight different hydroxylamines), (diacetoxyiodo)benzene (seven hydroxylamines), mercuric oxide (seven hydroxylamines), and iodine (four hydroxylamines), the ratios of isomeric nitrones observed at completion were identical, within the estimated experimental error, with the ratios calculated from those of simple oxidations and the

Table III
Effect of Degree of Completion of Oxidation on Product Ratios

Extent of reaction, %	% of B in nitrones produced	
	Y = p-NO_2	Y = p-Cl
13		64.2
46.5		60.1
67.5	68.2	
100	68.5	62.0

Table IV
Effect of Added Nitrone on Product Ratios in Oxidation of Dibenzylhydroxylamines by Iodine

$YC_7H_6N(OH)CH_2C_6H_5 \longrightarrow$
$YC_7H_6N(\rightarrow O)=CHC_6H_5$ (A) and $YC_7H_5=N(\rightarrow O)CH_2C_6H_5$ (B)

Y	Hydroxylamine, g	Nitrone added, g	% of B in product	
			Calcd	Found
p-NO_2	0.2	B (0.1)	74.6	76.8, 77.6
p-Cl	0.2	B (0.1)	74.0	73.6, 74.1
p-CH_3O	0.2	B (0.1)	70.6	70.2, 69.2
α-C_6H_5	0.2	B (0.1)	48.1	49.0, 49.0

assumption that the added nitrone remained unaltered throughout. The results obtained in the case of iodine oxidations are representative, and are presented in Table IV. In other experiments, pure nitrones were treated with oxidizing agents under the same experimental conditions; the recovered nitrones had not been isomerized.

Discussion

The foregoing results are best considered in the context of what is known about the oxidation of tertiary amines in general, of which N,N-disubstituted hydroxylamines constitute a special case. Two types of mechanism have been proposed, differing according to the initial (presumably rate-determining) step: removal of an electron from nitrogen to form an aminium cation radical, $R_3N\cdot^+$, or abstraction of hydride from an α carbon to form an aminocarbonium ion (immonium ion), $R_2N^+=CHR'$. In the former, the initial step is not product determining, but in the latter it is.

Abstraction of hydride has been considered principally in connection with oxidation by aqueous bromine[8] or triphenylmethyl carbonium ions.[8,9] For N-methyldibenzylamines with a substituent on one benzyl group, Hammett regression constants of −0.84 (aqueous Br_2) and −2.0 (Ph_3C^+) for oxidation to immonium ions were reported. This selectivity for different α hydrogens is consistent with the results of hydride extraction from other classes of substrate; electron-withdrawing substitution retards hydride abstraction, and electron donation facilitates it. This behavior is opposite to our experimental results with dibenzylhydroxylamines with nitro substituents. It can therefore be concluded that hydride abstraction is not the major pathway for oxidation of any of the oxidizing agents used in this study. (Hull et al.[10] have presented evidence that hydride abstraction may compete as a minor pathway with electron abstraction by ClO_2 as oxidizing agent for tertiary amines.)

Formation of an aminium cation radical as the first step in oxidation of tertiary amines has been demonstrated for a variety of oxidizing conditions, and the rates have been correlated with the ionization potentials of the amines. Ferricyanide ion,[11] cupric ion,[12] dibenzoyl peroxide,[1-] chlorine dioxide,[13] and electrolytic oxidation[13,14] are among the means studied. Product distribution from such oxidations of unsymmetrical tertiary amines has been less extensively studied, but investigations with substituted benzyldimethylamines conform to the generalization that factors that increase the acidity of an α hydrogen favor oxidation of that site to an alkylidene moiety (eq 3).[11,15,16] It should

$$ArCH_2N(CH_3)_2 \xrightarrow{(O)} ArCH=N^+(CH_3)_2 \text{ and } ArCH_2\overset{+}{N}(CH_3)=CH_2 \quad (3)$$

be noted that this is the opposite of the effect with hydride abstraction.

Audeh and Smith[11] have proposed that the product-determining step is loss of a proton from an α carbon of the aminium cation radical, a step that they expressed as an irreversible reaction, followed by oxidation of the resulting α-aminoalkyl radical to an immonium ion (eq 4). In the

$$(RCH_2)_3\overset{+}{N}\cdot \xrightarrow{-H^+} (RCH_2)_2N-\dot{C}HR \xrightarrow{(O)} (RCH_2)_2\overset{+}{N}=CHR \quad (4)$$

case of N,N-dialkylhydroxylamines, the hydroxyl group bears the most eminently acidic hydrogen, loss of which to form a nitroxide should predominate overwhelmingly over deprotonation from an α carbon. Such a step would not, however, be product determining; instead, the succeeding oxidation step to convert the nitroxide to a nitrone would fulfill that role.

If the assumption of Cowley and Waters[5] is correct that in the oxidation of hydroxylamines to nitrones, conversion of intermediate nitroxides to nitrones takes place by disproportionation, the product-determining step would be the same, regardless of the oxidizing agent used (cf. eq 2). Two other pathways deserve consideration. One of these assumes that deprotonation of hydroxylaminium cation radicals is actually reversible, and that the nitroxide or its conjugate acid may also be deprotonated at carbon, albeit very slowly (eq 5, 6). The product-determining step would

$$(RCH_2)_2N-O\cdot \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} (RCH_2)_2\overset{+\cdot}{N}-OH \longrightarrow RCH_2N(OH)\dot{C}HR \quad (5)$$

$$RCH_2N(OH)\dot{C}HR \xrightarrow{(O)} RCH_2N(\rightarrow O)=CHR \quad (6)$$

then be the same as that for oxidation of tertiary amines. The product distribution would be determined largely by the relative acidities of the α hydrogens and would also be independent of the oxidizing agent used so long as the last oxidation step is faster than reprotonation of the carbon radical to reform the hydroxylaminium cation radical. This mechanism was invoked by Johnson, Rodgers, and Trappe to explain their observation that autoxidation appeared to involve only the methyl group of N-methyl-N-alkyl hydroxylamines in basic medium.[6]

An alternative is that the nitroxide (or its conjugate acid) is attacked by more oxidizing agent, in effect removing H·, and thereby forming nitrone directly (eq 7). With such a

$$(RCH_2)_2N-O\cdot \xrightarrow{(O)} RCH_2N(\rightarrow O)=CHR \quad (7)$$

mechanism, the product distribution would show some sensitivity to the oxidizing agent used. The results shown in Table II show that such a dependence, varying from slight to moderate, does exist. It may be presumed to involve both the electronic demand of the oxidizing agent and its steric requirements. Mercuric oxide deviates more than the other oxidizing agents, a circumstance that must be con-

nected with the fact it is the only one of the group in which oxidation takes place on a solid surface.

Observation of a dependence of product distribution on oxidizing agent limits the mechanisms of eq 2, 5, and 6 to a minor role in the oxidation of hydroxylamines in comparison with eq 7. However, it does not preclude a minor competitive role for the deprotonation pathway of eq 6. For situations in which the rates of the two pathways are not extremely different, their relative importance might be influenced by changes in basicity of the reaction medium in such a way as to be reflected in observable changes in product ratio. The observations of the effect of different bases on oxidation by NBS may perhaps be due to an effect of this sort.

Some incidental observations on the effect of degree of completion of oxidation on product ratios provide further evidence against a significant role for the disproportionation path (eq 2); the reaction is second order in nitroxide in eq 2 but first order in eq 7. If the concentration of nitroxide varies in proportion to concentration of the hydroxylamine from which it is produced, the disproportionation path would contribute less toward the end of the reaction, so long as a substantial excess of oxidizing agent is present. The product distribution would thus vary with the stage of completion of the oxidation if the two pathways independently resulted in different product ratios. No dependence on degree of completion was observed in a limited variety of experiments (Table III). This evidence does not rigorously exclude disproportionation as a contributing pathway, but it does mean that either its contribution must be small, or the product distributions from the two paths are not substantially different.

We had originally considered that eq 7 might in some instances be sufficiently reversible to provide a path for the isomerization of unsymmetrical nitrones, alternative to the base-catalyzed prototropy examined in the accompanying paper. However, the fact that our oxidations produced mixtures of kinetically determined composition demonstrates that the reduced forms of the oxidizing agents used do not promote isomerization significantly. In addition, we attempted to equilibrate α-(*o*-chlorophenyl)-*N*-benzylnitrone by treatment with ferrous sulfate in ethanol, but no isomerization could be detected after 18 hr. Equation 7 is evidently not significantly reversible under the conditions of our experiments; eq 6, however, could be reversible without effecting equilibration of isomers.

In summary, the whole evidence points to the fact that in the oxidation of hydroxylamines to nitrones, the distribution of isomeric nitrones is determined kinetically, primarily by a step in which an intermediate nitroxide reacts with a second equivalent of oxidizing agent; alternative pathways may compete under certain circumstances, but their contribution remains essentially secondary. It is possible to influence the product distribution by choice of oxidizing agent; the effect is generally small among substrates with only electronic differences at the site of oxidation, somewhat larger where steric differences are involved. Iodine and mercuric oxide are somewhat more selective than NBS or (diacetoxyiodo)benzene.

Experimental Section

NMR spectra were determined on a Varian A-60 instrument, or, where specified, an A-100 instrument, using $CDCl_3$ solutions with tetramethylsilane as internal reference. Melting points are uncorrected. Thin layer chromatograms were prepared with Eastman Chromagram Type 6060 sheets (silica gel with fluorescent indicator) using chloroform or ethanol–chloroform mixtures for development. Analyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Dibenzylhydroxylamines. The N,N-disubstituted hydroxylamines were prepared by treating *N*-benzylhydroxylamines[7] with the appropriate benzyl halide in the presence of sodium carbonate, according to the general directions of Behrend and Leuchs.[17] The preparation of *N*-*p*-methylbenzyl-*N*-benzylhydroxylamine is representative.

A mixture of 4.0 g (32.5 mmol) of *N*-benzylhydroxylamine and 4.55 g (32.5 mmol) of *p*-methylbenzyl chloride in 25 ml of 70% ethanol with 3.46 g (32.5 mmol) of sodium carbonate was refluxed with stirring for 4 hr. Cooling and dilution with 200 ml of ice–water caused an oil to separate, which was extracted with 200 ml of ether. Evaporation of the dried ($MgSO_4$) extract left 6.08 g (82.5%) of crude product. Recrystallization from aqueous ethanol gave 3.94 g (54%) of *N*-*p*-methylbenzyl-*N*-benzylhydroxylamine, mp 92–98°; an analytical sample, mp 96–99°, was prepared by recrystallization from ligroin (bp 90–100°); ir (Nujol mull) 3025–3150, 1520, 1500, 1360, 1105, 1080, 1035, 850, 815, 755, and 710 cm^{-1}; NMR δ 2.26 (s, 3 H), 3.64 (s, 4 H), 7.16 and 7.04 (m, total 9 H).

The results are recorded in Table I (the ir spectra, not being particularly informative, are omitted).

Oxidations. For a given oxidizing agent, the procedure was essentially the same for each hydroxylamine. A representative example for each oxidizing agent is described.

***N*-Bromosuccinimide Oxidations.** A solution of 0.30 g (1.17 mmol) of *N*-*o*-nitrobenzyl-*N*-benzylhydroxylamine in 20 ml of chloroform was added to a stirred, cooled solution of 0.2808 g (1.17 mmol) of *N*-bromosuccinimide and 0.09 g (1.17 mmol) of pyridine in 30 ml of chloroform. The mixture was stirred for 10 min and then washed with 50 ml of water. Evaporation of the dried ($MgSO_4$) and filtered chloroform layer under aspirator vacuum left 0.281 g (94%) of mixed nitrones.

Diacetoxyiodobenzene Oxidations. A solution of 0.378 g (1.17 mmol) of diacetoxyiodobenzene (phenyliodoso acetate) in 20 ml of methylene chloride was added dropwise to a cooled solution of 0.30 g (1.7 mmol) of *N*-*o*-nitrobenzyl-*N*-benzylhydroxylamine and 0.23 g (2.34 mmol) of cyclohexylamine in 30 ml of methylene chloride. The mixture was then stirred for 1–5 hr, washed with two 50-ml portions, dried ($MgSO_4$), and filtered. Evaporation of the solvent under aspirator vacuum left a mixture of nitrones with some iodobenzene, which did not interfere with NMR analysis and was not removed.

Mercuric Oxide Oxidations. A suspension of 1.0 g of mercuric oxide in 30 ml of ether containing 0.20 g (0.775 mmol) of *N*-*o*-nitrobenzyl-*N*-benzylhydroxylamine was stirred for 3 hr at ambient temperature. Monitoring by TLC analysis showed incomplete reaction. A further 1.0 g of mercuric oxide was added and the mixture was stirred for 3 more hr, but TLC still showed incomplete reaction. A third 1.0-g portion of mercuric oxide was added and the mixture was stirred for 2 hr and then filtered. Evaporation left 0.181 g (91%) of mixed nitrones.

Iodine Oxidations. A solution of 0.207 g (0.83 mmol) of iodine in chloroform was added over a period of 0.5 hr to a solution of 0.20 g (0.82 mmol) of *N*-*p*-methoxybenzyl-*N*-benzylhydroxylamine and 0.13 g (1.64 mmol) of pyridine in 50 ml of chloroform, and the mixture was stirred for 0.5 hr. Washing with three 50-ml portions of water removed the small amount of precipitate that had formed. Evaporation of the dried ($MgSO_4$) and filtered solution under aspirator vacuum left 0.198 g (99%) of mixed nitrones.

Oxidations by *tert*-Butyl Hydroperoxide. A solution of 0.30 g (1.21 mmol) of *N*-*p*-chlorobenzyl-*N*-benzylhydroxylamine and 0.117 g (1.3 mmol) of *tert*-butyl hydroperoxide in 5 ml of benzene was heated at 55° for 3 hr and then at gentle reflux for 21 hr (TLC showed that reaction was complete at that time). The solvent was removed under aspirator vacuum, and the residue was used directly for NMR assay.

Oxidation by Ceric Ammonium Nitrate. A solution of 0.2 g (0.81 mmol) of *N*-*p*-chlorobenzyl-*N*-benzylhydroxylamine in 40 ml of ether was shaken for 5 min with a solution of 0.89 g (1.62 mmol) of ceric ammonium nitrate in 40 ml of water. The ether layer was separated, washed with 50 ml of dilute sodium carbonate solution, dried ($MgSO_4$), and filtered. Removal of the solvent under aspirator vacuum left 0.184 g (93%) of mixed nitrones.

NMR Analysis. The mixtures of nitrones were dissolved in $CDCl_3$ containing a trace of triethylamine, and analyzed according to the method in the preceding paper.

Registry No.—*N*-*p*-Nitrobenzylhydroxylamine, 2912-97-2; *N*-*p*-chlorobenzylhydroxylamine, 51307-68-7; *N*-*p*-methylbenzylhydroxylamine, 16814-17-8; *N*-*p*-methoxybenzylhydroxylamine, 51307-59-6; *N*-*m*-nitrobenzylhydroxylamine, 55606-47-8; *N*-*m*-

methoxybenzylhydroxylamine, 55606-48-9; *N*-*o*-nitrobenzylhydroxylamine, 37558-77-3; *N*-*o*-chlorobenzylhydroxylamine, 55606-45-6; *N*-*o*-methoxybenzylhydroxylamine, 55606-46-7; α-bromotoluene, 100-39-0; α-chlorotoluene, 100-44-7; *p*-nitro-α-bromotoluene, 100-11-8; *N*-benzylhydroxylamine, 622-30-0; *p*-methylbenzyl chloride, 104-82-5; *N*-bromosuccinimide, 128-08-5; phenyliodoso acetate, 3240-34-4; mercuric oxide, 21908-53-2; iodine, 7553-56-2; ceric ammonium nitrate, 16774-21-3.

References and Notes

(1) From the Doctoral Dissertation of Stewart E. Gloyer.
(2) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 2, W. A. Benjamin, New York, N.Y., 1966.
(3) N. M. Sheina and Z. A. Gallai, *Vestn. Mosk. Univ., Khim.*, **13**, 220 (1971); *Chem. Abstr.* **77**, 82880p (1972).
(4) C. J. W. Gutch and W. A. Waters, *J. Chem. Soc.*, 751 (1965).
(5) D. J. Cowley and W. A. Waters, *J. Chem. Soc. B*, 96 (1970).
(6) D. H. Johnson, M. A. T. Rodgers, and G. Trappe, *J. Chem. Soc.*, 1093 (1956).
(7) P. A. S. Smith and S. E. Gloyer, *J. Org. Chem.*, preceding paper in this issue.
(8) N. C. Deno and R. E. Fruit, Jr., *J. Am. Chem. Soc.*, **90**, 3502 (1968).
(9) H. Volz and H. H. Kiltz, *Justus Liebigs Ann. Chem.*, **752**, 86 (1971).
(10) L. A. Hull, G. T. Davis, D. H. Rosenblatt, H. K. R. Williams, and R. C. Weglein, *J. Am. Chem. Soc.*, **89**, 1163 (1967).
(11) C. A. Audeh and J. R. L. Smith, *J. Chem. Soc. B*, 1741 (1971); J. R. L. Smith and L. A. V. Mead, *J. Chem. Soc., Perkin Trans. 1*, 206 (1973).
(12) J. T. Yoke, III, J. F. Weiss, and G. Tollin, *Inorg. Chem.*, **2**, 1210 (1963).
(13) L. A. Hull, G. T. Davis, and R. H. Rosenblatt, *J. Am. Chem. Soc.*, **91**, 6247 (1969); *J. Phys. Chem.*, **73**, 2142 (1969).
(14) R. N. Adams, *Acc. Chem. Res.*, **2**, 175 (1969).
(15) C. A. Audeh and J. R. L. Smith, *J. Chem. Soc. B*, 1280 (1970); L. C. Portis, J. T. Klug, and C. K. Mann, *J. Org. Chem.*, **39**, 3488 (1974).
(16) D. H. Rosenblatt, L. A. Hull, D. C. DeLuca, G. T. Davis, R. C. Weglein, and H. K. R. Williams, *J. Am. Chem. Soc.*, **89**, 1158 (1967).
(17) R. Behrend and K. Leuchs, *Justus Liebigs Ann. Chem.*, **257**, 245 (1890).

Photochromism of Quinolylhydrazones. III.[1] The Mechanism of Isomerization of the Photocolored α-Quinolylimino-(*Z*)-hydrazone to the α-Quinolylamino-(*E*)-hydrazone

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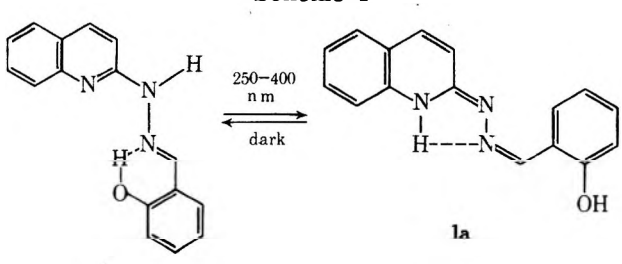
The kinetics and mechanism of the thermal decay of the photocolored form **1a** of salicylaldehyde 2-quinolylhydrazone (1) are reported. Two isomerization reactions, viz., α-imino- to α-aminoquinoline and $Z \rightarrow E$ hydrazone, are involved. The first conversion occurs via an intramolecular transfer of the phenolic hydrogen to the α-imino group. This is deduced on the basis of medium effect, concentration effect, and base inhibition studies. The decay of the 8-nitro colored form **2a** confirms this and implicates the quinoline NH as the source of the phenolic hydrogen of the uncolored form. The overall deuterium isotope effect of 1.84 denotes the non-rate-determining nature of the participation of the OH and NH. Since plots of the logarithm of the decay rate constant k vs. solvent Z or E_T (30) values show linear relationship and large negative $\Delta S^{\ddagger}$ values accompany the decay process, a rotation mechanism is postulated for the $Z \rightarrow E$ hydrazone isomerization. Also, acid catalysis substantiates the mechanistic scheme proposed for the decay process.

The photochromic phenomena of anils[2] and hydrazones[3] are generally observed only in a solid matrix. The instability of these colored forms in solution is typified by the *N*-salicylidene anil in the trans-quinonoid structure,[4] which showed a half-life of 1 msec at 30° in ethanol.[5a] The transient hydrazone photocolored species remains elusive. By contrast, the photochromism of salicylaldehyde 2-quinolylhydrazone (1) has been shown as follows (Scheme I).[1]

Scheme I



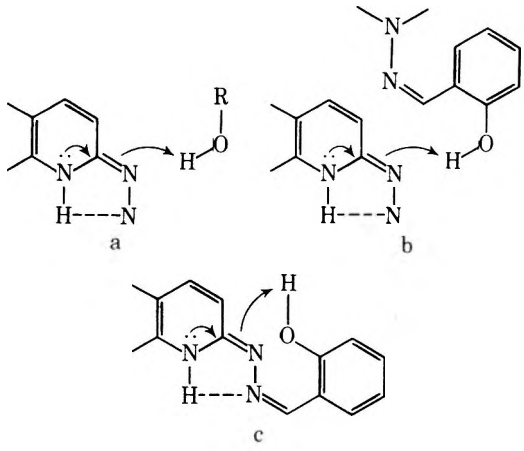
1 **1a**

The quinolylhydrazone 1 in ethanol is readily converted to the colored form **1a** when irradiated in the uv region of 250–400 nm at room temperature. This colored species has shown remarkable stability in both protic and aprotic solvents at room temperature. The availability and stability of **1a** thus afforded us an opportunity to investigate the relatively unexplored isomerization of α-heterocyclic imines and *Z* hydrazones. While *E,Z* isomerizations of the azomethine double bond in aldimines[5] and ketimines[6] have been the subjects of intensive studies, there is as yet no reported mechanism for the interconversions of hydrazones. This article details the kinetics and mechanisms of these isomerizations. The sequence of events reported herein also represents the first elucidated thermal decay process of the hydrazone photochromism.

Results and Discussion

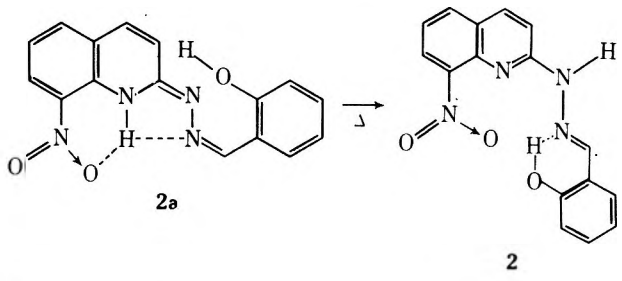
Intramolecular Hydrogen Transfer. In the isomerization of **1a** to **1**, involving imine → amine and $Z \rightarrow E$ hydrazone conversions, one or more hydrogen transfer steps must intervene. They may occur inter- or intramolecularly as shown in Scheme II. Scheme IIa supposes a hydrogen transfer between **1a** and a protic solvent. That this is not generally applicable is shown by (1) the instant conversion of **1a** to **1** when the colored form is heated to its melting point at 152° in an evacuated sealed tube, and (2) the decay constant of **1a** to **1** at 25° in an aprotic medium such as dimethyl sulfoxide (1.2×10^{-6} sec^{-1}) is similar to that in ethanol (3.0×10^{-6} sec^{-1}). Scheme IIb assumes intermolecular transfer between adjacent molecules of **1a**. Such a mechanism should be facilitated by increasing concentrations of **1a**. However, when the decay of **1a** was followed in ethanol at 25°, varying the concentration of **1a** from 4×10^{-5} *M* to 20×10^{-5} *M* caused only negligible change in the first-order rate constant (k, 10^{-6} sec^{-1}, 2.11 and 2.0, respectively). A corollary observation was made in methylcyclohexane, a solvent which facilitates aggregation of solute molecules. In this case, the decay constant k (10^{-6} sec^{-1}, 25°) actually decreased from 2.56 at 0.5×10^{-5} *M* to 1.25 at

Scheme II



ten times the concentration. While the concentration effect is insignificant, indicating the inoperation of Scheme IIb, the addition of 1 equiv of pyridine suppressed the rate of decay of **1a** in benzene (5.13×10^{-5} *M*, 25°) by a factor of 50. These rate data are therefore suggestive of the free phenolic proton being involved in an intramolecular protonation of the α-imine (cf. Scheme IIc). Further elucidation of the role of the phenolic proton was derived from the isomerization of the 8-nitro colored form **2a**. A KBr pellet of **2a** (1% by weight) was heated at 100° and monitored by ir spectroscopy. The sharp band at 3295 cm^{-1}, assignable only to the stretching mode of the unchelated phenolic OH, diminished gradually in intensity with a concomitant increase of a new sharp band at 3345 cm^{-1} for the exocyclic amino hydrogen of the uncolored form **2**. These assignments are firm since the quinoline NH in **2a** and the phenol OH in **2** are strongly chelated and should appear as broad, indistinct bands.[7] Furthermore, this 8-nitro photochromic pair also lends insight into the participation of the quinoline N hydrogen of the colored form in the decay process. Thus, the presence of the 8-nitro group in **2a** retarded the rate of decay by a factor of 5 compared to that of the parent colored form **1a** in ethanol at 79°. This may be attributed to the intramolecular chelation of the quinoline N hydrogen in **2a**, thus inhibiting its transfer to the adjacent hydrazone nitrogen which would labilize the carbon nitrogen double bond (Scheme III). Evidence of such internal

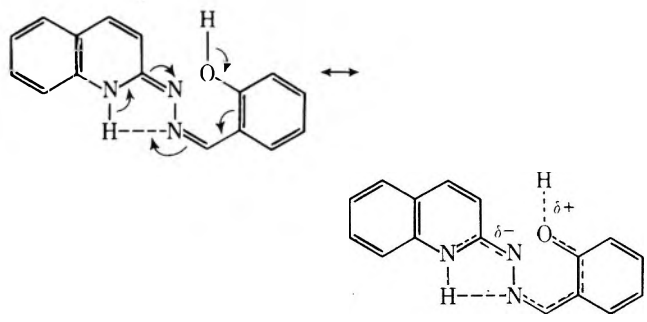
Scheme III



chelation is that the ν(asym,sym)[8] of the 8-nitro group in **2** at 1530 and 1352 cm^{-1}, respectively, are reduced to a weak band at 1530 cm^{-1} in **2a**.

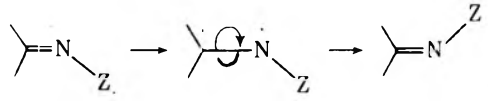
The net effects of these two intramolecular hydrogen transfers during the isomerization of the colored to the uncolored form are that (1) the α-amino hydrogen of **1** is derived from the phenolic proton of **1a** and (2) the ring N hydrogen of **1a** becomes the salicylidene hydrogen of **1**. It appears that specific isotope effect on the rate of decay of the colored form **1a** would detail the rate-determining nature of these steps. Specifically deuterated colored form **1a**, e.g., NH, OD, or ND, OH, could not be secured owing to deuterium scrambling even in aprotic solvents. In their place was prepared the N,O-dideuterated derivative of **1a**. By treating the 83% N,N,N′-trideuterated α-quinolylhydrazine with the 82% O-deuterated salicylaldehyde in benzene, a 70% N,O-dideuterated derivative of **1** was prepared, which, upon irradiation at 365 nm, was converted to **1a**. The percentage deuteration was made by ^1H NMR analysis. The decay rate constant *k* (10^{-3} min^{-1}, 56°) of the 70% O,N-dideuterated colored form in cyclohexane at 7.6×10^{-5} *M* was 7.54 ± 1.08 compared to 9.69 ± 0.88 for the undeuterated **1a** under the same conditions. These rate data translate to an overall kinetic isotope effect of 1.84. This is far short of the primary deuterium isotope effect of 9 for the tautomerization involving ND or 11 involving OD deduced by Hine.[9] Plausible interpretations of such weak isotope effect are (1) these hydrogen transfer steps are not rate determining, implying that the *Z* → *E* hydrazone isomerization is, and (2) the O–H and N–H bonds in **1a** are already stretched prior to the transfer steps (Scheme IV).

Scheme IV

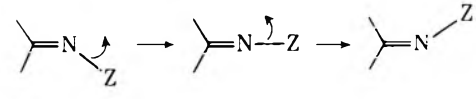


Rotation of the *Z* Hydrazone. In addition to the intramolecular hydrogen transfer steps deduced above, the salicylaldehyde hydrazone azomethine double bond must undergo *Z* → *E* isomerization to complete the decay of the colored form. Three potential mechanisms for such isomerization are shown as follows (Schemes V–VII).[10] Scheme V

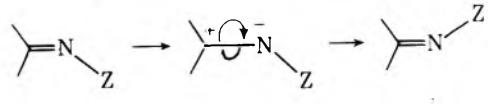
Scheme V



Scheme VI



Scheme VII



involves homolytic cleavage of the carbon–nitrogen double bond and closely parallels the rotational trans ⇄ cis isomerization of alkenes or azo compounds. This mechanism is usually dismissed because of the large activation energy involved in alkene isomerization ranging from 36 to 60 kcal mol^{-1} while that of azo compounds is even higher.[10] Scheme VI, the so-called "lateral shift" or inversion mechanism, is related to the inversion known for amino compounds.[11] The inversion mechanism is the preferred one to account for the low activation energy observed for aldimines and ketimines.[10] The third mechanism, Scheme VII,

Table I
Kinetic and Activation Parameters for the Decay of 1a at 25° [a]

Solvent	$k \times 10^7$, sec	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal mol^{-1}
1 Ethanol	30.20 (±0.0)	12.15 (±1.3)	−42.2 (±4.5)	24.7
2 Dimethyl sulfoxide	12.10 (±2.7)	5.9 (±1.8)	−62.8 (±5.2)	24.6
3 Methylcyclohexane	10.85 (±3.6)	9.0 (±1.6)	−53.1 (±4.9)	24.8
4 Dimethylformamide	6.8 (±0.6)	15.5 (±1.2)	−33.0 (±3.1)	25.3
5 Hexamethylphosphoramide	3.1 (±0.7)	17.1 (±1.1)	−28.5 (±2.9)	25.6
6 Dioxane	2.7 (±0.6)	14.6 (±1.3)	−37.5 (±1.6)	25.8
7 Toluene	2.4 (±0.1)	15.4 (±0.4)	−34.0 (±1.2)	25.5
8 *tert*-Butylbenzene	2.1 (±0.4)	10.9 (±0.9)	−49.9 (±2.7)	25.8
9 Benzene	1.1 (±0.0)	15.7 (±2.6)	−35.6 (±4.1)	26.3

[a] From a computer-assisted least-square routine. The concentration of 1a was ~4.3 × 10^{-5} *M* for all solvents.

known as rotation, involves polarization of the carbon–nitrogen double bond.[11] Unlike the nonionic inversion in Scheme VI, the rotation mechanism is particularly susceptible to solvent effects.[11] We therefore undertook a study of the kinetics and activation energies of the isomerization of 1a as a function of the solvent medium.

Table I summarizes the first-order rate constants k, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ obtained in nine different solvents of various types (i.e., protic, aprotic–dipolar, nonpolar, and aromatic). Attempts to correlate the solvent effect with rate in terms of the dielectric constant of the solvent resulted in a random distribution of points. This in itself does not indicate a nonpolar reaction, since Wiberg[12] has shown that the dielectric constant may not be useful in describing the solvent effect on a dipolar species. Furthermore, Frost and Pearson[13] contended that the correlation of rate with gross dielectric constant is very misleading, since the interaction of an ion or dipole with a nonpolar solvent is much greater than would be expected, this being particularly true of aromatic solvents, which are sometimes good for ionic reactions despite their low dielectric constant. Thus, other solvent polarity parameters, e.g., the Z values compiled by Kosower[14] and the E_T (30) proposed by Dimroth,[15] were employed. The Z values arise from the sensitivity of the charge transfer band of 1-alkylpyridinium iodides to solvent polarity.[14] The E_T (30) is based on solvent effect on the charge transfer transition energy of the pyridinium phenol betaines.[15] Both of the Z and E_T (30) vs. log k plots for the decay of the colored form 1a in these solvents at 25° give a linear relationship as shown in Figure 1. This linear correlation is indicative of a polar transition state for the rate-determining step, implicating the rotation scheme VII for the $Z \rightarrow E$ hydrazone isomerization.

Further inspection of Table I reveals a uniformly high negative entropy of activation for the decay reaction regardless of solvent types. This large negative $\Delta S^{\ddagger}$ is consonant with the polar rotation mechanism as depicted in Scheme VII. The substantial variation (29–63 eu) of the negative $\Delta S^{\ddagger}$ in the various solvents is worthy of note. According to Leffler,[16] large variations in $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ do not necessarily indicate a change in mechanism as long as there is a linear relationship between $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ from one solvent to the next. The linear relationship, known as the compensation law or the isokinetic relationship, is indeed observed as shown in Figure 2.

Comparison of these decay data with those reported for the $Z \rightarrow E$ isomerization of salicylaldehydephenylhydrazone[17] and *N*-salicylideneaniline[5a] is shown in Table II. It is seen that the rate constant and the activation energies for the α-quinolylimino-(*Z*)-hydrazone (1a) are quite comparable to those for the phenylhydrazone. However, the aniline anil, which isomerized about 100,000 times faster with one-third of the $\Delta S^{\ddagger}$ loss, is in a class by itself. Since anils

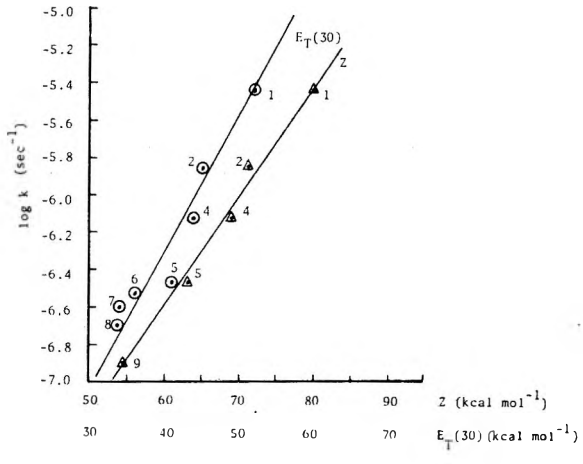


Figure 1. Plots of log k vs. solvent polarity parameters [Z,[14] E_T (30)[15]] for the decay of 1a. Numbers refer to solvent systems in Table I. [No Z or E_T (30) values are reported for methylcyclohexane (solvent 3)].

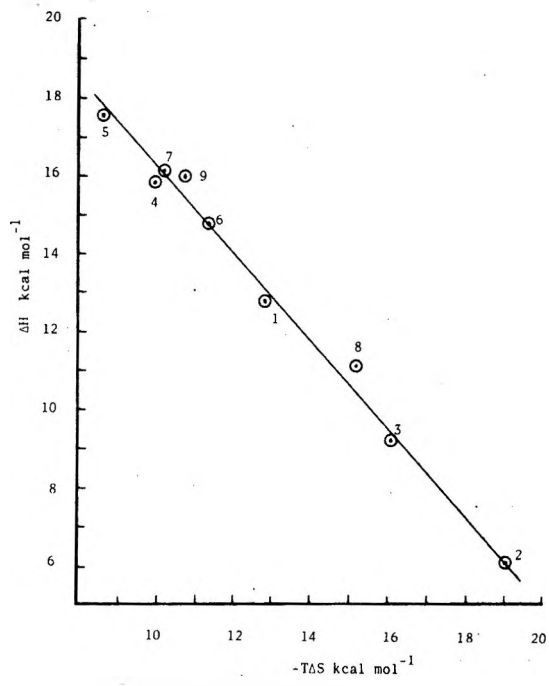


Figure 2. Isokinetic plot for the decay of 1a in nine solvent systems. Numbers refer to solvent systems in Table I.

Table II
Comparison of Kinetic and Activation Parameters of $Z \rightarrow E$ Isomerization

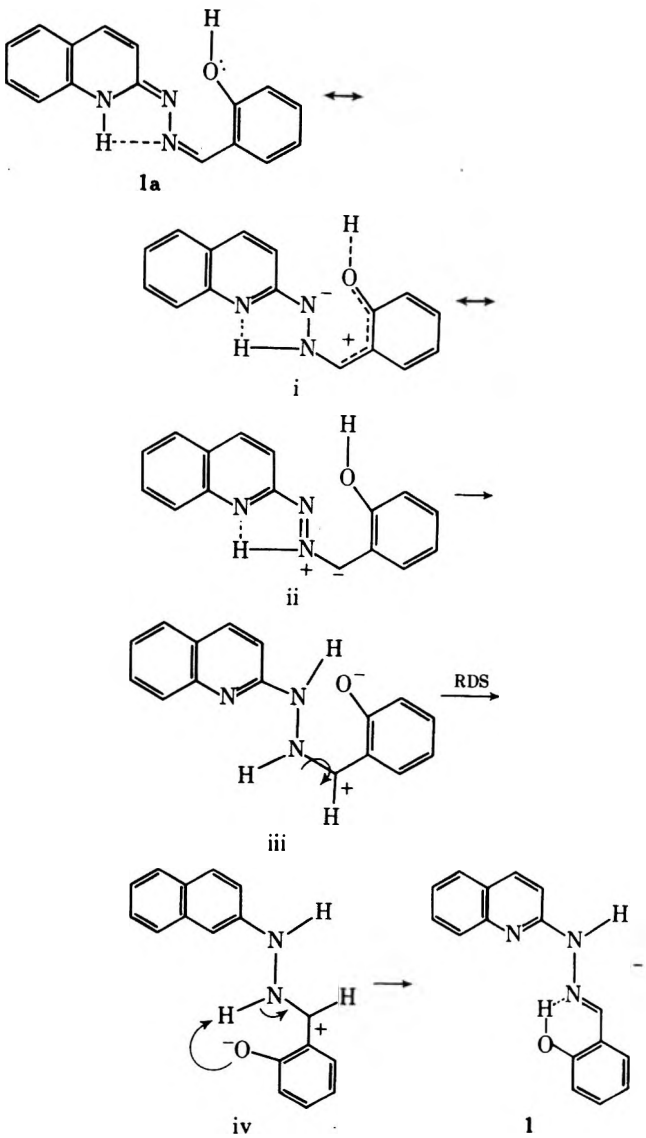
Compd	Solvent	k_1, sec^{-1} (°C)	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$
1a	Ethanol	3.7×10^{-6} (32)	12	−42	25
Salicylaldehyde-phenylhydrazone[a]	Ethanol–cyclohexane (3:1)	1.15×10^{-5} (37)	14	−34	24
N-Salicylidene-aniline[b]	Ethanol	1.67 (30)	14	−11	17

[a] Reference 17. [b] Reference 5a.

have been shown to undergo $Z \rightarrow E$ isomerization by inversion (Scheme VI),[5c] it appears most likely that the $Z \rightarrow E$ isomerization of **1a** and the phenylhydrazone proceeds via rotation (Scheme VII).

Decay Mechanism of the Colored Form 1a. Given the two intramolecular hydrogen transfers and the rotation mechanism of the *Z* hydrazone, the sequence of events can be arranged as shown in Scheme VIII. Thus, electron delocalization in **1a** affords the mesomeric forms i and ii. These dipolar structures allow the transfer of the quinoline N hydrogen to the *Z*-hydrazone nitrogen to form iii, thereby facilitating its rotational isomerization to iv. It then follows that the intramolecular migration of the phenolic proton to the α-imino nitrogen should precede the hydrazone double bond rotation. The reverse order would necessitate a most awkward intramolecular hydrogen rearrangement. The acid catalysis provides credence to this reaction sequence. Thus, the presence of 0.8 equiv of acetic acid in a 1×10^{-4} *M* solution of **1a** in ethanol at 32° increased the decay rate by a factor of 5. The probable site of protonation in **1a** is the α-imino nitrogen. The added proton source therefore obviates the need of the phenolic hydrogen transfer via the strained seven-membered ring to the α-imino nitrogen.

Scheme VIII



Experimental Section[18]

Salicylaldehyde 2-Quinolylhydrazone (1). A mixture of 1.59 g (10 mmol) of 2-hydrazinoquinoline (Eastman, recrystallized) and 1.22 g (10 mmol) of salicylaldehyde in 150 ml of 95% ethanol was refluxed for 5 hr. The solution was concentrated, the crystalline precipitate was collected, and recrystallized twice from ethanol, yielding 1.44 g (55%) of **1**: mp 203°; uv λ_{max} (EtOH) (log ε) 358 nm (4.387), 310 s (4.230), and 237 (4.406); NMR (Me_2SO-d_6) δ 11.10 (s, 2), 8.50 (s, 1), and 8.27–6.82 (m, 10).

Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.98, H, 4.98; N, 15.96. Found: C, 73.36; H, 5.11; N, 16.13.

Colored Form 1a. A solution of 0.1 g (0.4 mmol) of salicylaldehyde 2-quinolylhydrazone (**1**) in 125 ml of 95% ethanol was irradiated with a Sylvania Black Lamp Blue (366 nm) for 14 days. The solution was evaporated to dryness, the residue was dissolved in 25 ml of ether, and the latter was chromatographed on silica gel G preparative plates of 1 mm in thickness with chloroform as eluent. The uv fluorescent band nearest to the solvent was eluted with ether, and 0.09 g (90%) of the orange-colored form **1a** was isolated: mp 152°; uv λ_{max} (EtOH) (log ε) 400 nm (4.220), 298 (4.176), 289 (4.204), and 247 (4.344); NMR ($CDCl_3$) δ 11.30 (s, 1) and 7.99–6.65 (m, 12).

Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.89; H, 5.07; N, 15.73.

Salicylaldehyde 2-(8-Nitro)quinolylhydrazone (2). A mixture of 2.04 g (10 mmol) of 2-hydrazine-8-nitroquinoline (prepared from 2-chloro-8-nitroquinoline[19]) and 1.22 g (10 mmol) of salicylaldehyde in 150 ml of 2-propanol was refluxed for 5 hr. The solution was concentrated, and the crystalline precipitate was recrystallized twice from 2-propanol, giving 1.85 g (60%) of **2**: mp 204–206°; uv λ_{max} (EtOH) (log ε) 440 s nm (3.878), 370 (4.182), 335 (4.279), 302 (4.369), and 240 (4.450); NMR (Me_2SO-d_6) δ 12.02 (s, 1), 10.78 (s, 1), 8.77 (s, 1), and 8.53–6.93 (m, 9).

Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 61.90; H, 3.76; N, 18.07.

Colored Form 2a. A solution of 0.1 g (0.3 mmol) of **2** in 125 ml of an acetone–water (9:1) mixture was irradiated with a Sylvania Black Lamp Blue (366 nm) for 14 days. Upon standing and slow evaporation, 0.06 g (60%) of the colored form **2a** was obtained as red crystal: mp 206–208°; uv λ_{max} (EtOH) (log ε) 442 nm (4.164), 358 s (4.021), 295 (4.415), and 238 (4.433).

Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.32; H, 4.21; N, 17.94.

Kinetic Measurements. The rate studies were carried out in 1-cm quartz cuvettes which could be sealed with ground glass stoppers. The temperatures employed in the study were varied from room temperature to some temperature below the boiling point of the solvent employed by means of a constant-temperature bath. The absorbance of the colored species was determined in the various solvents using a Cary 14 spectrophotometer at zero time and at regular intervals after being placed in the constant-temperature bath. In all cases, four readings were made for each sample, and at least three different temperatures were used for each solvent sys-

tem. The first-order rate constant, k, was obtained from the straight line plot of log A vs. time. The thermodynamic values, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$, as well as the rate constant, $k_{25°}$, were determined by standard methods.[20] The activation parameters were determined by a computer-assisted least-square curve fit of plots of log k vs. $1/T$. Standard deviations were obtained from the equation

$$S = \sum[(X_i - X)^2/n - 1]^{1/2}$$

N,O-Dideuterated Derivative of 1a and the Isotope Effect. A mixture of 34.5 g (283 mmol) of salicylaldehyde and 12.0 g (611 mmol) of D_2O (99.8% D) in 25 ml of anhydrous dioxane was heated at reflux for 12 hr followed by distillation to remove the solvents. The process was repeated and the salicylaldehyde-*O*-*d* was distilled, bp 63° (3 mm), 82% deuteration by NMR integration of the residual OH resonance: (neat) δ 11.07 s (0.18 H), 9.7 s (1 H), 7.3 m (2 H), 6.8 m (2 H).

A mixture of 0.69 g (4 mmol) of 2-hydrazinoquinoline and 10 g (556 mmol) of D_2O (99.8% D) in 25 ml of anhydrous dioxane was refluxed under a dry nitrogen atmosphere for 72 hr. The solvent was removed by distillation and the process was repeated. The resulting N,N,N′-trideuterated 2-hydrazinoquinoline was recrystallized from ligroin, 83% deuteration by NMR integration: ($CDCl_3$) δ 7.78–6.62 m (6 H), 4.87 s (0.5 H).

A mixture of 0.123 g (1 mmol) of salicylaldehyde-*O*-*d* and 0.162 g (1 mmol) of N,N,N′-trideuterated 2-quinolylhydrazine in 5 ml of anhydrous benzene was heated at reflux for 4 hr. The solution was concentrated and the crystalline precipitate was collected and recrystallized twice from benzene to yield the N,O-dideuterated **1**, 70% deuteration, determined by NMR: (Me_2SO-d_6) δ 11.1 broad s (0.6 H), 8.5 s (1 H), 8.27–6.82 (10 H).

The uncolored, N,O-dideuterated salicylaldehyde-2-quinolylhydrazone (**1**) (2 mg) was placed in a 100-ml volumetric flask and dissolved in distilled, dried cyclohexane. The resulting solution was irradiated to the photostationary state. The absorbance at 400 nm was recorded on a Cary 14 spectrophotometer and samples of the solution were placed in a constant-temperature bath maintained at 56° for various lengths of time, with the absorbance being recorded periodically. From a plot of log A vs. time the rate constant k_D was determined to be $7.54 \pm 1.08 \times 10^{-3}$ min^{-1}. The entire process was repeated for the undeuterated **1** and the rate constant k_H was found to be $9.69 \pm 0.88 \times 10^{-3}$ min.$^{-1}$ The ratio k_H/k_D was found to be 1.84 after correction for the percentage deuterium in the sample by dividing by 0.70.

Acknowledgments. The decay data of **1a** in ethanol are taken from the Ph.D. Thesis of F. N. Bruscato, University of Louisville, 1969.

Registry No.—**1**, 55637-44-0; **1a**, 55570-67-7; **2**, 55570-68-8; **2a**, 55605-91-9; 2-hydrazinoquinoline, 15793-77-8; salicylaldehyde, 90-02-8; 2-hydrazino-8-nitroquinoline, 55570-69-9.

References and Notes

(1) Part II: J. L. Wong and M. F. Zady, *J. Chem. Soc., Chem. Commun.*, 684 (1973).
(2) R. Potashnik and M. Ottolenghi, *J. Chem. Phys.*, **51**, 3671 (1969).
(3) R. Exelby and R. Grinter, *Chem. Rev.*, **65**, 247 (1965).
(4) (a) R. S. Becker and W. F. Richey, *J. Am. Chem. Soc.*, **89**, 1298 (1967); (b) M. Ottolenghi and D. S. McClure, *J. Chem. Phys.*, **46**, 4620 (1967).
(5) (a) D. Anderson and G. Wettermark, *J. Am. Chem. Soc.*, **87**, 1433 (1965); (b) G. Wettermark and L. Dogliotti, *J. Chem. Phys.*, **40**, 1486 (1964); (c) G. Wettermark, J. Weinstein, J. Sousa, and L. Dogliotti, *J. Phys. Chem.*, **69**, 1584 (1965).
(6) (a) W. G. Herkstroeter, *J. Am. Chem. Soc.*, **95**, 8686 (1973); (b) H. Kessler and D. Leibfritz, *Tetrahedron*, **26**, 1805 (1970).
(7) H. H. Freeman, *J. Am. Chem. Soc.*, **83**, 2900 (1961).
(8) A. R. Katritzky and B. J. Ridgewell, *Spectrochim. Acta*, **20**, 589 (1964).
(9) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1961, p 72.
(10) C. G. McCarty, "The Chemistry of the Carbon Nitrogen Double Bond", S. Patai, Ed., Interscience, New York, N.Y., 1970, pp 405–408.
(11) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).
(12) K. B. Wiberg, "Physical Organic Chemistry", Wiley, New York, N.Y., 1964, p 385.
(13) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms", Wiley, New York, N.Y., 1961, p 142.
(14) E. M. Kosower, "An Introduction to Physical Organic Chemistry", Wiley, New York, N.Y., 1968, pp 293–315, 334.
(15) (a) K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, **661**, 1 (1963); (b) C. Reichardt, *Angew. Chem., Int. Ed. Engl.*, **4**, 29 (1965); (c) C. Reichardt and K. Dimroth, *Fortschr. Chem. Forsch.*, **11**, 1 (1968); (d) C. Reichardt, *Justus Liebigs Ann. Chem.*, **752**, 64 (1971).
(16) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).
(17) G. Condorelli and L. L. Costanza, *Boll. Sedute Accad. Gioenia Sci. Nat. Catania*, **8**, 753, 775 (1966).
(18) Ultraviolet spectra were obtained on a Cary 14 recording spectrophotometer. NMR spectra were run on a Varian A-60A or a Perkin-Elmer R-12 spectrometer with internal tetramethylsilane as standard. Infrared spectra were determined for KBr pellets with a Beckman IR-12 instrument. Melting points were uncorrected, and microanalyses were performed by M-H-W Laboratories, Garden City, Mich.
(19) (a) A. J. Deinet and R. E. Lutz, *J. Am. Chem. Soc.*, **68**, 1325 (1946); (b) T. Rudolph, F. Przystal, and J. P. Phillips, *J. Med. Chem.*, **10**, 981 (1967).
(20) I. Amdur and G. Hammes, "Chemical Kinetics", McGraw-Hill, New York, N.Y., 1966, p 55.

Large-Scale Synthesis of Diammonium Acetyl Phosphate[1]

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A detailed procedure for the large-scale synthesis of diammonium acetyl phosphate (**1**) is presented. Ketene is used to acylate 100% phosphoric acid in ethyl acetate at −10°, and the resulting mixture of mono- and polyacetyl phosphoric acids converted to **1** by treatment with anhydrous ammonia in ethyl acetate–methanol at −10°. The product is obtained as an easily filtered, crystalline solid in ca. 90% yield and ca. 90% purity.

One limitation to the use of enzymatic catalysis in large-scale organic synthesis has been the expense of many of the common cofactors. As part of an effort to devise techniques that would make enzymatically catalyzed reactions requiring adenosine triphosphate (ATP) useful in practical synthesis, we have developed the reaction sequence outlined in eq 1 and 2 as a method for regenerating ATP from AMP and/or ADP.[2]

$$\text{ATP} + \text{AMP} \underset{\text{kinase}}{\overset{\text{adenylate}}{\rightleftharpoons}} 2\text{ADP} \quad (1)$$

$$2\text{ADP} + 2\text{AcP} \xrightarrow[\text{kinase}]{\text{acetate}} 2\text{ATP} + 2\text{Ac} \quad (2)$$

ADP is produced from ATP and AMP by phosphoryl transfer catalyzed by adenylate kinase. ADP is converted to ATP by reaction with acetyl phosphate (AcP) catalyzed by acetate kinase. Acetyl phosphate, the ultimate phosphorylating agent in this sequence, had been synthesized previously from phosphoric acid by acylation with acetyl chloride,[3] ketene,[4] isopropenyl acetate,[5] and acetic anhydride,[6,7] and isolated as the lithium or silver salts.[8] All of these procedures contain difficult work-up and isolation sequences. None are suitable for the preparation of acetyl phosphate in large quantity. Here we report a synthesis of diammonium acetyl phosphate from phosphoric acid, ke-

tene, and ammonia, which yields product in easily isolated form. This synthesis provides the most practical method available for synthesizing large quantities of acetyl phosphate.

Results

The reaction of ketene with phosphoric acid in an inert solvent yields mono-, di-, and (presumably) triacetylphosphoric acids. The relative amount of monoacetylphosphoric acid produced depends on the ratio of reactants used and on the extent of hydration of the phosphoric acid: water that is present is converted to acetic acid and acetic anhydride. Dilution of the reaction mixture obtained from ketene and phosphoric acid with methanol, and treatment of the resulting solution with anhydrous ammonia at −10°, yields diammonium acetyl phosphate (1) as an easily filtered, crystalline solid.

$$CH_2{=}C{=}O + H_3PO_4\ [+ H_2O] \xrightarrow[-10^\circ]{\text{solvent}}$$

$$CH_3COPO_3H_2 + (CH_3CO)_2PO_2H +$$

$$(CH_3CO)_3PO\ [+ CH_3CO_2H + CH_3COCCH_2] \xrightarrow[CH_3OH,\ -10^\circ]{NH_3}$$

$$CH_3COP(O^-NH_4^+)_2 + CH_3CNH_2\ [+ CH_3CO^-NH_4^+] \quad (3)$$

1

Isolation of acetyl phosphate as its diammonium salt has a number of advantages over other isolation procedures. First, 1 is sparingly soluble in methanolic solutions, and precipitates as a crystalline, easily filterable solid. Ammonium acetate and acetamide are soluble in methanol and can be separated on the basis of solubilities. Previous procedures have involved neutralization of the acetylphosphoric acid in aqueous solutions, and have required either the use of silver(I) salts to effect precipitation or the filtration of the phosphate "slimes" generated by neutralization with lithium acetate, carbonate, or hydroxides, followed by precipitation with ethanol. In addition, removal of water from the dilithium acetyl phosphate required a time-consuming and not always successful lyophilization or related procedure. Second, ammonia is expected to attack the acetyl moiety of diacetyl phosphate more rapidly than that of monoacetyl phosphate.[9] This appears to underlie the unexpectedly high yields (>90%) of 1 obtained by this procedure. Although we have not studied the reactions that occur during introduction of ammonia into the initial reaction mixtures in any detail, it seems that the excess of ammonia present at the conclusion of this stage must convert di- and triacetyl phosphates to 1. Third, 1 is very soluble in water, and ammonium ion is innocuous to most (although not all) enzymes.[10] Thus 1 can be used directly in the regeneration of ATP. Ammonia is inexpensive compared with lithium and silver salts. Finally 1 has adequate storage and solution stability (vide infra).

The number of products that can be formed by reaction of ketene with phosphoric acid containing some water is large. This complexity, combined with uncertainties concerning the details of this reaction and of the subsequent reaction of the product mixture with ammonia, make it difficult to define a priori the number of equivalents of ketene required to maximize conversion of phosphoric acid to diammonium acetyl phosphate. In this work, the ratio of added ketene to phosphoric acid originally present has simply been varied, and the yield of 1 determined. Results of this study are summarized in Figure 1 for acylations of both 85 and 100% phosphoric acid. These data establish that the maximum conversion (90–95%) of 100% phosphoric acid to 1 occurs for molar ratios of ketene to phosphoric acid of approximately 1.7. The decrease in yield observed

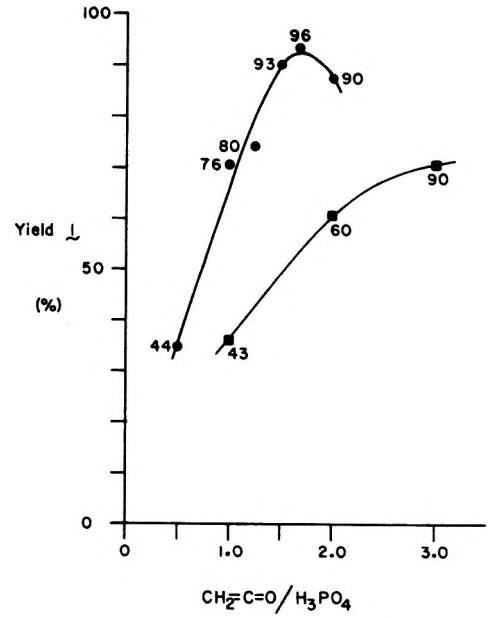

Figure 1. Yields of diammonium acetyl phosphate obtained following reaction of ketene with 100% phosphoric acid (●) and 85% phosphoric acid (■). Reactions were carried out in ethyl acetate solution at −10°, and the reaction mixtures were allowed to equilibrate for 2 hr at −10° before diluting with methanol and adding ammonia. The quantity ($CH_2{=}C{=}O/H_3PO_4$) is the number of moles of ketene added, divided by the total number of moles of phosphoric acid originally present. In 85% phosphoric acid, 1 mol of water is present for each mole of phosphoric acid. Yields are based on phosphoric acid. The numbers associated with each point represent the purity of the 1 isolated at that point; the major part of the impurity is ammonium phosphate in most instances.

for ratios greater than 2 reflects the fact that addition of ammonia to these reactions yields thick, difficultly filtered suspensions. The use of 85% phosphoric acid gave lower yields, apparently for the same reason. The effects of solvent, phosphoric acid water content, and temperature on yields of 1 were examined briefly: 100% phosphoric acid, prepared by dehydration of 85% phosphoric acid,[11] gave higher yields than dioxane diphosphate or 85% phosphoric acid; ethyl acetate was superior as a solvent to DMF, DME, di-*n*-butyl ether, and *n*-butyl acetate; raising the temperature above −10° during addition of ketene and equilibration resulted in lower yields.

The detailed course of the acylation of phosphoric acid with ketene has not been established.[12] In particular, it is not clear how rapidly intermolecular acyl or acetyl group transfer occurs. A qualitative observation made during this work does, however, suggest that intermolecular equilibration between diacetyl phosphoric acid and phosphoric acid occurs under the reaction conditions. A sample of 100% phosphoric acid was allowed to absorb 2 molar equiv of ketene. The resulting sample was treated with 1 additional equiv of phosphoric acid, allowed to equilibrate at −10° for 2 hr, and then worked up by the usual procedure, yielding 1 in 72% yield based on the *total* phosphoric acid involved in the mixture. Since the initial reaction mixture would have yielded ca. 45% of 1 (90%/2) on this basis had equilibration not occurred, the higher yield—which is also that obtained by direct reaction of 2 equiv of ketene with 2 equiv of phosphoric acid—suggests intermolecular equilibration.

$$(CH_3CO)_2PO_2H + H_3PO_4 \rightleftharpoons 2CH_3COPO_3H_2 \quad (4)$$

Ammonium ion, although normally innocuous as a component of an enzymatic reaction mixture, does occasionally reduce enzymatic activity,[10] and might interfere with other aspects of a synthetic sequence catalyzed by enzymes. It is possible to convert 1 to disodium acetyl phosphate by treatment with an ion exchange resin in water, although the yield is only moderate by the procedure we employed. It is also possible to use other amines (e.g., aniline) to neutralize the initial reaction mixture. The salts resulting from these reactions are less crystalline and more soluble in methanol, and this type of work-up offers no obvious advantages.

Compound 1 does contain a potential nucleophile (ammonia) in the presence of a reactive carbonyl group, and it was important to examine its stability. Solid 1 could be stored for extended periods at 4° without decomposition so long as it was protected from atmospheric moisture: no decrease in the purity of 1 in a desiccator was observed over 2 months at 4°. Storage in a desiccator for 1 month at 25° resulted in a 30% decrease in acetyl phosphate content. The solution stability of acetyl phosphate has been extensively studied.[9,13,14] In the region between pH 5.5 and 9.5, hydrolysis of dilithium acetyl phosphate takes place by P–O bond cleavage, apparently by a process involving metaphosphate anion.[15] Direct reaction with free amines does occur. The

$$CH_3COP(O^-)(O^-) \longrightarrow CH_3CO^- + PO_3^- \quad (5)$$

rate of addition of ammonia in equilibrium with ammonium ion would not, however, be expected to be competitive with the rate of reaction 5 at pH 6–8.[9] To check this prediction, the stability of 1 in buffered solutions at 39° was determined by observing its disappearance with time by means of the enzymatic assay. The hydrolysis of 1, followed to greater than 75% reaction, obeyed first-order kinetics from pH 5.83 to pH 9.30. At pH 6.9, the half-life was found to be 3 hr. The rate constants obtained in this work are in excellent agreement with those reported by Koshland for hydrolysis of dilithium acetyl phosphate.[13]

Experimental Section

General. All chemicals were reagent grade and were not further purified. Enzymes used in the assay of 1—acetate kinase (EC 2.7.2.1) and a commercial mixture of glucose 6-phosphate dehydrogenase (EC 1.1.1.49)/hexokinase (EC 2.7.1.1)—were obtained from Sigma Chemical Co. Authentic acetyl phosphate (Li, K salt), ADP (Na salt), and $NADP^+$ (Na salt) were also obtained from Sigma. Anhydrous ammonia was obtained from Matheson, and was used directly from the tank without purification. Phosphoric acid (100%) was made by the slow addition of 191.5 g of phosphorus pentoxide to 500 g of stirred 85% phosphoric acid at −10° (ice–acetone bath).[11] The final solution spontaneously crystallized after standing at room temperature for 48 hr. Ketene was produced by thermal cracking of acetone in a conventional apparatus similar to that described by Williams and Hurd.[16] The rate of generation, determined[17] by bubbling the output of the ketene generator through 50 ml of a cooled (0°), stirred solution of ethanolamine (3.184 *N*) in 2-propanol for 30 min and then titrating excess amine with standardized 1.0 *N* hydrochloric acid (Methyl Red as indicator), was found to be 0.198 ± 0.014 mol/hr under conditions used reproducibly throughout this work. Water used in enzymatic assays was distilled twice, the second time using a Corning Model AG-1b distillation apparatus. Small-volume aliquots for these assays were obtained using a Clay-Adams suction apparatus (obtained from Bectin Dickerson) and calibrated disposable micropipettes. Ultraviolet absorbance was measured using a Gilford Model 220 spectrophotometer. A Varian Model T-60 spectrometer was used for NMR assays. A Radiometer Model PHM 62 pH meter was used to determine pH values. Microanalysis were obtained by Midwest Microlab, Ltd., Indianapolis, Ind.

Diammonium Acetyl Phosphate (1). A 2-l. three-necked flask was fitted with a thermometer, a gas inlet tube, and an overhead stirrer. The stirrer shaft entered the flask through a fitting equipped with a side arm which served as a gas outlet. Ethyl acetate (750 ml) and 100% phosphoric acid (100 g, 1.02 mol) were transferred into the flask, and the resulting solution was cooled to −10° using an ethylene glycol–acetone–Dry Ice bath. Ketene was bubbled through the stirred solution for 10 hr (1.98 mol), after which 750 ml of methanol, precooled to −10°, was added. Anhydrous ammonia, directly from the tank, was passed through aluminum coils immersed in the cooling bath, then over the surface of the rapidly stirred solution, and finally out through a bubbler linked to the flask through the gas outlet on the stirrer. This addition was continued for 1.5 hr at a rate such that bubbles passed through the outlet bubbler at a rate of approximately one per second. During this time, the internal temperature of the solution gradually rose to −7° and then fell to −10°, signalling the end of the reaction. A total of 65 g of ammonia (3.82 mol) was used (as determined by weighing the tank before and after reaction), although not all was consumed by the reaction mixture. The fine solid which filled the flask was collected by suction filtration on a Buchner funnel. It was washed with 200 ml of methanol and 200 ml of anhydrous ether and transferred to a 1000-ml erlenmeyer flask. Methanol (350 ml) was added, and the resulting suspension was magnetically stirred for 10 min at room temperature. The solid was filtered as before and washed in succession with 150 ml of methanol and 500 ml of anhydrous ether. It was dried by covering the funnel with a piece of neoprene rubber, through which protruded a drying tube containing Drierite, and drawing air through it. Final drying to constant weight under vacuum gave 180.2 g of solid. Enzymatic assay (vide infra) showed that the solid contained 89% 1 by weight, corresponding to a 91% yield based on phosphoric acid. A NMR assay (vide infra) indicated a composition ratio of 91% 1, 4.4% acetamide, and 4.4% ammonium acetate. The sample was stored at 4° in a desiccator.

Anal. Calcd for $C_2H_{11}N_2O_5P$: C, 13.80; H, 6.37; N, 16.09. Found: C, 12.37; H, 6.56; N, 16.21.

Solvent was evaporated from the filtrate and the residue was dissolved in acetone. Filtration of this solution gave 266 mg of solid. Concentration of the filtrate and addition of ether gave 34.2 g (0.58 mol) of acetamide, mp 80–81.5 (lit. mp 81). Removal of solvent from the filtrate left 11.0 g of yellow oil of undetermined composition. The 1 and diammonium phosphate account for 100% of the phosphoric acid used originally. Diammonium acetyl phosphate, ammonium acetate, and acetamide collectively account for 80% of the ketene and 71% of the ammonia used.

Enzymatic Assay for 1. The enzymatic assay used to determine the yield and purity of 1 is based on three coupled enzymatic steps: reaction of adenosine diphosphate (ADP) and acetyl phosphate yielding adenosine triphosphate (ATP) catalyzed by acetate kinase; conversion of glucose to glucose 6-phosphate using this ATP catalyzed by hexokinase; and reduction of nicotinamide adenine dinucleotide phosphate ($NADP^+$) to NADPH by this glucose 6-phosphate catalyzed by glucose 6-phosphate dehydrogenase.

$$1 + ADP \xrightarrow{\text{acetate kinase}} ATP + CH_3CO_2^- \quad (6)$$

$$ATP + \text{D-glucose} \xrightarrow{\text{hexokinase}} ADP + \text{D-glucose 6-phosphate} \quad (7)$$

$$\text{D-Glucose 6-phosphate} + NADP^+ \xrightarrow[\text{6-phosphate dehydrogenase}]{\text{glucose}} \text{6-phospho-D-gluconic acid} + NADPH \quad (8)$$

The conditions used in the assay are such that the equilibrium constants for each reaction lie far to the right. Under these conditions, the number of equivalents of NADPH produced (measured spectrophotometrically at 340 nm) is equal to the number of equivalents of 1 added originally. This general assay scheme has been used previously.[18] The following standard solutions were prepared. Solution 1. To 300 mg of D-glucose and a mixture of 500 units of hexokinase and 250 units of D-glucose 6-phosphate dehydrogenase was added enough triethanolamine buffer (0.2 *M*, pH 7.6) containing magnesium chloride (0.03 *M*) to give 200 ml of solution. Solution 2. Water was added to 250 mg of ADP (Na salt) to give 1.0 ml

of solution. Solution 3. Water was added to 30 mg of $NADP^+$ (Na salt) to yield 1.0 ml of solution. Just prior to the assay, approximately 70 mg of 1 was brought to 10.0 ml with water (solution 4). To 5.0 ml of solution 1 was added 0.05 ml of solution 2, a 0.01-ml aliquot (ca. 8.5 units) of a suspension of acetate kinase in 3.2 *M* ammonium sulfate solution (supplied at 850 units/ml), and 0.05 ml of solution 3. The solution was allowed to incubate at 25° until its absorbance (measured at 340 nm using a 1-cm cell) had reached a plateau (ca. 3 min), and this absorbance (A_1) recorded. Another solution was prepared as above, but to this solution was added 0.01 ml of solution 4. The absorbance of this second solution (A_2) was then determined at 340 nm after a similar incubation. The absorbance A_1 corrects for the small amount of ATP present as a contaminant in the ADP, any NADPH contaminant in $NADP^+$, as well as other species which may have absorbance at 340 nm. For absorbances obtained using 1-cm cells, the following equation relates the difference, $(A_2 - A_1)$, to the numbers of moles of diammonium acetyl phosphate present in solution 4.

$$\text{moles of } \mathbf{1} = \frac{\text{total volume of assay solution}}{\epsilon_{NADPH}} \times 10^3(A_2 - A_1) = 8.20 \times 10^{-4}(A_2 - A_1)$$

NMR Assay for 1. Approximately 130 mg of the reaction product was dissolved in 0.4 ml of D_2O, and to this solution was added 0.01 ml of dioxane. The solution was stirred for 10 sec on a vortex-mixer, then transferred to an NMR tube, and the spectrum was recorded. The acetyl protons of 1 fall 1.63 ppm upfield from the dioxane protons, and are split into a doublet by coupling to phosphorus ($J \simeq 1.2$ Hz). Acetyl protons from acetamide present in the sample are found 1.75 ppm upfield from dioxane, while those from ammonium acetate are found 1.83 ppm upfield from dioxane. Integration of the dioxane peak and of the peaks due to 1 acetamide and ammonium acetate allows calculations of the percentages of these compounds found in the reaction mixtures.

Dianilinium Acetyl Phosphate. To 150 ml of ethyl acetate was added 20 g (0.204 mol) of 100% phosphoric acid, the solution was cooled to −10°, and ketene was bubbled through the stirred solution for 2 hr. A 75-ml portion of this solution was withdrawn, and to the remainder was added 125 ml of precooled methanol, followed by the dropwise addition of 30 g of aniline (2.5-fold excess) over a period of 10 min. During this time, the internal temperature of the solution remained at −10°. The resulting crystalline solid was collected by suction filtration on a sintered glass funnel, washed with 75 ml of acetone and 150 ml of ether, and dried by covering the funnel with a piece of neoprene rubber through which protruded a drying tube containing Drierite, and drawing air through the product. Enzymatic assay showed it to be 89.9% dianilinium acetyl phosphate. An NMR spectrum (DMSO-d_6) with dioxane as internal standard showed a broad multiplet (aromatic protons, 10 H, 3–4.2 ppm downfield from dioxane) and a doublet [acetyl protons, 3 H, 1.53 ppm upfield from dioxane ($J \simeq 2$ Hz)].

Anal. Calcd for $C_{14}H_{19}N_2O_5P$: C, 51.53; H, 5.87; N, 8.59. Found: C, 50.71; H, 5.95; N, 8.37.

Studies of the Rate of Hydrolysis of 1. Sodium phosphate–disodium phosphate buffers (0.2 *M* in total phosphate) were prepared with pH's 5.83, 6.90, and 8.00. A fourth solution (pH 9.30) was prepared from sodium carbonate–bicarbonate (0.2 *M*). The buffers were brought to 39°, and 50 ml of each was added to one of four 125-ml flasks containing ca. 70 mg of 1. The initial concentration of 1 in these solutions (ca. 8 m*M*) was determined by withdrawing a 50-μl aliquot and assaying enzymatically (vide supra). The decrease in concentration of 1 at 39° was followed until less than 25% remained. At least seven points were taken for each solution. The disappearance of 1 followed first-order kinetics, and led to these rate constants k_{obsd} (10^3 sec^{-1}) (pH): 4.33 (5.83); 3.78 (6.90); 3.78 (8.00); 4.35 (9.30).

Disodium Acetyl Phosphate. A 2 × 30 cm chromatography column (Pharmacia) was filled with 40 ml of the washed Bio-Rad AG MP-50 ion exchange resin (H^+ form, 100–200 mesh, 1.86 mequiv/ml) resin, and 100 ml of sodium hydroxide (1.0 *N*) was slowly (1 ml/min) passed through it. This neutralization was followed by washing with 250 ml of water. The column was equilibrated for 2 hr at 4°. Doubly distilled water was added to 1.0 g of 1 to make 4.0 ml of solution, and this solution was placed on the ion exchange column. Doubly distilled water was passed through the column at 1 ml/min, and 2.5-ml fractions were collected. These fractions were tested for the presence of acetyl phosphate by the hydroxylamine–ferric chloride test.[19] Fractions 1–6, pH 4.5, were devoid of acetyl phosphate; fractions 7–14, pH 5.5, contained acetyl phosphate. These fractions, when combined, were found to contain 85% of the initial acetyl phosphate by enzymatic assay.

Registry No.—**1**, 55660-58-7; ethyl acetate, 141-76-8; phosphoric acid, 7664-38-2; ketene, 463-51-4; ammonia, 7664-41-7; dianilinium acetyl phosphate, 55660-59-8; aniline, 62-53-3; disodium acetyl phosphate, 55660-60-1.

References and Notes

(1) Supported by the National Science Foundation (RANN), Grant GI 34284.
(2) C. R. Gardner, C. K. Colton, R. S. Langer, B. K. Hamilton, M. C. Archer, and G. M. Whitesides, "Enzyme Engineering", Vol. 2, E. K. Pye and L. B. Wingard, Jr., Ed., Plenum Press, New York, N.Y., 1974, p 209; G. M. Whitesides, A. Chmurny, P. Garrett, A. Lamotte, and C. K. Colton, *ibid.*, p 217.
(3) F. Lynen, *Chem. Ber.*, **73**, 367 (1940); (b) F. Lipmann and C. Tuttle, *J. Biol. Chem.*, **153**, 571 (1944).
(4) R. Bentley, *J. Am. Chem. Soc.*, **70**, 2183 (1948).
(5) F. Lipmann and E. R. Stadtman, *J. Biol. Chem.*, **185**, 549 (1950); D. E. Koshland, Jr., *J. Am. Chem. Soc.*, **73**, 4103 (1951).
(6) A. W. D. Avison, *J. Chem. Soc.*, 732 (1955); R. W. Porter, M. O. Modebe, and G. R. Stark, *J. Biol. Chem.*, **244**, 1846 (1969).
(7) E. Heyde, A. Nagabhushanian and J. F. Morrison, *Biochemistry*, **12**, 4718 (1973).
(8) E. Cherbuliez in "Organic Phosphorus Compounds", Vol. 6, G. M. Kosalopoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1973, p 211 ff.
(9) G. Di Sabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4393 (1961).
(10) Ammonium ion does act as an inhibitor (both competitive and noncompetitive) toward certain enzymes. For examples, see J. P. Hoare and K. J. Laidler, *J. Am. Chem. Soc.*, **72**, 2487 (1950); F. W. Sayre and E. Roberts, *J. Biol. Chem.*, **233**, 1128 (1958); P. Maeba and B. D. Sanwal, *Biochemistry*, **5**, 525 (1966). Also see R. J. P. Williams, *Q. Rev., Chem. Soc.*, **24**, 331 (1970); A. S. Mildman in "The Enzymes", Vol. II, P. D. Boyer, Ed., Academic Press, New York, N.Y., 1970, Chapter 9.
(11) R. N. Bell, *Anal. Chem.*, **19**, 97 (1947); L. F. Adrieth and O. F. Hill, *J. Chem. Educ.*, **25**, 80 (1948).
(12) A kinetic study of the acylation of carboxylic acids with dimethylketene in ether has been published: P. J. Lillford and D. P. N. Stachell, *J. Chem. Soc. B*, 885 (1968).
(13) D. E. Koshland, Jr., *J. Am. Chem. Soc.*, **74**, 2286 (1952).
(14) G. Di Sabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4400 (1961).
(15) J. Rebek and F. Gavina, *J. Am. Chem. Soc.*, **97**, 1591 (1975), and references cited therein.
(16) J. W. Williams and C. D. Hurd, *J. Org. Chem.*, **5**, 122 (1940).
(17) "Kirk-Othmer Encyclopedia of Chemical Technology", Vol. 8, 2nd ed., Interscience, New York, N.Y., 1952, p 109.
(18) R. S. Langer, Jr., "Enzymatic Regeneration of ATP", Thesis, Massachusetts Institute of Technology, 1974, p 434.
(19) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

The Ortho Effect in Hydrolysis of Phenyl Esters

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The effect of ortho substituents on the alkaline hydrolysis of substituted phenyl esters of acetic acid, *N,N*-dimethylcarbamic acid, diethylphosphoric acid, and *N*-methylcarbamic acid was analyzed using our recently developing method to correlate reactivity data of a set of ortho-, meta-, and para-substituted derivatives. The logarithmic value of the second-order rate constant was excellently correlated using $\log k = \rho\sigma_{o,m,p} + \delta E_s + fF + c$, where E_s and F are the Taft–Kutter–Hansch steric and the Swain–Lupton–Hansch field effect constants of ortho substituents, respectively. By means of the respective susceptibility constants, ρ, δ, and f, the role of ortho substituents in the hydrolysis reaction course was analyzed quantitatively.

Analyses of structure–reactivity relationships of hydrolytic reaction of phenyl phosphates and phenyl carbamates are important in order to gain better insight into their reactivities with acetylcholinesterase (AChE), which is believed to be the target for insecticidal action of these classes of compounds. A number of studies have been performed with the use of Hammett σ constants and related parameters.[1-7] Sometimes, the nature and site of the rate-determining process of the overall hydrolytic reaction sequence can be inferred from the value of the reaction constant ρ.[4-7] This approach is, however, only applicable to meta- and para-substituted derivatives. Since some ortho-substituted derivatives have been shown to be highly reactive with AChE,[8] it seems of significance to analyze the effect of ortho substituents and to know the role of "ortho effect" in the hydrolytic reaction course.

Recently, we have found that the logarithmic value of the alkaline catalyzed hydrolysis rate constant of substituted phenyl *N*-methylcarbamates is linearly related with the log K_A value of the corresponding phenols including ortho derivatives.[7] The effect of ortho substituents on the alkaline hydrolysis can be simulated by that on the acid dissociation of ortho-substituted phenols. However, the same procedure does not apply to other reactions. More recently, we have developed eq 1

$$\log k = \rho\sigma_{ortho} + \delta E_s + fF + c \quad (1)$$

to correlate reactivity data of a set of ortho-substituted derivatives including the unsubstituted parent compound.[9] In this equation, k is either the rate or equilibrium constant, E_s and F are the Taft–Kutter–Hansch steric[10,11] and Swain–Lupton field effect constants,[12] respectively, and ρ, δ, f, and c are susceptibility constants and the intercept which are determined by the method of least squares. It is assumed that (1) the total effect of ortho substituents is composed of ordinary polar, steric, and proximity polar effects, (2) the ordinary polar effect is equal to that of the corresponding para substituents, i.e., $\sigma_{ortho} = \sigma_{para}$, (3) the steric effect is represented by the E_s constant, and (4) the proximity polar effect is factored by the F constant. By mutual comparisons among eq 1, the corresponding Hammett equation (eq 2) and the combined equation (eq 3) for ortho-, meta-, and para-substituted derivatives, it has been shown that the proximity polar and steric effects of ortho substituents are excellently separable from the ordinary polar effect for a number of existing reactivity data.

$$\log k = \rho\sigma_{m,p} + c \quad (2)$$

$$\log k = \rho\sigma_{o,m,p} + \delta E_s^{ortho} + fF_{ortho} + c \quad (3)$$

In this paper, we have applied eq 1, 2, and 3 to the alkaline hydrolysis data of ortho-, meta-, and para-substituted phenyl diethyl phosphates, phenyl *N*-methylcarbamates, and phenyl *N,N*-dimethylcarbamates to analyze the ortho substituent effect on the hydrolytic reaction course. We have included, for comparison, a similar data set for substituted phenyl acetates. Phenyl acetates have been extensively used to delineate mechanisms of ester hydrolysis under various conditions[13-15] as well as with α-chymotrypsin.[16]

Materials and Method

Syntheses of Compounds. The phenyl acetates used are shown in Table I. Appropriate substituted phenol (0.1 mol) was stirred with acetyl chloride (0.2 mol) for 2 hr at room temperature and for 1 hr at 100°. The reaction mixture was poured onto ice and the oil which separated was extracted with ether, washed twice with saturated NaCl, dried over Na_2SO_4, and concentrated. The residual crude sample was purified either by repeated vacuum distillations or by recrystallizations from ethanol. The substituted phenyl dimethylcarbamates shown in Table I were synthesized as follows. To a solution of phosgene (0.12–0.15 mol) in anhydrous toluene (150 ml), an appropriate phenol (0.1 mol) in toluene (50 ml) was added dropwise with stirring at 0–5°. Subsequently anhydrous pyridine (0.11 mol) was added at 5–10°. Pyridine hydrochloride was filtered off and the filtrate was evacuated to remove excess phosgene. To the resulting toluene solution of the substituted phenyl chloroformate, 40% aqueous dimethylamine (22.5 g, 0.2 mol) was added at 10–15°. After the addition was complete, the toluene layer was washed three times with saturated NaCl, dried over Na_2SO_4, and evaporated in vacuo to give a crude sample of dimethylcarbamate which was purified either by repeated vacuum distillation or by recrystallizations from benzene–hexane. The ortho substituents were selected so that the simple correlation between F and E_s values is as low as possible. Some of compounds used which had not been previously reported were confirmed by elementary analysis for C and H.

Rate of Alkaline Hydrolysis. The reaction rate was followed spectrally using a Shimazu UV-200 double-beam spectrophotometer equipped with a thermostated cell at 25.0 ± 0.2°. The rate for phenyl acetates was measured at pH 9.14 ± 0.20 with 0.1 *M* Atkins–Pantin buffer (a mixture of 0.1 *M* Na_2CO_3 and 0.1 *M* H_3BO_3–KCl in a ratio (v/v) of 3.7:6.3), while that for dimethylcarbamates was at pH 13.95 ± 0.20 with 0.9 *N* NaOH. The initial concentration of substrate in the reaction mixture was 10^{-3}–10^{-4} *M*. Because of limited solubility of compounds, a certain amount of ethanol was contained in the reaction mixture: 10 vol % for dimethylcarbamates and 3 vol % for acetates. The pseudo-first-order rate constant, k_{hyd} in min^{-1}, was calculated from the initial rate of increase in the absorbance due to

Table I
Phenyl Esters of Acetic Acids and Dimethylcarbamic Acids[a]

Phenol substituents	Acetates mp or bp (mm), °C	Carbamates mp or bp (mm), °C	Phenol substituents	Acetates mp or bp (mm), °C	Carbamates mp or bp (mm), °C
H	81–82 (12)[b]	44–45[t]	*m*-Me	92–93 (13)[i]	129 (7)
o-F	79–80 (13)	113–114 (7)	*m*-Et	110–112 (19)[j]	
o-Cl	100 (9)[c]	130–131 (6)	*m*-OMe	127–128 (13)[k]	
o-Br	110–111 (13)[c]	148–149 (8)	*m*-NO_2	55[l]	62
o-I	126–127 (13)[d]	163–164 (7)	*m*-CN	58[m]	63–64
o-Me	87–88 (13)[e]	123–124 (7)	*m*-COMe		169–171 (7)
o-Et	105–106 (13)		*p*-F	81–82 (13)[n]	
o-*i*-Pr	103 (9)		*p*-Cl	109 (13)[o]	115 (0.3)[t]
o-*sec*-Bu		131–132 (8)	*p*-Br	120 (13)[p]	
o-*t*-Bu	112 (13)	107	*p*-Me	94 (14)[q]	52[t]
o-CF_3		46–47	*p*-Et	105–106 (13)[r]	
o-OMe	115 (13)[f]	142 (2)	*p*-*t*-Bu	119 (9)[j]	93–94
o-NO_2	41[g]	58	*p*-OMe	122 (14)[j]	66[t]
o-CN	143–144 (22)[h]		*p*-NO_2	79[l]	107–108[t]
m-F	77–78 (13)		*p*-CN	56[j]	67[t]
m-Cl		125–127 (4)	*p*-COMe	53[s]	123
m-Br	142 (34)[c]				

[a] All new compounds provided acceptable elemental analyses. [b] "Handbook of Table for Organic Compound Identification", 3rd ed. Chemical Rubber Publishing Co., Cleveland, Ohio, 1967, p 258. [c] W. J. Wohlleben, *Ber.*, **42**, 4369 (1909). [d] S. Buchan and H. McCombie, *J. Chem. Soc.*, 137 (1931). [e] K. Matsumoto and K. Han, *Bull. Chem. Soc. Jpn.*, **8**, 333 (1933). [f] F. Misani and M. T. Bogert, *J. Org. Chem.*, **10**, 347 (1945). [g] F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931). [h] B. Lach, *Chem. Ber.*, **17**, 1501 (1884). [i] K. Ono and M. Imoto, *Bull. Chem. Soc. Jpn.*, **11**, 127 (1936). [j] R. L. Van Etten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 3242 (1967). [k] F. Mauthner, *J. Prakt. Chem.*, **136**, 205 (1933). [l] T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **79**, 1663 (1957). [m] A. Clemm, *Ber.*, **24**, 826 (1891). [n] C. M. Suter, E. J. Lowson, and P. G. Smith, *J. Am. Chem. Soc.*, **61**, 161 (1939). [o] E. Klarmann, V. A. Shternov, and L. W. Gates, *ibid.*, **55**, 2576 (1933). [p] W. Autenrieth and P. Mühlinghaus, *Ber.*, **40**, 744 (1909). [q] J. Meisenheimer and L.-H. Chen, *Justus Liebigs Ann. Chem.*, **539**, 78 (1936). [r] W. S. Emerson, J. W. Heyd, V. E. Lucas, W. B. Cook, G. R. Owens, and R. W. Shotridge, *J. Am. Chem. Soc.*, **68**, 1665 (1946). [s] J. A. King and F. H. McMillan, *ibid.*, **68**, 2335 (1946). [t] R. D. O'Brien, B. D. Hilton, and L. Gilmour, *Mol. Pharmacol.*, **2**, 593 (1966).

Table II
Second-Order Rate Constant for the Alkaline Hydrolysis of Substituted Phenyl Acetates and *N,N*-Dimethylcarbamates

Substituent	Acetates[c] $10^{-2}\ k_s$,[a] $M^{-1}\ min^{-1}$	Carbamates[d] $10^{3}\ k_s$,[b] $M^{-1}\ min^{-1}$	Substituent	Acetates[e] $10^{-2}\ k_s$,[a] $M^{-1}\ min^{-1}$	Carbamates[f] $10^{3}\ k_s$,[b] $M^{-1}\ min^{-1}$
H	1.65	2.30	*m*-Me	1.45	2.00
o-F	4.63	3.18	*m*-Et	1.50	
o-Cl	3.35	2.06	*m*-OMe	2.22	2.57
o-Br	3.69	1.78	*m*-NO_2	12.2	14.7
o-I	3.30	1.30	*m*-CN	9.73	11.9
o-Me	0.74	0.64	*m*-COMe		5.62
o-Et	0.67		*p*-F	2.52	
o-*i*-Pr	0.61		*p*-Cl	3.64	5.88
o-*sec*-Bu		0.38	*p*-Br	3.33	
o-*t*-Bu	0.32	0.33	*p*-Me	1.45	1.89
o-CF_3		3.25	*p*-Et	1.21	
o-OMe	1.20	1.15	*p*-*t*-Bu	1.14	1.64
o-NO_2	13.1	4.51	*p*-OMe	1.43	2.11
o-CN	20.2		*p*-NO_2	18.6	25.0
m-F	4.66		*p*-CN	11.9	15.3
m-Cl		6.76	*p*-COMe	5.99	10.7
m-Br	4.70				

[a] 0.1 *M* Atkins-Pantin (Na_2CO_3-H_3BO_3) buffer, 3% ethanol, 25°. [b] 0.9 *N* NaOH, 10% ethanol, 25°. [c] Registry no. are, respectively, 122-79-2, 29650-44-0, 4525-75-1, 1829-37-4, 32865-61-5, 533-18-6, 3056-59-5, 1608-68-0, 3245-25-8, 613-70-7, 610-69-5, 5715-02-6, 701-83-7, 35065-86-2. [d] Registry no. are, respectively, 6969-90-0, 55682-12-7, 7305-01-3, 7305-04-6, 55682-13-8, 7305-06-8, 55379-70-9, 55682-14-9, 55682-15-0, 55682-16-1, 3373-86-2, 7305-02-4. [e] Registry no. are, respectively, 122-46-3, 3056-60-8, 5451-83-2, 1523-06-4, 55682-11-6, 405-51-6, 876-27-7, 1927-95-3, 140-39-6, 3245-23-6, 3056-64-2, 1200-06-2, 830-03-5, 13031-41-9, 13031-43-1. [f] Registry no. are, respectively, 7305-07-9, 7305-09-1, 7304-99-6, 55682-17-2, 2689-47-6, 7305-03-5, 7305-08-0, 5461-74-5, 7305-10-4, 7244-70-4, 14100-44-8, 52916-82-2.

the formation of phenoxide. The decrease in the substrate concentration was negligible and the rate of phenoxide formation was almost constant at least for the first 5 min under the present conditions. The second-order rate constant, k_{OH}, was estimated from k_{hyd} and pH values. The rate experiments were performed at least three times with different substrate concentrations. The average standard deviation in k_{OH} values is estimated as being 4%. k_{OH} values of phenyl acetates and dimethylcarbamates are listed in Table II. The rate constants of substituted phenyl diethyl phosphates are taken from the work of van Hooidonk and Ginjaar.[5] Those of phenyl *N*-methylcarbamates are

Table III
Log k Values Used in Correlations of Phenyl Diethyl Phosphates and Phenyl *N*-Methylcarbamates

	Substituent and log k, M^{-1} min^{-1}
Phosphates[a]	H: −1.56, *o*-Cl: −0.81, *o*-Br: −0.85, *o*-I: −0.94, *o*-C_2H_5: −1.94, *o*-*i*-C_3H_7: −1.99, *o*-OCH_3: −1.66, *o*-NO_2: 0.12, *m*-Cl: −1.03, *m*-Br: −1.00, *m*-CH_3: −1.67, *m*-OCH_3: −1.43, *m*-NO_2: −0.42, *p*-Cl: −1.16, *p*-Br: −1.12, *p*-I: −1.11, *p*-C_2H_5: −1.71, *p*-*i*-C_3H_7: −1.70, *p*-OCH_3: −1.78, *p*-SCH_3: −1.35, *p*-NH_2: −1.84, *p*-$COCH_3$: −0.71, *p*-CN: −0.42, *p*-NO_2: −0.18
N-Methylcarbamates[b]	H: 2.38, *o*-F: 3.89, *o*-Cl: 3.92, *o*-Br: 4.10, *o*-I: 4.01, *o*-CH_3: 1.67, *o*-C_2H_5: 1.67, *o*-*i*-C_3H_7: 1.69, *o*-C_3H_7: 1.66, *o*-*sec*-C_4H_9: 0.33, *o*-*t*-C_4H_9: 0.83, *o*-OCH_3: 2.53, *o*-OC_2H_5: 2.48, *o*-*i*-C_3H_7: 2.36, *o*-CN: 5.44, *o*-NO_2: 5.79, *m*-F: 3.30, *m*-Cl: 3.26, *m*-Br: 3.54, *m*-CH_3: 2.28, *m*-OCH_3: 2.55, *m*-CN: 4.10, *m*-NO_2: 4.44, *m*-$N(CH_3)_2$: 2.15, *p*-F: 2.40, *p*-Cl: 3.00, *p*-Br: 3.10, *p*-CH_3: 1.98, *p*-OCH_3: 1.79, *p*-CN: 5.00, *p*-NO_2: 5.66, 3,4-$(CH_3)_2$: 1.80

[a] From C. van Hooidonk and L. Ginjaar, *Recl. Trav. Chim. Pays-Bas*, 86, 449 (1967). [b] From T. Fujita, K. Kamoshita, T. Nishioka, and M. Nakajima, *Agric. Biol. Chem.*, 38, 1521 (1974).

previously reported values.[7] Their logarithm values are in Table III.

Substituent Parameters. The E_s value used in this work is not Taft $E_s°$ for the aromatic ortho substituents but the one for the aliphatic system,[10] which is a space-filling parameter as demonstrated by Charton.[17] For heteroatom substituents, the E_s value was estimated by eq 4

$$E_s = 3.484 - 1.839\, r_v \qquad (4)$$

where r_v is the average van der Waals radius according to Kutter and Hansch.[11] For the OR, SR, and NHR substituents, the values were calculated using oxygen, sulfur, and nitrogen radius only. For unsymmetrical top-type *o*-NO_2 group, two values of E_s were calculated corresponding to the group being either coplanar with or perpendicular to the reaction site by substituting the value of half-width or half-thickness of the group for r_v in eq 4. However, for reaction in this work, the value with the maximum dimension for the coplanar orientation gave much better correlations than the other. For these original E_s values, the point of reference is the methyl group, i.e., E_s(Me) = 0. In this work, however, the reference group is shifted to hydrogen for the sake of simplicity. The F values were first defined by Swain and Lupton,[12] but recently improved and extended by Hansch and coworkers.[18] The scale of the original set was not correct. The Taft σ_I constants[19] show rather small differences from the corresponding F values. The correlations using σ_I have been shown to be almost equivalent to or slightly poorer than those with eq 1 and 3 for various sets of reactivity data.[9] While we have selected here to use the Swain–Lupton–Hansch F constants, this does not necessarily mean that the Taft σ_I constants are not applicable to the current analyses. The relevant sets of substituent parameters are shown in Table IV.

Results

The three types of correlation, cor 1, 2, and 3, derived using eq 1, 2, and 3, respectively, are shown in Table V with some statistical values. The levels of significance of all the correlations presented in Table V are better than 99.5% as examined by the F test. Each term is justified above the 99% level by t test and represents a significant improvement above the 99% level over the corresponding equation minus that variable by F test, except for the E_s term in cor 1 of set 3, which is justified at the 97.5% level by t test and the 98.5% level by F test.

For phenyl acetates (set 1) and dimethylcarbamates (set 2), $\sigma°$ for the "insulated" substituent effect[20] is used to give correlations which are much better than those with σ and σ^-.[20] For meta- and para-substituted phenyl phosphates, a modified Yukawa–Tsuno equation[21] (eq 5)

$$\log k = \rho\sigma° + b\Delta\sigma + c;\ \Delta\sigma = \sigma^- - \sigma° \qquad (5)$$

(considering to a certain extent the through-resonance effect of para substituents) gives an excellent result (set 3, cor 2). The $b\Delta\sigma$ term is also statistically significant in cor 3 where the same effect is allowed for the corresponding ortho substituents. The ordinary polar effect of ortho substituents is expressed as $\sigma° + b(\sigma - \sigma°)/\rho$ in this case. However, in cor 1 for unsubstituted and ortho-substituted derivatives only, this term is statistically not significant. In this correlation, the *o*-NO_2 and *o*-OMe derivatives are those for which the values of σ and $\sigma°$ of substituent are different as apparent from Table IV. The value of $\Delta\sigma$ for the other six compounds is zero. The variation in the $\Delta\sigma$ value is so small that the contribution of this term cannot be established with statistical confidence.

The rate constants of meta- and para-substituted phenyl *N*-methylcarbamates are well correlated with σ^- (set 4, cor 2). However, when those of ortho-substituted derivatives are analyzed by assuming that $\sigma_{ortho} = \sigma_p^-$, the correlations give only poor results. If σ_{ortho} values are taken as σ_p instead of σ_p^-, the correlations are excellent (set 4, cor 1 and 3) where $\sigma\#$ (sigma mixed) is a set of σ_{ortho} (= σ_p), σ_m, and σ_p^-.

It is immediately apparent that, for each of the sets in Table V, ρ and c values of the usual Hammett equation for meta- and para-substituted derivatives (cor 2) are practically identical with those for ortho-substituted derivatives (cor 1) and for the combined data set (cor 3). The terms, δE_s and fF, in cor 1 correspond very well with those in cor 3. Thus, the assumptions which eq 1 is based upon hold generally only with a slight modification in the case of *N*-methylcarbamates.

Discussion

The hydrolysis of esters is generally regarded as following the addition intermediate path.[6,22] For the alkaline hydrolysis of phenyl esters, it is shown as Scheme I. Under conditions where a steady state is maintained for the addi-

Scheme I

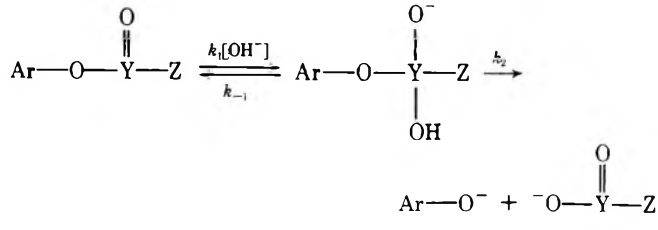


Table IV
Substituent Parameters Used for Correlations[a]

Substituent	σ_m[b]	σ_p[b]	σ_m°[c]	σ_p°[c]	σ_p^-[c]	E_s[d]	F[e]
H	0.0	0.0				0.0	0.0
Me	−0.07	−0.17		−0.12		−1.24	−0.04
Et	−0.07	−0.15		−0.13		−1.31	−0.05
i-Pr	−0.07[f]	−0.15		−0.16		−1.71	−0.05
n-Pr		−0.15[g]				−1.60	−0.06
sec-Bu		−0.15[g]		−0.16		−2.37	−0.05[g]
t-Bu	−0.10	−0.20		−0.17		−2.78	−0.07
OMe	0.12	−0.27	0.06	−0.16	−0.20[f]	−0.55	0.26
OEt	0.07[f]	−0.24	0.04[g]	−0.14[g]		−0.55	0.22
O-*i*-Pr		−0.45				−0.55	0.30
F	0.34	0.06	0.35	0.17	−0.02[f]	−0.49	0.43
Cl	0.37	0.23	0.37	0.27		−0.97	0.41
Br	0.39	0.23	0.38	0.26		−1.16	0.44
I	0.35	0.18	0.35	0.27		−1.40	0.40
CF_3	0.43	0.54			0.65	−2.40	0.38
COMe	0.38	0.50	0.38[f]	0.46	0.87[f]		
CN	0.56	0.66	0.62	0.69	0.90	−0.51	0.51
NO_2	0.71	0.78	0.70	0.82	1.24[f]	−1.01[h]	0.67
						−2.52[i]	
NH_2	−0.16	−0.66	−0.14	−0.38	−0.15		
NMe_2	−0.21[f]			−0.44		−0.61	0.10
SMe	0.15	0.0		0.08			

[a] Values used in this work are listed. When σ_p^- value is taken as σ_i° for substituents which do not undergo electron-withdrawing through-resonance, it is not shown. Likewise, if σ_m° value is equal to σ_m, it is not necessarily listed. [b] From the compilation of D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958), unless otherwise noted. [c] From ref 20 unless otherwise noted. [d] From ref 10 and 11; the point of reference is shifted to E_s of H; see text. [e] From ref 18. [f] From the compilation of M. S. Tute, *Adv. Drug Res.*, 6, 68 (1971). [g] Estimated from values of closely related substituents. [h] For the minimum steric effect of the perpendicular dimension. [i] For the maximum steric effect of the coplanar dimension.

tion intermediate, the overall second-order rate constant k_{sec} is expressed by the rate constants of elementary steps as eq 6. There are two extreme cases depending on the location of the rate-determining step.

$$k_{sec} = k_1k_2/(k_{-1} + k_2) \quad (6)$$

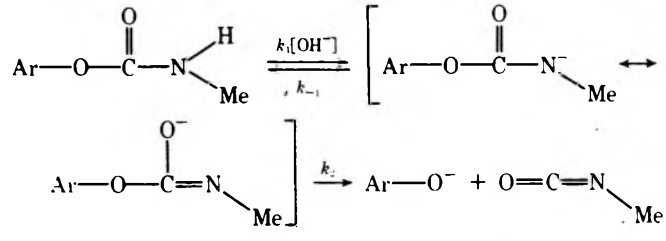
If the rate-determining step is the nucleophilic attack of OH^- on the carbonyl carbon and the phenoxide splitting occurs quickly, k_{sec} is reduced to k_1, since $k_2 \gg k_{-1}$ in eq 6. Since the site of reaction center in the rate-determining step is located at the second atom from the benzene ring, the rate constant k_{sec} is susceptible to the aromatic substituent effect probably to a degree similar to the acid dissociation of substituted benzoic acids (ρ = 1.0).[23] In fact, the ρ values for phenyl acetates and dimethylcarbamates are 1.18 and 1.16, respectively. Thus, for hydrolysis of these two series of esters, the hydroxide attack is rate limiting. The correlations with σ° indicate that the conjugation of the acyloxy group in phenyl acetates and dimethylcarbamates with the benzene ring occurs in neither initial nor intermediate state. Recently, Cohen and Takahashi[15] have shown evidence which supports the lack of the electron-attracting through-resonance effect of para substituents such as *p*-NO_2, -CN, and -$COCH_3$ on the phenoxy oxygen lone pair electrons in the hydrolysis of phenyl acetates. The steric inhibition of the conjugation of acyloxy group due to ortho substituents need not be considered.

The other extreme is the case where the addition occurs in a rapid equilibrium and the phenoxide splitting is rate limiting. Then, the overall second-order rate constant is expressed as $k_{sec} = k_2k_1/k_{-1}$, since $k_2 \ll k_{-1}$ in eq 6. In this case the reaction constant ρ will reflect the sum of those for steps k_1/k_{-1} and k_2. The ρ value for the preequilibrium step, k_1/k_{-1}, is expected to be around 1.0. The step k_2 can be considered to possess a ρ value about 2.0, similar to that for the dissociation of phenols.[23] Since the phenoxide splitting step, k_2, will be facilitated by the electron-attracting through-resonance effect and since it is more susceptible to the aromatic substituent effect than the preequilibrium intermediate formation, the rate constant is probably better correlated with σ^-.

The correlation for phenyl phosphates falls between the above described two extreme cases. Correlation 3 of set 3 indicates that the polar effect is best illustrated as a linear combination of σ° and σ^-: $1.42\sigma^\circ + 0.45(\sigma^- - \sigma^\circ) = 1.42(0.68\sigma^\circ + 0.32\sigma^-)$. The fact that the polar effect contains about 70% σ° character and the ρ value (1.42) is rather close to 1.0 suggests that the overall rate is mostly controlled by the step of hydroxide attack.

The ρ value for *N*-methylcarbamates (set 4) is close to what is expected for rate-determining phenoxide splitting mechanism with the use of σ^- for through-resonating para substituents. Unlike the above-described cases, however, the hydrolysis does not occur through the addition intermediate but via a quick preequilibrium deprotonation as shown in Scheme II.[4,7] Thus, the overall reaction constant,

Scheme II



ρ = 2.5, corresponds to the sum of those for the two consecutive steps. The deprotonation equilibrium seems to have a ρ value around 0.5, similar to the one for the acid dissociation of phenylacetic acids.[23] The fact that the correlations including ortho-substituted derivatives (cor 1 and 3) are

Table V
Correlation of Hydrolysis Data with Eq 1, 2, and 3[a]
$\log k = \rho\sigma + \delta E_s + fF + b\Delta\sigma + c$

Set no.	Esters and condition	Cor[b] no.	ρ	δ	f	b	c	n[c]	n_0[d]	s[e]	r[f]	F[g]
1	Acetates 3% EtOH–H_2O, 25° ($\log k_H$ = 2.22)	1	1.234σ° (±0.234)	0.185 (±0.045)	0.482[h] (±0.295)		2.263 (±0.085)	12	12	0.052	0.997	414.2
		2	1.174σ° (±0.057)				2.258 (±0.022)	18	0	0.037	0.996	1921.5
		3	1.180σ° (±0.054)	0.185 (±0.023)	0.538 (±0.094)		2.258 (±0.021)	29	12	0.041	0.997	1203.3
2	Dimethylcarbamates 10% EtOH–H_2O, 25° ($\log k_H$ = −2.64)	1	1.144σ° (±0.305)	0.232 (±0.102)			−2.684 (±0.168)	11	11	0.128	0.956	42.2
		2	1.145σ° (±0.096)				−2.591 (±0.041)	14	0	0.056	0.991	681.2
		3	1.164σ° (±0.121)	0.271 (±0.043)			−2.610 (±0.057)	24	11	0.095	0.983	302.0
3	Diethyl phosphates 2% i-PrOH–H_2O, 25° ($\log k_H$ = −1.56)	1	1.639σ° (±0.252)	0.090[i] (±0.060)	0.840 (±0.281)		−1.553 (±0.089)	8	8	0.034	0.999	1063.6
		2	1.405σ° (±0.090)			0.472[j] (±0.207)	−1.508 (±0.033)	17	0	0.052	0.996	785.3
		3	1.420σ° (±0.083)	0.134 (±0.047)	0.950 (±0.178)	0.445[j] (±0.181)	−1.510 (±0.028)	24	8	0.051	0.997	732.0
4	Methylcarbamates 10% EtOH–H_2O, 38° ($\log k_H$ = 2.38)	1	2.216σ (±0.349)	0.244 (±0.103)	3.233 (±0.471)		2.477 (±0.200)	16	16	0.133	0.997	605.9
		2	2.690σ^- (±0.161)				2.440 (±0.077)	17	0	0.128	0.994	1262.8
		3	2.541σ# (±0.144)	0.241 (±0.069)	2.989 (±0.285)		2.501 (±0.073)	32	16	0.148	0.994	802.1

[a] Unless otherwise noted, the value of ρ, δ, f, and b are justified by t test at better than the 99.5% level of significance. The figures in parentheses are the 95% confidence intervals. [b] Correlation number; see text. [c] The number of data used in the correlation. [d] The number of data of ortho-substituted derivatives including the unsubstituted ester. [e] Standard deviation. [f] Multiple correlation coefficient. [g] F value of the correlation. [h] Justified at a level between 99.5 and 99%. [i] Justified at a level between 99 and 97.5%. [j] $\Delta\sigma = \sigma^- - \sigma^\circ$.

excellent only when σ_{ortho} is taken as σ_{para} but not as σ^-_{para} indicates that the overlapping of phenoxy oxygen lone pair electrons with those of the benzene ring is seriously limited by ortho substituents and the electron-attracting through-resonance effect of ortho substituents is almost inhibited at the rate-limiting phenoxide splitting step.

It is interesting to compare correlations of set 4 with corresponding ones for log K_A of substituted phenols (eq 7–9). The ortho-substituted phenols are correlated with the use of σ and the whole set compounds are with σ# for the ordinary polar effect of substituents.[9] It is apparent that the correlations are quite similar to those for the N-methylcarbamate hydrolysis. In particular, the coefficients of three terms of eq 7 and 9 are nearly proportional to corresponding ones of cor 1 and 3 of set 4. The fact that the log K_A value of phenols is approximately linearly related with the log k value of phenyl N-methylcarbamate hydrolysis including ortho-substituted derivatives can be understood on this basis.

For ortho derivatives:

$$\log K_A = 2.196\ (\pm 0.749)\ \sigma + 0.199\ (\pm 0.148)\ E_s + 2.173\ (\pm 0.930)\ F - 9.727\ (\pm 0.308)$$
$$n = 14\ s = 0.203\ r = 0.990 \quad (7)$$

For meta and para derivatives:

$$\log K_A = 2.061\ (\pm 0.099)\ \sigma^- - 9.836\ (\pm 0.055)$$
$$n = 27\ s = 0.097\ r = 0.993 \quad (8)$$

For ortho, meta, and para derivatives:

$$\log K_A = 2.036\ (\pm 0.118)\ \sigma\# + 0.167\ (\pm 0.060)\ E_s + 2.395\ (\pm 0.260)\ F - 9.814\ (\pm 0.065)$$
$$n = 40\ s = 0.134\ r = 0.992 \quad (9)$$

The δ values for sets 1 and 2 are positive and close to each other (0.22 ± 0.03) indicating that the space-filling effect of ortho substituents is inhibitive of the reactivity and is similar between these two sets of phenyl esters. The sterically critical rate-determining step of these reactions is located at a quite similar geometrical position relative to the benzene ring. Since the steric inhibition of resonance does not seem to be important, the ortho substituents probably hinder the approach of nucleophile to the reaction site and/or prevent the formation of space-requiring tetrahedral addition intermediate according to their space-filling dimensions. Recently, the magnitude of δ values has been deduced to be a function of the distance between ortho substituent and the reaction site from 44 sets of analyses.[9] Nearly constant δ values have been found for eight benzoyl transfer (0.63 ± 0.14) and three phenylacetyl transfer (0.39 ± 0.01) reactions.[9]

The transition state of phenyl phosphates is more advanced on the reaction coordinate than that of the above esters as suggested by the polar effect of substituents being expressed as a linear combination of σ° and σ^-. Thus, their phenoxy-oxygen–phosphorus bond seems to be weakened and extended more than the corresponding bond of the above esters. However, this bond extension does not significantly modify the steric course of the hydrolysis, resulting in only slightly smaller δ value.

The δ value for set 4 for N-methylcarbamates is similar to values for sets 1 and 2. However, differing in the reaction mechanism from these systems, it probably indicates the susceptibility of critical phenoxide formation to the steric effect of ortho substituents. In fact, it may be taken as rather similar to the values in eq 7 and 9 for log K_A of phenols. The steric effect on the preequilibrium deprotonation

occurring at the third atom from the benzene ring does not seem to be involved in this δ value.

In the present correlations, the steric effect of o-NO_2 group is fit best with the E_s value for its maximum dimension. In the sterically critical step of hydrolysis reactions, the o-NO_2 group seems to remain coplanar with the benzene ring. The conjugation of the o-NO_2 group is not inhibited, while the intergroup through-resonance between o-NO_2 and acyloxy groups is not significant.

Substituent effects on the hydrolytic reaction course of phenyl acetates and dimethylcarbamates are very similar to each other including ortho-substituted derivatives as far as the ordinary polar and steric effects are concerned. However, the proximity polar effect of ortho substituents significantly differs between these two series. A distinct proximity effect appears to be involved for the ortho-substituted phenyl acetates (set 1, cor 1 and 3) while not significant for the ortho-substituted dimethylcarbamates (set 2, cor 1 and 3). As suggested in our recent analyses, the magnitude of f may be subject not only to the distance between reaction site and the benzene ring but also to the side chain structure to some extent.[9] Even though the geometrical location of the rate-limiting reaction site is similar to the above cases, the negative f value (-0.29 ± 0.05) has been found for three phenylacetyl transfer reactions.[9]

The large f value (3.0) for set 4 should come mostly from a high susceptibility of the rate-determining phenoxide formation step to the electron-withdrawing proximity polar effect of ortho substituents, which can be compared with that for the dissociation of phenols, 2.4 in eq 7 and 9. The difference may be attributed to the effect of ortho substituents on the preequilibrium deprotonation step. The f value, 0.90 ± 0.04, for set 3 is larger than that for set 1 of phenyl acetates. It may be mostly attributed to the step of addition intermediate formation, containing in part a component due to the phenoxide splitting.

The above work indicates that the ortho effect on the alkaline hydrolysis of phenyl esters can be analyzed quantitatively by means of δ and f terms of component effects overlapping on the ordinary polar effect of ortho substituents. The component effects participate in the total effect of ortho substituents generally to varying degrees according to reaction systems. We must be careful in discussing mechanism of reactions of these classes of compounds including ortho derivatives with enzyme systems so as to select reference reaction systems and conditions as close as possible to those of the enzymatic reactions.

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References and Notes

(1) T. R. Fukuto and R. L. Metcalf, *J. Agric. Food Chem.*, **4**, 930 (1956).
(2) C. Hansch, *J. Org. Chem.*, **35**, 620 (1970).
(3) R. D. O'Brien, B. H. Hilton, and L. Gilmour, *Mol. Pharmacol.*, **2**, 593 (1966).
(4) T. Vontor and M. Večeřa, *Collect. Czech. Chem. Commun.*, **38**, 516 (1973).
(5) C. van Hooidonk and L. Ginjaar, *Recl. Trav. Chim. Pays-Bas*, **86**, 449 (1967).
(6) S. A. Khan and A. J. Kirby, *J. Chem. Soc. B*, 1172 (1970).
(7) T. Fujita, K. Kamoshita, T. Nishioka, and M. Nakajima, *Agric. Biol. Chem.*, **38**, 1521 (1974).
(8) R. L. Metcalf, *Bull. W. H. O.*, **44**, 43 (1971).
(9) T. Fujita and T. Nishioka, *Prog. Phys. Org. Chem.*, in press.
(10) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1955, p 556.
(11) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).
(12) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4328 (1968).
(13) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, **86**, 418 (1964).
(14) R. L. van Etten, G. A. Clowes, J. F. Sebastian, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 3253 (1967).
(15) L. A. Cohen and S. Takahashi, *J. Am. Chem. Soc.*, **95**, 443 (1973).
(16) M. L. Bender and K. Nakamura, *J. Am. Chem. Soc.*, **84**, 2577 (1962).
(17) M. Charton, *J. Am. Chem. Soc.*, **91**, 615 (1969).
(18) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
(19) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958); **81**, 5343 (1959).
(20) O. Exner, *Adv. Linear Free Energy Relat.*, 27 (1972).
(21) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jpn.*, **32**, 965 (1959).
(22) A. J. Kirby in "Comprehensive Chemical Kinetics", Vol. 10, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, 1973, Chapter 2.
(23) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

3-Cycloalkenylindoles

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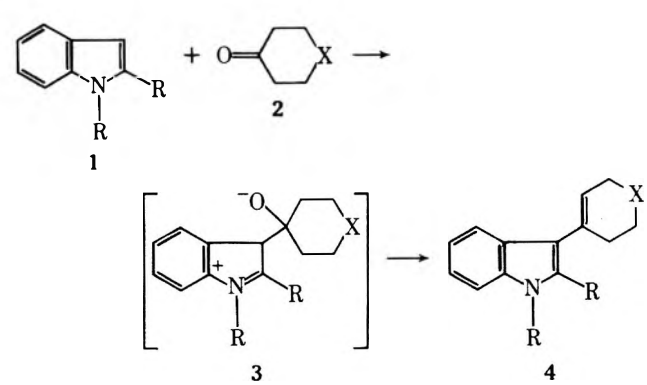
A simple method for the preparation of the title compounds 4 is described and demonstrated on a variety of indoles (1) and ketones (2). Some reactions of these new derivatives are discussed.

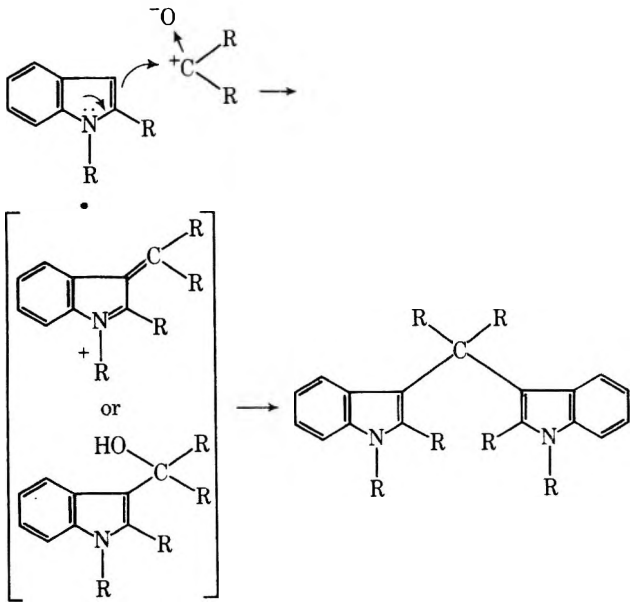
Reactions of indoles with ketones under acidic conditions are well documented.[1] The general course is electrophilic attack by the carbonyl carbon at the indole 3 position, leading via 3-methyleneindolenines or indolyl-3-carbinols to diindolylmethanes (Scheme I).

We found that cyclic ketones (2), contrary to this general observation, give 1:1 reaction products with 3-unsubstituted indoles (1). This reaction proceeds with a wide variety of cyclic ketones in excellent yields, affording indole derivatives of the general formula 4, hitherto little known[2,3] and accessible only via tedious de novo syntheses. Obviously, the intermediates 3 stabilize by water elimination.

The scope of this reaction was investigated using 1,2-



Scheme I



dimethylindole and a number of cyclic ketones (Table I) and secondly by combining *N*-methyl-4-piperidone with a number of indoles (Table II).

The variety of ketones leading to cycloalkenylindoles can be seen from Table I. The reaction did not proceed with the following cyclic ketones: tetrahydrofuranone, cyclopentanone, and adamantanone.

Some ketones were selected with the expectation to find biologically interesting compounds; e.g. **6** and **7** (4o) and their hydrogenation product **8** are cyclic tryptamines.

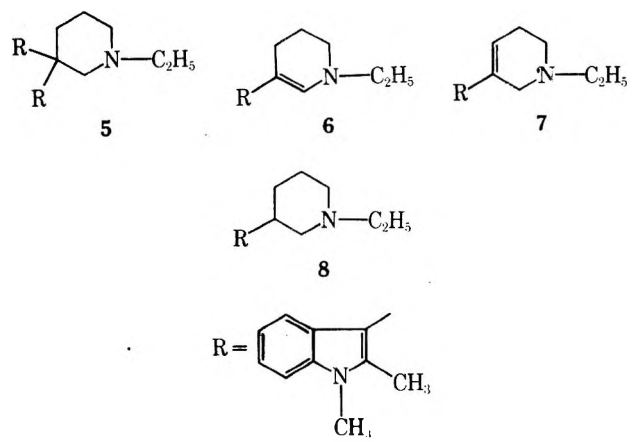
The same concept governed our choice of indoles in Table II, giving some preference to 5-substituted indoles.

Some reactions with unsymmetrically substituted ketones produced the expected mixture of isomers.

The product **4d**, obtained from 1,2-dimethylindole and ethyl cyclohexanone-2-carboxylate and subsequent saponification, is a mixture of the 1- and 2-unsaturated isomers, as shown by their NMR spectrum.

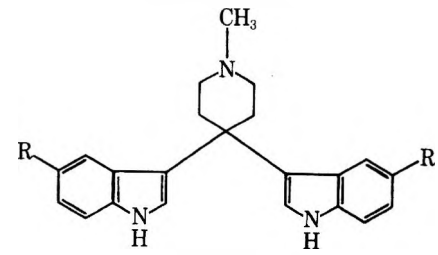
A similar mixture was detected by TLC in the case of **4m**. A small part of the α,β-unsaturated ester could be separated by column chromatography. The remaining mixture crystallized as hydrochlorides and showed an NMR spectrum indicative for a ratio of α,β:β,γ-unsaturated esters of 3:1.

The reaction of *N*-ethyl-3-piperidone with 1,2-dimethylindole resulted in three compounds which could be separated on silica: the dimer (**5**), the 2,3-piperideine (**6**), and the 3,4-piperideine (**7**).



Hydrogenation of either **6** or **7** gave the indolylpiperidine **8**.

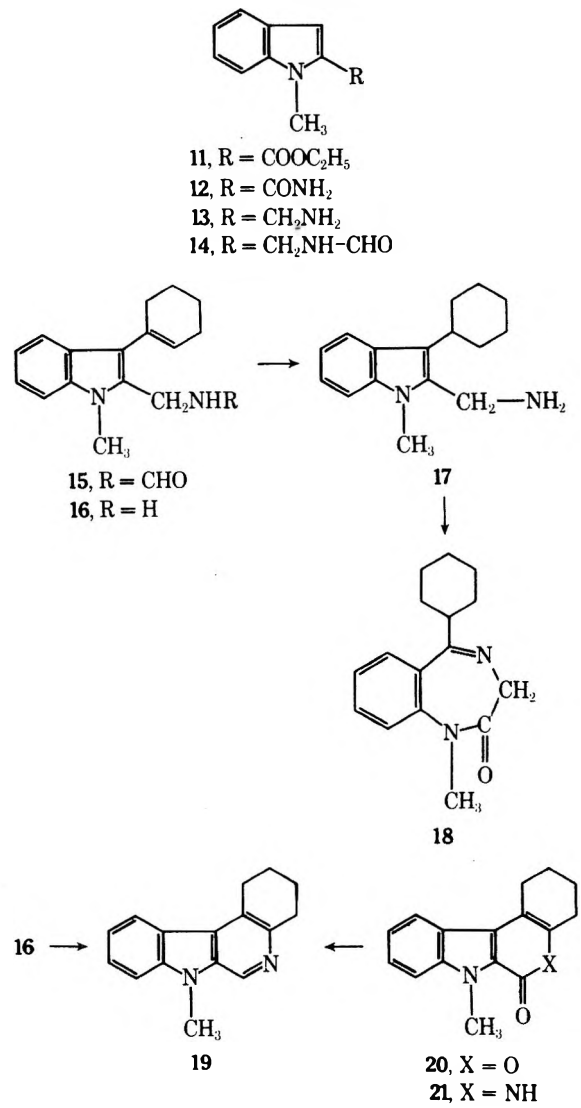
The 1,2,3-unsubstituted indoles gave under these conditions a considerable amount of the bisindolylcycloalkanes, **9** and **10**, in addition to the main products **4q** and **4r**.



9, R = H
10, R = OCH_3

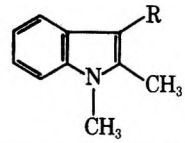
Ethyl 1-methylindole-2-carboxylate (**11**), 1-methylindole-2-carboxamide (**12**), and 1-methyl-2-aminomethylindole (**13**) failed to react with cyclohexanone and *N*-methyl-4-piperidone. We were especially interested in this reaction and succeeded finally with 1-methyl-2-formylaminomethylindole (**14**) and cyclohexanone (Scheme II). The resulting

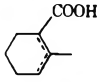
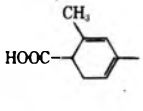
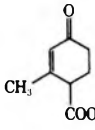
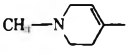
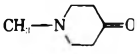
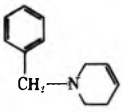
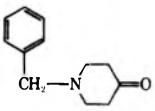
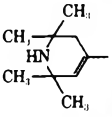
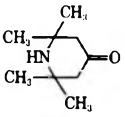
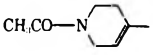
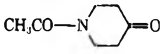
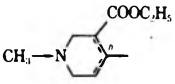
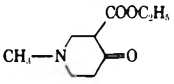
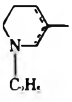
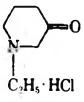
Scheme II



product (**15**), after hydrolysis and hydrogenation, smoothly underwent the chromium trioxide oxidation–rearrangement of Yamamoto et al.[4] to the benzodiazepine **18**. Under

Table I[a]



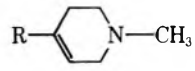
4	R	Ketone 2	Reaction time	Temp, °C	Yield, %	Mp, °C	Empirical formula	Calcd / Found	C, %	H, %	N, %
a			40 min	60–70	89	109	$C_{16}H_{19}N$	Calcd	85.28	8.50	6.22
								Found	85.54	8.35	6.30
b			4 hr	90	75	161[b]					
c			4 hr	60	85	165–168	$C_{16}H_{17}NO$	Calcd	80.30	7.16	5.85
								Found	80.10	7.34	5.87
d			1 hr	75	69[d]	153–155	$C_{17}H_{19}NO_2$	Calcd	75.81	7.11	5.20
								Found	75.76	7.05	5.28
e			90 min	75	30[e]	168–171	$C_{18}H_{19}NO_2$	Calcd	76.84	6.81	4.98
								Found	76.82	6.89	5.08
f			6 hr	70	97	118	$C_{15}H_{17}NS$	Calcd	74.05	7.04	5.76
								Found	73.99	6.89	5.82
g			30 min	60	95	79 270–275[f]	$C_{16}H_{20}N_2 \cdot HCl$	Calcd	69.40	7.66	10.11
								Found	69.07	7.55	9.89
h			2 hr	60	85	246[f]	$C_{22}H_{24}N_2 \cdot HCl$	Calcd	74.87	7.14	7.93
								Found	74.67	7.67	7.93
i			60 min	60	87	76 255–265[f]	$C_{15}H_{18}N_2 \cdot HCl$	Calcd	68.56	7.29	10.66
								Found	68.64	7.45	10.57
k			90 min	80	82	112	$C_{19}H_{26}N_2$	Calcd	80.80	9.28	9.92
								Found	80.45	9.31	9.97
l			3 hr	20	95	199	$C_{17}H_{20}N_2O$	Calcd	76.08	7.51	10.43
								Found	76.02	7.52	10.37
m			7 hr	110	67[h]	197[i]	$C_{19}H_{24}N_2O_2 \cdot HCl$	Calcd	65.41	7.22	8.03
								Found	65.66	6.94	8.10
n			23 hr	60	85	118 260[f]	$C_{18}H_{22}N_2 \cdot HCl$	Calcd	71.38	7.65	9.25
								Found	71.26	7.51	9.14
o			90 min	75	*k*						
p			13 hr	80	40	148	$C_{20}H_{24}N_2O_2$	Calcd	74.04	7.46	8.64
								Found	73.98	7.58	8.68

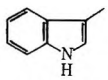
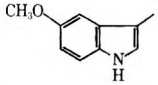
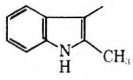
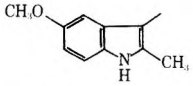
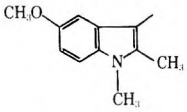
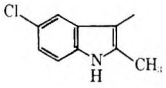
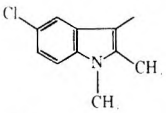
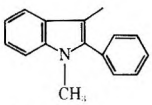
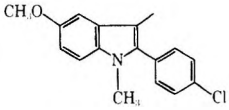
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in this table. [b] See also literature.[5] [c] Or from 3-ethoxy-2-cyclohexen-1-one. [d] The crude ester was saponified with KOH–ethanol to give this yield of crystalline acid, a mixture of two isomers. See text. [e] The crude ester was saponified, overall yield. [f] Hydrochloride. [g] 4-Piperidone monohydrate hydrochloride. [h] Mixture of both isomers. [i] 1,2-Dimethyl-3-[4-(1-methyl-3-ethoxycarbonyl-1,2,5,6-tetrahydropyridyl)]indole hydrochloride. [k] See text.

the same conditions, the unsaturated intermediate **16** cyclized and dehydrogenated to the carboline **19**, which we synthesized independently from the indolocoumarin **20**[5] via **21** as indicated in Scheme II.

The structures of **4** were verified by elemental analyses, spectral evidence (all show the characteristic vinyl proton at δ 5.8), and subsequent reactions. Hydrogenation, wherever attempted, yielded smoothly the cycloalkylindoles, as shown for **8**. Dehydrogenation of **4e** under the usual conditions afforded the expected substituted phenylindole **22**.

Table II[a]



4	R	Reaction time, hr	Temp, °C	Yield, %	Mp, °C	Empirical formula	Calcd / Found	C, %	H, %	N, %	Registry no.
q		4	90	45 + 30% 9	210–220[b] dec						120-72-9
r		2	reflux	50 + 35% 10	235 dec	$C_{15}H_{18}N_2O$	Calcd Found	74.34 74.24	7.48 7.63	11.56 11.60	1006-94-6
s		2	70	91	139–141	$C_{15}H_{18}N_2$	Calcd Found	79.60 79.53	8.02 7.89	12.38 12.48	95-20-5
t		1	70	88	137	$C_{16}H_{20}N_2O$	Calcd Found	74.96 74.87	7.86 7.72	10.93 11.03	1076-74-0
u		1	60	80	104	$C_{17}H_{22}N_2O$	Calcd Found	75.52 75.49	8.20 8.00	10.36 10.04	17591-06-9
v		2	60	85	155	$C_{15}H_{17}ClN_2$	Calcd Found	69.08 68.89	6.57 6.65	10.74 10.69	1075-35-0
w		1	60	63	95	$C_{16}H_{19}ClN_2$	Calcd Found	69.93 69.84	6.96 7.02	10.19 10.07	55556-49-5
x		8	80	60	103	$C_{21}H_{22}N_2$	Calcd Found	83.40 83.76	7.33 7.42	9.26 9.15	3558-24-5
y		6	80	50	251[c]	$C_{22}H_{23}ClN_2O \cdot HCl$	Calcd Found	65.50 66.09	5.99 6.34	6.94 6.89	55556-50-8

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compunds listed in this table. [b] See literature.[3] [c] Hydrochloride.

Experimental Section[9]

General Procedure for the Preparation of 3-Cycloalkenylindoles (4). The appropriate indole derivative (20 g) was dissolved in 400 ml of glacial acetic acid. When the temperature stated in Table I or II was reached, 100 ml of 2 *N* phosphoric acid and an 1.5–3 molar excess of the appropriate ketone was added. The mixture was stirred at this temperature for the time indicated. In some cases the end product was collected by filtration after cooling; in many cases the mixture was poured on ice–ammonia and the reaction products were extracted, mainly with ethyl acetate and worked up as usual. A typical[7] uv spectrum (**4g**): λ_{max} 230 nm (ϵ 24,000), 285 (6200).

3-(1,2-Dimethyl-3-indolyl)-*N*-ethyltetrahydropyridines (6 and 7). 1,2-Dimethylindole (10 g, 69 mmol) and 1-ethyl-3-piperidone hydrochloride (15 g, 91 mmol) were allowed to react as shown in the general procedure for **4o**. The resulting oil was separated on silica [20 cm column, 8 cm diameter, eluent chloroform–methanol (97:3)].

The first (**6**) of the three main reaction products (TLC) was an oil, 4.7 g, which gave a crystalline hydrochloride from ethanol–ether: mp 95–100°; 3.3 g (17%); NMR (D_2O) δ 8.4 (s, 1), 7.5–7.1 (m, 4), 4.2–3.8 (m, 4), 3.7 (s, 3), 2.5 (s, 3), 2.5–1.9 (m, 4), 1.6 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{17}H_{22}N_2$·HCl: C, 70.18; H, 7.98; N, 9.63. Found: C, 70.34; H, 7.76; N, 9.32.

The second fraction crystallized from ethanol and appeared to be 3,3-bis(1,2-dimethyl-3-indolyl)-1-ethylpiperidine (**5**): yield 2.2 g (16%); mp 182°; NMR ($CDCl_3$) δ 8.4–8.2 (m, 1), 8.3–7.8 (m, 1), 7.2–6.9 (m, 6), 4.0–1.5 (m, 10), 3.25 (s, 3), 3.20 (s, 3), 1.35 (s, 3), 1.30 (s, 3), 0.9 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{27}H_{33}N_3$: C, 81.15; H, 8.32; N, 10.51. Found: C, 80.91; H, 8.45; N, 10.31.

The major component eluted last from the column (**7**) yielding 9.8 g (56%) of a clear oil. It crystallized as the picrate from ethanol: mp 172°; NMR (DMSO-d_6) δ 9.6 (s, 1), 8.6 (s, 2), 7.6–6.9 (m, 4), 5.8 (s, broad, 1), 4.0 (s, 2), 3.7 (s, 3), 3.7–2.3 (m, 6), 2.4 (s, 3), 1.3 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{17}H_{22}N_2 \cdot C_6H_3N_3O_7$: C, 57.13; H, 5.21; N, 14.49. Found: C, 57.44; H, 5.24; N, 14.75.

3-(1,2-Dimethyl-3-indolyl)-*N*-ethylpiperidine Hydrochloride (8). Hydrogenation of either **6** or **7** in ethanol at room temperature and 50 psi over palladium on charcoal and subsequent treatment with hydrochloric acid afforded the title compound in almost quantitative yield: mp 250°; NMR ($CDCl_3$) δ 12.1 (s, 1), 7.8–6.9 (m, 4), 4.2–1.7 (m, 11), 3.6 (s, 3), 2.4 (s, 3), 1.4 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{17}H_{24}N_2$·HCl: C, 69.69; H, 8.60; N, 9.56. Found: C, 69.80; H, 8.71; N, 9.68.

4,4-Di(3-indolyl)-1-methylpiperidine (9). The reaction mixture from indole and a twofold excess of 1-methyl-4-piperidone (see general procedure for **4q**) was chromatographed on silica with chloroform–methanol–ammonia (70:29:1). The main fraction leaving the column first was compound **4q** (see Table II). The second fraction (30%) crystallized from methanol: mp 295–300°; NMR (DMSO-d_6) δ 10.8 (s, 2), 7.6–6.5 (m, 10), 2.8–2.3 (m, 8), 2.2 (s, 3).

Anal. Calcd for $C_{22}H_{23}N_3$: C, 80.20; H, 7.03; N, 12.75. Found: C, 80.14; H, 7.12; N, 12.67.

4,4-Bis(5-methoxy-3-indolyl)-1-methylpiperidine (10). This

compound was obtained analogously to 9, as a by-product in the preparation of **4r**: mp 275–280° dec from ethyl acetate; yield 35%; NMR (DMSO-d_6) δ 10.6 (s, 2), 7.5–6.5 (m, 8), 3.6 (s, 6), 2.7–2.4 (m, 8), 2.2 (s, 3).

Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.00; H, 6.98; N, 10.78. Found: C, 73.86; H, 7.15; N, 10.75.

1-Methyl-2-formylaminomethylindole (14). 1-Methyl-2-aminomethylindole (13[6] 1.8 g, 11 mmol) was heated to reflux for 6 hr in 20 ml of ethyl formate. The residue after evaporation was recrystallized from ethyl acetate–petroleum ether: yield 1.6 g (75%); mp 110–112°; NMR ($CDCl_3$) δ 8.0 (s, 1), 7.6–6.9 (m, 4), 6.3 (s, 2), 4.4 (d, 2, J = 6 Hz), 3.5 (s, 3).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.61; H, 6.65; N, 15.28.

1-Methyl-2-formylaminomethyl-3-cyclohexen(1)ylindole (15). A mixture of 14 (10 g, 50 mmol), cyclohexanone (20 ml, 190 mmol), glacial acetic acid (200 ml), and 4 N phosphoric acid (100 ml) was heated under stirring at 70° for 7 hr. After cooling to room temperature, water (40 ml) was added and the mixture was kept at 5° overnight. The crystalline reaction product was collected, washed with water, and recrystallized from ethanol: yield 5.9 g (42%); mp 178°; NMR ($CDCl_3$) δ 8.1 (s, 1), 7.7–6.9 (m, 4), 5.9 (s, 1), 5.6 (s, 1), 4.6 (d, 2, J = 6 Hz), 3.6 (s, 3), 2.5–2.0 (m, 4), 2.0–1.6 (m, 4).

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.54; H, 7.31; N, 10.73.

1-Methyl-2-aminomethyl-3-cyclohexen(1)ylindole (16). A solution of the above formyl compound (**15**, 17.3 g, 65 mmol) in 300 ml of ethanol and 15 ml of 30% sodium hydroxide was heated to reflux for 5 hr. The solution was filtered, concentrated in vacuo, and extracted with ether. The ether extracts were washed, dried, and evaporated. The solid residue (15.2 g, 97%) was used as such for the next step. A sample was crystallized from petroleum ether: mp 56°; NMR ($CDCl_3$) δ 7.6–6.8 (m, 4), 5.6 (s, 1), 3.9 (s, 2), 3.6 (s, 3), 2.5–2.0 (m, 4), 1.9–1.4 (m, 4), 1.2 (s, 2, NH_2).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 80.28; H, 8.50; N, 11.70.

1-Methyl-2-aminomethyl-3-cyclohexylindole (17). The above described unsaturated compound **16** (5.8 g, 24 mmol) was dissolved in 200 ml of ethanol and shaken with 0.5 g of palladium on charcoal (10%) at room temperature and about 40 psi hydrogen pressure for 3 days. The residue after filtration and evaporation was a light oil (5.8 g, 100%). Aside from the NMR spectrum, no attempt was made to characterize it. The spectrum was essentially unchanged from the one of the starting material; only the vinyl proton signal at δ 5.6 was missing and the cyclohexyl portion was more complex.

2-Oxo-1-methyl-5-cyclohexyl-2,3-dihydro-1*H*-1,4-benzodiazepine (18). The crude cyclohexylindole **17** (5.5 g, 23 mmol) was dissolved in 30 ml of glacial acetic acid and cooled to 15°. A solution of chromium trioxide (5 g) in 5 ml of water was added under stirring in such a way that the temperature remained between 15 and 18°. When the addition was completed, the mixture was allowed to stand at room temperature for 2 hr. It was poured on ice–ammonium hydroxide and the reaction products were extracted with ethyl acetate. The residue after washing, drying, and evaporation (3.8 g) was chromatographed on silica with chloroform–methanol (97:3).

The main fraction (R_f 0.7 on TLC) was dissolved in ether; a hydrochloride was precipitated with dry HCl, which was recrystallized from ethanol–ether. From this, the free base was liberated with sodium carbonate, which crystallized from ether: yield 0.9 g (16%); mp 98–100°; NMR ($CDCl_3$) δ 7.7–7.0 (m, 4), 4.5 (d, 1, J = 11 Hz), 3.5 (d, 1, J = 11 Hz),[8] 3.3 (s, 3), 3.0–0.6 (m, 11).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.53; H, 7.94; N, 10.45.

7-Methyl-6-oxo-1,2,3,4,5,6-hexahydroindolo[2,3-*c*]quinoline (21). 7-Methyl-1,2,3,4-tetrahydroindolo[2,3-c]coumarin (**20**, 4 g, 16 mmol)[5] was heated in 50 ml of ethanol, saturated with ammonia, for 7 days at 180° in a steel pressure vessel. The residue after evaporation was crystallized from ethanol by extraction from a Soxhlet apparatus: yield 3 g (75%); mp 280° dec; NMR (CF_3COOD) δ 8.2–7.3 (m, 4), 4.1 (s, 3), 3.3–2.7 (m, 4), 2.2–1.9 (m, 4).

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.29; H, 6.34; N, 11.03.

7-Methyl-1,2,3,4-tetrahydroindolo[2,3-*c*]quinoline (19). A. From 21. A mixture of the above compound **21** (3 g, 12 mmol), $LiAlH_4$ (2 g, 53 mmol), and 100 ml of anhydrous toluene was heated to reflux for 7 hours. The residue after the usual work-up was chromatographed on silica [chloroform–methanol (97:3)]. The main fraction (R_f 0.5) was the title compound. It crystallized as hydrochloride from ethanol–ether: yield 1.6 g (49%); mp 320–323°; NMR ($CDCl_3$) of the free base δ 8.4 (s, 1), 8.1–6.9 (m, 4), 3.6 (s, 3), 3.3–2.8 (m, 4), 2.1–1.7 (m, 4).

Anal. Calcd for $C_{16}H_{16}N_2$·HCl: C, 70.45; H, 6.28; N, 10.27; Cl, 13.00. Found: C, 69.98; H, 6.35; N, 10.34; Cl, 12.70.

B. From 16. 1-Methyl-2-aminomethyl-3-cyclohexen(1)ylindole (**16**, 7 g, 29 mmol) was dissolved in glacial acetic acid (100 ml). The solution was cooled to 15° and chromium trioxide (6 g) in water (7 ml) was added slowly with stirring. The mixture was worked up after 2 hr as described under **18**. The main fraction from column chromatography [silica, chloroform–methanol (97:3)] (2 g, 28%) was converted to the hydrochloride and was found identical with the above preparation.

4-(1,2-Dimethyl-3-indolyl)-2-methylbenzoic Acid (22). The cyclohexadiene derivative **4e** (0.4 g, 14 mmol) was heated to reflux in mesitylene (25 ml) under CO_2 with 0.3 g of palladium on charcoal (5%) for 2 hr. The residue after filtration and evaporation was recrystallized from ethanol: yield 0.2 g (50%); mp 205–207°; NMR (DMSO-d_6) δ 8.2–7.0 (m, 7), 3.8 (s, 3), 2.7 (s, 3), 2.5 (s, 3).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.46; H, 6.22; N, 5.02.

Acknowledgment. The author wishes to thank Miss E. Dubois and Mrs. A. Thomas for reliable technical assistance.

Registry No.—**1** (R = Me), 875-79-6; **2a**, 108-94-1; **2b**, 533-60-8; **2c**, 504-02-9; **2d**, 1655-07-8; **2e**, 487-51-4; **2f**, 1072-72-6; **2g**, 1445-73-4; **2h**, 3612-20-2; **2i**, 41661-47-6; **2k**, 826-36-8; **2l**, 32161-06-1; **2m**, 25012-72-0; **2n**, 532-24-1; **2o**, 41361-28-8; **2p**, 34286-16-3; **4a**, 55556-25-7; **4b**, 32544-46-0; **4c**, 55556-26-8; **4d** isomer 1, 55556-27-9; **4d** isomer 2, 55556-28-0; **4e**, 55556-29-1; **4f**, 55556-30-4; **4g**, 55556-31-5; **4h**, 55556-32-6; **4i**, 55556-33-7; **4k**, 55556-34-8; **4l**, 55556-35-9; **4m** isomer 1, 55556-36-0; **4m** isomer 2, 55556-37-1; **4n**, 55556-38-2; **4o** isomer 1, 55556-39-3; **4o** isomer 2, 55556-40-6; **4p**, 55606-54-7; **4q**, 17403-03-1; **4r**, 55556-41-7; **4s**, 55556-42-8; **4t**, 55556-43-9; **4u**, 55556-44-0; **4v**, 55556-45-1; **4w**, 55556-46-2; **4x**, 55556-47-3; **4y**, 55556-48-4; **5**, 55556-51-9; **6**, 55556-52-0; **7**, 55556-53-1; **8**, 55556-54-2; **9**, 55556-55-3; **10**, 55556-56-4; **13**, 55556-57-5; **14**, 55556-58-6; **15**, 55556-59-7; **16**, 55556-60-0; **17**, 55556-61-1; **18**, 31269-24-6; **19**, 55556-62-2; **20**, 32500-45-1; **21**, 55556-63-3; **22**, 55556-64-4; ethyl formate, 109-94-4.

References and Notes

(1) W. J. Houlihan, "Indoles Part One", Wiley-Interscience, New York, N.Y., 1972, p 105
(2) G. J. Zunecemu and G. N. Dorovchenko, *Usp. Khim.*, **41**, 1627 (1972).
(3) D. Beck and K. Schenker, *Helv. Chim. Acta*, **51**, 260 (1968).
(4) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968).
(5) K. Freter, *J. Org. Chem.*, **37**, 2010 (1972).
(6) From 1-methylindole-2-carboxamide by $LiAlH_4$ reduction, mp 255°.
(7) W. E. Noland and R. J. Sundberg, *J. Org. Chem.*, **28**, 884 (1963).
(8) The symmetrical wide quartet of the C_3 protons is typical for this class. See "Sadtler Standard NMR Spectra", Sadtler Research Laboratories, Philadelphia, Pa., 1970, Spectrum No. 8964M.
(9) Melting points were determined on a Fisher-Johns block and are uncorrected. Microanalyses were performed by Dr. A. B. Gygli, Toronto. The NMR spectra were taken on a Varian T-60 instrument.

Reductions of Conjugated Carbonyl Compounds with Cyanoborohydride in Acidic Media

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The reductions of a variety of conjugated aldehydes and ketones with $NaBH_3CN$ in acidic methanol and hexamethylphosphortriamide (HMPT) have been investigated. Alicyclic carbonyl compounds afforded principally the corresponding allylic alcohols in both solvents with methyl ethers as side products in methanol. The introduction of additional conjugation often resulted in reduction to allylic hydrocarbons, presumably via acid-induced ionization and hydride trapping. Formation of saturated alcohols was not observed in any alicyclic cases studied. Cyclic enones, on the other hand, gave mixtures of allylic and saturated alcohols resulting from competing 1,2 and 1,4 addition of cyanoborohydride.

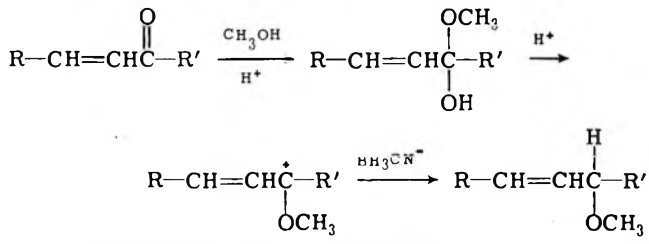
The problems often encountered in the reduction of α,β-unsaturated carbonyl systems with hydride reagents are legion.[1] In addition to affording the corresponding allylic alcohols, the reductions are often accompanied by such side reactions as concomitant reduction of the double bonds leading to saturated alcohols or, less commonly, reduction to enols which eventually give the saturated ketones. Such divergence in reduction products has been attributed to competing 1,2 vs. 1,4 attack by hydride, but predictions concerning the mode of attack for a particular substrate are difficult. In general, 1,4 addition competes favorably when the double bond is further conjugated with an aromatic ring,[2] contained in a five- or six-membered ring,[1b,3] or, at least with $NaBH_4$, conjugated with an additional carboxyl, cyano, or ester group.[4]

Our interest in the reducing capabilities of cyanoborohydride anion coupled with the unique (among metal hydrides) acid stability of the reagent prompted an exploration of its synthetic utility for effecting reductions of conjugated carbonyl systems. This article presents the results of such reductions with a variety of structurally different examples in two media, the polar protic solvent methanol and the polar aprotic solvent hexamethylphosphortriamide (HMPT).

Reductions in Acidic Methanol. As previously noted,[5] the carbonyl reducing capabilities of cyanoborohydride vary greatly with pH. Thus, in basic or neutral media, aldehydes and ketones are practically inert toward the reagent and adequate reduction rates are only obtained under acidic conditions where the carbonyl carbon is rendered more electrophilic by protonation. This was conveniently accomplished using Methyl Orange indicator and 2 N HCl to maintain the pH at about 3. Under these conditions most aldehydes and ketones are readily reduced at room temperature in 1–3 hr. Table I presents the reduction results for a selection of compounds chosen to determine the synthetic effectiveness and scope available in methanol. Both sodium and tetrabutylammonium[5b] cyanoborohydride were employed, but the latter displayed no advantage (entries 4, 7, 8).

Several features of the reductive results are noteworthy. First, the reduction of both alicyclic and β-aryl α,β-unsaturated carbonyls (entries 1–4, 6–9) gave products resulting only from 1,2 attack with no production of saturated alcohol observed. This qualitatively resembles previous investigations with $NaBH_4$ in methanol,[3b] although cyanoborohydride appears more discriminate toward carbonyl attack.[6]

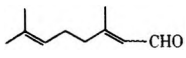
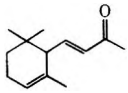
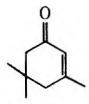
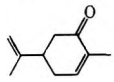
Unlike analogous reductions with borohydride, reductions in acidic methanol often afforded the corresponding methyl ethers in addition to the allylic alcohols. Ostensibly, these side products arise from protonation and ionization of the initially produced alcohol followed by solvent capture. The increase in the yields of such products with increasing conjugation is consistent with this interpretation. Thus, chalcone (entry 5) afforded only the corresponding methyl ether and the allylic hydrocarbon 1,3-diphenylpropene, this latter product apparently produced by hydride capture of the intermediate carbonium ion or displacement of the protonated alcohol. Indeed, treatment of the allylic alcohol chalcol with $NaBH_3CN$ in acidic methanol afforded the same two products. However, the formation of small amounts of methyl ethers from compounds containing less conjugation (entries 1, 6–8, 10) appears more complex than simple ionization of the intermediate allylic alcohols and subsequent solvent capture, since the alcohols were recovered unchanged when subjected to the reaction conditions. We envisioned that one possibility might involve an acid-induced reduction of initially generated acetals to methyl ethers in a similar fashion obtained in the reduction of acetals by mixed hydrides.[8] However, attempts to reduce 3-nitrobenzaldehyde dimethyl acetal with $NaBH_3CN$ in acidic methanol afforded only starting material. Other possibilities include the direct reduction of some allylic species (not the alcohol) or hydride trapping of an ion generated from an intermediate hemiacetal as shown below. This latter interpretation would also explain the absence of allylic hydrocarbon formation.



The reductions of cyclic ketones with $NaBH_3CN$ are considerably more prone to conjugate attack than the alicyclic analogs (entries 10 and 11), affording substantial or major amounts of the saturated alcohols. This parallels the situation in general for metal hydrides which provide hydride anion[3a,9] and is in agreement with previous reports of reductions of cyclic enones with $NaBH_3CN$ in acidic THF.[10]

Reductions in Acidic Hexamethylphosphortriamide (HMPT). The reductions of a variety of conjugated carbonyl compounds in acidic HMPT are presented in Table II. In general, the products paralleled those obtained in methanol with the exception that the nonnucleophilic HMPT precluded the formation of products stemming from solvent involvement. Thus, with alicyclic carbonyls (entries 23–27) and α,β-unsaturated β-aryl systems (entries

Table I
Reduction of Conjugated Carbonyl Compounds with Cyanoborohydride in Acidic Methanol

Entry	Compd	Registry no.	Reagent[a] (ratio hydride/compd)	Time, hr	Products, % yield[b] Allylic alcohol	Allylic hydrocarbon	Allylic ether	Saturated alcohol	Starting material
1	$C_6H_5CH{=}CHCOCH_3$	122-57-6	$NaBH_3CN$ (2)	1.5	77		11		
2	$C_6H_5C{\equiv}CCOCH_3$	1817-57-8	$NaBH_3CN$ (1)	1.25	70				15
3	$C_6H_5C{\equiv}CCOCH_3$		$NaBH_3CN$ (2)	1.5	89				
4	$C_6H_5C{\equiv}CCOCH_3$		TBAC (2)	1.5	80				
5	$C_6H_5CH{=}CHCOC_6H_5$	94-41-7	$NaBH_3CN$ (3)	2.5		48	26		12
6	$C_6H_5CH{=}CHCHO$	104-55-2	$NaBH_3CN$ (2)	1.5	80		8		
7	$C_6H_5CH{=}CHCHO$		TBAC (2)	1.5	58		10		
8		5392-40-5	TBAC (2)	2.0	69[c]		12		
9		127-41-3	$NaBH_3CN$ (2)	2.0	88				
10		78-59-1	$NaBH_3CN$ (2)	1.5	15		9	34	
11		99-49-0	$NaBH_3CN$ (2)	1.5	64			31	

[a] Solutions were acidified with 2 *N* HCl until the color change of Methyl Orange to red (ca. pH 3). [b] Overall yields were determined by isolation; relative percentages of mixture components were determined by GLC. [c] Composed of a mixture of geraniol and nerol.

12–15) exclusive 1,2 attack was observed and respectable yields of allylic alcohols obtained.[11] Likewise, the incorporation of further conjugation resulted in lower amounts (or absence) of allylic alcohols with a concurrent increase in the yields of allylic hydrocarbons (entries 16–22). As in methanol solvent, the allylic products from these highly conjugated systems most probably arise from hydride trapping of carbonium ions produced by protonation of initially formed alcohols. Thus, the relative yields of allylic alcohols and hydrocarbons were acid strength dependent with $NaBH_3CN$ (entries 19 and 20) and 1-(*p*-methoxyphenyl)-1-buten-3-one afforded both rearranged and unrearranged alkenes (entries 19–24). Unlike alicyclic systems, cyclic enones afforded substantial (entries 30–32) or exclusive (entries 28, 29) yields of the corresponding saturated alcohols resulting from 1,4 attack, again in analogy to the situation in methanol and THF.[10]

In summary, cyanoborohydride in acidic media provides a synthetically useful reagent system for the reduction of α,β-unsaturated carbonyls to the allylic alcohols provided that further conjugation is not present or the system is not a cyclic enone. In view of the general functional group selectivity possible with cyanoborohydride,[5] applications should be particularly attractive when other, normally sensitive, groups are present. Thus, although both aluminum hydride[12] and diisobutylaluminum hydride (DBAH)[13] are effective for reductions of conjugated systems to allylic alcohols, both are relatively powerful reducing reagents which would not tolerate the presence of many other functional groups in the molecule. For instance, DBAH readily reduces most common moieties[13b] including acids, esters, amides, epoxides, acetals, nitriles, and alkynes while cyanoborohydride leaves all of the above unmolested.[5] Aluminum hydride also shows poor discrimination among functional groups.[14]

Experimental Section

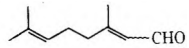
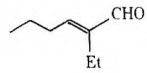
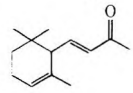
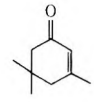
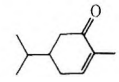
All melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrometer. Proton nuclear magnetic resonance spectra were obtained on Varian A-60 spectrometer typically as 10–20% solutions using tetramethylsilane (Me_4Si) as an internal reference. Microanalyses were performed by Chemanalytics Inc., Tempe, Ariz. Gas chromatographic (GLC) analyses of product mixtures and purified samples were performed on a Hewlett-Packard Model 5250B instrument coupled to an L & N Model W recorder equipped with a disk integrator. All analyses were carried out on either a 6 ft × 0.125 in. or 10 ft × 0.125 in. stainless steel column packed with 10% OV-1 or 20% Carbowax 20M on 80/100 mesh Chromosorb W (DMCS). Organic solvents were dried over anhydrous magnesium sulfate. Sodium cyanoborohydride, obtained from ALFA Inorganics, was purified by decolorizing with alkaline Norit-A in hot tetrahydrofuran (THF) followed by solvent removal at reduced pressure. All the other chemicals used were either commercially available or prepared by standard procedures. Hexamethylphosphortriamide (HMPT), obtained from Fisher Scientific Co., was distilled over CaH_2 and stored over 13 A molecular sieves. Authentic samples of products were either obtained commercially or prepared by standard procedures and compared with literature preparations: 4-phenyl-3-buten-2-ol and the methyl ether;[15a] 1-phenyl-1-butyn-3-ol;[15b] cinnamyl alcohol methyl ether;[15c] 3,7-dimethyl-2,6-octadien-1-ol methyl ether;[15d] 1,3-diphenyl-1-propen-3-ol[15e] and the methyl ether;[15f] isophorol;[15g] dihydrocarveol.[15h]

Tetrabutylammonium Cyanoborohydride (TBAC). The reagent was prepared in a similar manner as described for the corresponding borohydride.[16] Thus 33.95 g (0.10 mol) tetrabutylammonium hydrogen sulfate suspended in 50 ml of water was treated at room temperature with 35 ml of 5 *N* NaOH and a solution of 6.93 g (0.11 mol) of $NaBH_3CN$ in 40 ml of water. After 15 min, the mixture was extracted three times with methylene chloride, and the organic solution was washed with water and dried (K_2CO_3). The methylene chloride layer was then decolorized with carbon and concentrated at reduced pressure to afford 22.2 g (78%) of white, crystalline product. This material was pure enough for use in a reduction; the analytical sample was obtained by recrystallization from ethyl acetate, mp 144–145°.

Anal. Calcd for $C_{17}H_{39}N_2B$: C, 72.32; H, 13.92; Found: C, 72.18; H, 13.94.

General Reduction Procedure for α,β-Unsaturated Carbonyl Compounds with $NaBH_3CN$ or TBAC. Methanol Solvent. The procedure was similar to that described by Borch and coworkers for THF.[10a] All reductions were carried out at pH 3. Five millimoles of the carbonyl compound and 10 mmol of the reducing agent were dissolved in 10 ml of solvent containing a trace

Table II
Reduction of Conjugated Carbonyl Compounds with Cyanoborohydride in Acidic HMPT

Entry	Compd		Reagent (ratio hydride/compd)	Acidity, *M*	Time, hr	Products, % yield[a] Allylic alcohol	Allylic hydrocarbon	Saturated alcohol	Starting material
12	$C_6H_5CH{=}CHCOCH_3$		$NaBH_3CN$ (4)	1.9	1.0	58			
13	$C_6H_5CH{=}CHCOCH_3$		TBAC (4)	1.9	1.0	65			
14	$C_6H_5C{\equiv}CCOCH_3$		$NaBH_3CN$ (4)	1.9	1.0	71			
15	$C_6H_5C{\equiv}CCOCH_3$		TBAC (4)	1.9	1.0	64			
16	$C_6H_5CH{=}CHCOC_6H_5$		$NaBH_3CN$ (4)	0.75	1.0		53[b]		16[b]
17					10.0		61[b]		
18	$C_6H_5CH{=}CHCOC_6H_5$		TBAC (4)	0.75	1.0		46[b]		12[b]
19	p-$CH_3OC_6H_4CH{=}CHCOCH_3$	943-88-4	$NaBH_3CN$ (4)	0.25	1.25	20	59[c]		2
20				0.84	1.25		82[d]		
21			TBAC (4)	0.25	1.25	41	34[e]		4
22			TBAC (4)	0.84	1.25	41	36[f]		2
23			$NaBH_3CN$ (4)	1.9	1.5	79			
24			TBAC (4)	1.9	1.5	76			
25		645-62-5	$NaBH_3CN$ (4)	0.5	1.5	82			
26			$NaBH_3CN$ (4)	1.9	1.5	60			
27			TBAC (4)	1.9	1.5	63			
28			$NaBH_3CN$ (4)	1.9	1.0			57	
29			TBAC (4)	1.9	1.0			56	
30		43205-82-9	$NaBH_3CN$ (4)	1.9	1.0	18		48	
31	Cholest-4-en-3-one	601-57-0	$NaBH_3CN$ (4)	1.1	1.0	16		77	
32			TBAC (4)	0.75	1.0	14		80	

[a] Overall yields were determined by isolation; unless specified otherwise relative percentages of mixture components were determined by GLC. [b] Yields determined by GLC using internal standards. [c] Mixture of 1-(*p*-methoxyphenyl)butene (27%) and 1-(*p*-methoxyphenyl)-2-butene (32%). [d] Mixture of 1-(*p*-methoxyphenyl)butene (44%) and 1-(*p*-methoxyphenyl)-2-butene (38%). [e] Mixture of 1-(*p*-methoxyphenyl)butene (15%) and 1-(*p*-methoxyphenyl)-2-butene (19%). [f] Mixture of 1-(*p*-methoxyphenyl)butene (18%) and 1-(*p*-methoxyphenyl)-2-butene (18%).

amount of Methyl Orange indicator. A solution of 2 *N* HCl–solvent was added dropwise in order to maintain the red color. After stirring for the appropriate length of time (no more change in red color) the solvent was evaporated in vacuo. The residue was taken up in water (8 ml) and extracted with ether (3 × 25 ml) and the ether layer was dried and concentrated to obtain the product.

HMPT Solvent. To cold (0°) HMPT (10–15 ml) was added sufficient sulfuric acid to bring the acidity to the appropriate value listed in Table II for ketones or for aldehydes, followed by the addition of 5 mmol of the carbonyl compound and 20 mmol of the reducing agent ($NaBH_3CN$ or TBAC). The reaction mixture was stirred at 25° for the appropriate length of time (Table II). Water was added and stirring was continued for an additional 1 hr. The reaction mixture was extracted with ether, which was washed with water, dried, and concentrated on a rotary evaporator. The residue was analyzed by GLC on a 20% Carbowax 20M column and the products were identified by ir, NMR, or by comparison with authentic samples. In some cases the residue was further purified by using a short alumina column. The procedures are presented as representative examples below.

Reduction of Benzalacetone with TBAC. The reduction of 0.92 g (6.3 mmol) of the ketone with 25 mmol (7.05 g) of TBAC in 25 ml of HMPT containing 15 equiv of sulfuric acid for 1.25 hr at room temperature gave, after the usual work-up, 0.91 g of residue. The residue on distillation from a Kugelrohr apparatus gave 0.8 g (86%) of liquid which by GLC and NMR was identified as 4-phenyl-3-buten-2-ol by comparison with an authentic sample.

Reduction of Benzalacetophenone with $NaBH_3CN$ in Methanol (2.5 hr). Following the general procedure, the reduction of 1.03 g (5 mmol) of the ketone with 0.95 g (15 mmol) of $NaBH_3CN$ in 10 ml of methanol at pH 3 for 2.5 hr gave, after the usual work-up, 0.88 g (86%) of residue. Analysis by GLC (6 ft 10% OV-1 column) indicated the presence of 48% 1,3-diphenyl-1-propene, 26% 1,3-diphenylallyl methyl ether, and 12% starting material. No alcohol was detected in the product mixture.

Isophorol Methyl Ether. To a cold (0°), stirred solution of 2.8 g (20 mmol) of isophorol in 20 ml of HMPT was added 0.96 g (40 mmol) of NaH. After 30 min, 5.7 g(40 mmol) of methyl iodide was added slowly and the stirring was continued for an additional 2 hr. Water was then added, the mixture was extracted with ether (3 × 25 ml), and the ether solution was washed with water, dried, and concentrated. Distillation of the residue afforded 1.8 g (59%) of product: bp 46° (0.9 mm); $n^{25}D$ 1.4568; ir (neat) 2900 (s), 1670 (m), 1450 (s), 1380, 1370 (s), 1360 (vs), 1265 (w), 1200 (m), 1160, 1140 (w), 1125 (s), 1090 (vs), 1000 (w), 960, 940 (s), 810 cm^{-1} (m); NMR ($CDCl_3$) δ 0.95 (d, 6 H, *gem*-dimethyl), 1.1–1.85 (m, 4 H, $-CH_2-$), 1.65 (s, 3 H, vinylic methyl), 3.32 (s, 3 H, $-OCH_3$), 3.73 (m, 1 H, $-CHOCH_3$), 5.48 (broad, 1 H, vinylic).

Anal. Calcd $C_{10}H_{18}O$: C, 77.87, H, 11.76. Found: C, 78.36; H, 11.95.

Registry No.—$NaBH_3CN$, 25895-60-7; TBAC, 43064-96-6; tetrabutylammonium hydrogen sulfate, 32503-27-8; methanol, 67-56-1; HMPT, 680-31-9; isophorol methyl ether, 50987-46-7; isophorol, 470-99-5; methyl iodide, 74-88-4.

References and Notes

(1) (a) For a discussion and leading references, see H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, New York, N.Y., 1972, pp 89–96. (b) As an illustration of the divergence of product distributions from cyclic enones which may be obtained with different hydride reagents, see H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969). (c) Recently, exclusive 1,4 reduction of α,β-unsaturated systems to saturated ketones has been achieved using copper(I) hydride complexes; see R. K. Boeckman, Jr., and R. Michalak, *J. Am. Chem. Soc.*, **96**, 1623 (1974).

(2) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

(3) (a) W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965); (b) K. Iqbal and W. R. Jackson, *J. Chem. Soc. C*, 616 (1968).

(4) (a) J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963); (b) G. Luciani and F. Montanari, *Boll. Sci. Fac. Chim. Ind. Bologna*, **18**, 47 (1960).

(5) (a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971); (b) R. O. Hutchins and D. Kandasamy, *ibid.*, **95**, 6131 (1973).

(6) The increase in 1,2 addition by borohydride with increasing solvent polarity has been attributed to the ability of polar solvents (such as methanol) to more effectively stabilize the more charge-localized transition state of 1,2 addition.[3b] However, the rapid reaction of $NaBH_4$ with methanol[7] and the demonstrated preponderance of carbonyl attack by trialkoxyborohydride[3a] may account for much of the selectivity shown by borohydride. In addition, 1,4 attack of β-aryl conjugated systems involves loss of conjugation with the phenyl ring while no such loss occurs upon 1,2 addition.

(7) See H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, p 214, and references cited therein.

(8) (a) P. T. Lansbury and R. E. Macleay, *J. Org. Chem.*, **28**, 1940 (1963); (b) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962).

(9) See H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 89–97, and references cited therein.

(10) (a) Borch and coworkers obtained only cyclopentanol upon reduction of 2-cyclopentenone: R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971). (b) Steroidal α,β-unsaturated ketones also give substantial 1,4-addition products with $NaBH_3CN$ in acidic THF: M.-H. Boutique, R. Jacquesy, and Y. Petit, *Bull. Soc. Chim. Fr.*, **11**, 3062 (1973).

(11) The absence of allylic hydrocarbons in the reductions of alicyclic carbonyl compounds reinforces the previous suggestion that the allylic ethers formed from these systems in acidic methanol did not arise from acid-catalyzed reactions of the allylic alcohols; otherwise the corresponding reductions in HMPT should have produced some allylic hydrocarbons (compare entries 1 and 8 with entries 12, 13, 23, and 24).

(12) C. G. Scouten and H. C. Brown, *J. Org. Chem.*, **38**, 4092 (1973); H. C. Brown, E. F. Knights, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974).

(13) (a) K. E. Wilson, R. T. Seidner, and S. Masamune, *Chem. Commun.*, 213 (1970); (b) "The Use of Aluminum Alkyls in Organic Synthesis", Ethyl Corp., 1970 and 1973.

(14) Recently, Brown and Krisnamurthy have utilized 9-BBN to cleanly reduce conjugated systems to allylic alcohols. This reagent appears to offer good selectivity with respect to other functional groups: S. Krishnamurthy and H. C. Brown, presented at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975; S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **40**, 1864 (1975).

(15) (a) J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.*, 207 (1937); (b) G. A. Olah and C. U. Pittman, *J. Am. Chem. Soc.*, **87**, 5632 (1965); (c) B. Gredy, *Bull. Soc. Chim. Fr.*, 1093 (1936); (d) A. V. Semenovskii, V. A. Smit, T. N. Chernova, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **6**, 1068 (1965); (e) T. Sato and I. Homma, *Bull. Chem. Soc. Jpn.*, **44**, 1885 (1971); (f) E. Bergmann and T. Ukai, *Ber.*, **66**, 54 (1933); (g) H. Rubinstein, *J. Org. Chem.*, **27**, 3886 (1962); (h) C. V. Pigulevskii and I. S. Kozhima, *Zh. Obshch. Khim.*, **25**, 416 (1955); *Chem. Abstr.*, **50**, 2500*b* (1956).

(16) A. Brandstrom, U. Junggren, and B. Lamm, *Tetrahedron Lett.*, 3173 (1972).

Notes

Evidence of Significant Participation of the Less Stable Conformation in the Reduction of 2-Methylcyclohexanone by Sodium Borohydride

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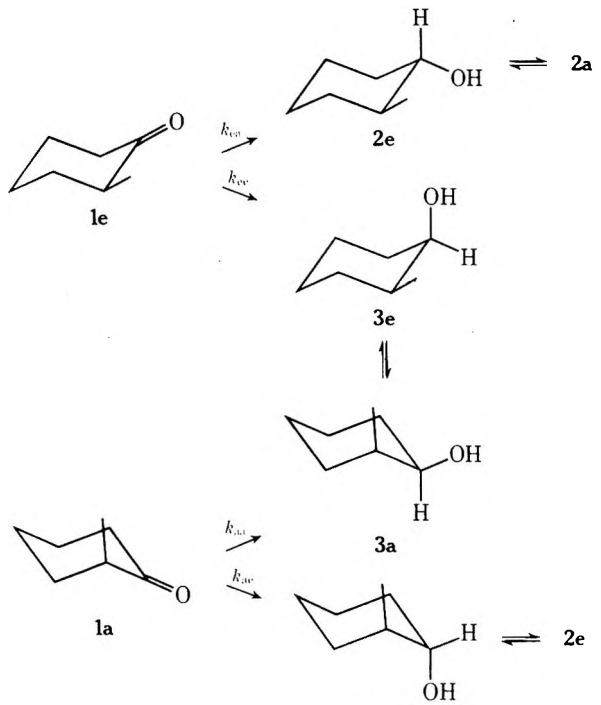
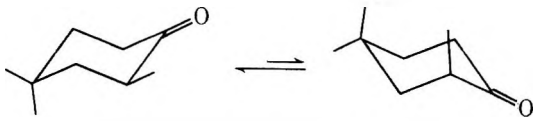
The reduction of conformationally mobile 2-alkylcyclohexanones by complex metal hydrides can, in principle, occur through two conformations: one with the alkyl group equatorial and the other with the alkyl group axial. Thus it is possible that both cis and trans alcohols may arise via two different routes, i.e., axial or equatorial attack on a given conformation (Scheme I).

From the point of view of investigating the origin of the stereoselectivity in reductions of cyclohexanones by complex metal hydrides, the question of just how each alcohol is formed is a vital one, and in a previous study[1] we demonstrated, by analysis of the relative magnitudes of activation enthalpies, that the trans alcohol **2** is derived almost exclusively from conformation **1e**. However, we were unable to determine whether the cis alcohol was derived from conformation **1a**, **1e**, or both, owing to experimentally indistinguishable values of $\Delta H^{\ddagger}$ for the two possible processes. Since we know, however, that conformation **1a** does not

Scheme I
Reduction of 2-Methylcyclohexanone



give rise to the trans alcohol,[1,2] a very simple experiment is possible that clarifies the origin of the cis alcohol. 2,4,4-Trimethylcyclohexanone (4) serves as a model for conformation 1e of 2-methylcyclohexanone, conformation 4a being virtually forbidden by virtue of the 1,3-diaxial interaction of the methyl groups. Thus the stereochemical product ratio from reduction of 4 represents to a good approximation that from the *equatorial conformation of 2-methylcyclohexanone* (1e), and a deviation from this of the observed product ratio of 2-methylcyclohexanone (1) is a measure of the contribution of the axial conformation (1a).



4e 4a

2,4,4-Trimethylcyclohexanone[3] is obtainable by ketone transposition of isophorone,[4,5] the penultimate intermediate providing an authentic sample of *trans*-2,4,4-trimethylcyclohexanol. Reduction of 2-methylcyclohexanone and 2,4,4-trimethylcyclohexanone under identical conditions by sodium borohydride gave 31 and 18%, respectively, of the cis isomer.

Regarding the rate of formation of the trans alcohol from 2-methylcyclohexanone as a single term E_A (that from conformation 1e), but the rate of formation of the cis alcohol as the sum of two terms E_E and A_A arising from the conformations with equatorial and axial methyl groups respectively, the stereochemical product ratio (cis:trans) can be written as

$$(A_A + E_E)/E_A = 31.69$$

Similarly, for reduction of 2,4,4-trimethylcyclohexanone[6]

$$E_E/E_A = 18/82$$

From these equations it follows that $A_A = 1.05E_E$ or, expressing A_A and E_E as percentages of the total reaction leading to *cis*-2-methylcyclohexanol, 51% of this product arises from axial attack on 1a while 49% of the product is derived by equatorial attack on the more stable conformation 1e. This result is in sharp contrast with formation of *trans*-2-methylcyclohexanol, which is derived almost exclusively from 1e.[1]

Conclusions

While some doubt must exist on the exactitude of the above figures (see ref 6), it appears that the *less* stable conformation of 2-alkylcyclohexanones plays at least a substantial role in the reduction to the cis alcohol. Any rationalization of stereochemical product ratio arising from reduction of these ketones should be consistent with this fact.

Experimental Section

2,4,4-Trimethylcyclohexanone (4) was prepared by oxidation[5] of *trans*-2,4,4-trimethylcyclohexanol, which was obtained by reduction and hydroboration of isophorone:[4] bp 191° [lit.[3] bp 191°]; $n^{21}D$ 1.4485 (lit. $n^{20}D$ 1.4493[3]); 2,4-dinitrophenylhydrazone mp 149–150° (lit.[9] mp 151.5°[2]). Ir and NMR spectra were in accord with published data.[9]

Reduction Procedures. Reductions were carried to completion in 2-propanol at 25° with a twofold molar excess of sodium borohydride as previously described.[1,10] GLC analyses were performed both on a Perkin-Elmer 990 gas chromatograph using a 50-ft S.C.O.T. TCEP column and on a Hewlett-Packard F & M Scientific 402 high efficiency gas chromatograph using a dual-packed column of Carbowax and TCEP, which gave base line separation of diastereomeric alcohols and ketone.[11] Both chromatographs were attached to an Infotronics CRS-208 electronic integrator for peak area determination. Reductions were performed in quadruplicate, and product ratios, which were determined both mechanically and electronically, were found to be reproducible within ±1%.

Registry No.—1, 583-60-8; 2, 7443-52-9; 3, 7443-70-1; 4, 2230-70-8; 4 2,4-dinitrophenylhydrazone, 2522-10-3; *trans*-2,4,4-trimethylcyclohexanol, 2518-25-4; sodium borohydride, 16940-66-2.

References and Notes

(1) D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, **96**, 543 (1974).
(2) J.-C. Richer, *J. Org. Chem.*, **30**, 324 (1965).
(3) I. Heilbron and H. M. Bunbury, Ed., "Dictionary of Organic Compounds", Vol. IV, Oxford University Press, London, 1953, p 599.
(4) J. Klein, E. Dunkelblum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).
(5) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 142.
(6) These equations make the assumption that 4,4 disubstitution does not affect the stereochemical product ratio of 1 other than conformational freezing; 4 substitution does tend to increase the overall rate of reduction;[7,8] however, despite differences in rate of reduction of 4-methyl- and 4-*tert*-butylcyclohexanone, stereochemical product ratios for reduction of these two ketones are identical.[8]
(7) B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).
(8) D. J. Phelps, Ph.D. Thesis, Carleton University, 1973.
(9) J.-J. Barieux and J. Gore, *Bull. Soc. Chim. Fr.*, 3978 (1971).
(10) D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, **50**, 388 (1972).
(11) We are very grateful to Professor B. Rickborn for details of this column (cf. footnote 62 of ref 7).

Effects of α Substitution on the Rate of Chloromercuriolactonization of Esters of γ,δ-Unsaturated Acids[1]

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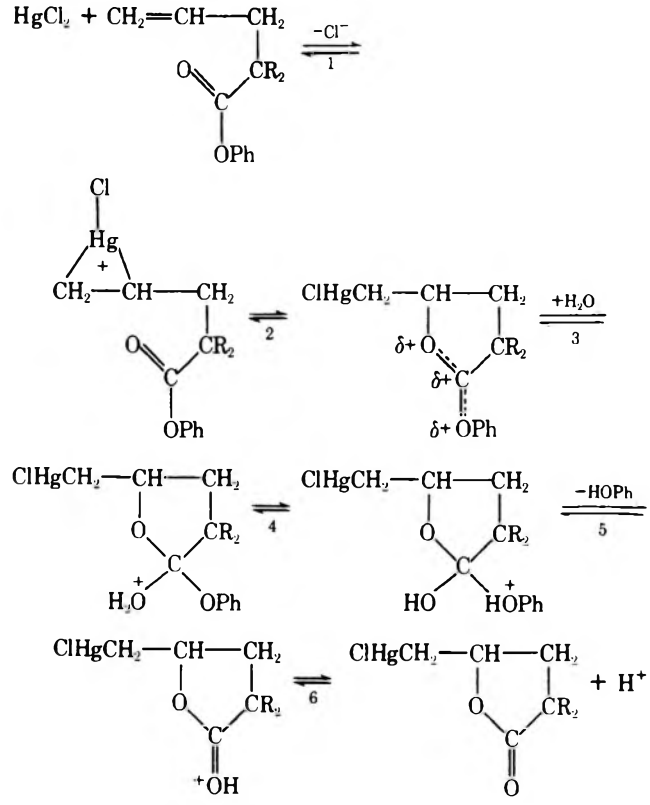
The chloromercuriolactonization of γ,δ-unsaturated acids and esters in aqueous ethanol has been studied by Rowland et al.[3] and do Amaral et al.[4] A mechanism for the reaction was proposed.[4]



Recently do Amaral and Melo studied the effect caused by substituents in the α position of the γ,δ-unsaturated acids on the rate of iodolactonization.[5]

In the present work, a kinetic investigation was undertaken in order to obtain rate information pertinent to the chloromercuriolactonization of esters of γ,δ-unsaturated acids referring specifically to effects caused by substituents on the α position of the esters.

Experimental Section

Materials. 4-Pentenoic acid was obtained from the Chemical Procurement Laboratories; 2-phenyl-2-pentenoic acid and 2,2-diphenyl-4-pentenoic acid were synthesized according to known procedures.[4] Phenyl allylacetate (I), phenyl allylphenylacetate (II), and phenyl allyldiphenylacetate (III) were prepared according to known procedures.[4] All other chemicals were reagent grade and were used without further purification.

Product Analysis. The products of the reaction of the esters with mercuric chloride were prepared according to known procedures,[4] and identified as δ-chloromercuri-γ-lactones:[4] from ester I, mp 81–82° (lit.[3,4] mp 81–82°); from ester II, mp 173° (lit.[4] mp 172.5–173.5°); from ester III, mp 203–204° (lit.[4] mp 203–204°).

Kinetic Measurements were carried out spectrophotometrically with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell holder through which water from a thermostated bath was continuously circulated. The required reaction temperature was measured inside the cell with an accuracy of ±0.05°. Reagent solutions were prepared in 50% aqueous ethanol (v/v) and had the following concentrations: ester solution, 4.0×10^{-4} *M*; mercuric chloride, 3.0×10^{-1} *M*; and sodium perchlorate, 1.0 *M*. Kinetic runs were carried out as follows. All reagents, except the ester solution, were pipetted into a reaction tube, mixed, and left in the water bath for 30 min for thermal equilibration. An ionic strength of 0.10 was obtained by addition of calculated volumes of sodium perchlorate solution. At zero time, a measured quantity of the ester solution was added to the mixture, which was then shaken and transferred rapidly to the reaction cell. The reaction kinetics were monitored by following the appearance of the liberated phenol at the appropriate wavelength until a constant reading was reached. In all cases a sufficient excess of mercuric chloride was used to ensure pseudo-first-order kinetic behavior. Observed first-order rate constants, k_{obsd}, were evaluated from plots of log $(OD_\infty - OD_t)$ against time and the expression $k_{obsd} = 0.693/t_{1/2}$, and expressed in min^{-1}. Second-order rate constants, k_2, were determined by dividing k_{obsd} by the mercuric chloride concentration, and expressed in $M^{-1}\ min^{-1}$.

Results and Discussion

Rate measurements have indicated that the reaction of esters of γ,δ-unsaturated acids and mercuric chloride to yield chloromercuriolactones is second order, first order in both ester and mercuric chloride.[4]

Rate constants for the reaction of phenyl allylacetate (I), phenyl allylphenylacetate (II), and phenyl allyldiphenylacetate (III) with mercuric chloride in aqueous ethanol were measured at three temperatures. Results are presented in Table I. From Table I it can be seen that α-phenyl groups increase the rate of the reaction at the three temperatures studied. This increase is more pronounced for ester III than for ester II. This observation is in accordance with the Thorpe–Ingold considerations about the effects exerted by substituents on the ease of ring formation.[6]

Table I
Second-Order Rate Constants Multiplied by 10^3, Expressed in $M^{-1}\ min^{-1}$, for the Reaction of Phenyl Allylacetate (I), Phenyl Allylphenylacetate (II), and Phenyl Allyldiphenylacetate (III) with Mercuric Chloride in Ethanol–Water (50% v/v) and Ionic Strength 0.10

Ester	25°	35°	45°
I	1.4	3.6	8.3
II[a]	6.3	15.8	35
III	120	200	350

[a] From ref 4.

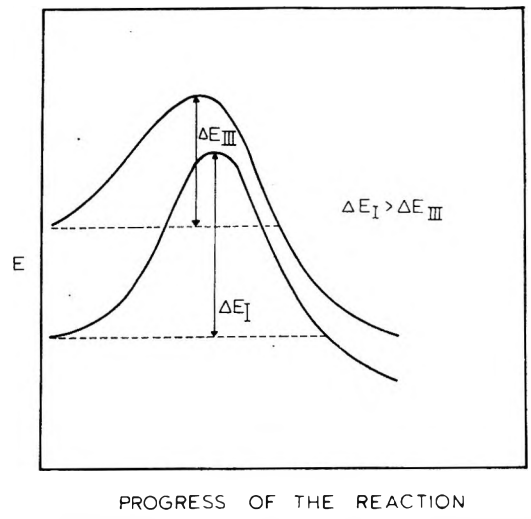


Figure 1. Potential energy profile for step 5 of the reaction path for the reactions of phenyl allylacetate (I) and phenyl allyldiphenylacetate (III) with mercuric chloride.

Arrhenius plots of log k_2 vs $1/T$ for the reaction of esters I, II, and III with mercuric chloride gave reasonably straight lines from which the activation energy, E_a, was determined by least-squares analysis (Table II). The enthalpy of activation, $\Delta S^\ddagger$, was calculated from the formula given by Schaleger and Long.[7] The activation parameters are shown in Table II. One notices from Table II that the values of entropy of activation become more negative with increasing degree of substitution at the α position of the ester substrate, and the values of the enthalpy of activation decrease in the same order.

Table II
Activation Parameters for the Reaction of Esters I, II, and III with Mercuric Chloride in Ethanol–Water (50% v/v) and Ionic Strength 0.10

Ester	E_a, kcal mol^{-1}	$\Delta H^\ddagger$, kcal mol^{-1}	$\Delta S^\ddagger$, eu	$\Delta G^\ddagger$, kcal mol^{-1}
I	18.0	17.4	−21.9	23.9
II	15.5	14.9	−27.3[a]	23.0[a]
III	10.4	9.8	−38.5	21.3

[a] Calculated from data in ref 4.

These results can be discussed in terms of the effect of the α-phenyl groups on the free energy of activation, $\Delta G^\ddagger$. The polar effect of the α-phenyl groups will be small because they are not directly attached to the carbonyl group. On the basis of a purely polar effect, one would expect a slight decrease in the rate going from ester III to ester I owing to the small electron-attracting properties of the phenyl group relative to hydrogen. We are left, therefore, with the possibility that these groups increase the reaction rate predominantly through a steric effect; that is, the more bulky the groups attached to the α carbon atom, the greater the reaction rate.

We have previously proposed that step 5, in which the phenol departs, is the rate-determining step for chloromercuriolactonization.[4] in the ground state for this reaction the conformational strain that results from the nearly eclipsed groups on the α and central carbon atom is greater in ester III than in ester I. In the transition state, the phe-

nol molecule starts to depart, and the central carbon–oxygen bond begins to acquire more sp^2 character.[8] As a result of this $sp^3 \rightarrow sp^2$ change,[9] bonds will spread out and there will be a relief from the eclipsing strain mentioned above.[10] The magnitude of such relief will depend on its original value in the ground state and is, of course, much greater for ester III than for ester I. In summary, this represents a higher initial energy and a lower energy difference, ΔE_a, between the ground and transition states of ester III than of ester I. Figure 1 illustrates this concept. The reported $\Delta S^{\ddagger}$ values, assuming constant contributions from the solvent, are also in accordance with the diagram given. $\Delta S^{\ddagger}$ changes from −38.5 to −21.9 eu in going from ester III to ester I. This means that the transition state of ester III is more ordered in relation to its ground state than in the case of ester I.

The increasing values of ΔE_a (or $\Delta H^{\ddagger}$) in going from ester III to ester I mean that in the former the transition state is reached earlier, and consequently is less sensitive to temperature variation. This conclusion can also be reached by a consideration of the much greater steric crowding present in the former ester's transitions state (vide supra).

Registry No.—I, 51231-09-5; II, 51231-03-9; III, 51231-12-0; mercuric chloride, 7487-94-7.

References and Notes

(1) Supported in part by the Fund for Overseas Research Grants and Education.
(2) Fellow of the Fundação de Amparo à Pesquisa do Estado de São Paulo.
(3) R. L. Rowland, W. L. Perry, and H. L. Friedman, *J. Am. Chem. Soc.*, **73**, 371 (1951).
(4) O. A. El Seoud, A. T. do Amaral, M. Moura Campos, and L. do Amaral, *J. Org. Chem.*, **39**, 1915 (1974).
(5) L. do Amaral and S. C. Melo, *J. Org. Chem.*, **38**, 800 (1973).
(6) C. K. Ingold, *J. Chem. Soc.*, **119**, 305 (1921).
(7) L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, **1**, 7 (1963).
(8) The degree of rupture of the central carbon and the phenol oxygen atoms does not change the basic idea given above. It does, however, change $\Delta F^{\ddagger}$ and hence the magnitude of steric acceleration.
(9) H. C. Brown, J. F. Brelluster, and H. Shexhter, *J. Am. Chem. Soc.*, **76**, 467 (1954); E. L. Eliel, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956.
(10) There will also be an angle strain on passing from the 109° of the sp^3 state to the 120° of the sp^2 state. Such strain will work against the sp^3–sp^2 change. Since such changes take place easily in the cyclopentane series, angular strain can be of minor importance as compared to conformational strain.

Reactions of Dichlorine Heptoxide and of Hypohalites with Alkyl Iodides[1]

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Stable aromatic polyvalent iodine compounds[2] are obtained from iodides with oxidizing reagents such as chlorine,[2] peracetic acid,[3] or dinitrogen pentoxide.[4] However, for aliphatic iodides, stable halogen adducts have been reported only with electron-withdrawing substituents such as fluorine[5,6,7] or sulfone.[8,9] Methyl iodide dichloride decomposes at −30° to give methyl chloride,[10] and similar reactions of alkyl iodides with peracetic acid[11] and with chlorine[12] have been studied kinetically at higher temperatures. The preparation of trifluoromethyl perchlorate from trifluoromethyl iodide and chlorine perchlorate has recently been reported.[13] The present work deals with reactions of alkyl iodides with dichlorine heptoxide and with hypohalites.

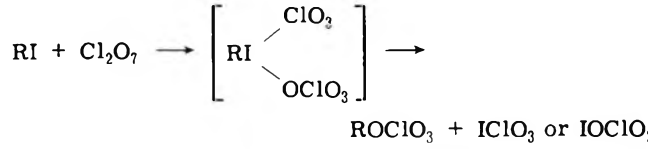
Ethyl iodide reacted rapidly at 0° with dichlorine heptoxide in carbon tetrachloride to give a white precipitate identified as iodine pentoxide. The composition of the soluble products was determined by NMR using a quantitative internal standard, and for a given reactant mixture the reproducibility of yields was 5–10%. With equimolar amounts of the reagents, or with an excess of dichlorine heptoxide, the products soluble in carbon tetrachloride were ethyl perchlorate (63% yield based on ethyl iodide), ethyl acetate (22%), and small amounts of diethyl ether (0–3%). With a 2:1 molar ratio of ethyl iodide to dichlorine heptoxide, the ethyl iodide was consumed completely to give ethyl perchlorate (33%), ethyl acetate (13%), and diethyl ether (21%). When a higher ratio of ethyl iodide to dichlorine heptoxide was used the additional ethyl iodide remained unreacted, and the same product mixture was obtained.

Since the above yields are all based on ethyl iodide consumed, almost the same total quantity of perchlorate is produced from 2 mol of ethyl iodide as from 1 mol. If the products of the experiment using 1 mol of ethyl iodide per mole of Cl_2O_7 are subtracted from the products of the 2-mol experiment, the second mole is seen to yield about 40% diethyl ether, 3% ethyl perchlorate, and 4% ethyl acetate. These results suggest that the equimolar reaction gives a by-product, not detectable by NMR, that converts additional ethyl iodide to ether.

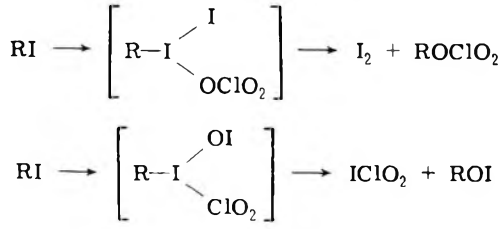
In the reaction of methyl iodide with dichlorine heptoxide similar products were obtained with the exception of the ester, presumably because of the greater oxidation resistance of the methyl group. Equimolar amounts of the reagents gave methyl perchlorate (45%) and dimethyl ether (12%), whereas a 2:1 ratio of methyl iodide to dichlorine heptoxide gave methyl perchlorate (24%) and dimethyl ether (26%). Thus, the first mole of methyl iodide gives predominantly perchlorate, and the second, ether.

In the above experiments the entire amount of ethyl iodide was added rapidly to the dichlorine heptoxide solution. To assess the stability of the implicated ether-forming intermediate, a series of experiments was carried out in which equimolar amounts of ethyl iodide and dichlorine heptoxide were reacted, the solutions were filtered, and after varying time intervals, a second mole of ethyl iodide was added. When this time interval was 15 min, 85% of the second mole was consumed; when the interval was 1 hr, 50% was consumed; and when it was 3 hr none of the added ethyl iodide was consumed.

Thus, the initial reaction of ethyl iodide with dichlorine heptoxide gives a compound, not visible by NMR, that reacts further with ethyl iodide at a rate slower than the initial reaction to give ether. Simple stoichiometry for the reaction of molar amounts of ethyl iodide and dichlorine heptoxide to form ethyl perchlorate would give perchloryl iodide or its isomer. Several paths can be envisioned for the



reaction of inorganic intermediates of this type with ethyl iodide. Displacement of iodine, possibly via a trivalent intermediate, could take place as follows. Reaction of these or



other ROX type intermediates with ethyl iodide could give ether. To shed light on the mechanism of ether formation, reactions of alkyl iodides with hypochlorites were studied.

$$RI + ROX \longrightarrow RI\begin{matrix}X\\ \diagup\\ \diagdown\\ OR\end{matrix} \longrightarrow ROR + IX$$

Chlorine oxide, Cl_2O, and I_2O_5 could be formed from $ICIO_3$ by a self-oxidation reaction, with transfer of oxygens from chlorine to iodine. The reaction of chlorine oxide with 2 mol of ethyl iodide in carbon tetrachloride at 0° was found to give ethyl chloride (40% yield), diethyl ether (20%), and ethyl acetate (8%). Since chloride was not detected in the dichlorine heptoxide reaction, chlorine oxide cannot be the reactive intermediate.

Ethyl hypochlorite was also treated with alkyl iodides at 0° in carbon tetrachloride. Equimolar amounts of ethyl hypochlorite and methyl iodide gave a quantitative yield of ethyl hypoiodite and methyl chloride. The latter was easily removed under vacuum to provide a convenient source of hypoiodite solution. Similarly, ethyl hypochlorite and ethyl iodide gave ethyl hypoiodite and ethyl chloride. The structure of ethyl hypoiodite was established by independent synthesis. Ethyl hypochlorite and iodine gave the same material contaminated with iodine chloride. This method has been reported for the synthesis of *tert*-butyl hypoiodite from *tert*-butyl hypochlorite.[14,15] Ethyl hypoiodite was

$$C_2H_5OCl + C_2H_5I \longrightarrow C_2H_5OI + C_2H_5Cl$$

$$C_2H_5OCl + CH_3I \longrightarrow C_2H_5OI + CH_3Cl$$

$$C_2H_5OCl + I_2 \longrightarrow C_2H_5OI + ICl$$

found to react with ethyl iodide to give diethyl ether and ethyl acetate. This result is significant with respect to the dichlorine heptoxide reaction since a hypoiodite is a possible intermediate. Other types of R–OX intermediates cannot be ruled out, however.

Experimental Section

NMR spectra were recorded with a Varian T-60 spectrometer and ir spectra were recorded with a Perkin-Elmer 700 spectrometer. A Varian 920 chromatograph with a 5 ft × 0.25 in. column of 12% QF-1 on Chromosorb W was used for GLC determinations.

Dichlorine heptoxide was utilized as a 0.3 *M* reagent in carbon tetrachloride, prepared by the previously described method.[16] Alkyl perchlorates are sensitive explosives if not diluted with solvent, and previously noted precautions should be observed.[16]

Reaction of Ethyl Iodide with Dichlorine Heptoxide. Ethyl iodide (0.0936 g, 0.6 mmol) was added dropwise with stirring to 2 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride at 0°. A granular solid, identified by elemental analysis as iodine pentoxide, and a purple solution were formed immediately. The solution was filtered. Analysis by NMR integration, using added chlorobenzene as a quantitative internal standard, showed 0.378 mmol of ethyl perchlorate (63%) and 0.066 mmol (22%) of ethyl acetate. A similar experiment using 0.187 g (1.2 mmol) of ethyl iodide and 2 ml of 0.3 *M* dichlorine heptoxide solution gave 0.40 mmol (33% based on ethyl iodide) of ethyl perchlorate, 0.078 mmol (13%) of ethyl acetate, and 0.126 mmol (21%) of diethyl ether. The identity of the components was confirmed by ir and GLC comparison with authentic samples.

Reaction of Methyl Iodide with Dichlorine Heptoxide. The reaction of 0.3 mmol of methyl iodide with 1 ml of 0.3 *M* dichlorine heptoxide reagent by the above procedure gave methyl perchlorate (45%) and dimethyl ether (12%). Similarly, 0.6 mmol of methyl iodide gave methyl perchlorate (24%) and dimethyl ether (26%).

Reaction of Ethyl Iodide with Chlorine Oxide. Ethyl iodide (0.0936 g, 0.6 mmol) was added to 1 ml of a 0.3 *M* solution of Cl_2O in carbon tetrachloride[17] with stirring at 0°. NMR analysis of the solution showed 0.24 mmol (40%) of ethyl chloride, 0.06 mmol (20%) of diethyl ether, and 0.024 mmol (8%) of ethyl acetate.

Reaction of Ethyl Hypochlorite with Alkyl Iodides. Methyl iodide (0.0852 g, 0.6 mmol) was added with stirring at 0° to a solution of 0.6 mmol of ethyl hypochlorite[18] in 2 ml of carbon tetrachloride. The NMR spectrum of the resulting colorless solution showed a quantitative yield of methyl chloride and of ethyl hypoiodite. The methyl chloride was removed under vacuum to give a solution of ethyl hypoiodite for spectral characterization: NMR (CCl_4) δ 4.37 (q, 2 H, J = 6.5 Hz, CH_2) and 1.32 ppm (t, 3 H, J = 6.5 Hz, CH_3); ir (CCl_4) 2970 (m), 1480 (m), 1450 (w), 1270 (m), 1240 (m), 1010 (s), and 870 cm^{-1}. The identical compound, contaminated by iodine chloride, was obtained by adding an equimolar amount of iodine to the ethyl hypochlorite solution, a procedure reported for the preparation of *tert*-butyl hypoiodite from *tert*-butyl hypochlorite.[14]

By the above procedure, the reaction of ethyl iodide with an equimolar amount of ethyl hypochlorite gave a quantitative yield of ethyl chloride and ethyl hypoiodite.

Reaction of Ethyl Hypoiodite with Ethyl Iodide. An equimolar amount of ethyl iodide was added at 0° to a solution of ethyl hypoiodite prepared as above. Reaction took place over a period of 1 hr, giving a purple solution. NMR analysis showed ethyl acetate (12%) and diethyl ether (41%).

Registry No.—Ethyl iodide, 75-03-6; dichlorine heptoxide, 10294-48-1; methyl iodide, 74-88-4; chlorine oxide, 7791-21-1; ethyl hypochlorite, 624-85-1; ethyl hypoiodite, 55661-06-8.

References and Notes

(1) This work was supported by the Office of Naval Research.
(2) For a review see D. F. Banks, *Chem. Rev.*, **66**, 243 (1966).
(3) K. H. Pansacker, *J. Chem. Soc.*, 107 (1953).
(4) M. Schmeisser, K. Dahmen, and P. Sartori, *Chem. Ber.*, **103**, 307 (1970).
(5) C. S. Rondesvedt, Jr., *J. Am. Chem. Soc.*, **91**, 3054 (1969).
(6) O. R. Chambers, G. Oates, and J. M. Winfield, *J. Chem. Soc., Chem. Commun.*, 839 (1972).
(7) J. Baumanns, L. Deneken, D. Naumann, and M. Schmeisser, *J. Fluorine Chem.*, **3**, 323 (1973).
(8) O. Exner, *Collect. Czech. Chem. Commun.*, **24**, 3567 (1959).
(9) J. L. Cotter, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 4692 (1962).
(10) J. Thiele and W. Peter, *Ber.*, **38**, 2842 (1905); *Justus Liebigs Ann. Chem.*, **369**, 119 (1909); J. Thiele and H. Haakh, *ibid.*, **369**, 131 (1909).
(11) Y. Ogata and K. Aoki, *J. Org. Chem.*, **34**, 3974 (1969).
(12) E. J. Corey and W. J. Wechter, *J. Am. Chem. Soc.*, **76**, 6040 (1954).
(13) C. J. Schack, D. Pilipovich, and K. O. Christe, *Inorg. Nucl. Chem. Lett.*, **10**, 449 (1974).
(14) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964).
(15) For a review of hypoiodite chemistry see J. Kalvoda and H. Heusler, *Synthesis*, 501 (1971).
(16) K. Baum and C. D. Beard, *J. Am. Chem. Soc.*, **96**, 3233 (1974).
(17) G. H. Cady, *Inorg. Synth.*, **5**, 156 (1957).
(18) C. Walling and J. A. McGuinness, *J. Am. Chem. Soc.*, **91**, 2053 (1969).

Restricted Rotation in Hindered Aryl Methyl Sulfoxides as Detected by Low-Temperature Proton Magnetic Resonance

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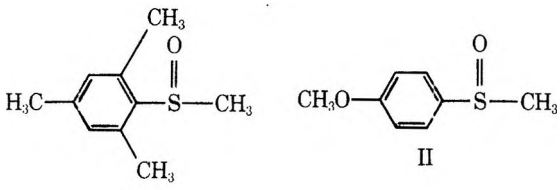
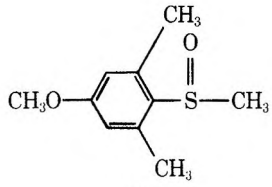
The degree of conjugation between an aromatic ring and the methylsulfinyl group has been the object of considerable attention in the recent literature. Katritsky et al.[1] on the basis of infrared spectral intensities have suggested that the MeSO group is a net resonance donor except when para to a strong electron-donating function. Results of a recent ^{13}C NMR examination,[2] however, do not support this concept. Also, rather little is known regarding the preferred conformations of methyl phenyl sulfoxides, although X-ray[3] and dipole moment[4] studies on the corresponding sulfones indicate a preference for the conformation in which the methyl group is orthogonal to the plane of the benzene ring.

In order to gain more insight into the above matters we have examined the ^1H NMR spectra of sulfoxides I, II, and III at various temperatures.



I

II

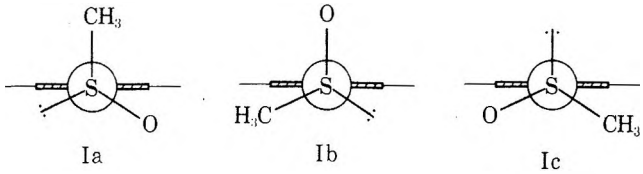


III

At room temperature in 1:1 CS_2–$CDCl_3$ solution, the ortho methyl protons of I appear as a singlet at δ 2.58. Below −87° this resonance separates into signals of 1:1 intensity separated by 29.8 Hz. Application of the Eyring equation yields a barrier ($\Delta G^{\ddagger}$) at −87° of 9.2 ± 0.3 kcal/mol. (The limiting chemical shifts for the anisochronous methyl groups at low temperature are δ 2.73 and 2.43, respectively.) It has been determined that the enthalpy of activation for atomic inversion at sulfur is 34 kcal/mol[5] for compound I. We therefore attribute the present observation to slow aryl–S rotation on the NMR time scale at low temperature.

Owing to peak overlap with the $SOCH_3$ and the para CH_3 resonance at low temperatures, detailed line shape analysis of this spectrum did not yield meaningful parameters.

If eclipsed forms are excluded, three possibilities exist for the conformation of a given enantiomer of I (shown below).

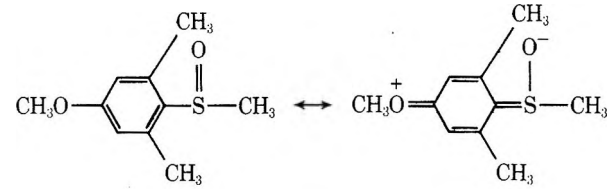


Ia Ib Ic

Since severe van der Waals repulsion is expected between methyl groups in Ib and Ic, Ia is likely to be favored. On the basis of the anisotropic effect of the S=O group[6] one can assign the ortho methyl resonance at lower field to the CH_3 which is cis to the S=O function.

The need for steric bulk at the ortho positions in order to render the aryl–S rotational process observable by ^1H NMR (at 100 MHz) is shown by the lack of change in the ^1H spectrum of II to −130°. This can be contrasted with the behavior of *p*-methoxybenzaldehyde,[7] in which the ortho ring protons show a shift difference of 1.46 ppm in the low-temperature limit, indicative of a barrier ($\Delta G^{\ddagger}$) of 9.4 kcal/mol at the coalescence temperature of −75°. Presumably the findings for II are a consequence of a lower degree of conjugation between the phenyl ring and the S atom, and the longer aryl–S bond.

Sulfoxide III was examined to ascertain the possible electronic influence of substitution on the rotational process. Katritsky's findings[1] suggest that resonance form IIIB may be a substantial contributor. If so, the rotational barrier in III should be higher than in I owing to the increased aryl–S double bond character.



IIIA IIIB

At room temperature in CD_2Cl_2 solution, III exhibits resonances at δ 6.61 (2 H, s), 3.82 (3 H, s), 2.90 (3 H, s), and 2.60 (6 H, s). On cooling, the resonance at δ 2.60 gradually broadens and coalescence is observed at −92°. The limiting chemical shifts at low temperature for the anisochronous CH_3 groups are 2.73 and 2.47 ppm. From the Eyring equation $\Delta G^{\ddagger}$ for aryl–S rotation is 8.9 ± 0.3 kcal/mol at −92°.

The similarity in the results for I and III is taken as evidence for minimal conjugative electron release by the para methoxy function into the aryl–S bond, in contrast to the earlier suggestion.[1] Further experiments using Fourier transform ^{13}C NMR are in progress with the aim of determining $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values.

Experimental Section

NMR spectra were recorded at 100 MHz on a Varian XL-100-12 spectrometer. Temperatures were calibrated with a copper–constantan thermocouple and are judged accurate to ±2°. Samples were contained in 5-mm tubes and were degassed via a freeze–pump–thaw cycle.

Compounds I and II were synthesized according to published procedures.[8] Elemental analyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich.

4-Methoxy-2,6-dimethylbenzenesulfonyl Chloride. Freshly distilled chlorosulfonic acid (10 g, 0.086 mol) was added at 0° to a stirred solution of 2.0 g (0.0147 mol) of 3,5-dimethylanisole (K and K laboratories) in 30 ml of dry chloroform. After a total addition time of 9 min, the reaction[9] mixture was poured into 50 g of crushed ice and extracted with ten 20-ml portions of chloroform. The chloroform extracts were then washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 2.9 g (54%) yield of the sulfonyl chloride as a viscous yellow liquid. The ^1H NMR spectrum in $CDCl_3$ exhibited resonances at δ 6.67 (2 H, s), 3.85 (3 H, s), and 2.70 (6 H, s).

4-Methoxy-2,6-dimethylthiophenol. In a 250-ml three-necked flask fitted with a pressure-equalized funnel, a reflux condenser, and a thermometer was placed 0.5 g (0.013 mol) of $LiAlH_4$ in 55 ml of dry ether. To this stirred slurry was added over 35 min a solution of the sulfonyl chloride (0.9 g, 0.0038 mol) in 100 ml of ether. After the initial reaction subsided, the mixture was stirred and gently refluxed for 4 hr. Excess hydride was decomposed by careful addition of water, followed by 10 ml of 10% H_2SO_4. After the evolution of H_2, a 10% excess of H_2SO_4 was added to dissolve the precipitate.

Acidification to pH 5–6 with 1 *N* HCl was followed by ether extraction. Drying over anhydrous magnesium sulfate, filtration, and evaporation of the solvent in vacuo gave 0.50 g (80%) of the thiophenol as a yellow, viscous liquid. Recrystallization from 30–60° petroleum ether yielded white needles, mp 101–102°. The ^1H NMR spectrum in $CDCl_3$ showed resonances at δ 6.65 (2 H, s), 3.75 (3 H, s), 2.94 (1 H, s), and 2.28 (6 H, s). Addition of D_2O diminished the peak at δ 2.94. Anal. Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19; O, 9.51; S, 19.05. Found: C, 64.20; H, 7.11; O, 9.62; S, 19.07.

4-Methoxy-2,6-dimethylphenyl Methyl Sulfide. A solution of 4-methoxy-2,6-dimethylthiophenol (0.5 g, 0.003 mol) in 3 ml of 2 *N* NaOH was stirred with dimethyl sulfate (0.76 g, 0.006 mol) for 3 hr at room temperature. Water (2 ml) was added to the reaction mixture and the organic component was extracted with four 10-ml portions of ether. The ether extracts were dried over anhydrous $CaCl_2$ and the solvent was evaporated to yield 0.42 g (73%) of the sulfide, bp 114–116° (9 mm). ^1H NMR in $CDCl_3$ has resonances at δ 6.80 (2 H, s), 3.86 (3 H, s), 2.62 (6 H, s), and 2.20 (3 H, s).

4-Methoxy-2,6-dimethylphenyl Methyl Sulfoxide. The sulfide (0.5 g, 0.0028 mol) in 4 ml of MeOH was added dropwise to a solution of sodium metaperiodate (0.6 g, 0.0028 mol) in 5 ml of water. After room temperature stirring overnight the sodium io-

date precipitate was removed by filtration and the filter cake was washed with 15 ml of $CHCl_3$. Extraction with $CHCl_3$, drying over anhydrous sodium sulfate, and removal of the solvent at reduced pressure yielded the sulfoxide as a brown oil. Recrystallization from benzene–petroleum ether gave 0.41 g (74%) of the sulfoxide: mp 71–72°; ^1H NMR ($CDCl_3$) δ 6.60 (2 H, s), 3.84 (3 H, s), 2.91 (3 H, s), and 2.60 (6 H, s).

Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.58; H, 7.12; S, 16.17; O, 16.13. Found: C, 60.46; H, 7.08; S, 16.18; O, 16.28.

Acknowledgments. Generous financial aid from the National Research Council of Canada and Carleton University President's Research Grants is acknowledged.

Registry No.—I, 7321-59-7; II, 3517-99-5; III, 55661-07-9; 4-methoxy-2,6-dimethylbenzenesulfonyl chloride, 55661-08-0; chlorosulfonic acid, 7790-94-5; 3,5-dimethylanisole, 874-63-5; 4-methoxy-2,6-dimethylthiophenol, 701-69-9; 4-methoxy-2,6-dimethylphenyl methyl sulfide, 55661-09-1; dimethyl sulfate, 77-78-1.

References and Notes

(1) N. C. Cutress, T. B. Grindley, A. R. Katritsky, M. Shome, and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 2*, 268 (1974).
(2) G. W. Buchanan, C. Reyes-Zamora, and D. E. Clarke, *Can. J. Chem.*, **52**, 3895 (1974).
(3) C. Rerat and G. Tsoucaris, *Bull. Soc. Fr. Mineral. Cristallogr.*, **87**, 100 (1964).
(4) H. Lumbroso and R. Passerini, *Bull. Soc. Chim. Fr.*, 1179 (1955).
(5) D. R. Rayner, E. G. Miller, P. Bickart, A. J. Gordon, and K. Mislow, *J. Am. Chem. Soc.*, **89**, 3139 (1967).
(6) R. D. G. Cooper, P. V. De Marco, J. C. Cheng, and N. D. Jones, *J. Am. Chem. Soc.*, **91**, 1408 (1969).
(7) R. E. Klinck, D. H. Marr, and J. B. Stothers, *Chem. Commun.*, 409 (1967).
(8) D. Landini, G. Modena, G. Sarrano, and F. Taddei, *J. Am. Chem. Soc.*, **91**, 6703 (1969).
(9) M. Baliah and M. Urna, *Tetrahedron*, **19**, 455 (1963).

Oxidation of Hydrocarbons. VI. Oxidation of Cycloalkanes by Ruthenium Tetroxide[1]

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The selective oxidation of saturated hydrocarbons by inorganic oxidants is an important and often difficult procedure because the required vigorous conditions also promote second-stage oxidation accompanied by C–C bond cleavage and subsequent degradation to carbon dioxide. The limited use of various transition metal oxides for such conversions has been recently reviewed.[2] In addition to other known methods we have found ruthenium tetroxide to be a convenient oxidant for cycloalkanes. Its value as a reagent for these reactions is enhanced because of its high solubility in nonpolar hydrocarbon solutions[3] and because it can be used in conjunction with inexpensive cooxidants such as aqueous sodium hypochlorite (household bleach).[4] Furthermore, the products are easily retrievable from the reaction mixture.

Experimental Section

All reactions were carried out as previously described[5] using either sodium metaperiodate or sodium hypochlorite as cooxidants. Since little difference in yields or products could be detected with either of these cooxidants, it would appear that most of the oxidative conversion is by ruthenium tetroxide, although the possibility of some direct oxidation of the intermediates by the cooxidants cannot be eliminated.[6]

Each reaction was initiated by combining 100 ml of cooxidant solution (1.46 *M* NaOCl or 0.46 *M* $NaIO_4$), 0.01 g of $RuO_2 \cdot 2H_2O$, and 5.0 ml of hydrocarbon in a flask. The flask was closed and the heterogenous mixture was agitated on a wrist shaker until all of the cooxidant had been consumed. The hydrocarbon layer was then separated and the remaining aqueous solution was made basic (pH ≥ 10) by the addition of 6 *M* NaOH and extracted with 3 × 50 ml of ether to recover nonacidic products and starting material. The remaining solution was acidified (pH ≤ 3) by the addition of concentrated H_2SO_4, saturated with NaCl, and extracted with 3 × 50 ml of ether to recover acidic products. Each set of ether extracts was combined, dried over anhydrous $MgSO_4$, and analyzed by GLC. They were then concentrated to 10 ml or less and the nonacidic products were separated and collected by preparative GLC. The isolated products were identified by GLC, TLC, NMR, ir, and melting points. The results are summarized in Table I. Each reaction was carried out three times and the average yield reported.

In a second series of experiments, the relative rates of reaction of cyclopentane, cyclohexane, cycloheptane, and cyclooctane were compared by subjecting all four compounds to oxidation under identical conditions. To 500 ml of 1.64 *M* NaOCl was added 20 mg of $RuO_2 \cdot 2H_2O$ and the solution was stirred until all of the ruthenium dioxide had been converted into ruthenium tetroxide. Ten milliliters of each substrate was then shaken with 50 ml of this solution and 1.00-ml aliquots were withdrawn and titrated periodically. The results of these experiments are found in Table II.

Results and Discussion

When a two-phase system is used, oxidation of the organic substrates by ruthenium tetroxide takes place in the nonaqueous phase. The ruthenium dioxide precipitate formed in this process then migrates to the interface (as in Scheme I), where it is converted back into ruthenium te-

Table I
Products from the Ruthenium Tetroxide Oxidation of Cycloalkanes

Alkane	Registry no.	Reaction time, days	Products	% yield[a]	Registry no.
Cyclopentane	287-92-3	7	Cyclopentanone	18	120-92-3
			Glutaric acid	63	110-94-1
Cyclohexane	110-82-7	8	Cyclohexanone	26 (23)	108-94-1
			Adipic acid	58 (45)	124-04-9
Cycloheptane	291-64-5	2	Cycloheptanone	68	502-42-1
			Pimelic acid	20	111-16-0
Cyclooctane	292-64-8	1	Cyclooctanone	55 (55)	502-49-8
			Suberic acid	23 (33)	505-48-6
trans-Decahydronaphthalene	493-02-7	1	*trans*-9-Decahydronaphthol	55	1654-87-1
			Decalones	7	21370-71-8
					16021-08-2

[a] The yields in parentheses were obtained using sodium periodate as the cooxidant; all other results were obtained using sodium hypochlorite as the cooxidant. In each case the yield calculation was based on the amount of cooxidant used.

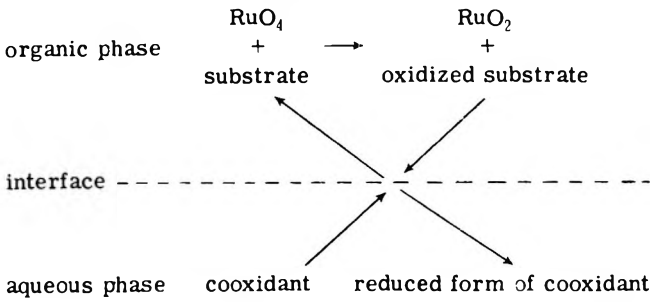
Table II
Relative Ratios for Reactions Involving Cycloalkanes

Reaction	Ring size 5	6	7	8
1. RuO_4 oxidation	1.5	1	2.5	8.7
2. Mn(VII) oxidation[b]	1.4	1	5.2	14.5
3. CrO_3 oxidation[c]	2.0	1	6.6	22.4
4. Acetolysis of tosylates[a,d]	14.0	1	25.3	191

[a] It has been proposed that these reactions proceed through carbonium ion intermediates. [b] Reference 10. [c] Reference 11. [d] Reference 9.

troxide by the cooxidant (which remains in the aqueous phase).

Scheme I



Consequently, it is likely that the organic substrates never come into direct contact with the cooxidant. The products (particularly if they are carboxylic acids) would, however, distribute between both phases and some second-stage oxidation could thus be the result of direct contact with the cooxidant. However, the fact that similar results were obtained when different cooxidants were used suggests that such reactions do not contribute significantly to the overall products obtained.

The results indicate that five- and six-membered rings have a greater tendency to undergo ring cleavage than the seven- and eight-membered rings. This may be due, at least in part, to the greater solubility of the corresponding cyclic ketones in aqueous solutions (where they would come into contact with cooxidant) or to the greater tendency for the smaller rings to undergo oxidative cleavage by ruthenium tetroxide. The reactions could be accelerated by working at a higher temperature, but because vigorous shaking is required to bring the two phases into contact, it is most convenient to work at room temperature. Despite the length of time required for a complete reaction, it would appear that this procedure compares favorably with other methods described in the literature for the oxidation of cyclic hydrocarbons.

Of particular interest is the observation that *trans*-decahydronaphthalene could be converted into *trans*-9-decahydronaphthol in about 60% yield. This suggests, as would be expected for an oxidative process, that tertiary carbon–hydrogen bonds are perferentially attacked.

In this work no solvent was used; however, an inert solvent such as carbon tetrachloride could be used if insufficient hydrocarbon was available.[7]

In a second series of experiments, the relative rates of reaction of cyclopentane, cyclohexane, cycloheptane, and cyclooctane were compared by subjecting all four compounds to oxidation under identical conditions and periodically determining the amount of unreduced cooxidant. In Table II, results of these experiments are described and compared with results that have been obtained from the oxidation of the same compounds by permanganate ion and hexavalent chromium. This comparison suggests that the mechanism is similar for all three oxidants and that the rate ratios are certainly different from those for the acetolysis of the corresponding tosylates. Since the latter reactions involve formation of carbonium ion intermediates,[8,9] it would appear that the oxidation reactions all proceed with homolytic carbon–hydrogen bond cleavage.

Acknowledgments. The authors are pleased to acknowledge the financial support of the National Research Council of Canada.

Registry No.—Ruthenium tetroxide, 20427-56-9.

References and Notes

(1) For parts IV and V see D. G. Lee and J. R. Brownridge, *J. Am. Chem. Soc.*, **96**, 5517 (1974), and U. A. Spitzer and D. G. Lee, *J. Org. Chem.*, **39**, 2468 (1974).
(2) D. G. Lee in "Oxidation, Techniques and Applications in Organic Synthesis, Vol. 1, R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1969, and references cited therein.
(3) T. J. Walsh and E. A. Hausman, *Treatise Anal. Chem. 1959*, (2) **8**, 379 (1963).
(4) S. Wolfe, S. K. Hasan, and J. R. Campbell, *J. Chem. Soc. D*, 1420 (1970).
(5) U. A. Spitzer and D. G. Lee, *J. Org. Chem.*, **39**, 2468 (1974).
(6) S. K. Chakrabartty and H. O. Kretschmer, *J. Chem. Soc., Perkin Trans. 1*, 222 (1974).
(7) D. G. Lee and M. van den Engh in "Oxidation in Organic Chemistry", Part B, W. S. Trahanovsky, Ed., Academic Press, New York, N.Y., 1973.
(8) C. Ruchardt, *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970).
(9) H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956).
(10) U. A. Spitzer, Ph.D. Thesis, University of British Columbia, 1973; U. A. Spitzer and R. Stewart, in preparation.
(11) F. Mares, J. Rocek, and J. Sicher, *Collect. Czech. Chem. Commun.*, **26**, 2355 (1961).

Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXX. Griseofulvin[1]

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While the ^1H nuclear magnetic resonance spectra of griseofulvin (**1a**) and its derivatives have been known and used for some time[3,4,5] and their ^{13}C satellites exploited in an analysis of the path of ^{13}C-enriched acetate in griseofulvin biosynthesis,[6] no direct ^{13}C nuclear magnetic resonance data are available for this system. Accordingly a ^{13}C NMR investigation of the spirocyclic antibiotic and four of its derivatives, epigriseofulvin (**1b**), isogriseofulvin (**2a**), 4′-demethoxyisogriseofulvin (**2b**), and dehydrogriseofulvin (**3**), was undertaken.

Proton-decoupled and single-frequency, off-resonance decoupled spectra of compounds **1–3** in hexadeuteriodimethyl sulfoxide solution were recorded and the residual coupling information used for the differentiation of the various carbon types. The carbon shifts of the five compounds are listed in Table I.

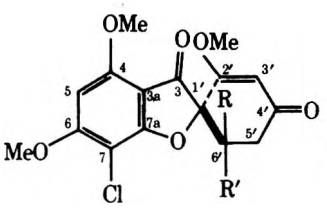
The C-methyl group is represented by the highest field signal in all spectra. The invariancy of the methyl shifts of the ring A methoxy groups permits assignment of the ring C methoxy shift by default. The ring A methoxy groups are distinguished from each other by the difference of the ef-

Table I
Carbon Chemical Shifts[a]

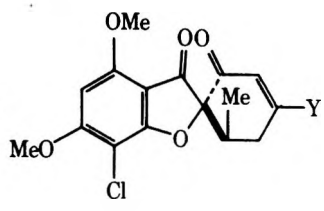
	1a	1b	2a[b]	2b	3
C(3)	191.2	192.3	190.3	189.4	188.0
C(3a)	104.1	105.1	104.0	103.8	103.5
C(4)	157.6	157.3	157.4	157.5	158.3
C(5)	91.2	91.2	90.8	91.1	91.7
C(6)	169.6	169.6	169.7	168.5	168.4
C(7)	95.3	95.6	95.1	95.1	95.8
C(7a)	164.5	164.2	164.0	164.1	164.8
C(1′)	90.1	89.4	94.3	95.1	88.2
C(2′)	170.3	167.9	188.0	189.4	167.5
C(3′)	104.7	105.8	99.2	125.8	103.5
C(4′)	195.6	195.7	178.8	154.1	185.6
C(5′)	39.5	40.1	32.3	30.6	128.9
C(6′)	35.4	34.2	34.3	36.1	146.8
Me	13.8	13.2	13.9	14.1	15.6
4-OMe	57.5	57.4	57.2	57.4	57.7
6-OMe	56.6	56.5	56.5	56.5	56.7
2′-OMe	57.1	56.8			56.7

[a] δ values in parts per million downfield from Me_4Si; δ(Me_4Si) = δ(Me_2SO-d_6) + 39.5 ppm. [b] The 4′-OMe shift is 56.2 ppm.

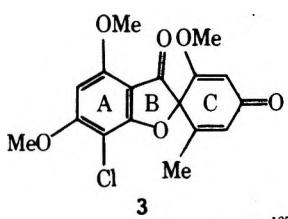
fect of *o*-chloro and *o*-acyl substituents. While ortho substituents have only a minimal influence on the methyl shift of ortho-substituted anisoles,[7] the similarity of the shift difference of the methyl groups of o-acetylanisole and o-chloroanisole in hexadeuteriodimethyl sulfoxide, depicted on formulas **4** and **5**, respectively, with that of the ring A methoxy groups of griseofulvin (**1a**) and its relatives points to the shifts of the latter methyl functions as designated.



1a, R = Me, R′ = H
b, R = H, R′ = Me



2a, Y = OMe
b, Y = H



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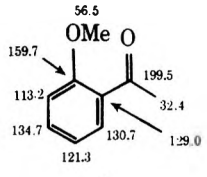

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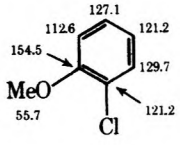

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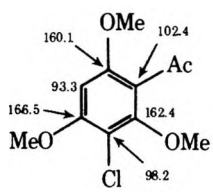
On the assumption of the carbonyl group of ring B being less affected by ring C changes than the ring C carbonyl group, carbon 3 can be assigned. The aromatic carbon shifts are derived from a calculated shift analysis of 3-chloro-2,4,6-trimethoxyacetophenone, an assumed model for ring A of the griseofulvin derivatives, based on the assumption that the additivity of individual substituent parameters holds even in a pentasubstituted aromatic system.[8] As the calculated shifts on formula **6** reveal, the δ values fall within 3 ppm of the experimental data for substances **1–3** despite the expected deviation from additivity



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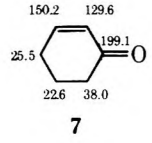

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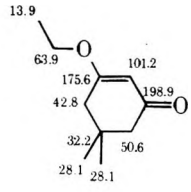

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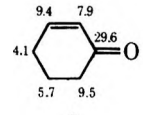
of substituent parameters within such a crowded ring system.

The tetrahedral ring C carbons of griseofulvin (**1a**), epigriseofulvin (**1b**), and isogriseofulvin (**2a**) are each unique in multiplicity and thus readily assigned. This is true also for the ring C, saturated carbons of compound **2b**, while the δ values of its ring C, trigonal carbons are based on those of the related centers in 2-cyclohexenone (**7**). Carbon 1′ is the sole ring C, nontrigonal site of dehydrogriseofulvin (**3**) and its C(5′) and C(6′) can be differentiated from the other, ring C olefinic centers by the difference of α and β effects of methyl and methoxy groups[8] and by the invariance of the C(3′) shift in **1a**, **1b**, **2a**, and **3**. Unambiguous shift assignment of C(2′) and C(4′) in these four substances requires a model study.

While a keto carbon can be expected to be downfield from an unsaturated, nonprotonated oxy carbon, even if the latter is β to the keto carbon and part of an α,β-unsaturated ketone system, this spectral relationship requires on examination of the C(2′) and C(4′) shifts of griseofulvin (**1a**) and isogriseofulvin (**2a**) that the C(1′) substituents exert a strongly shielding influence on C(2′). Since this is a most unusual β effect, verification of the C(2′) and C(4′) shift assignment is mandatory.[9] A ^{13}C NMR study of 5,5-dimethyl-3-ethoxy-2-cyclohexenone (dimedone ethyl ether) (**8**) including a Eu(DPM)$_3$ shift analysis was undertaken and paralleled by a similar investigation of 2-cyclohexenone (**7**)[11] in order to discount the effect of an europium contact shift component on the chemical shift difference of the carbonyl carbon.[12] The Δ_{Eu} values[12] of 2-cyclohexenone and the dimedone derivative, denoted on formulas **9** and **10**, respectively, verify the shift data indicated on



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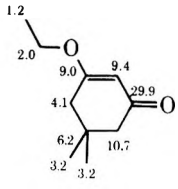

10

7 and **8**, respectively, and, in turn, corroborate the initial view on the shifts of C(2′) and C(4′) of **1a**, **1b**, **2a**, and **3**.

Inversion of the ring C methoxyenone chromophore, i.e., comparison of **1a** or **1b** with **2a**, changes the C(5′) shift by ca. 7.5 ppm, a Δδ value similar to that of C(4) and C(6) of the dimedone derivative **8**. The same effect is dampened strongly in the heavily substituted C(1′). Introduction of a double bond in conjugation with an even already conjugated ketone, i.e., the **1a** or **1b** → **3** change, strongly shields the carbonyl group. Since the methyl group of griseofulvin (**1a**) is known to be equatorially oriented[5] and since the methyl and C(6′) shifts of the antibiotic and epigriseofulvin (**1b**) are similar, the latter probably also possesses an equatorial methyl substituent.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian DP-60 spectrometer operating at 15.08 MHz in the Fourier transform mode. The δ values denoted on formulas **7** and **8** and the Δ_{Eu} values listed on **9** and **10** are for 0.5 *M* deuteriochloroform solutions [δ(Me_4Si) =

$\delta(CDCl_3)$ + 76.9 ppm]. The Δ_{Eu} values are $\Delta\delta$ values obtained by extrapolation to 1:1 molar ratio of ketone to $Eu(DPM)_3$ agent.

Registry No.—**1a**, 126-07-8; **1b**, 469-49-8; **2a**, 469-52-3; **2b**, 55658-69-0; **3**, 3573-90-8.

References and Notes

(1) For Part XXIX see E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gašić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell and P. M. Wovkulich in G. C. Levy, "Topics in Carbon-13 NMR Spectroscopy", Vol. II, Wiley, New York, N.Y., in press.
(2) Address correspondence to Department of Chemistry, Rice University, Houston, Texas 77001.
(3) G. F. H. Green, J. E. Page, and S. E. Saniforth, *J. Chem. Soc.*, **144** (1964).
(4) S. G. Levine and R. E. Hicks, *Tetrahedron Lett.*, 5409 (1968).
(5) S. G. Levine and R. E. Hicks, *Tetrahedron Lett.*, 311 (1971).
(6) M. Tanabe and G. Dertre, *J. Am. Chem. Soc.*, **88**, 4516 (1966).
(7) K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **44**, 2855 (1966).
(8) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972; J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(9) A disbelief of the β effect led to a misassignment of the keto carbon and olefinic oxy carbon of three synthetic intermediates on route to Lycopodium alkaloids. The two carbons in tricycles **49**, **51**, and **53** in the article cited in ref 10 now require signal reversal.
(10) E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, *J. Am. Chem. Soc.*, **95**, 8427 (1973).
(11) Some time after completion of the present work ^{13}C NMR and $Eu(DPM)_3$ shift analyses of **7** appeared in print: D. J. Chadwick and D. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1202 (1974).
(12) E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis, and F. M. Schell, *J. Am. Chem. Soc.*, **93**, 6271 (1971), and references cited therein.

Benzonorbornene-*endo*-2-carboxylic Acid and Its Methyl Ester[1]

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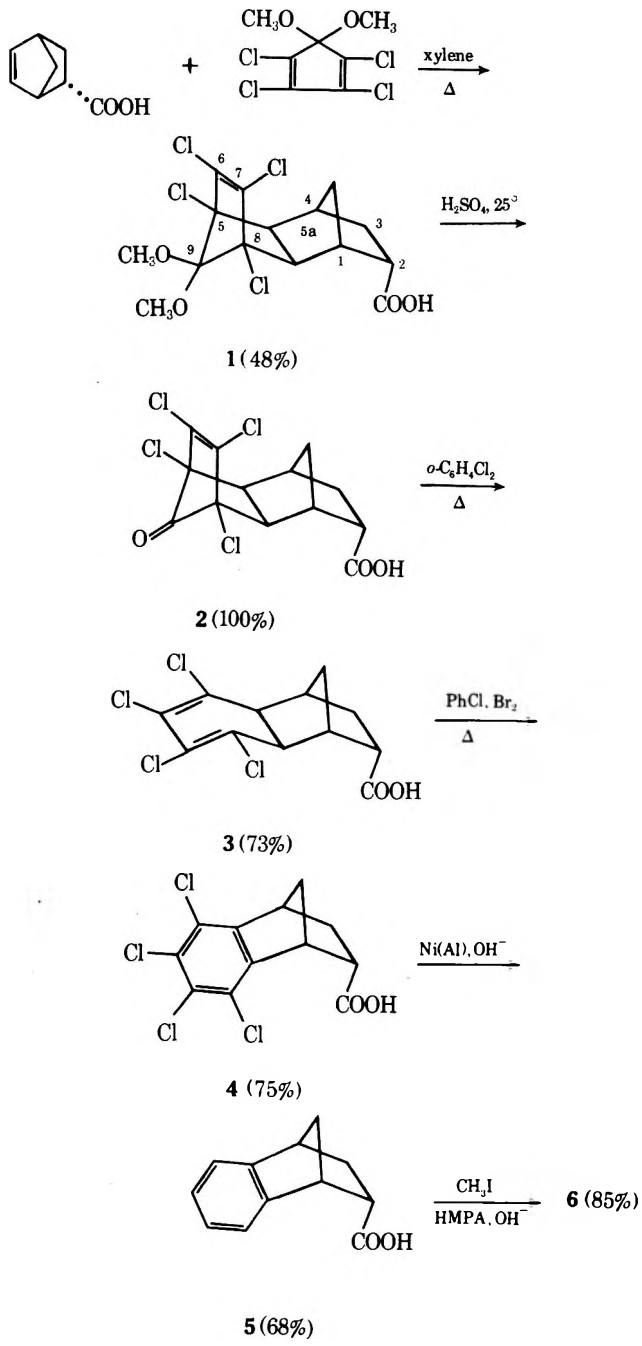
A need to confirm the structure of methyl benzonorbornene-*endo*-2-carboxylate (**6**) isolated in another study[2] led to the synthesis given in Scheme I. The sequence mirrors that used[3] to prepare the 1-carboxylic acid analog of **5** and requires no further discussion. However, the present use of the sequence involved an epimerizable acid function, in contrast to that earlier. The clean retention of configuration observed in **5** and **6**, with no trace of their exo epimers (both known[4]), shows that the sequence could have value as a general synthesis of ac-substituted benzonorbornenes of known stereochemistry, where ac = alicyclic in contrast to ar = aromatic.

Acid **5** was apparently unreported previous to our studies. However, two processes potentially capable of its synthesis have been reported. In the first, an ethyl ester possibly related to **6** was reported by Alder and Fremery,[5] but we have been unable to obtain **6** by their method (adduction of isoindene in situ with an acrylic ester). In the second, carbonation of the Grignard reagent obtained from *exo*-2-bromobenzonorbornene yielded only the exo 2 acid.[4]

Experimental Section

Melting points were taken on a calibrated Fisher-Johns block. Infrared spectra (ir) were determined on 1% KBr disks using a Perkin-Elmer Model 700 instrument. Only prominent or structurally significant absorptions are given (in microns). Nuclear magnetic resonance spectra (NMR) were taken in Me_2SO-d_6 solvent on a Varian A-60A spectrometer. Values are given in parts per million (δ) downfield from internal Me_4Si. Integration of signals agreed with the structural assignments. Mass spectra were taken on a Varian EM-600 instrument at 70 eV. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill.

Scheme I



5,6,7,8-Tetrachloro-9,9-dimethoxy-1,4:5,8-dimethano-1,2,3,4,5,5a,8,8a-octahydronaphthalene-*endo*-2-carboxylic Acid (1). A mixture of 5,5-dimethoxytetrachlorocyclopentadiene[6] (80.8 g, 0.306 mol) and norbornene-*endo*-2-carboxylic acid[7] (38.6 g, 0.263 mol) was refluxed in commercial xylene (150 ml) for 30 hr. Hexane (50 ml) was added and the solution was allowed to stand overnight. The precipitated material was collected and combined with some further material obtained by another treatment with hexane (100 ml): 53.5 g, 47.7%; mp 175–180°; ir 3.00–4.50, 5.88 (COOH), 6.24, 7.04, 7.69, 8.00, 8.40, 8.87, 9.52, 9.92, 10.38, 11.06, 13.15 μm; the compound was not soluble enough in the usual solvents to take a meaningful NMR spectrum. The analytical sample was obtained by recrystallization from xylene, mp 214–215°.

Anal. Calcd for $C_{15}H_{16}O_4Cl_4$: C, 44.80; H, 4.01. Found: C, 44.60; H, 4.01.

5,6,7,8-Tetrachloro-1,4-methano-1,2,3,4,5,5a,8,8a-octahydronaphthalene-*endo*-2-carboxylic Acid (3). Crude acid **1** (53.4 g, 0.133 mol) was added to concentrated sulfuric acid (250 ml) and stirred at 25° for 2 hr. The mixture then was poured over ice (625 g, the ratio of ice to sulfuric acid is critical, otherwise an oil results), stirred briefly, and filtered immediately. The solid so collected was crude keto acid **2** (47.3 g, quantitative yield) which was

used without purification in the next step. o-Dichlorobenzene (600 ml) was added to the crude 2 and the solution was refluxed for 4 hr. The volume was reduced to 250 ml and then diluted with hexane (200 ml). Acid 3 precipitated on standing. It was combined with further material obtained by additional reductions in volume and dilutions with hexane: 32 g, 73.4%; mp 180–185°, ir 3.00–4.50, 5.98 (COOH), 6.25 (C=C), 7.09, 8.14, 8.40, 10.99 μm; NMR, acid H indistinguishable,[8] 2.95 q (5a, 8a-H's, AB, J = 12 Hz), 2.8–1.2 m (all other H's). The analytical sample was produced upon recrystallization from methanol, mp 225–226°.

Anal. Calcd for $C_{12}H_{10}O_2Cl_4$: C, 43.94; H, 3.07. Found: C, 44.19; H, 3.11.

***ar*-Tetrachlorobenzonorbornene-*endo*-2-carboxylic Acid (4).** Crude acid 3 (32 g, 97.6 mmol) was added to chlorobenzene (160 ml) containing bromine (6.4 ml). The solution was refluxed for 4 hr, carefully decanted from ca. 0.5 ml of an immiscible tarry layer, and cooled. The acid 4 that precipitated was collected and combined with further crops obtained by evaporation and trituration with hexane: 23.8 g, 74.8%; mp 166–170°; ir 3.00–4.50, 5.92 (COOH), 7.06, 7.35, 7.79, 8.16, 8.26 μm; NMR, acid H indistinguishable,[8] 3.78 m, 3.67 m (H-1, 4), 2.5–1.2 m (all other H's). The analytical sample was obtained by recrystallization from n-octane, mp 215–216°.

Anal. Calcd for $C_{12}H_8O_2Cl_4$: C, 44.20; H, 2.48. Found: C, 44.18; H, 2.54.

Benzonorbornene-*endo*-2-carboxylic Acid (5). Crude acid 4 (19.6 g, 60 mmol), potassium hydroxide (85% material, 135 g), and water (1.36 l.) were stirred in a large flask while Raney nickel alloy (Alfa, 83.9 g) was added in portions over a 1.5-hr period. Considerable foaming occurred. After 3 hr the mixture was filtered and the residual solid was washed thoroughly with water. The washings were added to the original filtrate and the combined solution was acidified with hydrochloric acid (Congo Red endpoint). Extraction with ether several times then followed. Removal of the ether left crude acid 5: 7.7 g, 68.3%; mp 127–129°; ir and NMR spectra identical with those reported. The analytical sample was obtained from hexane, mp 130–131°, and the mixture melting point with material obtained otherwise[2] was undepressed.

Methyl Benzonorbornane-*endo*-2-carboxylate (6). Acid 5 (6.4 g, 34 mmol) was dissolved in hexamethylphosphoramide (85 ml) containing sodium hydroxide (8 ml of a 25% aqueous solution). Methyl iodide (19.3 g, 0.136 mol) was added and the solution was stirred at 25° for 5 hr.[9] Hydrochloric acid (5%, 170 ml) was added and the solution was extracted with ether several times. The ether extracts were washed with aqueous sodium bisulfite and dried (Na_2SO_4). Removal of the ether left quite pure ester 6: 5.8 g, 85%; m/e 202 (parent), retro-Diels–Alder fragments at 116 (base peak, isoindene), 115 (indene cation), 87 [CH_2=CHC(=$^+$OH)OCH_3, as expected].[10] The ester was chromatographed on silicone gum rubber column (10% SE-52 on Chromosorb W) at 180°. No exo ester was present (checked with authentic sample) and the retention time of 6 was identical (by coinjection) with 6 made otherwise.[2] Also, the ir and NMR spectra of the two samples were identical and showed no trace of any exo impurity.

Registry No.—1, 55606-62-7; 3, 55606-63-8; 4, 55606-64-9; 5, 54274-40-7; 6, 54164-81-7; 5,5-dimethoxytetrachlorocyclopentadiene, 2207-27-4; norbornene-*endo*-2-carboxylic acid, 1195-12-6; o-dichlorobenzene, 95-50-1.

References and Notes

(1) Studies of Benzonorbornene and Derivatives. VII. For Part VI, see J. W. Wilt and E. Vasiliauskas, *J. Org. Chem.*, **37**, 1467 (1972).
(2) J. W. Wilt and R. R. Rasmussen, *J. Org. Chem.*, **40**, 1031 (1975).
(3) J. W. Wilt, H. F. Dabek, Jr., J. P. Berliner, and C. A. Schneider, *J. Org. Chem.*, **35**, 2402 (1970).
(4) J. W. Wilt and P. Chenier, *J. Org. Chem.*, **35**, 1562 (1970).
(5) K. Alder and M. Fremery, *Tetrahedron*, **14**, 190 (1961). A 20% yield of an ethyl ester was obtained, with structural support coming from an unreported ir spectrum. The configuration of the ester was not discussed.
(6) J. S. Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 946 (1949).
(7) Prepared by addition of cyclopentadiene and acrylic acid. Cf. K. Alder et al., *Justus Liebigs Ann. Chem.*, **514**, 206 (1934).
(8) We have routinely experienced difficulty finding the acid proton in these compounds in Me_2SO-d_6 solvent. It is possible that these acids promote exchange even in this solvent.
(9) The method of J. E. Shaw et al., *Tetrahedron Lett.*, 688 (1973).
(10) Retro-Diels–Alder fragmentation (by several pathways) is the major source of MS peaks for norbornyl and benzonorbornenyl compounds. Cf. T. A. Eggelte and N. M. M. Nibbering, *J. Chem. Soc., Perkin Trans. 2*, 605 (1974); S. J. Cristol and G. Nachtigall, *J. Org. Chem.*, **32**, 3727 (1967); S. J. Cristol and A. L. Noreen, *J. Am. Chem. Soc.*, **91**, 3969 (1969); and ref 4.

Fluorinated Hydroquinones

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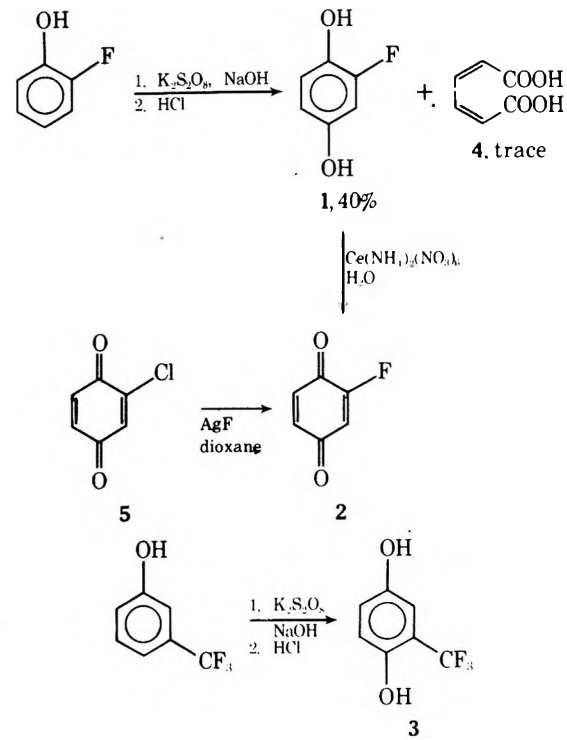
The fluorinated hydroquinones and benzoquinones possess interesting biological[1–3] and chemical[4–9] properties. Although some properties[2,3] of fluorohydroquinone (1) have been described, its preparation and spectroscopic characterization have not been detailed. A multistep preparation of fluorobenzoquinone (2) has been reported,[9] but its characterization was limited to elemental analysis. We now report simple preparations from commercially available starting materials of 1, 2, and trifluoromethylhydroquinone (3),[10] and polarographic half-wave potentials for oxidation of 1 and 3.

Fluorohydroquinone (1) was prepared in 40% yield by oxidation of o-fluorophenol with potassium persulfate[11] in aqueous alkali, followed by hydrolysis of the intermediate p-hydroxyphenyl potassium sulfate with dilute HCl. The compound, a white solid, mp 124–126°, was isolated by silica gel chromatography and recrystallization from chloroform. In addition to 1 and ca. 35% recovered o-fluorophenol, a small amount of *cis,cis*-2,4-hexadienedioic acid (4) was obtained from the reaction, possibly due to oxidation of o-hydroquinone derived from displacement of fluoride in the starting phenol by OH.

In a similar fashion, oxidation of m-hydroxybenzotrifluoride with potassium persulfate afforded trifluoromethylhydroquinone (3) in 6% yield together with 40% recovered phenol. The extremely low yield of product may be due in part to steric hindrance to attack of the persulfate anion by the bulky trifluoromethyl group.



Fluorobenzoquinone (2) was obtained as bright yellow crystals from oxidation of 1 with ceric ammonium nitrate[12] in water, followed by sublimation. The compound was extremely sensitive to base; a black tarry precipitate formed

Table I
$E_{1/2}$ for Monosubstituted Hydroquinones[a]

Substituent	$E_{1/2}$[b]
H	+0.060
Cl	+0.065
F	+0.050
CF_3	+0.133

[a] Aqueous solution, 0.10 *M* NaH_2PO_4 buffer, pH 6.5. [b] Vs. SCE.

instantly on adding 5% aqueous $NaHCO_3$ to an ethanolic solution of **2**.

The reported[13] synthesis of tetrafluorobenzoquinone from the tetrachloro derivative and potassium fluoride prompted attempts to convert chlorobenzoquinone (**5**) to **2** by this method. However, heating **5** neat with KF or in benzene or acetonitrile solution with KF solubilized with 18-crown-6[14] afforded only tars; no **2** was detected by GLC after complete disappearance of **5**. Treatment of **5** (7.2 g) with 2 equiv of silver fluoride in dioxane at 200° gave a dark oil from which 2.8 g of a 42:58 mixture (by GLC) of **2** and **5** could be isolated by silica gel chromatography.

The polarographic behavior of substituted hydroquinones has been extensively investigated.[15] Since little data are available on the effects of fluorine substitution, we have determined the polarographic half-wave potentials for **1** and **3**. At pH 6.5 in aqueous phosphate buffer, the compounds exhibited clean, reversible two-electron oxidation; at higher pH, erratic results were obtained owing to rapid base-catalyzed destruction of the corresponding quinones. The measured values of $E_{1/2}$ for **1**, **3**, and related compounds are given in Table I. The data indicate little effect on $E_{1/2}$ by monohalo substitution, presumably owing to a balancing of the electron-withdrawing inductive and electron-donating resonance effects of these substituents.[16] For the trifluoromethyl derivative, the strong electron-withdrawing effect[16] causes a significant increase in oxidation potential. A dependence of $E_{1/2}$ for monosubstituted quinones on both the inductive and resonance effects of the substituent has been previously noted.[17]

Experimental Section

General. *o*-Fluorophenol (PCR, Inc.), potassium persulfate (Fisher Scientific), ceric ammonium nitrate (Fisher), potassium fluoride (MCB, anhydrous), and silver fluoride (Ozark-Mahoning) were reagent grade and used as received. Chlorohydroquinone (Eastman) was recrystallized from chloroform. *m*-Hydroxybenzotrifluoride (Pierce Chemical Co.) was distilled before use, bp 67° (6 mm). Acetonitrile and dioxane were anhydrous reagent grade and were used directly from unopened bottles. Proton NMR spectra were run on a Varian A-60 instrument in the indicated solvents. Fluorine NMR spectra were run at 94.1 MHz on a Varian XL-100 instrument in the indicated solvents using F-11 as internal standard. GLC analyses were performed on a Hewlett-Packard 5700 instrument with thermal conductivity detector using a 10 ft × 0.25 in. 10% SE-30 column at 140°. Melting points were measured on a Thomas-Hoover melting point apparatus and are corrected.

Fluorohydroquinone (1). *o*-Fluorophenol (11.3 g, 0.100 mol) was dissolved in 400 ml of 6% aqueous NaOH. Solid potassium persulfate (27 g, 0.10 mol) was added to this stirred solution in several portions over 10 min. The dark mixture was stirred overnight at room temperature, then concentrated to ca. ⅓ its original volume on the rotary evaporator. The solution was neutralized with concentrated HCl and extracted once with 200 ml of ether. The aqueous solution was acidified with 100 ml of concentrated HCl, boiled for 1 hr, then concentrated to ca. 50 ml on the rotary evaporator. Addition of 200 ml of acetone precipitated the inorganic salts, which were removed by filtration. The filtrate was taken to dryness on the rotary evaporator and the dark residue, dissolved in acetone, was added to 15 g of silica gel. The solvent was removed and the material was added to a column of 100 g of silica gel packed in hexane. The column was eluted with 10% acetonitrile in chloroform, taking 75-ml fractions. Fractions 5–20 contained 5.3 g (41%) of product, showing a single spot on TLC. Further purification could be effected by dissolving the material in boiling chloroform (60 ml/g), concentrating the solution to ca. ⅓ its original volume, and cooling in an ice bath to give white plates: mp 122–123°; ir ($CHCl_3$) 3600 (s), 3300 (m), 1615 (m), 1520 cm^{-1} (s); proton NMR (Me_2SO-d_6) δ 6.23–6.97 (3 H, m), 8.97 (2 H, s); fluorine NMR (from F-11, Me_2SO-d_6) −134.3 ppm (m); mass spectrum, calcd for $C_6H_5O_2F$, *m/e* 128.0273; found, *m/e* 128.0259.

Anal. Calcd for $C_6H_5O_2F$: C, 56.26; H, 3.93. Found: C, 56.44; H, 4.03. The ether extract of the aqueous reaction solution was concentrated to an oil (4.0 g) which was identified as mostly unreacted *o*-fluorophenol by its NMR spectrum (δ 6.6–7.3, complex multiplet). A small amount of white solid was noted in the oil. Crystallization of the material from 30 ml of acetone gave 0.2 g of white crystals, identified as *cis,cis*-2,4-hexadienedioic acid: mp 199° (lit.[18] mp 194–195°); NMR (Me_2SO-d_6) δ 5.97 (2 H, doubled doublet, J_{12} = 7.8, J_{13} = 2.2 Hz), 7.72 (2 H, doubled doublet, J_{12} = 7.8, J_{13} = 2.2 Hz), 11.0 (2 H, broad singlet); mass spectrum, calcd for $C_6H_6O_4$, *m/e* 142.0266; found, *m/e* 142.0260.

Fluorobenzoquinone (2). Fluorohydroquinone (3.0 g, 0.023 mol) was added to a solution of 26 g (0.046 mol) of ceric ammonium nitrate in 150 ml of water. After stirring for 1 hr at room temperature the solution was extracted with 3 × 100 ml of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated on the rotary evaporator. The residue (2.3 g) was sublimed at 50° (0.5 mm) to give 2.2 g (78%) of bright yellow crystals: mp 78–79°; ir ($CHCl_3$) 3060 (m), 1695 (s), 1675 (s), 1605 (m), 1380 (w), 1350 (s), 1305 (s), 1290 (sh), 1230 (w), 1195 (s), 1165 (m), 1090 (s), 890 (s), 835 cm^{-1} (m); proton NMR ($CDCl_3$) δ 6.48 (1 H, doublet with fine structure), 6.85 (2 H, m); fluorine NMR (from F-11, $CDCl_3$) −112.3 ppm (m).

Anal. Calcd. for $C_6H_3O_2F$: C, 57.15; H, 2.40; F, 15.08. Found: C, 56.87; H, 2.44; F, 15.10.

Reaction of Chlorobenzoquinone with Silver(I) Fluoride. A mixture of 7.20 g (0.050 mol) of chlorobenzoquinone, 12.7 g (0.100 mol) of silver fluoride, and 40 ml of dioxane was heated under N_2 in a pressure bomb at 200° for 4 hr. After cooling to room temperature, the contents of the bomb were filtered and the filtrate was concentrated on the rotary evaporator to a dark oil (6.9 g). The oil was chromatographed on silica gel, eluting with chloroform. Fractions showing quinone by TLC (silica plates) were combined and concentrated to a yellow solid. GLC of this material showed a 42:58 mixture of fluorobenzoquinone and chlorobenzoquinone.

Trifluoromethylhydroquinone (3). *m*-Hydroxybenzotrifluoride (16.2 g, 0.100 mol) was dissolved in 350 ml of H_2O and 50 ml of 50% aqueous NaOH. Solid potassium persulfate (27 g, 0.10 mol) was added in portions over 10 min. The resulting mixture was stirred overnight at room temperature. The solution was concentrated to ca. ⅓ its original volume on the rotary evaporator, neutralized with concentrated HCl, and extracted with 200 ml of ether. The aqueous solution was acidified with an additional 100 ml of concentrated HCl and boiled for 1 hr. After cooling to room temperature, the solution was concentrated to ca. 50 ml on the rotary evaporator. Addition of 200 ml of acetone precipitated the inorganic salts, which were removed by filtration. The filtrate was concentrated to a black oil on the rotary evaporator. The residue was dissolved in 600 ml of ether, dried over $MgSO_4$ and concentrated to a black oil (5.5 g). The material was dissolved in acetone and added to 15 g of silica gel. The solvent was removed and the material was added to a column of 100 g of silica gel packed in chloroform. The column was eluted with 10% acetonitrile in chloroform; 50-ml fractions were taken. Fractions 10–16, showing a single spot on TLC, were combined and concentrated to a red solid. Trituration with chloroform and drying on the vacuum pump gave 1.0 g of white crystals: mp 106–107° (lit.[10] mp 109°); proton NMR (acetone-d_6) δ 6.9–7.1 (3 H, m), 8.32 (2 H, s); fluorine NMR (from F-11, acetone-d_6) −62.0 ppm (s); ir (KBr) 3350 (s), 1640 (w), 1610 (w), 1515 (s), 1490 (m), 1480 (m), 1380 (s), 1320 (s), 1265 (m), 1255 (m), 1220 (m), 1200 (s), 1170 (m), 1130 (s), 1050 cm^{-1} (s); mass spectrum, calcd for $C_7H_5O_2F_3$, *m/e* 178.0241; found, *m/e* 178.0238. The ether extract of the original aqueous solution was dried ($MgSO_4$) and concentrated on the rotary evaporator to a dark oil. Distillation of the oil gave 6.5 g of unreacted *m*-hydroxybenzotrifluoride, bp 67° (6 mm).

Registry No.—**1**, 55660-73-6; **2**, 367-28-2; **3**, 577-10-6; **4**, 1119-72-8; **5**, 695-99-8; *o*-fluorophenol, 367-12-4; potassium persulfate, 7727-21-1; ceric ammonium nitrate, 16774-21-3; silver(I) fluoride, 7775-41-9; *m*-hydroxybenzotrifluoride, 98-17-9.

References and Notes

(1) P. T. Sah and S. A. Peoples, *Arzneim.-Forsch.*, **11**, 27 (1961).
(2) L. R. Tehon, *Science*, **114**, 663 (1951).
(3) G. C. Finger, J. L. Finnerty, and H. G. Schneider, Abstracts, 116th National Meeting of the American Chemical Society, 1949, p 17K.
(4) W. E. Geiger and W. M. Gulick, *J. Am. Chem. Soc.*, **91**, 4657 (1969).
(5) E. Nield and J. C. Tatlow, *Tetrahedron*, **8**, 38 (1960).
(6) P. H. H. Fischer and H. Zimmermann, *Z. Naturforsh., Teil A*, **23**, 1399 (1968).
(7) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).
(8) G. C. Finger, F. H. Reed, D. M. Burness, D. M. Fort, and R. R. Blough, *J. Am. Chem. Soc.*, **73**, 145 (1951).
(9) H. H. Hodgson and D. E. Nicholson, *J. Chem. Soc.*, 645 (1941).
(10) W. B. Whalley, *J. Chem. Soc.*, 3016 (1949).
(11) W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948).
(12) T. Ho, *Synthesis*, 347 (1973).
(13) K. Wallenfels and W. Draber, *Chem. Ber.*, **90**, 2819 (1957).
(14) C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974).
(15) L. Meites, "Polarographic Techniques," 2nd ed, Interscience, New York, N.Y., 1965.
(16) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, N.Y., 1969, pp 33–40.
(17) P. Zuman, *Collect. Czech. Chem. Commun.*, **27**, 2035 (1962).
(18) "The Merck Index", 8th ed, Merck and Co., Inc., Rahway, N.J., 1968, p 704.

Hydration of *p*-Nitrobenzaldehyde[1a]

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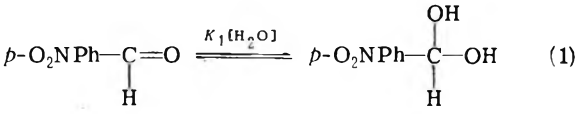
Although measurable hydration in neutral solution has been observed by Laviron, Troncin, and Tirouflet[2] for *o*-nitrobenzaldehyde and by Greenzaid[3] for 4-trimethylammoniobenzaldehyde iodide, it has been assumed[3,4] that the equilibrium constant, K_1, for this hydration reaction (eq 1)



(1)

of *p*-nitrobenzaldehyde is negligibly small, and to the author's knowledge no experimental evidence supporting a significant extent of hydration of this aldehyde in neutral or weakly acidic aqueous solution has previously been reported. Several recent observations in this laboratory indicate that the value of $K_1[H_2O]$, although small, is measurable and has an approximate value of 0.25 ± 0.1 at 25°, corresponding to approximately 20% hydration of the aldehyde. This finding means that a small but significant correction of observed rate and equilibrium constants for reactions of *p*-nitrobenzaldehyde is required in kinetic studies, especially when this aldehyde is compared with other, less significantly hydrated, substituted benzaldehydes in structure–reactivity correlations.

The following three experimental observations provide strong qualitative evidence that *p*-nitrobenzaldehyde is significantly hydrated in neutral aqueous solution, and are consistent with an approximate value for $K_1[H_2O]$ of 0.25 ± 0.1.

(1) Upon addition of a sample of *p*-nitrobenzaldehyde in acetonitrile solution to 0.1 *M* aqueous potassium acetate–acetic acid buffer, pH 4.6, a time-dependent absorbance change at 268 nm with a pseudo-first-order rate constant of approximately 5×10^{-2} sec^{-1} is observed (curve A, Figure 1). This result is most easily accounted for by the establishment of an equilibrium between the unhydrated and hydrated forms of the aldehyde. If an estimate is made for the absorbance of the hydrate at 268 nm, based on the absorbance of the corresponding bisulfite addition product, the magnitude of the observed absorbance change corresponds to 17 ± 1% hydration of the aldehyde at equilibrium.

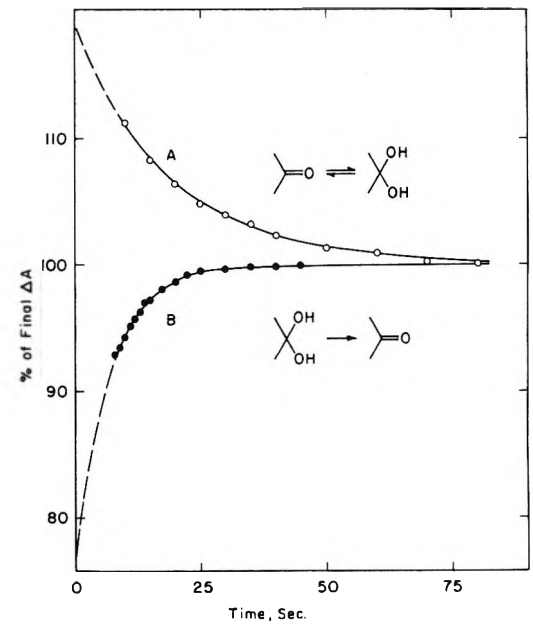
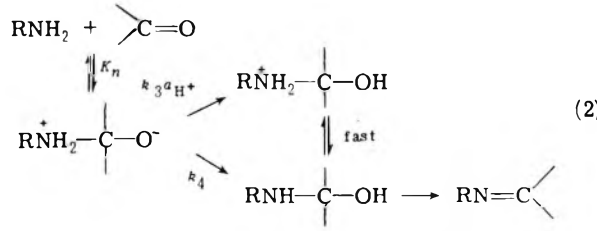


Figure 1. Time-dependent absorbance changes observed upon addition of *p*-nitrobenzaldehyde in acetonitrile solution to 0.1 *M* aqueous acetic acid–potassium acetate buffer, pH 4.6 (curve A), and *p*-nitrobenzaldehyde in aqueous solution to 0.5 *M* aqueous semicarbazide buffer, pH 2.8 (curve B). The spectral changes of curves A and B were followed at 268 and 320 nm, respectively, and corresponded to absolute absorbance changes of 0.080 (curve A) and 0.38 (curve B) for a total concentration of aldehyde in the reaction mixtures of 10^{-4} *M*. The broken portions of the curves represent extrapolated values determined from semilogarithmic plots of $(A_{obsd} - A_{final})$ or $(A_{final} - A_{obsd})$ against time.

(2) Addition of an *aqueous* solution of *p*-nitrobenzaldehyde to semicarbazide buffer, 88% acid, pH 2.8, causes an immediate burst of absorbance at 320 nm, followed by a measurably slow increase in absorbance to a final stable value (curve B, Figure 1). Under these conditions, the rate-determining step for semicarbazone formation is the proton transfer step, k_3 and k_4, in the formation of the cationic or neutral tetrahedral intermediate (eq 2),[5] and hence pre-



(2)

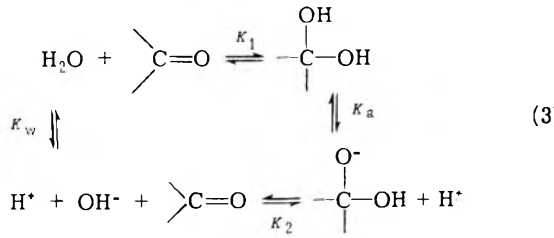
equilibrium accumulation of this intermediate is not responsible for the observed biphasic kinetics. The second phase that is observed in the reaction between *p*-nitrobenzaldehyde and 0.5 *M* (total) semicarbazide at pH 2.8 has a pseudo-first-order rate constant of 0.15 sec^{-1}, approximately 15 times slower than the pseudo-first-order rate constant, $K_n(k_3a_{H^+} + k_4)$ $[H_2NC(O)NHNH_2]$, of 2.3 sec^{-1} for buffer-independent semicarbazone formation under these conditions calculated from published rate constants.[5] The second phase of the reaction is less than first order in semicarbazide, as indicated by the fact that the pseudo-first-order rate constants for this process in the presence of

0.2 and 0.4 M total semicarbazide differ only by approximately 20%. This biphasic behavior is most easily explained[6] if the initial burst represents very rapid conversion of the free aldehyde to the semicarbazone, whereas the second phase of the reaction involves rate-limiting conversion of the fraction present as the hydrate to the free aldehyde. An extent of hydration of 23 ± 2% is calculated from the magnitude of the absorbance change corresponding to the second phase of the reaction.

(3) The 90-MHz Fourier transform NMR spectrum of a saturated solution of p-nitrobenzaldehyde in 25% CD_3CN–75% D_2O shows small peaks at δ 6.06 and 7.65 ppm that are assigned to the α proton of the hydrate and to the aromatic protons of the hydrate,[3] respectively. The ratio of the area of the peak at δ 6.06 to that of the peak corresponding to the aldehydic proton at 10.0 ppm is approximately 1.0:7.6 and the ratio of the areas of peaks for the aromatic protons in the hydrated (δ 7.65) and unhydrated (δ 8.2) aldehydes is approximately 1.0:8.2. This finding provides qualitative confirmatory evidence for the hydration of the aldehyde, and the value of approximately 11–12% hydration in D_2O containing 25% acetonitrile is consistent with the slightly greater extent of hydration observed in completely aqueous solutions.

These results for p-nitrobenzaldehyde are comparable with the observed value[2] of 0.43 for $K_1[H_2O]$ for o-nitrobenzaldehyde and with a calculated value of 0.08 for m-nitrobenzaldehyde.[3]

The value of 0.25 ± 0.1 for $K_1[H_2O]$ for p-nitrobenzaldehyde is consistent with the known equilibrium constant for formation of the anionic hydrate from p-nitrobenzaldehyde and hydroxide ion[3,4] and a value for the pK_a of the hydrate estimated from structure–reactivity correlations. From the interrelationship[3] of the equilibria shown in eq 3,



(3)

a pK_a value of 12.1 ± 0.2 for the hydrate may be calculated from $K_1[H_2O]$ = 0.25 ± 0.10 and K_2 = 18 ± 3 M^{-1}, obtained from $K_1[H_2O]$ and the observed[3,4,7] equilibrium constant of 14.8 ± 1.5 M^{-1} for the addition of hydroxide ion to hydrated plus unhydrated p-nitrobenzaldehyde in aqueous solution at 25°. A pK_a of 12.1 ± 0.2 is consistent with a value of pK_a = 12.3 estimated as follows. From the observed pK_a of 9.18 for 1,1-dihydroxy-1-(m-nitrophenyl)-2,2,2-trifluoroethane[8] and a ρ value of 1.11, the pK_a of the corresponding p-nitro compound is estimated to be 9.08. Substitution of the CF_3 group by CH_3 should give a ΔpK_a of 3.5 if ρ_I for ionization of the hydroxyl group[9] is taken as 8.4 and σ_I[10] for CF_3 is 0.42. This gives pK_a = 12.58 for 1,1-dihydroxy-1-(p-nitrophenyl)ethane, and substitution of H for CH_3 is expected to decrease the pK by ~0.3 unit,[9] giving pK = 12.28 for p-nitrobenzaldehyde hydrate.

The observed equilibrium constant of 0.25 ± 0.1 for hydration of p-nitrobenzaldehyde is also consistent with a predicted value of 0.18 ± 0.04 from the structure–reactivity correlation of Sander and Jencks[6] for addition of nucleophiles to aromatic aldehydes. Based on γ values of 1.13, 0.46, and −3.58 for methoxyamine,[11] semicarbazide, and water, respectively, and equilibrium constants of 40 and 125 M^{-1} for the addition of semicarbazide[13] and methoxyamine[12] to p-nitrobenzaldehyde, log K_1 = −2.5 ± 0.1, corresponding to $K_1[H_2O]$ = 0.18 ± 0.04, was calculated from the relationship $\Delta \log K_{eq} = \Delta\gamma$.

Experimental Section

Semicarbazide hydrochloride was recrystallized and p-nitrobenzaldehyde was recrystallized or sublimed. Glass-distilled water was used in all reactions. Kinetics were followed at 25° and ionic strength 1.0, maintained with potassium chloride. Formation of the hydrated aldehyde was followed at 268 nm using a Cary 118 recording spectrophotometer, after addition of 50 μl of a 5×10^{-3} M solution of p-nitrobenzaldehyde in acetonitrile to 2.5 ml of aqueous acetic acid–potassium acetate buffer solution. The reaction follows pseudo-first-order kinetics, and the absorbance change due to hydration of the aldehyde was determined from the intercept at time zero of a linear semilogarithmic plot of ($A_{final} - A_{obsd}$) against time. The absorbance expected for the fully hydrated aldehyde was estimated using the sulfite addition product as a model: after completion of the hydration reaction, 30 μl of Na_2SO_3–$NaHSO_3$ (1:1) solution, 1 M in SO_3^{2-} plus HSO_2^-, was added to the reaction mixture and the absorbance was measured. A correction of approximately 4% was applied for the absorbance of the sulfite–bisulfite solution alone. ΔA_{hyd} for complete hydration of the aldehyde was taken as ($A_0 - A_{SO_3^{2-}}$) where A_0 is the extrapolated value for the absorbance at zero time and $A_{SO_3^{2-}}$ is the absorbance of the sulfite addition product. The fraction of aldehyde converted to the hydrate, α, is then given by $\Delta A_{obsd}/\Delta A_{hyd}$, where ΔA_{obsd} is the observed time-dependent absorbance change. The equilibrium constant, $K_1[H_2O]$, for hydration is $\alpha/(1 - \alpha)$. For a typical experiment under these conditions using a concentration of approximately 10^{-4} M total aldehyde, observed values of A_0, A_{final}, and $A_{SO_3^{2-}}$ were 1.415, 1.335, and 0.903, respectively.

Time-dependent dehydration of the hydrated aldehyde was followed by measurement of the change in absorbance at 320 nm upon addition of 50 μl of a (2.5–5) × 10^{-3} M aqueous solution of p-nitrobenzaldehyde to 2.5 ml of semicarbazide buffer solution, 88% acid, ionic strength 1.0. The total absorbance change, ΔA_{tot}, for semicarbazone formation from hydrated plus unhydrated aldehyde was obtained by correction of the final absorbance value for the small (~11%) absorbance of p-nitrobenzaldehyde at 320 nm. The observed time-dependent absorbance change, ΔA_{obsd}, due to slow conversion of the hydrate to the aldehyde, was determined from the intercept at time zero of a semilogarithmic plot of ($A_{final} - A_{obsd}$) beginning 8–10 sec after mixing. The fraction, α, of aldehyde present as the hydrate in the initial solution is then given by $\Delta A_{obsd}/\Delta A_{tot}$. The *time-dependent* absorbance change observed upon mixing an acetonitrile solution of p-nitrobenzaldehyde with the semicarbazide buffer was negligible, the final absorbance value being reached too rapidly to measure under our conditions, as expected for a solution in which no hydrated aldehyde is present at time zero.

Analogous experiments using a Gilford Model 2000 spectrophotometer equipped with a rapid-mixing syringe,[14] and reaction mixtures containing 12% acetonitrile, gave results that were consistent with those described above.

The 90-MHz Fourier transform NMR spectrum of a saturated solution of p-nitrobenzaldehyde in 75% D_2O–25% acetonitrile (by weight) was determined using a Bruker WH90 Fourier transform NMR spectrometer. Chemical shifts relative to tetramethylsilane were determined from the observed chemical shifts relative to acetonitrile (δ 2.0 ppm).

Acknowledgment. The author is grateful to Professor William P. Jencks for helpful discussions, and to Professor A. Redfield and Dr. Arthur Cooper for obtaining the NMR spectrum.

Registry No.—p-Nitrobenzaldehyde, 555-16-8; p-nitrotoluene-α,α-diol, 55649-04-2.

References and Notes

(1) (a) Supported by grants from the National Science Foundation (GB 31740) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247). (b) Department of Chemistry, University of Vermont, Burlington, Vt. 05401.
(2) E. Laviron, H. Troncin, and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 524 (1962).
(3) P. Greenzaid, *J. Org. Chem.*, **38**, 3164 (1973).
(4) W. J. Bover and P. Zuman, *J. Chem. Soc., Perkin Trans. 2*, 786 (1973).
(5) J. M. Sayer, B. Pinsky, A. Schonbrunn, and W. Washtien, *J. Am. Chem. Soc.*, **96**, 7998 (1974).
(6) E. G. SANDER AND W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 6154 (1968).

(7) A value of 14 M^{-1} measured at ionic strength 1.0 is identical within experimental error with the reported values.
(8) R. Stewart and R. Van der Linden, *Can. J. Chem.*, **38**, 399 (1960).
(9) J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 1436 (1974).
(10) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(11) Calculated from K_e = 13.4 M^{-1} for addition to *p*-chlorobenzaldehyde (ref 12).
(12) S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7986 (1974).
(13) B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).
(14) B. Perlmutter-Hayman and M. A. Wolff, *Isr. J. Chem.*, **3**, 155 (1965).

Electrophilic Substitution in 1,8-Di-*tert*-butylnaphthalenes

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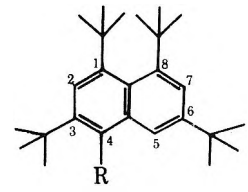
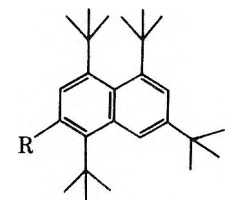
In previous reports from our laboratories on 1,8-di-*tert*-butylnaphthalenes, the focus has been primarily on synthetic and spectroscopic studies.[2] This note describes our results with probing the strained system via electrophilic aromatic substitution.

Nitration of 1,3,6,8-tetra-*tert*-butylnaphthalene (**1**) was accomplished using acetyl nitrate at −40°, followed by warming to 25°, conditions used previously for substitution on azulene, (18)annulene, and 1,3,6,8-tetramethylnaphthalene.[3] NMR and TLC of the crude reaction mixture revealed the presence of a single product which after purification yielded 4-nitro-1,3,6,8-tetra-*tert*-butylnaphthalene (**2**) in 54% yield. The structural assignment was based on its NMR spectrum (Table I), particularly the shielded peri proton at δ 7.04. This value is shifted upfield by 0.17 ppm compared to the parent compound **1**, expected since the nitro group is rotated so that its shielding cone interacts strongly with the peri H. Similar results have been obtained with methylnitronaphthalenes by Wells.[4] Our reaction conditions and results may be compared to those for *o*-di-*tert*-butylbenzene which is nitrated using concentrated nitric acid in acetic acid to afford products with no nitro insertion ortho to *tert*-butyl.[5]

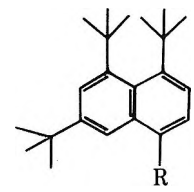
Bromination of **1** was effected in good yield with dioxane dibromide, a reagent normally used for bromination of phenols.[6] The NMR of the product (Table I) is consistent with both a rearranged structure **4** and the direct product **3**. In particular, the *tert*-butyl chemical shift of δ 1.64 is interpretable as an uncrowded peri-*tert*-butyl which is complementary to a neighboring peri H at δ 8.07. A reductive dehalogenation with butyllithium was performed on **3** to yield **1**, confirming lack of rearrangement in the bromination. Thus, the chemical shifts are due to the deshielding effects



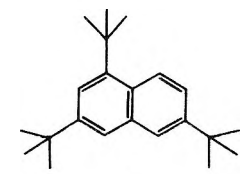
1, R = H
2, R = NO_2
3, R = Br



4, R = Br
9, R = H



5, R = H
6, R = Br
7, R = I



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of the bromine. These bromination conditions were also applied to 1,3,8-tri-*tert*-butylnaphthalene (**5**) to afford 5-bromo-1,3,8-tri-*tert*-butylnaphthalene (**6**). The lesser deshielding of the peri proton by bromine compared to that in **3** can be explained by the lack of buttressing of the bromine by the *tert*-butyl.[7] The photochemical behavior of **6** has been reported.[2] These brominations also may be compared to those of *o*-di-*tert*-butylbenzene, which requires $FeBr_3$ catalysis for rapid reaction and which results in some dealkylation as well as substitution.[5] Lastly, 5-iodo-1,3,8-tri-*tert*-butylnaphthalene (**7**) was prepared by treating **5** with iodine and yellow mercuric oxide, a combination of reagents previously used for iodination of thiophene.[8]

These results, i.e., regiospecific attack at the 4 position, are consistent with our previous study of the acid sensitivity of peri *tert*-butylnaphthalenes which demonstrated greatest reactivity at the 4 position. From the NMR data accumulated in this series, we are now able to assign α and β protons in the entire series with more certainty. Using the data obtained in unstrained naphthalene **8** as a standard, we can conclude that there is, in fact, a decrease in ring current in the naphthalenes which are strained and thus distorted from planarity. This decrease in ring current appears to result in a shielding of approximately 0.3 ppm and is consistent with the distortion effects observed with other spectroscopic techniques applied to the naphthalenes and the similar NMR observation made with 1,2,3,5-tetra-*tert*-butylbenzene.[9]

Experimental Section[10]

4-Nitro-1,3,6,8-tetra-*tert*-butylnaphthalene (2). A solution of 30 mg (0.08 mmol) of naphthalene **1**[2] in 2 ml of acetic anhydride was placed in a Dry Ice–ethanol bath and allowed to stir until it reached −40°. To this solution was added acetyl nitrate (2 ml over a 10-min period) prepared as follows: 160 mg of $Cu(NO_3)_2$ was

Table I
NMR Data for *tert*-Butylnaphthalenes. Chemical Shift and *J* (Hertz), CCl_4

Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
9[a]	1.22	7.43 (2)	1.42	7.90 (2)	1.57	7.28 (8)	7.10 (8)	1.24
8[a]	1.65	7.78 (2)	1.43	7.57 (2)	7.57 (2)	1.43	7.48 (2, 9.2)	8.34 (9.2)
1[a]	1.30	7.48 (2)	1.40	7.22 (2)	7.22 (2)	1.40	7.48 (2)	1.30
2	1.33	7.62	1.48	NO_2	7.04 (2)	1.42	7.65 (2)	1.33
3	1.30	7.59	1.64	Br	8.07 (2)	1.45	7.59 (2)	1.28
6	1.30	7.63 (2.5)	1.47	7.79 (2.5)	Br	7.48 (8)	7.32 (8)	1.32
7	1.28	7.61 (2)	1.45	7.66 (2)	I	7.80 (8)	7.19 (8)	1.28

[a] Data taken from ref 2a.

added to 10 ml of acetic anhydride and 5 ml of acetic acid and then gently heated in a water bath. Ten minutes after the acetyl nitrate was added, the reaction was allowed to warm to room temperature. Water was then added and the reaction was worked up in a conventional manner. Preparative TLC of the product on silica gel eluting with hexane afforded 22 mg of nitronaphthalene (2) whose NMR was essentially identical with that of the analytical sample obtained by recrystallization from methanol (18.5 mg, 54% yield), mp 124.5–125.5°.

Anal. Calcd for $C_{26}H_{39}NO_2$: C, 78.98; H, 9.80; N, 3.40. Found: C, 78.89; H, 9.90; N, 3.43.

4-Bromo-1,3,6,8-tetra-*tert*-butylnaphthalene (3). A solution of 50 mg (0.14 mmol) of naphthalene 1[2] in 4 ml of anhydrous ether was cooled in an ice–salt bath (−3°) and treated with a solution of 110 mg (0.41 mmol) of dioxane dibromide in 4 ml of ether. The reaction was complete in 45 min. The solution was allowed to warm to room temperature, diluted with ether, washed with sodium thiosulfate solution, and worked up in the usual manner. Preparative TLC of the product on silica gel eluting with hexane afforded 41 mg of crude bromo product whose NMR was essentially identical with that of the analytical sample prepared by recrystallization from 80:20 ethanol–ethyl acetate (27 mg, 39%), mp 142.5–144.0°.

Anal. Calcd for $C_{26}H_{39}Br$: C, 72.72; H, 9.01; Br, 18.65. Found: C, 72.46; H, 9.14; Br, 18.68.

Debromination of Bromonaphthalene 3. A solution of 18 mg (0.04 mmol) of bromonaphthalene 3 in 2 ml of anhydrous ether was prepared in an oven-dried flask equipped with a serum cap. Excess butyllithium in hexane was then injected into the solution. After the resulting solution was stirred for 1.5 hr, 10 ml of water was added. The solution was then worked up in the normal way to afford 13 mg of naphthalene 1 identical with an authentic sample by TLC and NMR comparison.

5-Bromo-1,3,8-tri-*tert*-butylnaphthalene (6). To an anhydrous ether solution of 60 mg (0.2 mmol) of 1,3,8-tri-*tert*-butylnaphthalene (5)[2] was added an ether solution of 100 mg (0.4 mmol) of dioxane dibromide. The reaction was cooled in an ice–salt bath initially and then allowed to warm to room temperature over a 2-hr period. Work-up included washing the ether with 15% sodium thiosulfate. The crude product was an oil which was distilled in a Kugelrohr, oven temperature 120° (0.1 Torr), to afford 60 mg (90%) of bromonaphthalene 6 as a clear oil.

Anal. Calcd for $C_{22}H_{31}Br$: C, 70.57; H, 8.35; Br, 21.34. Found: C, 70.40; H, 8.36; Br, 21.32.

5-Iodo-1,3,8-tri-*tert*-butylnaphthalene (7). To a solution of 131 mg (1 mmol) of iodine and 50 mg (0.5 mmol) of naphthalene 5[2] in 3 ml of benzene was added 110 mg (0.5 mmol) of mercuric oxide (yellow). The mixture was stirred overnight after which time it became orange colored. Work-up afforded a mixture of product 7 (28 mg) and starting material which was separated by preparative TLC on silica gel. Crude 7 was rechromatographed on silica and then distilled at 65° and 1 Torr to yield 18 mg of a clear oil which was used as the analytical sample.

Anal. Calcd for $C_{22}H_{31}I$: C, 62.57; H, 7.35; I, 30.08. Found: C, 62.89; H, 7.60; I, 29.70.

Registry No.—1, 22495-86-9; 2, 55669-70-0; 3, 55669-71-1; 5, 22495-89-2; 6, 53535-11-8; 7, 55669-72-2; acetyl nitrate, 591-09-3; dioxane dibromide, 21992-70-1.

References and Notes

(1) (a) Partial support of this research by the Fordham University Research Council is gratefully acknowledged. (b) Taken in part from the Undergraduate Research Participation Report of E. S.

(2) (a) Synthesis: R. W. Franck and E. Leser, *J. Org. Chem.*, **35**, 3932 (1970). (b) NMR: J. E. Andersen, R. W. Franck, and W. L. Mandella, *J. Am. Chem. Soc.*, **94**, 4608 (1972). (c) Photochemistry: W. L. Mandella, R. W. Franck, and K. J. Falci, *J. Org. Chem.*, **40**, 327 (1975). ESR: I. Goldberg, H. Crowe, and R. W. Franck, *J. Phys. Chem.*, **79**, 1740 (1975).

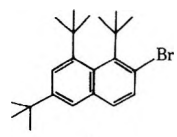
(3) (a) A. G. Andersen, Jr., J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953) (azulene); (b) Y. Gaoni and F. Sondheimer, *ibid.*, **86**, 521 (1964) (annulene); (c) unpublished results, E. Soykan (1,3,6,8-tetramethylnaphthalene).

(4) P. R. Wells, *Aust. J. Chem.*, **17**, 967 (1964).

(5) A. W. Burgstahler, P.-L. Chien, and M. O. Abdel-Rahman, *J. Am. Chem. Soc.*, **86**, 5281 (1964).

(6) (a) L. A. Yanovskaya, A. P. Terent'ev, and L. I. Belenkii, *J. Gen. Chem. USSR (Engl. Transl.)*, **22**, 1592 (1952); (b) J. D. Billimore and N. F. McLagan, *J. Chem. Soc.*, 3257 (1954).

(7) This could also be explained by postulating i as the product. However, a significant effect on a *tert*-butyl resonance would have been a requirement for this structure.



i

(8) W. Minnis, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 357.

(9) (a) E. M. Arnett, J. C. Sanda, J. M. Bollinger, and M. Barber, *J. Am. Chem. Soc.*, **89**, 5389 (1967); (b) E. M. Arnett and J. M. Bollinger, *Tetrahedron Lett.*, 3803 (1964).

(10) Microanalyses were performed by Spang Laboratories, Ann Arbor, Mich.

Synthesis of Benzoquinone-1,4-aldehyde Diacetate

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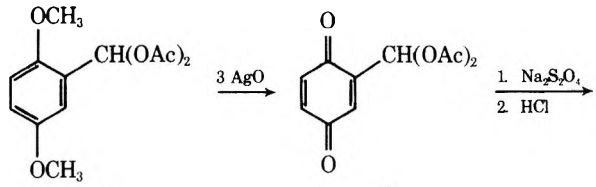
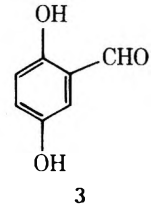
The oxidative demethylation of unsubstituted and several substituted hydroquinone and naphthohydroquinone ethers to give the corresponding quinones with argentic oxide (AgO) in excellent yields was reported by Rapoport and coworkers.[1] In our efforts related to the demethylation of 2,5-dimethoxybenzaldehyde,[2] we examined this method in order to see if benzoquinone-1,4-aldehyde could be readily obtained. Aldehydic groups are reported to remain intact under the specified mild reaction conditions.[1]

Treatment of 2,5-dimethoxybenzaldehyde with argentic oxide in the presence of nitric acid produced only small amounts of benzoquinone-1,4-aldehyde, as evidenced by the detection of traces of gentisaldehyde (by TLC) after reduction of the reaction products with sodium dithionite. In contrast, reaction of 2,5-dimethoxybenzaldehyde diacetate (1)[3] with 3 equiv of argentic oxide in the presence of 6 *N* HNO_3 produced the previously unreported benzoquinone-1,4-aldehyde diacetate (2) in 96% yield. The spectral data



1 2



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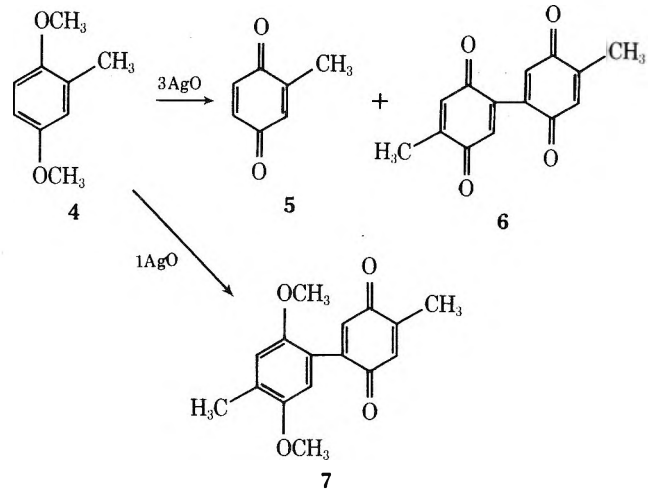
and elemental analysis agree with structure 2, and further proof was provided by the reduction of 2 with sodium dithionite, followed by hydrolysis to give gentisaldehyde (3) in 69% yield. In our attempts to further extend this method to monosubstituted alkylhydroquinone ethers, difficulties were encountered. For example, oxidation of 2,5-dimethoxytoluene (4) with argentic oxide gave a mixture of the expected methyl-1,4-benzoquinone (5) and 4,4′-dimethylbiphenyl-2,5,2′,5′-diquinone (6) in approximately equal amounts with an overall yield of 83%. The formation of 6 was due to the arylation of 5 by the starting ether 4, as evidenced by the isolation of 7, when only 1 equiv of argentic oxide was used. The formation of diquinones was also re-

ported in the oxidation of 1,4-dimethoxybenzene and 2,5-dimethoxytoluene with ceric sulfate and a threefold increase in diquinone was observed with the latter,[4] suggesting that with electron-donating substituents arylation becomes a competing pathway.

The reduction of the electron-donating ability of the methyl group by introducing two acetoxy groups in 1 changed the reaction to cause exclusive demethylation. However, the fact that arylation occurs with 1,4-dimethoxybenzene if ceric sulfate is being used as oxidizing agent, while argentic oxide produced exclusively 1,4-benzoquinone, indicates that the oxidative demethylation reaction is sensitive to both the substituent and the oxidizing agent used.



Experimental Section

Oxidative Demethylation of 2,5-Dimethoxybenzaldehyde Diacetate (1).[3] To a suspension of 3.4 g (27.4 mmol) of AgO (supplied by Alfa Inorganics) in a solution of 2.1 g (7.8 mmol) of **1** in 80 ml of THF (freshly distilled over CaH_2) under stirring was added 8 ml of 6 *N* HNO_3, and after 3 min (by this time all AgO was dissolved) the reaction mixture was diluted with 160 ml of chloroform and 40 ml of water and stirred. The organic layer was separated, washed with water, dried (anhydrous $MgSO_4$), and evaporated to give 1.8 g of **2** (96%), mp 88–90°. By TLC examination (8:2 benzene–ether, silica gel plate) it was found to be pure. A recrystallized (2-propanol) sample had mp 90–92°; NMR ($CDCl_3$) δ 2.13 (s, 6, $OCOCH_3$), 6.83 (s, 3, 1,4-benzoquinone), 7.61 [s, 1, $CH(OAc)_2$]; ir ($CHCl_3$) 1666 (1,4-benzoquinone C=O), 1765 cm^{-1} (acetate C=O).

Anal. Calcd for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.37; H, 4.20.

Formation of Gentisaldehyde (3) from 2. A solution of 1.0 g (42 mmol) of **2** in 200 ml of ether was shaken with aqueous sodium dithionite in a separatory funnel until the ether layer turned colorless. The ether layer was separated, washed with water, and stirred with 50 ml of 1 *N* HCl for 2 hr (the reaction was followed by TLC, silica gel plates, 8:2 benzene–methanol). From the ether layer 0.4 g (69%) of gentisaldehyde was isolated, mp 90–92°. It was found to be identical with an authentic sample of **3**.

Oxidation of 2,5-Dimethoxytoluene (4). A. The oxidation was carried out with 0.3 g (2 mmol) of **4** using 0.86 g (6 mmol) of AgO and 3 ml of 6 *N* HNO_3 following the procedure given for **1**, which yielded 0.2 g of solid from which were separated by trituration with ether, followed by recrystallization (2-propanol), 0.1 g (42%) of **6**, mp 189–190° (lit.[4] mp 178.5–179.5°), as an ether-insoluble component and 0.1 g (41%) of **5**, mp 64–65°, as an ether-soluble component. **5** was compared with an authentic sample. **6** was confirmed based on its NMR spectrum ($CDCl_3$): δ 2.08 (d, 6, CH_3), 6.70 (m, 2, 1,4-benzoquinone, H adjacent to methyl group), 6.78 (s, 2, 1,4-benzoquinone, H adjacent to carbonyl group).

Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.17; H, 4.10.

B. When 0.3 g of **4** was oxidized with 0.3 g (2 mmol) of AgO and 2 ml of 6 *N* HNO_3 in the manner described above, besides the unconverted **4** (separated by *n*-hexane trituration), 0.1 g (37%) of **7**, mp 150–152°, was isolated, which melted at 154–155° after recrystallization from 2-propanol (lit.[5] mp 153°), NMR ($CDCl_3$) δ 2.03 (d, 3, CH_3 on quinone), 2.21 (s, 3, CH_3 on aromatic), 3.70 (s, 3, OCH_3), 3.73 (d, 3, OCH_3), 6.58 (m, 2, aromatic), 6.71 (m, 2, *p*-benzoquinone).

Registry No.—**1**, 55669-73-3; **2**, 55669-74-4; **3**, 1194-98-5; **4**, 24599-58-4; **5**, 553-97-9; **6**, 4388-07-2; **7**, 19965-46-9; silver oxide, 1301-96-8; sodium dithionite, 7775-14-6.

References and Notes

(1) C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 227 (1972); **96**, 8046 (1974).
(2) H. Ulrich, D. V. Rao, B. Tucker, and A. A. R. Sayigh, *J. Org. Chem.*, **39**, 2437 (1974); we have also prepared gentisaldehyde from 2,5-dimethoxybenzaldehyde with 48% HBr in acetic anhydride at 100–105° for 6 hr in 60% yield.
(3) R. Preuss and R. Menzel, *Arch. Pharm. (Weinheim, Ger.)*, **291**, 377 (1958); *Chem. Abstr.*, **53**, 5175*d* (1959).
(4) Y.-H. C. Giza, K. A. Kun, and H. G. Cassidy, *J. Org. Chem.*, **27**, 679 (1962).
(5) T. Posternak, W. Alcalay, R. Luzzati, and A. Tardent, *Helv. Chim. Acta*, **31**, 525 (1948).

Phenylcarbene from 3,5-Diphenyl-1-pyrazoline

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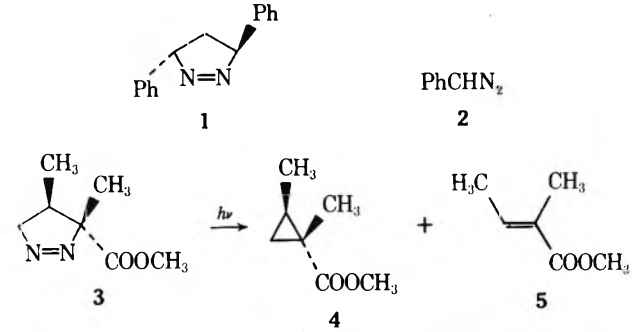
Thermal and photochemical extrusion of nitrogen from 1-pyrazolines has often been studied as a means of generating 1,3-diradicals.[1] In work directed toward observing such species,[2] we have recently noted an interesting alternate mode of decomposition in the case of *trans*-3,5-diphenyl-1-pyrazoline (**1**).

Previous workers[3–7] have suggested that retro-1,3-dipolar addition to give diazomethane (or a derivative) and an olefin may be a competing pathway of decomposition of some 1-pyrazolines. Thus, Rinehart and Van Auken[3] reported that irradiation of **3** gave methyl tiglate (**5**) as a side product in the formation of the cyclopropane (**4**). Their



conclusion was that a reversal of the formation of **3** from **5** and diazomethane had occurred, although direct fragmentation to methylene, nitrogen, and olefin could not be ruled out. Similarly, it has been suggested, based on product analysis, that several bicyclic pyrazolines decompose by retro-1,3-dipolar addition.[4,5]

In the present case, direct evidence is adduced for a carbene-generating pathway in the photolysis of **1**. A triplet ESR spectrum was observed when **1** was irradiated for short periods with ultraviolet light at 5.5 K either neat or in dilute toluene solution (see Table I). The spectrum from the neat sample was identical with the phenylcarbene spectrum obtained by irradiating phenyldiazomethane under the same conditions.[8] In addition to the carbene spectrum, the samples of **1** and **2** in toluene also gave weak spectra at-

Table I
ESR Absorptions[a]

Sample	Solvent	Absorptions, G[b]
1	Toluene	1640, 2200, 3035, 3170, 3420, 3535, 4870, 5860
1	Toluene-d_8	2200, 4870, 5860
1	Neat	2200, 3285,[c] 4870, 5860
2	Toluene	2200, 3140, 3210, 3370, 4870, 5860

[a] Microwave frequency 9.206 GHz. [b] In all samples except neat 1, a weak monoradical absorption at 3285 G was observed, which was also seen with toluene alone. [c] A strong monoradical absorption.

Table II
Analysis of Photolysis of 1

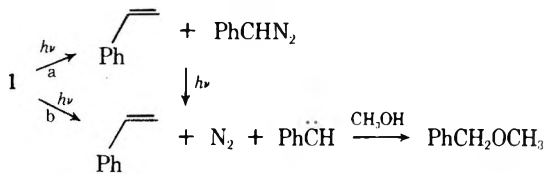
Compd	%[a]
Styrene	9 ± 2
Benzyl methyl ether	15 ± 3
cis-1,2-Diphenylcyclopropane	13 ± 1
trans-1,2-Diphenylcyclopropane	67 ± 4

[a] Disk integration corrected for relative response factors; low precision is due to tailing of methanol.

tributable to a triplet pair of benzyl radicals,[9] presumably formed by attack of phenyl carbene on the solvent. Significantly, the radical pair spectrum was absent when 1 was irradiated in toluene-d_8.

In order to assess the relative importance of carbene formation in the photolysis of 1, a trapping experiment was performed. The reaction was examined at room temperature with methanol serving as both solvent and carbene trap[10] (see Scheme I). A dilute solution of 1 in methanol was irradiated for 45 min, giving a mixture which was analyzed by VPC (Table II).

Scheme I



The results show that a minimum of about 10% of the photolysis proceeds to styrene and phenylcarbene. A considerably larger fraction of the reaction may actually follow this path, since it is unknown how much of the diphenylcyclopropanes result from addition of phenyl carbene to styrene. In fact, under conditions in which the olefin is a more reactive substrate than the reaction medium, the carbene pathway of decomposition may well go undetected. This possibility may explain why Overberger and Anselme[11] reported only diphenylcyclopropane as the product of photolysis of 1.

Present data cannot distinguish between a retro-1,3-dipolar addition (path a) and direct fragmentation (path b). A third possibility, that the carbene and styrene arise from the diphenylcyclopropanes, as is observed with shorter wavelength light,[10] is eliminated on the basis of control experiments. Regardless of whether path a or b is correct, it is clear that this alternate mode of decomposition is a complicating factor in the use of pyrazolines as diradical precursors. Although the generality of the carbene pathway is not known, its occurrence in 1 indicates that it must be considered in all cases before firm conclusions can be made about diradical species that may or may not be involved in the decomposition of 1-pyrazolines.

Experimental Section

Materials and Apparatus. *trans*-3,5-Diphenyl-1-pyrazoline[12] (1) and phenyldiazomethane[13] (2) were prepared by published procedures. A mixture of *cis*- and *trans*-1,2-diphenylcyclopropane was prepared by refluxing overnight a solution of 1 in benzene. Toluene was passed through a 1:1 mixture of alumina and silica gel prior to use. Toluene-d_8 (Stohler Isotope Chemicals) was used as received. Dilute toluene solutions (10% w/v, *ca.* 0.05 *M*) of 1, 2, and the mixture of cyclopropanes in 4 mm o.d. quartz tubing were degassed (three freeze–thaw cycles at 10^{-3} Torr) and sealed on a vacuum line.

A Varian E-9 spectrometer equipped with an Air Products and Chemicals Heli-Tran LTD-3-110 liquid helium transfer apparatus was used to record the ESR spectra. Gas chromatographic analysis was performed on a Varian Aerograph 1200 instrument equipped with a disk integrator. The column was 20% Carbowax 6000 on Chromosorb W, 6 ft × 0.125 in. at 80–180°.

Low-Temperature Photolyses. The samples were rapidly chilled in liquid nitrogen before being placed in the quartz dewar, which had been cooled to 5.5 K. A calibrated gold (0.07% iron) vs. chromel thermocouple sealed in a sample tube showed that the temperature at the sample varied from 5 to 6 K depending on the flow rate of helium.

The samples were irradiated for 5 min or less with a 2000-W mercury–xenon lamp operated at about 1300 W and filtered by water and Pyrex. Longer irradiation caused a reduction in the intensity of the spectra. The spectra are summarized in Table I. The sample containing the diphenylcyclopropanes gave no observable spectrum.

Room Temperature Photolyses. Samples of 1 and the diphenylcyclopropanes were dissolved in methanol (1% w/v, ~0.05 *M*) and placed in a water-jacketed Pyrex photolysis apparatus. Irradiation with a Hanovia medium-pressure 550-W lamp was continued for 45 min. In the case of the solution of 1, evolution of nitrogen was over in 35 min. The photolysis solutions were analyzed by gas chromatography (see Table II). Styrene and benzyl methyl ether were identified in the product mixture from 1 by coinjection of authentic samples on several different columns. A weighed mixture of styrene, benzyl methyl ether, and the diphenylcyclopropanes was also analyzed to calibrate the detector response. The irradiated diphenylcyclopropane solution did not contain styrene or benzyl methyl ether. In another experiment, a solution of 1 in methanol was refluxed for 24 hr. Only diphenylcyclopropanes were found in the product mixture.

Acknowledgment. Acknowledgment is made to the National Science Foundation (Grant GP-37481X) for support of this research.

Registry No.—1, 10514-16-6; 2, 766-91-6; phenylcarbene, 3101-08-4.

References and Notes

(1) See, for example, R. J. Crawford and A. Mishra, *J. Am. Chem. Soc.*, **88**, 3963 (1966).
(2) G. L. Closs and S. L. Buchwalter, *J. Am. Chem. Soc.*, **97**, 3857 (1975).
(3) K. L. Rinehart, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **82**, 5251 (1960); **84**, 3736 (1962).
(4) M. Franck-Neumann, *Tetrahedron Lett.*, 2659 (1969).
(5) D. H. White, P. B. Condit, and R. G. Bergman, *J. Am. Chem. Soc.*, **94**, 1348 (1972); R. A. Keppel and R. G. Bergman, *ibid.*, **94**, 1350 (1972); D. F. Eaton, R. G. Bergman and G. S. Hammond, *ibid.*, **94**, 1351 (1972).
(6) D. E. McGreer and W. S. Wu, *Can. J. Chem.*, **45**, 461 (1967).
(7) R. Moore, A. Mishra, and R. J. Crawford, *Can. J. Chem.*, **46**, 3305 (1968).
(8) The carbene spectrum was similar to that reported previously; cf. A. M.

Trozzolo, R. W. Murray, and E. Wasserman, *J. Am. Chem. Soc.*, **84**, 4990 (1962).
(9) The radical pair spectra derived from **1** and **2** were not identical, which is consistent with previous observations by M. Trifunac; cf. M. Trifunac, Ph.D. Thesis, The University of Chicago, 1974.
(10) H. Kristinsson, K. N. Mehrotra, G. W. Griffin, R. C. Petterson, and C. S. Irving, *Chem. Ind. (London)*, 1562 (1966).
(11) C. G. Overberger and J.-P. Anselme, *J. Am. Chem. Soc.*, **86**, 658 (1968).
(12) J.-P. Anselme, *Org. Prep. Proced.*, **1**, 73 (1969).
(13) P. Yates and B. L. Shapiro, *J. Org. Chem.*, **23**, 759 (1958).

Synthesis of 7-Azanorbornene and *N*-Methyl-7-azanorbornene

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A number of substituted 7-azanorbornanes,[1] 7-azabenzonorbornenes,[2,3] and 7-azanorbornadienes[4-8] have been reported. However, only one fully characterized *non*-ring-substituted 7-azanorbornene, *N*-phthalimido-7-azanorbornene, has been synthesized.[9] We now describe syntheses of 7-azanorbornene (**1**) and of the corresponding N-methylated amine (**2**).

In an earlier communication,[10] we reported the anomalous reduction of isolated carbon–carbon double bonds in *N*-carbethoxy-7-azanorbornene and in *N*-carbethoxy-2,3-benzo-7-azanorbornadiene by lithium aluminum hydride (or Vitride). In the present study, the successful synthesis of *N*-methyl-7-azanorbornene (**2**) was accomplished by diisobutylaluminum hydride reduction of *N*-carbethoxy-7-azanorbornene. The syntheses of **2** and of the parent (unsubstituted) amine (**1**), outlined in Scheme I, provide the first practical routes to the 7-azanorbornenyl system.

The starting material, *N*-benzyl-7-azanorbornadiene-2,3-dicarboxylic acid (**3**),[11] is obtained in 15–20% yield by Diels–Alder addition of acetylenedicarboxylic acid to *N*-benzylpyrrole.[12] Hydrogenation–hydrogenolysis of **3** affords **4**, which is then converted to the *N*-tosyl or *N*-carbethoxy derivative **5** and **6**. Electrolytic oxidative bisdecarboxylation of **5** and **6** gave the corresponding olefins **7** and **8**, which were further reduced to **1** and **2**, respectively.

Experimental Section

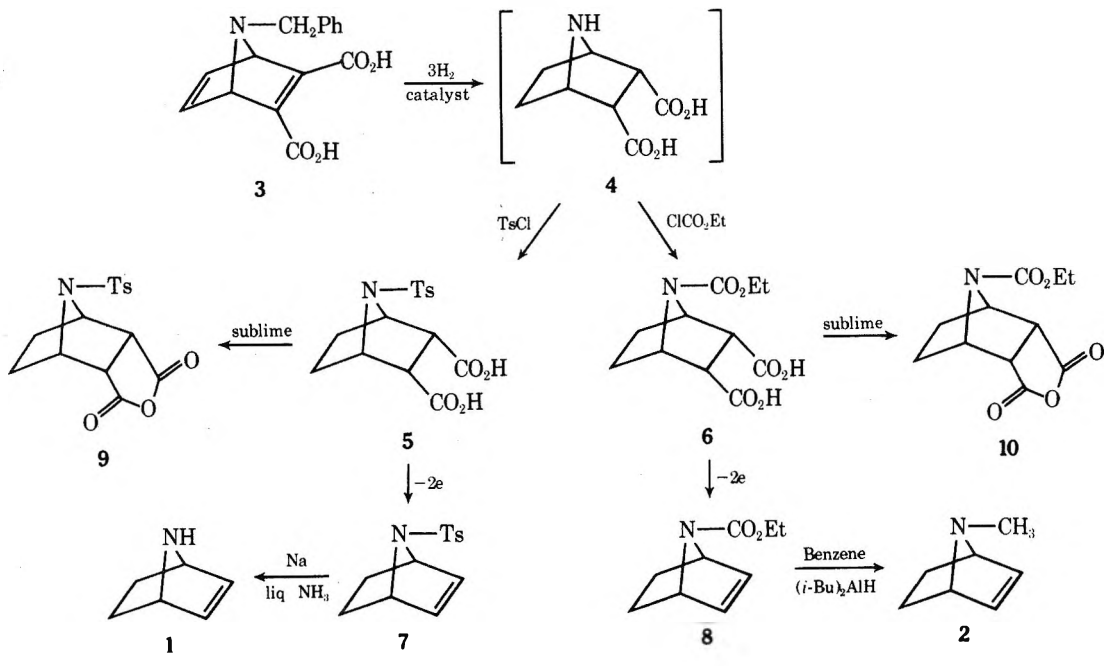
Melting points are uncorrected. NMR spectra were obtained on a Varian T-60 NMR spectrometer (Me_4Si internal standard). Ir spectra were obtained on a Perkin-Elmer Model IR-8 infrared spectrophotometer. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-7E mass spectrometer (70 eV); in order to obtain the molecular ion for compounds **1**, **2**, **7**, and **8**, it was necessary to cool the filament chamber to ambient temperature.

***N*-Carbethoxy-7-azanorbornane-*endo,endo*-2,3-dicarboxylic Acid (6).** *N*-Benzyl-7-azanorbornadiene-2,3-dicarboxylic acid[11] (**3**, 10.0 g, 36.9 mmol) was dissolved in excess aqueous sodium carbonate solution (100 ml). The resulting solution was hydrogenated (45 psig) over 10% palladized charcoal catalyst on a Parr apparatus. After 3 equiv of hydrogen had been taken up, the catalyst was removed by filtration. To the filtrate containing the hydrogenation product (**4**) was added excess ethyl chloroformate, and the resulting solution was stirred overnight at room temperature. The solution was then acidified with dilute aqueous hydrochloric acid and extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and then concentrated, affording **6** as a colorless syrup (8.20 g, 86.4%). Diacid **6** was characterized via the corresponding anhydride, **10**, which could be obtained via sublimation of syrupy **6** at 110° (0.1 mm). This procedure afforded **10** (5.80 g, 65.8%), which recrystallized from ether–hexane to afford colorless crystals: mp 111.5–112.8°; NMR ($CDCl_3$) δ 1.30 (t, J = 6 Hz, 3 H, $-OCH_2CH_3$), 1.61–2.1 (complex m, 4 H, 5,6-exo and endo ring protons), 3.73 (m, 2 H, 2,3-exo ring protons), 4.15 (q, J = 6 Hz, 2 H, $-OCH_2CH_3$), 4.70 [m, 2 H, 1,4 (bridgehead) protons]; ir (KBr) 2980 (w), 1860 (s), 1785 (s), 1690 (s), 900 cm^{-1} (s); mass spectrum *m/e* 239 (molecular ion), 141 (base peak), 140, 139, 122, 68.

Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48. Found: C, 55.30; H, 5.35.

***N*-Carbethoxy-7-azanorbornene (8).** Compound **6** (5.00 g, 19.5 mmol) was dissolved in an electrolysis solution which consisted of water (20 ml), triethylamine (2.5 ml), and pyridine (175 ml). A direct current (80 V, initial current 350 mA, Pt wire electrodes) was passed through this solution for 15 hr while the solution was maintained at 20° via external cooling. At the conclusion of the electrolysis, the current had dropped to 40 mA. The solution was then quenched with dilute, aqueous hydrochloric acid, and the resulting solution was extracted with diethyl ether (500 ml). The ether layer was then extracted with 10% aqueous sodium hydroxide solution to recover unreacted **6** (0.60 g). The ether layer was dried (Na_2SO_4), filtered, and then concentrated to afford crude **8**.

Scheme I



The crude product was further purified via column chromatography on neutral alumina (hexane eluent); this procedure afforded pure 8 [749 mg, 26.2% based on consumed (unrecovered) 6] as a colorless, sweet-smelling oil, bp ca. 50° (0.14 mm, microdistillation). An analytical sample of 8 was obtained via preparative VPC [0.25 in. × 10 ft column, 20% FFAP on Chromosorb W, all VPC components (injector, column, and detector) at 140°, He flow rate 100–110 ml/min]: NMR ($CDCl_3$) δ 1.13 (m, 2 H, 5,6-endo ring protons), 1.26 (t, J = 6 Hz, 3 H, $-OCH_2CH_3$), 1.90 (m, 2 H, 5,6-exo ring protons), 4.07 (q, J = 6 Hz, 2 H, $-OCH_2CH_3$), 4.74 [m, 2 H, 1,4 (bridgehead) protons], 6.24 [unsymmetrical t, 2 H, 2,3 (vinyl) protons]; ir (film) 3020 (w), 2995 (w), 1710 (s, br), 1270 (m), 690 cm^{-1} (m); mass spectrum m/e 167 (molecular ion), 139, 94, 80, 66, 41, 39 (base peak).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84. Found: C, 64.88; H, 7.87.

***N*-Methyl-7-azanorbornene (2).** *N*-Carbethoxy-7-azanorbornene (8, 749 mg, 4.49 mmol) was dissolved in benzene (30 ml). To the resulting solution was added a benzene solution (23 ml) of diisobutylaluminum hydride (0.61 mmol/ml). After stirring for 4 hr at room temperature, an additional 5 ml of the benzene solution of diisobutylaluminum hydride was added (total 28 ml, 17.1 mmol of diisobutylaluminum hydride). After stirring for an additional 4 hr at room temperature, the reaction was quenched with excess methanol until precipitation of aluminum methoxide was complete. The reaction mixture was then filtered and combined with an equal volume of a saturated solution of picric acid in 95% ethanol, whereupon yellow crystals of *N*-methyl-7-azanorbornene picrate precipitated almost immediately. Recrystallization from 95% ethanol afforded the pure picrate (1.30 g, 85.6%) as yellow needles, mp 225° dec.

Anal. Calcd for $C_{13}H_{14}N_4O_7$: C, 46.16; H, 4.17. Found: C, 45.93; H, 3.98.

The free base (2) was obtained by treating the above picrate with concentrated, aqueous KOH solution. The resulting mixture was extracted with chloroform, and the free amine (2) was isolated via preparative VPC [0.25 in. × 4 ft column, 28% Pennwalt 223 on 80/100 mesh Gas-Chrom R containing 4% KOH, all VPC components (injector, column, and detector) at 100–110°, *nitrogen* carrier gas, N_2 flow rate ca. 100–110 ml/min]: NMR ($CDCl_3$) δ 0.98 (m, 2 H, 5,6-endo ring protons), 1.87 (m, 2 H, 5,6-exo ring protons), 2.05 (s, 3 H, NCH_3), 3.70 [m, 2 H, 1,4 (bridgehead) protons], 5.98 [br s, 2 H, 2,3 (vinyl) protons]; ir (film) 3080 (w), 2990 (w), 690 cm^{-1} (m); mass spectrum m/e 109 (molecular ion), 94, 81, 80, 66, 53, 42, 39 (base peak).

***N*-Tosyl-7-azanorbornane-*endo,endo*-2,3-dicarboxylic Acid (5).** Compound 5 was prepared using the same procedure which was previously employed for the synthesis of 6. Hydrogenation–hydrogenolysis of 3 (10.0 g, 36.9 mmol) followed by treatment of the resulting solution with excess *p*-toluenesulfonyl chloride afforded crude 5 (12.0 g, 95.5%). The crude product was further purified by sublimation at 150° (0.05 mm), which afforded the corresponding acid anhydride (9). Compound 9 recrystallized from acetone to afford a colorless, microcrystalline solid, mp 230–232°. Hydrolysis of 9 afforded pure 5: NMR (pyridine-d_5) δ 1.53–2.50 (m, 4 H, 5,6-exo and endo ring protons), 2.30 (s, 3 H, $ArCH_3$), 3.90 (m, 2 H, 2,3-exo ring protons), 4.70 [m, 2 H, 1,4 (bridgehead) protons], 5.50 (s, 2 H, –COOH), 7.63 (AA′BB′ pattern, 4 H, aryl ring protons). Compound 5 was further characterized via the corresponding anhydride (9); ir of 9 (KBr) 3070 (w), 2980 (w), 1865 (s), 1785 (s), 1335 (sh), 1140 (sh), 1590 (w), 905 cm^{-1} (s); mass spectrum m/e 321 (molecular ion), 223, 166, 155, 122, 91, 68 (base peak).

Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70. Found: C, 56.16; H, 4.92.

***N*-Tosyl-7-azanorbornene (7).** Compound 5 (2.3 g, 6.8 mmol) was dissolved in an electrolyte solution (100 ml) which was prepared as described previously for the synthesis of 8 from 6. A direct current (80 V, initial current 160 mA) was passed through this solution for 12 hr while the solution temperature was maintained at 20° via external cooling. At the conclusion of the electrolysis, the current had dropped to 50 mA. Work-up of the reaction was carried out as described for the synthesis of 8 from 6. The crude product was purified via elution chromatography on neutral alumina (hexane eluent). Compound 7 (204 mg, 12.1%) was thereby obtained. Recrystallization of 7 from hexane afforded an analytical sample as colorless needles: mp 91.5–92.0°; NMR ($CDCl_3$) δ 1.07 (m, 2 H, 5,6-endo ring protons), 2.03 (m, 2 H, 5,6-exo ring protons), 2.42 (s, 3 H, $ArCH_3$), 4.64 [m, 2 H, 1,4 (bridgehead) protons], 5.73 [unsymmetrical t, 2 H, 2,3 (vinyl) protons], 7.41 (AA′BB′ pattern, 4 H, aryl ring protons); ir (KBr) 3090 (w), 2995 (w), 2960 (w), 1590 (w), 1335 (s), 1150 (s), 690 cm^{-1} (s); mass spectrum m/e 249 (molecular ion), 221, 155, 106, 91 (base peak), 65, 58.

Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06. Found: C, 62.50; H, 5.99.

7-Azanorbornene (1). Compound 7 (204 mg, 0.82 mmol) was dissolved in a solution of diethyl ether (10 ml) in liquid ammonia (20 ml). Excess, clean sodium metal was added portionwise until the blue color of solvated electrons persisted for 1 min. The reaction mixture was then concentrated, and the residue was dissolved in diethyl ether and extracted with dilute aqueous hydrochloric acid. The aqueous phase was rendered strongly basic (KOH) and the resulting solution was extracted with chloroform (10 ml). The chloroform extracts were dried and carefully concentrated, affording 1 as a colorless liquid (70 mg, 90%): NMR ($CDCl_3$) δ 1.02 (m, 2 H, 5,6-endo ring protons), 1.75 (m, 2 H, 5,6-exo ring protons), 1.76 (s, 1 H, –NH, disappears upon addition of D_2O), 4.12 [m, 2 H, 1,4 (bridgehead) protons], 6.23 [unsymmetrical t, 2 H, 2,3 (vinyl) protons]; ir (film) 3250 (br), 3070 (w), 2960 (s), 1650 (br), 1260 (m), 790 cm^{-1} (s); mass spectrum m/e 95 (molecular ion), 80, 67, 66, 51, 42, 39 (base peak), 28. Compound 1 was further characterized via its picrate. When 1 was added to a solution of picric acid (excess) in 95% ethanol, precipitation of 7-azanorbornene picrate occurred almost immediately. Recrystallization of the picrate from 95% ethanol afforded yellow needles, mp 208–210° dec.

Anal. Calcd for $C_{12}H_{12}N_4O_7$: C, 44.45; H, 3.73; N, 17.28. Found: C, 44.21; H, 3.85; N, 17.30.

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Registry No.—1, 55590-24-4; 1 picrate, 55590-25-5; 2, 55590-26-6; 2 picrate, 55590-27-7; 3, 34354-00-2; 4, 55658-14-5; 5, 55658-15-6; 6, 55590-28-8; 7, 55590-29-9; 8, 55258-01-0; 9, 17037-46-6; 10, 55590-30-2.

References and Notes

(1) R. R. Fraser and R. B. Swingle, *Can. J. Chem.*, **48**, 2065 (1970).
(2) V. Rautenstrauch, *Chem. Commun.*, 1122 (1969).
(3) P. Rosso, J. Oberdier, and J. Sweeton, *Tetrahedron Lett.*, 3947 (1971).
(4) R. Kitzing, R. Fuchs, M. Joyeux, and H. Prinzbach, *Helv. Chim. Acta*, **51**, 888 (1968).
(5) R. C. Bansal, A. W. McCulloch, and A. G. McInnes, *Can. J. Chem.*, **47**, 2391 (1969).
(6) L. Mandell and W. A. Blanchard, *J. Am. Chem. Soc.*, **79**, 2343 (1957).
(7) J. C. Blazejewski, D. Cantacuzene, and C. Wakselman, *Tetrahedron Lett.*, 363 (1975).
(8) G. W. Gribble, N. R. Easton, Jr., and T. Eaton, *Tetrahedron Lett.*, 1075 (1970).
(9) L. Hoesch and A. S. Dreiding, *Chimia*, **26**, 629 (1972).
(10) A. P. Marchand and R. W. Allen, *Tetrahedron Lett.*, 67 (1975).
(11) A. Shafi'ee and G. Hite, *J. Org. Chem.*, **33**, 3435 (1968).
(12) A. D. Josey, R. J. Tuite, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 1597 (1960).

Addition of *tert*-Butylcyanoketene to Imino Ethers. Steric Effects on Product Formation

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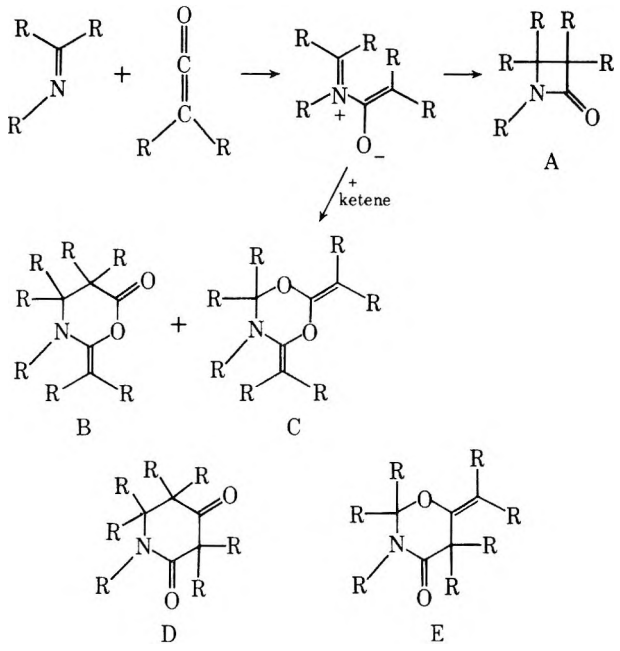
In connection with a series of studies on additions to imino ethers,[1] we have investigated ketene additions to cyclic and acyclic imino ethers here. Ketenes were first shown by Staudinger to add to imines to give β-lactams A in 1907.[2] In many cases 2:1 adducts are formed at the expense of the β-lactam, however.[3–17] Although originally assigned the piperidinedione structure D,[4–9] most 2:1 adducts have since been shown to be oxazinones B.[3,10–13] In a few cases the dioxazines C have been formed too.[14–17] Compounds of structure E are known,[18–26] but not from 1,4-dipolar addi-

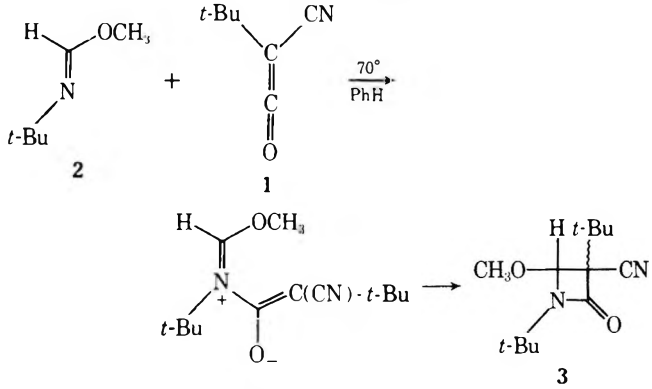


tions. With unhindered imines in the presence of Lewis acid catalysts, a few 1:2 adducts from addition of a second molecule of imine to the 1,4 dipole are obtained;[3,27,28] and a 1:1:1 adduct from trapping of a 1,4 dipole with phenyl isocyanate is known.[29,30]

The pattern of reactivity in these reactions indicates that 1:1 β-lactams are usually preferred over 2:1 adducts when there are bulky groups on nitrogen and in solvents of low polarity.[3,13] In addition, it appears that dioxazines C are favored over oxazinones B when the iminium ion is strained[16,17] or when there is steric hindrance to ring closure through carbon.[17] Steric hindrance at nitrogen in the imino ethers **2** and **5** might particularly favor β-lactam formation, so additions to **5** were tried in an attempt to make the bicyclic β-lactam **4**.

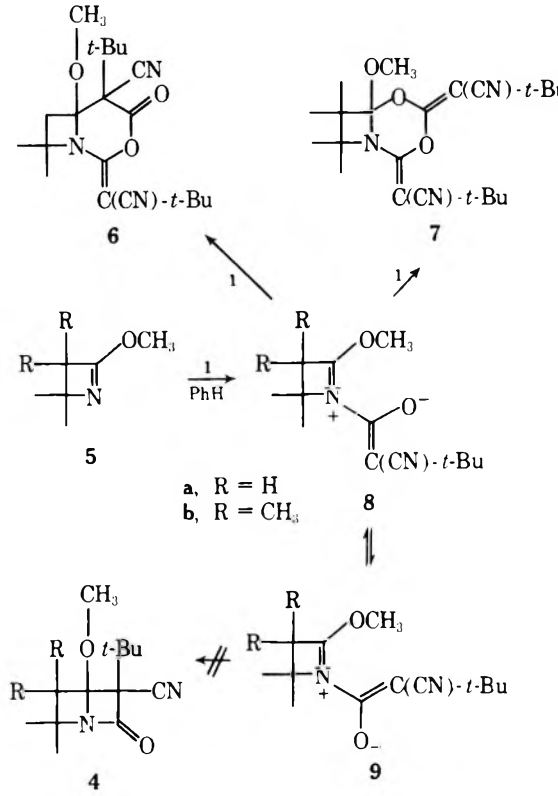
Results and Discussion

A convenient source of a sterically hindered ketene, *tert*-butylcyanoketene (**1**), is from thermolysis of 2,5-diazido-3,6-di-*tert*-butylquinone.[31] Treatment of methyl *N*-*tert*-butylformimidate (**2**) with a slight excess of ketene **1** in refluxing benzene results in a 90% isolated yield of 1,3-di-*tert*-butyl-3-cyano-4-methoxy-2-azetidinone (**3**). This reaction is analogous to those of imines with bulky substituents on nitrogen which yield β-lactams.[1-3,13] No 2:1 cycloadducts were detected; the reaction gives only **3** from NMR and ir analysis of the crude reaction mixture.



To study the steric effect and to look for the interesting bicyclic amide **4**, additions to methoxyazetines **5** were tested. These 4,4-dimethyl substituted methoxyazetines represent analogs of **2** where the *tert*-butyl group is effectively pulled back by incorporation into the azetine ring. Treatment of 2-methoxy-4,4-dimethylazetine (**5a**) with 2 equiv of **1** at room temperature in benzene resulted in the isolation by chromatography of a crystalline 2:1 adduct in low yield. The oxazinone structure **6** for this adduct was chosen on the basis of the infrared bands at 1755 and 1700 cm^{-1}, although the 1755-cm^{-1} band was much weaker.[3,10-12] It was also noted that this adduct melted with decomposition and vigorous evolution of a gas shown to be isobutylene by mass spectrometry. The presence of a carbonyl in **6** was confirmed by the occurrence of a ^{13}C NMR peak at 187.4 ppm. The rest of the ^{13}C spectrum was also consistent with structure **6**. The ultraviolet spectrum showed only end absorption as expected for **6**. The desired β-lactam **4** could not be detected by NMR or ir spectroscopy in the reaction mixture.

Treatment of 2-methoxy-3,3,4,4-tetramethylazetine (**5b**) with ketene **1** showed no evidence of β-lactam formation, but resulted in formation of the 2:1 adduct **7** in moderate yield. Lack of even a weak band from 1700 to 1800 cm^{-1} in the infrared spectrum and lack of any carbonyl band in the ^{13}C spectrum led to the assignment of the dioxazine structure **7** to this adduct rather than an oxazinone structure analogous to **6**. The ^{13}C spectral bands and the infrared bands at 1705 and 1625 cm^{-1} are consistent with structure **7**.[14-17] A strong ultraviolet band at 232 nm with a shoulder at 275 nm also distinguishes the dioxazine structure **7** from the oxazinone structure of **6**.



Formation of the β-lactam **3** is favored[3,13] over formation of 2:1 adducts. This is probably because the 1,4-dipolar ion prefers the conformation shown, which cannot give the usual oxazinone B or dioxazine C adducts by concerted 1,4-dipolar addition of another ketene. Although the carbon of the ketene is quite hindered, the imino ether carbon is not very hindered in **2**; and C–C closure to give the β-lactam **3** occurs readily. The dipolar ions **8** and **9** from the cyclic imino ethers **5** feel enough relief of the steric hindrance of the bulky *gem*-dimethyl substituents next to nitrogen that conformer **8** may now be preferred over **9**. Greater ste-

ric hindrance at the imine carbon in **5** vs. **2** also makes ring closure to the β-lactam **4** more difficult from **9**. In contrast to **5a**, the usual oxazinone[3,10-13] adduct B from ketene additions to imines is not formed from the azetine **5b**. This again is probably because steric hindrance at the imine carbon in **8b** makes C–C bond closure to an oxazinone less favorable than in **8a**, which lacks the 3,3-dimethyl substitution.

Experimental Section

All melting points are uncorrected. Ir spectra were obtained in solution with a matched reference cell on a Perkin-Elmer 337 grating infrared spectrometer. NMR spectra were obtained on a 60-MHz Varian Associates T-60 spectrometer and a CFT-20 spectrometer. Mass spectra were obtained on a MS-902 spectrometer, and uv spectra were obtained on a Cary 15 spectrophotometer.

Materials. The 2,5-diazido-3,6-di-*tert*-butylquinone and imino ethers were made according to published procedures.[1,32]

1,3-Di-*tert*-butyl-3-cyano-4-methoxy-2-azetidinone (3). A solution of 153 mg (0.51 mmol) of 2,5-diazido-3,6-di-*tert*-butylquinone[31] dissolved in 10 ml of benzene was heated to 70°. The initially orange solution turns yellow after 1 hr indicating conversion to the cyano-*tert*-butylketene **1**. With the solution at room temperature, a solution of 100 mg (0.87 mmol) of methyl *N*-*tert*-butylformimidate (**2**) in 1.5 ml of benzene was added. The solution was heated at 70° overnight. The reaction was quantitative by NMR and ir analysis. Removal of volatiles left 186 mg (90%) of β-lactam **3**. Recrystallization from hexanes and ether gave 86 mg of **3**: mp 104–106°; ir (CCl_4) 2230 w, 1780 s, 1370, 1345, 1100 cm^{-1}; ^1H NMR (CCl_4) δ 1.12 (s, 9 H), 1.33 (s, 9 H), 3.40 (s, 3 H), 4.65 (s, 1 H); mass spectrum (70 eV) *m/e* 238.1708 (calcd for $C_{13}H_{22}N_2O_2$, 238.1681); *m/e* (rel intensity) 238 (M^+, 0.2), 223 (0.2), 208 (0.4), 185 (0.5), 184 (4), 169 (1), 168 (12), 140 (9), 139 (36), 125 (7), 124 (100), 115 (1), 110 (1), 108 (4), 100 (7), 96 (2), 86 (2), 84 (7), 68 (2), 67 (1), 66 (1), 60 (4), 58 (3), 57 (27), 56 (7), 55 (4), 53 (4), 44 (2), 43 (2), 42 (5), 41 (22), 40 (2), 39 (6).

Reaction of Azetine 5a with Ketene 1. Adding 142 mg (1.26 mmol) of 2-methoxy-4,4-dimethylazetine (**5a**) in 5 ml of benzene to a solution of ketene **1** (2.54 mmol) generated from 382 mg (1.27 mmol) of azidoquinone[31] gave immediately at 25° a mixture of products. Isolation of 39 mg (10%) of white solid **6** was achieved by column chromatography on alumina using ether–hexane (10:90) elution: mp 155–157° dec (with C_4H_8 evolution by mass spectral analysis); uv (EtOH) end absorption λ 220 nm (ε 2900); ir (CCl_4) 2960 (m), 2230 (w), 1755 (m), 1700 (s), 1470, 1460, 1262, 1247, 1233, 1198, 1189, 1142, 1112, 1060, 1049, 861 cm^{-1}; ^1H NMR (CCl_4) δ 1.26 (s, 9 H), 1.36 (s, 9 H), 1.67 (s, 3 H), 1.83 (s, 3 H), 2.53 and 2.80 (AB, J = 13.5 Hz), 3.56 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ_{Me_4Si} 187.4 (C=O), 160.7 [=C(–N–)O–], 116.2 (CN), 115.3 (CN), 92.9, 65.3, 62.9, 61.9, 52.3, 40.7, 39.7, 39.3, 28.3 (*t*-Bu), 26.5, 23.7; mass spectrum (70 eV) *m/e* 359.2216 (calcd for $C_{20}H_{29}N_3O_3$, 359.2209); *m/e* (rel intensity) 359 (M^+, 0.23), 344 (0.55), 328 (0.15), 316 (1.1), 304 (3), 303 (34), 288 (9), 272 (3), 271 (6), 256 (5), 247 (5), 216 (12), 192 (12), 178 (6), 163 (5), 153 (12), 152 (9), 151 (100), 140 (3), 139 (3), 138 (6), 124 (9), 114 (6), 108 (12), 94 (6), 84 (28), 83 (5), 82 (6), 73 (19), 68 (5), 67 (5), 58 (12), 57 (47), 56 (19), 55 (9), 53 (9), 43 (6), 42 (8), 41 (41), 39 (8). Some methyl 2-cyano-3,3-dimethylbutanoate [ir (CH_2Cl_2) 2950, 2240 (w) 1750 cm^{-1}; ^1H NMR (CH_2Cl_2) δ 1.17 (s, 9 H), 2.84 (s, 1 H), 3.76 (s, 3 H)][31] was formed in the reaction mixture and found in early chromatography fractions, but no other pure substances could be isolated from the chromatography.

Reaction of Azetine 5b with Ketene 1. Addition of 282 mg (2.00 mmol) of 2-methoxy-3,3,4,4-tetramethylazetine (**5b**) in 5 ml of benzene to a solution of ketene **1** (4.00 mmol) generated from 604 mg (2.00 mmol) of azidoquinone in 10 ml of benzene at 25° resulted in an oil after removal of the volatiles. Upon addition of ether, a white solid **7** precipitated, mp 122–126°. Recrystallization from benzene–hexanes gave 326 mg (42%): mp 131–133°; uv (EtOH) λ_{max} 232 nm (ε 8850), 275 (sh, ε 550); ir (CCl_4) 2950 (s), 2230 (vw), 2200 (w), 1925 (vw), 1870 (vw), 1705 (s), 1625 (w), 1400, 1380, 1370, 1230, 1125, 1032, 891 cm^{-1}; ^1H NMR (CCl_4) δ 1.08 (s, 3 H), 1.19 (s, 3 H), 1.38 (s, 18 H), 1.44 (s, 3 H), 1.46 (s, 3 H), 3.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ_{Me_4Si} no C=O, 159.3 [=C(–N–)O–], 155.5 [=C(–O–)$_2$], 117.3, 116.5, 115.2, 108.2, 71.8, 55.2, 54.3, 51.5, 45.6, 36.9, 36.2, 30.2 (*t*-Bu), 28.3 (*t*-Bu), 24.2, 20.4, 19.1, 17.3; mass spectrum (70 eV) *m/e* 387.2511 (calcd for $C_{22}H_{33}N_3O_3$, 387.2522); *m/e* (rel intensity) 387 (M^+, 0.33), 333 (0.9), 318 (1.3), 304 (0.9), 303 (5), 264 (0.8), 249 (4), 248 (23), 246 (5), 236 (1.2), 221 (3), 192 (5), 190 (1.7), 186 (1.3), 181 (3), 180 (3), 175 (3), 165 (5), 144 (2), 143 (7), 142 (2), 141 (15), 140 (4), 127 (2), 126 (10), 124 (5), 123 (15), 111 (5), 109 (4), 108 (45), 98 (3), 96 (4), 94 (2), 85 (5), 84 (24), 83 (9), 82 (3), 80 (3), 73 (16), 70 (13), 69 (23), 68 (5), 67 (3), 59 (3), 58 (45), 57 (100), 56 (8), 55 (12), 54 (4), 53 (20), 52 (3), 43 (9), 42 (16), 41 (53), 39 (17).

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Registry No.—**1**, 29342-22-1; **2**, 49680-36-6; **3**, 55712-07-7; **5a**, 23974-38-1; **5b**, 49680-46-8; **6**, 55712-08-8; **7**, 55712-09-9; 2,5-diazido-3,6-di-*tert*-butylquinone, 29342-21-0; methyl 2-cyano-3,3-dimethylbutanoate, 55712-10-2.

References and Notes

(1) See D. H. Aue and D. Thomas, *J. Org. Chem.*, **39**, 3857 (1974); **40**, 2356 (1975); **40**, 2360 (1975).
(2) H. Staudinger, *Justus Liebigs Ann. Chem.*, **356**, 51 (1907).
(3) J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971).
(4) H. Staudinger, *Justus Liebigs Ann. Chem.*, **370**, 13 (1910).
(5) H. Staudinger, *Ber.*, **40**, 1145 (1907).
(6) H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of the Penicillin", Princeton University Press, Princeton, N. J., 1949.
(7) L. E. Muller and J. Hamer, "1,2-Cycloaddition Reactions", Interscience, New York, N.Y., 1967.
(8) R. D. Kimbrough, *J. Org. Chem.*, **29**, 1242, 1246 (1964).
(9) J. C. Sheehan and E. J. Corey, *Org. React.*, **9**, 388 (1957).
(10) J. C. Martin, V. A. Hoyle, Jr., and K. C. Brannock, *Tetrahedron Lett.*, 3589 (1965).
(11) R. N. Pratt, G. A. Taylor, and S. A. Proctor, *J. Chem. Soc. C*, 1569 (1967).
(12) M. J. Haddadin and A. Hassner, *J. Org. Chem.*, 38, 2650 (1973).
(13) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes", A. T. Bloomquist, Ed., Academic Press, New York, N.Y., 1967.
(14) J. C. Martin, R. D. Burpitt, P. G. Gott, M. Harris, and R. H. Meen, *J. Org. Chem.*, **36**, 2205 (1971).
(15) F. P. Woerner, H. Reimlinger, and R. Merenyi, *Chem. Ber.*, **104**, 2786 (1971).
(16) A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).
(17) A. Hassner, M. J. Haddadin, and A. B. Levy, *Tetrahedron Lett.*, 1015 (1973).
(18) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **15**, 1334 (1967).
(19) R. N. Lacey, *J. Chem. Soc.*, 839 (1954).
(20) R. N. Lacey, *J. Chem. Soc.*, 845 (1954).
(21) R. N. Lacey and W. R. Ward, *J. Chem. Soc.*, 2134 (1958).
(22) R. Hoffmann, E. Schmidt, K. Wamsler, A. Reichle, and F. Moosmüller, German Patent 960,458 (1957); *Chem. Abstr.*, **53**, 16077 (1959).
(23) G. Kleineberg and E. Ziegler, *Monatsh. Chem.*, **94**, 502 (1963).
(24) G. Kleineberg and H. Mundl, *Monatsh. Chem.*, **94**, 544 (1963).
(25) G. Kleineberg, E. Ziegler, and H. Mundl, *Monatsh. Chem.*, **97**, 10 (1966).
(26) H. Stetter and K. Kiehs, *Chem. Ber.*, **98**, 2099 (1965).
(27) D. H. Clemens and W. D. Emmons, *J. Org. Chem.*, **26**, 949 (1961).
(28) J. Thesing and K. Hoffmann, *Chem. Ber.*, **90**, 229 (1957).
(29) R. Huisgen, K. Herbig, and M. Morikawa, *Chem. Ber.*, **100**, 1107 (1967).
(30) R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968).
(31) H. W. Moore and W. Weyler, Jr., *J. Am. Chem. Soc.*, **92**, 4132 (1970).

A Method for Catalytic Dehalogenations via Trialkyltin Hydrides[7]

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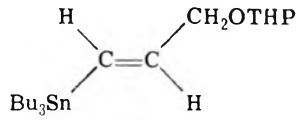
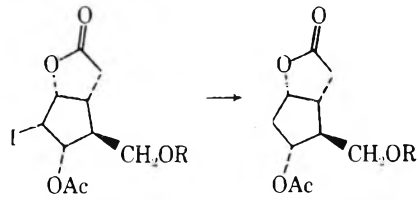
This note describes a method for the catalytic dehalogenation of organic halides with trialkyltin hydrides. The chief impetus for the development of a catalytic process was our interest in devising a simpler and more convenient procedure for the generation of the valuable prostaglandin intermediate II from the halolactone precursor I. Previous-

Table I

Substrate (mmol)	Product	Mmol of $NaBH_4$	R, R_3SnCl (mmol)	Conditions	Yield, %
$PhCH_2CH_2CH_2Br$ (1)	$PhCH_2CH_2CH_3$	2	Bu (0.1)	2.5 hr, 25°	86[b]
$PhCH_2CH_2CH_2Br$ (1)	$PhCH_2CH_2CH_3$	2	Bu (0.1)	0.5 hr, 25°, $h\nu$	88[b]
Ia (0.27)	IIa	0.41	Bu (0.027)	20 min, 10°, $h\nu$	93[a]
Ia (0.156)	IIa	0.195	Me (0.032)	20 min, 15°, $h\nu$	94[a]
n-$C_{14}H_{29}Br$ (0.35)	n-$C_{14}H_{30}$	0.56	Bu (0.035)	0.5 hr, 25°, $h\nu$	100[b]
Ib (0.078)	IIb	0.117	Me (0.026)	15 min, 15°, $h\nu$	88[a]
p-BrC_6H_4NHAc (0.08)	C_6H_5NHAc	0.1	Bu (0.008)	3 hr, 25°, $h\nu$	96[a]
$HC{\equiv}CCH_2OTHP$ (5.64)	 III	6.1	Bu (6.1)	3 hr, reflux	73.5[a]

[a] Isolated yields. [b] Yields determined by VPC.



Ia, R = CH_3 IIa, R = CH_3
b, R = $CH_2C_6H_5$ b, R = $CH_2C_6H_5$

ly tin hydrides have usually been employed in stoichiometric amounts (either preformed or generated in situ from the nonvolatile polymethylhydrosiloxane and trialkyltin oxides).[1,2] The product, once formed by these procedures, must be separated from a full 1 equiv of trialkyltin halide. A catalytic method has been described using stoichiometric amounts of lithium aluminum hydride;[1] however, the reactivity of lithium aluminum hydride greatly limits the method's usefulness.

In our procedure the organic halide and 0.1–0.3 equiv of the trialkyltin chloride are dissolved in absolute ethanol and a solution of sodium borohydride in ethanol is added rapidly. In most experiments the reaction was carried out in Pyrex with irradiation by a 100-W mercury floodlamp so that reaction occurred rapidly at or below room temperature. The catalytic cycle is given in eq 1 and 2.

$$2R_3SnX + 2NaBH_4 \longrightarrow 2R_3SnH + 2NaCl + B_2H_6 \quad (1)$$

$$R_3SnH + R'X \longrightarrow R_3SnX + R'H \quad (2)$$

Ethanol is used as the solvent in order to trap the resulting diborane.[3]

Our results are summarized in Table I. As can be seen, ester and lactone functions do not interfere with this procedure.[4] The ethanolic solution of tributyltin hydride produced by our method also can be used in the hydrostannation reaction, illustrated by the preparation of the synthetically useful[5] *trans*-1-tri-*n*-butylstannyl-1-propene-3-tetrahydropyranyl ether (III).

Experimental Section

All reactions were performed under argon with carefully degassed solvents.

2-Oxa-3-oxo-6-*syn*-methoxymethyl-7-*anti*-acetoxy-*cis*-bicyclo[3.3.0]octane (IIa). To the iodide Ia (0.0553 g, 0.156 mmol) and trimethyltin chloride (0.0063 g, 0.0316 mmol) in 3 ml of air-free absolute ethanol cooled to 15° was rapidly added via syringe sodium borohydride (0.0076 g, 0.195 mmol) dissolved in 1.5 ml of ethanol. The solution was irradiated with a 100-W mercury floodlamp. Initially gas was rapidly evolved. After 20 min no starting material remained. Oxalic acid (0.0010 g) was added (to convert any trimethyltin hydride to the tin ester) followed 5 min later by 20 ml of CH_2Cl_2. The solution was washed once with saturated sodium bicarbonate and dried over anhydrous magnesium sulfate and the solvent was evaporated to give as a slightly yellow oil a mixture of hexamethylditin and IIa. Chromatographic separation on silica gel (eluent 1:1 benzene–ether) gave 0.0336 g (94%) of IIa, the spectral data for which were identical with those for authentic material.[6]

***trans*-1-Tri-*n*-butylstannyl-1-propene-3-tetrahydropyranyl Ether (III).** To tri-*n*-butyltin chloride (2.00 g, 6.1 mmol) in 5 ml of absolute ethanol was added dropwise sodium borohydride (0.23 g, 6.1 mmol) in 10 ml of ethanol. The solution became warm, gas was vigorously evolved, and sodium chloride precipitated. After stirring at 25° for 10 min, propargyl tetrahydropyranyl ether (0.790 g, 5.46 mmol) was added and the solution was refluxed for 3.5 hr, cooled, treated with 30 ml of pentane, and filtered. Evaporation of the solvent gave a clear oil containing (by ir and NMR) only III and tri-*n*-butyltin hydride. Distillation gave 1.78 g (73.5%) of III, bp 140–150° (0.1 mm), identical with material prepared by the direct reaction of isolated tri-*n*-butyltin hydride with propargyl tetrahydropyranyl ether.

Registry No.—Ia, 55721-21-6; Ib, 55721-22-7; IIa, 37745-51-0; IIb, 52689-80-2; III, 55723-10-9; $PhCH_2CH_2CH_2Br$, 637-59-2; n-$C_{14}H_{29}Br$, 112-71-0; p-BrC_6H_4NHAc, 103-88-8; $HC{\equiv}CCH_2OTHP$, 6089-04-9; $PhCH_2CH_2CH_3$, 103-65-1; n-$C_{14}H_{30}$, 629-59-4; C_6H_5HNAc, 103-84-4; $NaBH_4$, 16940-66-2; Bu_3SnCl, 1461-22-9; Me_3SnCl, 1066-45-1.

References and Notes

(1) H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963); H. G. Kuivila, *Acc. Chem. Res.*, **1**, 299 (1968).
(2) G. L. Grady and H. G. Kuivila, *J. Org. Chem.*, **34**, 2014 (1969).
(3) See E. R. Birnbaum and P. H. Javora, *J. Organomet. Chem.*, **9**, 379 (1967).
(4) Some reduction is observed if unnecessarily extended reaction times are used.
(5) E. J. Corey and R. H. Wollenberg, *J. Org. Chem.*, in press.
(6) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.*, **92**, 397 (1970).
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Reduction of Epoxides to Olefins with Low Valent Titanium

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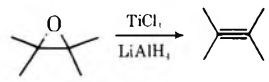
The reduction of epoxides to olefins is of some importance in synthesis, and a variety of methods have been devised to accomplish the transformation.[1] Among these methods has been the use of strongly reducing metals or

Table I
Reduction of Epoxides to Olefins with $TiCl_3$–$LiAlH_4$

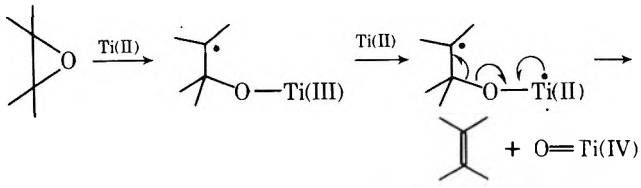


Substrate	Registry no.	Yield, %	Registry no.
α-Methylstyrene oxide	2085-88-3	36	98-83-9
Cyclooctene oxide	286-62-4	53	931-88-4
1-Dodecene oxide	2855-19-8	69	112-41-4
1-Decene oxide	2404-44-6	65	872-05-9
Cholesterol oxide	55700-78-2	75	57-88-5
cis-5-Decene oxide	36229-64-8	70 (4:1 trans/cis)	7433-78-5 (cis)
trans-5-Decene oxide	2165-61-9	70 (4:1 trans/cis)	7433-56-9 (trans)

metal salts including chromous ion,[2] zinc–copper couple,[3] magnesium amalgam,[4] zinc,[5] low valent tungsten complexes,[6] and $FeCl_3$–BuLi.[7] We have recently been studying the use of low valent titanium species as reducing agents for organic systems[8] and therefore examined the possible reduction of some epoxides.

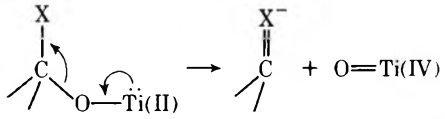
We have found that Ti(II), prepared by reaction of dry $TiCl_3$ with 0.25 molar equiv of $LiAlH_4$ in tetrahydrofuran, is a convenient and efficient reagent for converting epoxides to olefins. Some of our results are given in Table I.

The mechanism of epoxide reduction with Ti(II) is probably similar to that proposed by Kochi[2] for the chromous ion reduction. Central to this postulate is the implication



that the reaction must proceed with loss of olefin stereochemistry, as observed for reductions with chromous ion[2] and ion,[7] but not with low-valent tungsten.[6] This is in fact observed as shown in Table I. Both *cis*- and *trans*-5-decene oxide give the identical 81:19 mixture of *trans*- and *cis*-5-decene on treatment with $TiCl_3$–$LiAlH_4$. A control experiment established the stability of *cis*-5-decene under the reaction conditions.

Yet a further implication of this mechanistic postulate is the expectation that whenever a Ti(II)–oxygen bond is formed next to a group, X, which can stabilize free radicals, then deoxygenation should occur. We have confirmed this expectation in reactions with halohydrins (X = CBr) and cyanohydrins (X = CN), and we are currently studying these and other cases in detail.[9]



From a synthetic point of view, use of $TiCl_3$–$LiAlH_4$ for epoxide reduction appears competitive with use of other reagents. A major advantage of the present procedure, however, is the ease with which the reagent may be prepared. A 4:1 ball-milled mixture of $TiCl_3$ and $LiAlH_4$ prepared for our evaluation by Alfa Inorganics has proven to be indefinitely stable in the absence of solvent and extremely convenient to use as a one-bottle source of reagent.[10]

Experimental Section

General Reaction Procedure. The titanium reagent was prepared in either of two ways.

Method A. Lithium aluminum hydride (0.20 g, 5.0 mmol) was added in small portions to a stirred slurry of $TiCl_3$ (3.08 g, 20.0 mmol) in 60 ml of dry tetrahydrofuran under an inert atmosphere (argon or nitrogen) at room temperature. Hydrogen evolution was immediate, and the resulting fine black suspension was stirred for 15 min before use.

Method B. Alternatively, a 4:1 premix of $TiCl_3$ and $LiAlH_4$[10] (effective mol wt 164, 3.28 g, 20.0 mmol) was added with stirring and in small portions to 60 ml of dry THF at room temperature under an inert atmosphere. Hydrogen evolution occurred immediately and the fine black suspension was stirred 15 min before use.

A solution of epoxide (10 mmol) in 10 ml of dry THF was added to the Ti(II) reagent, and the reaction mixture was refluxed for 3 hr. The reaction mixture was then cooled to room temperature and quenched by addition of 60 ml of water. The organic layer was diluted with ether, then drawn off, washed with water and with brine, dried ($MgSO_4$), and concentrated to yield the product. With the exception of cholesterol, yields were determined by GLC with appropriate internal standards added. Products were identified by comparison with authentic samples. The results are presented in Table I.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

References and Notes

(1) For a list of methods, see I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Wiley-Interscience, New York, N.Y., 1971, pp 502–504.
(2) J. K. Kochi, D. M. Singleton, and L. J. Andrews, *Tetrahedron*, **24**, 3503 (1968).
(3) S. M. Kupchan and M. Maruyama, *J. Org. Chem.*, **36**, 1187 (1971).
(4) F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Chem. Commun.*, 144 (1970).
(5) K. B. Sharpless, *Chem. Commun.*, 1450 (1970).
(6) K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Am. Chem. Soc.*, **94**, 6538 (1972).
(7) T. Fujisawa, K. Sugimoto, and H. Ohta, *Chem. Lett.*, 883 (1974).
(8) J. E. Mc Murry, *Acc. Chem. Res.*, **7**, 281 (1974).
(9) J. E. Mc Murry and T. Hoz, unpublished results.
(10) We thank Mr. Robert Wade, Alfa Inorganics, Beverly, Mass., for preparing this premix, which is commercially available as "Mc Murry's Reagent".

A Simple One-Step Alternative to the Malonic Ester Synthesis

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The classical malonic ester synthesis involving discrete alkylation and decarbalkoxylation steps remains, in spite of attempts at replacement, the standard method for effecting two-carbon homologation of alkyl halides. Although nor-

Table I
Reaction of Alkyl Halides with the Dilithium Salt of Monoethyl Malonate
RX + LiCH(COOLi)COOEt → RCH_2COOEt

RX		RCH_2COOEt		Yield, %[a]
Methallyl chloride	563-47-3	$CH_2{=}C(CH_3)CH_2CH_2COOEt$	4911-54-0	71
Allyl bromide	106-95-6	$CH_2{=}CHCH_2CH_2COOEt$	1968-40-7	80
Benzyl chloride	100-44-7	$PhCH_2CH_2COOEt$	2021-28-5	75
Ethyl chloroacetate	105-39-5	Diethyl succinate	123-25-1	98
Chloroacetone	78-95-5	$CH_3COCH_2CH_2COOEt$	539-88-8	25
Ethyl iodide	75-03-6	$CH_3CH_2CH_2COOEt$	105-54-4	60
n-Butyl bromide	109-65-9	$CH_3(CH_2)_4COOEt$	123-66-0	80
n-Decyl bromide	112-29-8	$CH_3(CH_2)_{10}COOEt$	106-33-2	60
2-Bromopropane	79-26-3	$(CH_3)_2CHCH_2COOEt$	108-64-5	50
2-Bromobutane	78-76-2	$CH_3CH_2CH(CH_3)CH_2COOEt$	5870-68-8	22

[a] Yields given represent distilled product.

mally a three-step alkylation, saponification, decarboxylation sequence is used,[1] a recently introduced variation, in which decarbalkoxylation can be effected in a single step, seems to give better overall yields.[2]

Ideally, one could simplify the procedure still further by alkylating directly with lithio ethyl acetate, but this does not seem to be feasible. Lithio ethyl acetate can be readily prepared at −78° and caused to undergo aldol addition to simple carbonyl compounds.[3] In reaction with alkyl halides, however, it reacts poorly, giving the product in 20–30% yields.[4] Lithio *tert*-butyl acetate seems to alkylate well,[4] but the use of *tert*-butyl esters can introduce unwanted complications in synthesis.

A further possibility is the alkylation of an acid dianion according to Creger's method,[5,6] but again this does not seem to be feasible. Although the dianions of substituted acetic acids alkylate well, especially when the solvent modification of Pfeffer and Silbert is used,[7,8] the parent dilithioacetate reacts poorly. Even were this reaction to go well, a separate esterification step would be required.

We reasoned that these difficulties could be resolved, and the malonic ester synthesis simplified considerably, if one were to alkylate with the dianion of monoethyl malonate. On simple warming of the reaction, the intermediate alkylated monoethyl malonate should decarboxylate, giving the desired product directly. The starting material is readily available by partial saponification of diethyl malonate.[9]

$$RX + \underset{LiCHCOOEt}{\overset{COOLi}{|}} \longrightarrow \underset{RCHCOOEt}{\overset{COOLi}{|}} \longrightarrow RCH_2COOEt$$

The expected reaction does in fact proceed as planned, giving the ester products in fair to excellent yields. Some of our results are given in Table I.

As can be seen from Table I activated halides (R = allylic, benzylic) alkylate in excellent yields. Primary halides also give good results, but, as expected, secondary halides react less well.

In summary, we feel that this new method is clearly superior to the classical malonic ester synthesis both in yield and in ease of operation, and we expect that it will find use in synthesis.

Experimental Section

General Reaction Procedure. Isopropylcyclohexylamine (4.15 g, 29.4 mmol) was dissolved in 10 ml of dry tetrahydrofuran (THF) under a nitrogen atmosphere, and the temperature of the solution was lowered to −78° by means of a Dry Ice bath. *n*-Butyllithium (14.3 ml of 2.06 *M* solution in hexane, 29.4 mmol) was then added via syringe. Monoethyl malonate (1.94 g, 14.7 mmol) in 10 ml of THF was added, and the reaction was allowed to warm to ice temperature to form the dianion. After 15 min of stirring, 4.0 ml of dry hexamethylphosphoramide was added, followed by addition of the alkyl halide (14.7 mmol) in 5 ml of dry THF. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hr to effect alkylation. After this time the reaction mixture was refluxed (68°) overnight to effect decarboxylation.

After cooling, the reaction mixture was poured into water and extracted with ether. The ether extracts were washed with dilute hydrochloric acid, with saturated sodium bicarbonate, and with brine, then dried ($MgSO_4$), filtered, and concentrated at the rotary evaporator. The residue was distilled to yield the product.

Product identification was made through a combination of spectroscopic methods (ir, NMR, mass spectra) and through comparison of the product boiling points with literature values.

Acknowledgment. We thank the National Institutes of Health for their support of this work through Grant CA11277.

Registry No.—Monoethyl malonate, 1071-46-1.

References and Notes

(1) For a representative procedure, see G. B. Heisig and F. H. Stodola, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 213.
(2) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).
(3) M. W. Rathke, *J. Am. Chem. Soc.*, **92**, 3222 (1970).
(4) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(5) P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967).
(6) P. L. Creger, *J. Am. Chem. Soc.*, **92**, 1397 (1970).
(7) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35**, 262 (1970).
(8) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, *J. Org. Chem.*, **37**, 451 (1972).
(9) R. E. Strube, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 417.

Complete Stereochemistry of Tenulin. Carbon-13 Nuclear Magnetic Resonance Spectra of Tenulin Derivatives

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Determination of the gross structure of the sesquiterpene lactone tenulin (1)[1] was an early example of the successful use of ^1H NMR spectrometry in natural products chemistry. Subsequently, the relative and absolute configuration of tenulin at C-1, C-5, C-7, and C-10 was deduced by

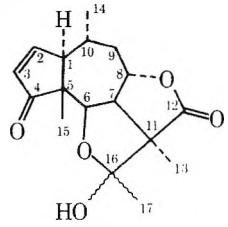
Table I
^{13}C NMR Spectra of Tenulin and Derivatives

	1a	1b	2a	2b	3	4	5	6	7	8
C-1	54.3	54.7	48.3	48.6	150.1	48.4	52.7	47.3	173.2	47.8
C-2	162.6	162.3	24.7	24.2	122.7	24.4	161.1	24.3	138.4	23.0
C-3	130.4	130.0	34.6	34.5	39.7	34.4	130.3	35.1	207.0	35.8
C-4	212.7	212.3	221.6	221.2	217.6	220.3	210.6	219.8	37.2	209.7
C-5	56.3	55.3	54.5	53.4	53.5	53.4[a]	54.5	54.3	44.0	64.0
C-6	77.4	74.0	78.4	74.8	78.6	49.1	66.0	67.5	66.0	201.6
C-7	63.3	63.8	61.7	62.0	60.2	59.6	55.1	53.6	58.4	61.8
C-8	76.5	76.0	76.1	75.6	75.5	75.3	75.8	75.9	75.8	76.5
C-9	42.9	42.5	42.4	42.0	41.3	41.8	44.7	44.9	38.1	44.9
C-10	28.4	28.0	30.8	30.3	291.8	30.3	27.2	29.5	31.3	29.2
C-11	58.8	58.8	58.5	58.3	56.5	54.4[a]	37.0	37.0	41.2	36.8
C-12	176.4	176.42	175.6	177.6	175.4	75.4	177.4	177.6	178.0	177.2
C-13	18.3[a]	19.0[a]	18.0[a]	18.5[a]	21.2[a]	21.3[a]	20.6[a]	20.6[a]	20.6	20.1
C-14	19.6[a]	20.4[a]	13.7	13.8	16.2	13.7	19.7	14.8	8.12[a]	14.8
C-15	19.9[a]	20.4[a]	19.8[a]	19.6[a]	19.2[a]	19.7[a]	13.9	13.8	12.0[a]	18.7
C-16	108.4	105.2	107.6	104.4	161.4	162.0	169.2	169.2		
C-17	24.7	27.3	24.6	26.8	83.7	82.7	20.0[a]	19.8[a]		

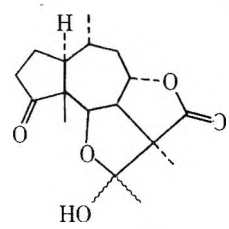
[a] Assignments may be interchanged.

analysis of the complex interrelationships between isotenulin (4) and its congeners,[2] their ORD curves,[2,3] and an X-ray analysis of 2-bromoisotenulin.[4,5] Although the stereochemistry of tenulin at C-11 and C-16 has not been specified previously, fusion of the γ-lactone and five-membered hemiketal rings is only possible if the C-11 methyl group is α (11*R*). Consequently, the only remaining point of uncertainty in the structure of tenulin was the configuration at C-16.

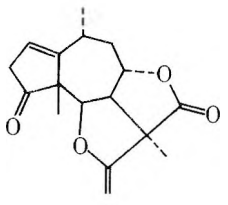
In the course of collecting ^{13}C NMR spectra of various sesquiterpene lactones, we noticed that spectra of chromatographically pure tenulin (1) and dihydrotenulin (2) consistently exhibited two sets of signals (Table I) whereas samples of pyrotenulin (3) and anhydrodihydrotenulin (4), formed by dehydration of 1 and 2, respectively, and other transformation products such as isotenulin (5), dihydroisotenulin (6), and deacetylneotenulin (7)[6] were spectroscopically homogeneous. The observation that chemical shift differences between members of the two sets were greatest for C-16 and for carbon atoms in close proximity to C-16 such as C-8, C-11, and C-12 (for assignments see below) permitted the deduction that tenulin as isolated from the plant consists of a mixture of C-16 epimers.[7]



1a, C-17 Me α
b, C-17 Me β



2a, C-17 Me α
b, C-17 Me β



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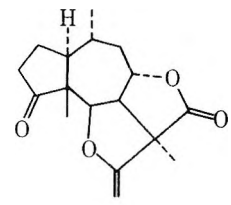

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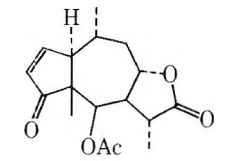

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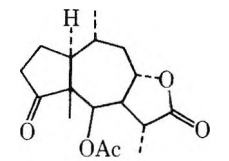

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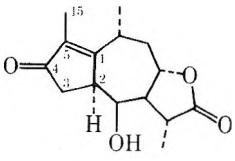

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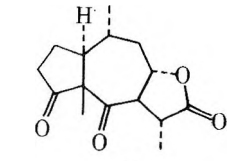

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Further evidence for this rather anticlimactic finale to nearly 40 years of research on tenulin was provided by examining the ^{1}H NMR spectra of 1 and 2 at higher fields. At 90 and particularly at 270 MHz two sets of signals in the approximate ratio 4:1 characteristic of H-6, H-13, and H-17 in the two separate isomers were reasonably well resolved, whereas other signals not obscured by the methylene and methinyl envelope (H-14, H-8, and H-15 of 1 and 2 as well as H-1, H-2, and H-3 of 1) remained superimposed and quite sharp.[8] Since the H-6 doublet of the two minor isomers appears at lower field (4.57 vs. 4.45 ppm in 1), we infer that it represents H-6 of epimers **1b** and **2b** in which H-6 is cis to the hydroxyl group attached to C-16.

Assignments to most signals in the ^{13}C NMR spectra of 1 and 2 are fairly obvious on the basis of multiplicities, chemical shift data in the literature, and comparison with signals in the spectra of compounds 3–8. Thus a triplet near 42 ppm, one of three representing the methylene carbons of 2, is assigned to C-9 by comparison with 1 and 3–8, leaving the 24.5-ppm triplet to C-2 and the 33.7-ppm triplet to the more deshielded C-3. The identity of a methinyl doublet near 76 ppm, fairly constant throughout the series, as that of C-8 was established by single-frequency off-resonance decoupling; although superposition of signals in the ^{1}H NMR spectra of 1 and 2 prevented direct identification of the slightly more deshielded (in 1–3) methinyl doublet of C-6, comparison with the spectra of 5, where single-frequency off-resonance decoupling of C-6, now at somewhat higher fields, was possible, and 8, where C-6 is a carbonyl carbon, left no ambiguity.[9] The most shielded methinyl is clearly that of C-10, thus permitting assignment of C-7, which should be more affected by the changes at C-11, by default. The doublet of C-1 can be recognized by its upfield

shift on hydrogenation of 1 to 2 and 5 to 6 and by its conversion to a singlet—far downfield—in the spectrum of 3.

The chemical shifts of the various carbonyl carbons may be deduced from known parameters of cyclopentenones, cyclopentanones, cycloheptanones, substituted esters (or lactones), and acetates.[10] The upfield shift in the cyclopentanone carbonyl frequency of 8 relative to 6 is notable. Among the remaining nonprotonated carbon atoms, C-16 of 1 and 2 is unique; recognition is eased by its downfield shift in 3–6 and disappearance in 7 and 8. Differentiation between C-5 and C-11 of 1 and 2 is based on comparison with the spectra of 5, 6, and 8 where the upfield shift of one of the signals, that of C-11, and the relative constancy of the second, that of C-5, which moves downfield on oxidation of the neighboring carbon atom, leaves no ambiguity.

Among the methyl signals, assignment of the quartet at lowest field to C-17 is based on single-frequency off-resonance decoupling in 1 and its conversion to a triplet near 86 ppm, characteristic of vinyl ethers, in the spectra of 3 and 4. Differentiation between the remaining methyl signals is difficult because of the superposition of methyl frequencies in the proton NMR spectra. Inspection of Table I reveals a significant upfield shift of one of the methyl signals upon hydrogenation (compare 1 with 2 and 5 with 6) and an upfield shift of a second methyl signal upon opening the hemiacetal ring (compare 1 with 4 and 2 with 6). We assume that the signals affected are those of C-14 and C-15, because (a) the chemical shift of C-13 should not be affected significantly by hydrogenation, (b) conversion of 1 to 2 or 2 to 4 produces a small downfield shift of one of the methyl signals which must be that of C-13, and (c) 5–8 all exhibit at least one relatively invariant signal in the 19–20-ppm region which again must be attributed to C-13. Comparison of 3 and 4 with 2, and 6 and 8 with 5, suggests that the signal which moves upfield on hydrogenation is that of C-14, the shift probably being associated with the introduction of a hydrogen atom peri to C-14. The signal which is shifted upfield on opening of the hemiacetal ring (and downfield on conversion of 6 to 8) is therefore that of C-15, although the reasons for the upfield shift are not clear as opening of the hemiacetal ring would appear to result in removal of a gauche interaction.

Experimental Section

Spectra were recorded on a Bruker HFX-270 instrument in $CDCl_3$ (1–4, 6) and Me_2SO-d_6 (5) solution, using Fourier transform techniques.

Registry No.—1a, 55721-12-5; 1b, 55780-22-8; 2a, 55660-88-3; 2b, 55700-79-3; 3, 55660-89-4; 4, 55660-90-7; 5, 10092-04-3; 6, 55700-80-6; 7, 54933-23-2; 8, 55660-91-8.

References and Notes

(1) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Am. Chem. Soc.*, **84**, 3857 (1962).
(2) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963).
(3) C. Djerassi, J. Osiecki, and W. Herz, *J. Org. Chem.*, **22**, 1361 (1957).
(4) D. Rogers and Mazhar-ul-Haque, *Proc. Chem. Soc.*, 92 (1963).
(5) Mazhar-ul-Haque, D. Rogers, and C. N. Caughlan, *J. Chem. Soc., Perkin Trans.* **2**, 223 (1974).
(6) The stereochemistry shown in the formula is based on a recent X-ray analysis (private communication from Dr. P. J. Cox, University of Glasgow).
(7) Anhydrodihydrotenulin (4) can be prepared from 2 in >80% yield.[1] Consequently the unlikely (because of the H-6 and H-8 proton shifts) possibility that 1 and 2 are 4:1 mixtures of C-8 epimers (the existence of a C-6 epimer of 1 is not possible) and that purification of 3, 4, and 5 has resulted in fractionation of the more abundant isomer product can be dismissed.
(8) Reexamination of 60-MHz traces recorded 15 years ago revealed a weak doublet (H-6 of minor isomer) partially obscured by the H-6 doublet of the major isomer and two shoulders on the sharp singlets of H-13 and H-17.
(9) The downfield shift of C-9 and the upfield shifts of C-1, C-4, C-5, C-6, and C-7 on going from 1 to 5 (and 2 to 6) are due partially to changes in electron density at C-6 and partially to changes in conformation of ring B and subsequent alterations of spatial relationships on opening the hemiacetal ring.
(10) The conversion of C-6 from sp^3 to sp^2 must be responsible for the surprisingly large upfield shift of C-4 in going from 6 to 8.

Reaction of (+)-1,3-Dimethylallene with Lead Tetraacetate

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Although there has been a great deal of interest in the reaction of lead tetraacetate (LTA) with alkenes,[1] there have been few examples utilizing this reaction with allenes. An earlier study by Laforge and Acree[2] reported that the major product of the reaction of acyclic allenes with LTA was a diacetate. More specifically, the reaction of 1,3-dimethylallene with LTA in acetic acid was also assumed to afford a diacetate. In a more recent disclosure, we have shown that the electrophilic addition of LTA to (−)-1,2-cyclononadiene in acetic acid solvent afforded (+)-3-acetoxycyclononyne by a suprafacial addition.[3] This was a particularly interesting result since the dominant pathway in the oxymercuration[3] and the oxythallation[4] of 1,2-cyclononadiene has been shown to be antarafacial addition to an alkene–metal π complex. The above results of Laforge and Acree[2] with acyclic allenes and our own results[3] with a cyclic allene, which afforded an alkyne as the major product, prompted us to examine the orientation and the stereochemistry of the addition of LTA to (+)-1,3-dimethylallene (1). We now report that the electrophilic addition of LTA to 1 also proceeds principally by a suprafacial pathway affording (*S*)-(+)-4-acetoxy-2-pentyne as the major product.

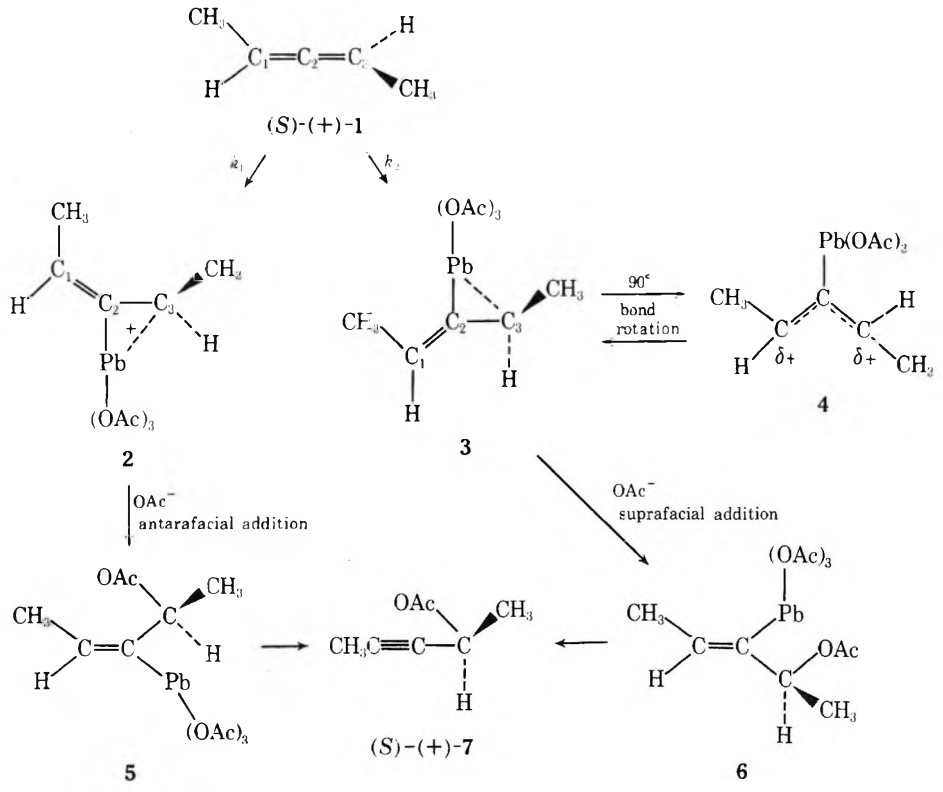
Results and Discussion

When 1,3-dimethylallene (1) was treated with LTA in acetic acid solvent, gas chromatographic analysis (GLC) showed that the major product of the reaction was 4-acetoxy-2-pentyne (7). When the reaction was carried out with optically active (*S*)-(+)-1,[5] $[\alpha]D$ +22.4°, the product 7 had $[\alpha]D$ +6.6° (Scheme I). The absolute configuration of 7 was established as *S* by saponification of 7 followed by catalytic hydrogenation of 4-hydroxy-2-pentyne to (*S*)-(+)-2-pentanol (8), $[\alpha]D$ +1.4°. The stereochemistry of 7 was also established by direct hydrogenation of 7 to (+)-2-acetoxypentane (9). The absolute configuration of 9 was established by conversion of (*S*)-(+)-2-pentanol, $[\alpha]D$ +12.2°, of known configuration to (*S*)-(+)-9, $[\alpha]D$ +13.8°, by the action of acetyl chloride (Scheme II).

The relative stereospecificity of the addition of LTA to 1 was determined in the following manner. The rotation of optically pure (+)-2-pentanol is 18.8°.[7] Therefore, the optical purity of 2-pentanol having $[\alpha]D$ +1.4° is approximately 7.4%. The optical purity of the allene 1, $[\alpha]D$ +22.4°, from which 8 was derived may also be estimated to be about 13% based upon a calculated rotation for optically pure (*R*)-(−)-1 of −174° (EtOH).[6b] Thus, we may conclude that the stereospecificity of LTA addition to 1 is at least 57%. The specificity could conceivably be higher since our data cannot exclude some racemization of the allene or the acetoxypentyne under the reaction conditions.

In the reaction of 1 with LTA, there are two possible

Scheme I

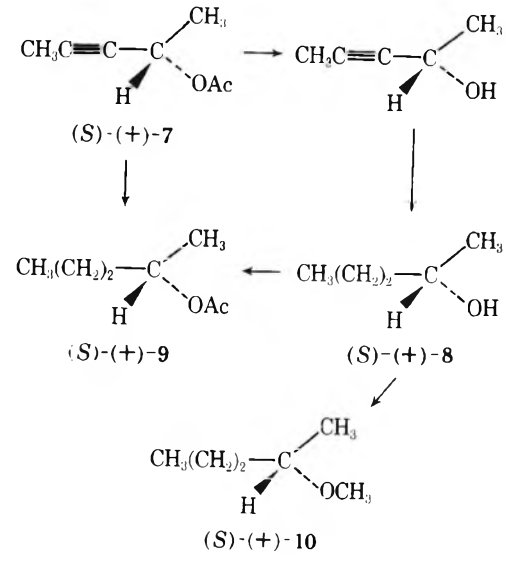


pathways for approach of the attacking electrophilic lead reagent. The stereochemistry of the formation of (+)-7 from (+)-1 can either result from antarafacial addition to 2 or suprafacial addition to 3. Because the vinyllead intermediates 5 and 6 are labile and not isolable, a definitive mechanism is not attainable. However, examination of molecular models suggest that attack of $Pb(OAc)_3^+$ from the least hindered side as in 2 results in an intermediate having a potential methyl–methyl steric interaction. Although approach of the electrophile affording 3 is hindered by the methyl substituent at the vinyl terminus, the resulting plumbonium ion 3 is less sterically crowded, having only hydrogen–methyl interactions. Any rehybridization at C_2 affording the nonlinear structures 2 and 3 will further accentuate steric repulsions in the transition state for antarafacial acetate anion addition to the π complex. The transition state for a suprafacial addition to such a π complex should require that the metal ion be unsymmetrically bonded to the double bond in order that a more nearly empty p orbital at C_3 is available. Moreover, rehybridization at C_2 makes antarafacial addition of acetate ion to 2 more difficult because of steric hindrance.

We therefore suggest that (+)-7 arises principally via suprafacial addition to intermediate 3 followed by the loss of the metal and alkyne formation. Further support for the suggested mechanism comes from the observation that suprafacial addition of LTA to 1,2-cyclononadiene has been unequivocally established.[3] The methoxymercuration[5a] of (−)-1 has also been shown to proceed by solvent attack on a π complex comparable to 3 which affords (+)-2-methoxypentane upon reduction. In the latter case, antarafacial addition was observed and the resulting vinylmercurial was sufficiently stable to be isolated. The vinylmercurials corresponding to 5 and 6 were formed in a ratio of 17:83. A steric argument was also offered in explanation of these results.[5a] A mixture of cis and trans pentenes has also been reported in the oxythallation of racemic 1.[10]

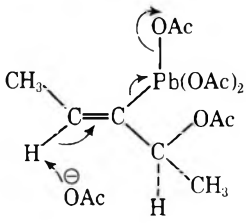
The isolation of an optically active product in this reaction precludes exclusive product formation via the planar resonance stabilized allyl cation 4, since attack by solvent on 4 would result in a racemic product. It should also be recognized that antarafacial addition to 2 or 3 will result in a reduction in stereospecificity. Our data are consistent with the formation of a π-bridged plumbonium ion intermediate that is sufficiently stabilized to prevent extensive carbon–carbon rotation affording 4. The rotational barrier in allyl cation has been calculated to be 34.8 kcal/mol.[9] However, the position of equilibrium in the present case would depend upon the relative stabilities of the bridged plumbonium ion 3 and the allyl cation 4.

Scheme II



The mechanism for the formation of an alkyne in this reaction is also worthy of comment. The carbon–lead bond in 6 is obviously considerably more labile than either the carbon–mercury[5] or carbon–thallium bond[4,10] in their corre-

sponding vinyl metal acetates. The formation of 7 from 6 may occur via anti elimination as depicted in 11. Alternatively, ionization of the labile carbon–lead bond forming a vinyl cation may be involved. An anti elimination on the acetoxonium ion 12 will also afford 7. Although our results



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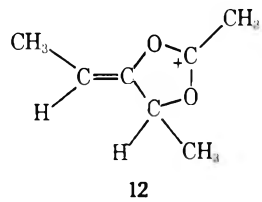

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cannot distinguish between these pathways, the fact that the vinylmercury and vinylthallium derivatives are formed as discrete intermediates suggests that a similar vinyllead compound is involved that suffers ionization of the carbon–lead bond either in concert with or prior to elimination.

In conclusion, the oxyplumbation of 1 proceeds with relatively high stereospecificity by a suprafacial addition. The formation of an alkyne in these reactions appears to be general for cyclic[3] and acyclic dialkyl-substituted allenes under these reaction conditions, since 1,3-diethylallene also affords 3-acetoxy-4-heptyne as the major product upon reaction with LTA in acetic acid.

Experimental Section

Materials. Lead tetraacetate was purchased from Arapahoe Chemicals, Boulder, Colo. The nickel acetate was purchased from Allied Chemicals, Morristown, N.J. Methyllithium and 2-butene were purchased from Matheson Coleman and Bell, Norwood, Ohio. The (+)-2-pentanol was purchased from Norse Laboratories, Santa Barbara, Calif. The (+)-α-pinene was purchased from Aldrich Chemical Co., St. Paul, Minn.

Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. NMR spectra were recorded with a Varian A-60A spectrometer, and chemical shifts are reported in parts per million downfield from internal Me_4Si.

1,1-Dibromo-2,3-*cis*-dimethylcyclopropane. To 1 l. of *tert*-butyl alcohol, distilled from CaH, was added 40 g (1 mol) of potassium under argon. After 3 hr of vigorous stirring with mild heating, the potassium was consumed and 1 l. of sodium-dried heptane was added. The *tert*-butyl alcohol was removed by distillation until a head temperature of 92° was attained. The flask was equipped with a Dry Ice condenser, the thick white slurry was cooled to 0°, and 68 g (1 mol) of *cis*-2-butene was distilled into the flask. Bromoform (253 g, 1 mol) was added dropwise over a 3-hr period. After stirring overnight at 25°, the reaction was quenched by the addition of water. The aqueous layer was extracted with 3 × 50 ml of pentane and the combined organic fractions were dried ($MgSO_4$). The solution was concentrated by simple distillation and vacuum distilled to yield 180 g (80%) of dibromide, bp 40° (5 mm).

1,3-Dimethylallene (1). To 48.6 g (2 mol) of 40 mesh magnesium powder in 360 ml of dry THF was added dropwise 91.2 g (0.40 mol) of 1,1-dibromo-*cis*-2,3-dimethylcyclopropane at a rate that maintained gentle reflux. When the addition was complete, the dimethylallene was removed by flash distillation. The THF–allene mixture was fractionally distilled and the first fraction, bp 48–50°, contained 2.5 g of dimethylallene in greater than 90% purity. Succeeding fractions (contaminated with THF) yielded 3.25 g (65% pure) and 16 g (25% pure) of dimethylallene, overall GLC yield 36%. The allene had ir 3020 (s), 2970 (s), 1970 (m), 1450 (m), 1280 (m), 950 (m), 865 cm^{-1} (s); NMR (CCl_4) δ 1.62 (d, 6, J = 6 Hz), 4.92 (m, 2).

Partial Resolution of Dimethylallene (1). Using the method of Caserio,[5a] 7.0 g (~0.10 mol) of racemic dimethylallene (1) was treated with optically active tetraisopinocampheyldiborane, prepared from (+)-α-pinene, $[\alpha]D$ +46° (neat), at 0° for 3 hr with stirring. The reaction mixture was vacuum distilled (4 mm, 25°) until no more volatiles could be collected. Allene was collected by GLC (15 ft × 0.25 in., 10% SE-30 on Chromosorb W, injection port temperature 40° and detector 60°) and had $[\alpha]D$ +22.4° (c 2.09, Et_2O). Collection of the allene at higher temperatures resulted in partial racemization.

Lead Tetraacetate Oxidation of 1,3-Dimethylallene (1). To 0.34 g (0.005 mol) of dimethylallene, $[\alpha]D$ +22.44° (c 2.2, Et_2O), as a 30% solution in THF was added 12 ml of glacial acetic acid and 2.22 g (0.005 mol) of LTA. The flask was stoppered and allowed to stir at room temperature for 20 hr. Ether was added and a precipitate of lead diacetate was removed by filtration. The organic layer was washed with H_2O and aqueous bicarbonate. Drying ($MgSO_4$) and removal of solvent afforded 0.26 g (41.4%) of crude product consisting of 57% of 4-acetoxy-2-pentyne and two other products that were tentatively identified as diacetates. The acetylene 7 after purification by GLC had $[\alpha]D$ +6.6° (c 3.92, Et_2O). A duplicate experiment afforded 7 having $[\alpha]D$ +6.9° (c 3.95, Et_2O): ir 2275 (s), 1740 (s), 1365 (m), 1230 (s), 1170 (m), 1055 cm^{-1} (m); NMR (CCl_4) δ 1.40 (d, 3, J = 7 Hz), 1.82 (d, 3, J = 2 Hz), 1.97 (s, 3) 5.32 (m, 1); mass spectrum m/e (rel intensity) 125 (6), 111 (37), 84 (45), 83 (1), 69 (33), 67 (45), 66 (100), 65 (43), 55 (8), 43 (76), 42 (6), 41 (64), 40 (33).

(*S*)-(+)-2-Pentanol (8). To 0.39 g (0.3 mmol) of 7 in 1 ml of absolute ethanol was added 0.045 g of K_2CO_3. The reaction mixture was stirred for 3 hr. The solid material was removed by filtration and 0.01 g of PtO_2 and a crystal of $NaNO_2$ (to decrease hydrogenolysis) were added to the solution which was hydrogenated at atmospheric pressure until uptake of H_2 ceased. The 2-pentanol isolated by GLC had $[\alpha]D$ +1.36° (c 1.1, CH_2Cl_2). The infrared spectrum of 8 was identical with that of an authentic sample of racemic 8.

(*S*)-(+)-2-Acetoxypentane (9). A. To a solution of 1.0 g (10 mmol) of (+)-2-pentanol (8), $[\alpha]D$ +12.2° (neat), and 5 ml of freshly distilled pyridine was added dropwise 0.85 g (12 mmol) of acetyl chloride. After complete addition, 20 ml of ether was added and the solution was washed with 2 × 25 ml of 5% HCl solution and 3 × 20 ml of water. After drying ($MgSO_4$), the solution was concentrated and afforded 9, $[\alpha]D$ + 13.8° (c 2.4, CCl_4).

B. Catalytic reduction of 7, $[\alpha]^{25}D$ +9.8° (c 7.87, CH_2Cl_2), using the method of Brown[11] and the procedure given by Caserio,[5a] gave a low yield of 2-acetoxypentane, $[\alpha]^{25}D$ +2.1° (c 0.49, $CHCl_3$), that had ir and NMR spectra identical with those of an authentic sample of 9. The low yield was presumably due to extensive hydrogenolysis.

(*S*)-(+)-2-Methoxypentane. A solution of 1.0 g (10 mmol) of (+)-2-pentanol (8), $[\alpha]D$ +12.2° (neat), 3.0 g (20 mmol) of methyl iodide, 20 ml of hexane, and 1.0 g (20 mmol) of sodium hydride (57% oil dispersion) was refluxed for 4 hr. Excess sodium hydride was destroyed by adding wet ether to the mixture. The organic layer was washed with 2 × 20 ml of a saturated NaCl solution and dried ($MgSO_4$). GLC collection (10 ft × 0.25 in., 20% SE-30 on Chromosorb W, 90°) gave 10 that had $[\alpha]D$ +9.8° (c 5.2, CCl_4).

Lead Tetraacetate Oxidation of Diethylallene. A mixture of 1.60 g (10 mmol) of diethylallene, 6.75 g (15 mmol) of lead tetraacetate, and 75 ml of glacial acetic acid was stirred at room temperature for 16 hr. The mixture was poured into a separatory funnel and 50 ml of water and 100 ml of ether were added. The ether layer was washed with 4 × 50 ml of water, 2 × 50 ml of a saturated sodium bicarbonate solution, and 50 ml of a saturated NaCl solution. The solution was dried ($MgSO_4$) and concentrated. Upon GLC analysis and collection, the major product peak (>75%) was identified as 3-acetoxy-4-heptyne: ir 2970 (m), 2940 (m), 2240 (w), 1740 (s), 1370 (m), 1230 (s), 1020 cm^{-1} (m); NMR (CCl_4) δ 1.10 (m), 1.98 (s), 2.1 (m), 5.22 (m).

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Registry No.—(±)-1, 28383-16-6; (+)-1, 23190-25-2; 7, 55621-89-1; 8, 26184-62-3; 9, 55621-90-4; 10, 55621-91-5; 1,1-dibromo-2,3-*cis*-dimethylcyclopropane, 3591-57-9; *cis*-2-butene, 590-18-1; bromoform, 75-25-2; tetraisopinocamphenyldiborane, 16997-72-1; lead tetraacetate, 546-67-8; acetyl chloride, 75-36-5; methyl iodide, 74-88-4; diethyl allene, 2454-31-1; 3-acetoxy-4-heptyne, 55621-92-6.

References and Notes

(1) (a) W. Kitching, *Organomet. Chem. Rev.*, **3**, 61 (1968); (b) R. Criegee, "Oxidation in Organic Chemistry", K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965, Chapter 5; (c) W. Kitching, *Rev. Pure Appl. Chem.*, **19**, 1 (1969).
(2) F. B. Laforge and F. Acree, Jr., *J. Org. Chem.*, **6**, 208 (1941).
(3) R. D. Bach, U. Mazur, R. N. Brummel, and L. H. Lin, *J. Am. Chem. Soc.*, **93**, 7120 (1971).
(4) R. D. Bach and J. W. Holubka, *J. Am. Chem. Soc.*, **96**, 7814 (1974).

(5) (a) W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90**, 6741 (1968); (b) W. M. Jones and J. Walbrick, *Tetrahedron Lett.*, 5229 (1968); (c) P. Crabbé, E. Velarde, H. W. Anderson, S. D. Clark, W. R. Moore, A. F. Drake, and S. F. Mason, *Chem. Commun.*, 1261 (1971).
(6) (a) M. Raban and K. Mislow, *Top. Stereochem.*, **2**, 215 (1967) (b) J. H. Brewster, *ibid.*, **2**, 35 (1967); (c) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966).
(7) The highest observed rotation for 2-pentanol in benzene solvent is 13.7°.[5a] However, a gas chromatographic study has determined that the absolute rotation of 2-pentanol is 18.8°.[8] Optically active 2-methoxypentane (**10**) having $[\alpha]_D$ +9.9° has been estimated[5a] to be 58% optically pure. We have prepared **10** having $[\alpha]_D$ +9.8° from **8** having $[\alpha]_D$ +12.2° which was presumed to be 65% optically pure, in fair agreement with the above value.
(8) E. Gil-Av, R. Charles-Sigler, G. Fischer, and D. Nurok, *J. Gas Chromatogr.*, **4**, 51 (1966).
(9) L. Radom, P. C. Hariharan, J. A. Pople, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 6531 (1973).
(10) R. K. Sharma and E. D. Martinel, *J. Chem. Soc., Chem. Commun.*, 1129 (1972).
(11) H. C. Brown, K. Sivasankaran, and C. A. Brown, *J. Am. Chem. Soc.*, **85**, 1003 (1963).

Thermal Rearrangements of 4,5-Diphenyl-2*H*-imidazoles

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Some time ago Weiss reported that 2,2,4,5-tetraphenyl- and 2,2-dibenzyl-4,5-diphenyl-2*H*-imidazoles (**3c, 5a**) thermally rearrange to the corresponding 1*H*-imidazoles with migration of a phenyl or benzyl group, respectively.[2] The apparent similarity of this rearrangement to the [1,5] sigmatropic shifts of geminal dimethylcyclopentadienes,[3] spirodienes,[4] and 2*H*-pyrroles[5] prompted us to investigate this reaction, particularly since Weiss had claimed that 2,2-dimethyl-4,5-diphenyl-2*H*-imidazole (**3a**) did not rearrange thermally and that 2,2-pentamethylene-4,5-diphenyl-2*H*-imidazole (**1c**) decomposed when heated.[6]

The 2*H*-imidazoles were prepared by condensing the appropriate ketone with benzil in refluxing acetic acid[2] or *N,N*-dimethylformamide containing excess ammonium acetate. Cyclobutanone yielded only rearranged product (**2a**) and cycloheptanone and cyclooctanone gave the required product together with large amounts of colored products.

We studied the rearrangement by heating samples of the 2*H*-imidazoles, with or without solvent, under nitrogen in sealed ampoules or NMR tubes in a thermostatted microtube furnace. Rate studies were generally carried out in the melt without solvent and measured by integration of the NMR signals of rearranged product relative to the signals of the aromatic protons or the unrearranged reactant. Under nitrogen the reaction showed first-order kinetics to about 5 half-lives at several temperatures. Failure to purge with nitrogen resulted in side reactions, indicated by darkening of the reaction and appearance of many additional peaks in the NMR spectra. The kinetic and activation data are presented in Table I.

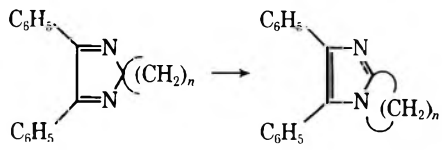
Three mechanisms have been documented for the thermal rearrangements of the analogous carbocyclic geminal dialkylcyclopentadienes and spirodienes. These are (a) a diradical route involving opening of a cycloalkane ring as observed for spiro[2,4]hepta-4,6-diene;[4b,7] (b) a suprafacial and stereospecific [1,5] alkyl shift as reported for *cis*- and *trans*-6,9-dimethylspiro[4,4]nona-1,3-diene;[8] and (c) a radical chain process, observed in geminal dimethyl cyclopentadienes, which competes with b, initiated by dissociation into cyclopentadienyl and methyl radicals.[9] Analogous stepwise and concerted processes are presumably available for 2*H*-imidazoles.

Table I
Kinetic and Activation Data for the Rearrangement of 2*H*-Imidazoles

Compd	Temp, K	k, sec^{-1}	E_a, kcal/mol	$\Delta S^{\ddagger}$, cal/deg mol	Rel rate at 550 K
1b	510	1.11×10^{-3}	44.1	+11	1000
	524	3.49×10^{-3}			
	545	1.90×10^{-2}			
1c	573	3.59×10^{-4}	49.4	+9	4
	582	6.68×10^{-4}			
	593	1.72×10^{-3}			
	601	2.70×10^{-3}			
1d	560	3.32×10^{-4}	45.9	+4	8
	573	8.07×10^{-4}			
	587	2.20×10^{-3}			
1e	555	4.50×10^{-3}	41.9	+3	140
	574	1.57×10^{-2}			
1f	564	5.71×10^{-3}	37.6	−5	100
	581	1.53×10^{-2}			
1g	543	1.87×10^{-3}	39.7	−1	120
	560	5.69×10^{-3}			
	576	1.54×10^{-2}			
3a	588	2.20×10^{-4}	40.5	−7	1
	603	6.66×10^{-4}			
3b	560	9.81×10^{-4}	41.2	−2	25
	573	2.40×10^{-3}			
	583	4.42×10^{-3}			
5a	498	9.33×10^{-5}	39.8	0	175
	513	2.79×10^{-4}			
	528	9.17×10^{-4}			
	543	2.58×10^{-3}			
5b	545	1.52×10^{-3}			
5c	543	6.24×10^{-3}			
5d	543	3.29×10^{-2}			
5e	543	5.92×10^{-4}			

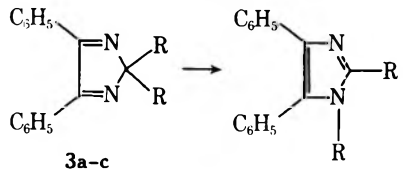
An approximate E_a for the stepwise processes of 67 kcal/mol is obtained, assuming that dissociation is rate determining, by subtracting the gain in stabilization energy in forming the delocalized imidazolyl radical (13 kcal/mol)[10] from the C–C bond dissociation energy (80 kcal/mol).[11a] Heterolytic dissociation would yield a higher value. This result is higher than the experimentally determined values for the 2*H*-imidazoles, which suggests that stepwise processes are not involved in the thermal rearrangements of these compounds. Nonetheless, significant differences in reaction rates (interpolated or extrapolated to 550 K) and activation parameters were observed as a possible consequence of ring strain differences in the polymethylene rings, delocalization and substituent effects in the migrating groups, and medium effects.

The inability of **1a** to withstand the conditions of synthesis and its consequent rearrangement to **2a** may be the result of the 27 kcal/mol strain energy of the cyclobutane ring.[12] Similarly **1b** rearranges 250 times faster than **1c** because of the 6.5 kcal/mol strain in cyclopentane compared with cyclohexane. The carbocyclic analogs show a similar effect: spiro[4,4]nona-1,3-diene rearranges 1000 times faster than spiro[4,5]deca-1,3-diene.[4c] On the other hand, the increased rearrangement rate of **1d–g** parallels the strain in the medium-sized rings. Although the strain in medium rings is generally greater than cyclopentane, the tenfold greater rate of **1b** compared to **1d–g** may be a consequence of differences in conformational rigidity in the transition states.



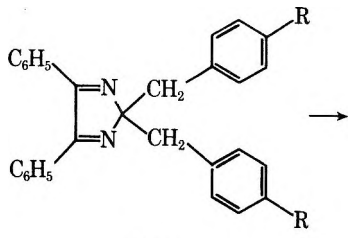
1a-g 2a-g

a, $n = 3$; b, $n = 4$; c, $n = 5$; d, $n = 6$; e, $n = 7$; f, $n = 9$; g, $n = 11$

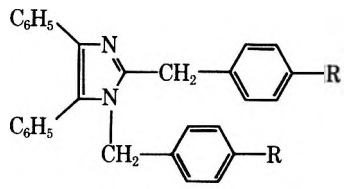


3a-c 4a-c

a, R = CH_3; b, R = C_2H_5; c, R = C_6H_5



5a-e



6a-e

a, R = H; b, R = Cl; c, R = CH_3; d, R = OCH_3; e, R = NO_2

The approximate limiting activation energy can be modified to reflect the ring strain in the reactants, but even this correction results in values of E_a higher than the experimental values. Thus increased ground-state energy due to ring strain does not result in intervention of a stepwise mechanism.

As concerted reactions are synchronous only if bond breaking and making occur at the same rate,[13] departures from synchronous reaction are to be anticipated if the reactants and products have different strain energies. The extent of this departure is difficult to determine in the absence of reliable methods for determining approximate activation energies for synchronous reactions of this kind. One approach has been to equate the extent of strain in the transition state with half of the difference in strain between the reactant and product.[4c] Results of this procedure are equivocal but application of this idea to the present work reveals a parallel between strain differences[14] and the values of $\Delta S^{\ddagger}$. As low values of $\Delta S^{\ddagger}$ are indicative of concerted processes and as strain differences between cycloalkanes and the next larger cycloalkenes decrease with increasing ring size,[12] a shift towards more synchronous reactions occurs as ring size increases.

The rearrangement of **3a** to **4a** and **3b** to **4b**, where considerations of ring strain do not apply, are about 100 times and 5 times slower than, for example, **1g** to **2g**. These differences in rate may be the consequence of anchoring the migrating terminus by the flexible polymethylene chain. Similar differences in migratory aptitudes of methyl and ethyl groups have been observed recently in the case of 2,2-dialkyl-2*H*-indene rearrangements.[15]

We find that the rearrangement of 2*H*-imidazoles is rather insensitive to solvent, so measuring the reaction rates in the melt appears to be a valid procedure. The rearrangement of **1b** and **5a** in a variety of solvents of differing polarity and dielectric constant was carried out and the results are in Table II. In addition the clean first-order kinetics observed while the composition of the melt is changing during a reaction is consistent with a minimal medium effect.

Table II
Effect of Solvent on Rearrangement Rate

Solvent	k_1, sec^{-1} at 470 K: 1b → 2b	k_1, sec^{-1} at 470 K: 5a → 6a
Melt	5.12×10^{-5}	1.50×10^{-5}
Diphenyl ether	4.46×10^{-5}	8.9×10^{-6} [b]
Triphenylmethane		1.4×10^{-5} (8.8×10^{-5})[a]
Benzyl alcohol	8.5×10^{-5} [b]	3.2×10^{-5} [b]
Nitrobenzene	1.37×10^{-4}	5.8×10^{-5} [b]
1,3,5-Trichlorobenzene		4.9×10^{-5}

[a] At 498 K. [b] Followed to about 1 half-life.

We carried out a Hammett $\sigma^+\rho$ investigation of the rearrangement of **5a–e** to **6a–e** at 543 K. The ρ value was −1.15, though the linear correlation was not particularly good (r = 0.92) with marked upward curvature. The small value of ρ obtained here when compared with the large values found for reactions known to involve benzylic carbonium ions[16] argues, at least for this series of compounds, for a concerted mechanism, though the negative slope implies some charge development.

These results do not totally rule out a stepwise mechanism involving radicals, though the greater rate of rearrangement of **5a** compared to, for example, **3a** does not appear to be a consequence of dissociation into resonance-stabilized benzylic and imidazolyl radicals (the benzylic resonance energy is 13 kcal/mol[11b]), as the E_a values are quite similar for these compounds. We have carried out both trapping and crossover experiments to expose the intervention of radicals. Reactions of **3b** and **5a** run in triphenylmethane (molar ratio 1:2) to about 3 half-lives at 560 K failed to reveal any 2-methyl-4,5-diphenylimidazole in the former and any toluene in the latter case. Crossovers between **3a** and **3b** and between **3b** and **5a** were attempted. The disparity in reaction rates was compensated for by

Table III
2*H*-Imidazoles[e]

Compd	% yield	Mp, °C	NMR,[f] δ
1b	73	105–108	2.11 (8 H, s)
1c	66	107–108[a]	1.78 (10 H, s)
1d	60	141–143	1.92 (12 H, s)
1e	38	136–138	1.94 (14 H, s)
1f	48	146–148	1.73 (18 H, s)
1g	80	143–144	1.60 (22 H, s)
3a	75	78–79[b]	1.62 (6 H, s)
3b	50	105–106	0.81 (6 H, t), 2.20 (4 H, q)
5a	60	88–89[c]	2.88 (4 H, s)
5b	80	126–128	2.87 (4 H, s)
5c	40[d]	109–110	2.30 (6 H, s), 2.85 (4 H, s)
5d	30[d]	127–128	2.84 (4 H, s), 3.76 (6 H, s)
5e	40	151–152	2.96 (4 H, s)

[a] Reference 2, 107–108°. [b] Reference 2, 78–79°. [c] Reference 2, 88–89°. [d] *N,N*-Dimethylformamide as reaction solvent. [e] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds in table except **1c**, **3a**, and **5a**, which were not new. Ed. [f] Aryl proton signals omitted.

Table IV
1*H*-Imidazoles[a]

Compd	Mp, °C	NMR, δ[f]
2a	154–155	2.58 (2 H, m), 2.92 (2 H, m), 3.87 (2 H, t)
2b	137–138	1.87 (4 H, m), 2.76 (2 H, m), 3.62 (2 H, m)
2c	138–140[a]	1.81 (6 H, m), 2.80 (2 H, m), 3.56 (2 H, m)
2d	146–148	1.80 (8 H, m), 2.80 (2 H, m), 3.58 (2 H, m)
2e	140–143	1.68 (10 H, m), 2.76 (2H, m), 3.65 (2 H, m)
2f	146–147	1.46 (14 H, m), 2.74 (2 H, m), 3.68 (2 H, m)
2g	146–148	1.37 (18 H, m), 2.68 (2 H, t), 3.72 (2 H, t)
4a	121–122[b]	2.38 (3 H, s), 3.32 (3 H, s), 7.30 (10 H, m)
4b	126–128	1.09 (3 H, t), 1.41 (3 H, t), 2.52 (2 H, q), 3.70 (2 H, q)
6a	147–148[c]	3.88 (2 H, s), 4.46 (2 H, s)
6b	131–134	3.87 (2 H, s), 4.50 (2 H, s)
6c	117–119	2.31 (6 H, s), 3.80 (2 H, s), 4.40 (2 H, s)
6d	131–133	3.72 (2 H, s), 3.81 (6 H, s), 4.38 (2 H, s)
6e	159–161	4.06 (2 H, s), 4.68 (2 H, s)

[a] 138–140°. [b] 121–122°. P. Beak and J. L. Meisels, *J. Am. Chem. Soc.*, **89**, 2375 (1967). [c] 147–148°, ref 2. [d] Satisfactory analytical values were reported for all compounds in table except **2c**, **4a**, and **6d**, which were not new. Ed. [e] Aryl proton signals omitted.

using a reactant ratio favoring the less reactive component. Inside the limits of the analytical methods no crossover was detected. Trapping of radicals, however, has not been realized in those cases where their intervention has been proved in similar rearrangements.[3,9]

We conclude that thermal rearrangement of 2*H*-imidazoles is concerted but not necessarily synchronous.

Experimental Section

General. NMR spectra were obtained on Varian T-60 or Jeol Minimar 100 spectrometers in carbon tetrachloride or deuteriochloroform with tetramethylsilane as internal standard. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. GLC was done with an Aerograph 600C with flame ionization and mass spectra were obtained on a Varian EM-600 with direct inlet.

Reactants. These were prepared as described by Weiss.[2] A molar ratio of benzil, ketone, and ammonium acetate of 1:1:10 in glacial acetic acid (2.5 *M* in ammonium acetate) gave optimum yields. Products were purified by recrystallization from aqueous methanol or benzene–petroleum naphtha. Colored by-products occurred in all preparations. For **1d** and **1e** these constituted a significant portion of the crude reaction product. Table III contains data for the 2*H*-imidazoles.

Products. Samples of the appropriate 2*H*-imidazoles (0.5–1.0 g) were heated in nitrogen-purged, evacuated ampoules for about 30–90 min at about 550 K followed by recrystallization from aqueous methanol. The products were isolated in 70–80% yield. Data for the 1*H*-imidazoles are in Table IV.

Kinetic Procedure. Approximately 50 mg of the 2*H*-imidazole was placed in each of six NMR tubes which were purged with nitrogen and capped. The tubes were inserted in a multiposition thermostatted microtube furnace to within 0.5 cm of the cap. Tubes were withdrawn at noted times and quenched in ice water and the contents were dissolved in a suitable solvent. NMR spectra were recorded and the integrals of the signals were carefully and reproducibly determined. Reactions in solution were carried out in nitrogen-purged, evacuated ampoules at about 1 *M* concentration. The contents of the ampoules were diluted with deuteriochloroform and the NMR spectra were recorded as previously.

Calculations. The first-order rate constants were determined from plots of $\log a/(a-x)$ vs. time, where x is the normalized integral of the downfield protons on the methylene groups at positions 1 and 2 ($>NCH_2-$ and $=CCH_2$) in the product and a is 4 (6 in the case of **3a**), the number of protons on the methylene groups at position 2 [$>C(CH_2)_2$] of the reactant. The phenyl protons served as an internal standard of ten protons. Alternatively for **3a** and **5a–e**, a was the integral of the total aliphatic protons and x was the integral of those due to the product, occurring at lower field. All runs were replicated and the rate constants showed a precision of ±3%. E_a and $\Delta S^{\ddagger}$ were determined as described by Bunnett[17] and were judged to be within ±0.5 kcal/mol and ±2 cal/deg mol, respectively.

Trapping and Crossover Experiments. Mixtures of **3b** or **5a** in triphenylmethane (molar ratio 1:2) were heated in evacuated ampoules at 560 K for about 3 half-lives (10–30 min). For **3b** the contents were examined by TLC (SiO_2 or Al_2O_3 with benzene, methylene chloride, or ethyl acetate elution). Only **3b**, **4b**, and triphenylmethane were detected; no 2-ethyl-4,5-diphenylimidazole was found. An independent test showed that it could have been detected if present in <5% concentration. For **5a** examination of the contents of the ampoule by GLC (6 ft × 0.125 in., 5% XF-1150 on Gaskrom Q at 125°) or MS failed to reveal any toluene.

Mixtures of **3a** and **3b** (molar ratio 5:1) and **3b** and **5a** (molar ratio 4:1) were ground in a mortar and loaded into ampoules which were purged with nitrogen, evacuated, and sealed. After heating at about 590 K for 30–90 min the contents of the ampoules were examined by TLC (SiO_2 with elution by benzene or methylene chloride). Only reactants and expected products were detected in each case. Independent tests showed that the crossover products, 1-methyl-2-ethyl-4,5-diphenylimidazole and 1-ethyl-2-benzyl-4,5-diphenylimidazole, were separable from the other products and could be detected if present in < 5% concentration.

Registry No.—**1b**, 55682-24-1; **1c**, 5396-98-5; **1d**, 55682-25-2; **1e**, 55682-26-3; **1f**, 55682-27-4; **1g**, 55682-28-5; **2a**, 55682-29-6; **2b**, 55682-30-9; **2c**, 16340-54-8; **2d**, 55682-31-0; **2e**, 55682-32-1; **2f**, 55682-33-2; **2g**, 55682-34-3; **3a**, 31839-62-0; **3b**, 55682-35-4; **4a**, 16340-59-3; **4b**, 55682-36-5; **5a**, 55682-37-6; **5b**, 55682-38-7; **5c**, 55682-39-8; **5d**, 55682-40-1; **5e**, 55682-41-2; **6a**, 55682-42-3; **6b**, 55682-43-4; **6c**, 55682-44-5; **6d**, 55682-45-6; **6e**, 55682-46-7.

References and Notes

(1) Abstracted in part from the B.S. (Honors) Thesis of T.R.F., Hobart College, 1974.
(2) M. Weiss, *J. Am. Chem. Soc.*, **74**, 5193 (1952).
(3) J. W. de Haan and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **84**, 1594 (1965); **87**, 298 (1968).
(4) (a) B. A. Kazanskii, E. V. Sobolev, V. T. Aleksanyan, L. A. Nakhapetyan, and M. Yu, *Dokl. Akad. Nauk SSSR*, **159**, 839 (1964); (b) J. M. E. Krekels, J. W. de Haan, and H. Kloosterziel, *Tetrahedron Lett.*, 2751 (1970); (c) L. M. Dané, J. W. de Haan, and H. Kloosterziel, *ibid.*, 2755 (1970).
(5) J. M. Patterson, J. D. Ferry, J. W. de Haan, and M. R. Boyd, *J. Am. Chem. Soc.*, **97**, 360 (1975).
(6) The nomenclature in this article, while not always conforming to *Chemical Abstracts* conventions, allows ready comparison between reactants and products.
(7) E. T. McBee, J. A. Bosoms, and C. J. Morton, *J. Org. Chem.*, **31**, 768 (1966); P. H. Mazzocchi, *Tetrahedron Lett.*, 989 (1969).
(8) M. A. M. Boersma, J. W. de Haan, H. Kloosterziel, and L. J. M. Van de Ven, *Chem. Commun.*, 1168 (1970).
(9) M. R. Willcott, III, and I. M. Rathburn, III, *J. Am. Chem. Soc.*, **96**, 938 (1974).
(10) A. F. Bedford, P. B. Edmondson, and C. T. Mortimer, *J. Chem. Soc.*, 2927 (1962); M. J. S. Dewar, A. J. Harget, and N. Trinajstic, *J. Am. Chem. Soc.*, **91**, 6321 (1969).
(11) S. W. Benson, "Thermochemical Kinetics", Wiley, New York, N.Y., 1968: (a) p 215; (b) p 86.
(12) Data for ring strain is from P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.*, **92**, 2377 (1970), and E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 180.

(13) K. N. Houk, "Survey of Progress in Chemistry", Vol. 6, A. F. Scott, Ed., Academic Press, New York, N.Y., 1973, p 128.
(14) Strain in the carbocyclic rings of the 2,2-polymethylene-2*H*-imidazoles should correlate with the cycloalkanes. In the absence of data for the analogs of 1,2-polymethylene-1*H*-imidazoles (lactams) cis cycloalkenes can be used noting that the rigid cis double bond represents the fusion to the imidazole ring.
(15) W. R. Dolbier, Jr., L. McCullagh, D. Rolison, and K. E. Anapolle, *J. Am. Chem. Soc.*, **97**, 934 (1975).
(16) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, p 208.
(17) J. F. Bunnett in "Techniques of Organic Chemistry", S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N.Y., 1961, p 199.

On the Regioselectivity of Lewis Acid Catalyzed Diels–Alder Reactions of Methylcyclopentadiene[1]

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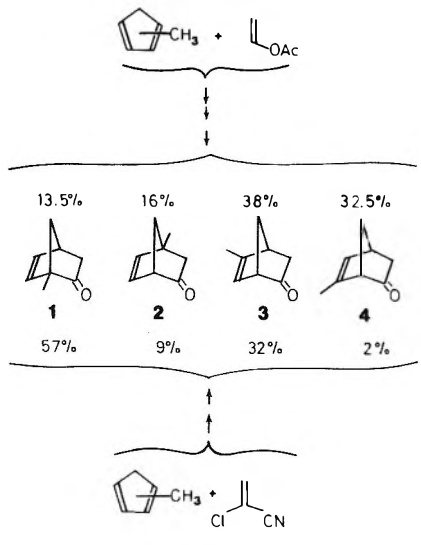
In connection with our investigation of bicyclic systems, 1-methyl-5-norbornen-2-one (1) was of interest as a precursor for 1,2-dimethyl-5-norbornen-2-yl derivatives. This compound had been obtained earlier, together with 4- (2), 5- (3), and 6-methyl-5-norbornen-2-one (4), by the Diels–Alder reaction of methylcyclopentadiene and vinyl acetate at 180° followed by a two-step conversion of the adduct to the ketone mixture (lithium aluminum hydride reduction followed by oxidation).[2] However, as shown by the upper part of Chart I, the desired isomer is the minor component of the mixture and thus this did not appear to be a suitable approach for preparing large amounts of 1. From the 1:2 and 3:4 ratios it is clear that very little regioselectivity is observed for the uncatalyzed Diels–Alder addition of 1- and 2-methylcyclopentadiene.

Chart I



The equilibrium composition of the three isomeric methylcyclopentadienes is 45% 1-methyl-, 54% 2-methyl-, and 1% 5-methylcyclopentadiene.[3] The formation of over twice as much 3 + 4 as 1 + 2 shows that there is considerable isomerization of 1-methyl- to 2-methylcyclopentadiene which leads to unwanted isomers.

From various reports in the literature [4-6] it appeared that regioselectivity as well as rate should be increased by Lewis acid catalysts, and we now report that this is indeed the case. As shown by the lower part of Chart I, the cupric fluoroborate[7] catalyzed Diels–Alder reaction of the equilibrium mixture of the isomeric methylcyclopentadienes and α-chloroacrylonitrile in benzene at 0–5°, followed by hydrolysis, gives a mixture containing 57% of the desired ketone (1) together with 9% 2, 32% 3, and 2% 4. Only trace amounts of unidentified contaminants were detected by GC. Satisfactory yields of pure 1 could be obtained by careful fractionation.

Comparison of the 1:2 and 3:4 ratios for the catalyzed and uncatalyzed reactions shows that cupric fluoroborate causes a remarkable increase in regioselectivity as well as in rate. Similar results have been reported for other dienes and the earlier interpretations[4,6] appear adequate for the present case.

It is noteworthy that the (1 + 2):(3 + 4) ratios show that 2-methylcyclopentadiene is more reactive than the 1-methyl isomer for the high-temperature uncatalyzed reaction whereas the reverse is true for the catalyzed reaction. Also, the amount of 1 + 2 obtained from the catalyzed reaction, relative to the amount of the 1-methyl isomer in the diene, suggests that there is isomerization of 2-methylcyclopentadiene to the 1-methyl isomer under the conditions of the catalyzed Diels–Alder reaction.

Experimental Section

1-Methyl-5-norbornen-2-one (1). Monomeric methylcyclopentadiene was prepared just before use by distillation of methylcyclopentadiene dimer. In a typical experiment a solution of 40 g (0.50 mol) of methylcyclopentadiene, 175 g (2 mol) of α-chloroacrylonitrile, and 75 ml of benzene[8] was cooled to 0–5° and 35.6 g (0.15 mol) of dry cupric fluoroborate was added slowly. The reaction mixture was stirred for 4 hr at 0–5°, after which brine containing sodium potassium tartrate was added. The resulting mixture was extracted with ether. After concentration of the ether extract under reduced pressure 500 ml of dimethyl sulfoxide was added to the residual oil. A hot solution of 1.25 mol of potassium hydroxide in 50 ml of water was added to the dimethyl sulfoxide solution and the resulting mixture was stirred at room temperature for 10 hr, after which the mixture was washed with water and extracted with ether. The ether extract was dried ($MgSO_4$) and the ether was removed under reduced pressure. Capillary GC (SE-30, 100 ft, 80°) showed that the residual oil consisted of 1, 4- (2), 5- (3), and 6-methyl-5-norbornen-2-one (4) in a ratio of 57:9:32:2. Only trace amounts of unidentified contaminants were present. Distillation of the crude product, 46–53° (10 mm), gave 50 g (82%) of a colorless mixture of the four products. All ketones were isolated in pure form by preparative GC (10% Carbowax, 10 ft, 80°) and identified by the NMR spectra, which corresponded in detail to the NMR data reported earlier.[2b] The desired ketone (1) is the most volatile isomer and can be separated and purified by fractionation with a spinning band column, bp 46–47° (10 mm), NMR (CCl_4) δ 6.46 (q, 1 H), 5.72 (d, 1 H), 3.05 (s, 1 H), 1.68–2.24 (m, 4 H), 1.2 (s, 3 H).

Registry No.—1, 19740-13-7; 2, 22405-38-5; 3, 22405-40-9; 4, 19740-15-9; methylcyclopentadiene, 26519-91-5; α-chloroacrylonitrile, 920-37-6.

References and Notes

(1) This work was supported by the National Science Foundation (GP-6555X) and the Air Force Office of Scientific Research (AFOSR-71-1974).
(2) (a) H. Krieger and S.-E. Mason, *Suom. Kemistil. B*, **43**, 318 (1970); (b) S.-E. Mason and H. Krieger, *ibid.*, **42**, 3 (1969).
(3) S. McLean and P. Haynes, *Tetrahedron Lett.*, 2385 (1964).
(4) T. Inukai and T. Kojima, *J. Org. Chem.*, **36**, 924 (1971), and references cited therein.
(5) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(6) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, **24**, 2575 (1968); K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).
(7) (a) E. J. Corey, N. H. Weinshenker, T. K. Schaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969); (b) E. J. corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971).
(8) The benzene facilitates isolation of the products.

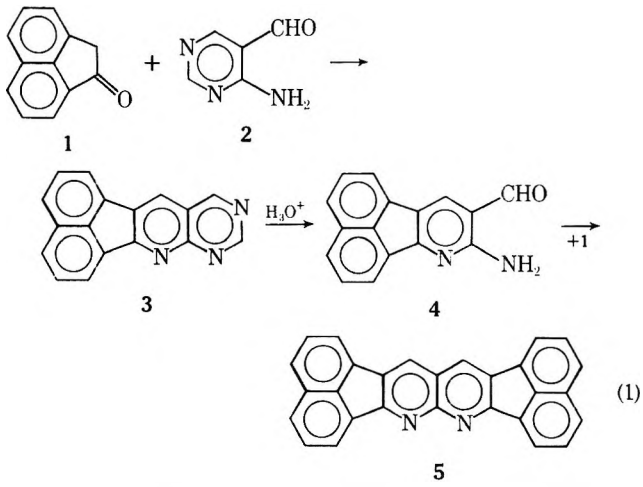
A New Annelation Sequence. Polycondensed 1,8-Naphthyridines

Summary: Friedländer condensations of compounds containing the ortho aminoaldehyde functional groups—readily obtained from aromatic cyclic ketones and 4-aminopyrimidine-5-carboxaldehyde—with aromatic ketones leads to symmetrically and nonsymmetrically fused 1,8-naphthyridines with equal ease.

Sir: The object of the research which is outlined herein has been the development of a general synthetic method for the introduction of the 1,8-naphthyridine heterocyclic ring system into fused polycyclic frameworks of different architecture. The remarkable properties and stability of "black orlon"—itself composed of a linearly annelated sequence of partially oxygenated 1,8-naphthyridine units[1]—made synthesis of such systems desirable.

Incorporation of this heterocyclic system into larger units has met with limited success even in the case of simple benzo-fused systems.[2] The reported obstacles[3] of converting oxo or amino functional groups into the unsubstituted heterocyclic unit made the one-step construction of the unsubstituted 1,8-naphthyridine moiety imperative. The Friedländer condensation of compounds containing the ortho aminoaldehyde functional groups offers such opportunity. This report describes a facile annelation sequence leading to fused 1,8-naphthyridines starting from readily accessible aromatic keto methylenes.

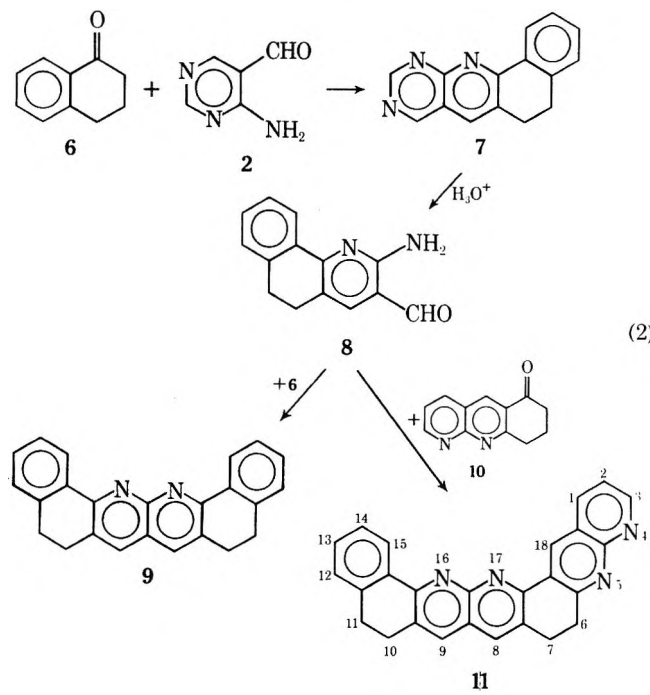
The synthetic strategy relies on our earlier observation[4] that pyrido[2,3-*d*]pyrimidines can be used as latent 2-aminonicotinaldehydes by acid-catalyzed hydrolysis of their pyrimidine moiety. It became thus necessary to first assemble fused polycyclic systems containing a terminal pyrimidine moiety. This was achieved by Friedländer condensation of 4-aminopyrimidine-5-carboxaldehyde (**2**) and aromatic cyclic keto methylenes as illustrated in eq 1.



(1)

To a refluxing ethanolic solution of acenaphthenone and **2** were added a few drops of methanolic KOH (20%); a precipitate was formed within a few minutes. The reaction mixture was further refluxed for 12 hr to give acenaphtho[1′,2′:5,6]pyrido[2,3-*d*]pyrimidine (**3**) in 95% yield, mp 269–270°.[5] Covalent hydration[6] of **3** followed by irreversible ring opening of the pyrimidine moiety, carried out by heating in 2 *N* HCl for 4 hr, provided 8-aminoacenaphtho[1,2-*b*]pyridine-9-carboxaldehyde (**4**) in 95% yield, mp 215–217.[5] This newly formed ortho aminoaldehyde was readily recondensed with starting acenaphthenone to form diacenaphtho[1,2-*b*:1′,2′-*g*]-1,8-naphthyridine (**5**) in quantitative yield, mp 422 (bright yellow needles from pyridine).[5]

A similar sequence of Friedländer condensations was followed in the synthesis of the hexacyclic 1-phenanthridino[2,3-*b*]-1-phenanthridine (**9**) using α-tetralone in the consecutive cyclizations as outlined in eq 2.



(2)

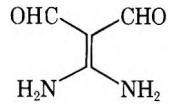
Friedländer condensation of **2** with the less reactive α-tetralone resulted in the formation of 5,6-dihydropyrimido[4,5-*b*]-1-phenanthridine in 85% yield, mp 223.5–224°.[5] Hydrolytic cleavage of this heterocyclic system was best carried out in dilute hydrochloric acid (0.01 *N*) to generate the highly fluorescent 2-amino-5,6-dihydro-1-phenanthridine-3-carboxaldehyde (**8**) in 90% yield, mp 130.5–131°.[5] Reutilization of α-tetralone in the second Friedländer condensation gave **9** in 90% yield, mp 255–256°.[5]

The isolation of compounds containing the ortho aminoaldehyde functional group in this annelation sequence allows for the synthesis of nonsymmetrical, fused 1,8-naphthyridines as exemplified by the facile synthesis of the heptacyclic 6,7,10,11-tetrahydro(1-phenanthridino)[2,3-*b*]pyrido[2,3-*j*]-1,7-phenanthroline (**11**) from α-tetralone and 6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**10**).[7] To a refluxing solution of **8** and **10** in ethanol were added a few drops of methanolic KOH (20%). A precipitate formed slowly. The mixture was refluxed for 48 hr to yield **11** in 85% yield, mp 329° dec.[5]

The key step in this annelation sequence leading to polycondensed 1,8-naphthyridines is the use of cyclic keto methylenes for the introduction of the pyrido[2,3-*d*]pyrimidine moiety in a polycondensed framework (Friedländer condensations of 4-aminopyrimidine-5-carboxaldehyde represent a new and facile entry into such systems) and

reuse of the same functionality in a second ring formation reaction. This two-step sequence can therefore be directed with equal ease to the synthesis of symmetric and nonsymmetric polycondensed 1,8-naphthyridines depending on whether or not the same ketone is supplied in the second condensation. The general availability of cyclic keto methylenes ensures a successful application of this new sequence for a multitude of polycondensed systems.

Finally, it is interesting to note that this sequence formally represents a double Friedländer condensation of aromatic keto methylenes with the unknown diaminomethylene malonaldehyde.



Acknowledgment. This research was sponsored by the U.S. Army Research Office—Durham, N.C. We wish to express appreciation to Professor M. Szwarc without whose help this investigation would not have been possible. We thank Dr. G. Evens for carrying out some preliminary experiments.

Supplementary Material Available. Experimental details and full analytical and spectroscopic data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2566.

References and Notes

(1) C. G. Overberger and J. A. Moore, *Adv. Polym. Sci.*, **7**, 125–127 (1970), and references cited therein.
(2) C. V. Wilson, "Chemistry of Heterocyclic Compounds", Vol. 12, Arnold Weissberger, Ed., Interscience, New York, N.Y., 1958, pp 91–99.
(3) J. V. Crawford and E. R. Webster, "Chemistry of Heterocyclic Compounds", Vol. 2, Arnold Weissberger, Ed., Interscience, New York, 1951, pp 117–119.
(4) G. Evens and P. Caluwe, *J. Org. Chem.*, **40**, 1438 (1975).
(5) See paragraph at the end of paper regarding supplementary material.
(6) For a review on covalent hydration, see A. Albert and W. L. F. Armarego, *Adv. Heterocycl. Chem.*, **4**, 1 (1965).
(7) T. G. Majewicz and P. Caluwe, unpublished work.

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Neighboring Group Assistance in Azabicyclic Derivatives. Tremendous Rate Accelerations in 2-Aza-6-halobicyclo[2.2.2]- and 6-Aza-4-halobicyclo[3.2.1]octanes

Summary: The incorporation of a nitrogen atom into the 2 position of bicyclo[2.2.2]octane and the 6 position of bicyclo[3.2.1]octane results in exceptional solvolytic rate enhancements (up to 10^9) of halo substituents located 1,3 from the nitrogen compared to similar carbon–carbon σ bond participation and 1,3-nitrogen participation in alicyclic compounds.

Sir: Although considerable effort has been devoted to investigations of participation and skeletal rearrangements in carbobicyclic structures,[1] relatively limited attention has been accorded analogous systems containing heteroatoms[2–4] in spite of the well-established ability of several atoms to offer neighboring group assistance in solvolytic and related reactions.

Table I
Rates of Solvolysis of Azabicyclic and Related Compounds in 80% Aqueous Ethanol

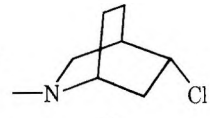
Compd	Temp, °C	k, min^{-1}	Rel rate
1	0	8.53	4×10^8
2	75	4.48×10^{-6}	1[a]
3	0	6.22×10^{-5}	2.4×10^3
4	85	2.5×10^{-3}	2.8×10^{2}[a]
5	0	>42	1.7×10^9
6	0	>42	1.7×10^9

[a] Corrected to 0°.

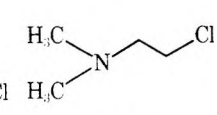
We wish to report that the incorporation of a nitrogen into the 2 position of bicyclo[2.2.2]octane and the 6 position of bicyclo[3.2.1]octane results in exceptional solvolytic rate enhancement of halo substituents located cross-ring and exo compared to similar carbon–carbon σ bond participation in these systems and even analogous 1,3-nitrogen participation in alicyclic compounds. Table I presents rate data for a variety of compounds chosen to compare various participation possibilities in bicyclic derivatives (**1**, **2**, **4–6**) and the open-chain equivalent (**3**). As evident, the ability of nitrogen to enhance the solvolysis of a 6-*exo*-chloro group is phenomenal, the rate being over 10^8 *as fast as a 5-chloro substituent and ca.* $\sim 10^5$ *as fast as N,N-dimethylamino-2-chloroethane (3)*! The effect on a 6-bromo substituent is equally dramatic. Both the bicyclo[2.2.2] and the bicyclo[3.2.1] compounds **5** and **6** were solvolyzed so rapidly (half-lives <1 sec at 0°) that accurate rate data could not be obtained. Nevertheless, a lower limit estimate of $\sim 10^9$–10^{10} compared with **2** illustrates that nitrogen possesses super assisting ability in these systems.

Compounds **5** and **6** (and to a lesser extent **1**) were so reactive in the free amine state that they could be isolated only as the HBr salts **5a** and **6a**.[5] Treatment of either **5a** or

1
1a HCl salt



2
2a HCl salt



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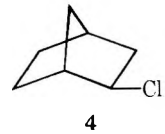
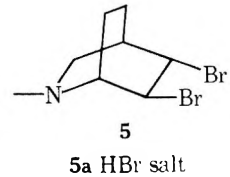
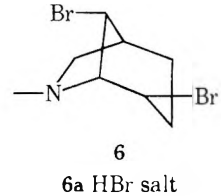
3a HCl salt



4

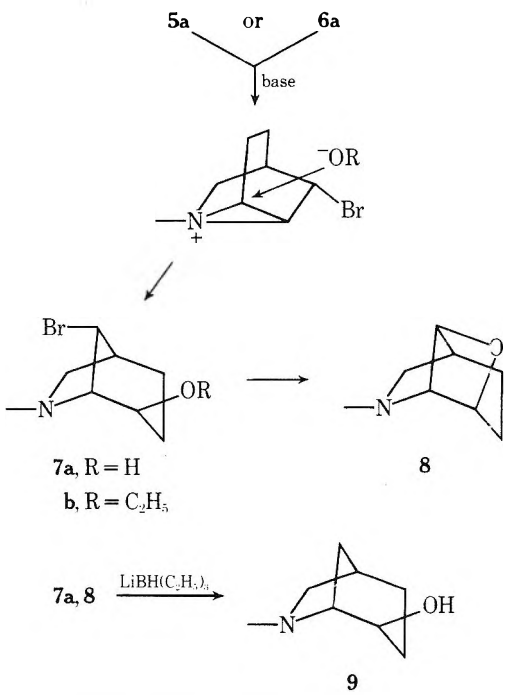


5
5a HBr salt



6
6a HBr salt

6a with ethanolic ethoxide or hydroxide in aqueous *tert*-butyl alcohol initially gave the *exo*-4-hydroxy derivative **7a** with the latter reagent or the corresponding ethyl ether **7b** with the former. The hydroxy compounds **7a** was converted to the tricyclic ether **8** upon longer reaction time. Reduction of either **7a** or **8** with lithium triethylborohydride ("Super-hydride")[7] afforded 4-*exo*-hydroxyl-2-methyl-2-azabicyclo[3.2.1]octane (**9**).[8] Evidently, release of the free amine by base results in rapid formation of the cyclic aziridinium ion which is opened by base to the more stable bicyclo[3.2.1] derivative **7a**. Further reaction with base furnishes the ether **8** by internal cyclization.



The astounding rate enhancement observed for **1a**, **5a**, and **6a** is reminiscent of the acceleration found for bicyclic α-amino halides compared with carbocyclic analogs ($\sim 10^3$–10^8)[2g-i] and the observation that most α-amino halides exist in the iminium salt form.[9] Apparently, favorably disposing nitrogen for displacement of halogens results in extremely rapid reactions. In the present case, locking the geometry such that the departing halogen and the attacking nitrogen are rigidly held antiplaner provides an especially favorable orientation for facile participation.[10]

Acknowledgment. The authors wish to express their gratitude to Dr. Grant Krow for a spectrum of **9** and helpful discussions. L.R. expresses his thanks to NDEA for a fellowship.

Supplementary Material Available. The synthesis and characterization of the compounds employed in this investigation along with other experimental details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2567.

References and Notes

(1) For reviews and discussions of the voluminous studies concerning participation and rearrangements in bicyclo systems and the attendant controversy concerning the nature of the intermediates see (a) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N.Y., 1963, Part I, p 213; (b) G. A. Olah and P. v. R. Schleyer, Ed., "Carbonium Ions," Wiley, New York, N.Y., 1972, Vol. III; (c) G. D. Sargent, Quart. Rev. (*London*), **20**, 301 (1966); (d) P. D. Bartlett, Ed., "Nonclassical Ions," W. A. Benjamin, New York, N.Y., 1965; (e) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972.

(2) For examples of investigations suggesting assistance by nitrogen in bicyclic systems see (a) J. W. Huffman, T. Kamiya, and C. B. S. Rao, *J. Org. Chem.*, **32**, 700 (1967); (b) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Am. Chem. Soc.*, **79**, 6337 (1957), and **80**, 4677 (1958); (c) S. Archer, T. R. Lewis, M. R. Bell, and J. W. Schulenberg, *ibid.*, **83**, 2386 (1961); (d) J. D. Hobson and W. D. Riddell, *Chem. Commun.*, 1180 (1968); (e) G. Büchi, D. L. Coffen, K. Kocis, P. E. Sounet, and F. E. Ziegler, *J. Am. Chem. Soc.*, **88**, 3099 (1966); (f) L. A. Paquette and J. F. Kelly, *J. Org. Chem.*, **36**, 442 (1971); (g) H. O. Krabbenhoft, J. R. Wiseman, and C. B. Quinn, *J. Am. Chem. Soc.*, **96**, 258 (1974); (h) R. D. Fisher, T. D. Bogard, and P. Kovacic, *ibid.*, **94**, 7599 (1972), and **95**, 3646 (1973); (i) P. G. Gassman, R. L. Cryberg, and K. Shudo, *ibid.*, **94**, 7600 (1972).

(3) Pertinent studies of rearrangement and participation of oxygen containing bicyclics include (a) J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, **79**, 2533 (1957); (b) L. A. Paquette and P. C. Storm, *ibid.*, **92**, 4295 (1970); (c) L. A. Spurlock and R. G. Fayter, Jr., *ibid.*, **94**, 2707 (1972); (d) J. Wolinsky, R. O. Hutchins, and J. H. Thorstenson, *Tetrahedron*, **27**, 753 (1971).

(4) R. E. Ireland and H. A. Smith, *Chem. Ind.* (*London*), 1252 (1959), invoked sulfur involvement in the solvolysis of 8-thiabicyclo[3.2.1]octyl derivatives.

(5) Bromination of the parent alkene 2-methyl-2-azabicyclo[2.2.2]oct-5-ene in CCl_4 followed by treatment of the resulting dibromo-*N*-bromine complex with acetone gave **5a**. Refluxing **5a** in acetone gave essentially complete conversion to the rearranged salt **6a**. A similar predominance of the [3.2.1] over the [2.2.2] ring system was noted by Huffman and coworkers[2a] with isoquinuclidones. Apparently, the bicyclo[3.2.1] skeleton is the more thermodynamically stable as is the case with the carbocyclic analog.[6] However, Büchi has observed[2e] that nitrogen migrations in certain iboga alkaloid intermediates favor the bicyclo[2.2.2] system. Ostensibly, other (probably steric) factors play a decisive role in determining the stability in these complex derivatives.

(6) P. v. R. Schleyer, K. R. Blanchard, and C. D. Woody, *J. Am. Chem. Soc.*, **85**, 1358 (1963).

(7) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **95**, 1669 (1973); S. Krishnamurthy, R. M. Schubert, and H. C. Brown, *ibid.*, **95**, 8486 (1973).

(8) An ir spectrum of authentic **9** was kindly supplied by Professor Grant Krow (Temple University); cf. P. G. Gassman and J. H. Dygos, *Tetrahedron Lett.*, 4745 (1970).

(9) H. Bohme and K. Osmers, *Chem. Ber.*, **105**, 2237 (1972), and references cited therein.

(10) The importance of bond allignment in rearrangements of bicyclic systems has recently been discussed; cf. A. Nickon and R. C. Weglein, *J. Am. Chem. Soc.*, **97**, 1271 (1975).

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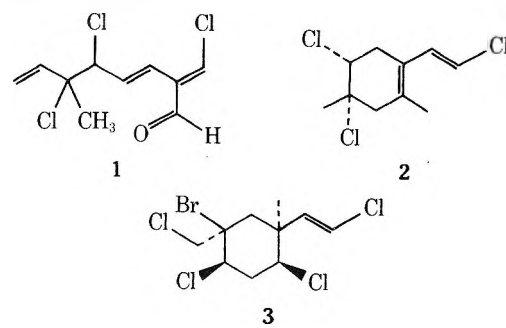
Plocamene B, a New Cyclic Monoterpene Skeleton from a Red Marine Alga

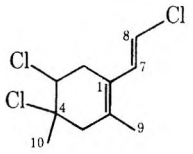
Summary: A nonisoprenoid trichloromonoterpene, plocamene B, has been isolated and characterized from Northern California collections of the red alga *Plocamium violaceum*.

Sir: Very recently we reported an acyclic polychlorinated monoterpene aldehyde **1** as a major component from the red alga *Plocamium cartilagineum*.[1] Our observation that semipurified extracts from this alga possess marked antiinsecticidal activity against mosquito larvae[2a] prompted us to examine a related, less common alga, *P. violaceum*. We report below the characterization of a major metabolite from this latter alga, plocamene B (**2**), which has a nonisoprenoid monoterpene skeleton and displays moderate toxicity to lab test fish.[2b]

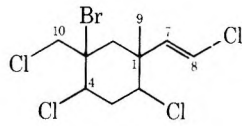


Collections were made of *P. violaceum* in the fall of 1974 [week of Sept 15] from several different intertidal locations north of Santa Cruz. Separate extractions ($CHCl_3$) of each batch of frozen thalli yielded about equal amounts of essential oils. Preliminary analysis of the crude, nonpolar fractions for halomonoterpenes by GC/MS showed (see

Table I
CMR Data at 25.1 MHz



2



3

Carbon	Ppm[a]	J (Hz)[b]	Pattern[c]	Carbon	Ppm	J (Hz)	Pattern
9	18.4	128.4	q	10	38.8	155.7	t
10	30.3	129.4	q	9	27.4	129.4	q
6	34.5	127.0	t	3	38.3	134.3	t
3	48.5	127.0	t	6	48.8	131.7	t
5	64.1	148.9	d	4	64.1	146.5	d
4	69.3		s	5	71.3		s
8	117.7	194.1, 9.8	dd	8	119.5	192.9, 9.8	dd
1,2	123.8		s	1	42.0		s
	129.8		s	2	59.0	146.5	d
7	130.3	162.1, 13.4	dd	7	135.4	156.1	br d

[a] Relative to TMS ($CDCl_3$ solvent). [b] Error, ±1 Hz. [c] From ^1H coupled spectra.[6]

paragraph at end of paper regarding supplementary material) that the relative levels of the major components varied significantly between collection locations. Although the origin of this effect is at present unclear, this observation was useful in facilitating our isolation work.

Chromatographic purification (silica gel column) of the oil from *P. violaceum* of Davenport Landing gave fractions which were further purified by HPLC (Porasil-A). This procedure enabled isolation of the two major components which were both crystalline. The major compound of shortest GC retention time (mp 100–101°, $[\alpha]_D$ −48°) was unknown, and support of our assignment as structure **2** is presented below.[3] The longer retention time component had spectral properties[4] and mp 70–71° ($[\alpha]_D$ −81°) identical with violacene (**3**) recently reported from *Plocamium*.[5]

The mass spectrum of plocamene B [*m/e* 238, 240, 242, 244; 203, 205, 207; 167 (base peak), 169; 131] required the formula $C_{10}H_{13}Cl_3$. The appearance of four vinyl carbons, including two quaternary ones, in the ^{13}C NMR of plocamene B (Table I) together with its molecular formula required a monocyclic constitution. Moreover, a substituted diene chrompohore was implied by its uv λ_{max} (EtOH) 245 nm (ε 16,000). Close inspection of its ^1H NMR at 100 MHz (Figure 1, benzene-d_6) confirmed the presence of 13 H's of

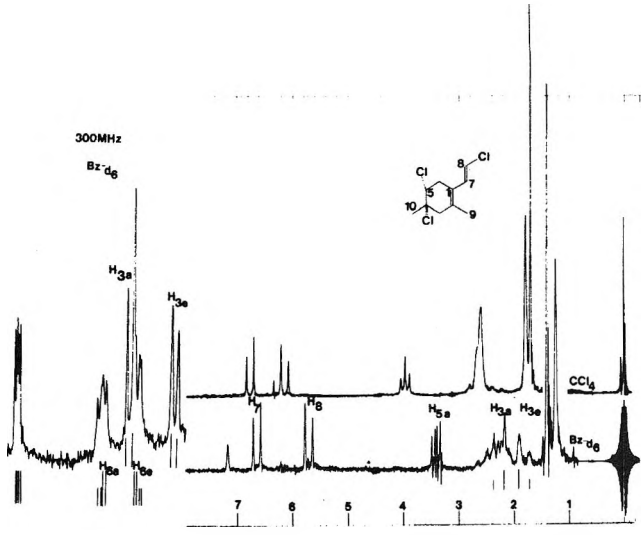
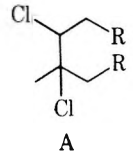


Figure 1. NMR spectra of plocamene B (**2**) at 100 and 300 MHz.

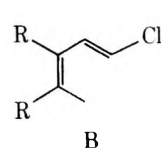
the following subgroups: (a) quaternary CH_3 (δ 1.4); (b) allylic CH_3 (1.22); (c) isolated $-CH_2-$, AB quartet [1.8 and 2.3δ (J = 17 Hz)]; (d) a $-CHXCH_2-$ ABX pattern [1.6–2.6 and 3.35 (J = 20, 10.0, 5.5 Hz)]; and (e) an (*E*)-vinyl AB quartet [5.5 and 6.6 (J = 13.5 Hz)]. Further verification of the above interpretation for the region δ 1.6–2.6 as an overlapping AB and ABX pattern was achieved via a 300-MHz ^1H NMR spectrum. This spectral region was first order at that higher frequency, and J's could be determined by direct measurement. Finally, the distinct broadening observable for the allylic methyl relative to the quaternary methyl concurrent with enhanced half-width of the highfield AB doublet relative to the one at lower field must arise from long range coupling.

A full assignment of the ^{13}C NMR of plocamene B (Table I) was aided by considering both δ and J_{CH} values. The direct J_{CH} data in Table I were obtained by comparison of the broad-band ^1H CW decoupled spectra to the ^1H coupled spectra obtained via a pulse decoupling technique.[6] A knowledge of J_{CH} enables an unambiguous distinction of carbons of similar chemical shift and constitution, but of differing substituent electronegativity.[7] As an example, the (*E*)-vinyl double bond of **2** shows carbon resonances at 117.7 and 130.3 ppm which display J_{CH} = 194.1 and 162.1 Hz, respectively. Based on those observed J's, these peaks could be assigned as shown in the table. A reverse assignment, on the other hand, might have been predicted on the basis of chemical shifts and multiplicities alone.[8]

The carbon shifts of plocamene B (**2**) were remarkably similar to those observed for violacene (**3**). Consequently, the combined spectral data for **2** were most consistent with the two partial structures shown below as A and B. The structure elucidation now involved determination of both the regiochemistry of the ring connection between fragments A and B and the relative stereochemistry between the adjacent chiral centers in fragment A.



A



B

The NMR data provided a means for directly addressing each of these questions. Union of A and B to give a 1,3-

dimethyl orientation as in structure 2 provides a constitutional arrangement consistent with the long range coupling between the equatorial H_{3e} and the vinyl CH_3.[9] The J's between H_5 and the adjacent $-CH_2-$ are consistent with an equatorial Cl at C_5. Carbon chemical shifts, especially in cyclohexane ring systems, are extremely sensitive to stereochemical factors.[8,10] Hence, in methylcyclohexane the axial methyl is shielded relative to the equatorial one by 6 ppm,[10a] and the methyl shielding in *cis*- and *trans*-9-methyldecalin differ by 12 ppm.[10b] The similarity of the shift position for the equatorial methyl in methylcyclohexane (24 ppm) and the equatorial quaternary methyl in 3 (27.4 ppm) vs. that of the quaternary methyl in 2 (30.3 ppm) suggests its stereochemistry to be equatorial.[11]

Chemical conformation of the proposed structure of 2 was provided by aromatization of 2 to (*E*)-1-chloro-2-(2,4-dimethylphenyl)ethylene (4) by 1,5-diazobicyclo[5.4.0]undec-5-ene (DBU) in THF. Compound 4 was treated with O_3 to yield 2,4-dimethylbenzaldehyde (5) which was in turn prepared directly from commercial 2,4-dimethylbenzoic acid (6).[12]

We have observed by GC/MS five isomers of formula $C_{10}H_{13}Cl_3$ from various collections of *P. violaceum*. Comparative mass spectral data [especially intense fragmentation to an aromatic nucleus $(C_{10}H_{11})^+$, *m/e* 131] indicates that four of the uncharacterized $C_{10}H_{13}Cl_3$ isomers probably have a trialkyl six-membered ring with no points of geminate alkyl substitution.[13] Thus, plocamene B may be just the first representative of a host of nonisoprenoid monoterpenes from red alga. Migration of methyl from C_1 or vinyl from C_2 are the simplest possibilities to link plocamene B to the isoprenoid biosynthetic manifold. The nucleus of the former precursor, however, represents an uncommon tail-to-tail isoprenoid arrangement, and there are, as yet, no literature examples of the carbon constitution of this envisioned precursor.[14]

Acknowledgment. We thank Professor I. Abbott (Hopkins Marine Station) for guidance in alga identification. Mr. Dennis Taylor (Finnigan Corp.) kindly provided GC/MS data, and Professor R. Wing (UCR) provided the 300-MHz NMR spectra. We also thank the UCSC Committee on Research for support of this research.

Supplementary Material Available. The GC/MS traces showing halomonoterpene distribution of *P. violaceum* from two different intertidal locations north of Santa Cruz will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2568.

References and Notes

(1) P. Crews and E. Kho, *J. Org. Chem.*, **39**, 3303 (1974).
(2) (a) These tests assay for a variety of insect growth effects, such as immediate mortality, growth inhibitory effects, juvenile hormone effects, and antimolting effects. This testing program is being carried out through a collaboration with Zoecon Corp. Research Division, Biology Department. We hope in the near future to present a detailed account of these results. (b) A bioassay using gold fish has been patterned after a literature description: G. J. Bakus and G. Green, *Science*, **185**, 951 (1974).
(3) Examples to date of halo monoterpenes from red marine algae include (a) ref 1; (b) ref 5; (c) N. Ichikawa, Y. Naya, and S. Enomoto, *Chem. Lett.*, 1333 (1974).
(4) We initially named this compound plocamene A and its ^1H NMR (δ) showed (in benzene-d_6, 100 MHz) (a) CH_3, s, 0.62 (1.25 in CCl_4); (b) $-CH_2-$, AB q, 1.34 and 1.57 (J = 15 Hz); (c) $-ClCHCH_2CHCl-$, ABX_2 m, H_{3e}, doubled t, 1.78 (J = 13, 4, 4 Hz), H_{3a}, q, 2.19 (J = 13, 12, 12 Hz), H_{2a} and H_{4a}, dd, 2.55 and 3.52 (J = 12 and 4 Hz); (d) $-CH_2-$, AB q, 2.85 and 3.40 (J = 10 Hz); (e) H_7 and H_8, AB q, 5.50 and 6.30 (J = 13 Hz) (note that many of these J's are first order approximations). This spectrum is closely comparable with that of violacene (3)[5] at 300 MHZ (solvent unspecified).
(5) J. S. Mynderse and D. J. Faulkner, *J. Am. Chem. Soc.*, **96**, 6771 (1974).
(6) This methodology has been previously described: O. Ganson and W. Shittenhelm, *J. Am. Chem. Soc.*, **93**, 4294 (1972).
(7) Some examples of the variation of J_{CH} with substituent electronegativity are (a) G. E. Maciel and K. D. Summerhays, *J. Am. Chem. Soc.*, **93**, 520 (1971); (b) M. E. Freeburger and L. Spialter, *ibid.*, **93**, 1894 (1971); (c) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, Chapter 10.
(8) G. C. Levy and G. R. Nelson, "Carbon-13 Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, Chapter 3.
(9) The ^1H NMR spectra of β-ionone (Varian Catalog, Vol. II, #617) and β-cyclocitral [prepared according to R. N. Gedge et al., *Can. J. Chem.*, **49**, 1764 (1971)] both show greatly broadened vinylic methyls. See P. Crews, *J. Am. Chem. Soc.*, **95**, 636 (1973), and references within for a discussion of long range J's.
(10) (a) F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *J. Am. Chem. Soc.*, **93**, 258 (1971); (b) J. L. Gough, J. P. Guthrie, and J. B. Stothers, *Chem. Commun.*, 979 (1972); (c) J. B. Stothers and N. K. Wilson, *Top. Stereochem.*, **8**, 1 (1974).
(11) It would appear that only a small chemical shift difference should be observed for a CH_3 geminate to a vinyl vs. geminate to a Cl. Compare Tables 3.7 and 3.18 of ref 8.
(12) (a) Purchased from Aldrich Chemical Co. (b) The physical properties of 4 and 5 were consistent with their structures.
(13) Based upon comparison of the individual mass spectral data from our lab; however, see also ref 5.
(14) The biosynthesis of head-to-head terpenes has recently been investigated: (a) R. M. Coates and W. H. Robinson, *J. Am. Chem. Soc.*, **94**, 5921 (1972); (b) C. D. Poulter, O. J. Muscio, C. J. Spillner, and R. G. Goodfellow, *ibid.*, **94**, 5923 (1972).

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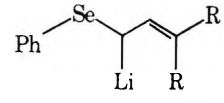
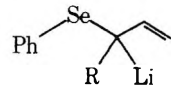
Organoselenium Chemistry. Synthetic Transformations Based on Allyl Selenide Anions[1]

Summary: Enones and allyl alcohols are formed when substituted allyl selenides, prepared by alkylation or silylation of allyl selenide anions, are oxidized.

Sir: Lithium reagents derived from allyl sulfides,[2,3a] sulfoxides,[3] sulfones,[4] phosphonates,[5] ethers,[6a,b] and amines[6c,d] have been used to perform useful synthetic transformations. We have been exploring the chemistry of α-lithio selenoxides and selenides[7,8] and report here preliminary results on the deprotonation of a variety of allyl selenides, their reaction with representative electrophiles, and some transformations of these alkylation products. Alkyllithium reagents can rarely be used for the deprotonation of selenides or selenoxides since extensive cleavage reactions often occur.[7,8] We have found lithium diisopropylamide (LDA) in tetrahydrofuran a useful base for this purpose. In sterically hindered situations lithium diethylamide is superior.

The lithium reagents 1–5 are formed using LDA in tetrahydrofuran under the conditions indicated. β-Methylallyl



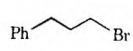
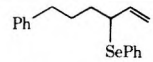
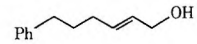
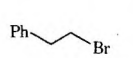
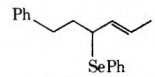
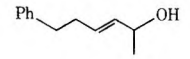
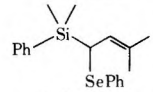
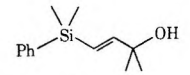
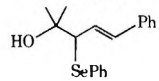
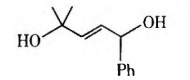
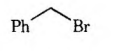
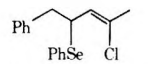
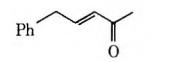
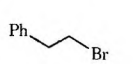
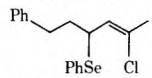
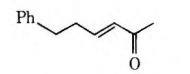
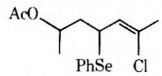
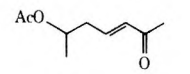
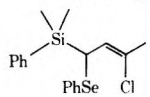
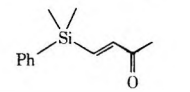


R	Conditions
1 H, H	−78°, <10 min
2 CH_3, H	−78°, 20 min
3 CH_3, CH_3	0°, 20 min
4 Ph, H	−78°, <5 min
5 CH_3, Cl	−78°, <5 min

6a, R = $Si(CH_3)_3$
b, R = CH_3

phenyl selenide can also be deprotonated and the anion behaves quite similarly to 1. Attempts to extend the procedure to α-substituted allyl anions (6) have been successful only for the α-trimethylsilyl derivative **6a**, which can be

Table I
Transformation of Phenylselenoallyllithium Reagents to Allylic Alcohols and Enones by Alkylation and Subsequent Oxidation

Anion	Electrophile	Selenide[a]	Product[b]	Yield, %[c]
1				68
2				80
3	$(CH_3)_2PhSiCl$			74
4				55
5				70
5				85
5				80[d]
5	$(CH_3)_2PhSiCl$			63

[a] The selenides from 2 and 5 were mixtures of geometric isomers. Small amounts of γ-alkylation products were also formed. [b] All compounds were adequately characterized by spectral methods. [c] Yields are for material isolated by preparative thin layer chromatography. [d] The crude reaction mixture from 5 and propylene oxide was treated with excess acetic anhydride.

formed by deprotonation of the selenide using lithium diethylamide[9] (less hindered bases such as lithium isobutylamide result in desilylation). α-Methylallyl phenyl selenide is not cleanly deprotonated to **6b** under conditions we have tried.

The anions 1–5 are powerful nucleophiles; the reactions with the electrophiles shown in Table I were carried out at −78° and were complete in <15 min. Secondary halides also react, but higher temperatures and/or longer reaction times are required. The problem of α vs. γ alkylation is similar to that found for the related sulfur systems.[2a,3a] Alkylation usually occurs predominantly α (~80% for 1, >90% for 2 and 3, ~50% for 4; γ-alkylation products for 5 appear to be formed to a small extent, but these are usually rather unstable). Other electrophiles such as chlorosilanes or carbonyl compounds give more variable α/γ ratios with 1: trimethylchlorosilane (82/18), dimethylphenylchlorosilane (41/59), acetophenone (15/85). The γ-substitution products are usually a 1:1 mixture of *E*:*Z* isomers.

A solution to the problem of γ alkylation for allyl sulfide anions has been found through the use of substituent groups on sulfur having chelating potential.[2b–d,3a] For example, much improved α/γ ratios were observed for the anions of 2-pyridyl allyl sulfide when compared with the phenyl analog. Unfortunately the lithium reagent prepared by deprotonation of 2-pyridyl allyl selenide[10] does not give increased α/γ ratios (70/30 for methyl iodide, 60/40 for trimethylchlorosilane). This may be because complexation with the diisopropylamine present prevents the chelation with the pyridine nitrogen.[11]

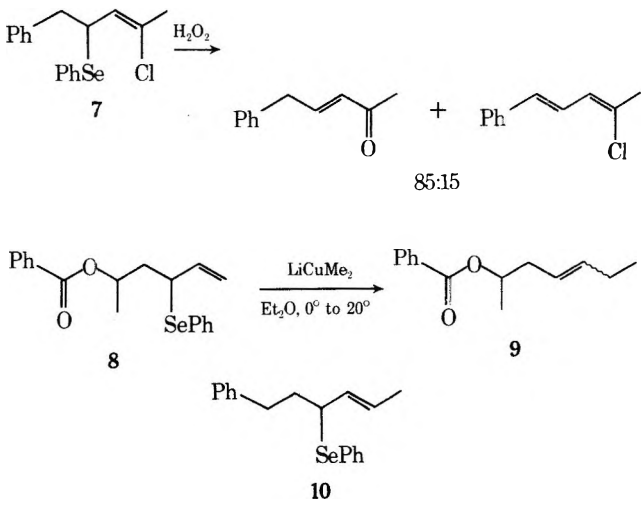
Transformations of the alkylation products of functionalized allyl anions are of several types. Allyl sulfides,[2a–f] sulfones,[4] and phosphonates[5] have been reductively cleaved; allyl vinyl sulfides[2i–j] and dithiocarbamates[2k–l] undergo [3.3] sigmatropic rearrangements; and allyl sulfoxides undergo reversible [2.3] sigmatropic rearrangements. Evans has developed the last reaction into a versatile synthesis of allylic alcohols.[3]

Table I lists a number of transformations involving [2.3] sigmatropic shifts of allyl selenoxides.[12] In all cases selenides were oxidized using the two-phase pyridine buffered hydrogen peroxide/dichloromethane procedure (15 min at 25°)[13] previously described.[14,15] This procedure is convenient and results in clean rearrangement of the intermediate selenoxide giving eventually an allylic alcohol. Excess oxidant is used so that no volatile selenium-containing compounds remain after oxidation, and no trapping agent to cleave the allyl selenenate is needed. Selenium appears as benzeneseleninic acid which is removed by extraction (and can be reduced back to diphenyl diselenide in high yield).

The anion 5 is formed rapidly even at −100°, attesting to the substantial acidifying effect of chlorine (compare with 3). Alkylation of 5 with primary halides proceeds cleanly and in high yield at −78°. Not surprisingly, 5 is rather unstable. It is decomposed significantly after 30 min at −78° in THF so that alkylation with secondary bromides or epoxides does not occur in acceptable yields. Oxidation of the alkylation products of 5 by the usual two phase H_2O_2/CH_2Cl_2 procedure leads cleanly and in high yield to enones. The starting selenide is prepared from the readily available 1,3-dichloro-2-butene by nucleophilic displacement with PhSeNa. Transformations using 5 are similar to the α,β-unsaturated aldehyde synthesis based on 1,3-bis(methylthio)allyllithium developed by Corey, Erickson, and Noyori.[2g] Lansbury and Rhodes[16] have reported that 3-chloro-2-buten-1-yl sulfoxide and amine oxide rearrange readily to give methyl vinyl ketone.

The allyl selenoxide [2.3] shift proceeds more rapidly than selenoxide syn elimination[17] or "sila-Pummerer" rearrangement.[18] A small amount of diene (12% yield) is formed upon oxidation of 7. Here elimination is enhanced by the phenyl substituent, and the [2.3] shift is probably slowed down by the γ substituents.

We have observed that allyl selenides such as 8 react with lithium dimethylcuprate above 0° to give product in



which methyl has replaced phenylseleno.[19] The transformation of 8 to 9 proceeds with allylic rearrangement giving a mixture of cis and trans isomers. The route from 1 to 8 to 9 results in overall 1,3 disubstitution of an allyl fragment, first by an electrophile, then by a nucleophile. Cinnamyl phenyl selenide gives unrearranged olefin (1-phenyl-1-butene, 65%) upon treatment with dimethylcuprate in ether. Alkylation products of phenyl crotyl selenide (i.e., 10) undergo reaction with dimethylcuprate sluggishly, and the reaction is likely to be limited to the less highly substituted allyl selenides such as 8. Aryl selenides with electron-attracting substituents may undergo more facile displacements by cuprate, and we are exploring this possibility.

Acknowledgment. The donors of the Petroleum Research Foundation, administered by the American Chemical Society, the National Science Foundation, and the Wisconsin Alumni Research Foundation provided generous support for this work.

References and Notes

(1) These results were presented in part at the American Chemical Society Midwest Regional Meeting, Iowa City, Iowa, Nov 8, 1974.
(2) (a) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 5629 (1968); 3707 (1969); *Tetrahedron*, **27**, 5861 (1971). (b) T. Mukaiyama, K. Narasaka, K. Maekawa, and M. Furusato, *Bull. Chem. Soc. Jpn.*, **44**, 2285 (1971). (c) K. Narasaka, M. Hayashi, and T. Mukaiyama, *Chem. Lett.*, 259 (1972). (d) K. Hirai, H. Matsuda, and Y. Kishida, *Tetranedron Lett.*, 4359 (1971). (e) K. Kondo, A. Negishi, K. Matsui, D. Tunemoto, and S. Masamune, *Chem. Commun.*, 1311 (1972). (f) P. L. Stotter and R. E. Hornish, *J. Am. Chem. Soc.*, **95**, 4444 (1973). (g) E. J. Corey, B. W. Erickson, and R. Noyori, *ibid.*, **93**, 1724 (1971). (h) K. Oshima, H. Takahashi, H. Yamamoto, and H. Nozaki, *ibid.*, **95**, 2693 (1973). (i) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, **95**, 4446 (1973). (j) H. Takahashi, K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, **95**, 5803 (1973). (k) T. Hayashi, *Tetrahedron Lett.*, 339 (1974). (l) T. Nakai, H. Shiono, and M. Okawara, *ibid.*, 3625 (1974). (m) J. P. Marino and W. B. Mesbergen, *J. Am. Chem. Soc.*, **96**, 4050 (1974).
(3) (a) D. A. Evans, *Acc. Chem. Res.*, **7**, 147 (1974); (b) D. A. Evans, G. C. Andrews, and C. L. Sims, *J. Am. Chem. Soc.*, **93**, 4956 (1971); (c) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, 1385, 1389 (1973).
(4) (a) M. Julia and D. Arnould, *Bull. Soc. Chim. Fr.*, 743, 746 (1973); (b) P. A. Grieco and Y. Masaki, *J. Org. Chem.*, **39**, 2135 (1974).
(5) K. Kondo, A. Negishi, and D. Tunemoto, *Angew. Chem., Int. Ed. Engl.*, **13**, 407 (1974).
(6) (a) D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, 96, 5560 (1974); (b) W. C. Still and T. L. Macdonald, *ibid.*, **96**, 5561 (1974); (c) H. Ahlbrecht and J. Eichler, *Synthesis*, **9**, 672 (1974); (d) M. Julia, A. Schouteeten, and M. Baillarge, *Tetrahedron Lett.*, 3433 (1974).
(7) H. J. Reich and S. K. Shah, *J. Am. Chem. Soc.*, **97**, 3250 (1975).
(8) Several selenium stabilized anions have been prepared: (a) D. Seebach and N. Peleties, *Angew. Chem.*, **81**, 465 (1969), *Chem. Ber.*, **105**, 511 (1972); (b) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973); (c) R. H. Mitchell, *Chem. Commun.*, 990 (1974); (d) W. Dumont, P. Bayet, and A. Krief, *Angew. Chem., Int. Ed. Engl.*, **13**, 804 (1974); (e) D. Seebach and A. K. Beck, *ibid.*, **13**, 806 (1974).
(9) Anions of this type may have some use in the preparation of functionalized vinyl silanes: G. Stork, M. E. Jung, E. Colvin, and Y. Noel, *J. Am. Chem. Soc.*, **96**, 3684 (1974).
(10) Prepared by alkylation of 2-selenopyridine [H. G. Mautner, S.-H Chu, and C. M. Lee, *J. Org. Chem.*, **27**, 3671 (1962)] with allyl chloride.
(11) Addition of hexamethylphosphoric triamide destroys the α selectivity of chelated sulfur-substituted allyllithium reagents.[3a]
(12) K. B. Sharpless and R. F. Lauer [*J. Am. Chem. Soc.*, **95**, 2697 (1973)] first reported the [2.3] sigmatropic rearrangement of allyl selenoxides.
(13) Oxidation with hydrogen peroxide in ethanol sometimes results in complex mixtures of products.
(14) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Org. Chem.*, **39**, 2133 (1974).
(15) The minor amounts of γ-alkylation products are converted into materials readily removed during aqueous work-up or subsequent purification.
(16) P. T. Lansbury and J. E. Rhodes, *Chem. Commun.*, 21 (1974).
(17) Low-temperature (−67°) ozonolysis of allyl phenyl selenide gives the selenoxide which can be observed by low-temperature NMR. Rearrangement accompanied by further transformations occs at −40° with a half-life of <60 min. The selenoxide elimination of alkyl selenoxides, on the other hand, does not occur rapidly until temperatures above 0° are reached.
(18) (a) A. G. Brook and D. G. Anderson, *Can. J. Chem.*, **46**, 2115 (1968); (b) F. A. Carey and O. Hernandez, *J. Org. Chem.*, **38**, 2670 (1973).
(19) Allylic halides[20a] and acetates[20b] undergo displacement by alkyl cuprates.
(20) (a) E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 3911 (1967). (b) P. Rona, L. Tökes, J. Tremble, and P. Crabbé, *Chem. Commun.*, 43 (1969); R. J. Anderson, C. A. Henrick, and J. B. Sidall, *J. Am. Chem. Soc.*, **92**, 735 (1970).

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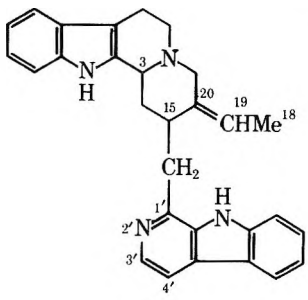
Synthesis and Stereochemistry of (±)-3′,4′-Dihydrousambarensine

Summary: A total synthesis of (±)-3′,4′-dihydrousambarensine has been carried out which confirms the structure and defines the stereochemistry of the alkaloid as **2a.**

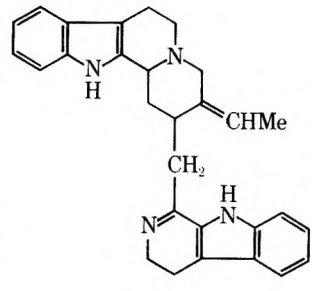
Sir: Largely on the basis of spectral data,[1] formulas 1 and 2 were recently suggested for the *Strychnos usambarensis* alkaloids, usambarensine and 3′,4′-dihydrousambarensine. However, no stereostructures have been assigned to these substances, all unusual, indole analogs of the more familiar Ipecacuanha type, which possess isoquinoline rings as the heterocyclic entities. Using totally synthetic starting material of secure stereochemistry, namely, methyl (±)-geissoschizoate (**3a**),[2] we have carried out the first synthesis of 3′,4′-dihydrousambarensine, which not only establishes the gross structure but also defines the geometry and chirality of the natural product as indicated in **2a**.[3]

(±)-Geissoschizoic acid, prepared by saponification of methyl (±)-geissoschizoate (**3a**), was condensed with tryptamine in the presence of dicyclohexylcarbodiimide (dimethoxyethane–dimethylformamide at room temperature) to give tryptamide **4a**. Cyclization of the latter by means of $POCl_3$ in $CHCl_3$ provided, after preparative TLC, (±)-dihydrousambarensine (**2a**), indistinguishable from the natural product on the basis of TLC, uv, ir, and NMR as well as high resolution mass spectral comparisons. That no inversion occurred at the potentially epimerizable center C-3 during the synthesis of (±)-**2a** was substantiated by the result of a parallel series starting with methyl (±)-epigeissoschizoate (**3b**). After successive treatment of this ester with boron tribromide[4] and tryptamine in dichloromethane–benzene, tryptamide **4b** was obtained. On $POCl_3$–$CHCl_3$ cyclization, the amide **4b** generated base **2b**, isomeric with, but different from, natural 3′,4′-dihydrousambarensine, on the basis of TLC and ir spectral properties. In view of the foregoing, the stereochemistry of **3a** corresponds to that of synthetic (±) base **2a**, which accordingly must possess the cis relationship for C-3 and C-15 as well as for the olefinic methyl (C-18) and the C-15 center.

Obviously derived biogenetically from two tryptamine

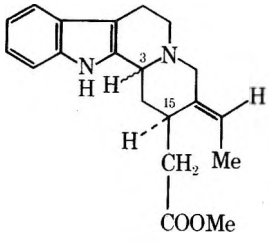


1

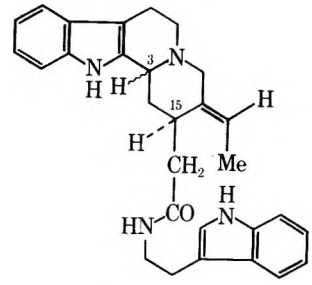


2

a, 3,15 cis, 18-Me cis to C-15
b, 3,15 trans, 18-Me cis to C-15



3a, 3α-H
b, 3β-H



4a, 3α-H
b, 3β-H

residues and a C_9 terpenoid component, dihydrousambarensine features stereochemical relationships characteristic of (1) terpene-derived indole alkaloids bearing ethylidene groups, normally possessing cis geometry, and (2) the emetine type, having the cis relationship of C-3 and C-15. Further, the oxidation levels of the heterorings in natural products **1**, **2**, and tetrahydro-**2** corresponds exactly to those of the isoquinoline units in emetine, psychotrine, and emetamine.[5] These similarities constitute a remarkable overlap of the various structural features which characterize the two alkaloid classes and suggest action on precursor substrates of very similar—perhaps identical—enzyme species.

Acknowledgment. The authors thank Dr. L. Angenot, University de Liege, for providing a sample of natural dihydrousambarensine, and Professor E. E. van Tamelen, Stanford University, for his kind interest in this work.

Supplementary Material Available. The experimental procedures for the reactions described in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $2.50 for photocopy or $4.00 for microfiche, referring to code number JOC-75-2572.

References and Notes

(1) L. Angenot and N. G. Bisset, *J. Pharm. Belg.*, **26** (5), 585 (1971); *Chem. Abstr.*, **76**, 72694w (1972).
(2) K. Yamada, K. Aoki, T. Kato, D. Uemura, and E. E. van Tamelen, *J. Chem. Soc., Chem. Commun.*, 908 (1974).
(3) The C-3,C-15 stereochemical assignment has been changed from the original 3β,15α to 3α,15α (personal communication from Dr. L. Angenot; *cf.* L. Angenot, Ph.D. Thesis, University de Liege, 1973, pp 66–69).
(4) H. Yazawa, K. Tanaka and K. Kariyone, *Tetrahedron Lett.*, 3955 (1974).
(5) H. T. Openshaw in "Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand-Reinhold, 1970, pp 85–115.

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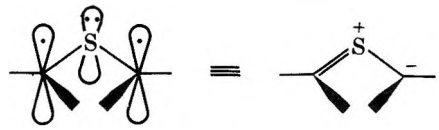
Thiocarbonyl Ylides.[1] Stereochemical Properties of 4-*tert*-Butylcyclohexyl Derivatives

Summary: The stereoisomeric thiocarbonyl ylides derived formally from 4-*tert*-butylcyclohexanone undergo ring closure in a conrotatory manner providing spirocyclic thiiranes, which may be desulfurized.

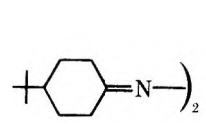
Sir: Thiocarbonyl ylides (**1**) have revealed their usefulness as tools for theory and as building blocks for synthesis.[2]



1

Methods developed previously by us make now available various aliphatically substituted members of this class of reactive intermediates.[2a] We offer here further insight into the stereochemical properties of thiocarbonyl ylides and in the following articles some applications of the derived products.[3]

Treatment of the azine (**2**) of 4-*tert*-butylcyclohexanone with hydrogen sulfide under pressure gives a mixture of 1,3,4-thiadiazolidines (**3**). Dehydrogenation of this mixture with dimethylazodicarboxylate gives a mixture of **4**, **5**, and **6**.[4,5] The yield is quantitative based on **2**. Separation of **4**



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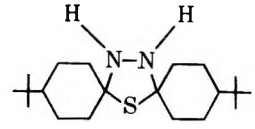
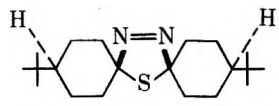
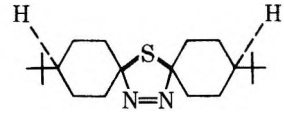


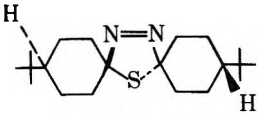
3 (mixture of stereoisomers)



4 (trans,trans), 34%



5 (cis,cis), 23%



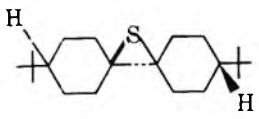
6 (cis,trans), 43%

and **5** from **6** is achieved by extraction with *n*-pentane in which **6** is totally insoluble. Chromatography over aluminum oxide allows separation of **4** and **5**. The isomers **4**–**6** were pure as determined by ^{1}H NMR and ^{13}C NMR spectroscopy[6] and chromatography.[7]

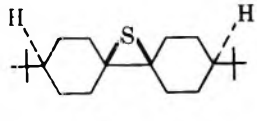
The stereochemistry of **6** was readily ascertained from the observation of two *tert*-butyl absorptions (δ 0.915 and 0.95 in $CDCl_3$) of equivalent intensity in the ^{1}H NMR spectrum. Moreover in the proton decoupled ^{13}C NMR spectrum eight lines (four pairs) for the ring carbon atoms were noted demonstrating the nonequivalence of the rings. Distinction between **4** and **5** (*tert*-butyl absorptions at δ 0.90 and 0.92, respectively, in $CDCl_3$) was made on the basis of selective shifts observed in the ^{1}H NMR spectrum induced by Eu(FOD)$_3$. In **5** the axial hydrogens adjacent to the quaternary ring carbon atoms project into the vicinity of the azo bridge, which provides a good complexing site.[8] Absorptions for these protons[9] are shifted strongly downfield on addition of Eu(FOD)$_3$, but in **4** where this steric feature is absent Eu(FOD)$_3$ influences the ^{1}H NMR spectra only

trivially. The configurational assignment was substantiated independently by oxidizing **4** and **5** to their respective sulfoxides (not shown); here two of the axial protons adjacent to the ring quaternary carbons in the sulfoxide **4** project into the vicinity of the sulfur–oxygen bond and undergo the anticipated downfield shift in C_6D_6 solution.[10] This effect is, as predicted, absent in the sulfoxide of **5**.

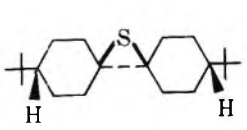
Pyrolysis in boiling methylcyclohexane of **4** or **5** either separately or as a mixture (most convenient for synthetic purposes) gave in quantitative yield a single thiirane **7**, mp 208–214° dec. The observation of two *tert*-butyl absorptions of equal intensity in the ^1H NMR spectrum (at δ 0.915 and 0.95 in $CDCl_3$) as well as clear evidence in the proton decoupled ^{13}C NMR spectrum for the nonequivalence of the cyclohexyl rings established the cis,trans structure.



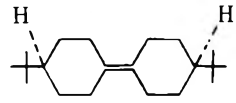
7 (cis, trans)



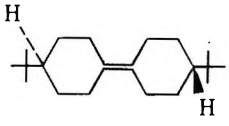
8 (trans,trans)



9 (cis, cis)



10 (syn)

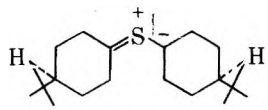


11 (anti)

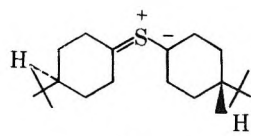
Pyrolysis of **6** under similar conditions gave in quantitative yield also a *single* thiirane, mp 224–228° dec, with a single *tert*-butyl absorption at δ 0.90 in the ^1H NMR spectrum ($CDCl_3$). ^{13}C NMR spectroscopy confirmed reflection symmetry of the cyclohexyl rings. The spectroscopic data establish the product as **8** or **9** but allow no distinction between the two. A choice between these structural possibilities was made on the basis of chemical reactivity considerations. In refluxing xylene with tri-*n*-butylphosphine **7** and **8** or **9** gave (after chromatography and recrystallization) in 90 and 70% yields, respectively, the isomeric olefins **10** and **11**, mp 137–138.5 and 183–183.5°, respectively. Compound **7** reacted much more slowly (roughly factor 100) than **8** or **9** although both reactions were clean and quantitative before work-up. Desulfurization of thiiranes by phosphorous compounds involves initial attack at sulfur followed by or concomitant with release of the alkene.[11] Steric requirements in the transition state are expected to be greater than in the ground state and reaction will be slowed at an axial relative to an equatorial position on a cyclohexyl ring owing to increased 1,3-diaxial repulsions.[12] In **7** two sets of such interactions are present, in **8** there are four such interactions, and in **9** none. The rate differences are in accord with structure **9**, which appears to be the thermodynamically less favored isomer owing to nonbonded repulsions between the axial hydrogens of the two rings, which are forced to face each other.

It has been firmly established that in general the Δ^3-1,3,4-thiadiazoline ring system loses nitrogen readily on thermolysis producing a reactive thiocarbonyl ylide intermediate.[2a] The fact that **4** and **5** afford the *same* thiirane **7** indicates the formation of a common thiocarbonyl ylide **12**, *conrotatory* ring closure of which produces **7**. This implies that the terminal carbons of the thiocarbonyl ylide segment of **12** are effectively sp^2 hybridized. The two possible conrotatory motions for ring closure of **12** are enantiomeric.

Pyrolysis of **6** produces both enantiomers of **13** (**12** with the thiocarbonyl ylide segment completely planar is meso);



12



13

the two possible directions for conrotatory ring closure are diastereomeric and lead, respectively, to **8** or **9**. The exclusive formation of **9** provides an extreme example of the fairly general tendency of exothermic carbon–carbon bond forming reactions to afford the more strained isomer,[13] in this case through predictable axial–axial ring closure.[14]

Acknowledgement. We are indebted to Dr. M. P. Doyle and W. Mungall of Hope College, Holland, Mich., and to that institution for making it possible for J.K.K. to participate in an undergraduate exchange program with this university.

References and Notes

(1) Thione ylides: E. M. Burgess and H. R. Penton, Jr., *J. Org. Chem.*, **39**, 2885 (1974).
(2) Thiocarbonyl ylides and their applications: (a) J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, **37**, 4045 (1972); (b) R. M. Kellogg and W. L. Prins, *ibid.*, **39**, 2366 (1974); (c) T. Beetz and R. M. Kellogg, *J. Am. Chem. Soc.*, **95**, 7925 (1973); (d) P. Raynolds, S. Zonnebelt, S. Bakker, and R. M. Kellogg, *ibid.*, **96**, 3146 (1974); (e) A. G. Schultz, *J. Org. Chem.*, **39**, 3185 (1974); (f) A. G. Schultz and M. B. DeTar, *J. Am. Chem. Soc.*, **96**, 296 (1974); (g) W. J. Middleton, *J. Org. Chem.*, **31**, 3731 (1966); (h) S. Mitamura, M. Takaku, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **47**, 3152 (1974). See also (i) S. Tamagaki, K. Sakaki, and S. Oae, *ibid.*, **47**, 3084 (1974); (j) J. P. Synder, *J. Am. Chem. Soc.*, **96**, 5005 (1974); (k) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, **95**, 7301 (1973); (l) R. Hoffmann, H. Fujimoto, J. R. Swenson, and C.-C. Wan, *ibid.*, **95**, 7644 (1973).
(3) R. M. Kellogg and J. K. Kaiser, *J. Org. Chem.*, following paper in this issue; in press.
(4) For brevity no perspective drawings are given. Some of the stereochemical points may not be obvious unless models are used.
(5) Compound **5** was isolated earlier[2a] and its reactions were briefly investigated. Reinvestigation and improvement of experimental methodology led to the obtainment of all stereoisomers.
(6) ^{13}C NMR and other pertinent data will be reported in detail in a full publication.
(7) Satisfactory elemental analyses were obtained for all new compounds reported here.
(8) M. Franck-Neumann and M. Sedrati, *Org. Magn. Reson.*, **5**, 217 (1973).
(9) Identified by well-established precedent: (a) J. W. Emsly, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance", Vol. 2, Pergamon Press, Oxford, 1966, p 703; (b) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966).
(10) (a) K. Kondo and A. Negishi, *Tetrahedron*, **27**, 4821 (1971); (b) B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Am. Chem. Soc.*, **91**, 3839 (1969).
(11) D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, **82**, 4736 (1960).
(12) This is an extrapolation of a well-known argument to explain rate differences in S_N2 reactions of cis and trans-substituted cyclohexane derivatives. See, for example, (a) E. L. Eliel, E. W. Della, and M. Rogic, *J. Org. Chem.*, **30**, 855 (1965); (b) A. R. Katritzky, P. G. Lehman, and B. B. Shapiro, *J. Chem. Soc. B.*, 1308 (1971); (c) E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961); (d) E. A. S. Cavell, N. B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960); (e) R. C. Cookson, *Chem. Ind. (London)*, 337 (1953).
(13) (a) M. Schlosser, *Bull. Soc. Chim. Fr.*, 455 (1971); (b) R. Hoffmann, C. C. Levin, and R. A. Moss, *J. Am. Chem. Soc.*, **95**, 629 (1973).
(14) See, for analogy, M. Chérest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).

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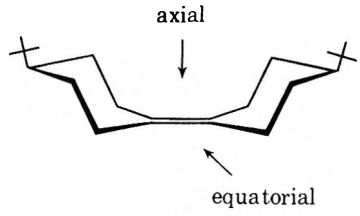
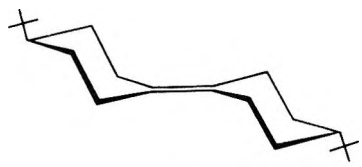
Reaction of Singlet Oxygen with Conformationally Fixed Cyclohexylidenecyclohexanes. Failure of an All Suprafacial Mechanism

Summary: Conformationally fixed C_{2v} and C_{2h} conformers of cyclohexylidenecyclohexane react with singlet oxygen in benzene solution to give in differing ratios two stereoisomeric allylic hydroperoxides, a result not in accord with an all suprafacial mechanism for the "ene" reaction.

Sir: For the "ene" reaction of alkenes with singlet oxygen there must be available an allylic hydrogen aligned roughly parallel to the plane formed by the π bond.[1] In this light the alkenes **1** and **2**[2] possess instructive structural features for elucidation of stereochemical aspects of singlet oxygen reactions. In all-chair conformations **1** and **2** belong, respectively, to C_{2v} and C_{2h} point groups and as such should be conformationally fixed models for the two all-chair conformations that cyclohexylidenecyclohexane may adopt in principle.[3] Only the equatorial face of **1** is available for a concerted all suprafacial "ene" reaction, whereas the axial face is structurally related to adamantylideneadamantane, photooxygenation of which gives a 1,2-dioxetane.[4,5] The alkene faces of **2** are equivalent but with regard to any one face only that alkylidene carbon furthest from the axial allylic hydrogen can bond in a concerted all suprafacial concerted "ene" reaction (axial rather than equatorial bonding).



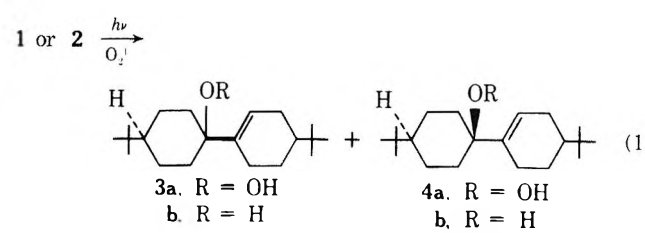
1



2

^{1}H NMR, ^{13}C NMR, and ir spectra of **1** and **2** are virtually superimposable. Substantiation of the presumed double-chair conformations for both **1** and **2** is obtained from analysis of the ^{1}H NMR spectra (100 MHz). Particularly revealing is a broadened doublet, J = 12.5 Hz, at δ 2.67 in $CDCl_3$, which is assigned to the equatorial allylic protons, which have a normal J_{gem} but small J_{vic} coupling in the chair conformation. This absorption is absent in the (temperature averaged) spectrum of cyclohexylidenecyclohexane at room temperature. Full details will be reported subsequently.

Both **1** and **2** (150 mg in 150 ml of benzene, *meso*-tetraphenylporphine sensitizer, $K_2Cr_2O_7$ filter) react smoothly with singlet oxygen. The rate of consumption is as great as that of cyclohexylidenecyclohexane itself.[6a] Within the limits of sensitivity of the detection techniques,[6b] quantitative conversion to two products assigned structures **3a** and **4a** occurred (eq 1). From **1** the ratio of **3a**:**4a** was 60:40; from **2** this ratio was 33:67. Although ir, ^{1}H NMR, and mass spectra were in accord with expectation for **3a** and **4a**, neither compound has been purified sufficiently to give a sharp melting point. The structures were verified through subsequent conversions (see below). The hydroperoxides did not



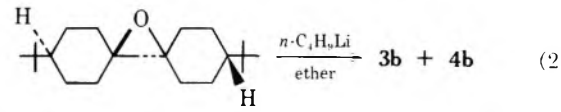
3a, R = OH
b, R = H

4a, R = OH
b, R = H

(1)

interconvert or undergo other rearrangements on standing at ambient temperature in solution for at least 1 day. Attempts to use gas chromatography caused decomposition to both 4-*tert*-butylcyclohexanone and a mixture of epoxides.[6a,7]

Reduction of crude photooxygenation mixtures with $NaBH_4$ in methanol gave quantitatively in ratios identical with the original peroxide composition the alcohols **3b** and **4b**. In our hands especially **4b** was difficult to work with owing to its ready dehydration.[8] The alcohols were ultimately separated by thin layer chromatography and purified by careful recrystallization, **3b**, mp 154–155.5°, and **4b**, mp 180.5–183°.[9] Stereochemistry is assigned to **3b** and **4b** (and by analogy to **3a** and **4a** on the basis that reduction does not affect configuration) from the much faster elution of the latter on aluminum oxide.[10] Independent structural confirmation for these structures was obtained through conversion of **2** to epoxide **5** with *meta*-chloroperbenzoic acid, followed by ring opening of **5** with strong base producing a mixture of **3b** and **4b** (eq 2). The ring opening pro-



5 (2)

ceeded only sluggishly with butyllithium and exhibited no pronounced stereoselectivity.[11]

There is no obvious reason to suppose a breakdown of the normal stereoelectronic requirement for an axially oriented allylic hydrogen in the "ene" reaction of **1** and **2**. Both olefins are fixed in double-chair conformations and the low activation energies for reaction with singlet oxygen (1.3 kcal/mol for cyclohexylidenecyclohexane in methanol)[12] indicate that the rate-determining reaction should occur through these conformations (specifically the Curtin–Hammett principle is not violated).[13,14] Subject to these restrictions, the obtainment of **4a** from **1** and **3a** from **2** is inconsistent with complete suprafacial participation of the alkenes reacting from all-chair conformations. Other explanations are demanded. Possibilities include a previously undetected antarafacial component to the "ene" reaction or the initial irreversible formation of an intermediate, perhaps a peroxirane,[5] which lives sufficiently long to be able to react, if necessary, from an attainable but energetically unfavorable flexible form in which a quasi axial hydrogen is presented.

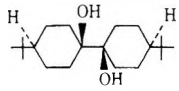
We are currently engaged in experiments to test these and other ideas.

References and Notes

(1) (a) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961). (b) For an excellent review of singlet oxygen reactions, see R. W. Denny and A. Nickon, *Org. React.*, **20**, 133 (1973).
(2) R. M. Kellogg, M. Noteboom, and J. K. Kaiser, *J. Org. Chem.*, preceding paper in this issue.
(3) Cyclohexylidenecyclohexane is known to have C_{2h} geometry in the crystal: K. Sasvari and M. Low, *Acta Cryst.*, **19**, 840 (1965).
(4) (a) J. H. Wieringa, J. Strating, H. Wynberg, and W. Adam, *Tetrahedron Lett.*, 169 (1972). (b) Both a 1,2-dioxetane and an epoxide are obtained from 7′,7′-binorbornylidene: P. D. Bartlett and M. S. Ho, *J. Am. Chem. Soc.*, **96**, 627 (1974). (c) Related observations have been made with bisbicyclo[3.3.1]-9-nonylidene: H. K. Keul, Dissertation, Karlsruhe, 1973.
(5) The factors affecting the competition between different modes of reac-

tion for singlet oxygen are the subject of much current interest: (a) N. M. Hasty and D. R. Kearns, *J. Am. Chem. Soc.*, **95**, 3380 (1973); (b) A. P. Schaap and G. R. Faler, *ibid.*, **95**, 3381 (1973); (c) P. A. Burns and C. S. Foote, *ibid.*, **96**, 4339 (1974); (d) L. N. Stephenson, D. E. McClure, and P. K. Sysak, *ibid.*, **95**, 7888 (1973).

(6) (a) Investigation of photooxygenation: G. O. Schenck and K. H. Schulte-Elte, *Justus Liebigs Ann. Chem.*, **618**, 185 (1958). (b) In benzene *t*-Bu absorptions of starting material and products are well separated and can be monitored accurately using wide sweep widths. Although they cannot be detected by the ^{1}H NMR method under these conditions other products are certainly present. Crude photooxygenation mixtures in boiling dioxane with 9,10-dibromoanthracene chemiluminesce well. When photooxygenated in methylene chloride using Methylene Blue as sensitizer, **1** after reduction gave 5–10% glycol i, likely arising from reduc-



i

tion of a 1,2-dioxetane. In a reinvestigation of the photooxygenation of cyclohexylidenecyclohexane, after reduction with $NaBH_4$ there was found in addition to the previously reported 1-(1-cyclohexenyl)-1-cyclohexanol the glycol and the epoxide of cyclohexylidenecyclohexane in the ratio 98:1:1 (by GPC).

(7) See also (a) W. F. Brill, *J. Am. Chem. Soc.*, **87**, 3286 (1965). (b) G. O. Schenck, O. A. Neumüller, and W. Eisfeld, *Justus Liebigs Ann. Chem.*, **618**, 202 (1958).

(8) Dienes are formed. Note that loss of water from **3a** and **4a** leads to two isomeric dienes.

(9) Spectral data were in accord with the proposed structures, in particular a single vinylic proton was observed in the ^{1}H NMR spectra. Satisfactory analytical data have been obtained for all new compounds except **3a** and **4a**.

(10) (a) K. Savard, *J. Biol. Chem.*, **202**, 457 (1953); (b) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); (c) S. Winstein and N. S. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955); (d) E. W. Garbisch, Jr., and D. B. Patterson, *ibid.*, **85**, 3228 (1963).

(11) Compare with R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, **92**, 2064 (1970).

(12) E. Koch, *Tetrahedron*, **24**, 6295 (1968).

(13) For extensive applications of this argument, see K. Gollnick, *Adv. Photochem.*, **6**, 1 (1968).

(14) D. Y. Curtin, *Record. Chem. Progr.*, **15**, 111 (1954).

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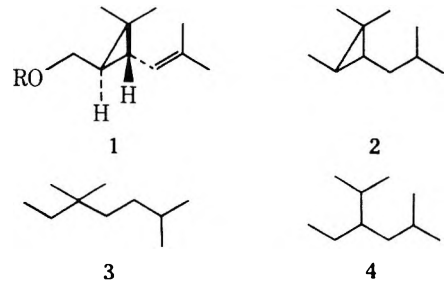
Studies on the Biogenesis of Non-Head-to-Tail Monoterpenes. The Isolation of (1*R*,3*R*)-Chrysanthemol from *Artemesia ludoviciana*[1]

Summary: The isolation of optically pure (1*R*,3*R*)-chrysanthemol from the leaves of *Artemesia ludoviciana* supports the hypothetical involvement of the corresponding pyrophosphate as a cruical intermediate in the biosynthesis of non-head-to-tail monoterpenes.

Sir: As part of a continuing study of the biosynthesis of the biologically important triterpene, squalene, we have been investigating the simpler but presumably analogous non-head-to-tail monoterpenes. Although there has been little experimental verification of any biosynthetic pathway, the available data[2] coupled with biogenetic analogies to presqualene alcohol and the known chemical[3] interconversions of the chrysanthemyl carbon skeleton with other non-head-to-tail monoterpene carbon skeletons have led to a unified hypothesis for the biosynthesis of these compounds.[4] This hypothesis requires (1*R*,3*R*)-chrysanthemyl pyrophosphate (**1**, R = pyrophosphate) as a key intermediate in the formation of the chrysanthemyl (**2**), artemesyl (**3**), and santolinyl (**4**) types of irregular monoterpenes. With the ubiquitous occurrence of phosphatases in plants, it might be expected that any plants producing **1** (R = pyrophosphate) would also have the corresponding alcohol, (1*R*,3*R*)-chrysanthemol (**1**, R = H), present.



1 2

3 4

In support of the proposed biosynthetic scheme, we wish to report the isolation of **1** (R = H) from the leaves of the sage brush, *Artemesia ludoviciana*, and further in accord with the hypothesis the natural chrysanthemol is optically pure possessing the 1*R*,3*R* absolute configuration.

The essential oils from 4 kg of fresh leaves of *A. ludoviciana* collected near Salt Lake City[5] were obtained by extraction of the plant material with pentane. Removal of the solvent and vacuum, bulb-to-bulb distillation of the remaining volatiles gave 12.5 ml of a mixture containing approximately 2% chrysanthemol as evidenced by VPC comparison to known **1** (R = H) on a 500-ft capillary column. The mixture was subjected to a vacuum distillation on a 60-cm annular spinning band column and the fractions enriched in **1** (R = H) were combined and further separated by a succession of high-pressure liquid chromatographies on a 170–200 mesh Florisil column using 1:10 ethyl acetate–hexane as the eluting solvent system. VPC analysis indicated an increase from 70 to 90 to 98% purity in the successive runs. The final purification was accomplished by preparative VPC on a 20 ft × ⅜ in. Carbowax 20M column to give 25 mg of 100% pure chrysanthemol. Spectral comparisons (NMR and ir) with authentic material as well as VPC coinjections confirmed the structure. Synthetic **1** (R = H) prepared by reduction of 97% (1*R*,3*R*)-chrysanthemic acid via its methyl ester[6] possessed an $[\alpha]_D$ of +46.9° (c 1.7, methylcyclohexane) while the isolated material had $[\alpha]_D$ +49.7° (c = 1.1, methylcyclohexane), indicating that the natural chrysanthemol is essentially 100% 1*R*,3*R*.

Evidence that the isolated **1** (R = H) could have been derived in vivo from the corresponding pyrophosphate was provided by allied studies in which we have clearly demonstrated enzymatic including phosphatase activity in leaf preparations of *A. ludoviciana*. In particular we have observed the facile conversion of known **1** (R = pyrophosphate) to **1** (R = H) in vitro by these leaf preparations.

References and Notes

(1) This work was supported by a grant from the National Institutes of Health (R01 GM20196).

(2) M. P. Crowley, P. J. Godin, H. S. Inglis, M. Snarey, and E. M. Thain, *Biochem. Biophys. Acta*, **60**, 312 (1962); G. W. Waller, G. M. Frost, G. M. Burleson, D. Brannon, and L. H. Zalkow, *Phytochemistry*, **7**, 213 (1968); D. V. Banthorpe and B. V. Charlwood, *Nature (London)*, **232**, 285 (1971); G. Pattenden and R. Storer, *Tetrahedron Lett.*, 3473 (1973); G. Pattenden, C. R. Popplestone, and R. Storer, *J. Chem. Soc., Chem. Commun.*, 290 (1975).

(3) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 1453 (1967); T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *J. Org. Chem.*, **36**, 1968 (1971); C. D. Poulter, S. G. Moesinger, and W. W. Epstein, *Tetrahedron Lett.*, 67 (1972); L. Crombie, P. A. Firth, R. P. Noughton, D. A. Whiting, and D. K. Woods, *J. Chem. Soc., Perkin Trans. 1*, 642 (1972); T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *Chem. Lett.*, 503 (1972).

(4) W. W. Epstein and C. D. Poulter, *Phytochemistry*, **12**, 737 (1973); R. B. Bates and S. K. Paknikar, *Tetrahedron Lett.*, 1453 (1965).

(5) Voucher Specimen 84025 of the University of Utah Herbarium contains a pressed sample of the *Artemesia ludoviciana* used in this study.

(6) We wish to thank Professor C. D. Poulter of this department for the sample used in our comparisons.

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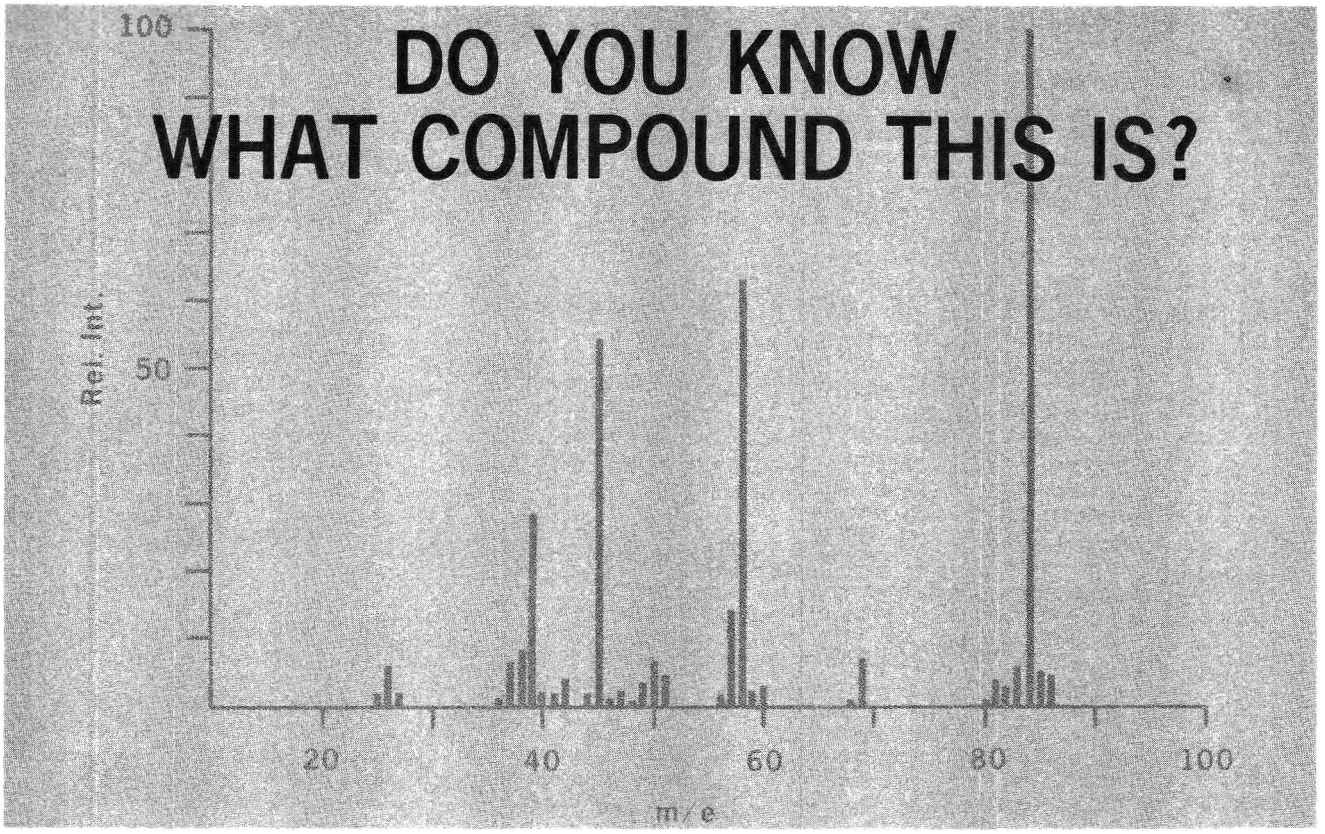

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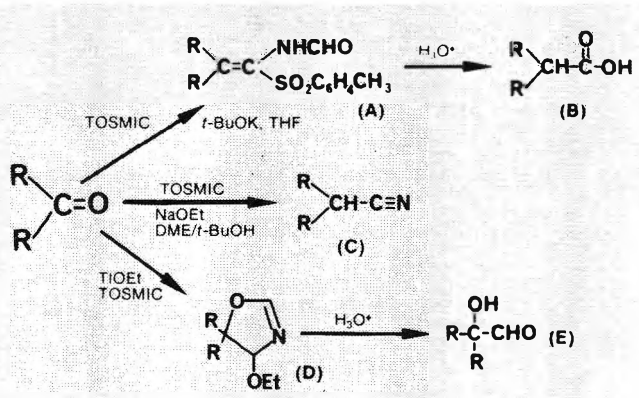

4-Ethoxyoxazolines (D)[3] which serve as excellent intermediates for a new and simple synthesis of **α-hydroxyaldehydes** (E)[4] are formed from the reaction of *TOSMIC* with ketones in the presence of thallous ethoxide.

TOSMIC also permits the synthesis of many difficult-to-prepare heterocycles. For example, the reaction of *TOSMIC* with an aldehyde and potassium carbonate in refluxing methanol affords the **5-substituted oxazole** (F)[5] in excellent yield *via* the intermediate **4-tosyl-Δ²-oxazoline. 4-Tosyl-5-substituted oxazoles** (G) are obtained from acid chlorides or anhydrides.[5] *TOSMIC* and imidoyl chlorides react, in the presence of sodium hydride, to give **4-tosyl-5-substituted imidazoles** (H)[6] while **5-substituted imidazoles** (I) are formed in the analogous reaction with aldimines.[7] Whereas ethyl benzoate does not react readily with the anion of *TOSMIC*,[5] carboxymethyl dithioates give **4-tosyl-5-substituted thiazoles** (J).[8] Diazonium salts react to give **1,2,4-triazoles** (K). Reaction of *TOSMIC* anion with Michael acceptors gives **pyrroles** (L) unsubstituted in the 1 and 2 positions.[9]

References:

1. U. Schöllkopf, R. Schröder, and E. Blume, *Ann. Chem.*, **766**, 130 (1972); U. Schöllkopf and R. Schröder, *Angew. Chem., Intern. Ed. Engl.*, **11**, 311 (1972).
2. O.H. Oldenziel and A.M. van Leusen, *Syn. Comm.*, **2**, 281 (1972); *Tetrahedron Lett.*, 1357 (1973).
3. O.H. Oldenziel and A.M. van Leusen, *Tetrahedron Lett.*, 163 (1974).
4. O.H. Oldenziel and A.M. van Leusen, *ibid.*, 167 (1974).
5. A.M. van Leusen, B.E. Hoogenboom, and H. Siderius, *ibid.*, 2369 (1972).
6. A.M. van Leusen and O.H. Oldenziel, *ibid.*, 2373 (1972).
7. O.H. Oldenziel, private communication.
8. O.H. Oldenziel and A.M. van Leusen, *Tetrahedron Lett.*, 2777 (1972).
9. A.M. van Leusen, H. Siderius, B.E. Hoogenboom, and D. van Leusen, *ibid.*, 5337 (1972).

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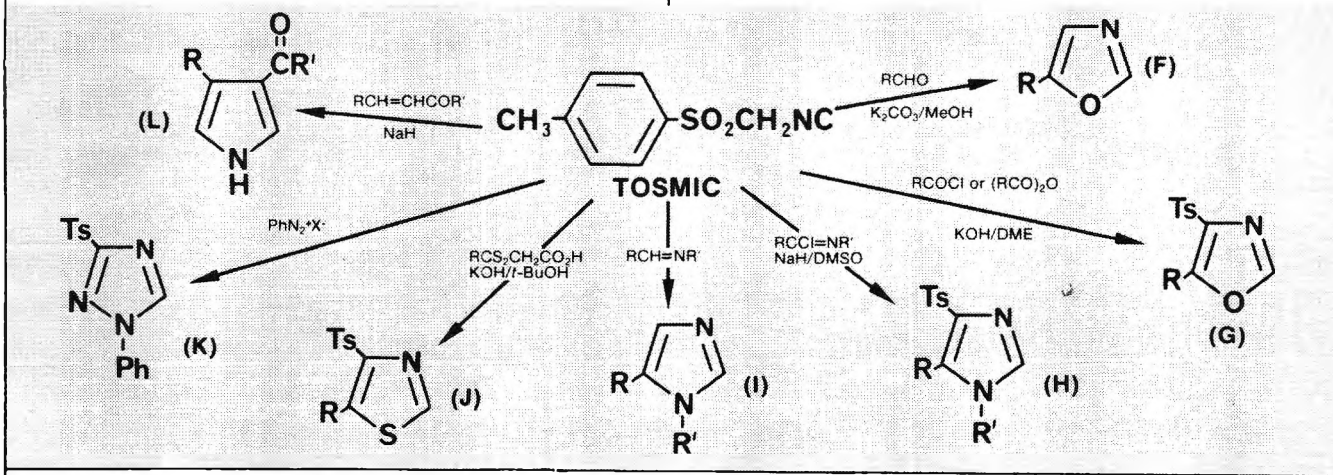

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