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Preparation and Properties of Ternary Iminium Salts of Pyrrole Aldehydes and Ketones. Synthesis of 4-Substituted Pyrrole-2-carboxaldehydes

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Received August 20, 1971

Ternary iminium salts were readily prepared from pyrrole aldehydes and methyl pyrryl ketones. Reaction of 1-(pyrrol-2-ylmethylene)pyrrolidinium perchlorate (1) with 1–3 equiv of bromine provides, after hydrolysis, 4-bromo-, 4,5-dibromo-, and 3,4,5-tribromopyrrole-2-carboxaldehydes. Reaction of 1 with sulfuryl chloride, acyl chlorides, and dichloromethyl methyl ether was found useful in preparing 4-chloro-, 4-acyl-, and 4-formyl-pyrrole-2-carboxaldehydes relatively free of 5 isomers. Conversion of acylated aldehydes to 3-acyl- and 3-alkyl-pyrroles is described.

The synthesis of β-substituted pyrroles is generally accomplished by ring closures, alkylations and acylations of metallopyrroles, and electrophilic substitution upon pyrroles bearing an electronegative substituent on the α position.[1] The first method is limited by the availability of suitably constituted acyclic precursors, while the other two methods are limited by concurrent and consecutive substitution reactions.

Our interest in preparing isoprenoid heterocyclics for screening as mimics of insect juvenile hormones led us to consider using an α substituent with a formal positive charge as a meta-directing group for electrophilic substitution on the pyrrole ring. We recently reported[2] that bromination of 1-(pyrrol-2-ylmethylene)pyrrolidinium perchlorate (1) at 0° gave a monobrominated product, 2, in high yield. Conversion of this salt to 4-bromopyrrole-2-carboxaldehyde (3) with aqueous $NaHCO_3$ also proceeded in high yield. The product contained only ~0.5% of the 5-bromo aldehyde as inferred by glpc. We now report the preparation and physical properties of such ternary iminium salts and the investigation of the synthetic utility of 1 using some of the common electrophilic substitution reactions.

Preparation and Properties of the Salts.—Leonard and Paukstelis[3] described the preparations and properties of ternary iminium perchlorates from a variety of aldehydes and ketones. Some of the condensations they reported proceeded spontaneously with evolution of heat, whereas others required the removal of water to drive them to completion. The salts (Table I) were prepared under forcing conditions (benzene, reflux).[3] It was possible to prepare the pyrrolidinium perchlorate and use it directly in the condensation step. However, it was necessary to ensure alkalinity by adding a few drops of pyrrolidine prior to the condensation step in order to promote the condensation and to reduce the color of the product. Phenyl pyrryl ketones did not react with pyrrolidinium perchlorate under these conditions.

The infrared spectra of the salts, taken as 1% solu-

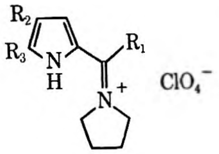
TABLE I

CHARACTERIZATION OF SALTS[a]

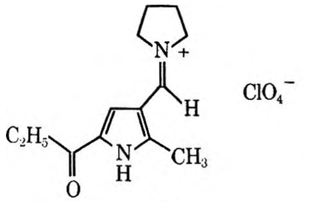
Compd	Yield, %	Mp, °C[b]	Spectral data[c]
1	>95	101–102.5	ir 3240, 1643 cm^{-1};[d] uv sh 260 (4.01), 289 (4.32);[e] nmr ref 2
6	9.5[f]	111–112	ir 3250, 1597; uv sh 273 (3.57), 323 (4.42)
7	90	155–157	ir 3200, 1712, 1643; uv 233 (4.11), 294 (4.23), 336 (3.97), sh 358 (3.45)
8	86	187–188	ir 3220, 1710, 1596; uv 238 (4.01), sh 297 (3.98), 332 (4.38), sh 354 (3.47)
9	86	209–211	ir 3350, 1717, 1640
10	90	256–258	ir 3430, 1620; uv 243 (4.21), 262 (4.13), 293 (4.17), sh 343 (2.80)

[a] Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Satisfactory analytical data (±0.4% for C, H, N, Br, Cl, and I) were reported for all new compounds listed in the table: Ed. [b] Melting points were obtained with a Fisher-Johns apparatus and are uncorrected. [c] Infrared spectra were determined with Perkin-Elmer Models 137 and 521 infrared spectrophotometers; ultraviolet spectra were obtained in ethanol with a Carey 14 recording spectrophotometer; and nmr spectra were obtained with Varian T-60 and HA-100-A instruments. Chemical shifts are given in parts per million from TMS. Piperidine was added to facilitate NH exchange. [d] 1% in ethylene dichloride. [e] λ_{max}, mμ (log ε). [f] Recovered 65.3% of the ketone after 2-hr reflux in benzene.

(1) (a) K. Schofield, "Heteroaromatic Nitrogen Compounds. Pyrroles and Pyridines," Butterworths, London, 1967. (b) A. J. Castro, W. G. Duncan and A. K. Leong, *J. Amer. Chem. Soc.*, **91**, 4304 (1969).
(2) P. E. Sonnet, *J. Org. Chem.*, **36**, 1005 (1971).
(3) N. J. Leonard and J. V. Paukstelis, *ibid.*, **28**, 3021 (1963).



Compd	R_1	R_2	R_3
1	H	H	H
6	CH_3	H	H
7	H	$CO_2C_2H_5$	CH_3
8	CH_3	$CO_2C_2H_5$	CH_3



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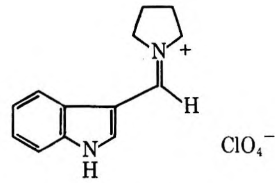

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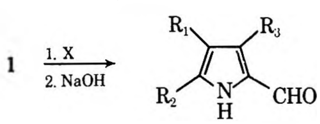
tions in ethylene dichloride, exhibited broad NH absorption due to hydrogen bonding. A comparison of the positions of the bands for compounds **1**, **6**, **7**, and **8** indicates that the carbethoxy groups in **7** and **8** increase the acidity of these two compounds, as evidenced by stronger hydrogen bonding. The C=N band is unaffected by its position on the ring or the presence of a carbethoxy group and appears at 1640–1643 cm^{-1} for PyCH=N<$^+$ and 1596–1597 cm^{-1} for $PyC(CH_3)$=N<$^+$.

Halogenation.—Treatment of **1** with 2 equiv of bromine followed by hydrolysis produced the 4,5-dibromo compound **11** (Scheme I, Table II). Nmr

SCHEME I



11–17

	X	R^1	R^2	R^3
11	$2Br_2$	Br	Br	H
12	$3Br_2$	Br	Br	Br
13	SO_2Cl_2	Cl	H	H
14	$2SO_2Cl_2$	Cl	Cl	H
15	SO_2Cl_2, then Br_2	Cl	Br	H
16	Br_2, then SO_2Cl_2	Br	Cl	H
17	$Tl(TFA)_3$, then KI	I	H	H

documented the loss of H-5 and a change in multiplicity of the aldehyde proton from the doublet of **3** caused by long-range splitting ($J_{CHO\text{-}5}$ = 1.0 Hz) to a sharp singlet. The third equivalent of bromine reacted with the dibromo salt in refluxing acetic acid, and the tribromo compound, **12**, was obtained therefrom by hydrolysis.

The corresponding salt of furfural[3] was recovered unchanged after treatment with 1 equiv of bromine (ethylene dichloride, 24-hr reflux, and acetic acid, 3-hr reflux). This illustrated the deactivation of the furan ring by the positively charged substituent.

The reaction of sulfuryl chloride with pyrrole-2-carboxyaldehyde reportedly gave a complex mixture from which a 9% yield of the 5-chloro compound was obtained.[4] Sulfuryl chloride reacted with **1** in ethylene dichloride to produce the 4-chloride **13** in good yield contaminated by small amounts of the 4,5-dichloride

(4) P. Hodge and R. W. Rickards, *J. Chem. Soc.*, 459 (1965).

TABLE II

CHARACTERIZATION OF OTHER NEW COMPOUNDS[a]

Compd	Yield, %	Mp, °C	Spectral data
3	92	122.5–124.5	ir 3460, 1671; uv 253 (3.85), 298 (4.10)
11	>95	158–159.5	ir 3443, 3210, 1671; uv 250 (3.72), 303 (4.18); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 6.92 (s, H-3), 9.43 (s, CHO)
12	>95	202 dec	ir 3432, ~3180, 1666; uv sh 270 (3.73), 308 (4.21); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 9.52 (s, CHO)
13	82	129–129.5	ir 3467, 3260, 1672; uv 252 (3.84), 302 (4.16); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 6.90 (d, J = 1.5 Hz, H-3), 7.12 (b s, H-5), 9.53 (b s, CHO)
14	85	143.5–145	ir 3444, 3210, 1671; uv 252 (3.61), 302 (3.70); nmr (3:1 $CDCl_2$DMSO-d_6) δ 6.93 (s, H-3), 9.47 (s, CHO)
15	71	149.5–150	ir 3444, 3190, 1670; uv 250 (3.68), 303 (4.20); nmr DMSO-d_6) δ 7.17 (s, H-3), 9.48 (s, CHO)
16	71[b]	148–149.5	ir 3445, 3200, 1671; uv 250 (3.71), 302 (4.18); nmr DMSO-d_6) δ 7.18 (s, H-3), 9.48 (s, CHO)
17	27	118–120	ir 3460, 3270, 1670; uv 257 (3.95), 303 (4.07); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 7.03 (d, J = 1.4 Hz, H-3), 7.15 (b s, H-5) 9.55 (b s, CHO)
18	48[c]	70.5–71.5	ir 3210, 1630;[d] nmr ($CDCl_3$) δ 7.41 (m, H-2), 6.68 (m, H-4), 6.77 (m, H-5)[e]
19	89[c]	99.5–101.5	ir 3130, 1670;[d] nmr (3:1 $CDCl_3$–DMSO-d_6) δ 7.37 (m, H-2), 7.73 (m, H-5), 9.63 (b s, CHO)[e]
20	74[c]	81.5–83	ir 3150, 1630;[d] nmr (CCl_4) δ 6.58 (m, H-4), 6.75 (m, H-5), 7.45 (m, H-2)[e]
21	33[c]	59.5–60.5	ir 3150, 1620;[d] nmr $(CCl)_4$ δ 6.58 (m, H-4), 6.75 (m, H-5), 7.45 (m, H-2)[e]
22	53[f]		ir 3380, 772, 704;[d,g] nmr (CCl_4) δ 5.95 (m, H-4), 6.37 (m, H-2), 6.48 (m, H-5)[e]
23	51[f]		ir 3380, 772, 707[d,g]
24	50[h]	160–162	ir 1690;[d] nmr (DMSO-d_6) δ 7.42 (s, H-3), 11.33 (b s, CO_2H, NH)[e]

[a] Footnotes *a–f* of Table I apply to this table except that infrared spectra were obtained as 10^{-3} *M* solutions in CCl_4. [b] All yields are of crude product which were generally >90% of the stated compound. In this case, 16 comprised ~58% of the crude product by glpc. [c] Yield calculated from 1. [d] Nujol mull; values approximate. [e] No piperidine added to this solution. [f] Yield calculated from the ketone. [g] Infrared bands characteristic of 3-alkylpyrroles; ref 18. [h] Yield calculated from 1 after recrystallization from toluene.

and a material, probably the 5 isomer, showing a lesser retention time by glpc than **13**. Substitution in the 4 position was typically verified with the nmr spectral data, which showed the aldehyde proton split into a doublet and coupling of the remaining aryl protons of the magnitude expected for cross-ring coupling.[5] Compound 14, the dichloride, was easily prepared using 2 equiv of sulfuryl chloride, but the trichloroaldehyde could not be formed in refluxing ethylene dichloride.

Although the mixed dihalides 15 and 16 were successfully prepared, such reactions may incur displacement and rearrangement,[6,7] and the investigator is sometimes challenged with products that occur in the reaction mixtures as complexes[8] or have very similar physical properties which would thwart assignment of structure.[7a] When 1 was first chlorinated and then brominated, the crude product was primarily a mixed dihalide showing a glpc peak well separated from contaminants of shorter retention times, the principle one being the monochloropyrrole 13. The sharp melting point of the purified dihalide and its glpc retention time suggested that it was a single compound and a simple pyrrole derivative to which we assigned the structure 15.

Bromination of 1 followed by chlorination produced a mixed dihalide plus the 4,5-dibromide 11, with the latter predominating. When the intermediate brominated salt was stripped of HBr and the reaction mixture was reconstituted with fresh solvent prior to the addition of sulfuryl chloride, the product was free of 11 and consisted mainly of a mixed dihalide with essentially the same melting point as 15 (undepressed on admixture) and its nmr and uv spectral properties as well as its glpc behavior were indistinguishable from those of 15. However, the infrared spectra (Nujol mull and $CHCl_3$) showed a small but significant difference, namely, 15, 993 and 997 cm^{-1}; 16, 993 and 1002 cm^{-1}. In addition, the formation of 16 was almost completely inhibited by the addition of 2,6-diisopropylphenol in the chlorination step. Although dichlorination of 1 can be achieved at room temperature in ethylene dichloride, chlorination of the 4-brominated salt was much slower and, in fact, proceeded only to a slight extent in acetonitrile (64 hr). Thus the chlorination of the 4-brominated salt was apparently a free-radical reaction. Since reaction of a radical is expected to occur at position 5 on a pyrrole substituted in the 2 position with an electronegative substitutent,[8] this evidence of a radical pathway lends support to structure 16 (rather than rearrangement to 15) for this dihalide.

Iodinations of 1 with iodine in acetic acid or iodic acid[9] were unsuccessful. The 4-iodopyrrole-2-carboxaldehyde 17 was prepared, albeit in low yield, by treatment with $Tl(TFA)_3$[10] followed by KI.

Spectra of the haloaldehydes in dilute solution revealed both free and intramolecularly hydrogen bonded NH stretching modes. In general a β halogen lowered the free NH band to 3460–3467 cm^{-1}, α plus β halogens shifted this band to 3443–3445 cm^{-1}, and the third halogen displaced it a like amount to 3432 cm^{-1}. The presence of halogen atoms has been reported to increase the acidity of pyrroles,[4] and the considerably greater power of an electronegative substituent (*e.g.*, NO_2) in the α position has been made the basis of the chemical separation of isomers.[11] The stretching frequencies of the hydrogen-bonded NH of these haloaldehydes underscored this fact. Each of the three 4-haloaldehydes, 3, 13, and 17, absorbed most intensely at ~3260–3270 cm^{-1}. The 4,5-dihaloaldehydes and the tribromoaldehyde absorbed at ~3180–3210 cm^{-1}. The uv spectra of these compounds, excepting 12, were all very similar. The 250-mμ band was shifted to 270 mμ in the tribromoaldehyde 12. This band was seen at 265 mμ with 3,4-dichloropyrrole-2-carboxaldehyde.[8] A tentative explanation for this is a resonance interaction between the formyl group and the electron-donating ortho bromine atom. Such interaction is well documented for para-disubstituted benzene rings [12]

Acylation.—The Friedel–Crafts alkylation of pyrrole-2-carboxyaldehyde with isopropyl bromide was reported to proceed cleanly to 4-isopropylpyrrole-2-carboxaldehyde in high yield.[13] We turned our attention, therefore, to acylation reactions instead. The acetylation of 1 has been reported to occur with greater success than the analogous reaction of pyrrole-2-carboxaldehyde.[2] The acetylated aldehyde was converted in good yield to the acid by oxidation with Ag_2O. An improvement in the method of decarboxylation would make this an excellent route for β-acylpyrroles. In fact, 3-palmitoylpyrrole (18) was prepared in greater than 40% yield from pyrrole. Acylation of 1 with palmitoyl chloride and oxidation of the resulting 4-palmitoylpyrrole-2-carboxaldehyde (19) to the acid proceeded well with some modification necessitated by the low solubility of 19. The acid melted at 182–184° with gas evolution, and the decarboxylation was carried out easily at ~190–200°. Similarly, isopentyl pyrrol-3-yl ketone (20) (the nitrogen analog of perilla ketone[14]) and 3,7-dimethyloctyl pyrrol-3-yl ketone (21) were prepared. An attempt to improve the yield of methylpyrrol-3-yl ketone by heating the acid *in vacuo* at ~190–200° resulted in sublimation of the unreacted acid. The longer chains of the other acids lower their melting points considerably. Apparently a melt or its equivalent in molecular mobility is necessary for the decarboxylation. Because we were interested in screening the corresponding β-alkylpyrroles, 20 and 21 were reduced with $LiAlH_4$ to produce the air-sensitive 22 and 23, respectively (Scheme II).

Acylation of 1 with α-methyl-$\Delta^{1,\alpha}$-cyclohexaneacetyl chloride failed. Reaction of the corresponding acid[15] with $SiCl_4$ followed by addition of 1 and $SnCl_4$, a method which successfully produced thiophenes with unsaturated isoprenoid side chains,[16] likewise failed. In both cases the infrared spectra of the crude products indicated that considerable γ-lactone had formed.

Formylation.—When 1 was subjected to the Vilsmeier–Haack formylation procedure there was es-

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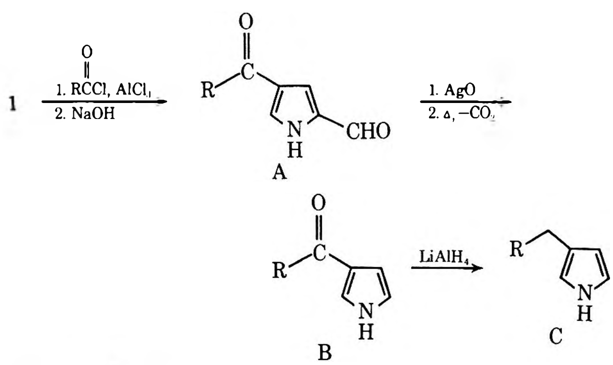
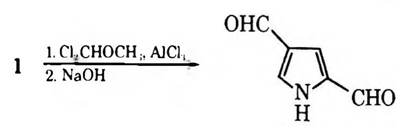
SCHEME II



A, 19, R = $C_{15}H_{31}$
B, 18, R = $C_{15}H_{31}$
20, R = $CH_3CH(CH_3)CH_2CH_2-$
21, R = $CH_3CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2CH_2-$
C, 22, R = $CH_3CH(CH_3)CH_2CH_2-$
23, R = $CH_3CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2CH_2-$

sentially no reaction. The Friedel–Crafts formylation using dichloromethyl methyl ether and $AlCl_3$ gave yields of 40–50% of pyrrole-2,4-dicarboxaldehyde (**24**).[17] Other Lewis acid catalysts ($ZnCl_2$, $SnCl_4$, $BF_3 \cdot Et_2O$) provided only tars and unchanged starting aldehyde.



24

Nitration.—The nitration of pyrrole-2-carboxaldehyde with acetyl nitrate has been described.[18] We found that nitration of this aldehyde with concentrated HNO_3 produced a greater quantity of crude product and the relative amounts of 4 and 5 isomers was 64:36 at −2°. The reaction of **1** under these conditions was much slower, but the ratio of mononitration products was not materially changed (67:33). The corresponding salt of the weaker base morpholine gave an even slower reaction producing a 64:36 product ratio. Evidently the salts are hydrolyzed to the aldehyde and it is this species which is nitrated. Reaction of the aldehyde with concentrated HNO_3 at −20° increased the ratio of 4:5 to 75:25.

Treatment of the aldehyde with acetyl nitrate at −2° in our hands gave a ratio of 37:63, indicating that protonation of the aldehyde in concentrated HNO_3 was responsible for a greater percentage of 4 isomer in the nitration product obtained therefrom. Nitration of benzaldehyde, for example, produces 72% *m*-nitrobenzaldehyde from fuming HNO_3 and 91% from oleum.[19] A nitration of pyrrole-2-carboxaldehyde in oleum resulted in a fire. Compound **1**, however, was converted to a dinitropyrrole-2-carboxaldehyde, which was characterized as the corresponding carboxylic acid, **24**. The assignment of the 4,5-dinitro structure is by analogy with the other electrophilic substitutions discussed. Apparently the salt is nitrated (it cannot hydrolyze to aldehyde first), but under these conditions dinitration occurs.

Miscellaneous Reactions.—Compound **1** gave no reaction under the usual conditions of the Mannich reaction,[20] nor did it react with formaldehyde under the influence of acid in ethanol to produce either a dipyrrylmethane or an alkoxymethylpyrrole. Moreover, **1** did not react with pyrrole (the production of a Mannich base, dipyrrolylmethane, was attempted). Both oxalyl chloride and phosgene failed to react with **1** in refluxing ethylene dichloride. Phosgenation with $AlCl_3$ produced tars, and phosgenation using *N,N*-dimethylaniline followed by treatment with methanol gave a crude mixture that probably contained primarily N-acylated material (1765 cm^{-1}). Chloromethylation with chloromethyl methyl ether and $AlCl_3$ gave only tarry material.

Summary.—The low reactivity of **1** limits electrophilic substitution reactions to only the more reactive electrophiles. However, considerably greater specificity for 4 substitution occurred as compared to analogous reactions of pyrrole-2-carboxaldehyde in the case of halogenation. Much better yields of acylation (4 isomer) and formylation (4 isomer) products can be obtained by using **1**. The iminium group is so deactivating that the salt derived from furfural could not be brominated.

The haloaldehydes may serve as sources of the otherwise not readily available halocarboxylic esters. These could serve as intermediates for the synthesis of, *e.g.*, pyoluteorin[21] and, in fact, we have found that the 4-haloaldehydes and corresponding methyl carboxylates are active as trail-marking chemicals for the Texas leaf-cutting ant, *Atta texana* (Buckley).[22] In addition the acylaldehydes are useful in preparing 3-acyl- and 3-alkylpyrroles.

Experimental Section

Gas chromatographic analyses were carried out with an Aerograph Model A-700 instrument employing principally an SE-30 column (5% on acid-washed Chromosorb W, 3.05 m × 0.32 cm) at 150–200°. Mention of a proprietary product in this paper does not constitute endorsement by USDA.

1-(Pyrrol-2-yl)ethylidenepyrrolidinium Perchlorate (6).—The preparation of 1 has been reported.[2] Typically, the methyl substituent slowed the condensation and an example of lowered yield and recovered starting material is given here. Pyrrolidinium perchlorate (0.02 mol), 0.02 mol of methyl pyrrol-2-yl ketone,[23] and 2 drops of pyrrolidine were heated under reflux in 50 ml of C_6H_6 for 2 hr using a Dean–Stark trap. The mixture was cooled and decanted, and the resiude was washed with Et_2O. Removal of the solvents from the washings yielded 1.4 g of the ketone. The residual oil was washed with H_2O, dissolved in ethylene dichloride, and dried (Na_2SO_4). Removal of solvent followed by crystallization from anhydrous Et_2O gave 0.50 g of **6**.

4,5-Dibromopyrrole-2-carboxaldehyde (11).—Bromine (1.60 g) in 10 ml of ethylene dichloride (EDC) was added dropwise to a solution of 1.25 g of **1** in 25 ml of EDC at 5–7°. The mixture was allowed to stand at room temperature overnight. The solvent was stripped to give the dibrominated salt, mp 158–159.5° (EDC). A mixture of 0.5 g of NaOH, 0.5 g of this salt, and 20 ml of EtOH (1:1) was swirled till homogeneous. After 1 hr, the mixture was acidified (HCl) and extracted with Et_2O; the extract was dried ($MgSO_4$) and concentrated to give 0.31 g of **11**.

3,4,5-Tribromopyrrole-2-carboxaldehyde (12).—The 4,5-dibromo salt (2.03 g) and 1 equiv of bromine were heated under re-
the product was filtered with C_6H_6, giving 2.15 g (88.5%) of tribromo salt, mp ~245° dec (CH_3CN–Et_2O). A mixture of this salt (0.70 g), 0.50 g of NaOH, and 20 ml of EtOH–H_2O (1:1) was heated until the mixture became homogeneous (~10 min),

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cooled to room temperature, and then worked up as described for 11. The yield of 12 was 0.48 g.

4-Chloropyrrole-2-carboxaldehyde (13) and 4,5-Dichloropyrrole-2-carboxaldehyde (14).—The procedures for preparing these compounds were analogous to those employed for the bromo aldehydes, except that the sulfuryl chloride was substituted for bromine. The monochlorinated salt melted at 126–128° (EDC–Et_2O) and the dichloro salt at 209–214° (EDC–Et_2O).

5-Bromo-4-chloropyrrole-2-carboxaldehyde (15).—Chlorination was carried out on 1 in the usual way. After 1 hr the mixture was cooled and 1 equiv of bromine in EDC was added. The mixture was stirred overnight at ambient temperature and the product was hydrolyzed in the usual manner. Recrystallization twice from C_6H_6–petroleum ether (bp 30–60°) gave the product, mp 149.5–150°.

4-Bromo-5-chloropyrrole-2-carboxaldehyde (16).—The procedure was as for 15 except that the addition of halogenators was reversed and the intermediate bromo salt was freed of HBr by stripping the solvent. After hydrolysis the crude product was analyzed by glpc as 58% 16, with the remainder mainly 4-bromo aldehyde. The crude product (1.6 g) was placed on 5 g of alumina and added to a 48-g column of alumina in C_6H_6–petroleum ether (1:1). The 4-bromoaldehyde (0.15 g) was obtained by elution with C_6H_6–Et_2O. The dihalide 16 was obtained with EtOAc–Et_2O and, finally, MeOH–C_6H_6 and weighed (0.80 g). Recrystallization twice from C_6H_6 gave product of 91% purity (glpc), mp 148.5–149.5°.

4-Iodopyrrole-2-carboxaldehyde (17).—To a suspension of 1.25 g of 1 in 10 ml of TFA was added 7.2 g of $Tl(TFA)_3$[10] and the mixture was heated under reflux overnight. The mixture was cooled and stripped of solvent. The product was treated with 6.5 g of KI in 25 ml of H_2O. After 15 min some $KHSO_3$ was added and the mixture was made alkaline with aqueous NaOH and filtered. The orange solid obtained was warmed on a steam bath with 1 g of NaOH in 10 ml each of H_2O and EtOH for 40 min. The mixture was cooled, filtered, acidified with HCl, and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated to give 0.3 g of 17. The glpc analysis revealed a minor component of low retention which may be the 5 isomer.

4-Palmitoylpyrrole-2-carboxaldehyde (19) and Similar Acylations of 1.—To a solution of 1.25 g of 1 in 25 ml of EDC was added 1.47 g of $AlCl_3$. To the resulting violet solution, cooled to 0°, was added 1.27 g of palmitoyl chloride in 5 ml of EDC. The mixture was kept at 0° overnight and then poured over crushed ice; 20 ml of H_2O containing 1 g of NaOH was added thereto, and the mixture was stirred vigorously for 15 min. It was then acidified (HCl) and extracted with $CHCl_3$. The extract was washed to neutrality, dried ($MgSO_4$), and concentrated, giving 1.48 g of 19. Acylations of 1 with 4-methylvaleryl chloride and 4,8-dimethylnonanoyl chloride were carried out in a similar manner. The oily keto aldehydes obtained were oxidized directly to keto acids.

4-Palmitoylpyrrole-2-carboxylic Acid and Similar Oxidations of 4-Acylpyrrole-2-carboxaldehydes.—The crude aldehyde obtained above (2.96 g) was dissolved in 100 ml of EtOH to which was added a solution of 2.50 g of $AgNO_3$ in 35 ml of H_2O. The mixture was heated under reflux and a solution of 7.1 g of NaOH in 75 ml of H_2O was added in a slow stream. The mixture was heated for 1 hr with vigorous stirring and filtered by suction, and the precipitate was washed with H_2O. The filtrate was diluted with two volumes of H_2O and acidified (HCl). The crystalline acid (2.44 g) was collected by filtration, mp 182–184° dec (EtOH). Oxidations of the other keto aldehydes were carried out in the same way to give the crystalline acids: 4-(4-methylvaleroyl)pyrrole-2-carboxylic acid, mp 213–213.5° (aqueous EtOH), and 4-(4,8-dimethylnonanoyl)pyrrole-2-carboxylic acid, mp 181–183° (aqueous EtOH).

3-Palmitoylpyrrole (Pentadecyl Pyrrol-3-yl Ketone) (18) and Decarboxylations of 4-Acylpyrrole-2-carboxylic Acids to 20 and 21.—The 4-palmitoylpyrrole-2-carboxylic acid (2.0 g) was heated under N_2 at 190–200° with magnetic stirring for 5 hr. The mixture was cooled and extracted with hot benzene and the extract was filtered and stripped. The residue was recrystallized from hexane to give 1.30 g of 18. Decarboxylation of 4-(4-methylvaleroylpyrrole-2-carboxylic acid (486 mg) was acflux in 20 ml of AcOH for 2.5 hr. The AcOH was stripped and complished by heating to melting (~215°) at 1 mm. After 1.25 hr, 325 mg of 20 was obtained from the condenser. Another 17 mg was obtained by working up the pot residue as above. Decarboxylation of 4-(4,8-dimethylnonanoyl)pyrrole-2-carboxylic acid was best conducted at atmospheric pressure. The product, however, was purified by passage through alumina with hexane–Et_2O; only 1.64 g of 21 was obtained from 5.00 g of the acid.

Reductions of 3-Acylpyrroles to 3-Alkylpyrroles 22 and 23.—The acylpyrrole 20 (1.24 g) was added in portions to a slurry of 0.5 g of $LiAlH_4$ in 40 ml of anhydrous Et_2O. The mixture was heated under reflux for 45 min and then worked up in the usual way. The product was subjected to short-path distillation, bp 58–60° (0.15 mm), 0.60 g (53%). Similarly, 21 was converted to 23. The crude product was purified by distillation in a Hickman still, bath temperature 120–130° (0.05 mm), yield 51%.

Pyrrole-2,4-dicarboxaldehyde (24).—To a solution of 1 (1.25 g) and $AlCl_3$ (1.47 g) in 20 ml of EDC kept at 0° was added 0.86 g of Cl_2CHOCH_3. The mixture was stirred without cooling for 0.5 hr, decomposed with ice, and made alkaline with aqueous NaOH; after 5 min of vigorous stirring, it was acidified (HCl) and extracted continuously with ether for 16 hr. The crude product was dissolved in EtOAc and filtered through 10 g of alumina to give 0.26 g (43%) of 24, mp 154° (lit.[17] mp 151.5–152°). The glpc trace showed this material to be virtually free of any isomer of lesser retention time, *i.e.*, 2,5-dialdehyde.

Nitration of 1 with Concentrated HNO_3.—The salt 1 (1.25 g) was added in portions to 20 ml of concentrated HNO_3 cooled to 0° and stirred magnetically. The mixture became homogeneous in ~15 min and was then stored at −20° overnight. The mixture was poured over ice and made alkaline with aqueous NaOH, and after 5 min was acidified (HCl) and extracted continuously with Et_2O for 5 hr. The solvent was stripped from the extract and the crude product was extracted with hot benzene. Removal of the benzene left 0.53 g of red solid. Recrystallization from benzene gave a product showing two glpc peaks (see text). Several preparations were combined and submitted to column chromatography using Brockman neutral alumina, activity I. Material corresponding to the longer retention glpc peak was eluted with Et_2O–C_6H_6. It was identical (glpc, ir) with a known sample of 4-nitroaldehyde, mp 140–141.5° (lit. mp 142°)[24] with no depression on admixture with an authentic sample.[25] A sample of the shorter retention component was obtained by elution with EtOAc–Et_2O, mp 181.5–183° (lit. mp 185°).[23]

Nitration of 1 in Oleum.—The salt 1 (5.0 g) was added in small portions to a vigorously stirred solution of 2 g of 90% HNO_3 in 9 ml of 30% SO_3–H_2SO_4 kept at <0° under N. The amber solution was stored at −2° for 16 hr. The mixture was poured over crushed ice and filtered to give 4.5 g of yellow solid. The aldehyde could not be freed of pyrrolidine and so this product (a salt) was oxidized directly to the acid 24. The yellow solid, 1 g, was added to 220 ml of 1 *N* NaOH, and a solution of 1.1 g of $AgNO_3$ in 100 ml of H_2O was added thereto. The mixture was warmed to 40° and stirred for 0.5 hr. The mixture was filtered, brought to neutrality with dilute HCl, and extracted continuously with Et_2O for 16 hr. The extract was dried ($MgSO_4$) and concentrated to a yellow-brown solid (0.7 g). Extraction of this material with toluene gave 0.45 g of 24, mp 160–162°.

Registry No.—1, 27521-94-4; 1 (dibromo derivative), 33515-46-7; 1 (tribromo derivative), 33515-47-8; 1 (monochloro derivative), 33515-48-9; 1 (dichloro derivative), 33515-49-0; 3, 931-33-9; 6, 33515-51-4; 7, 33515-52-5; 8, 33515-53-6; 9, 33515-54-7; 10, 33515-55-8; 11, 932-82-1; 12, 33515-57-0; 13, 33515-58-1; 14, 33515-59-2; 15, 33515-60-5; 16, 33515-61-6; 17, 33515-62-7; 18, 33515-63-8; 19, 33578-91-5; 20, 33515-64-9; 21, 33545-28-7; 22, 33515-65-0; 23, 33515-66-1; 24, 23999-91-9; 4-palmitoylpyrrole-2-carboxylic acid, 33515-68-3; 4-(4-methylvaleroyl)pyrrole-2-carboxylic acid, 33515-69-4; 4-(4,8-dimethylnonanoyl)pyrrole-2-carboxylic acid, 33515-70-7.

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Reduction of Nitroaryls by Dodecacarbonyltriiron–Methanol[1]

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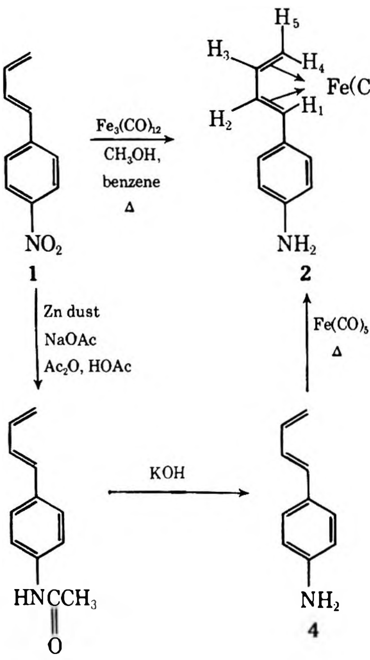
Methanolic solutions of dodecacarbonyltriiron [$Fe_3(CO)_{12}$] *specifically* reduce the nitro group of nitroaryls to a primary amine in the presence of functional groups often encountered in aromatic synthesis (*e.g.*, C=C, C=O, CO_2R, NHAc). High yields result. The effective reducing agent is the hydridoundecacarbonyltriferrate anion. Aspects of the synthetic scope and mechanistic pathway are discussed.

Our interest in the use of dodecacarbonyltriiron-methanol systems for the reduction of nitro groups arose from an attempt to prepare *p*-nitrophenylbutadienetricarbonyliron. Reaction of *p*-nitrophenylbutadiene (1) with a molar amount of dodecacarbonyltriiron [$Fe_3(CO)_{12}$] gave a mixture of amines 2 and 4. With a two fold excess of $Fe_3(CO)_{12}$, an 80% yield of complex 2 was obtained; the structure was confirmed by the alternative synthesis outlined in Scheme I. The

SCHEME I



source of proton for the reduction was apparently the methanol included in the $Fe_3(CO)_{12}$ reagent as a stabilizer (*ca.* 10% by weight).[4] Without methanol no amine was obtained; instead the reaction yielded a complex (*vide infra*).

Since 1 was reduced in high yield without loss of the sensitive functional group, other nitroaryls were tested in order to broaden the synthetic applicability. The conditions used are outlined in eq 1. The compounds

$$\underset{0.01\ M}{ArNO_2} + \underset{0.01\ M}{Fe_3(CO)_{12}} + \underset{\substack{2.5\ ml \\ (0.1\ M)}}{CH_3OH} \xrightarrow[\substack{reflux \\ 10\text{–}17\ hr}]{\text{excess benzene,}} ArNH_2 \quad (1)$$

reduced are listed in Table I. Conditions were not optimized for each compound. Yield analyses were carried out either using vapor phase chromatography (vpc) (internal standard) or by product isolation.

TABLE I

YIELDS OBTAINED FROM REACTION OF $ArNO_2$ AND $Fe_3(CO)_{12}$ WITH METHANOL IN BENZENE

$NO_2C_6H_4X$, X	$NH_2C_6H_4X$, Yield of amine, %
H	77[a]
p-Cl	86[a]
o-Cl	83[a]
p-CH_3	73[a]
o-CH_3	87[a]
m-NH_2	95[a]
p-NH_2	63[a]
m-NO_2	77[a,c]
p-CO_2Et	83[a]
o-Br	86[a]
p-OCH_3	84[a]
p-OH	38[b]
m-OH	66[b]
p-$COCH_3$	91[b]
p-$NHCOCH_3$	77[b]
p-CH=CHCH=CH_2	80[b,d]
o-Biphenyl	93[b]

[a] Determined by vpc. [b] Isolated yield. [c] Using a twofold excess of reagent. [d] Isolated as the tricarbonyliron complex.

Reduction of the nitro group is specific and takes place in relatively high yields with a variety of substituents (Table I). Acid- or base-sensitive groups survive; carbonyl and olefin groups remain unaltered. Only amine results; no azo, azoxy, or carbonyl insertion products are formed.[5] Complete reduction takes place with less than a stoichiometric quantity of $Fe_3(CO)_{12}$ (Table IV); however, the reaction is not catalytic. Shorter reaction times may improve yields (Table V).

Several mechanistic questions required answers: What happens to the oxygens from the $-NO_2$ group? What is the role of the $Fe_3(CO)_{12}$ and the purpose of the methanol? Are intermediates such as polynuclear carbonyliron anions or organometallic complexes involved?

Results and Discussion

Some of the oxygen appears as carbon dioxide; only 1 mol of CO_2 is found (Table III). One of the oxygens of the $-NO_2$ function must be lost by oxidation of ligand carbon monoxide. The other oxygen is lost by another route. Insoluble iron residues result and appear to be iron oxides; loss of oxygen to iron may be involved.

(1) This work was supported by the National Science Foundation. It was presented at Metrochem '71, San Juan, Puerto Rico, April 30–May 3, 1971, Abstracts of Papers, p 19.

(2) Abstracted in part from the Ph.D. Thesis of Lawrence Katz, Adelphi University, April 1971.

(3) Abstracted in part from the M.S. Thesis of Carol Olsen, Adelphi University, June 1971.

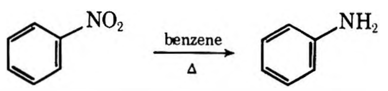
(4) $Fe(CO)_5$, $Fe_2(CO)_9$, and $Fe_3(CO)_{12}$ supplied by Alfa Inorganics, Beverly, Mass.

(5) (a) H. Alper and J. T. Edward, *Can. J. Chem.*, **48**, 1543 (1970); (b) Professor H. Alper, private communication.

Dodecacarbonyltriiron and methanol, in the absence of nitroaryl, gave an unstable, pyrophoric red solid (eq 2). An absorption maximum at 543 mμ (MeOH)

$$Fe_3(CO)_{12} + CH_3OH \xrightarrow[\text{benzene, 7.5 hr}]{\Delta} \text{Red solid on filtration} \quad (2)$$
$$\lambda_{max}\ (MeOH)\ 602\ m\mu \qquad \lambda_{max}\ (MeOH)\ 543\ m\mu$$

suggested the hydridoundecacarbonyltriferrate anion $[HFe_3(CO)_{11}^-]$ $[HFe_3(CO)_{11}^-$, λ_{max} 540 mμ;[6b] $Fe_3(CO)_{12}$, λ_{max} 605 mμ[6a]]. Two salts of this anion were brick red to black, pyrophoric crystalline solids; visible spectra corresponded to the isolated red solid {$Et_3NH[HFe_3(CO)_{11}]$ (**5**), λ_{max} 540 mμ;[6a] $Me_4N[HFe_3(CO)_{11}]$} (**6**), λ_{max} 540 mμ[6a]]. Thus, $Fe_3(CO)_{12}$ is converted into an active hydrido species which is the effective reducing agent. The reaction time is important; after 7.5 hr the 602-mμ absorption of the $Fe_3(CO)_{12}$ is lost and only the 543-mμ absorption remains. When nitrobenzene was introduced into the reducing system which showed absence of the $Fe_3(CO)_{12}$ (602 mμ) but presence of the suspected $HFe_3(CO)_{11}^-$ anion (543 mμ), aniline was formed. The salts **5**[6a] and **6**[7a] also reduce nitrobenzene to aniline (eq 3).



(3)

a. $Fe_3(CO)_{12}$ + CH_3OH reflux in benzene for 8 hr, then add $PhNO_2$	34% (37% $PhNO_2$)
b. $Et_3NH[HFe_3(CO)_{11}]$(**5**)[6a]	62%
c. $Me_4N[HFe_3(CO)_{11}]$(**6**)[7a]	32%
d. $Fe(CO)_5$ + CH_3OH	0

Differences in yield are noted. In system a (eq 3) not all of the nitrobenzene is reduced, and the yield of aniline is low; this is probably due to loss of $HFe_3(CO)_{11}^-$ anion through decomposition or conversion to less active polynuclear carbonyliron species. Salt **5** gave aniline in yields close to the optimum obtained in the original reaction medium (eq 1, Table I). However, salt **6** reproducibly gave half as much aniline as did **5**. The apparent difference is the proton in **5**. Thus, a proton source is required. In salt **6**, therefore, the hydrido species acts not only as a reducing agent but also as a proton source (eq 4).[7] The methanol

$$HFe_3(CO)_{11}^- \longrightarrow H^+ + Fe_3(CO)_{11}^{2-} \quad (4)$$

reacts with the $Fe_3(CO)_{12}$ to form the hydrido species and acts as a proton source.

Pentacarbonyliron[4] and methanol did not reduce nitrobenzene. Alper[5] used these reagents to convert nitroaryls[5a] into azo, azoxy and/or amino compounds, and nitroalkyls[5b] into formamides and/or ureas. A key difference is the solvent and temperature for reaction: dry diglyme and 130° in his system *vs.* dry benzene and 80° in our system. Differences in the effective reagent and reaction pathway are apparent.

Hieber and Brendel[7] established the formation of the $HFe_3(CO)_{11}^-$ anion from methanol and $Fe_3(CO)_{12}$.

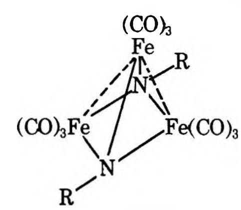
$$3Fe_3(CO)_{12} \xrightarrow{MeOH} Fe(MeOH)_n[Fe_3(CO)_{11}] + 5Fe(CO)_5$$
$$2Fe(MeOH)_n[Fe_3(CO)_{11}] \longrightarrow Fe(OMe)_2 + Fe(MeOH)_n[HFe_3(CO)_{11}]_2$$
$$Fe(MeOH)_n[HFe_3(CO)_{11}]_2 \longrightarrow Fe(OMe)_2 + 2H_2Fe_3(CO)_{11}$$

Pentacarbonyliron can be detected in our product mixtures.

The nature of the intermediates remains. Since only one oxygen is lost by oxidation of ligand carbon monoxide to carbon dioxide, nitrosobenzene may be generated. This possibility was eliminated, since reduction of nitrosobenzene with **6** or with $Fe_3(CO)_{12}$ and methanol in benzene gave azobenzene, azoxybenzene, and a substantial quantity of CO_2 in addition to aniline. Since no azobenzene or azoxybenzene is observed in the reduction of nitrobenzene with either reagent, free nitrosobenzene is not involved.

When nitrobenzene was treated with methanol-free $Fe_3(CO)_{12}$[8] in anhydrous benzene, a complex (**7b**, 18%) and azobenzene (4%) resulted. The empirical formula of **7b** was established as $C_{21}H_{10}N_2O_9Fe_3$ by analysis. The mass spectrum had a parent peak at *m/e* 602 (±1) (2%) and showed successive loss of carbon monoxide units in the fragmentation pattern. The isotopic distribution of elements in the fragments agrees with the number of iron atoms (Table VI). The large peak at *m/e* 91 (±1) suggests that a Ph–N group might be present. The nuclear magnetic resonance spectrum of **7b** shows only an aromatic singlet and indicates only one type of aryl moiety.

Complex **7b** was compared spectrally to complex **7a** reported by Dekker and Knox.[9,10] The structure



7a, R = CH_3
b, R = Ph

of **7a** proposed by these workers[9] was confirmed by X-ray analysis.[11] Mössbauer spectra[12,13] showed identical oxidation states for the irons in both complexes. Thus, phenylnitrene or its complex **7b** may be intermediates.

A nitrobenzene reduction was stopped after 4 hr; work-up yielded no complex, only aniline and unreacted nitrobenzene. Should complex **7b** or free phenylnitrene be intermediates, their reduction must take place as fast as their formation. Dekker and Knox[9] proposed formation of **7a** through a triplet nitrene; complex **7b** might also arise in a similar way. However, reaction of nitrobenzene with methanol-free Fe_3-

(6) (a) J. R. Case and M. C. Whiting, *J. Chem. Soc.*, 4632 (1960); these workers describe the reduction of nitromethane with ethanolic solutions of $KHFe(CO)_4$; methylamine and ferric hydroxide result after 12 hr. (b) W. Hieber and H. Beutner, *Z. Naturforsch.*, **17b**, 211 (1962).

(7) (a) W. Hieber and G. Brendel, *Z. Anorg. Allg. Chem.*, **289**, 324, 338 (1957); (b) F. Calderozzo, R. Ercoli, and G. Natta in "Organic Syntheses *via* Metal Carbonyls," I. Wender and P. Pino, Ed., Interscience, New York, N. Y., 1968, pp 101, 109.

(8) Dodecacarbonyltriiron[4] was made methanol free by keeping the reagent at 0.5 mm for at least 5 hr; the quantity of reagent (6–10 g) gave constant weight readings after 5 hr.

(9) M. Dekker and G. R. Knox, *Chem. Commun.*, 1243 (1967).

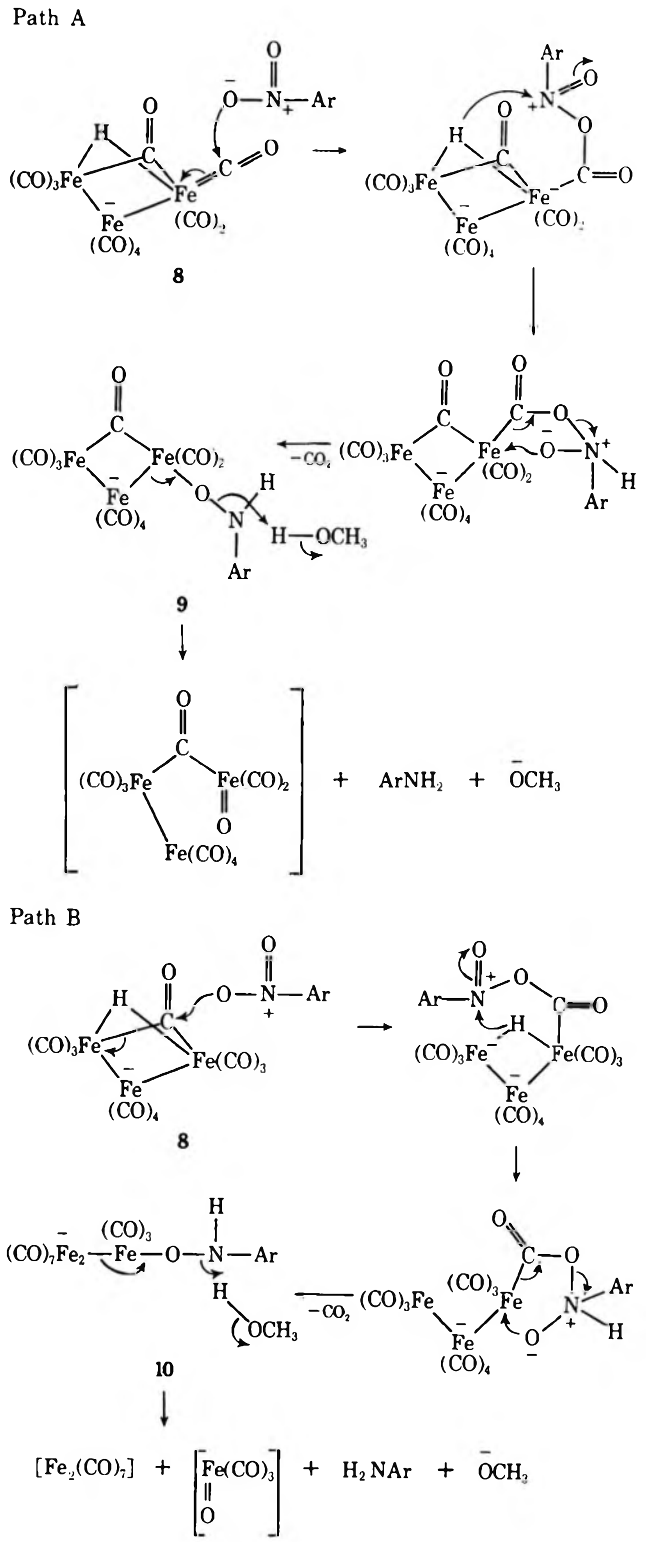
(10) We thank Professor G. R. Knox for kindly supplying a sample of **7a** and the spectra: λ_{max} (cyclohexane) ($\epsilon \times 10^3$) 311 (8.8), 356 (4.5), 410 (sh) (3.4), and 519 mμ (2.3); ν (CS_2) 2062 (vs), 2043 (vs), 2011 (s), 1979 (sh), 1960 cm^{-1} (sh) (C≡O).

(11) R. J. Doedens, *Inorg. Chem.*, **8**, 570 (1969).

(12) Mössbauer spectra of **7a** and **7b** were determined by Dr. F. Ross, Brookhaven National Laboratory, Brookhaven, N. Y.

(13) Professor R. Greatrex, The University of Newcastle upon Tyne, England, kindly provided data for Mössbauer spectrum of **7a**.

SCHEME II

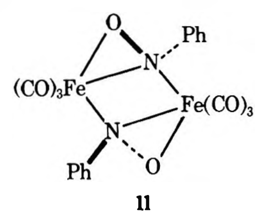


$(CO)_{12}$[8] in cyclohexane gave no *N*-phenylcyclohexylamine;[14,15] complex **7b** resulted (6%). A free nitrene appears unlikely.

Alper[5a] treated *o*-nitrobiphenyl with $Fe(CO)_5$ in hot butyl ether and found *o*-aminobiphenyl (58%) and carbazole (15%). Carbazole formation was taken as evidence for a nitrene intermediate.[5a,14] *o*-Nitrobiphenyl was treated with $Fe_3(CO)_{12}$. With methanol-free $Fe_3(CO)_{12}$[8] in anhydrous benzene, carbazole (1.3%) was found. Other products were isolated: *o*-aminobiphenyl (53%), *o*-hydrazobiphenyl (17%), and *o*-azobiphenyl (10%). Traces of a green complex were also found. In the presence of methanol, 1 mol of CO_2 was generated, but only *o*-aminobiphenyl (93%) was isolated; no carbazole was found. Therefore, though amine or coupling products may arise from a nitrene intermediate, either complexed or free,[5,9,14,15] a nitrene intermediate seems unlikely in the reduction of nitro groups to amines using methanol and $Fe_3(CO)_{12}$.

A rationalization for the reduction is presented in Scheme II. Attack of nitroxide oxygen on ligand carbon monoxide is the probable first step. This is similar to the proposal of Alper and Edward[5a] for the reduction of compounds with the N–O linkage. The site of attack could be either at a terminal carbonyl (path A) or at the bridging carbonyl (path B) of the $HFe_3(CO)_{11}^-$ anion (**8**).[16] A definitive choice between path A or path B cannot be made; however, the bridging carbonyl should be more susceptible to nucleophilic attack[17-19] and may account for the relative ease of the reaction [*vs.* $Fe(CO)_5$[5]]. Since nitroso intermediates have been discounted, transfer of the bridging hydrogen as a hydride ion[20] must follow and takes place before CO_2 loss. The complexed *N*-oxide can then decompose by attack on iron[21] with loss of 1 mol of CO_2. The new complex (**9** or **10**) can decompose by abstraction of a proton from methanol or from the $HFe_3(CO)_{11}^-$ anion,[7,20] if no other proton source is available; a nitrene or nitrene complex is never passed through.

The closest model for complexes of type **9** and **10** is bis(phenylnitroso)hexacarbonyldiiron (**11**) prepared by



11

Koerner von Gustorff and Jun.[22] Reduction of **11** gives aniline and small amounts of nitrosobenzene. The presence of aniline suggests that complexes of this type may be involved.

(14) J. E. Kmiecik, *J. Org. Chem.*, **30**, 2014 (1965), and references cited therein.

(15) J. H. Hall, J. W. Hill, and H. Tsai, *Tetrahedron Lett.*, 2211 (1965), and references cited therein; phenylnitrene inserts into cyclohexane to give *N*-phenylcyclohexylamine.

(16) The structure of the hydrodoundecacarbonyltriferrate anion has been determined: (a) L. F. Dahl and J. F. Blount, *Inorg. Chem.*, **4**, 1373 (1965); (b) K. Farmery, M. Kilner, R. Greatrex, and N. N. Greenwood, *J. Chem. Soc. A*, 2339 (1969).

(17) A bridging CO is more like an organic carbonyl group than is a terminal CO. It has also been noted that Lewis basicity may be a general property of the bridging carbonyl ligand.[18]

(18) N. J. Nelson, N. E. Kime, and D. F. Shriver, *J. Amer. Chem. Soc.*, **91**, 5173 (1969).

(19) See also (a) Sr. A. Alich, N. J. Nelson, and D. F. Shriver, *Chem. Commun.*, 254 (1971); (b) J. C. Katz and C. D. Turnipseed, *ibid.*, 41 (1970).

(20) P. L. Pausen, "Organometallic Chemistry," St. Martins Press, New York, N. Y., 1967, pp 91, 92.

(21) Ligand displacement on iron by $M^+–O^-$ (where M is N, S, P, As) is known; see (a) W. Strohmeier, J. F. Guttenberger, and G. Popp, *Chem. Ber.*, **98**, 2248 (1965); (b) W. Hieber and A. Lipp, *ibid.*, **92**, 2085 (1959); (c) W. Hubel in "Organic Syntheses *via* Metal Carbonyls," I. Wender and P. Pino, Ed., Interscience, New York, N. Y., 1968, p 322. (d) See also H. Alper, *Organometal. Chem. Syn.*, **1**, 69 (1970).

(22) (a) E. Koerner von Gustorf and M. J. Jun, *Z. Naturforsch.*, **20B**, 521 (1965); prepared photochemically from $Fe(CO)_5$ and nitrobenzene. (b) E. Koerner von Gustorf, M. C. Henry, R. E. Sacher, and C. DiPietro, *ibid.*, **21B**, 1152 (1966).

The carbonyliron fragments[23] which remain would undergo further decomposition and/or regeneration of the starting reagent, $Fe_3(CO)_{12}$; the latter is likely since a less than molar ratio of reagent brings about reduction. We hope to obtain more information on this reaction from further experiments.

Experimental Section

General.—Capillary melting points were taken with a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared (ir) spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer, calibrated with the 1944 and the 1601 cm^{-1} bands of polystyrene. Nuclear magnetic resonance (nmr) spectra were determined with a Varian A-60 spectrometer; the chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane used as internal standard; coupling constants (J) are accurate to ± 0.5 Hz. Vapor phase chromatography (vpc) was carried out isothermally on an F & M Model 720 thermal conductivity gas chromatograph using the following aluminum columns: A, 2 ft × 0.25 in., 10% UCW98 on Chromosorb P 60/80 mesh; B, 4 ft × 0.25 in., similarly packed; C, 2 ft × 0.25 in., 10% Carbowax 1540 on Chromosorb W, acid washed, 60/80 mesh. The reaction products were determined quantitatively by the internal standardization method.[24] Relative percentages were calculated with a Disc integrator, made by Disc Instruments, Inc. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6D mass spectrometer. Ultraviolet (uv) and visible spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer and standardized using holmium oxide glass. Mössbauer spectra were recorded at Brookhaven National Laboratory.[12] Analyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., or Spang Microanalytical Laboratory, Ann Arbor, Mich. Column chromatography was carried out using the "Dry Column" method of Loev[25] on silica gel approximately grade III (60–200 mesh). The commercial nitroaryls were purified by recrystallization or distillation. The standards were commercial samples or material isolated from the reduction reactions.

1-(*p*-Acetamidophenyl)-1,3-butadiene (3).—To a stirred solution of 35.04 g (0.20 mol) of 1-(*p*-nitrophenyl)-1,3-butadiene (1)[26] in 850 ml of glacial acetic acid, 850 ml of acetic anhydride, and 60 g of sodium acetate was added 100 g (1.53 g-atoms) of zinc dust over 20 min. The solution was stirred for an additional 2 hr at room temperature. Excess zinc and sodium acetate were removed by suction filtration, and the yellow solution was concentrated under reduced pressure. The yellow solid was allowed to stand overnight in contact with 1 l. of dilute ammonium hydroxide; the solid was broken up, placed in a Büchner funnel, and washed with several liters of water. The air-dry solid was dissolved in 800 ml of benzene, filtered, decolorized with Norit, and cooled in a refrigerator. The yellow crystals were dried on a Büchner funnel and washed with water. The yield was 20.5 g (55%) of yellow solid, mp 139–145°. The analytical sample was recrystallized twice from benzene as a very light yellow powder: mp 161–163° (corrected) (sealed evacuated tube); ir ν ($CHCl_3$) 3434 (NH), 1690 (C=O), 1601, 1588, and 1514 cm^{-1}; nmr δ (DMSO-d_6) 9.94 (broad s, 1, –NHAc), 7.25–7.80 [$(AB)_2$ q, d at 7.64, J = 9 Hz, d at 7.40, J = 9 Hz, 4, ArH), 6.20–6.90 (m, 3, –HC=CHCH=), 5.03–5.57 (m, 2, =CH_2), and 2.10 (s, 3, –$COCH_3$).

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.00; H, 7.00; N, 7.47. Found: C, 77.09; H, 7.13; N, 7.24.

1-(*p*-Aminophenyl)-1,3-butadiene (4).—A solution of 17.6 g of potassium hydroxide in 12.6 ml of water was diluted to 50 ml with methanol before adding 7.70 g (41.0 mmol) of 1-(*p*-acetamidophenyl)-1,3-butadiene (3). The mixture was heated for 15 min on a steam bath, with stirring; 5 ml of water was added; and heating was continued for 15 min. Ether extraction yielded 4.22 g of a red liquid which was distilled to yield 2.22 g (37%) of colorless liquid, bp 84–86° (0.04–0.05 mm). The analytical sample of 4 was redistilled: ir ν (CCl_4) 3477 and 3392 (NH_2), 1621, 1601, and 1516 cm^{-1}; nmr δ (CCl_4) 6.17–7.12 [$(AB)_2$ q, d at 6.98, J = 8 Hz, d at 6.33, J = 8 Hz, 4, ArH), 5.92–6.49 (m, 3, –CH=CH=CH=), 4.79–5.27 (m, 2, =CH_2), and 3.43 (broad s, 2, $ArNH_2$).

Anal. Calcd for $C_{10}H_{11}N$: C, 82.75; H, 7.63; N, 9.65. Found: C, 82.60; H, 7.50; N, 9.71.

Its phenylthiourea derivative was prepared by heating with an excess of phenyl isothiocyanate. Several recrystallizations from aqueous ethanol gave an off-white solid, mp 137–140° dec.

Anal. Calcd for $C_{17}H_{16}N_2S \cdot H_2O$: C, 68.55; H, 6.08. Found: C, 68.66; H, 5.73.

1-(*p*-Aminophenyl)-1,3-butadienetricarbonyliron (2). **A.**—A mixture of 2.18 g (15.0 mmol) of 1-(*p*-aminophenyl)-1,3-butadiene (4) and 15 ml (23 g, 0.11 mol) of pentacarbonyliron[4] was heated under nitrogen, with stirring, at 110–115° for 24 hr. Removal of excess $Fe(CO)_5$ yielded a yellow solid. Its acetone solution was filtered, and upon solvent removal a tarry solid remained. This solid was heated with four 125-ml portions of ligroin (bp 60–90°) and the combined solutions were cooled to −78°. The yellow crystals weighed 0.38 g. The filtrate was concentrated to yield an additional 0.49 g. Evaporation to dryness followed by recrystallization of the residue from petroleum ether (bp 30–60°) yielded an additional 0.53 g. The total yield was 1.40 g (33%), mp 77.5–78.5°. The analytical sample was recrystallized from petroleum ether as golden crystals: mp 95.5–96° (corrected); ir ν (CCl_4) 3482 and 3402 (NH_2), 2047, 1980, and 1973 (C≡O), and 1257 cm^{-1} (CN); nmr δ ($CDCl_3$) 6.16–7.35 [$(AB)_2$ q, d at 8.05, J = 8 Hz, d at 6.49, J = 8 Hz, 4, ArH), 5.75 (dd, 1, J = 10 Hz, H_2, complexed vinyl proton), 5.05–5.54 (m, 1, H_3, complexed vinyl proton), 3.48 (broad s, 2, $ArNH_2$), 2.10 (d, 1, J = 9.5 Hz, H_1, complexed vinyl proton), 1.77 (dd, 1, J = 7.5 Hz, H_5, complexed vinyl proton), and 0.52 (dd, 1, J = 9.5, 2.5 Hz, H_4, complexed terminal vinyl proton).

Anal. Calcd for $C_{13}H_{11}FeNO_3$: C, 54.80; H, 3.89; N, 4.92. Found: C, 55.08; H, 3.68; N, 5.21.

B.—A mixture of 1.75 g (10.0 mmol) of 1-(*p*-nitrophenyl)-1,3-butadiene (1), 12.0 g of dodecacarbonyltriiron[4] (containing *ca.* 10% methanol), and 2.5 ml of methanol in 100 ml of benzene was stirred at 70° for 15 hr. The mixture was filtered, decolorized with charcoal, and evaporated. The residue was triturated with pentane and filtered to give 2.27 g (80%) of yellow-gold solid, mp 80–86°. Two recrystallizations from petroleum ether gave a pure sample, mp 95.5–96.5° (corrected), no depression by mixture melting point with previously obtained material.

General Reaction Procedure for the Reduction of Nitroaryls. **A.**—The nitroaryl (10 mmol) was refluxed overnight with either 5.0 g (methanol free)[8] or with 6.0 g of $Fe_3(CO)_{12}$[4] (containing *ca.* 10% methanol) (*ca.* 10 mmol) and 2.5 ml of absolute methanol in 100 ml of benzene under nitrogen. The reaction mixture was filtered, and the collected residue was washed with 100–200 ml of a solvent for the amino product. The filtrate was then concentrated to *ca.* 25 ml on a rotary evaporator. An internal standard (equivalent to 10 mmol of arylamine) was added. Product identification and relative percentages were determined by vpc, calibrating with authentic mixtures. Details are presented in Table II and yields are summarized in Table I.

B.—For certain arylamines, the product was isolated by evaporating a filtered solution to dryness. *p*-Aminophenyl gave a solid from benzene, 0.42 g (38%), mp 160–180° dec (lit.[27] mp 186°). *m*-Aminophenol yielded crystals from benzene, 0.72 g (66%), mp 120.5–121.5° (lit.[27] mp 123°). *p*-Aminoacetophenone was recrystallized from ligroin (bp 90–120°), 1.23 g (91%), mp 104–105° (lit.[27] mp 106°). *p*-Aminoacetanilide gave crystals from benzene, 1.16 g (77%), mp 158–160° (lit.[27] mp 162–162.5°).

Determination of Evolved Carbon Dioxide.—Escaping CO_2 gas was trapped in a moisture-protected tube of Ascarite[28] connected to the top of the reflux condenser. A positive stream of dry, CO_2-free nitrogen gas was bubbled through the reaction mixture. The results are given in Table III.

Reduction of Nitrobenzene.—Nitrobenzene was reduced using general reaction procedure A and varying the quantity of $Fe_3(CO)_{12}$. The results are presented in Table IV.

Time Study of the Reduction of Nitrobenzene with Dodeca-

(23) The chemistry of such species is unknown; however, organometallic oxo metal complexes are known; see M. Cousins and M. L. H. Green, *J. Chem. Soc.*, 1567 (1964).

(24) (a) L. Szepesey, "Gas Chromatography," English translation by E. D. Morgan, Iliffe Books, London, 1970, pp 133, 134, 266. (b) A. E. Messner, D. M. Rosie, and P. A. Argabright, *Anal. Chem.*, **31**, 230 (1959).

(25) B. Loev and M. M. Goodman, *Chem. Ind. (London)*. 2026 (1967).

(26) G. A. Ropp and E. C. Coyner in "Organic Syntheses," Collect. Vol., IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 727.

(27) R. C. Weast and S. M. Selby, Ed., "Handbook of Chemistry and Physics," 48th ed, The Chemical Rubber Co., Cleveland, Ohio, 1967.

(28) Purchased from Arthur H. Thomas Co., Philadelphia, Pa.

TABLE II

CONDITIONS FOR REDUCTION OF NITROARYLS

X	Reaction conditions	Vpc analysis: Column and column temp, °C	Vpc analysis: Internal standard	Vpc analysis: Amine, %
H	*a*	A, 100	Nitrobenzene[e]	77
	b	A, 100	Nitrobenzene[e]	76
p-Cl	*a*	A, 162	Biphenyl[e]	89
	b	A, 160	Biphenyl[e]	82
o-Cl	*a*	A, 125	Biphenyl[e]	89
	b	A, 122	Biphenyl[e]	84
p-CH_3	*a*	A, 125	Biphenyl[e]	73
	b	A, 125	Biphenyl[e]	73
o-CH_3	*a*	A, 120	Biphenyl[e]	87
m-NH_2	*a*	C, 170	*p*-Bromoaniline[f]	95
p-NH_2	*a*	C, 150	*p*-Bromoaniline[f]	63
m-NO_2	*c*	C, 170	*p*-Bromoaniline[f]	77
p-CO_2Et	*b*	C, 170	*p*-Bromoaniline[f]	83
o-Br	*b*	A, 125	Biphenyl[e]	86
p-OCH_3	*b*	C, 140	*p*-Bromoaniline[e]	84
p-OH	*b, d*			38[d]
m-OH	*b, d*			66[d]
p-$COCH_3$	*b, d*			91[d]
p-$NHCOCH_3$	*b, d*			77[d]

[a] General reaction A using 5.0 g of methanol-free $Fe_3(CO)_{12}$. [b] General reaction A using 6.0 g of $Fe_3(CO)_{12}$ containing *ca.* 10% CH_3OH. [c] General reaction A using 10.0 g of $Fe_3(CO)_{12}$ containing *ca.* 10% CH_3OH and 5.0 ml of CH_3OH. [d] Product isolated. [e] 0.01 mol of standard added. [f] 0.005 mol of standard added.

TABLE III

EVOLVED CARBON DIOXIDE DURING REDUCTION

X	Avg CO_2, %
H	101
p-Cl	95
o-Cl	84
p-CH_3	106
p-OCH_3	104
o-Br	84
p-$COCH_3$	85
p-$NHCOCH_3$	103
p-$CO_2CH_2CH_3$	87
o-Biphenyl	99

carbonyltriiron[4]–Methanol.—A mixture containing 1.23 g (10.0 mmol) of nitrobenzene, 5.03 g (10.0 mmol) of methanol-free $Fe_3(CO)_{12}$[8], 2.5 ml of methanol, and 2.35 g (10.0 mmol) of *p*-dibromobenzene was refluxed, with stirring, under nitrogen. At 0.5-hr intervals 0.5-ml aliquots were removed, filtered, and analyzed by vpc (column A, 74°). The results are presented in Table V. A control showed no loss of *p*-dibromobenzene under reaction conditions.

Further Studies on the Reduction of Nitrobenzene to Aniline with Dodecacarbonyltriiron–Methanol. A.—A mixture containing 6.0 g of $Fe_3(CO)_{12}$[4] (containing *ca.* 10% methanol) and 2.5 ml of methanol in 100 ml of benzene was refluxed, with stirring, under nitrogen. After 5 hr, 0.25-ml aliquots were removed at 15-min intervals.[29] Filtration of these aliquots yielded a red solid (kept under nitrogen) (*vide infra*) and a green solution. The filtrates were volumetrically diluted with cyclohexane and the absorbance at 602 mμ was monitored. The $Fe_3(CO)_{12}$ was consumed after 7.5 hr.

After 8 hr, 1.23 g (10.0 mmol) of nitrobenzene in 5 ml of benzene was added and the mixture was refluxed for an additional 16 hr. The solution was filtered and 2.36 g (10.0 mmol) of *p*-dibromobenzene was added. The yield of aniline (column A, 74°), was 37%; in addition, unreacted nitrobenzene (34%) was present.

B.—A mixture containing 0.62 g (5.0 mmol) of nitrobenzene, 3.20 g of $Fe_3(CO)_{12}$[4] (containing *ca.* 10% methanol), and 1.5 ml of methanol in 50 ml of benzene was refluxed for 4 hr, with stirring, under nitrogen. The green filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in a minimum quantity of methylene chloride, a small amount of silica gel was added, and the solvent was removed *in vacuo*. The dried mixture of silica gel and residue was added to the top of a column containing 70 g of silica gel.

The first fraction, eluted with petroleum ether, contained $Fe_3(CO)_{12}$. The second fraction, eluted with benzene, contained traces of a yellow solid: ir ν (CS_2) 2084 (mw), 2050 (s), and 2043 cm^{-1} (vs) (C≡O); the material rapidly deteriorated. Other fractions eluted with more polar solvents, contained only nitrobenzene and aniline.

(29) Up to 5 hr the solution is heterogeneous. After 5 hr the solution is homogeneous.

TABLE IV

STUDY OF THE RELATIONSHIP OF THE REACTANTS IN NITROBENZENE REDUCTION

Mole ratio[a]	Vpc column[b,c]	Yield of aniline, %	Yield of nitrobenzene, %
1:3	A	75	0
1:2	A	77	0
1:1	A	77	0
1:0.8	B	70	0
1:0.75	A	75	16
1:0.7	B	66	5
1:0.6	B	64	18
1:0.5	B	46	30
1:0.4	B	37	42
1:0.2	B	22	69

[a] $C_6H_5NO_2$:$Fe_3(CO)_{12}$ (methanol-free). [b] Column temperature maintained at 100°. [c] Internal standard, *p*-dibromobenzene.

TABLE V

RELATIVE PER CENT OF ANILINE AND NITROBENZENE WITH TIME

Time, hr	Nitrobenzene, %	Aniline, %
0.5	80	6
1.0	65	16
1.5	59	20
2.0	47	27
2.5	42	47
3.0	19	60
3.5	7	65
4.0	4	73
5.0	0	79
5.5	0	80
6.5	0	78
7.0	0	84
7.5	0	84
17	0	76

Reaction of Dodecacarbonyltriiron and Methanol in Benzene.—A mixture containing 6.0 g of $Fe_3(CO)_{12}$[4] (containing *ca.* 10% methanol), 2.5 ml of methanol, and 100 ml of benzene was refluxed under nitrogen with stirring. After 5 hr,[29] samples were filtered. The red solid formed a red solution in methanol: visible max 543 mμ; ir ν (DMF) 2040 (sh), 1998, 1964 (C≡O), and 1829 cm^{-1} (w) (bridging C=O); ν (cyclohexane) 2043, 1999, 1953 (C≡O), and 1812 cm^{-1} (bridging C=O).

Preparation of Hydridoundecacarbonyltriferrate Salts. A. Triethylammonium Hydridoundecacarbonyltriferrate (5).—This complex was prepared from pentacarbonyliron[4] and triethylamine as described by Case and Whiting.[6a] The impure material was usually pyrophoric. The recrystallized material (aqueous methanol) was obtained as large, dark red needles (stable for several weeks at 0°): visible max (MeOH) 545 mμ (ε 2.4 × 10^3); ir ν (DMF) 3540 (broad) (NH), 1947 (sh), 1975 (s), 1999 (vs), and 2062 cm^{-1} (vw) (C≡O) {lit.[6a] visible max (EtOH) 540 mμ (ε 3.06 × 10^3); lit.[30] ir [for unspecified salt of $HFe_3(CO)_{11}^-$] ν (DMF) 1950 (w), 1980 (m), 2004 (s), and 2070 cm^{-1} (vw) (C≡O)}.

B. Tetramethylammonium Hydridoundecacarbonyltriferrate (6).—This complex was prepared from dodecacarbonyltriiron[4] in

(30) W. F. Edgell, M. T. Yang, B. J. Bulkin, R. Bayer, and N. Koizumi, *J. Amer. Chem. Soc.*, **87**, 3080 (1965).

alkaline methanol by neutralization and treatment with tetramethylammonium iodide as described by Heiber and Brendel.[7a] This salt was always *pyrophoric* when impure. The dark red crystals from acetone were dried *in vacuo:* visible max (MeOH) 545 mμ (ε 2.7 × 10³); ir ν (DMF) 1962 (sh) and 1973 (m), 1997 (vs) and 2066 cm⁻¹ (w) (C≡O) [lit.[6a] visible max (aqueous MeOH) 540 mμ (ε 3.09 × 10³); lit.[30] ir, see A].

Reduction of Nitrobenzene with Hydridoundecacarbonyltriferrate Salts. A. Reduction with 5.—A mixture containing 1.23 g (10.0 mmol) of nitrobenzene, 5.79 g (10.0 mmol) of **5**, and 100 ml of dry benzene was refluxed for 15 hr under nitrogen. The reaction was worked up as in general reaction procedure A. The yield of aniline (column A, 74°) was 62%. A second reaction was carried out using 5.0 mmol of **5**. The yield of aniline (column A, 74°) was 38%.

B. Reduction with 6.—A mixture containing 551 mg (1.00 mmol) of **6** and 123 mg (1.00 mmol) of nitrobenzene in 10 ml of dry benzene was refluxed for 15 hr under nitrogen. The solution was worked up as above. The yield of aniline (column A, 74°) was 34%.

Reaction of Nitrobenzene with Dodecacarbonyltriiron in the Absence of Methanol. Formation of Bis(phenylnitrino)enneacarbonyltriiron (7b). A.—A mixture containing 2.46 g (20.0 mmol) of nitrobenzene and 10.1 g (20.0 mmol) of methanol-free $Fe_3(CO)_{12}$[8] in 200 ml of dry benzene was refluxed for 15 hr under nitrogen. The solution was filtered, the residue was washed with dichloromethane, and the combined solutions were evaporated *in vacuo*. The red-purple residue was taken up in a minimum amount of dichloromethane, mixed with a small amount of silica gel, and evaporated to dryness *in vacuo*. This silica gel was added to the top of a column containing 200 g of silica gel. The first fraction, a diffuse green band eluted with petroleum ether, was $Fe_3(CO)_{12}$. The second fraction, a purple-red band eluted with petroleum ether, yielded 1.19 g of black crystals, mp 143–145° (corrected) (18%). The analytical sample was recrystallized from pentane, black crystals: mp 143° (corrected); λ_{max} (cyclohexane) (ε × 10⁴) 330 (1.17), 365 (1.02), and 553 mμ (0.31); ir ν (CS_2) 2067 (vs), 2043 (s), 2022 (s), 1972 (vw), and 1956 cm⁻¹ (vw) (C≡O); nmr δ ($CDCl_3$) 6.96 (s, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 602 (2), 574 (90), 546 (97), 518 (5), 490 (49), 462 (81), 434 (97), 406 (86), 378 (39), 166 (24), 91 (93), 77 (99), 65 (95), 64 (50), 40 (45), 32 (46), and 28 (100); mol wt calcd for $C_{21}H_{10}N_2Fe_3O_9$, 602. The isotope distributions for four principle fragments are given in Table VI.

TABLE VI

MASS SPECTRA OF ISOTOPE PEAKS OF 7b

Peak	Found, %	Calcd, %
+1	31.9	29.7
574		assuming 100
−2	19.5	19.1
+1	28.0	28.6
546		assuming 100
−2	19.1	19.1
+1	26.8	26.4
490		assuming 100
−2	21.4	19.1
+1	25.2	24.2
462		assuming 100
−2	19.6	19.1

Anal. Calcd for $C_{21}H_{10}N_2Fe_3O_9$: C, 41.85; H, 1.80; N, 4.65. Found: C, 41.64; H, 1.77; N, 4.60.

The third fraction, eluted with petroleum ether, gave azobenzene, 38 mg (4%) of orange needles, mp 66–67° (corrected), no depression by mixture melting point with authentic material.

B.—A refluxing mixture containing 11.02 g (21.90 mmol) of methanol-free $Fe_3(CO)_{12}$[8] and 4.37 g (35.4 mmol) of nitrobenzene in 219 ml of dry benzene generated 98% of theoretical carbon dioxide. Column chromatography as described in A yielded 860 mg (8%) of **7b** and 840 mg (26%) of azobenzene.

C.—A mixture containing 615 mg (5.00 mmol) of nitrobenzene and 2.52 g (5.00 mmol) of methanol-free $Fe_3(CO)_{12}$[8] in 50 ml of cyclohexane was refluxed for 15.5 hr under nitrogen. Vpc[31] of the filtrate showed no detectable *N*-phenylcyclohexylamine. Column chromatography of the filtrate as described in A, using 42 g of silica gel, yielded 173 mg (6%) of **7b**.

Reduction of o-Nitrobiphenyl with Dodecacarbonyltriiron–Methanol.—*o*-Nitrobiphenyl, 1.99 g (10.0 mmol), when treated with 6.0 g of $Fe_3(CO)_{12}$[4] (containing *ca.* 10% methanol) according to general reaction procedure A, generated 436 mg (9.90 mmol, 99%) of carbon dioxide. After filtering, the filtrate was reduced in volume, a small amount of silica gel was added, and the solvent was evaporated *in vacuo*. This silica gel was added to the top of a column containing 100 g of silica gel. *o*-Aminobiphenyl, 1.57 g (92.5%), mp 46.5–47.5 (corrected) (lit.[27] mp 49–50°), was eluted with benzene.

Reaction of o-Nitrobiphenyl with Dodecacarbonyltriiron.—*o*-Nitrobiphenyl, 1.99 g (10.0 mmol), was treated with 5.03 g (10.0 mmol) of methanol-free $Fe_3(CO)_{12}$[8] in 100 ml of dry benzene as above. Carbon dioxide, 220 mg (5.0 mmol, 50%), was trapped. A similar work-up and column chromatography were carried out. Elution with petroleum ether removed $Fe_3(CO)_{12}$ and unidentified trace solids. Elution with carbon tetrachloride yielded 180 mg (10%) of *o*-azobiphenyl, orange needles from hexane, mp 138–140° (corrected) (lit.[27] mp 145°); its spectral characteristics were identical with those of authentic material.

Prior to recrystallization, solid from the above fraction was taken up in petroleum ether; 15 mg of an insoluble white solid remained, mp 239.5–242° (corrected). An additional 7 mg of insoluble white solid was obtained from the column by further elution with carbon tetrachloride. The combined 22 mg (1.3%) of material was carbazole (lit.[27] mp 247°), no depression on mixture melting point with authentic material. Elution with benzene yielded 900 mg (54%) of *o*-aminobiphenyl, mp 42–45° (corrected) (lit.[27] mp 49–50°). The solid was converted into the acetamide and gave a white solid from ligroin (bp 90–120°), mp 119–120° (corrected) (lit.[27] mp 121°). Elution with chloroform yielded 280 mg (17%) of *o*-hydrazobiphenyl, crystals from alcohol, mp 183.5–184.5° (corrected) (lit.[27] mp 182°).

Elution with more polar solvents yielded trace amounts of uncomplexed materials which were not characterized.

Repetition of this experiment with a different batch of methanol-free $Fe_3(CO)_{12}$[8,32] and carefully dried solvents gave similar results.

Reduction of Nitrosobenzene. A. With Dodecacarbonyltriiron–Methanol.—Nitrosobenzene, 1.07 g (10.0 mmol), $Fe_3(CO)_{12}$, 6.0 g (containing *ca.* 10% methanol), and methanol, 2.5 ml, when refluxed for 16 hr in 100 ml of benzene, with stirring and under nitrogen, yielded aniline (55%).[33] Azobenzene and azoxybenzene were detected, although the yields were not determined.[34]

B. With 6.—Nitrosobenzene, 96.3 mg (0.900 mmol), and **6**, 495 mg (0.900 mmol), in 9 ml of benzene were refluxed for 17 hr, with stirring, under nitrogen. Carbon dioxide, 36 mg (0.83 mmol, 92%), was trapped. The yield of aniline was 26%.[33] In addition, azobenzene (22%) and azoxybenzene (31%) were found.[35]

Reactions of Bis(phenylnitroso)hexacarbonyldiiron (11).[22] **A. With Dodecacarbonyltriiron–Methanol.**—A mixture containing 494 mg (1.00 mmol) of **11**, 1.25 g of $Fe_3(CO)_{12}$[4] (containing *ca.* 10% methanol, *ca.* 2 mmol), and 0.5 ml of methanol in 20 ml of benzene was refluxed for 16.5 hr, with stirring, under nitrogen. The yield of aniline was 55%.[33]

B. With 5.—A mixture containing 494 mg (1.00 mmol) of **11** and 579 mg (1.00 mmol) of **5** in 20 ml of dry benzene was refluxed for 15.5 hr, with stirring, under nitrogen. Trapped carbon dioxide totaled 15%. The yield of aniline was 21%;[33] a 2% yield of nitrosobenzene was also detected.[36] With 2.0 mmol

(31) Aniline detected, column B, 74°; the column was cleaned by raising the temperature to 160°. A sample was analyzed at 160° for *N*-phenylcyclohexylamine against prepared samples of known composition.

(32) Complex **7b** formed in a reaction using reagent from the same batch without aniline formation.

(33) Aniline analysis was carried out as previously described (column B, 80°; *p*-dibromobenzene).

(34) The oven temperature was raised to 185° removing azobenzene and azoxybenzene. These compounds were collected and compared to authentic samples: identical infrared spectra, no depressions on mixture melting point.

(35) Yields of azobenzene and azoxybenzene were determined against prepared samples of known composition (column B, 185°; *p*-dibromobenzene).

(36) Presence and yield of nitrosobenzene was determined by comparison to prepared samples of known composition (column B, 80°; *p*-dibromobenzene).

of 5, the carbon dioxide trapped amounted to 17%, the aniline found was 44%,[33] and the nitrosobenzene detected[36] was 4%. A third reaction with 4.0 mmol of 5 also gave carbon dioxide (11%), aniline (44%),[33] and nitrosobenzene (4%).[36]

Registry No.—**2**, 33479-92-4; **3**, 33482-90-5; **4**, 33537-34-7; **4** (phenylthiourea derivative), 33482-91-6; **5**, 18129-63-0; **6**, 33479-90-2; **7b**, 33519-79-8; **11**, 33479-91-3; dodecacarbonyltriiron, 15444-70-9; methanol, 67-56-1; nitrobenzene, 98-95-3; aniline, 62-53-3; *o*-nitrobiphenyl, 86-00-0; nitrosobenzene, 586-96-9.

The Isomerization and Disproportionation of Acylcobalt Carbonyls

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When acylcobalt carbonyls, $RCOCo(CO)_4$, are left standing under a nitrogen atmosphere, they not only slowly isomerize but disproportionate irreversibly to yield a mixture of aldehydes and olefins. Thus when R is n-C_3H_7, the products are n- and isobutyraldehyde and propylene, formed in accordance with the reaction scheme shown in Chart I. The report that nonpolar solvents inhibit the isomerization of acylcobalt carbonyls is confirmed, but this failure is now shown to arise because of the competing disproportionation reaction. In nonpolar solvents the olefin–metal hydride π complex required as an intermediate for the isomerization reacts with the acyl compounds to produce the aldehyde and olefin. With polar solvents, however, the π complex is rapidly converted to the σ complex and thence to the isomerized acylcobalt compound. The implications of these reactions for the mechanism of the oxo reaction in which the acylcobalt carbonyls play a vital role are discussed.

Although the room temperature, spontaneous interconversion of branched and straight chain acylcobalt carbonyls (eq 1) is well documented,[1-6] certain features

$$RCH_2CH_2COCo(CO)_n \rightleftharpoons \underset{COCo(CO)_n}{\overset{RCHCH_3}{|}} \quad (n = 3 \text{ or } 4) \tag{1}$$

of the isomerization are difficult to explain. Furthermore, these acyl compounds are intermediates in the oxo reaction and whether such interconversions affect the product distribution of the aldehydes, especially in the stoichiometric hydroformylation, has not been explicitly ascertained. Accordingly we undertook an investigation of this reaction in an effort to elaborate the details of the interconversion.

In our initial experiments we planned to prepare the acylcobalt carbonyls by the published procedure (eq 2)

$$RCOX + NaCo(CO)_4 \longrightarrow RCOCo(CO)_4 + NaX \tag{2}$$

and, after a lapse of time during which interconversion of the acyl compounds would be permitted to proceed, we planned to hydrogenolyze the resulting mixture with $HCo(CO)_4$ (eq 3) in order to duplicate the last step of the stoichiometric hydroformylation.

$$RCOCo(CO)_n + HCo(CO)_4 \longrightarrow RCHO + Co_2(CO)_{4+n} \tag{3}$$

In the course of studying this reaction, we found, much to our surprise, that aldehydes were formed even before the $HCo(CO)_4$ was added, and that in addition, olefins possessing one carbon less than the starting acyl compound were also formed. This observation indicated that not only were the acylcobalt carbonyls undergoing isomerization but they were disproportionating as well.

(1) Y. Takegami, C. Yokokowa, Y. Watanabe, H. Masada, and Y. Okuda, *Bull. Chem. Soc. Jap.*, **37**, 1190 (1964).
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(4) Y. Takegami, Y. Watanabe, H. Masada, Y. Okuda, K. Kubo, and C. Yokokowa, *ibid.*, **39**, 1495 (1966).
(5) Y. Takegami, C. Yokokowa, and Y. Watanabe, *ibid.*, **39**, 2430 (1966).
(6) Y. Takegami, Y. Watanabe, H. Masada, and T. Mitsudo, *ibid.*, **42**, 206 (1969).

Results and Discussion

Treatment of n- and isobutyrylcobalt tetracarbonyl under three different sets of conditions gave the results shown in Table I. These results are most conveniently

TABLE I

ISOMERIZATION AND DISPROPORTIONATION OF n- AND ISOBUTYRYLCOBALT CARBONYL[a]

Butyrylcobalt carbonyl	Atm	Solvent	—Butyraldehydes— Yield, mmol[b]	n, %	Iso, %
n	CO	Pentane	0.15	95	5
Iso	CO	Pentane	0.08	0	100
n	N_2	Pentane	0.55	77	23
Iso	N_2	Pentane	0.55	8	92
n	N_2	Ethyl ether	0.27	51	49
Iso	N_2	Ethyl ether	0.07	21	79

[a] 2.6 mmol of $NaCo(CO)_4$, 2 mmol of acyl chloride in 10 ml of solvent for 24 hr. [b] The yields of propylene were proportional to the yields of aldehydes.

discussed in terms of the reaction scheme shown in Chart I.

Under 1 atm of CO, relatively little of anything happens in 24 hr to either of the acylcobalt carbonyls, probably because the first steps in the reaction sequence involve the loss of CO and hence the reaction is inhibited. However, when the reaction is repeated under N_2 rather than under CO, extensive isomerization and disproportionation occurs. The total yield of aldehydes is the same (perhaps fortuitously, exactly the same, 55%) regardless of the structure of the starting isomer. The yield is based on the stoichiometry

$$2RCOCo(CO)_n \longrightarrow RCHO + R_{-H} + Co_2(CO)_{2n} \tag{4}$$

Under our conditions, the reaction does not go to completion because of the self-inhibiting effect of the CO liberated during the reaction. When ethyl ether rather than pentane is used as a solvent, there is much more extensive interconversion of isomers but appreciably less disproportionation; with isobutyrylcobalt carbonyl, practically no disproportionation occurs.

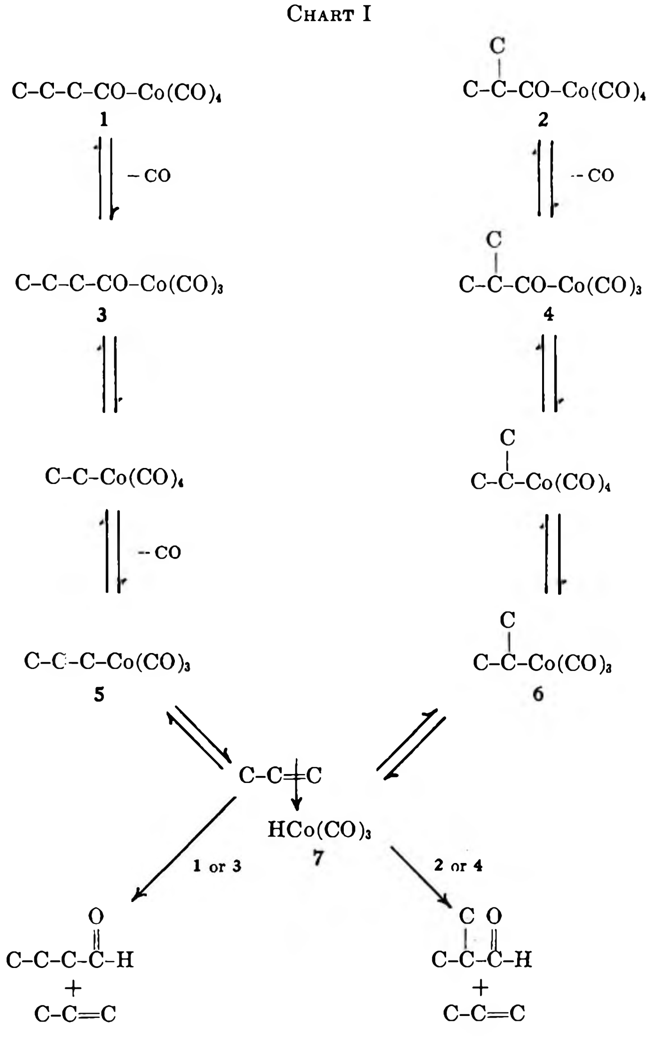
TABLE II

ISOMERIZATION AND DISPROPORTIONATION OF $RCOCo(CO)_4$ [R = n-C_4H_9 AND $CH_3CH(CH_3)CH_2$][a]

$RCOCo(CO)_4$	Hexane, ml	1-Pentene, mmol	C_6 Aldehydes			Butenes			
			Yield[b]	st[c]	br[d]	Yield[b]	1-	*cis*-2-	*trans*-2-
Pentanoyl	10	0	0.30	75.0	25.0	0.47	29.7	28.1	42.2
2-Methylbutanoyl	10	0	0.40	3.0	97.0	0.31	35.7	25.5	38.8
Pentanoyl	10	10	0.28[e]	31.5	68.5	0.48	29.0	28.6	42.4
2-Methylbutanoyl	10	10	0.21[e]	32.0	68.0	0.56	29.5	27.4	43.1
Pentanoyl	0	100[f]	0.01	*g*	*g*	0.26	31.6	29.7	38.7
2-Methylbutanoyl	0	100[f]	0.03	*g*	*g*	0.13	33.3	29.8	36.0

[a] 2.6 mmol of $NaCo(CO)_4$ and 2 mmol of acyl chloride under N_2 for 24 hr. [b] mmol. [c] Per cent straight chain. [d] Per cent branched chain. [e] A small amount of C_6 aldehydes was observed. [f] The recovered pentene was largely (>95%) 1-pentene and some pentane was present. [g] Too small for accurate determination but approximately 90% branched.

CHART I



It is well known[7] that coordinating solvents (S) promote the rearrangement of metal hydride–π olefin complexes to the corresponding σ complexes (eq 5). In

$$>C{\ddagger}C< \; + \; S \longrightarrow \; >CH\text{-}C< \quad (\text{MH on } \pi \text{ complex; MS on } \sigma) \qquad (5)$$

pentane, there is a relatively high concentration of π complex **7** (Chart I) which furnishes the MH required for the hydrogenolysis of $RCOCo(CO)_n$ to aldehyde. In ether, the σ complexes **5** and **6** are favored, relative to the π complex, and the relative unavailability of MH reduces the rate of hydrogenolysis to aldehyde. Previous reports[8] that propionylcobalt tetracarbonyl does not undergo disproportionation at room temperature are probably in error because ethyl ether was used as a solvent and the reaction time of 30 min was probably too short to observe the slow disproportionation.

Although the disproportionation of C_4 acylcobalt carbonyls leads to propylene as the only olefin, similar disproportionation of C_5 acylcobalt carbonyls can lead to a mixture of C_4 olefins. The results obtained from the disproportionation of pentanoyl- and 2-methylbutanoyl cobalt carbonyls are shown in Table II. One surprising feature of these data is that approximately the same mixture of butenes is obtained from the disproportionation of either of the isomeric acyl compounds. This mixture of butenes does not result from the interconversion of butenes catalyzed by $HCo(CO)_4$, since, if 1-pentene (1.1 ml = 10 mmol) is added to the mixture, essentially no isomerization to 2-pentene can be detected. The results can be rationalized on the basis of an extension of the scheme shown in Chart I. The interconversion of $\sigma \rightleftarrows \pi$ complexes is very fast compared to the final displacement of the butenes; thus the same mixture of butenes is obtained independent of the starting acyl compound. When 1-pentene is used as solvent (Table II), appreciable butenes are still formed but no aldehydes are produced because, although the liberated $HCo(CO)_3$ is tightly bound in π complexes, the large excess of olefin traps the hydrocarbonyl. The possibility that σ alkylcobalt carbonyls react with acylcobalt carbonyls to form alkenes and aldehydes in the disproportionation reaction, although unlikely, cannot be completely ruled out. The dramatic effect on the change in aldehyde distribution produced by the presence of 1-pentene is very puzzling and requires further investigation.

When the stoichiometric hydroformylation is carried out under CO, the yield of aldehyde depends on the relative rates of the two major reactions,[9] eq 6 and 7. In

$$RCH{=}CH_2 + HCo(CO)_4 + CO \longrightarrow RCH_2CH_2COCo(CO)_4 \qquad (6)$$

$$RCH_2CHCOCo(CO)_4 + HCo(CO)_4 \longrightarrow RCH_2CH_2CHO + Co_2(CO)_8 \qquad (7)$$

the presence of excess olefin reaction 6 is accelerated and the yield of aldehyde is depressed because the $HCo(CO)_4$ required for reaction 7 is consumed in reaction 6. As a result, when all the $HCo(CO)_4$ has disappeared, substantial cobalt is present as acylcobalt carbonyls. We have demonstrated above that, in the absence of an atmosphere of CO, the acylcobalt compounds isomerize and disproportionate. Thus we might expect that at

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(8) R. F. Heck and D. S. Breslow *J. Amer. Chem. Soc.*, **83**, 4023 (1961).

(9) L. Kirch and M. Orchin, *ibid.*, **81**, 3597 (1959).

the conclusion of a stoichiometric reaction conducted with excess olefin under CO, were the CO replaced with N_2, enhanced yields of aldehyde might be observed. This prediction was fully confirmed, as the data in Table III show. It will be noted from this table that the

TABLE III

STOICHIOMETRIC HYDROFORMYLATION OF 1-PENTENE[a]

Reaction time, hr	Yield of hexanals, %	Composition of hexanals, % Straight	Branched
16[b]	60.5	78.2	21.8
19	73.4	70.8	29.2
24	77.5	69.1	30.9
42	77.5	68.4	31.6

[a] 1.8 mmol of $HCo(CO)_4$, 10 mmol of 1-pentene, 13 ml of pentane. [b] After 16 hr the CO was replaced by N_2.

additional aldehyde formed (17%) after replacement of CO by N_2 is relatively richer in branched aldehyde. We have found that the distribution of aldehydes in the stoichiometric reaction carried out from its inception under N_2 favors the branched aldehydes; a 37% yield of total aldehydes consisting of 44% straight-chain and 56% branched-chain aldehyde is obtained. Incidentally, if this reaction is allowed to stand for an additional long period (44 hr), there is, as expected, no further change in yield or product distribution.

We have commented earlier on the effect of solvents on the isomerization and disproportionation of acylcobalt compounds. The effect of solvents on the stoichiometric hydroformylation reaction should be consistent with their effect on the isomerization and disproportionation of the acylcobalt compounds. We have written the formation of the acylcobalt carbonyls in one step as eq 6. In considering the yield of aldehydes in the stoichiometric reaction under N_2 and in the presence of excess olefin, the intermediate steps to the acylcarbonyl are important and require analysis. The first step is unquestionably the loss of CO and the complexation between olefin and $HCo(CO)_3$. The presence of CO or other nucleophiles should slow this reaction. On the other hand, the presence of ether solvents results in the acceleration of the rate of the $\pi \rightarrow \sigma$ conversion and the equilibrium is strongly in favor of the σ complex. The concentration of uncomplexed $HCo(CO)_3$ is relatively high, thereby increasing the yield of aldehyde. The data of Table IV show that the pres-

TABLE IV

STOICHIOMETRIC HYDROFORMYLATION OF 1- and *cis*-2-PENTENE IN PENTANE. EFFECT OF ETHYL ETHER[a]

Ether, ml	Pentene	Aldehydes Yield, %	st,[b] %	br,[c] %
0	1-	42	43	57
0	2-	30	41	59
4	1-	51	53	47
4	2-	38	47	53
7	1-	62	58	42
7	2-	41	50	50

[a] 1.8 mmol of $HCo(CO)_4$; 10 mmol of pentene; total solvent 10 ml; 4 hr under N_2 and then quenched with PPh_3. [b] Straight chain. [c] Branched chain.

ence of ether does increase the yield of aldehydes in the stoichiometric hydroformylation of both 1- and 2-pentene.

The stoichiometric hydroformylation of terminal olefins under N_2 in the presence of excess olefin is characterized by extensive isomerization of the olefin. The double bond isomerization catalyzed by $HCo(CO)_4$ involves a series of $\sigma \rightleftharpoons \pi$ interconversions and displacement of the π-complexed olefin by free, starting olefin. The less favored the π complexes are relative to σ complexes, the less opportunity for isomerization, and vice versa. Accordingly, one might expect that a hydroformylation reaction conducted in ether solvents should lead to less olefin isomerization than similar reactions conducted in a nonpolar solvent. The results shown in Table V confirm this expectation.

TABLE V

EFFECT OF SOLVENT ON ISOMERIZATION OF 1-PENTENE[a]

Solvent	$HCo(CO)_4$, mmol	Recovered pentene 1-	2-(*cis*- + *trans*-)
Pentane	0.3	7	93
Pentane	0.6	5	95
Ethyl ether	0.3	94	6
Ethyl ether	0.6	78	22
Tetrahydrofuran	0.3	97	3
Tetrahydrofuran	0.6	94	6
Dioxane[b]	0.6	100	0

[a] 10 ml of solvent; 10 mmol of 1-pentene; under N_2. After 4 hr, the reaction was quenched with PPh_3. [b] Evolution of a small amount of gas was observed.

Finally, it should be noted that the rate of acylcobalt carbonyl isomerization is so slow that such interconversion would not normally affect the distribution of products in either the catalytic reaction carried out under at least 30 atm of CO or in the stoichiometric reaction carried out under CO.

Experimental Section

Acyl chlorides were commercial products and were distilled before use. $NaCo(CO)_4$ solutions in absolute tetrahydrofuran (THF) were prepared from NaOH and $Co_2(CO)_8$.[10] Most experiments reported in the tables were repeated about three times.

A. Isomerization and Disproportionation of Acylcobalt Carbonyls Prepared from Acyl Chlorides and $NaCo(CO)_4$.—A solution of $NaCo(CO)_4$ in dry THF was introduced into a 100-ml flask fitted with a side arm. This operation was carried out in a drybox under N_2. The THF was eliminated by distillation *in vacuo* and replaced by the desired solvent. In order to eliminate all the THF it was necessary to heat the $NaCo(CO)_4$ to 60–80° in a good vacuum (oil pump). The desired solvent was then introduced, and again eliminated, by evacuation at 60–80°. This operation was repeated three times. When pentane was the solvent of choice, the $NaCo(CO)_4$ was insoluble and hence the yields of aldehydes and olefins were more difficult to reproduce than when ether solvents were employed. However, the ratios of aldehydes and of olefins in all cases were obtained with good precision. The $NaCo(CO)_4$ and solvent, together with a known quantity of reference compound (for the determination of yields), was connected to a gas burette. After filling the burette and the flask with 1 atm of CO or N_2, the acyl chloride was introduced by means of a syringe. The reaction was stopped by adding PPh_3 in ethyl ether; the phosphine converts all cobalt carbonyls to insoluble phosphine derivatives. When butenes were present, the mixture was cooled with Dry Ice–acetone and liquid samples were removed for analysis. The reaction product was then distilled at room temperature at low pressure (about 1 mm) and the aldehydes were analyzed by glc. All transfers were carried out in a drybox and in the absence of oxygen, and magnetic stirring was used m all reactions.

B. Isomerization and Disproportionation of Acylcobalt

(10) W. F. Edgell and J. Lyford, *Inorg. Chem.*, **9**, 1932 (1970).

Carbonyls during the Stoichiometric Hydroformylation.—Solvent, olefin, and reference compound were introduced into the 100-ml flask connected to a gas burette. The flask and the burette were filled with 1 atm of CO and then a solution of $HCo(CO)_4$ was introduced. After 16 hr of stirring, the flask was cooled with Dry Ice–acetone and N_2 was flushed through until complete elimination of CO took place. The solution was stirred at room temperature and the samples, which were taken after treatment with PPh_3, were analyzed by glc.

Registry No.—*n*-$BuCOCo(CO_4)$, 33520-58-0; *i*-$BuCOCo(CO_4)$, 33520-59-1; 1-pentene, 109-67-1.

Acknowledgment.—The authors are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this investigation.

Silicon-Containing Carbanions. I. Synthesis of Vinyl Thioethers and Vinylphosphonates *via* Silicon-Modified Organolithium Reagents

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Received September 9, 1971

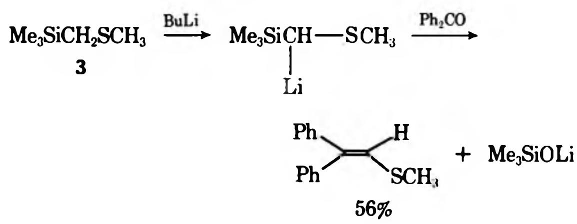
Reactions of diethyl 1-lithio-1-trimethylsilylmethylphosphonate (1) and 1-trimethylsilyl-1-phenylthiomethyllithium (2) with representative aldehydes and ketones are reported which provide useful routes to diethyl vinylphosphonates (6a–g) and vinyl phenylthioethers (18a–g) by loss of Me_3SiOLi from the presumed intermediate resulting from attack of the organolithium reagent at the carbonyl group. It was found that the exocyclic vinylphosphonate 6e from cyclohexanone and 1 isomerized to the endocyclic isomer 7 under the reaction conditions. The reactions are not highly stereoselective in that 1 and 2 usually give cis–trans mixtures of olefins from aldehydes and unsymmetrical ketones. Methylation and benzoylation of 1 are described. Reaction of $Me_3SiCH_2OCH_3$ resulted in nucleophilic attack at silicon when *n*-butyllithium was used and proton abstraction from the methyl group when *tert*-butyllithium was used.

A number of silicon-containing ylides[1] and organometallics[2] have been described in which electron delocalization into silicon 3d orbitals may be important. While the extent of this delocalization remains to be established, the synthetic versatility of carbanions and the expectation of stabilization with modification of chemical reactivity resulting from silicon bonded directly to the carbanionic center suggests the desirability of thorough examination into the reactions of such intermediates.

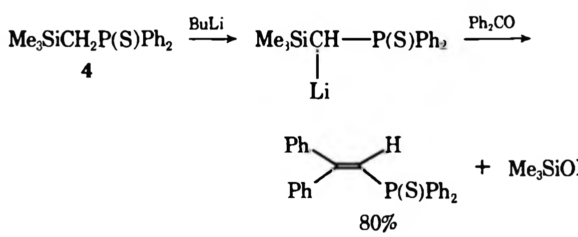
This report describes the generation and some reactions of diethyl 1-lithio-1-trimethylsilylmethylphosphonate (1) and 1-trimethylsilyl-1-phenylthiomethyllithium (2).

1 2

Peterson[3] made the important discoveries that metalation of methylthiomethyltrimethylsilane (3) and (trimethylsilylmethyl)diphenylphosphine sulfide (4) occurred readily using *n*-butyllithium and that the resulting lithio reagents reacted with benzophenone to afford olefins resulting from loss of Me_3SiOLi (eq 1 and 2).



(1)



(2)

The lithio reagent from 3 yielded equal amounts of *cis*- and *trans*-2-phenylvinyl methylthioether (64%) when treated with benzaldehyde.

As will be seen from the results to be described these reactions are very general and provide convenient routes to a number of interesting hetero-substituted olefins.

Results and Discussion

Synthesis of Diethyl Vinylphosphonates.—Diethyl trimethylsilylmethylphosphonate (5) is conveniently prepared by the Arbusov reaction between chloromethyltrimethylsilane and triethyl phosphite.[4] Treatment of 5 in tetrahydrofuran with *n*-butyllithium in *n*-hexane generates the lithio derivative 1, which reacts with aldehydes and ketones to give good yields of substituted diethyl vinylphosphonates (6) according to eq 3. The results are summarized in Table I.

Most of the compounds listed in Table I have previously been prepared by Wysocki and Griffin by the Wadsworth–Emmons procedure employing $CH_2[P(O)(OEt)_2]_2$ in KO-*tert*-Bu–THF.[5] The structures of 6a–e were confirmed by comparison of their physical

(1) (a) N. E. Miller, *J. Amer. Chem. Soc.*, **87**, 390 (1965); (b) N. E. Miller, *Inorg. Chem.*, **4**, 1458 (1965); (c) N. E. Miller and D. R. Mathiason, *ibid.*, **7**, 709 (1968); (d) H. Schmidbaur and W. Malisch, *Chem. Ber.*, **103**, 3448 (1970), and previous papers in this series; (e) D. Seyferth and G. Singh, *J. Amer. Chem. Soc.*, **87**, 4156 (1965); (f) H. Gilman and R. A. Tomasi, *J. Org. Chem.*, **27**, 3647 (1962).

(2) (a) D. J. Peterson, *J. Organometal. Chem.*, **9**, 373 (1967); (b) M. A. Cook, C. Eaborn, A. E. Jukes, and D. R. M. Walton, *ibid.*, **24**, 529 (1970); (c) T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Lett.*, 1137 (1970).

(3) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).

(4) A. R. Gilbert, U. S. Patent 2,768,193 (Oct 23, 1956); *Chem. Abstr.*, **51**, 5816 (1957).

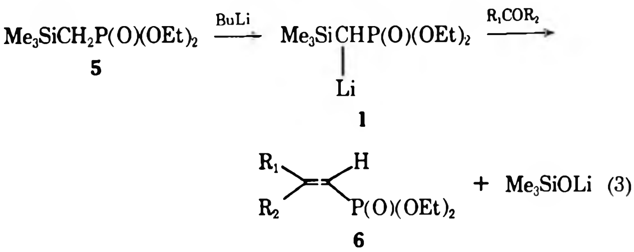
(5) D. C. Wysocki, Ph.D. Thesis, University of Pittsburgh, 1967; C. E. Griffin, adviser. See *Diss. Abstr. B*, **28**, 1437 (1967), for a summary.

Table I

Reactions of 1 with Aldehydes and Ketones

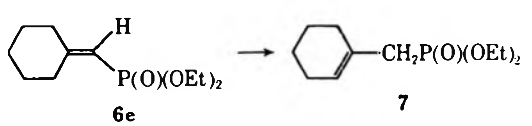
Carbonyl component	Product	R_1	R_2	Yield,[a] %
Benzaldehyde	6a	Ph	H	63[b,c]
Benzophenone	6b	Ph	Ph	83[c]
Fluorenone	6c			42[c]
Acetone	6d	CH_3	CH_3	55[c]
Cyclohexanone	6e + 7	$-(CH_2)_5-$		65[c]
Isobutyraldehyde	6f + 6g	H	$(CH_3)_2CH$	92[d]

[a] Isolated yields of pure product; not corrected for recovered starting material. [b] Reported by W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961). [c] Reported by D. C. Wysocki, Ph.D. Thesis, University of Pittsburgh, 1967. [d] Cis:trans ratio 2.4:1.

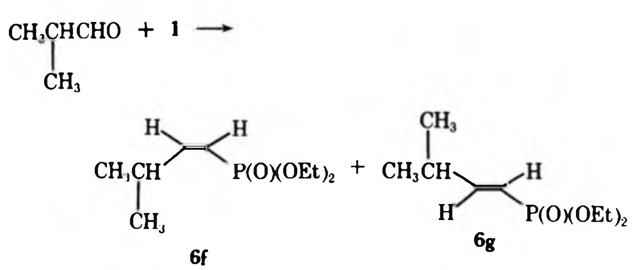


properties, particularly nmr spectra, with those reported by Wysocki.[5]

Several features of these reactions bear mentioning. First, while cyclohexanone reacted normally with **1** it was found that the initial product **6e** was unstable under the reaction conditions and was isomerized to the more stable endocyclic double bond isomer **7**.[6] By direct glpc analysis of a reaction mixture it was determined that after 5 min at −67° the ratio of the endocyclic double bond isomer **7** to the exocyclic isomer **6e** was 4.5:1 and increased to 17:1 after 88 hr at 25°.



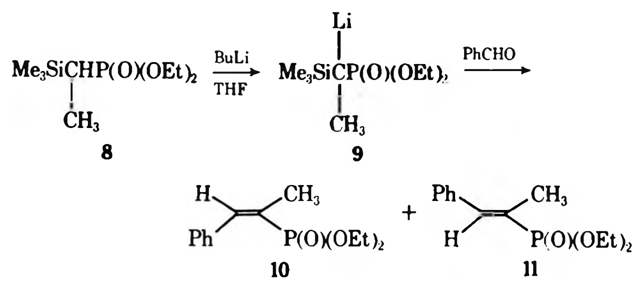
No simple pattern of stereoselective vinylphosphonate formation from **1** and aldehydes is evident, since reaction with benzaldehyde affords diethyl *trans*-2-phenylvinylphosphonate (**6a**) while reaction with isobutyraldehyde gives a mixture of diethyl *cis*- and *trans*-2-isopropylvinylphosphonate (**6f** and **6g**) in which the cis:trans ratio is 2.4:1.[7]



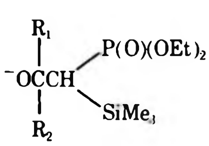
Assignment of stereochemistry to the isomers **6f** and **6g** was made from consideration of their nmr spectra at 100 MHz. The signals resulting from the vinyl protons in the compound assigned the cis geometry appeared as 12 lines which were determined by first-order analysis to result from splitting of the resonance of the vinyl proton at higher field into a doublet of doublets by coupling to the geminal phosphorus nucleus (J = 20 Hz) and to the vicinal vinyl proton (J = 12 Hz). The resonance of the lower field vinyl proton appeared as a doublet of doublets of doublets because of splitting by the vinyl proton, the proton of the isopropyl group (J = 10 Hz) and phosphorus (J = 52 Hz). The magnitude of the vicinal phosphorus coupling is consistent with a trans orientation of H and P while the vinyl coupling is consistent with cis orientation of H and H.[5,8]

Assignment of the trans stereochemistry to the minor isomer follows from the observation that the vicinal vinyl H–H coupling constant was larger (18 Hz) and the vicinal H–P coupling constant smaller (23 Hz) than for the cis isomer.

Alkylation of **1** with methyl iodide was carried out in 86% yield to give diethyl 1-trimethylsilylethylphosphonate (**8**). The derived anion (**9**) was formed readily from the reaction of **8** with *n*-butyllithium in tetrahydrofuran as evidenced by quantitative incorporation of deuterium when D_2O was added, but was much less reactive than **1** toward benzaldehyde. The vinylphosphonate which resulted from **9** on reaction with benzaldehyde was isolated in 38% yield on distillation and was determined to be an 8:1 mixture of cis and trans isomers **10**[5] (major) and **11**[5] (minor) by glpc.



The formation of vinylphosphonates by loss of Me_3SiOLi from intermediate **12** rather than formation of vinylsilanes by loss of $(EtO)_2P(O)(OLi)$ is consistent with current thinking regarding reactions of phosphonate carbanions.[9] The β-hydroxyphosphonates re-



sulting from addition of phosphonate carbanions to carbonyls lose diethyl phosphate only when the carbon atom bearing phosphorus carries an additional electron-withdrawing substituent, while base-catalyzed elimination of β-hydroxysilanes occurs readily.[2c,3]

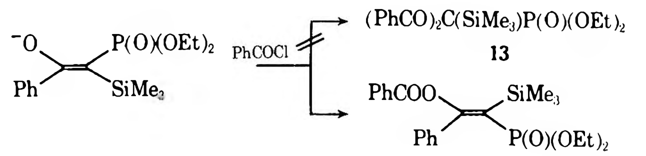
(6) For a discussion of related isomerizations, see F. S. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(7) For a thorough examination of the mechanistic features relating to stereoselectivity of Wittig reactions, see M. Schlosser, *Top. Stereochem.*, **5**, 1 (1969).

(8) (a) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1825 (1966); (b) W. A. Anderson, R. Freeman, and C. A. Reilly, *J. Chem. Phys.*, **39**, 1518 (1963); (c) W. M. Daniewski, M. Gordon, and C. E. Griffin, *J. Org. Chem.*, **31**, 2083 (1966); T. M. Timofeeva, B. I. Ionin, Y. L. Kleiman, N. V. Morkovin, and A. A. Petrov, *J. Gen. Chem. USSR*, **38**, 1208 (1968).

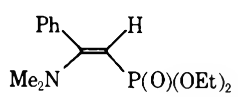
(9) E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5654 (1966); (b) A. N. Pudovik and G. E. Yastrebova, *Russ. Chem. Rev.*, **39**, 562 (1970).

Reaction of **1** with several different benzoylating agents (benzoyl chloride, methyl benzoate, and *N,N*-dimethylbenzamide) resulted in the novel finding that a different product was obtained from each reagent. When benzoyl chloride was used there was isolated a stable crystalline compound, mp 94–95°, which analyzed correctly for $C_{22}H_{29}SiO_5P$ corresponding to a yield of 58% for reaction of 1 equiv of **1** with 2 equiv of benzoyl chloride. The product was more stable than expected for structure **13** to be correct[10] and examination of its ir spectrum removed **13** from consideration. An intense absorption at 1750 cm^{-1} is too low in energy to arise from the carbonyl stretching of an aromatic ketone, but is consistent with that of a benzoyl ester and leads to the assignment of **14** for the compound.



Formation of **14** by O-acylation of the initial intermediate is reasonable, since C-acylation is seriously hindered by the Me_3Si and $P(O)(OEt)_2$ substituents.[11]

Monobenzoylation of **1** was effected by using methyl benzoate to afford a 56% yield of $PhCOCH_2P(O)(OEt)_2$ in what constitutes a useful alternative to the Arbusov reaction for the synthesis of β-ketophosphonates. This product may result from hydrolytic cleavage of $PhCOCH(SiMe_3)P(O)(OEt)_2$ during isolation. Reaction of **1** with *N,N*-dimethylbenzamide was less effective but interesting in that the unusual enamine **15** was isolated directly in 24% yield.



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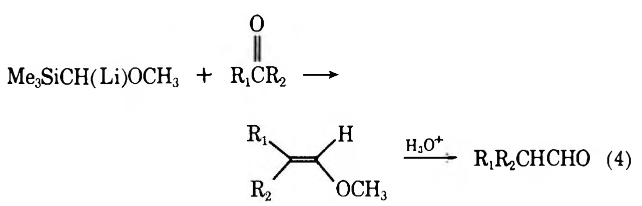
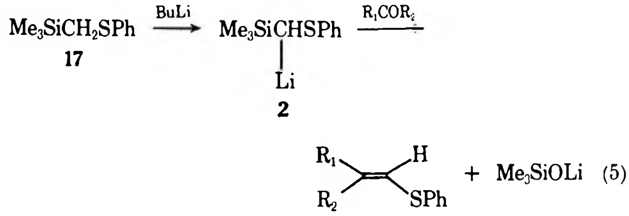
Synthesis of Vinyl Phenylthioethers.—The reagent $Me_3SiCH(Li)OCH_3$ would be useful for extension of carbonyl chains *via* enol ethers according to eq 4.



Attempts to generate the required organolithium derivative by proton abstraction from $Me_3SiCH_2OCH_3$ (**16**)[12] were not successful. When *n*-butyllithium was used, **16** was cleaved to yield *n*-butyltrimethylsilane as the only identifiable product after quenching with D_2O.[13] To minimize nucleophilic attack at silicon, *tert*-butyllithium was used as the base and was observed to abstract a proton from the Si-methyl group to give $CH_3OCH_2Si(CH_3)_2CH_2Li$ rather than $CH_3OCH(Li)Si(CH_3)_3$. In this experiment methyl iodide was added to the organometallic and $CH_3OCH_2Si(CH_3)_2CH_2CH_3$ was isolated in 50% yield.

Extension of the carbonyl chain could also be accomplished by way of vinyl thioether intermediates which, however, suffer from the disadvantage of being more difficult to hydrolyze than enol ethers.[14,15] Vinyl phenylthioethers (**18**) were readily prepared from a variety of aldehydes and ketones by reaction with **2** in tetrahydrofuran at 0–25° (eq 5). In contrast to the oxygen analog, **2** was generated quantitatively from phenylthiomethyltrimethylsilane (**17**)[16] by metalation



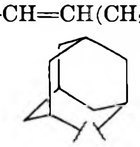
18

with *n*-butyllithium at 0° at the methylene group without any evidence of cleavage.

The reactions of **2** with several aldehydes and ketones are summarized in Table II. The ease with which

TABLE II

REACTIONS OF 2 WITH ALDEHYDES AND KETONES

Carbonyl component	Product	R_1	R_2	Yield,[a] %
Benzaldehyde	**18a**	Ph	H	71[b]
Benzophenone	**18b**	Ph	Ph	82[c]
Acetone	**18c**	CH_3	CH_3	50
Cyclohexanone	**18d**	$-(CH_2)_5-$		65
Pinacolone	**18e**	*tert*-Bu	CH_3	55[d]
Cyclohexenone	**18f**	$-CH{=}CH(CH_2)_3-$		75
Adamantanone	**18g**			80

[a] Isolated yields of product; not corrected for recovered starting material. The yield of **18c** is approximate since separation from **17** by distillation was difficult. [b] The cis:trans ratio was 2:1; see A. A. Oswald, K. Griesbaum, B. E. Hudson, Jr., and J. M. Bregman, *J. Amer. Chem. Soc.*, **86**, 2877 (1964), for nmr spectra of isomers. [c] E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966); H. K. Reimlinger, *Chem. Ind.* (*London*), 1682 (1966). [d] Isomer ratio 3:2.

these reactions are carried out (see Experimental Section), the generally good yields obtained even with hindered ketones (55% from pinacolone), and 1,2 addition to an α,β-unsaturated ketone (cyclohexenone) make this method a highly desirable one for the synthesis of vinyl thioethers and as part of a general method for converting R_1R_2CO to R_1R_2CHCHO. Alternative and analogous methods for preparing vinyl thioethers employing sulfur-substituted phosphonate

(10) C. R. Hauser and C. R. Hance, *J. Amer. Chem. Soc.*, **74**, 5091 (1952); W. K. Musker and G. L. Larson, *J. Organometal. Chem.*, **6**, 627 (1966).

(11) This reaction is similar to the O benzoylation of $Me_2S^+CH{=}C(O^-)Ph$ with benzoyl chloride reported by A. W. Johnson and R. T. Amel, *Tetrahedron Lett.*, 819 (1966). We thank a referee for bringing this reference to our attention.

(12) J. L. Speier, *J. Amer. Chem. Soc.*, **70**, 4142 (1948).

(13) A referee has pointed out that this cleavage is analogous to that which occurs in Schollkpof's procedure for preparation of methoxymethyllithium.

$$CH_3OCH_2SnR_3 + n\text{-BuLi} \longrightarrow CH_3OCH_2Li + BuSnR_3$$

See U. Schollkopf in E. Muller, Ed., "Methoden der Organischen Chemie," Vol. 13, Georg Thieme Verlag, Stuttgart, 1970, pp 87, 253.

(14) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

(15) There has been much recent progress in the improvement of methods for hydrolysis of vinyl thioethers. See E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971); B. W. Erickson, Ph.D. Thesis, Harvard, 1970; T. Mukaiyama, S. Fukuyama, and T. Kumamoto, *Tetrahedron Lett.*, 3787 (1968); H. J. Bestmann and J. Angerer, *ibid.*, 3665 (1969).

(16) G. D. Cooper, *J. Amer. Chem. Soc.*, **76**, 3713 (1954).

carbanions have been reported,[17] but these anions appear to be less reactive than 2 and, in some cases, tend to decompose under the reaction conditions.

Experimental Section

Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra were measured on a Perkin-Elmer 337 grating instrument as KBr discs for solids and pressed films for liquids. Melting points are corrected and were determined on a Thomas-Hoover apparatus. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV.

Microanalyses were performed by Alfred Bernhardt, Engelskirchen, West Germany.

Gas chromatographic analysis of product mixtures and purification of analytical samples were carried out on a Varian Aerograph A-90P3 instrument equipped with a thermal conductivity detector and disc integrator.

All reactions were carried out in an atmosphere of dry nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride. *n*-Butyllithium in *n*-hexane was purchased from Alfa Inorganics.

General Procedure for Synthesis of Diethyl Vinylphosphonates (6).—*n*-Butyllithium (25 mmol as a 23% solution in hexane) was added to a solution of 5.6 g (25 mmol) of diethyl trimethylsilylmethylphosphonate (6) in 10 ml of tetrahydrofuran and allowed to stir for 1.5 hr. To the yellow solution of 1 was added 25 mmol of the carbonyl compound and after 2 hr at 25° brine (25 ml) was added. The layers were separated, and the aqueous phase was extracted with ether, dried ($MgSO_4$), and evaporated. Distillation or recrystallization of the residue afforded the purified product. The nmr, ir, and uv spectra of **7a–c**, **10**, and **11** have been thoroughly discussed by Wysocki and Griffin. The spectral and analytical data for the previously unreported diethyl vinylphosphonates and related compounds follow.

Diethyl 1-Cyclohexenylmethylphosphonate (7).—The endocyclic olefin 7 was separated from its exocyclic isomer **6e** by preparative glpc on a 10-ft 20% Carbowax 20M on firebrick column: retention time 21 (7), 26 min (6e); nmr ($CDCl_3$) δ 1.32 (t, 6 J = 7 Hz, CH_3CH_2O), 1.6 (m, 4, ring CH_2), 2.1 (m, 4, allylic CH_2), 2.52 (d, 2, J = 22 Hz, CH_2P), 4.11 (q, 4, J = 7 Hz, CH_3CH_2OP), 5.6 (m, 1, C=CH).

Anal. Calcd for $C_{11}H_{21}O_3P$: C, 56.88; H, 9.11; P, 13.34. Found: C, 56.78; H, 9.28; P, 13.07.

Diethyl *cis*-3-Methyl-1-butenylphosphonate (6f).—The cis and trans products from reaction of isobutylraldehyde with 1 were separated by preparative glpc on a Carbowax column at 150°. The major product was eluted first and identified as **6f** (cis) by its nmr spectrum (100 MHz) in $CDCl_3$): δ 1.10 (d, 6, J = 7 Hz, CH_3CH), 1.4 (t, 6, J = 7 Hz, CH_3CH_2O), 3.32 [m, 1, $(CH_3)_2CH$], 4.10 (q, 4, J = 7 Hz, CH_3CH_2O), 5.4 [d, d, 1, J_{HH} = 12, J_{HP} = 20 Hz, HC(=)P], 6.2 [d, d, d, 1, J_{HH} = 12, J_{HH} = 10, J_{HP} = 52 Hz, $(CH_3)_2CHC$=CH].

Anal. Calcd for $C_9H_{19}O_3P$: C, 52.42; H, 9.28; P, 15.02. Found: C, 52.17; H, 9.10; P, 14.86.

Diethyl *trans*-3-Methyl-1-butenylphosphonate (6g).—The minor isomer isolated from the reaction described above was identified as **6g** (trans) by its nmr spectrum (100 MHz, $CDCl_3$): δ 1.10 (d, 6, J = 7 Hz, CH_3CH), 1.36 t, [6, J = 7 Hz, CH_3CH_2O), 4.10 (q, 4, J = 7 Hz, CH_3CH_2O), 5.58 [t, 1, $J_{HH} \cong J_{HP} \cong$ 18 Hz, HC(=)P], 6.8 (d, d, d, 1, J_{HH} = 18, J_{HH} = 7, J_{HP} = 23 Hz, HC=CP).

Anal. Calcd for $C_9H_{19}O_3P$: C, 52.42; H, 9.28; P, 15.02. Found: C, 52.43; H, 9.39; P, 14.94.

Methylation of 1-Lithio-1-trimethylsilylmethylphosphonate.—Methyl iodide (3.55 g, 25 mmol) was added slowly with cooling to a solution of 25 mmol of 1 in 10 ml of THF. The reaction mixture was worked up as previously described after 5.5 hr and the crude product was distilled to yield 5.1 g (86%) of diethyl 1-trimethylsilylethylphosphonate (8), bp 72–75° (1 mm).

Anal. Calcd for $C_9H_{23}SiO_3P$: C, 39.48; H, 8.61; P, 20.36. Found: C, 39.31; H, 8.74; P, 20.26.

A number of attempts to methylate 5 using sodium hydride in a variety of solvents did not yield useful results owing to formation of mixtures of di-, mono-, and nonmethylated products.

(17) M. Green, *J. Chem. Soc.*, 1324 (1963). I. Shabak and J. Almog, *Synthesis*, 170 (1969); 145 (1970).

Hydrogen–Deuterium Exchange of 8.—To a solution of 4.1 g (18.5 mmol) of 8 in 10 ml of THF was added 5.1 g of butyllithium (23% in hexane). After 1 hr, D_2O was added, the solution was extracted with ether, and the product was distilled, yielding 3.3 g (80%) of 8 completely deuterated at the α position. This was evident from the nmr spectrum ($CDCl_3$): δ 0.15 [s, 9, $(CH_3)_3Si$], 1.21 (d, 3, J_{HP} = 23 Hz, CH_3CDP), 1.31 (t, 6, J = 7 Hz, CH_3CH_2O), 4.10 (q, 4, J = 7 Hz, CH_3CH_2O). The presence of the molecular ion peak at m/e 239 in the mass spectrum confirmed deuterium incorporation.

Benzoylation of 1-Lithio-1-trimethylsilylmethylphosphonate.—To a solution of 25 mmol of 1 in tetrahydrofuran was added 3.5 g (25 mmol) of benzoyl chloride while cooling in ice. After 1 hr at 25° the reaction mixture was worked up according to the general procedure to yield 8.3 g of crude product which partially crystallized on standing. Recrystallization from ethanol gave 3.0 g (58%) of diethyl 1-trimethylsilyl-2-phenyl-2-benzoyloxyvinylphosphonate (14): mp 94–95°; ir (KBr) 1750, 1250, 1060, 1030, 970, 960, 930, 860, 805, 770, 710 cm^{-1}; nmr ($CDCl_3$) δ 0.10 (s, 9, CH_3Si), 1.25 (t, 6, J = 7 Hz, CH_3CH_2O), 4.10 (quintet, 4, J = 7 Hz, CH_2OP), 7.5 (m, 4, aromatic), 8.15 (m, 1, aromatic).

Anal. Calcd for $C_{22}H_{29}SiO_5P$: C, 61.09; H, 6.76; P, 7.16. Found: C, 61.28; H, 6.85; P, 7.12.

Reaction of 1 with Methyl Benzoate.—The preceding experiment was repeated employing methyl benzoate to afford, after distillation at 165° (1.8 mm), 3.6 g (56%) of diethyl benzoylmethylphosphonate, which was identical with authentic material prepared by reaction of triethyl phosphite with phenacyl bromide.

Reaction of 1 with *N,N*-Dimethylbenzamide.—Use of 25 mmol of *N,N*-dimethylbenzamide in a similar experiment yielded 1.68 g (24%) of diethyl 2-phenyl-2-dimethylaminovinylphosphonate: bp 163° (1 mm); ir (CCl_4) 3000, 1600, 1230, 1060, 1030, 950, 860, 700 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (t, 6, J = 7 Hz, CH_3CH_2O), 2.78 (s, 6, CH_3N), 3.80 (quintet, 4, J = 7 Hz, CH_2OP), 4.21 (d, 1, J = 10 Hz, CCH), 7.41 (s, 5, aromatic).

Anal. Calcd for $C_{14}H_{22}NO_3P$: C, 59.35; H, 7.83; P, 10.93; N, 4.94. Found: C, 59.20; H, 7.93; P, 11.08; N, 4.88.

Substantial amounts (19 mmol) of unreacted *N,N*-dimethylbenzamide were recovered.

Metalation of Methoxymethyltrimethylsilane (16) with *tert*-Butyllithium.—*tert*-Butyllithium (20 mmol) in pentane was added to a solution of 2.4 g (20 mmol) of 16 in 10 ml of tetrahydrofuran. After stirring for 30 min at 25°, the solution was cooled in an ice bath while 2.84 g (20 mmol) of methyl iodide was added. The ice bath was removed and the solution was allowed to stand for 2 hr at 25°, water was added, and the mixture was extracted thoroughly with ether. The ether solution was dried ($MgSO_4$) and distilled to yield 1.4 g (54%) of methoxymethylethyldimethylsilane: bp 109°; nmr ($CDCl_3$) δ 0.05 [s, 6, $(CH_3)_2Si$], 0.60 (2, CCH_2) 0.9 (3, CH_3C) (both multiplets distorted because $\nu/J \cong 3$), 3.1 (s, 2, $SiCH_2O$), 3.35 (s, 3, CH_3O).

Anal. Calcd for $C_6H_{16}OSi$: C, 54.48; H, 12.19; Si, 21.23. Found: C, 54.19; H, 12.01; Si, 21.23.

General Procedure for Synthesis of Vinyl Phenylthioethers (18).—To a solution of 3.92 g (20 mmol) of 17 in 10 ml of tetrahydrofuran at 0° was added 20 mmol of *n*-butyllithium in hexane. The resulting yellow solution was stirred for 15 min at 0°, a solution of 20 mmol of the carbonyl compound in 5 ml of tetrahydrofuran was added, and the reaction mixture was stirred for 15 min at 0°, then 15 min at 25°. Brine (15 ml) was added and the product was extracted with two 10-ml portions of ether, dried ($MgSO_4$), filtered, and evaporated to yield the crude product.

1-Phenylthio-2-phenylethylene (18a).—The crude product from 2.12 g of benzaldehyde and 2 was purified by distillation, bp 154° (0.8 mm), to yield 3.0 g (71%) of **18a** as a mixture of cis and trans isomers along with 0.9 g (23%) of recovered 17. The cis:trans ratio was 2:1 as determined from the nmr spectrum of the mixture (see footnote *b*, Table II).

1-Phenylthio-2,2-diphenylethylene (18b).—Recrystallization of the crude residue from reaction of 2 with benzophenone from hexane gave **18b** (82%), mp 66–68°. A further recrystallization from hexane raised the melting point to 71–73° [reported 71.5–73° (footnote *c*, Table II)].

1-Phenylthio-2-methyl-1-propene (18c).—Distillation of the crude product from reaction of acetone with 2 gave as a first fraction 1.5 g, bp 81° (1 mm), of product contaminated with *ca.* 20% of 17. Subsequent fractions were composed of **18c** and 17 in varying amounts. The analytical sample was obtained by preparative glpc on a 10-ft 20% SE-30 on Chromosorb column at 165°: nmr ($CDCl_3$) δ 1.90 (s, 6, CH_3), 5.92 (s, 1, =CH), 7.3 (s, 5, PhS).

Anal. Calcd for $C_{10}H_{12}S$: C, 73.11; H, 7.36. Found: C, 72.99; H, 7.31.

Phenylthiomethylenecyclohexane (**18d**).—Distillation of the residue afforded 2.62 g (65%) of **18d**: bp 133° (1.1 mm); nmr ($CDCl_3$) δ 1.58 (br s, 6, CH_2), 2.3 (m, 4, allylic CH_2), 5.90 (s, 1, C=CH), 7.30 (s, 5, Ph).

Anal. Calcd for $C_{13}H_{16}S$: C, 76.41; H, 7.89. Found: C, 76.22; H, 7.74.

1-Phenylthio-2,3,3-trimethyl-1-butene (**18e**).—Fractional distillation of the crude product from reaction of pinacolone with **2** resulted in the recovery of 1.7 g (45%) of **17** and isolation of 2.1 g (55%) of **18e**, bp 110° (1.2 mm), as a mixture of cis and trans isomers. The mixture was *ca.* 3:2 by nmr analysis of the crude product. No assignment is being made at present as to which isomer is the major component and which is the minor component. Major component: nmr ($CDCl_3$) δ 1.28 (s, 9, *tert*-Bu), 1.85 (s, 3, CH_3), 5.90 (m, 1, C=CH), 7.28 (m, 5, SPh). Minor component: nmr ($CDCl_3$) δ 1.13 (s, 9, *tert*-Bu), 1.82 (s, 3, CH_3), 6.03 (s, 1, C=CH), 7.28 (m, 5, SPh).

A sample of the mixture was purified by preparative glpc on Carbowax at 190°.

Anal. Calcd for $C_{13}H_{18}S$: C, 75.66; H, 8.79. Found: C, 75.51; H, 8.64.

3-Phenylthiomethylene-1-cyclohexene (**18f**).—Distillation of the crude product afforded 3.0 g (75%) of **18f** as a mixture of cis and trans isomers: bp 131° (0.55 mm); nmr ($CDCl_3$) δ 1.75 (m, 2, CH_2), 2–2.7 (m, 4, allylic CH_2), 5.8–6.8 (m, 3, C=CH), 7.3 (m, 5, SPh).

The analytical sample of the mixture was obtained by preparative glpc on Carbowax at 190°.

Anal. Calcd for $C_{13}H_{14}S$: C, 77.17; H, 6.97. Found: C, 76.95; H, 6.87.

2-Phenylthiomethyleneadamantane (**18g**).—The nmr of the crude product indicated an 80% yield of **18g**. Recrystallization from absolute ethanol gave the analytical sample: mp 65°; nmr ($CDCl_3$) δ 1.90 (s, 12, CH_2 and bridgehead CH), 2.58 (br s, 1, allylic CH), 3.16 (br s, 1, allylic CH), 5.80 (s, 1, C=CH), 7.20 (s, 5, SPh).

Anal. Calcd for $C_{17}H_{20}S$: C, 79.63; H, 7.86. Found: C, 79.58; H, 7.69.

Registry No.—**1**, 33521-83-4; **2**, 30536-77-7; **6f**, 18689-34-4; **6g**, 33536-50-4; **7**, 33521-85-6; **8**, 33521-86-7; **14**, 33536-51-5; **18c**, 13640-71-6; **18d**, 33521-88-9; *cis*-**18e**, 33536-52-6; *trans*-**18e**, 33536-53-7; *cis*-**18f**, 33536-54-8; *trans*-**18f**, 33536-55-9; **18g**, 33521-89-0; diethyl 2-phenyl-2-dimethylaminovinylphosphonate, 33521-90-3; methoxymethylethyldimethylsilane, 33521-91-4.

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The Lithium Salt Catalyzed Rearrangement of Epoxides. II. Glycidic Esters[1,2]

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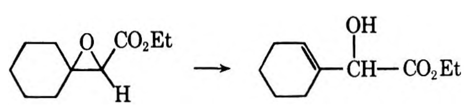
The rearrangement of glycidic esters catalyzed by lithium salts and other Lewis acids has been explored. Lithium halide catalyst leads to a mixture of products derived from both α and β cleavage of the oxirane. Lithium perchlorate causes β cleavage of 3,3-disubstituted glycidic esters, with subsequent elimination yielding the 2-hydroxy-3-alkenoic acid ester product. Catalytic hydrogenation gives the glycolic ester, which on oxidation affords the corresponding glyoxylic ester. Attempted isomerization of a 2-hydroxy-3-alkenoate by ethanolic sodium ethoxide gave instead double bond reduction. The presumed intermediate glyoxylic ester is similarly reduced under these conditions.

The availability of glycidic esters from the Darzens condensation is an attractive feature for synthesis, and consequently we were interested in examining the behavior of these materials under the conditions of lithium salt catalyzed epoxide rearrangement.[2,3] Simple alkyl-substituted epoxides rearrange to carbonyl compounds with these catalysts, *via* either hydrogen or alkyl migration. Glycidic esters can undergo epoxide scission at either the α or β carbon, and a sizable number of further products from these ring-opened intermediates can be envisioned.

Earlier studies using protic or Lewis acid catalysts have in fact led to a variety of rearrangement products. Boron trifluoride is an effective catalyst for phenyl-substituted glycidates, where, depending on the starting material structure, either α-keto ester[4] products or products of carboethoxy migration[5] may result. Hydrogen chloride at elevated temperature has been used to convert ethyl 3,3-diphenylglycidate to ethyl diphenylglyoxylate,[6] whereas sulfuric acid is reported[7] to cause rearrangement of compound **1a** to **2a** as shown in eq 1.



1a **2a** (1)

A similar result using hydrochloric acid catalyst has been noted by Camps and coworkers.[8] In contrast, ethyl dimethylglyoxylate was obtained in low yield in acid treatment of 3-methyl-2,3-epoxybutanoate.[9]

Also relevant to the present study is the report that Grignard reagents in reaction with glycidic esters yield exclusively α addition, α-hydroxy product,[10] presumably by initial rearrangement to the glyoxylate ester followed by addition. This mechanism is supported by the fact that Darzens[11] has actually isolated the α-

(1) Supported in part by the National Science Foundation, GP-6043.

(2) Part I: B. Rickborn and R. M. Gerkin, *J. Amer. Chem. Soc.*, **93**, 1693 (1971).

(3) B. Rickborn and R. M. Gerkin, *ibid.*, **90**, 4193 (1968).

(4) H. O. House, J. W. Blaker, and D. A. Madden, *ibid.*, **80**, 6386 (1958).

(5) S. P. Singh and J. Kagan, *ibid.*, **91**, 6198 (1969).

(6) F. F. Blicke and J. A. Faust, *ibid.*, **76**, 3156 (1954).

(7) W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *ibid.*, **75**, 4995 (1953).

(8) F. Camps, J. Castells, and J. Pascual, *J. Org. Chem.*, **31**, 3510 (1966).

(9) E. Vogel and H. Schinz, *Helv. Chim. Acta*, **33**, 116 (1950).

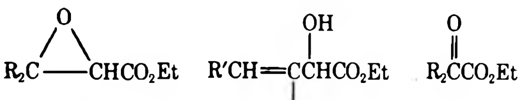
(10) E. P. Kohler, N. K. Richtmeyer, and W. F. Hester, *J. Amer. Chem. Soc.*, **53**, 205 (1931).

(11) G. Darzens, *C. R. Acad. Sci.*, **152**, 443 (1911).

keto ester (in low yield) from the addition of organozinc reagent to ethyl 3,3-dimethylglycidate.

Results and Discussion

The rearrangement of some β-dialkylglycidic esters catalyzed by lithium and magnesium halides is shown in eq 2 and the results are presented in Table I.



(2)

1a, $R_2 = (CH_2)_5$
b, $R_2 = (CH_2)_4$
c, $R_2 = (CH_2)_6$
d, $R = CH_2CH_3$
e, $R = CH_3$

2 **3**

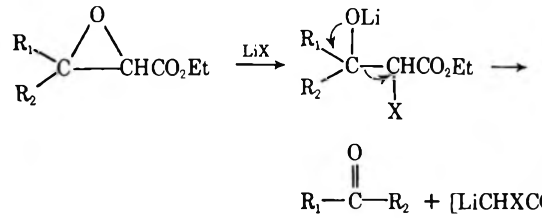
TABLE I
METAL HALIDE CATALYZED REARRANGEMENT OF GLYCIDIC ESTERS[a]

Ester	Salt	Product distribution, % 2	3	Yield,[b] %	Time,[c] hr
1a	LiBr·HMPA	94	6	26	70
	LiI	60	40	14	7
1b	LiBr·HMPA	10	90	65	3
	LiI	4	96[d]	17	0.6
1c	LiBr·HMPA	51	49	36	216
	LiI	12	88	36	1.5
1d	MgI_2	87	13	52	44
1e	LiBr·HMPA	0	100	8	22
	LiI	0	100	37	1
	LiI·HMPA	6	94	51	3.3
	LiI[e]	0	100	33	40
	$MgBr_2 \cdot Et_2O$[f]	39	61		0.5
	$MgBr_2$[f]	33	67	66	0.5
	$MgCl_2$·HMPA[g]	35	65[d]	46	44
	MgI_2	8	92	82	1.5

[a] Unless otherwise noted, the reactions were carried out in benzene solvent with [salt] = 0.21 and $[\text{ester}]_{\text{init}}$ = 0.35. [b] Yields were determined by vpc using an inert internal standard. [c] Approximate time required for disappearance of the starting glycidic ester. [d] A small amount of unidentified product, of approximately the same retention time as 2, was formed in this run. [e] CH_2Cl_2 solvent. [f] 0.1 *M*. [g] 0.35 *M*.

The products **2** and **3** both arise from cleavage of the oxirane ring at the β carbon, followed by elimination or hydrogen migration. Both products could arise by a carbonium ion process, or might involve an intermediate halohydrin salt. Evidence favoring the latter mechanism in the LiBr reaction of alkyl-substituted epoxides has been presented earlier.[2] Attempts to further delineate this question using glycidic esters with a secondary (as opposed to tertiary) β carbon have not given tractable products, although facile reaction mitigates against a carbonium ion process.

Lithium bromide, solubilized with 1 mol of hexamethylphosphoramide (HMPA), gives at best moderate yields of rearranged material, and in several instances (Table I) this material is a mixture of both **2** and **3**. Other metal halides were explored in an effort to increase the yield or improve the selectivity of the rearrangement process. The use of very hygroscopic LiI (which does not require HMPA for solubility) in general leads to a shorter reaction time and an increase in the glyoxylate product, **3**, relative to **2**. The overall yield, however, does not seem to vary in a uniform manner. The yield is directly related to the relative amounts of α- and β-cleavage processes that occur; it appears that α cleavage of the oxirane leads to reverse Darzens condensation, as shown in eq 3.[12] Thus in the reaction of **1a** with LiBr·HMPA and LiI, 12 and 34%



(3)

of cyclohexanone, respectively, was recovered from the reaction mixture. Similarly in the reaction of **1c**, cycloheptanone accounted for at least 22 (LiBr·HMPA) and 44% (LiI) of the starting glycidic ester. Fragmentation products were not pursued with the other systems examined. However, it seems reasonable to conclude from the yield data in Table I that the lithium halide reaction does not exhibit significant regioselectivity, *i.e.*, preference for reaction by α or β cleavage. It should be noted that the amounts of rearrangement and fragmentation may not be directly correlatable to the extents of β- and α-halide attack, since the halohydrin lithium salt may reclose to epoxide. This kind of rapid prior equilibrium has been established in the reaction of simple aliphatic epoxides.[2] In contrast, there is evidence that a magnesium salt of a halohydrin may not revert to epoxide as readily as it is rearranged.[13] We have examined one system, **1e**, with both lithium and magnesium halides (see Table I) and find that the latter in general lead to enhanced rearrangement yields (more β cleavage) but diminished selectivity in the rearrangement product mixture.

Control experiments with **2a** and a mixture of **2b** and **3b** established that the rearrangement products are stable under the reaction conditions; *i.e.*, they are neither interconverted nor transformed to other materials.

The lithium perchlorate catalyzed rearrangement of simple epoxides occurs by a carbonium ion mechanism.[2] A similar process with a glycidic ester should lead to exclusive β cleavage. In fact, the $LiClO_4$ reaction proved to be quite regioselective and hence synthetically useful. Results are given in Table II. The overall yields range from good to excellent, and, for the three spiro compounds examined, there is observed highly

TABLE II
REARRANGEMENT OF GLYCIDIC ESTERS BY $LiClO_4$ AND H_2SO_4

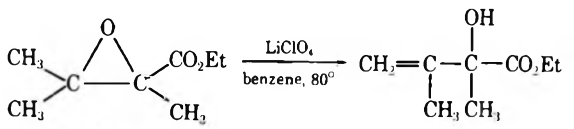
Ester	Catalyst	Product distribution, % 2	3	Yield, %	Time, hr
1a	$LiClO_4$	99.5	0.5	95	2.8
1b	$LiClO_4$	92	8	82	0.25
1c	$LiClO_4$	99	1	98	0.04
1e	$LiClO_4$	66	34	58	0.25
1a	H_2SO_4	100	0	70	2
1b	H_2SO_4	96	4	43	0.05
1c	H_2SO_4	100	0	54	0.05
1e	H_2SO_4	60	40	35	0.5

(12) Related "dealdolization" is known to occur in some instances under Darzens condensation conditions; see F. W. Bachelor and R. K. Bansal, *J. Org. Chem.*, **34**, 3600 (1969).

(13) H. O. House, *J. Amer. Chem. Soc.*, **77**, 5083 (1955).

selective formation of the allylic alcohol product **2**. Only in the case where elimination would involve abstraction of a primary proton (to give **2e**) is a significant quantity of α-keto ester formed. In general, the $LiClO_4$ catalyzed reaction is faster than a comparable metal halide catalyzed rearrangement. The relative rates of the various spiro systems with $LiClO_4$ (Table II) is as anticipated for a carbonium ion process,[14] *i.e.*, with the six-membered ring reacting slower than either the five- or seven-membered glycidate.

Also in keeping with the carbonium ion mechanism, systems lacking the tertiary β center, *e.g.*, ethyl 2,3-epoxybutyrate, fail to react at all with $LiClO_4$. Similarly, no evidence for α cleavage is observed; no ketone fragmentation product could be detected in the reactions cf **1a** and **1c**. One system containing both α and β tertiary centers was examined (**4**), and again exclusive β cleavage was observed, leading to **5** in essentially quantitative yield.[15] Control experiments again established that the rearrangement products (Table II) were not interconverted.



(4)

4 **5**

For purposes of comparison with the $LiClO_4$ catalyzed reaction, the rearrangement of the same glycidic esters by sulfuric acid in ether was examined. The data are also shown in Table II. The ratio of products **2** and **3** is quite similar for both catalysts, with sulfuric acid showing somewhat higher selectivity for **2**. However, the overall yields of rearrangement products were uniformly higher using $LiClO_4$.

The preference for formation of allylic alcohol product **2** in the $LiClO_4$ and protic acid catalyzed rearrangements is likely a result of the unfavorable electronic situation of the transition state leading to **3**. The same factor that prevents α cleavage of the glycidic ester, *i.e.*, generation of a positive charge adjacent to the ethoxycarbonyl group, must also come into play in the transition state for rearrangement of the β-cleaved intermediate. It is worth noting that allylic alcohol products were never observed in the lithium salt rearrangements of alkyl-substituted epoxides.[2]

A high-yield synthesis of glyoxylic esters (**3**) using glycidic ester starting materials is accomplished by subjecting the $LiClO_4$ rearrangement product mixture to catalytic hydrogenation (to give ethyl glycolates) followed by chromic acid oxidation to **3**. For the synthesis of β-disubstituted glyoxylic esters, this procedure compares quite favorably with other methods in the literature.[16]

(14) (a) H. C. Brown and M. Borokowski, *J. Amer. Chem. Soc.*, **74**, 1894 (1952); (b) H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

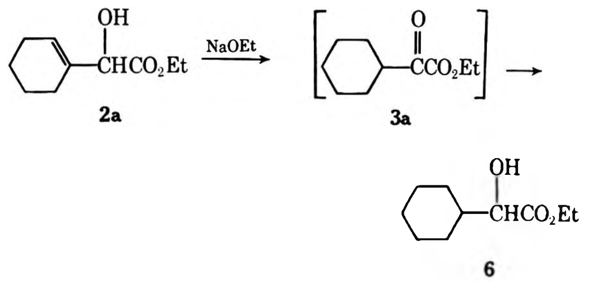
(15) Compound **4** proved to be inert to LiBr·HMPA, presumably because of steric hindrance to attack by bromide.

(16) Procedures for the formation of glyoxylic acids, esters, and closely related materials are found in (a) R. Rambaud, *Bull. Soc. Chim. Fr.*, 1317 (1941); (b) F. Kögl and A. J. Ultee, Jr., *Recl. Trav. Chim. Pays-Bas*, **69**, 1576 (1960); (c) J. D. Chanley, *J. Amer. Chem. Soc.*, **70**, 244 (1948); (d) F. F. Blicke and M. U. Tsao, *ibid.*, **66**, 1645 (1944); (e) J. Kollontisch, *J. Chem. Soc. A*, 456 (1966); (f) J. Lubochinsky and P. Maitte, *C. R. Acad. Sci., Ser. C*, **263**, 732 (1966); (g) E. Baer and M. Kates, *J. Amer. Chem. Soc.*, **67**, 1482 (1945); (h) J. W. Cornforth, *Org. Syn.*, **31**, 59 (1951); (i) E. Zbiral and E. Werner, *Tetrahedron Lett.*, 2001 (1966); (j) F. Adickes and G. Andreesen, *Justus Liebigs Ann. Chem.*, **555**, 41 (1943); (k) R. Fischer and T. Wieland, *Chem. Ber.*, **93**, 1387 (1963); (l) J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Amer. Chem. Soc.*, **81**, 2715 (1959); (m) E. Müller and B. Zeeh, *Tetrahedron Lett.*, 3951 (1965); (n) J. B. Wright, *J. Amer. Chem. Soc.*, **77**, 4883 (1955); (o) W. W. Wisaksono and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **80**, 846 (1961); (p) N. Rabjohn and C. A. Harbert, *J. Org. Chem.*, **35**, 3240 (1970); (q) M. Igarashi and H. Midorikawa, *Bull. Chem. Soc. Jap.*, **34**, 1543 (1961). (r) NOTE ADDED IN PROOF.—A useful general preparative method for α-keto esters has recently appeared: E. L. Eliel and A. A. Hartmann, *J. Org. Chem.*, **37**, 505 (1972).

Rambaud[17] has reported that mild base treatment can effect the rearrangement shown in eq 5.

$$CH_2{=}CHCH(OH)CO_2Et \xrightarrow[H_2O]{K_2CO_3} CH_3CH_2C(=O)CO_2K\ (30\%) \quad (5)$$

In an effort to convert **2a** directly to the glyoxylic ester **3a**, it was treated with sodium ethoxide in refluxing ethanol. A rather slow reaction occurred giving exclusively the glycolic ester **6** (eq 6). This unusual



(6)

ethoxide-induced reduction of a double bond presumably occurs *via* rearrangement to the glyoxylic ester **3a** followed by hydride donation from the alkoxide to yield **6**. The intermediacy of **3a** is given credence by a separate experiment in which it was shown that **3a** is in fact reduced to **6** under identical conditions, in a reaction that occurs considerably faster than the **2a** to **6** interconversion.[18]

Experimental Section

Glycidic Esters.—Ethyl chloroacetate, ethyl 2-bromopropionate, acetone, 3-pentanone, cyclopentanone, cyclohexanone, and cycloheptanone were used as obtained from commercial sources. The Johnson procedure[20] for the Darzens condensation gave the following materials in moderate to good yields: ethyl 1-oxaspiro[2.5]octane-2-carboxylate (**1a**), bp 90° (1.5 Torr);[20] ethyl 1-oxaspiro[2.4]heptane-2-carboxylate (**1b**), bp 72° (1 Torr);[21] ethyl 3-ethyl-2,3-epoxypentanoate (**1d**), bp 109–110° (25 Torr);[22] ethyl 3-methyl-2,3-epoxybutanoate (**1e**), bp 82–84° (25 Torr);[7] ethyl 2,3-dimethyl-2,3-epoxybutanoate (**4**), bp 83–87° (25 Torr).[23]

Ethyl 1-oxaspiro[2.6]nonane-2-carboxylate (1c) had bp 90° (1 Torr); nmr δ 1.25 (t, 3, J = 7 Hz), 1.3–1.9 (m, 13), 3.10 (s, 1), 4.10 ppm (q, 2, J = 7 Hz); ir (thin film) 860, 920, 1036, 1198, 1293, 1730, 1750,[24] 2845, 2915, and 2975 cm^{-1}.

(17) R. Rambaud, *Bull. Soc. Chim. Fr.*, **1**, 1342 (1934); R. Rambaud and M. L. Dondon, *C. R. Acad. Sci., Paris*, **223**, 381 (1946).

(18) Ethoxymagnesium halides have been reported to similarly reduce glyoxylic esters.[19]

(19) I. I. Lapkin and N. A. Karavanov, *Zh. Obshch. Khim.*, **30**, 2677 (1960).

(20) R. H. Hunt, L. J. Chinn, and W. S. Johnson, *Org. Syn.*, **34**, 54 (1954).

(21) M. S. Newman, *J. Amer. Chem. Soc.*, **57**, 732 (1935).

(22 B. Phillips, P. S. Starcher, and D. L. MacPeek, British Patent 863, 446 (1961); *Chem. Abstr.*, **55**, 25982d (1961).

(23) A. Oku, M. Okano, T. Shono, and R. Oda, *Kogyo Kagaku Zasshi*, **68**, 821 (1965).

(24) A double carbonyl absorption is characteristic of glycidic esters.[25] Conversely, the glyoxylic esters **3a** and **3d** exhibited a single carbonyl absorption, as reported for pyruvic acid and its esters.[26]

(25) G. Chiurdoglu, M. Mathieu, R. Baudet, A. Delsemme, M. Planchon, and P. Tullen, *Bull. Soc. Chim. Belg.*, **65**, 664 (1956).

(26) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., London, 1958, p 141.

Anal.[27] Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.33; H, 8.89.

Rearrangements.—Small-scale runs were made in refluxing benzene under a nitrogen atmosphere using the appropriate lithium salt and glycidic ester (and HMPA where noted); the extent of rearrangement and product yields were determined by vpc examination of water-washed samples. The inert internal standards employed for vpc analysis were *p*-dibromobenzene, *p*-chlorobromobenzene, and bromobenzene. Vpc response factors were determined for mixtures of **1e**, **2e**, and **3e**; no corrections were needed for these isomeric materials, and identical response factors were therefore assumed for other isomeric sets.

Preparative scale rearrangements were carried out as in the following example. Glycidic ester 1a, 10.8 g (0.06 mol), and 1.6 g of $LiClO_4$[28] in 25 ml of benzene gave after 1 hr at reflux 8.8 g (81%) of a mixture, bp 116–118° (10 Torr), which was 0.5% (by vpc) of ethyl 2-keto-2-cyclohexylacetate (**3a**) and 99.5% of ethyl 2-hydroxy-2-(1-cyclohexenyl)acetate (**2a**): nmr δ 1.41 (t, 3 H), *J* = 8 Hz), 1.50–2.50 (broad m, 8 H), 4.10 (s, OH), 4.72 (q, 2 H, *J* = 8 Hz), 4.93 (s, 1 H), 6.47 ppm (broad s, 1 H); ir 1735, 3100–3650 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$ (**2a**): C, 65.19; H, 8.75. Found: C, 65.05; H, 8.65.

On a larger scale, 100 g of **1a** and 10 g of $LiClO_4$ in 450 ml of benzene gave after 72 hr 96.0 g (96%) of **2a**.

Similarly 14.4 g (0.10 mol) of **1e** gave 8.0 g (56%) of a mixture, bp 68–69° (10 Torr), consisting of 72% of **2e**[9] (ethyl 2-hydroxy-3-methyl-3-butenoate) and 28% of **3e**[9] (ethyl 2-keto-3-methylbutanoate). A viscous pot residue (3.7 g) was recovered after distillation but was not further examined.

Compound **1d**, 8.3 g (0.05 mol), gave a distillate, bp 80–81° (5 Torr), which contained 1% (vpc) of ethyl 2-keto-3-ethylpentanoate (**3d**) and 99% of a mixture of *cis*- and *trans*-ethyl 2-hydroxy-3-ethyl-3-pentenoate (**2d**): nmr δ 0.90 (t, 3 H, *J* = 7 Hz), 1.20 (t, 3 H, *J* = 7 Hz), 1.59 and 1.63 (two d, *J* = 6 and 7 Hz, respectively, relative areas *ca.* 2:1, 3 H total, allylic CH_3), 1.92 (t, 2 H, *J* = 7 Hz), 3.33 (broad d, OH), 4.03 (q, 2 H, *J* = 7 Hz), 4.28 and 4.82 (broadened singlets, relative areas *ca.* 2:1, 1 H total, carbinol CH), 5.35 ppm (broad q, *J* = 6–7 Hz, vinyl H); ir 1730, 3150–3650 cm^{-1}. *Anal.* Calcd for $CH_{16}O_3$ (*cis*- and *trans*-**2d**): C, 62.77; H, 9.36. Found: C, 63.09; H, 9.16.

Glycidic ester **1b**, 10.1 g (0.06 mol), gave 8.3 g (82%) of a mixture, bp 105–107° (10 Torr), consisting of 90% ethyl 2-hydroxy-2-(1-cyclopentenyl)acetate (**2b**) and 10% ethyl 2-keto-2-cyclopentylacetate (**3b**); pure samples were obtained by preparative vpc.

Compound **2b** had nmr δ 1.20–2.70 (multiplet, 9 H), 3.17 (s, OH), 4.15 (q, 2 H, *J* = 7 Hz), 4.57 (s, 1 H), 5.62 ppm (broad s, 1 H). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.50; H, 8.29. Found: C, 63.31; H, 8.12.

Glyoxylic ester **3b** had nmr δ 1.32 (t, 3 H, *J* = 7 Hz), 1.60–2.10 (m, 8 H), 3.10–3.75 (m, *tert*-CH), 4.19 ppm (q, 2 H, *J* = 7 Hz); ir 1730 cm^{-1}. *Anal.* Found: C, 63.76; H, 8.65.

Glycidic ester **4** gave in essentially quantitative yield (vpc) ethyl 2-hydroxy-2,3-dimethyl-3-butenoate (**5**), identified by its spectral characteristics: nmr δ 1.22 (t, 3 H, *J* = 7 Hz), 1.42 (s, 3 H), 1.70 (s, 3 H), 3.40 (broad s, OH), 4.08 (q, 2 H, *J* = 7 Hz), 4.72 and 4.92 ppm (broad singlets, 1 H each, vinyl); ir 1730, 3200–3650 cm^{-1}. *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.69; H, 8.97.

Overall conversion of glycidate to glyoxylate is illustrated by the reaction of **1c**; 19.8 g (0.10 mol) in 5 min in refluxing benzene with $LiClO_4$ gave 17.0 g (86%) of distillate, bp 89° (0.5 Torr). This was nearly pure **2c**, with *ca.* 1% **3c**. The distillate had nmr δ 1.20–2.35 (m, 13 H), 2.99 (s, OH), 4.12 (q, 2 H, *J* = 7 Hz), 4.23 (s, 1 H), 5.78 ppm (t, 1 H, *J* = 6 Hz); ir 1730, 3150–3700 cm^{-1}.

A portion, 13.8 g (0.07 mol), of the distillate was reduced on a Parr shaker, 3 atm H_2, using PtO_2 catalyst and absolute ethanol solvent. Distillation gave 11.5 g (83%) of ethyl cycloheptylglycolate, which was contaminated by the *ca.* 1% of **3c** present in the starting material: bp 124–127° (9 Torr); nmr δ 1.12–2.10 (m, 16 H), 3.23 (broad s, OH), 3.88–4.02 (m, 1 H), 4.15 ppm (q, 2 H, *J* = 7 Hz); ir 1730, 3150–3650 cm^{-1}.

A portion, 7.5 g (0.038 mol), of this material was subjected to Jones oxidation (CrO_3, aqueous acid, acetone, 0°) to give 6.1 g g (82%) of pure **3c**: bp 127–128° (10 Torr); nmr δ 1.23–2.00 (m, 16 H), 2.82–3.27 (m, *tert*-CH), 4.12 ppm (q, 2 H, *J* = 7 Hz); ir 1730, shoulder at 1750 cm^{-1}. *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.64, H, 9.15. Found: C, 66.36; H, 8.88.

Similarly **2b** was reduced to give ethyl 2-hydroxy-2-cyclopentylacetate: nmr δ 1.27 (t, 3 H, *J* = 7 Hz), 1.20–2.30 (m, 9 H), 3.47 (s, OH), 3.95–4.33 ppm (m, 3 H, containing ester quartet, *J* = 7 Hz); ir 1730, 3150–3600 cm^{-1}. *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.84; H, 9.57. Oxidation gave **3b**, confirming its structure.

The mixture of **2d** and **3d** described earlier was similarly reduced and gave ethyl 2-hydroxy-3-ethylpentanoate: bp 88° (11 Torr); δ 0.7–1.70 (m, 14 H), 3.21 (s, OH), 4.10 (s, 1 H), 4.17 ppm (q, 2 H, *J* = 7 Hz); ir 1730, 3150–3650 cm^{-1}. *Anal.* Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.26; H, 10.63. Oxidation as above furnished **3d**: bp 79–81° (10 Torr); nmr δ 0.90 (t, 6 H, *J* = 7 Hz), 1.05–1.82 (m, 7 H, containing t, *J* = 7 Hz), 2.80 (quintet, 1 H, *J* = 6 Hz), 4.17 ppm (q, 2 H, *J* = 7 Hz); ir 1730 cm^{-1}. *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 63.10; H, 9.35.

Attempted Base-Catalyzed Rearrangement of 2a.—A mixture of 0.2 g of sodium ethoxide and 1 g of **2a** in 25 ml of absolute ethanol was refluxed under nitrogen for 44 hr. Vpc analysis after neutralization and isolation showed a mixture consisting of 83% of starting material and 17% of ethyl cyclohexylglycolate,[29] which had an ir spectrum identical with that of the material obtained on catalytic reduction of **2a**.

Compound **3a** was similarly treated with sodium ethoxide; after 14 hr 32% had been converted to ethyl cyclohexylglycolate.

Registry No.—**1c**, 6975-19-5; **2a**, 33487-17-1; **2b**, 33487-18-2; **2c**, 33487-19-3; *cis*-**2d**, 33495-64-6; *trans*-**2d**, 33495-65-7; **2e**, 33537-17-6; **3b**, 33537-18-7; **3c**, 33487-20-6; **3d**, 33487-21-7; **3e**, 20201-24-5; **5**, 33487-23-9; ethyl 2-hydroxy-2-cyclopentylacetate, 33487-24-0; ethyl 2-hydroxy-3-ethylpentanoate, 33487-25-1.

(27) Analyses by C. F. Geiger, 312 E. Yale St., Ontario, Calif.

(28) Although the $LiClO_4$ is catalytic, the reaction exhibits autoinhibition, making advisable the use of relatively large amounts of the salt. In general a $LiClO_4$ to glycidate mole ratio of 0.25 gave satisfactory results.

(29) I. I. Lapkin and N. A. Karavanov, *Zh. Obshch. Khim.*, **30**, 1638 (1960).

Linear Dimerization and Codimerization of 1,3,7-Octatriene

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The linear dimerization of 1,3,7-octatriene *via* π-allylpalladium complexes in homogeneous reactions yields in high selectivity *n*-hexadecapentaenes. The same catalysts also prove active for the codimerization of 1,3,7-octatriene with various other polyolefins such as 1,3,6-heptatriene, 1,3,6-octatriene, 1,3,7,11-dodecatetraene, and 1,5,7,10,15-hexadecapentaene producing linear olefins in the C_{16}–C_{24} carbon range. The addition of phosphine ligands alters the course of the reaction and branched dimers are formed.

Over the last decade, oligomerization reactions of olefins *via* π-allylic intermediates of various transition metal complexes have seen a prodigious growth.[1,2] Although often not too well understood, they represent an exciting development in coordination chemistry and are finding increasing interest in both the academic and industrial world. Especially the linear and cyclic oligomerization of 1,3-dienes has demonstrated great usefulness for the synthesis of numerous novel and known organic compounds.[3] Many attempts to oligomerize other dienes such as isoprene, piperylene, dimethylbutadiene, and chloroprene have been disclosed. It can be generalized that catalysis with dienes other than butadiene directed at open chain or cyclic oligomers is complicated by the concomitant formation of the various, possible isomers. The products and their distribution often can be altered by modifying the catalysts with ligands such as phosphines or phosphites. However, very few cases are known in which dienes other than butadiene have cleanly been oligomerized to predominantly one product.

In this paper, a remarkably selective dimerization reaction of trienes to predominantly linear products in the n-C_{12}–C_{24} range will be described. This dimerization represents a facile route to a variety of novel linear compounds. Long straight carbon chains play an important role in nature, especially in fatty acids, fatty alcohols, sphingosines, and pheromones. It can be envisaged that linear natural products may be synthesized by utilizing the described type of oligomers as starting materials for further chemical reactions. Our major experimental research efforts were focused on the dimerization of 1,3,7-octatriene, which was available in large quantities in our laboratory.[4]

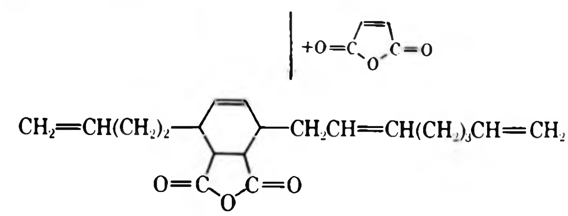
Results and Discussion

The addition of catalytic amounts of bis-π-allylpalladium[5] to a cis,trans mixture of 1,3,7-octatriene yielded four linear hexadecapentaenes containing one major isomer in >70% selectivity. Microanalysis and molecular weight measurements indicated an empirical formula of $C_{16}H_{24}$. Proof of linearity rested on hydrogenation of the dimer mixture giving n-hexadecane in 97% selectivity. For a structure assignment, the major isomer was arduously trapped by glc fractionation. All attempts to locate spectroscopically (nmr, ir, uv) the exact position of the five double bonds proved impossible in our hands. These spectroscopic data fit various possible double bond isomers. However, they clearly indicated the presence of two terminal and three internal double bonds of which two are conjugated. Additional evidence was needed for a correct structure assignment.

An ozone analysis was attempted; however, the results obtained did not unambiguously distinguish among the various possible isomers. At this point, it became obvious that the location of the position of the conjugated diene fragment would be helpful for an exact structure assignment. Therefore, a Diels–Alder reaction with maleic anhydride was carried out. The nmr data in addition to ir and high-resolution mass spectral analysis of both the hydrogenated and nonhydrogenated product have led to the structure assignment 3-(octadienyl-2,7)-6-(butenyl-3)-1,2,3,6-tetrahydrophthalic anhydride (2) pointing at a diene conjugation in 5–7 position.

$CH_2{=}CH(CH_2)_2CH{=}CHCH{=}CHCH_2CH{=}CH(CH_2)_3CH{=}CH_2$

1



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Having located the conjugated diene unit in the predominant isomer of the dimerization of 1,3,7-octatriene, the nmr and ir data were in agreement with the structure 1,5,7,10,15-hexadecapentaene (1).

Definitive structure assignment is lacking for the three minor n-hexadecapentaene isomers. All attempts of separating and trapping by glc failed because of nearly identical retention times; however, spectroscopic evidence (nmr, uv, ir) of the combined mixture suggested that only different cis and trans isomers have been formed. This is not too surprising. The presence of various cis and trans isomers in oligomerization products of 1,3-dienes has frequently been observed.[6]

During the course of our studies to increase conversions of the dimerization reaction which never exceeded 60%, it was noted that the unreacted 1,3,7-octatriene[7] consisted of predominantly cis isomer. In this way, it was possible to synthesize pure cis-1,3,7-octatriene

(1) C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Logos Press, London, 1967.

(2) J. P. Candlin, K. A. Taylor, and D. T. Thompson, "Reactions of Transition Metal Complexes," Elsevier, New York, N. Y., 1968.

(3) P. Heimbach, P. W. Jolly, and G. Wilke, *Advan. Organometal. Chem.*, **8**, 29 (1970).

(4) E. J. Smutny, *J. Amer. Chem. Soc.*, **89**, 6793 (1967).

(5) W. Keim, Thesis Technichsche Hochschule Aachen, 1964.

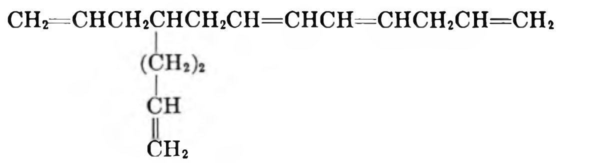
(6) G. Wilke, *et al.*, *Angew. Chem., Int. Ed. Engl.*, **2**, 105 (1963).

(7) The octatriene-1,3,7 used for the dimerization was composed of ~60% *trans*-1,3,7-octatriene and 40% *cis*-1,3,7-octatriene.

starting from the trans and cis mixture. Further investigation of this interesting finding confirmed that pure *cis*-1,3,7-octatriene did not undergo dimerization or isomerization under the catalytic influence of bis-π-allylpalladium. Unfortunately, experimental evidence regarding the inhibiting effect of the cis isomer is lacking due to unavailability of sizable amounts of *pure trans*-1,3,7-octatriene. The above observation once more demonstrates the remarkable degree of selectivity and specificity when working in homogeneous catalysis with transition metal complexes.

Other Palladium Catalysts.—It is known that a certain transition metal catalyzed reaction is not necessarily restricted to a particular transition metal complex. Proper modification of the ligands will often lead to more active and more stable catalysts. Indeed, comparable activity was demonstrated with bis-π-allylpalladium and π-allylpalladium acetate. The system π-allylpalladium chloride–sodium phenoxide was found to be only half as active. Little or no catalysis was observed with the following complexes: $(\pi\text{-}C_3H_5PdC)_2$,[8a] $(\pi\text{-}C_3H_5PdCF_3COO)_2$,[8b] $Pd(CH_3COO)_2$,[9] $Pd(CH_3COO)_2$–$AlEt_3$, $Pd(CH_3COO)_2$–C_3H_5MgCl, $(Ph_3P)_4Pd$, $(Ph_3P)_3Pd$, $PdCl_2/NaOPh$.

Interestingly, attempts to modify the bis-π-allylpalladium by addition of 1 mol of triphenylphosphine per mole of bis-π-allylpalladium altered the course of the reaction and a new dimer in yields of up to 50% was formed. Spectroscopic (ir, nmr, high-resolution mass) data are consistent with the structure 4-(butenyl-3)-dodecatetraene-1,6,8,11 (**3**). Attempts to alter the

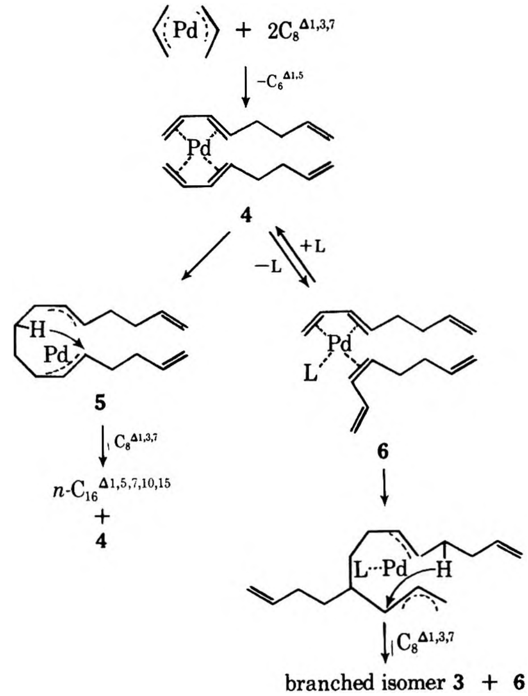


3

dimerization of 1,3,7-octatriene toward the branched dimer exclusively failed. The addition of alkylphosphines and triphenylarsins was found to have a deleterious effect. The various ligands studied and the order of their effectiveness is as follows: diphenylphosphinoethane ≈ triphenylphosphine > phenol >>> pyridine, acetic acid, dipyridyl, triphenylarsine.

The mechanism proposed for the dimerization of 1,3,7-octatriene is depicted in Scheme I. The initial step is the coordination of two 1,3,7-octatrienes to bis-π-allylpalladium yielding intermediate **4**. Simultaneously, the two π-allyl groups in bis-π-allylpalladium are displaced by forming 1,5-hexadiene, a product identified in the reaction mixture. A carbon–carbon coupling of the C_8 units in **4** gives the bis-π-allyl intermediate **5**, which is coordinatively unsaturated and coordinates to incoming 1,3,7-octatriene under concomitant displacement of 1,5,7,10,15-hexadecapentaene (**1**). In this way, the intermediate **4** is regenerated and the catalytic cycle completed. An arrow in **5** indicates the allylic hydrogen shift which is necessary for the displacement of the C_{16} chain. Carbon–carbon couplings accompanied by allylic hydrogen

SCHEME I



shifts have frequently been discussed to explain oligomerization reactions of conjugated dienes.[10-14]

The formation of the branched C_{16} isomer **3** can also be derived from the intermediate **4**. Ligands such as triphenylphosphine coordinate to palladium in **4**, thus displacing a coordinated olefin as depicted in **6**. Again, a carbon–carbon coupling and allylic hydrogen shift is needed to form the branched isomer **3**. The fact that, in the presence of triphenylphosphine, the linear dimer is also formed can be explained by the donor properties of triphenylphosphine. It is well established in the literature that triphenylphosphine is not very strongly bonded to a transition metal complex and the equilibrium **4** ⇄ **6** can be considered. The proposed scheme explains in a reasonable manner the formation of the products. It is in agreement with current aspects of transition metal catalyzed oligomerization of conjugated dienes but should not be taken too literally.

Codimerization of 1,3,7-Octatriene.—The proposed mechanism indicated the feasibility of codimerization of 1,3,7-octatriene with other polyolefins possessing a conjugated diene unit as in 1,3,6-octatriene, 1,3,7,11-dodecatetraene, and 1,5,7,10,15-hexadecapentaene. Indeed, bis-π-allylpalladium is an active catalyst for the linear codimerization of 1,3,7-octatriene with various polyolefins as listed in Table I. In view of the immense difficulties encountered in locating the double bonds in the 1,3,7-octatriene dimer, no attempts have been made to characterize the olefinic dimerization products. Identification and characterization were carried out by hydrogenation. Table I summarizes

(8) (a) A. J. Wilkinson, *et al.*, *J. Chem. Soc.*, 1585 (1964); (b) B. L. Shaw and S. D. Robinsons, *J. Organometal. Chem.*, **3**, 367 (1965).

(9) G. Wilkinson, *et al.*, *J. Chem. Soc.*, 3632 (1965).

(10) G. Wilke, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, **9** (1966).

(11) G. Wilke, *et al.*, *Angew. Chem.*, **78**, 157 (1966); *ibid.*, *Int. Ed. Engl.*, **5**, 151 (1966).

(12) H. Muller, D. Wittenberg, H. Seibt, and E. Scharf, *ibid.*, *Int. Ed. Engl.*, **4**, 327 (1965).

(13) T. Saito, Y. Uchida, A. Misono, A. Yamamoto, K. Morifugi, and S. Ikeka, *J. Organometal. Chem.*, **6**, 572 (1966).

(14) G. Allegra, F. LoGiudice, and G. Natta, *Chem. Commun.*, 1263 (1967).

Table I

Linear Codimerization of 1,3,7-Octatriene with Polyolefins Containing a 1,3-Diene Unit

Reaction	Reactants: Olefin A (ml)	Reactants: Olefin B (ml)	Reaction: Pd catalyst, mg	Reaction: Time, days	Reaction: Temp, °C	Reaction: Concn, % $C_8H_{12}\Delta^{1,3,7}$	Products: Before hydrogen	Products: After hydrogen	Products: Distribution
a	n-$C_8H_{12}\Delta^{1,3,7}$ (5)	$C_4H_6\Delta^{1,3}$ (20)	230	4	25	32	n-$C_{12}H_{18}\Delta^{1,3,6,10}$[a]	n-$C_{12}H_{26}$	95
							n-$C_{16}H_{24}$ (5)[b]	n-$C_{16}H_{34}$	~5
b	n-$C_8H_{12}\Delta^{1,3,7}$ (2)	n-$C_7H_{10}\Delta^{1,3,6}$ (4)	123	2	25	49	n-$C_{15}H_{22}$ (5)	n-$C_{15}H_{32}$	44
							n-$C_{16}H_{24}$ (5)	n-$C_{16}H_{34}$	37
							n-$C_{14}H_{20}$ (5)	n-$C_{14}H_{30}$	19
c	n-$C_8H_{12}\Delta^{1,3,7}$ (5)	n-$C_{12}H_{18}\Delta^{1,3,7,11}$ (5)	110	2	25	24	n-$C_{20}H_{30}$ (6)	n-$C_{20}H_{42}$	44
							n-$C_{16}H_{24}$ (5)	n-$C_{16}H_{34}$	56
							n-$C_{24}H_{36}$ (7)	n-$C_{24}H_{50}$	Trace
d	n-$C_8H_{12}\Delta^{1,3,7}$ (5)	n-$C_{16}H_{24}\Delta^{1,5,7,10,15}$ (5)	50	1	25	15	n-$C_{24}H_{36}$ (7)	n-$C_{24}H_{50}$	30
							n-$C_{16}H_{24}$ (5)	n-$C_{16}H_{34}$	60
e	n-$C_8H_{12}\Delta^{1,3,7}$ (5)	n-$C_8H_{12}\Delta^{1,3,6}$ (5)	100	2	25	45	n-$C_{16}H_{24}$ (5)	n-$C_{16}H_{34}$	97
f	n-$C_{12}H_{18}\Delta^{1,3,7,11}$ (5)		60	2	25	~10	n-$C_{24}H_{36}$ (7)[c]	n-$C_{24}H_{50}$	85
g	n-$C_7H_{10}\Delta^{1,3,6}$ (10)		103	2	25	6	n-$C_{14}H_{20}$ (5)	n-$C_{14}H_{30}$	95

[a] 90% selectivity. [b] Number of double bonds in parentheses. [c] Two isomers.

the results obtained. Principally, it is possible to linearly codimerize 1,3,7-octatriene with dienes (reaction a), trienes (reactions b, e), tetraenes (reaction c), and pentaenes (reaction d). However, besides codimerization, normal dimerization of the 1,3,7-octatriene and the coolefin takes place. For instance, the codimerization of 1,3,7-octatriene with 1,3,7,11-dodecatetraene (Table I, reaction c) yields, in addition to n-eicosane, n-hexadecane and n-tetracosane. The ratio of these three products can be influenced by altering the concentration of 1,3,7-octatriene to 1,3,7,11-dodecatetraene.

The results of Table I also show that the linear dimerization is not unique to 1,3,7-octatriene and linear dimerization can be carried out with other triene or polyenes as shown in reactions f and g.

In our experiments, no emphasis has been placed on yield and selectivity since the detection of catalytic activity and proof of feasibility of codimerization have been the primary design.

Generalizing, it can be stated that bis-π-allylpalladium is an excellent catalyst for the linear oligomerization of trienes or polyenes containing a 1,3-diene unit. Disappointingly, however, all attempts to codimerize 1,3,7-octatriene with compounds of the general type CH_2=CHCH=CHY (Y = functional group such as OH, CN, Cl) or CH_2=CHCHX (X = O, CN) have been unsuccessful so far.

Experimental Section

Oligomerization Procedure.—All reactions were carried out under the exclusion of oxygen and water. In general, the reactants and the palladium catalyst were charged into a glass ampoule and stirred magnetically. Reaction temperatures above 25° were maintained with a preheated silicone oil bath. The progress of the reaction was monitored by glc analysis. The products were isolated by glc trapping or distillation in the conventional manner. To avoid possible product isomerization during work-up, the active palladium catalyst was reduced to the metal by reduction with gaseous carbon monoxide at atmospheric pressure and removed by filtration. Product identification rests on nmr, ir, uv, and mass spectral analyses before and after hydrogenation. Whenever possible, glc emergence times of the hydrogenated products were compared with those of authentic samples.

1,5,7,10,15-Hexadecapentaenes (1).—A mixture of 53.7 g of 1,3,7-octatriene and 693 mg of bis-π-allylpalladium was charged into a two-neck round-bottom flask and stoppered. After a reaction period of 3 days at ambient temperature, glc analysis of the product mixture showed a 54% octatriene conversion to 97% n-hexadecapentaenes (70% selectivity to n-$C_{16}H_{24}\Delta^{1,5,7,10,15}$) and 3% yield of butenyldodecatetraenes. Distillation at reduced pressure gave 26.9 g of hexadecapentaenes [bp 93° (2 mm)]. Linearity of the dimer mixture rested on comparison of the hydrogenated dimer product with an authentic sample of n-hexadecane by mass spectral analyses and glc emergence times. Mass spectral analysis of 1 confirmed the empirical formula, 216. Nmr spectrum[15] of 1 ($CDCl_3$): 4.8–6.6 (m, 12, vinyl plus terminal vinyl), 2.85 (t, 2, J = 6 Hz, double allylic), 1.9–2.3 (m, 8, allylic), 1.5 ppm (g, 2, J = 7 Hz, aliphatic methylene). The ir spectrum exhibited strong bands indicative of terminal and internal cis and trans double bonds (1005, 996, 910, 778 cm^{-1}). The ultraviolet spectrum had a λ_{max} 232 (ϵ 31,000).

Anal. Calcd for $C_{16}H_{24}$: C, 88.9; H, 11.1. Found: C, 88.7; H, 11.1.

The unreacted 1,3,7-octatriene consisted of the cis isomer.

Hexadecapentaene–Maleic Anhydride Adduct 2.—A reaction mixture of 1.58 g (7.32 mmol) of 1,5,7,10,15-hexadecapentaene and 0.72 g (7.34 mmol) of maleic anhydride was heated under reflux of benzene (20 ml) for 4 hr. Glc analysis showed that reaction with maleic anhydride to give predominantly (90%) one isomer had taken place. The product was isolated by glc trapping using a 6 ft × 0.25 in. o.d. SE-30 chromatographic column. Mass spectral analyses confirmed the empirical formulas, 314 and 322 [bp 180° (1 mm)], for the product before and after hydrogenation. Nmr spectrum of 2 ($CDCl_3$): 4.9–6.0 (m, 10, vinyl plus terminal vinyl), 2.9–3.1 (m, 2, substitute succinic anhydride), 1.3–2.6 ppm (m, 14, allylic plus substituted allylic plus aliphatic methylene). Mass spectral analysis of the hydrogenated 2 confirmed the location of the anhydride adduct on the linear carbon skeletal chain.

4-(Butenyl-3)-dodecatetraene-1,6,8,11 (3).—A reaction mixture of 10 ml of 1,3,7-octatriene, 67 mg of bis-π-allylpalladium, and 94 mg of triphenylphosphine was charged into a glass ampoule. After a reaction period of 2 days at 65° glc analysis showed a 70% octatriene conversion to give 51% yield of n-hexadecapentaenes and 49% yield of butenyldodecatetraenes [95% selectivity to 4-(butenyl-3)dodecatetraene-1,6,8,11]. Mass spectral analyses confirmed the empirical formulas, 216 and 226, of the branched C_{16} product before and after hydrogenation. Nmr spectrum of 3 ($CDCl_3$): 4.8–6.5 (m, 13, vinyl plus terminal vinyl), 2.95 (m, 2, double allylic), 1.3–2.5 ppm (m, 9, allylic plus aliphatic methylene).

Linear Codimerization of 1,3,7-Octatriene with Polyolefins Containing a 1,3-Diene Unit.—The general procedure followed for the codimerization reaction was to charge the appropriate olefin reactants and the bis-π-allylpalladium catalyst into a glass ampoule and seal in the normal manner. After a reaction period of 1–2 days at 25°, the per cent conversion to products was determined by glc analysis. The codimer products were isolated by glc trapping, and their empirical formulas were obtained by mass spectral analyses. Linearity proof rested on mass spectral analysis, nmr analysis, and glc emergence times of the hydrogenated codimers with authentic samples. The data obtained are summarized in Table I.

(15) Nmr spectra of compounds 1–3 will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche.

Registry No.—1, 33143-72-5; 2, 33212-34-2; 3, 33143-73-6; 1,3,7-octatriene, 1002-35-3; π-allylpalladium, 12240-87-8; 1,3,6-heptatriene, 1002-27-3; 1,3,6-octatriene, 929-20-4; 1,3,7,11-dodecatetraene, 22005-88-5.

Acknowledgment.—We wish to thank Dr. P. A. Wadsworth, Jr., for the numerous mass spectral measurements and his helpful suggestions for structure determinations.

Oligomerization and Co-oligomerizations of Allene

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A systematic study of the oligomerization of allene was undertaken. *Via* temperature and concentration variation one could control reasonably the relative proportions of the various oligimers formed. The oligomerization was found to proceed from the dimer, 1,2-dimethylenecyclobutane, and through various [2 + 2] and [2 + 4] cycloadditions, sigmatropic rearrangements, and electrocyclic reactions. Co-oligomerizations of allene with 1,2-cyclononadiene and tetramethylallene were found to incorporate only *one* molecule of the substituted allene and they proceeded *via* pathways similar to that for allene itself.

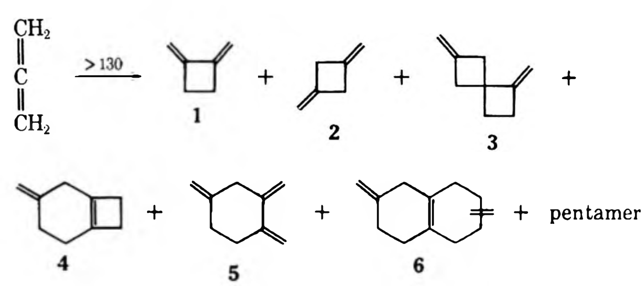
In spite of the amount of recent work which has been devoted to the dimerization and further oligomerization reactions of allene,[2] there has been little or no discussion of the detailed *pathways* to the various oligomers which are formed. Nor has any attempt been made to regulate this process so as to obtain preferentially one oligomer or another.

In order to investigate the secondary deuterium isotope effects of the allene dimerization it was necessary for us to seek conditions for a high yield (~90%) conversion of allene to 1,2-dimethylenecyclopropane. In the course of this work various data were accumulated which enable us now to be able to present a concise picture of this *very interesting* oligomerization process which apparently proceeds by a simple sequence of competitive [2 + 2] and [2 + 4] cycloadditions, sigmatropic rearrangements, and electrocyclic reactions.

It also became of interest to investigate the relative abilities of other allenic hydrocarbons, namely 1,2-cyclononadiene and tetramethylallene, to co-oligomerize with allene. There is essentially no information in the literature dealing with the relative ability of allene to codimerize or co-oligomerize with other allenic hydrocarbons. Not only were the results of these studies found to be consistent with those conclusions derived from our earlier investigation of allene itself, but much new and interesting chemical information was gleaned from these systems.

Results and Discussion

Allene Oligomerization.—The key innovation of this study as compared to those that have preceded it derived from the idea of pyrolyzing allene at relatively low concentration in benzene. Vacuum line techniques combined with gas–liquid phase chromatography (glpc) allowed quantitative analysis, isolation, and characterization of the various oligomers, which were in all cases but one proven to be identical with those described earlier by Weinstein.[2a–d]



As can be seen from Table I, 1,2-dimethylenecyclobutane, dimer 1, is the major constituent of the oligomerization product mixture at the lower temperatures. In fact, if the weight ratio of allene to benzene was decreased to 1:3.0 at 130°, the yield of dimer after 24 hr could be increased to as high as 91%, although the conversion dropped off to 5%.

Curiously, dimer 2 was detected only in those runs at higher temperatures (>160°), and its mole fraction increased as the temperature was increased, a maximum value of >0.05 being reached, in our study, at 200°. It had been shown earlier that the process 1 → 2 did not take place even at temperatures as high as 450°.[3] Since, as it will be shown below, all higher oligomers derive solely and logically from dimer 1, this means that >95% of all dimerizations of allene result in the formation of 1,2-dimethylenecyclobutane.

While the dimerization of allene to form 1,2-dimethylenecyclobutane (1,2-DMC) can be most consistently thought of as proceeding *via* a two-step mechanism[2e,4] very little can be said at this time about the mechanism of the process leading to 1,3-dimethylenecyclobutane (1,3-DMC). What can be said is that, since less than 1% of 1,3-DMC is formed at temperatures below 160° and yet >5% is formed at 200°, it is necessary that the entropy requirements for 1,2- and 1,3-dimethylenecyclobutane formation *cannot* be nearly the same. Moreover, the $\Delta S^{\ddagger}$ for 1,2-dimethylenecyclobutane formation must have a significantly larger negative value. This can easily be rationalized in terms of the greater

(1) (a) Taken in part from the Ph.D. Dissertation of Sheng-Hong Dai, University of Florida, June 1971; (b) Alfred P. Sloan Foundation Fellow, 1971–1972.

(2) (a) B. Weinstein and A. H. Fenselau, *Tetrahedron Lett.*, 1463 (1963); (b) B. Weinstein and A. H. Fenselau, *J. Chem. Soc. C*, 368 (1967); (c) B. Weinstein and A. H. Fenselau, *J. Org. Chem.*, **32**, 2278 (1967); (d) B. Weinstein and A. H. Fenselau, *ibid.*, **32**, 2988 (1967); (e) a recent review discusses substituted allene dimerizations and [2 + 2] cycloadditions—J. E. Baldwin and R. H. Fleming, "Fortschritte der Chemischen Forschung," Band 15, Heft 3, Springer-Verlag, West Berlin, 1970, pp 281–310.

(3) W. v. E. Doering and W. R. Dolbier, Jr., *J. Amer. Chem. Soc.*, **89**, 4534 (1967).

(4) W. R. Dolbier, Jr., and Sheng-Hong Dai, *ibid.*, **92**, 1774 (1970).

TABLE I

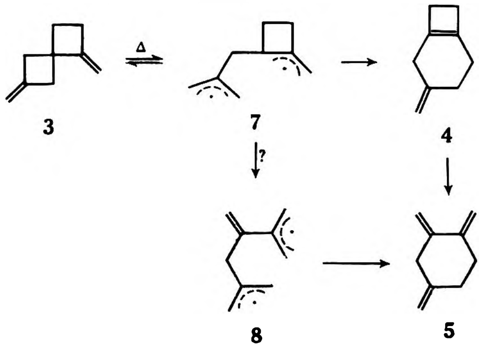
PRODUCTS FROM ALLENE OLIGOMERIZATIONS IN BENZENE

Reaction temp, °C	Reaction time, hr	Wt ratio, PhH/allene	Allene, reacted, %	Mole fraction of products 1	2	3	4	5	6	Pentamer
130 ± 2	24	1.66	6–8	0.869		0.045	0.059	0.027		
135 ± 2	24	1.53	8.5	0.862		0.047	0.074	0.014		
140 ± 2	24	1.24	10	0.774		0.096	0.068	0.062		
160 ± 2	15	1.46	30	0.394	0.011	0.131	0.021	0.079	0.312	0.052
175 ± 2	24	2.20	42	0.118	0.012	0.140		0.023	0.547	0.162
200 ± 4	24	2.18	85	0.075	0.057	0.023		0.019	0.622	0.196
200 ± 5	24	3.80	80	0.108	0.052	0.050		0.026	0.582	0.176

steric requirements for C-2–C-2′ approach than for C-2–C-1′ approach in the respective rate-determining transition states.

A careful investigation of the trimer products **3**, **4**, and **5** revealed some very interesting chemistry (Scheme I). At first glance it seemed obvious that **3**

SCHEME I



and **4** are formed by competitive [2 + 2] and [2 + 4] processes, respectively, and that **5** derives from **4** *via* simple electrocyclic ring opening.

However, considering Table I it is apparent that things are not quite that simple. In the higher temperature runs, tetramer **6** and the pentamers have obviously increased in concentration at the expense of *all three* trimers, although tetramer **6** can logically only be obtained from [2 + 4] addition to trimer **5**. Indeed we found that, under the reaction conditions, trimer **3** could be converted quantitatively into a mixture of **4** and **5**. (See Table II.) The reaction was complete at

TABLE II

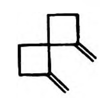
PYROLYSES OF 1,6-DIMETHYLENESPIRO[3.3]HEPTANE (**3**)

Pyrolysis temp, °C	Pyrolysis time, hr	Phase	Ratio 3	5	4
140–145	24	Acetone-d_6 solution	98.5	1.4	
160 ± 3	12	Acetone-d_6 solution	91.0	8.5	0.5
170 ± 2	12	Benzene solution	81.0	19.0	
175 ± 3	5	Acetone-d_6 solution	88.7	11.0	0.3
185 ± 5	18	Gas phase	9.0	91.0	
275 ± 5	3.5	Gas phase	0	100	

185° after 18 hr. Less than 1% of **4** could actually be detected in the product mixture after pyrolysis, but it was shown that conversion of **4** to **5** is very rapid under these conditions. (See Table I). The alternative possibility of the process proceeding *via* a radical ring cleavage process *via* **8** has not yet been ruled out as contributing at least partially to the mechanistic pathway. A concerted Cope rearrangement alternative pathway was not considered a realistic possibility owing to the lack of proximity of the two ends of this 1,5-hexadiene system.

If the probable pathway *via* **4** can indeed be proven correct, this will provide a unique example of a reaction where both [2 + 2] and [2 + 4] cycloadducts are formed competitively, along with concomitant rearrangement of the [2 + 2] to the [2 + 4] adduct. This seems a likely system to be able to observe competitive [2 + 2] and [2 + 4] closure from a diradical intermediate. Such an investigation is presently underway.

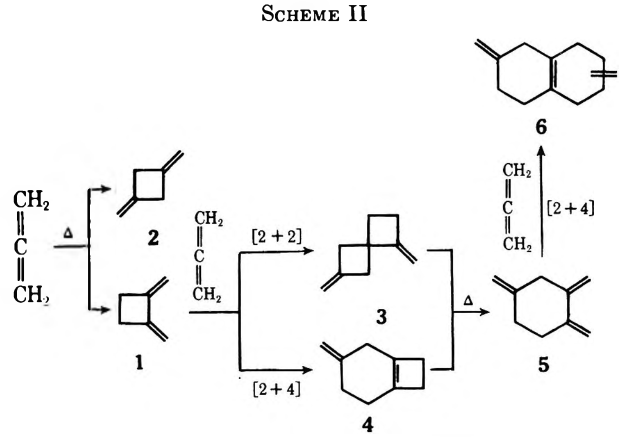
Needless to say, the smooth conversion of **3** to **5** without doubt establishes the identity of the trimer **3** which Weinstein had not been able to distinguish from the isomeric structure **9**.[2b] Actually the nmr spectrum of **3** also is *much* more consistent with structure **3** than **9**.



9

With an understanding of the thermal properties of trimer **3**, one can now rationalize easily the entire process of oligomerization of allene as a sequence of competitive [2 + 2] and [2 + 4] cycloadditions, sigmatropic rearrangements, and electrocyclic reactions with essentially all of the oligomerization beginning with the formation of 1,2-DMC (Scheme II).

SCHEME II



One last point deserves mentioning. While trimer formation involved competitive [2 + 2] and [2 + 4] cycloadditions, tetramer formation from **5** apparently involves only two, competitive [2 + 4] cycloadditions. No [2 + 2] dimers could be detected by glpc. This observation has some experimental precedent, since Bartlett has shown that the interatomic distance between C-1 and C-4 of the diene system has much to do with its relative rates of [2 + 2] and [2 + 4] cycloadditions.[5] Indeed he found that the ratio of [2 + 2] to [2 + 4] cycloaddition between 1,1,2,2-dichlorodifluoroethylene and 1,2-DMC was >99, while for 1,2-dimethylenecyclohexane it was 0.8.

Co-oligomerization of Allene and 1,2-Cyclononadiene.—1,2-Cyclononadiene (CND) is the smallest cyclic allene which is relatively free of ring strain, and its properties and reactions have been studied extensively.[6] The dimerization takes place with ease at 120°, forming a remarkably pure mixture of dimers in high yield. Unlike parent allene, no higher oligomers could be detected.

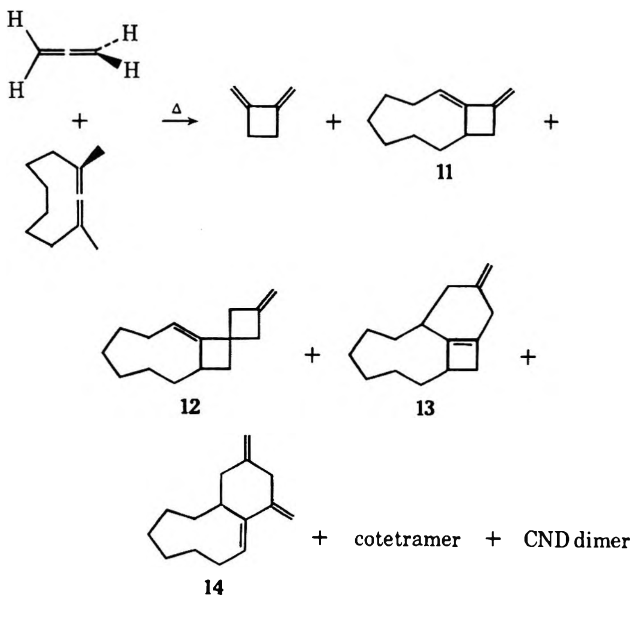
It was a desire to take advantage or the reactivity and simplicity of 1,2-cyclononadiene which prompted the study of its reaction with allene.

The reaction was carried out under a variety of conditions in a sealed tube with no solvent. After each pyrolysis, the allene was allowed to evaporate slowly, and the components in the residual liquid were separated and isolated by glpc. The results of several reactions are summarized in Table III.

Table III

Co-oligomerization of Allene and CND

Ratio, allene/CND	Temp, °C	Time, hr	Relative ratio: 11	12,13, 14	Cotetramer + CND dimer	Reacted CND, %
6.3	135 ± 2	21.5	56	10	34	82
6.0	146 ± 2	11.0	16	46	38	90
9.6	152 ± 2	8	7	38	55	100
12.0	136 ± 3	24	70	22	8	85
12.4	147 ± 3	9	16	36	48	100



Codimer **11** was formed but became the major product only under conditions where allene was used in >10-fold excess and the temperature was maintained at <140°. The structure assignment of **11** was based upon its elemental analysis and its spectral characteristics in the uv, nmr, and ir (see Experimental Section).

15 **16**

The presence of uv absorption obviously eliminates **15** as a possible structure for codimer, and geometrical isomer **16** could be ruled out by the fact that the codimer was thermally stable. Heating the codimer in a large excess of pentane at 265° for 3.5 hr led to complete recovery of the sample with negligible rearrangement having occurred.[7] A significant amount of **16** would have easily been detected by the observation of a [1,5] hydrogen shift, which is well-precedented for such systems.[8]

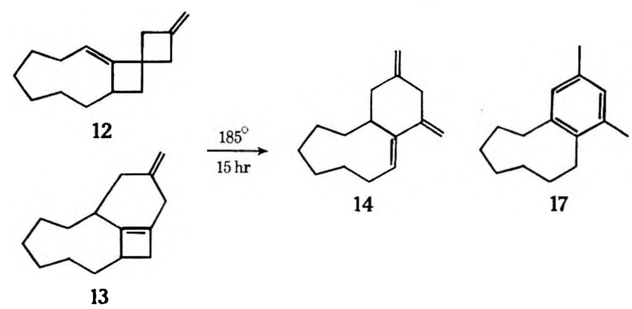
Three trimers eluted on the gc after the dimer and were characterized chemically and spectroscopically to have the structures **12**, **13**, and **14**.[9] A key factor in determining their structures was a pyrolytic study which showed that, similar to the case for the allene trimers **3**, **4**, and **5**, two of the cotrimers, assigned structures **12** and **13**, rearranged thermally to the third trimer, **14** (Table IV). A clean separation of the three

Table IV

Pyrolysis of Allene–CND Cotrimers 12, 13, and 14

Pyrolysis temp, °C	Time, hr	Starting sample	Product ratio: 14	21	17
185	12	Mainly 14	50		50
185	15	Mixture of 12 and 13	50		50
246	6	Mixture of three		78	22
255	5	Mainly 14		80	20
275	3.5	Mixture of three		73	27

trimers could not be achieved preparatively by glpc, but enriched samples were used to obtain the nmr spec-



tra described in the Experimental Section. A mixture of **12** and **13** was heated at 185° for 15 hr with the result that a 50:50 mixture of the third trimer and a new compound **17** was obtained. **17** was characterized by its elemental analysis to be isomeric with the trimers. Moreover, it was shown spectroscopically to be a benzene derivative with two nonidentical methyl groups and two aromatic hydrogens. Structure **17** not only best fits the data, but is consistent with the structural assignment of **13** and **14**.

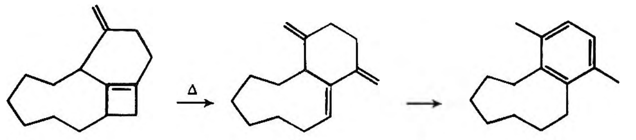
(5) P. D. Bartlett and K. E. Schueller, *J. Amer. Chem. Soc.*, **90**, 6071, 6077 (1968).

(6) (a) L. Skattebøl and S. Solomon, *ibid.*, **87**, 4506 (1965); (b) W. R. Moore, R. D. Bach, and T. M. Ozretich, *ibid.*, **91**, 5918 (1969); (c) W. R. Moore and W. R. Moser, *J. Org. Chem.*, **35**, 908 (1970); (d) W. R. Moore and W. R. Moser, *J. Amer. Chem. Soc.*, **92**, 5469 (1970).

(7) Polymerization of **11** occurs quite readily in concentrated solution; *i.e.*, a total loss of **11** was observed after storage as a 30% solution in benzene at 0° for 30 days.

(8) E. F. Kiefer and C. N. Tanna, *J. Amer. Chem. Soc.*, **91**, 4478 (1969).

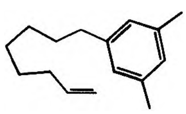
(9) A cotetramer (one CND and three allenes) was detected by glpc, as indicated in Table III, but it was not fully characterized.



18 19 20

Structures **18** and **19** can thus be ruled out as alternatives to **13** and **14**, since they could only reasonably lead to aromatic compound **20**, which has two *identical* methyl groups.

An additional pyrolysis product, interestingly, was obtained when the pyrolysis temperature was raised above 245°. This new product was formed equally well from any of the three trimers but was not found to be formed from **17**. Largely on the basis of elemental analysis and the observation in the nmr of two *identical* benzene-bound methyl groups, *three* aromatic protons, and *three* vinylic protons, the structure **21** was assigned to this product.



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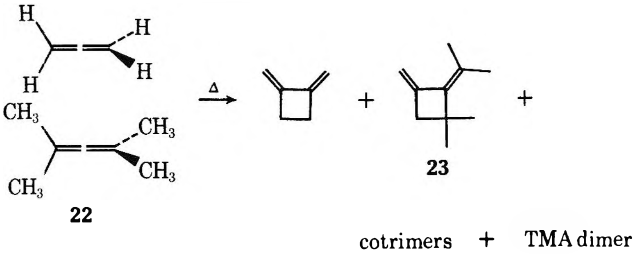
The picture of this co-oligomerization is now very clear, with the process being almost identical with that of parent allene oligomerization. There are, however, some key differences in the two reactions which should be mentioned. First, CND apparently is *not* an effective dienophile nor an effective [2 + 2] reagent with the codimer. Thus only *one* unit of CND becomes involved in the co-oligomerization process, and that in the initial [2 + 2] cycloaddition step. Second, in its [2 + 2] cycloadditions with allene, the codimer is reactive *only* at the unsubstituted methylene group. Most likely this is due to a steric effect on carbon–carbon bond formation at the other, substituted methylene position. Notice that the particular orientation of the [2 + 4] trimer adducts (**13** and **14**) also indicates a greater degree of bond formation in the [2 + 4] transition state at the *unsubstituted* methylene group. Finally, while the thermodynamic driving force to aromatization is unquestioned, the thermal conversion of the trimers to aromatic species **17** and **21** was not expected. The allene trimers did *not* undergo this conversion, and there is no precedent for unimolecular aromatization of such species. Certainly there is no orbital symmetry allowed pathway that can easily be envisioned.

Codimerization of Allene and Tetramethylallene.—Since tetramethylallene (TMA) is an open-chain allene and thus can have *no* ring strain, it appeared of interest to compare its reactivity in codimerization with allene with that of CND.

The reaction was carried out in essentially the same



22 23

cotrimers + TMA dimer

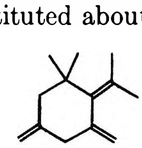
manner as the CND–allene co-oligomerization. However, in this case, only a three- to fourfold excess of allene was needed to ensure dominant codimer formation. Table V shows the results of runs under variable conditions.

TABLE V

CODIMERIZATION OF ALLENE AND TMA

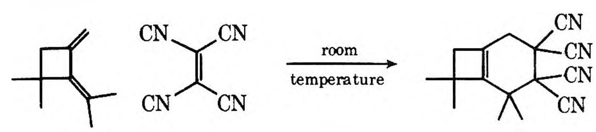
Mole ratio (Allene/TMA)	Reaction temp, °C	Time, hr	TMA conversion	Codimer **23**, g (%)
3	147 ± 3	15	30	0.87 (61)
4	140 ± 2	12	21	0.41 (74)
3.7	155 ± 3	12	45	1.05 (73)
3.7	160 ± 3	12	52	1.12 (44)

tions. The analysis of the cotrimer fraction was not fully accomplished, although a good quantity of it was obtained in the run at 155°, and a mixture of cotrimers could be clearly separated from TMA dimer by glpc. Although the cotrimers were not able to be separated, nmr indicated that a cotrimer with a triene structure, most likely **24**, constituted about 70% of the cotrimer



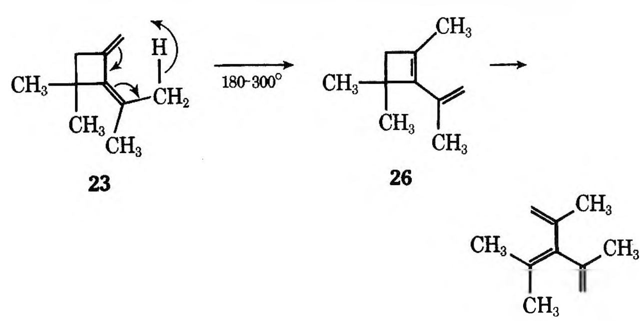
24

mixture. However, the definitive study in this system was limited to the chemistry of the dimer, which was established spectroscopically to have the structure **23**. Additional evidence included the formation of a 1:1 Diels–Alder adduct (**25**) with TCNE in acetone at room temperature.



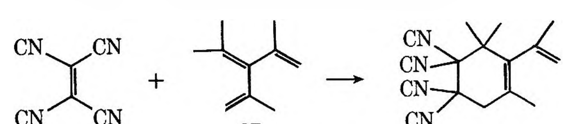
23 25

Additional interesting chemistry of the codimer **23** has been explored. As expected it undergoes a thermal 1,5-hydrogen shift to produce **26**, which then ring opens under the reactions conditions to form triene **27**.



23 26 27

As can be seen from Table VI, significant amounts of **26** can be detected at pyrolysis temperatures <210°, but at temperatures >250°, only **27** was observed. A 1:1 Diels–Alder adduct of TCNE and triene **27** could



27 28

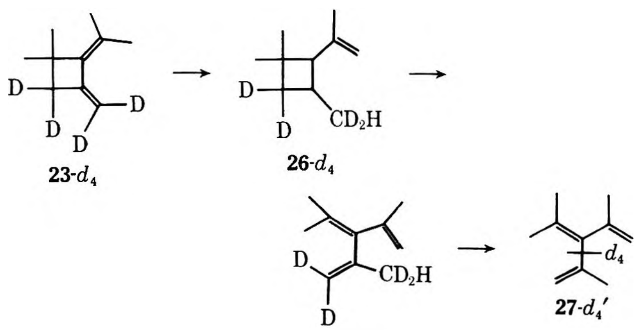
TABLE VI
PYROLYSIS OF CODIMER 23

Pyrolysis temp, °C	Time, hr	Solvent	Mole ratio 23	26	27
180	12	C_6D_6	78	12	10
210	6	C_6D_6	59	13	28
270	6		0	0	100
200[a]	20	C_6D_6	72	12	16[b]
210[a]	6	C_6D_6	70	11	19[b]
300[a]	10	C_6D_6	0	0	100[c]

[a] Tetradeuterio starting material used. [b] Nmr of the trienic product showed the deuterium to be relatively unequilibrated. [c] Nmr showed *complete* equilibration of the deuteriums of the triene **27**.

be prepared at room temperature with adduct structure **28** deduced from elemental analysis and spectra.

An interesting aspect of the chemistry of triene **27** was its ability to undergo thermally degenerate 1,5-hydrogen shifts. In order to detect such a process the codimer **23**-d_4 was prepared from allene-d_4[10] and TMA. Pyrolysis of **23**-d_4 at 210° for 6 hr yielded 19% of **27**-d_4 and 11% of **26**-d_4, **27**-d_4 showing a ratio of methyl to



23-d_4 **26**-d_4 **27**-d_4 **27**-d_4'

vinyl protons in the nmr of 4.8. (A ratio of 5.0 is expected for the initially formed **27**-d_4.) After heating codimer **23**-d_4 for 10 hr at 300°, however, only triene **27**-d_4' was recovered, and the ratio of methyl to vinyl protons had attained the totally equilibrated value of 3.0. That the four deuteriums were indeed randomly distributed was verified by the formation of the Diels–Alder adduct of this triene with TCNE. The nmr integrations from this adduct were identical with those from the TCNE adduct of the undeuterated triene **27**.

Conclusions

Allenes are one of the types of reactive olefinic species which undergo thermal [2 + 2] cycloadditions. Such reactions are not common for simple olefins, and only several fluoro- and chlorofluoroalkenes can match the ability of allenes in cyclobutane ring-forming reactions.[11] The relative reactivity of allenes seems to be reflected by their relative abilities to dimerize. For instance, perfluoroallene affords a high yield of dimer at 40°,[12] CND at 130°,[6] TMA at 150°,[13] allene above 175°, and acrylonitrile above 250°.[14] Thus a qualitative order of decreasing reactivity can be arranged as follows: fluoro or fluorochloroallenes and alkenes > cycloallenes > methylated allenes > allene > activated alkenes ≫ unactivated alkenes.

Therefore any satisfactory codimerization between two different olefinic species in the above series can only be achieved by using an excess of the *less* reactive olefin; otherwise the major product will just be the dimer of the more reactive species. This idea is certainly supported by our codimerization studies.

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(11) A review of [2 + 2] cycloadditions: J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962).
(12) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 1339 (1967).
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(14) E. C. Coyner and W. S. Hillman, *J. Amer. Chem. Soc.*, **71**, 324 (1949).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Gas chromatographic separations were performed using a Model A-90-P3 Varian Aerograph gas chromatograph equipped with a Varian Model G2010 10-in. strip chart recorder. Infrared spectra were recorded on Perkin-Elmer Model 137 and Beckman IR-10 spectrometers; mass spectra on a Hitachi Model RMU-6E spectrometer; uv spectra on a Cary-15 recording spectrophotometer; and nmr spectra on a Varian A-60A spectrometer. Tetramethylsilane was used as an internal standard for the nmr spectra.

Allene Oligomerization.—A summary of the oligomerization conditions and product distributions is shown in Table I. Each reaction was carried out in a sealed thick-walled tube of 12–15 ml capacity. The detailed experimental procedure for the 175° run will serve as an example.

To a 15-ml tube was added 1.76 g of benzene, and allene (0.80 g) was transferred to the tube *via* vacuum line. The tube was sealed under vacuum, wrapped with glass wool, and heated at 175° for 24 hr in a tube furnace. Then the tube was cooled to −78°, a pin hole was opened at the point of the seal, and the unreacted allene was allowed to evaporate and transfer from −78 to −195° on the vacuum line; 0.46 g of allene was found to be unreacted (~58% recovery). The residual liquid was characterized by glpc using a 10% 10 ft × 1/4 in. Carbowax 1500 column at 80° to estimate the relative amounts of dimers and trimers, and a 8 ft × 1/4 in. 20% SE-30 silicone oil column at 135° for estimating the trimers, tetramers, and pentamers. Benzene, dimers, and trimers were separated from less volatile tetramers and pentamers by vacuum line transfer at room temperature to −195°. The tetramers and pentamers weighed 0.24 g. Dimers were collected from gc using glass spiral traps cooled to −78°, while simple 4-mm, v-shaped tubes were used at room temperature to collect the tetramers and pentamers. The spectra of the dimers were identical with those reported in the literature,[2b] while those for the trimers and tetramers are given below.

1,6-Dimethylenespiro[3.3]heptane (3)[2b] had ir (NaCl plate) 3055, 2915, 1755, 1675, 1408, 1220, 1055, and 878 cm^{-1}; nmr (CCl_4) δ 4.68 (t, *J* = 2.3 cps, 1 H), 4.50 (pent, *J* = 2.1 cps, 3 H), 2.57 (sext, 4 H), 2.40 (m, 1 H), 2.29 (m, 1 H), and 1.60–1.97 (m, 2 H); mass spectrum (70 eV) *m/e* 120 (10) (p), 91 (85), 79 (85), and 39 (100).

3-Methylenebicyclo[4.2.0]octa-1(6)-ene (4)[2b] had nmr (CCl_4) δ 4.74 (m, 2 H), 2.65 (m, 2 H), 2.43 (s, 4 H), 2.18 (s, 4 H); mass spectrum (70 eV) *m/e* 120 (67) (p), 105 (100), 92 (40), 91 (95), 79 (64), 77 (50), 51 (45), 39 (98).

1,2,4-Trimethylenecyclohexane (5)[2b] had ir (NaCl plate) 3082, 2950, 2910, 2855, 1680, 1650, 1630, 1440, 1430, 1265, 1178, 952, 880, 802, 736, and 678 cm^{-1}; nmr (CCl_4) δ 2.24 (s, 4 H), 2.90 (pent, 2 H), 4.59 (m, 4 H), and 4.99 (m, 2 H); mass spectrum (70 eV) *m/e* 120 (p).

Dimethylene-9,10-octalins (6)[2c] had ir (NaCl plate) 3072, 2900, 2840, 1650, 1440, and 885 cm^{-1}; nmr (CCl_4) δ 4.70 (s, 4 H), 2.65 (s, 4 H), 2.22 (t, 8 H); mass spectrum (70 eV) *m/e* 160 (95) (p), 91 (100).

Pyrolyses of 1,4-Dimethylenespiro[3.3]heptane (3).—A summary of the results is shown in Table II. The gas-phase reactions were carried out under vacuum at low sample pressure in a 500-ml Pyrex tube heated in a tube furnace. Solution pyrolyses were carried out as a *ca.* 10% solution in a sealed 5-ml tube.

Allene–1,2-Cyclononadiene Co-oligomerization.—All reactions were carried out in 25-ml thick-walled tubes. A summary of the results is shown in Table III. A typical reaction and isolation of products is described below.

CND (3.4 g, 27.9 mmol) was added to a 25-ml thick-walled tube and 13.5 g (0.34 mol) of allene was added *via* vacuum line. The tube was sealed under N_2 and heated at 136° for 24 hr. After cooling to −78°, the tube was opened and the excess allene was allowed to transfer to −195°. The residual liquid was analyzed by glpc using the SE-30 column at 175°. The ratio of components was as follows: 1,2-dimethylenecyclobutane, 8.4; unreacted CND, 3.1; codimer **11**, 9.5; cotrimers **12**, **13**, and **14**, 3.0; cotetramer and CND dimer, 1.0. The conversion of CND was 79% and the yield of codimer **11** was 70%. Codimer **11** and the cotrimers were concentrated by distillation, the portion distilling from 50–110° (4 mm) being used for preparative glpc.

Codimer 11 (11-Methylenebicyclo[7.2.0]undec-1(2)-ene) had bp 70–80° (5 mm); ir (NaCl plate) 3040, 2890, 2815, 1730, 1660, 1645, 1462, 1440, 1344, 1264, 1075, 1040, 1008, 862, and 795 cm^{-1}; uv λ_{max} 255 mμ (ϵ 14,100), 240 (12,000), and 260 (10,100); nmr (CCl_4) δ 5.51 (t, J = 8.4 cps, 1 H), 4.97 (t, J = 2.5 cps, 1 H), 4.46 (t, J = 2.1 cps, 1 H), 2.70 (d, J = 9.9 cps, 2 H), 1.97 (d, J = 9.9 cps, 1 H), and 2.0–1.0 (broad, 12 H); mass spectrum (70 eV) m/e 162 (15) (p), 105 (50), 93 (70), 91 (72), 81 (60), 80 (75), 79 (100), 77 (50), 67 (40), 41 (50), 39 (55).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.58; H, 11.32.

Cotrimer 14 (11,13-Dimethylenebicyclo[7.4.0]tridec-1(2)-ene) had bp 90–110° (5 mm); ir 3015, 2870, 2800, 1665, 1455, 1429, 885, and 865 cm^{-1}; nmr (vinylic only) (CCl_4) δ 5.82 (t, J = 8.5 cps, 1 H), 4.93 (sext, 1 H), 4.80 (m, 1 H), and 4.09 (m, 2 H); mass spectrum (70 eV) m/e 202 (25) (p), 145 (25), 119 (100), 105 (75), 91 (60).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.07; H, 10.99.

Cotrimer 13 (3-Methylenetricyclo[10.1.1.0^{5,13}]tridec-1(13)-ene) had bp 90–110° (5 mm); nmr (CCl_4) vinylic at δ 4.72 (pent, J = 2.3 cps, 2 H) and doubly allylic at δ 2.62 (m, 2 H), allylic at 1.80–2.35 (broad, 6 H) and others at 0.90–1.80 (broad, 12 H).

Cotrimer 12 (Spiro[3-methylenecyclobutane-1,11′-bicyclo-[7.2.0]undec-1(2)-ene]) had bp 90–110° (5 mm); nmr (CCl_4) vinylic protons at δ 4.74 (pent, 4 H) and 5.33 (*t*, J = 8.1 cps, 1 H).

Pyrolysis of Allene–CND Cotrimers 12, 13, and 14.—A summary of the pyrolyses is shown in Table IV. All were carried out by heating the cotrimers in a large excess of pentane (~5% solution) sealed in a thick-walled glass tube. The products were analyzed and purified by glpc using the SE-30 column.

3,5-Dimethyl-1,2-benzocyclononane (17) had ir (NaCl plate) 2860, 2810, 1610, 1575, 1465, 1440, 1365, 1340, 1030, 855, 820, and 805 cm^{-1}; nmr δ 6.78 (s, 2 H), 2.56–2.95 (broad, 4 H), 2.26 (s, 3 H), 2.22 (s, 3 H), and 1.10–1.95 (broad, 10 H); mass spectrum (70 eV) m/e 202 (100) (p), 159 (60), 145 (55), 133 (65), 119 (53).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.43; H, 10.60.

9-(3,5-Dimethylphenyl)-1-nonene (21) had ir (NaCl plate) 3635, 2980, 2900, 2836, 1642, 1620, 1499, 1450, 1375, 1160, 996, 915, 821, and 730 cm^{-1}; nmr (CCl_4) δ 6.84 (s, 3 H), 5.45–6.01 (m, 1 H), 4.98–5.08 (m, 1 H), 4.80 (m, 1 H), 2.36–2.72 (broad t, 2), 2.25 (s, 6), 1.80–2.24 (broad, 2), 1.22–1.80 (broad, 6); mass spectrum (70 eV) m/e 202 (20) (p), 145 (25), 119 (100).

Pyrolysis of Allene–CND Codimer (11).—The pyrolysis was carried out as for the cotrimers, at 265° for 3.5 hr. The nmr spectrum of the recovered material showed only starting material absorptions.

Allene–Tetramethylallene Codimerization.—The results of this reaction are summarized in Table V. A typical example of reaction, isolation, and purification of codimer is described below.

Tetramethylallene (3.21 g, 33.4 mmol) was added to a thick-walled tube of ~15 ml capacity, and 4.10 g (103 mmol) of allene was transferred to it *via* vacuum line. After sealing under N_2 and wrapping with glass wool, the tube was heated in a tube furnace at 145–150° for 15 hr. Then after cooling to −78°, the tube was opened and allene was transferred as before. The volatile products (3.2 g) were isolated by vacuum line transfer at room temperature and the residual oil (0.5 g) was weighed in the tube. The volatile fraction was then examined by glpc using the SE-30 column at 90°. Three major components were detected, 1,2-dimethylenecyclobutane, TMA, and codimer **23**, in a ratio of 1.0:4.2:1.5. The codimer **23**, 0.87 g (61% based on reacted TMA), was collected from the gc using a glass spiral trap cooled to −78° as a colorless liquid: ir (NaCl plate) 3060, 2915, 2850, 2700, 1740, 1670, 1640, 1445, 1418, 1358, 1270, 1230, 1102, 1016, 890, and 859 cm^{-1}; uv λ_{max} 253 mμ (ϵ 14,300) with a shoulder at 261 (11,400); nmr (CCl_4) δ 1.24 (s, 6 H), 1.60 (s, 3 H), 1.72 (s, 3 H), 2.32 (t, J = 2.5 cps, 2 H), 4.83 (m, 1 H), and 5.14 (t, J = 2.5 cps, 1 H); mass spectrum (*inter alia*) (70 eV) m/e 136 (p)b.

The nmr of the tetradeuterio species, **23**-d_4, showed singlets at δ 1.26 (6 H), 1.61 (3 H), and 1.73 (3 H).

23 reacted quantitatively with TCNE at room temperature in acetone to produce the 1:1 Diels–Alder adduct: pale yellow; mp 131–132° (*n*-heptane); nmr (C_6D_6) δ 2.41 (m, 2 H), 1.90 (m, 2 H), 1.25 (s, 6 H), and 0.98 (s, 6 H); ir (KBr) 2960, 2880, 2260, 1470, 1435, 1402, 1380, 1370, 1308, 1260, 1230, 1180, 1160, 1145, 1105, 1075, 1023, 839, and 670 cm^{-1}; mass spectrum m/e 264 (p).

Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.72; H, 6.07; N, 21.21. Found: C, 72.62; H, 6.20; N, 21.32.

Pyrolysis of Codimer 23 (3,3-Dimethyl-2-isopropylidene-methylenecyclobutane).—Each pyrolysis was carried out using 0.15 to 0.85 g of codimer **23** in a 500-ml Pyrex tube sealed under vacuum. Table VI summarizes the results. The ratio of products was approximated from nmr spectra of product mixtures. The triene (**27**) product was isolated by glpc and characterized: ir (NaCl plate), 3050, 2895, 2710, 1880, 1620, 1428, 1363, 1098, 896, and 880 cm^{-1}; uv (EtOH) λ_{max} 225 mμ (ϵ 5600); nmr (C_6D_6) δ 4.98 (m, 2 H), 4.76 (m, 2 H), 1.74 (m, 6 H), and 1.70 (s, 6 H); mass spectrum m/e 136 (p).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.08; H, 11.84.

Triene **27** was found to react rapidly with TCNE at room temperature to form its Diels–Alder adduct **28**: pale green; mp 96–98° (benzene); ir (KBr), 3042, 2960, 2261, 1848, 1659, 1630, 1440, 1400, 1380, 1274, 1173, 1105, 1040, 940, 840, and 690 cm^{-1}; uv λ_{max} (*n*-hexane) 263 mμ (ϵ 3300) with a shoulder at 272; nmr (C_6D_6) δ 1.24 (s, 6 H), 2.33 (s, 2 H), 1.15 (m, 3 H), 1.44 (m, 3 H), 4.35 (m, 1 H), and 4.84 (m, 1 H).

Anal. Calcd for $C_{16}H_{16}N$: C, 72.72; H, 6.07; N, 21.21. Found: C, 72.66; H, 6.23; N, 21.26.

The vinylcyclobutene intermediate product, **26**, present only in small quantities, was not isolated but was clearly present as indicated by the nmr (C_6D_6): a singlet at δ 1.31 (6 H); a multiplet (obscured by codimer) at 1.75–1.80 (3 H); a multiplet at 1.85 (3 H); a multiplet at 1.95 (2 H); and a multiplet at 4.86–5.18 ppm (2 H) (obscured by codimer). Upon further heating this component was shown to convert to triene **27**.

Registry No.—**3**, 4696-20-2; **11**, 33487-27-3; **12**, 33487-28-4; **13**, 33487-29-5; **14**, 33487-30-8; **17**, 33487-31-9; **21**, 33487-32-0; **23**, 33487-33-1; **25**, 33487-34-2; **27**, 33487-35-3; **28**, 33487-36-4.

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Oligonucleotide Synthesis. II. The Use of Substituted Trityl Groups

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Several new substituted trityl protecting groups have been prepared and investigated. They are di(*p*-benzyloxyphenyl)phenylmethanol (**2a**), (*p*-hydroxyphenyl)diphenylmethanol (**2b**), (*p*-acetoxyphenyl)diphenylmethanol (**2c**), (*m*-hydroxyphenyl)diphenylmethanol (**2d**), (*m*-acetoxyphenyl)diphenylmethanol (**2e**), and (*p*-bromophenacyloxyphenyl)diphenylmethanol (**2f**). Comparison of the rates of detritylation of the corresponding 5′-trityladenosine derivatives by acetic acid showed that the (*p*-hydroxyphenyl)diphenylmethyl group could be removed under mild conditions in a reasonable length of time. However, this group cannot be used directly in oligonucleotide synthesis, without protection of the phenolic function. Consequently the trityl chloride (*p*-bromophenacyloxyphenyl)diphenylmethyl chloride (BPTrCl) (**3f**) was used as the phenacyl ester is cleaved by mild reduction with zinc and acetic acid to give the *p*-hydroxytrityl group. Two dinucleoside monophosphates TpT (**5a**) and d-UpT (**5b**) have been synthesized using the BPTr group for protection of the 5′-hydroxyl position. The removal of the protecting group was studied both in the presence and absence of other acyl protecting groups. Application to the ribose series was investigated by the preparation of the dinucleoside monophosphate 5′-BPTr-UpU (**12**) and the trinucleoside diphosphate 5′-BPTr-UpUpU (**15**). Removal of the BPTr group from these compounds was achieved with 20% acetic acid and zinc dust. However, it was found that the presence of other acyl protecting groups complicated the detritylation when using zinc and acetic acid, so that for further synthetic work detritylation was achieved with formic acid.

The selective protection of reactive groups in nucleosides and nucleotides is of utmost importance for the successful chemical synthesis of oligo- and polynucleotides of predetermined base sequence.[1] Acid-labile protecting groups such as the trityl group (Tr)[2] and its mono- (MMTr), di- (DMTr), and trimethoxy (TMTr) derivatives are widely used for protection of the 5′ primary hydroxyl function of nucleosides.[3] The introduction of methoxy groups increases the ease of removal of the trityl groups, but also increases the rate of reaction with the secondary hydroxyl groups and the amino functions of the bases.[3] As a result the most widely used trityl group is the MMTr.

As part of a general program on the synthesis of polynucleotides of predetermined base sequence, we have undertaken a study of substituted trityl chlorides to investigate whether improvements could be made of their ease of removal while maintaining selectivity toward the 5′-hydroxyl group. In particular, we have developed the use of the *p*-bromophenacyloxytrityl group and report its use in oligonucleotide synthesis.

Results

The trityl alcohols di(*p*-benzyloxyphenyl)phenylmethanol (DPTrOH, **2a**), (*p*-hydroxyphenyl)diphenylmethanol (*p*-HOTrOH, **2b**), and (*m*-hydroxyphenyl)diphenylmethanol (*m*-HOTrOH, **2d**) were prepared from the corresponding ketones (**1a**, **1b**, and **1d**) *via* a Grignard reaction with phenylmagnesium bromide.[4] The trityl chloride DPTrCl (**3a**) was prepared from **2a** by chlorination with acetyl chloride. Treatment of the methanol **2b** with acetyl chloride gave the corresponding acetoxy derivative (*p*-acetoxyphenyl)diphenylmethyl chloride (**3c**), and, similarly, *m*-acetoxytrityl chloride (**3e**) was prepared from **2d**. Attempts to prepare *p*- and *m*-hydroxytrityl chlorides (**3b** and **3d**) by treatment with hydrogen chloride in ether in the presence of calcium chloride were unsuccessful.

(*p*-Bromophenacyloxyphenyl)diphenylmethyl choride (BPTrCl, **3f**) was synthesized by reacting the trityl alcohol **2b** with *p*-bromophenacyl bromide and then chlorinating the intermediate trityl alcohol (**2f**) with acetyl chloride.

On treating the trityl alcohol **2f** with zinc dust and 80% acetic acid at room temperature, it was completely reduced to *p*-HOTrOH (**2b**) in under 1 hr. In 20% acetic acid containing zinc the compound was significantly reduced (>25%) in 1 hr and the reaction was complete in 16 hr. No reduction was observed in the absence of the zinc dust or when ethanol was substituted for acetic acid.

The trityl chlorides **3a**, **3c**, **3e**, and **3f** were used to prepare the 5′-protected derivatives 5′-DPTr-A (**4a**), 5′-(*p*-AcOTr)-A (**4c**), 5′-(*m*-AcOTr)-A (**4e**), and 5′-BPTr-A (**4f**). In the deoxyribose series 5′-BPTr-T (**5a**), 5′-BPTr-dU (**5b**), 5′-BPTr-dA (**5c**), and 5′-BPTr-dG (**5d**) were prepared. Deactylation of **4c** and **4e** with ammonia afforded 5′-(*p*-HOTr)-A (**4b**) and 5′-(*m*-HOTr)-A (**4d**), respectively.

The rates of detritylation of the protected ribonucleosides **4a–f** were studied and compared with those of 5′-MMTr-A and 5′-DMTr-A, and the results are summarized in Table I. Detritylation of **4f** was also studied in the presence of zinc dust.

The intermediate *p*-HOTr derivatives **4b** and **6a–d** were isolated by preparative tlc from the corresponding BPTr nucleosides by treatment with 30% acetic acid and zinc dust for 45 min together with unprotected nucleoside.

The use of the BPTr group in oligonucleotide synthesis was demonstrated by the preparation of the deoxyribodinucleoside monophosphates TpT (**7a**) and d-UpT (**7b**) as shown in Scheme I. In these syntheses, the 3′-hydroxyl function of the phosphorylating moiety was protected with the dihydrocinnamoyl group, which is removable by alkaline pH or enzymatically by α-chymotrypsin at neutral pH.[5]

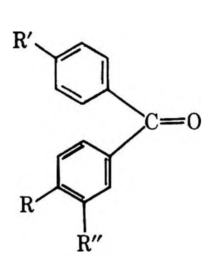
(1) H. Kössel, H. Buchi, T. M. Jacob, A. R. Morgan, S. A. Narang, E. Ohtsuka, R. D. Wells, and H. G. Khorana, *Angew. Chem., Int. Ed. Engl.*, **8**, 387 (1969); H. G. Khorana, *Fed. Proc. Fed. Amer. Soc. Exp. Biol.*, **19**, 931 (1960).

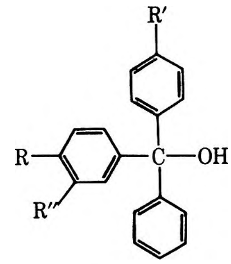
(2) The system of abbreviations used in this paper is that of H. G. Khorana's group; compare, for example, H. Kössel, H. Buchi, and H. G. Khorana, *J. Amer. Chem. Soc.*, **89**, 2185 (1967).

(3) M. Smith, D. H. Rammler, T. H. Goldberg, and H. G. Khorana, *ibid.*, **84**, 430 (1962).

(4) Preparative methods were adapted from M. Gomberg and L. H. Cone, *Justus Liebigs Ann. Chem.*, **370**, 142 (1909).

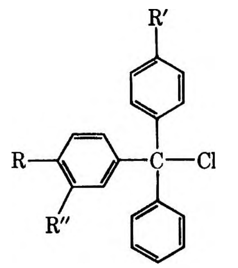
(5) The rationale for using the dihydrocinnamoyl protecting group is described in H. S. Sachdev and N. A. Starkovsky, *Tetrahedron Lett.*, **9**, 733 (1969).



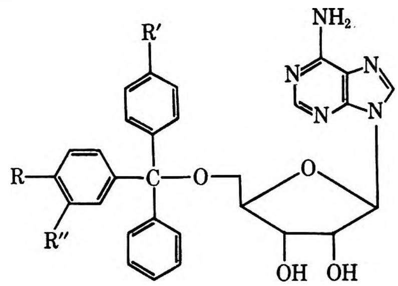


1a, R = R′ = OC_6H_5; R″ = H
b, R = OH; R′ = R″ = H
d, R = OH; R = R′ = H

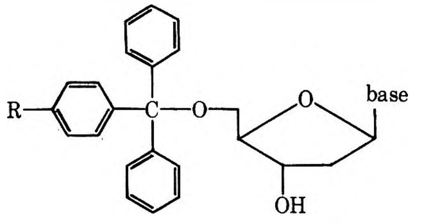
2a, R = R′ = OC_6H_5; R″ = H
b, R = OH; R′ = R″ = H
c, R = OAc; R′ = R″ = H
d, R″ = OH; R = R′ = H
e, R″ = OAc; R = R′ = H
f, R = $OCH_2COC_6H_4Br$; R′ = R″ = H



3a, R = R′ = OC_6H_5; R′ = H
b, R = OH; R′ = R″ = H
c, R = OAc; R′ = R″ = H
3d, R″ = OH; R = R′ = H
e, R″ = OAc; R = R′ = H
f, R = $OCH_2COC_6H_4Br$; R′ = R″ = H



4a, R = R′ = OC_6H_5; R″ = H
b, R = OH; R′ = R″ = H
c, R = OAc; R′ = R″ = H
4d, R″ = OH; R = R′ = H
e, R″ = OAc; R = R′ = H
f, R = $OCH_2COC_6H_4Br$; R′ = R″ = H



5a, R = $OCH_2COC_6H_4Br$; base = Thy
b, R = $OCH_2COC_6H_4Br$; base = Ura
c, R = $OCH_2COC_6H_4Br$; base = Ade
d, R = $OCH_2COC_6H_4Br$; base = Gua
6a, R = OH; base = Thy
b, R = OH; base = Ura
c, R = OH; base = Ade
d, R = OH; base = Gua

Detritylation of **7a** and **7b** was studied in detail and the results are shown in Scheme II. The BPTr group could be removed slowly from **7a** by 80% acetic acid alone (8–24 hr).

The application of this protecting group to ribooligonucleotide synthesis was studied. The mononucleotide 5′-BrTr-U(OAc)-3′-p (**11**) was prepared by reaction of uridine 2′,3′-cyclic phosphate with BPTrCl followed by incubation with pancreatic ribonuclease to open the 2′,3′-cyclic phosphate and protection of the 2′-hydroxyl function by acetylation. The protected monomer was condensed in the usual way[6] with dibenzoyluridine to prepare the ribodinucleoside monophosphate **12** as shown in Scheme III.

TABLE I
TIME REQUIRED FOR FULL DEPROTECTION OF 5′-TRITYLADENOSINE COMPOUNDS WITH ACETIC ACID AT ROOM TEMPERATURE[a]

Compound	Time 80% HOAc	40% HOAc	20% HOAc
5′-MMTr-A	1 hr	48 hr	1 week
5′-DMTr-A	15 min	3 hr	48 hr
5′-DPTr-A (4a)	15 min	3 hr	1 week
5′-(p-HOTr)-A (4b)	1 hr	1 hr	6 hr
5′-(p-AcOTr)-A (4c)	1 week		
5′-(m-HOTr)-A (4d)	48 hr	1 week	
5′-(m-AcOTr)-A (4e)	1 week		
5′-BPTr-A (4f)	5 hr	1 week	
5′-BPTr-A + zinc[b] (4f)	1 hr	2 hr	24 hr

[a] 15–20 μmol of 5′-trityladenosine in 0.2 ml of acetic acid. [b] 20 mg of zinc dust.

The acyl protecting groups were removed from **12** by treatment with ammonia for 16 hr to give 5′-BPTr-UpU (**15**) (see Scheme IV). Detailed studies showed that the BrTr group was removed from both **12** and **15** by 20% acetic acid and zinc in under 1 hr, but the detritylation of **15** proved to be cleaner than that of the fully protected dinucleoside monophosphate **12**. In the case of **12** several side products, which were not identified, were also formed. Similar results were obtained with 10, 40, and 50% acetic acid and zinc. However, it was found that a brief treatment with formic acid also removed the BPTr group cleanly from the fully protected dinucleoside monophosphate.

As a result, for further synthetic work the BPTr group was removed from **12** by treatment with 90% formic acid for 10 min, to give **13**. Condensation of **13** with **11** gave the fully protected trinucleoside diphosphate **14** (see Scheme III).

The series of reactions summarized in Scheme V were carried out. Detritylation of the fully protected trinucleoside diphosphate **14** again proved to be more difficult than that of the partially protected trimer **18**, and as in the case of the dinucleoside monophosphates a brief treatment with formic acid gave better results.

We were unable to find conditions under which appreciable amounts of the intermediate p-HOTr protected dinucleoside monophosphates and trinucleoside diphosphates could be isolated. The p-HOTr group was obviously removed as fast as it was formed with 20% and even with 10% acetic acid.

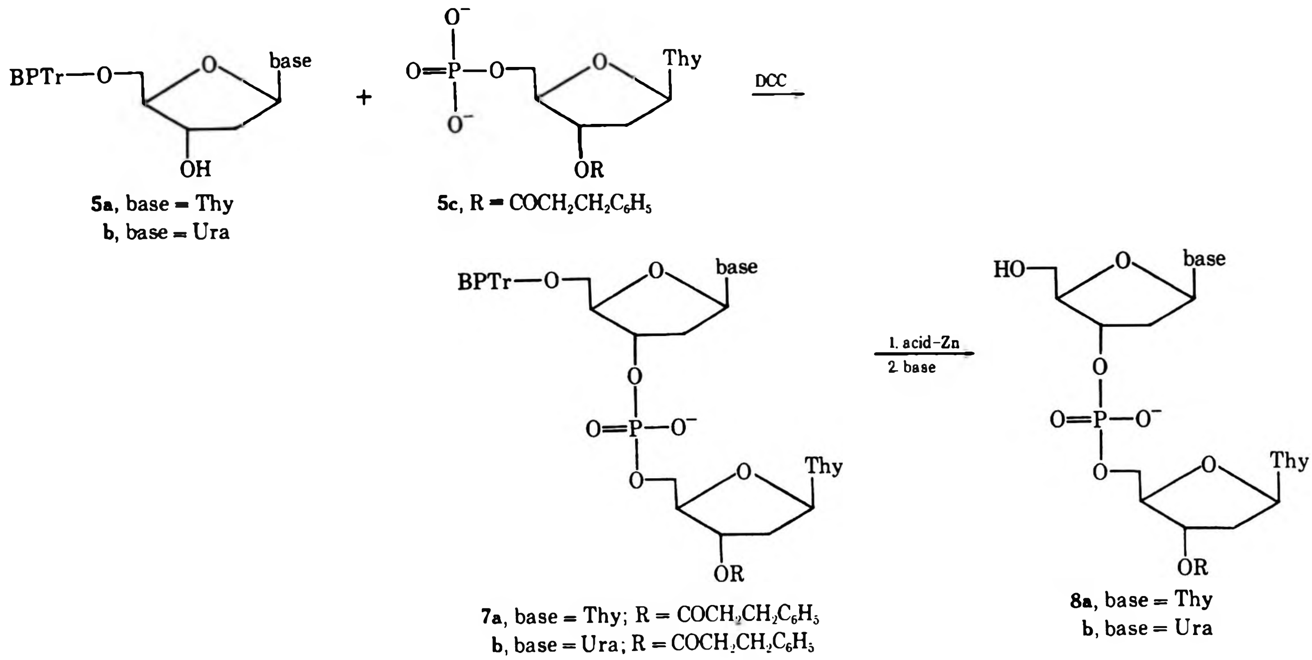
The identity of the dimers TpT, d-UpT, UpU (**16**), and the trimer UpUpU (**19**) was confirmed by degradation with snake venom phosphodiesterase.[7]

Discussion

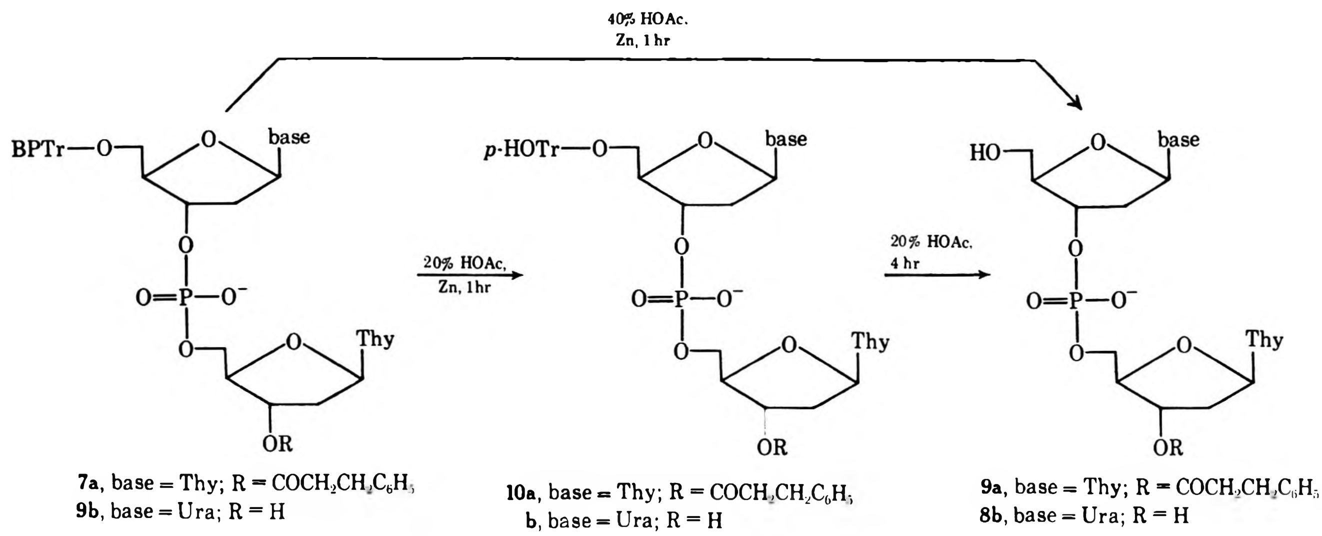
At present the MMTr and DMTr groups are the most frequently used acid-labile protecting groups for the 5′-hydroxyl functions of nucleosides. The DMTr group can be removed under milder conditions than the MMTr group, but it is also less specific for the primary hydroxyl function. In addition, the greater lability of

(6) S. A. Narang, T. M. Jacob, and H. G. Khorana, *J. Amer. Chem. Soc.*, **87**, 2988 (1965).
(7) H. G. Khorana, A. F. Turner, and J. P. Vizsolyi, *ibid.*, **83**, 686 (1961); H. G. Khorana and J. P. Vizsolyi, *ibid.*, **83**, 675 (1961).

SCHEME I



SCHEME II



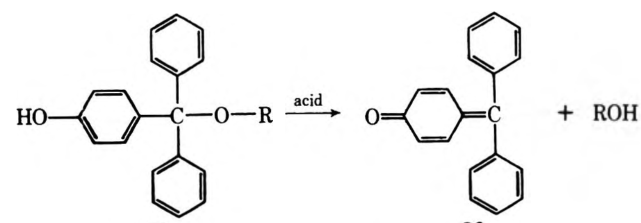
this trityl group can lead to unwanted removal of the protecting group during a synthetic sequence.

We have used these two groups for comparison with the substituted trityl groups described in this paper. Particular attention has been given to the selectivity of the trityl chlorides for primary and secondary hydroxyl functions and to the ease of removal from nucleosides.

The DPTr group was synthesized in order to determine the effect of size on the selectivity of a trityl group. This bulky trityl group showed excellent selectivity for the primary hydroxy function, no other isomer being observed. Similarly, BPTrCl reacted selectively with the 5′-hydroxyl group of nucleosides to give excellent yields of the protected compounds.

The *p*-HOTr group was synthesized as detritylation of a nucleoside protected by this group should be particularly easy because of the formation of the fuchsone form (**20**) of the trityl alcohol in the presence of acid.

(*p*-Hydroxyphenyl)diphenylmethanol (**2b**) is peculiar in that when crystallized from ammoniacal alco-



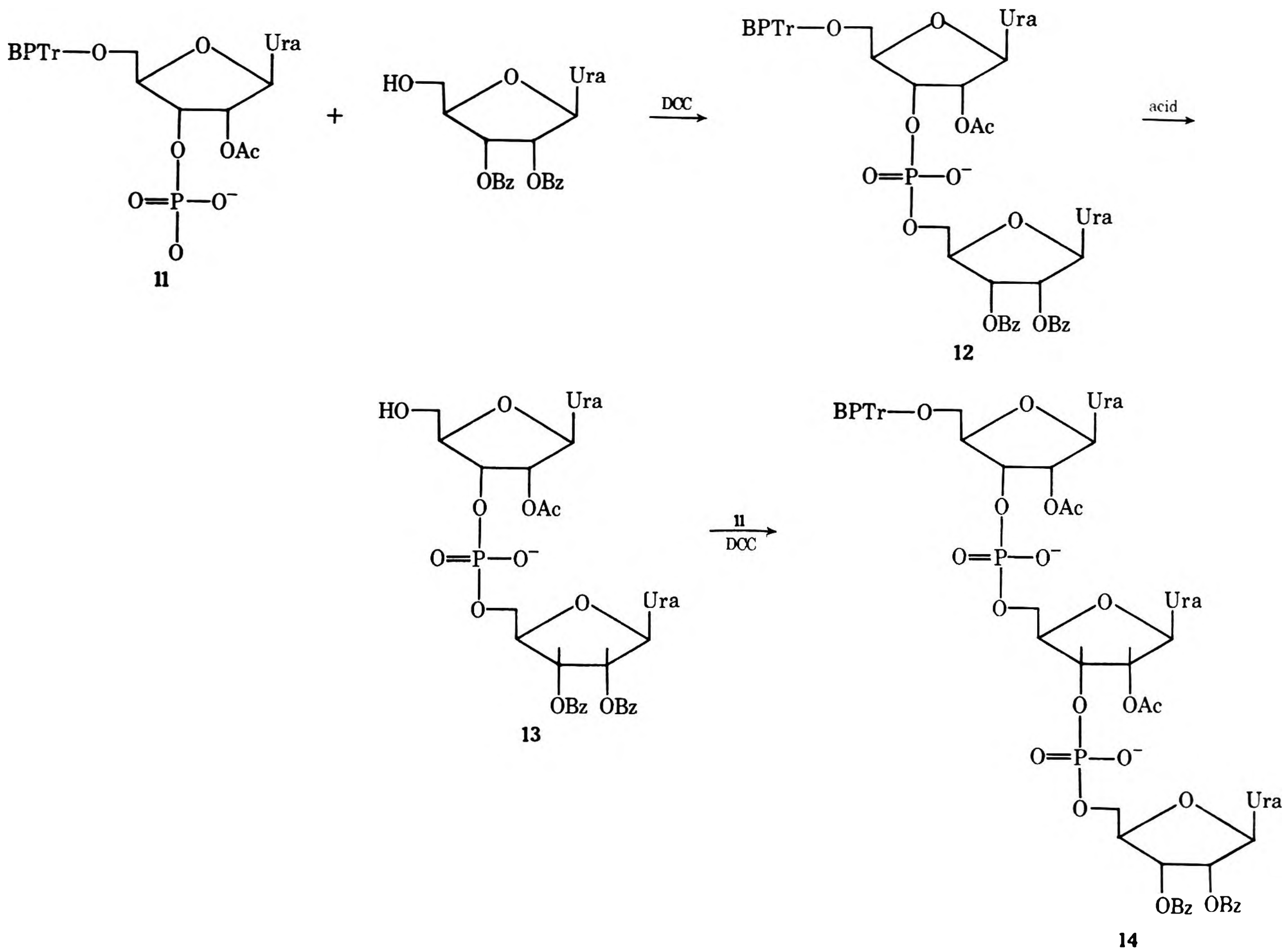
2b *p*-HOTrOR **20** fuchsone form

hol the crystals are colorless, whereas those obtained from 50% acetic acid are yellow. The yellow color is thought to be due to the presence of the fuchsone.[8]

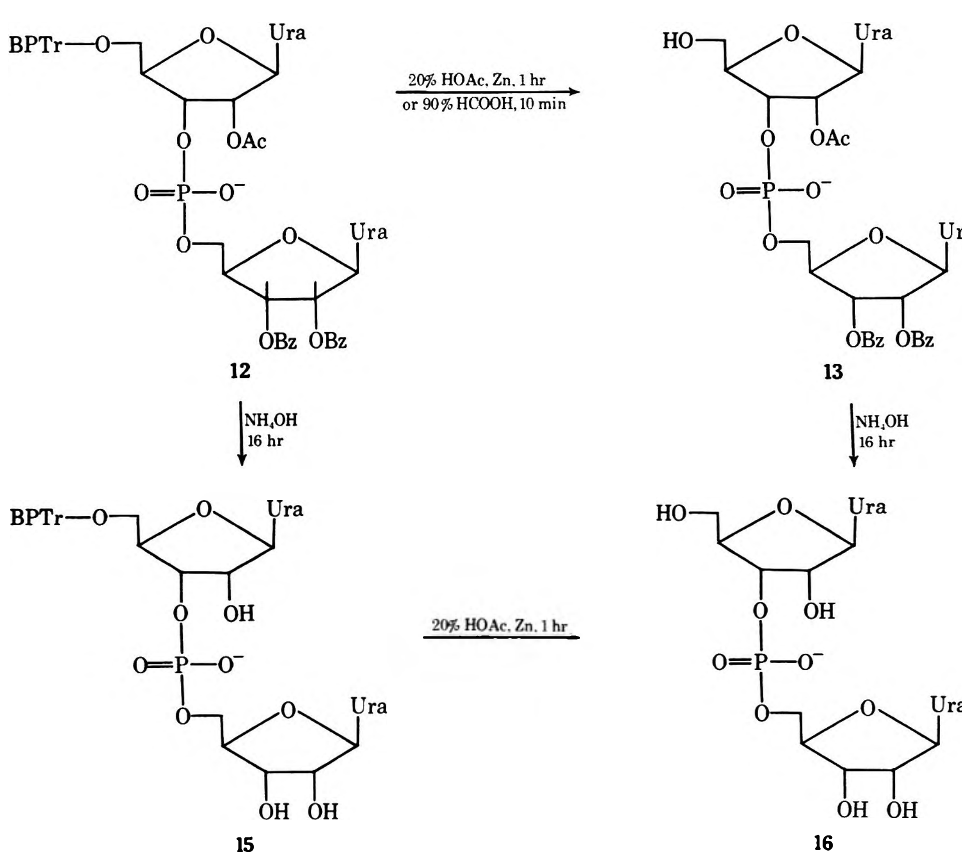
However, the *p*-HOTr group cannot be used directly in oligonucleotide synthesis for two reasons. Firstly, during the condensation step the phenolic function must be protected as sulfonyl chlorides, used as condensing agents, will react with phenols to form sulfonic esters, and, secondly, the corresponding trityl chloride

(8) L. C. Anderson and M. Gomberg, *J. Amer. Chem. Soc.*, **35**, 203 (1913); K. I. Beynon and S. T. Bowden, *J. Chem. Soc.*, 4247 (1957).

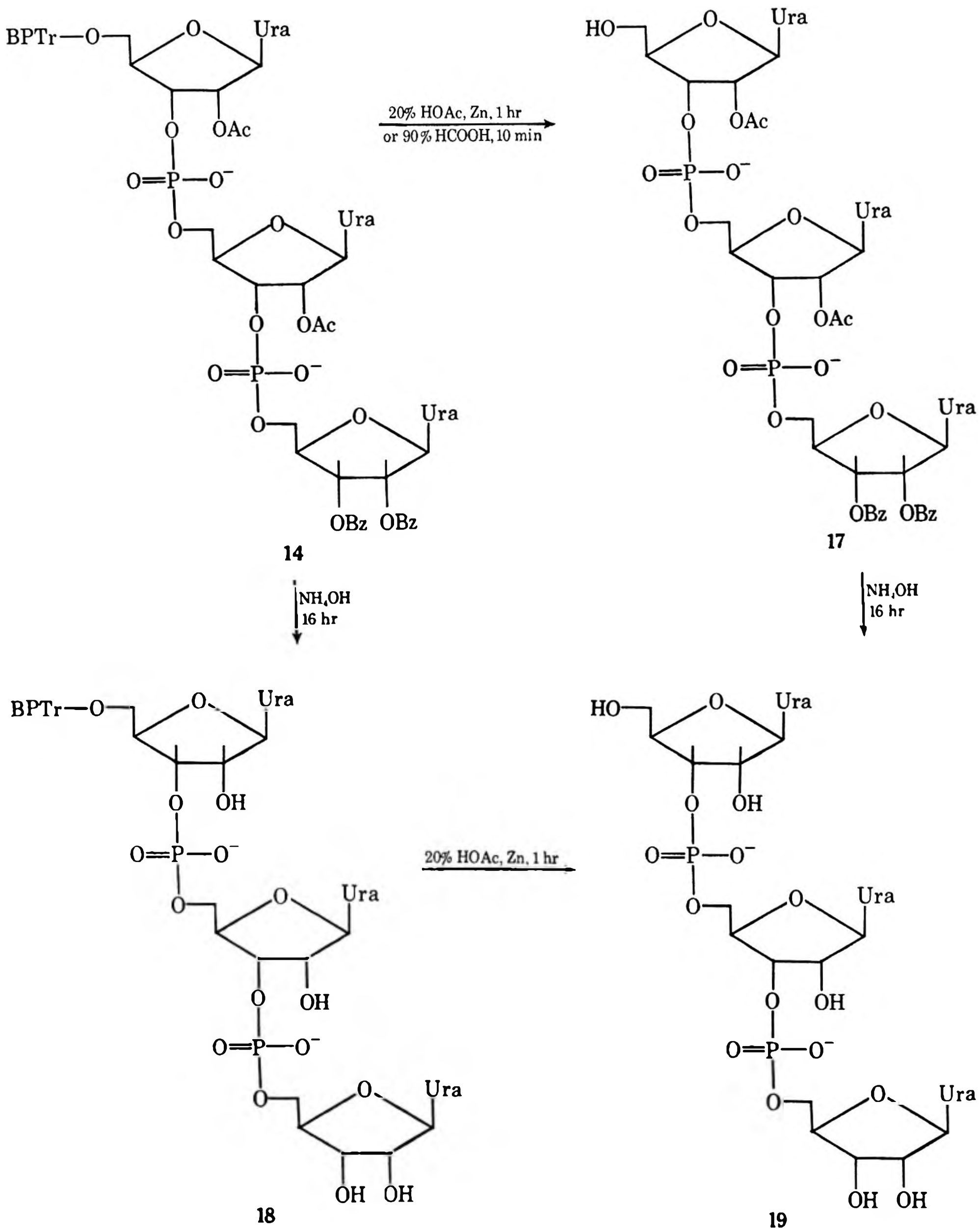
SCHEME III



SCHEME IV



SCHEME V

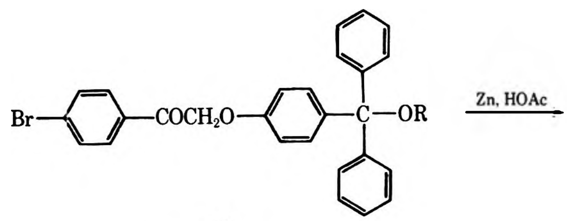


p-HOTrCl is unstable and loses HCl spontaneously to give **20**.[9] The synthesis of *m*-HOTrCl by chlorination of the methanol *m*-HOTrOH with acetyl chloride has been reported.[9] However, we were unable to repeat this work, as we obtained only the acetoxy derivative *m*-AcOTrCl in high yield from this reaction. Similarly *p*-AcOTrCl[10] was the only product from the reaction of *p*-HOTrOH with acetyl chloride. Treatment of either trityl alcohol with dry hydrogen chloride in ether in the presence of calcium chloride was also unsuccessful.

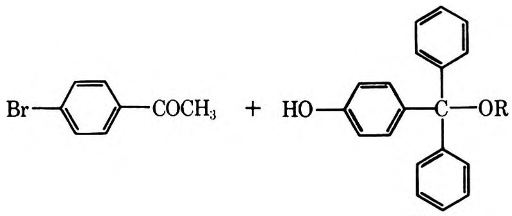
The phenolic function of the *p*-HOTr group could be protected by the acetyl group as 5′-(*p*-AcOTr)-A (**4c**) could be deacetylated readily with ammonia to give 5′-(*p*-HOTr)-A (**4b**). However, the acetyl group was not thought to be the ideal protecting group during oligonucleotide synthesis, as other alkali-labile protecting groups are used both in the ribose and deoxyribose series. Consequently a phenacyl ether, which can be removed by reductive cleavage with zinc and dilute acid,[11] was utilized to protect the phenolic function of the *p*-HOTr group.

Comparison of the ease of detritylation of all these substituted trityl compounds was carried out using the corresponding 5′-trityladenosine derivatives, 5′-MMTr-A and 5′-DMTr-A, and the results are shown in Table I. The DPTr group was hydrolyzed by 80 and 60% acetic acid at a rate comparable to the DMTr group but much slower with 20% acid. It should be noted that complete and rapid removal of the trityl group in the presence of alkali-labile base-protecting groups frequently leads to depurination, so that it is advisable when complete deprotection is sought to submit the protected compound first to treatment with alkali and then with acid.[12-14] However, in the

(9) S. T. Bowden and K. I. Beynon, *J. Chem. Soc.*, 4253 (1957).
(10) M. Gomberg, *J. Amer. Chem. Soc.*, **35**, 209 (1913).
(11) J. B. Hendrickson and C. Kandall, *Tetrahedron Lett.*, 343 (1970).
(12) P. T. Gilham and H. G. Khorana, *J. Amer. Chem. Soc.*, **80**, 6212 (1958).
(13) H. Schaller, G. Weiman, B. Lerch, and H. G. Khorana, *ibid.*, **85**, 3821 (1963).
(14) H. Schaller and H. G. Khorana, *ibid.*, **85**, 3828 (1963).



2f
p-bromophenacyloxytrityl-OR
(BPTrOR)



2b
p-HOTrOR

sequential synthesis of oligonucleotides, it is essential to be able to remove the trityl group efficiently while keeping the alkali-labile base protecting groups intact. As a check on the use of removal of the DPTr group under these conditions $N,N',O^{2'},O^{3'}$-tetrabenzoyladenosine was synthesized by successive tritylation, benzoylation, and detritylation of adenosine using the DPTr group. The yield and purity of the product was slightly better than that obtained using the DMTr group.

Both acetoxytrityl groups, as expected, proved to be very resistant to hydrolysis. The *m*-HOTr group was similar. However, the *p*-HOTr group could be removed rapidly be acetic acid and, in fact, more easily with 20% acetic acid than either the MMTr or DMTr groups. The BPTr group on treatment with acetic acid alone was relatively resistant, but on addition of zinc dust detritylation took place at a rate comparable to the DMTr group. Detritylation occurred in two stages, the first, and rate-determining step, being removal of the phenacyl ether to give the *p*-HOTr derivative. Attempts to find conditions under which the *p*-HOTr derivative could be isolated quantitatively failed as under all conditions investigated the compound was isolated together with the free nucleoside.

In the deoxyribose series the nucleosides thymidine, deoxyuridine, deoxyadenosine, and deoxyguanosine were protected with the BPTr group. Detritylation of these compounds was studied giving particular attention, in the case of deoxyadenosine and deoxyguanosine, to depurination.[12-14] As can be seen from Table II, detritylation could be achieved without depurination with 20 and 40% acetic acid and zinc, although some depurination was detected with 80% acid. Depurination was more noticeable with deoxyguanosine than with deoxyadensoine.

From these results it can be seen that the BPTr group combined the best properties of all the substituted trityl groups investigated. It showed excellent selectivity for the 5′-hydroxyl function of nucleosides because of its large size, and could be removed easily with acetic acid containing zinc dust. In the absence of zinc dust the group was resistant to hydrolysis. In oligonucleotide synthesis it is obviously advantageous to use a hydrolysis resistant group such as the BPTr

TABLE II
TIME REQUIRED FOR FULL DEPROTECTION OF 5′-BPTr NUCLEOSIDES BY ACETIC ACID AND ZINC AT ROOM TEMPERATURE[a]

Compound	Time, hr		
	80% HOAc	40% HOAc	20% HOAc
5′-BPTr-A (**4f**)	1	2	24
5′-BPTr-T (**5a**)	1	2	8
5′-BPTr-dU (**5b**)	1	2	8
5′-BPTr-dA (**5c**)	1 (2%)[b]	2 (<1%)	8 (<1%)
5′-BPTr-dG (**5d**)	1 (5%)[b]	2 (1%)	8 (<1%)

[a] 15–20 μmol of 5′-trityl nucleoside in 0.2 ml of acetic acid containing 20 mg of zinc dust. [b] % depurination as measured by elution of spots from paper chromatograms and measurement of absorbance at λ_{max}.

group, which at the correct time can be converted into a more labile group.

The use of this protecting group in synthesis was demonstrated by the preparation of the deoxyribodinucleoside monophosphates TpT (**8a**) and d-UpT (**8b**) as shown in Scheme I. Removal of the BPTr group was studied in one case (**8a**) before and in the other (**8b**) after removal of the dihydrocinnamoyl group from the 3′-hydroxyl position. The presence of other protecting groups appeared to have no effect on the ease of removal of the BPTr group.

The results on the detritylation of the two deoxyribodinucleoside monophosphates paralleled the results at the monomer level. The BPTr group can be removed rapidly and completely by mild acid and zinc. In the absence of zinc the BPTr group was stable.

In the ribose series the dinucleoside monophosphate UpU (**16**) and the trinucleoside diphosphate UpUpU (**19**) were synthesized utilizing the BPTr group. It was found that the BPTr group could be removed from ribose dinucleoside monophosphates and trinucleoside diphosphates under very mild conditions, but when other acyl protecting groups were present the removal was complicated by the formation of side products which we were unable to identify. There was no evidence of hydrolysis of the glycosidic bonds.

However, it was noted that a brief treatment with formic acid removed the BPTr group without any complications at both the dinucleoside monophosphate and trinucleoside diphosphate levels. This was, therefore, the method of choice for these particular compounds for further synthetic work.

It appears from these results that the *p*-bromophenacyloxytrityl group, while eminently suitable for use in synthesis in the deoxyribose series, is not the ideal diprotecting group when used in the ribose series. The *p*-HOTr group itself is entirely satisfactory being removed rapidly by mildly acidic conditions (less than 20% acetic acid), but a better protecting group for the phenolic function, than the *p*-bromophenacyl ether, is mandatory.

Experimental Section

General Methods.—Paper chromatography was carried out by the descending technique using Whatman No. 1 or Whatman No. 3MM paper. The solvent systems used were (A) ethyl alcohol-1 *M* ammonium acetate (pH 7.5) (7:3, v/v); (B) ethyl acetate–ethanol (9:1); (C) *n*-PrOH-concentrated NH_4OH-H_2O (55:10:35); (D) *i*-PrOH-concentrated NH_4OH-H_2O (7:1:2). Thin layer chromatography was carried out on silica gel plates (F-254 E Merck).

The trityl groups or substituted trityl groups in compounds were detected by spraying the chromatograms with 10% aqueous perchloric acid and drying in warm air. The trityl-containing compounds appeared yellow or orange. The presence of phenolic functions was detected by lightly spraying the chromatograms with a saturated solution of *p*-nitrobenzenediazonium fluoroborate followed by spraying with 20% sodium bicarbonate solution. Compounds containing phenolic functions appeared as pink spots.

Reagent grade pyridine was purified by distillation over chlorosulfonic acid and potassium hydroxide and stored over 4A molecular sieve beads (Linde Co.). All evaporations were carried under reduced pressure below 25°. Whenever necessary, reagents and reaction mixtures were rendered anhydrous by repeated evaporation of added dry pyridine *in vacuo*.

Enzymatic degradations were carried out by standard methods.[7]

Melting points are uncorrected. Elemental analyses were carried out by Dr. C. Fitz, Needham Heights, Mass.

The amounts of nucleotides in solution were estimated by their absorption at neutral pH at 260 mμ.

Adaptations of published procedures were used to prepare 5′-MMTr-A,[15] 5′-DMTr-A,[15] 2′,3′-dibenzoyluridine,[13] *p*-HOTrOH,[8,9] *m*-HOTrOH,[8,9] DPTrOH,[8,9] DPTrCl,[9] *p*-AcOTrCl,[10] and *m*-AcOTrCl.[10]

(*p*-Bromophenacyloxyphenyl)diphenylmethanol (2f).—(*p*-Hydroxyphenyl)diphenylmethanol (**2b**) (5.52 g, 20 mmol), *p*-bromophenacyl bromide (5.56 g, 20 mmol), and powdered potassium carbonate (20 g) were stirred overnight in dry acetone (200 ml) at 30°. The reaction mixture was filtered and evaporated to dryness. The residue was crystallized from methanol (20 ml) to give 8.0 g (88%) of **2f**: mp 118–120°; λ_{max} (EtOH) 260 mμ (ε 21,800); ir (Nujol) 2.80, 2.92, 5.84, 6.20, 6.30, 8.15, 8.44, 9.10 μ.

Anal. Calcd for $C_{27}H_{21}O_3Br$: C, 68.5; H, 4.5; Br, 16.9. Found: C, 68.2; H, 4.7; Br, 16.5.

(*p*-Bromophenacyloxyphenyl)diphenylmethyl Chloride (3f).—The above methanol (2f) (1 g) was dissolved in acetyl chloride (15 ml) with warming. The deep yellow solution was kept at room temperature 15 min, diluted to 125 ml with petroleum ether (bp 30–60°), and kept at 0° overnight. Colorless crystals of **3f** separated and were filtered, washed with dry petroleum ether, and dried *in vacuo* to give 0.91 g (88%) of product which decomposed without melting.

Anal. Calcd for $C_{27}H_{20}O_2BrCl$: C, 65.8; H, 4.1; Br, 16.3; Cl, 7.2. Found: C, 65.6; H, 4.3; Br, 14.3; Cl, 6.8.

Action of Zinc Dust and Acetic Acid on BPTrOH.—When a 0.5% solution of the trityl alcohol in acetic acid (clarified, if necessary, by the addition of a few drops of acetone) was kept at room temperature overnight and then examined by tlc (silica gel, solvent B), no degradation of the compound was observed. In the presence of zinc dust (100 mg), however, the compound was significantly hydrolyzed (>25%) to *p*-HOTrOH in 20% acetic acid in 1 hr. Hydrolysis was complete with 80% acetic acid containing zinc dust in 1 hr. No hydrolysis was observed when ethanol was substituted for acetic acid.

Preparation of 5′-Trityladenosine Derivatives.—Compounds **4a**, **4c**, **4e**, and **4f** were prepared as follows. A solution of adenosine (1.5 g, 5.22 mmol), dried by repeated evaporation from anhydrous pyridine, in a mixture of dry dimethylformamide (35 ml) and pyridine (65 ml) was treated with a solution of the trityl chloride (5.2 mmol) in dry dimethylformamide (10 ml). After standing at room temperature for 5 days, the reaction mixture was poured into ice-cold water (800 ml). The precipitate thus obtained was washed with water, dried over P_2O_5 *in vacuo*, and recrystallized from ethyl acetate–benzene. Information concerning the properties of substituted trityladenosines is given in Table III.

5′-(*p*-Hydroxyphenyl)diphenylmethyladenosine (4b).—A solution of **4c** (0.6 g, 0.83 mmol) in dimethylformamide (5 ml) was treated with aqueous 58% ammonium hydroxide (5 ml) and the mixture stirred for 6 hr at room temperature. After evaporation under reduced pressure to a dry residue, the product was crystallized twice from ethanol to give 0.50 g (82%) of **4b**, mp 192–193°.

5′-(*m*-Hydroxyphenyl)diphenylmethyladenosine (4d).—This compound was prepared in the same way as the above compound from **4e** as crystals (78% yield), mp 182–184°.

(15) R. Lohrmann and H. G. Khorana, *J. Amer. Chem. Soc.*, **86**, 4188 (1964).

TABLE III

PROPERTIES AND YIELDS OF 5′-TRITYL NUCLEOSIDES AND NUCLEOTIDES

Compound	Yield, %	R_f Tlc, silica, solvent B	R_f Whatman No. 1, solvent A
5′-DPTr-A (4a)	53	0.57	0.85
5′-(*p*-HOTr)-A (4b)	82[a]	0.37	0.84
5′-(*p*-AcOTr)-A (4c)	60	0.41	0.84
5′-(*m*-HOTr)-A (4d)	78[a]	0.36	0.84
5′-(*m*-AcOTr)-A (4e)	65	0.39	0.84
5′-BPTr-A (4f)	88	0.52	0.82
5′-BPTr-T (5a)	90	0.80	0.97
5′-BPTr-dU (5b)	73	0.75	0.86
5′-BPTr-dA (5c)	91	0.65	0.83
5′-BPTr-dG (5d)	89	0.65	0.80
5′-(*p*-HOTr)-T (6a)	49	0.72	0.90
5′-(*p*-HOTr)-dU (6b)	40	0.65	0.85
5′-(*p*-HOTr)-dA (6c)	39	0.50	0.75
5′-(*p*-HOTr)-dG (6d)	33	0.51	0.72
5′-BPTr-TpT-DHC (7a)	42		0.83
5′-BPTr-dUpT-DHC (7b)	54		0.85
5′-BPTr-dUpT (9d)	94		0.80
5′-(*p*-HOTr)-TpT-DHC (10a)	31		0.78
5′-(*p*-HOTr)-dUpT (10b)	50		0.69
5′-BPTr-U(OAc)-3′-p (11)	97		0.79
5′-BPTr-U(OAc)pU(OBz)$_2$ (12)	47		0.83
5′-BPTr-U(OAc)pU(OAc)pU(OBz)$_2$ (14)	34		0.84
5′-BPTr-UpU (15)	83		0.75
5′-BPTr-UpUpU (18)	83		0.63

[a] Obtained by alkaline hydrolysis of the corresponding acetoxy derivatives.

Preparation of 5′-BPTr Deoxyribonucleosides.—Compounds **5a–d** were prepared as follows. A pyridine solution (2 ml) of the deoxyribonucleoside (1.0 mmol) was treated at 0° with BPTrCl (0.54 g, 1.1 mmol) for 4 hr and then overnight at room temperature. Water (100 ml) was added and the mixture extracted with methylene chloride (three 100-ml portions). The organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* and the residue recrystallized from benzene. The yields and properties of these compounds are summarized in Table III.

Detritylation Experiments.—Samples of the 5′-trityladenosine compounds (**4a–f**, **5a–d**, and MMTr-A and DMTr-A) (1.5–2 μmol) were treated with 20, 40, and 89% acetic acid (0.2 ml) at room temperature. The reactions were followed by tlc using silica plates (solvent B) and on Whatman No. 1 paper (solvent A). The results are summarized in Tables I and II.

The detritylation of **4f** and **5a–d** was also studied under the same conditions in the presence of zinc dust (20 mg).

Preparation of 5′-(*p*-HOTr) Derivatives from the Corresponding 5′-BPTr Nucleosides (4b from 4f, 6a from 5a, 6b from 5b, 6c from 5c, and 6d from 5d).—Samples of **4b** and **5a–d** (0.1 mmol) were treated with 30% acetic acid (2 ml) and zinc dust (200 mg) for 45 min at room temperature. The solutions were filtered, neutralized to stop the reactions, and chromatographed on preparative tlc (silica, solvent B). Bands of product were eluted and crystallized from benzene. Yields were: **4b**, 41% (adenosine 32%); **6a**, 49% (thymidine 33%); **6b**, 40% (deoxyuridine 37%); **6c**, 39% (deoxyadenosine 29%); and **6d**, 33% (deoxyguanosine 28%).

5′-(*p*-Bromophenacyloxytrityl)thymidylyl-(3′–5′)-3′-dihydrocinnamoylthymidine (5′-BPTr-TpT-DHC, 7a).—A mixture of 5′-(*p*-bromophenacyloxytrityl)thymidine (**5a**, 353 mg, 0.5 mmol) and 3′-dihydrocinnamoylthymidine 5′-monophosphate[5] (414 mg, 0.91 mmol) together with dry Dowex 50W-X8 (pyridinium) resin (1.0 g) were dried by azeotroping with pyridine. The mixture was dissolved in dry pyridine (7 ml) and a solution of dicyclohexylcarbodiimide (840 mg, 4.08 mmol) in pyridine (1 ml) was added; the mixture was stirred at room temperature for 5 days. The solution was cooled and treated with an equal volume of water and after standing 2 hr extracted with three portions of cyclohexane (40 ml). The aqueous layer was stored overnight at 0° and then filtered and concentrated *in vacuo*. The product was isolated by paper chromatography on Whatman No. 3MM, solvent A, to give the protected dinucleoside monophosphate, 245 mg (42%), R_f 0.83 (solvent A).

Thymidylyl-(3′–5′)-thymidine (8a).—A sample of 5′-BPTr-TpT-DHC (7a, 20 mg) was treated with acetic acid (40%) (1 ml) and zinc dust (25 mg) for 1 hr and the solution chromatographed on Whatman No. 3MM (solvent D). The band at R_f 0.67 was eluted and the solution lyophilized to give TpT-DHC (9a, 11 mg (91%). The dihydrocinnamoyl group was removed from this dinucleoside monophosphate by the enzyme α-chymotrypsin (see ref 5) to give TpT (8a).

5′-(p-Hydroxytrityl)thymidylyl-(3′–5′)-3′-dihydrocinnamoylthymidine (5′-(p-HOTr)-TpT-DHC, 10a).—The hydrolysis of 5′-BPTr-TpT-DHC (7a) (150 OD's) was studied using 20, 40, and 60% acetic acid (0.1 ml) and zinc dust (2 mg) and followed by tlc (cellulose, solvent A). In 1 hr using 60 or 40% acetic acid there was complete detritylation to give TpT-DHC (9a). However, on using 20% acid and zinc for 1 hr the intermediate 5′-(p-HOTr)-TpT-DHC (10a) could be isolated by paper chromatography (solvent A) together with TpT-DHC (9a). The yields follow: **10a**, 15 OD_{260} units (31%), and **9a**, 18 OD_{260} units (39%). After standing for 4 hr the only product was **9a**.

Similar studies were made using 40, 60, and 80% acetic acid in the absence of zinc dust. Only in the case of 80% acetic acid was any hydrolysis observable after 24 hr.

d-5′-(p-Bromophenacyloxytrityl)uridylyl-(3′–5′)-3′-dihydrocinnamoylthymidine (5′-BrTr-dUpT-DHC, 7b).—This was prepared in the same way as 7a using 5′-BrTr-dU (5b, 300 mg, 0.44 mmol) and pT-DHC (350 mg, 0.77 mmol). The product was isolated by chromatography on Whatman No. 3MM (solvent A), followed by lyophilization after removal of the salts, to give the dinucleoside monophosphate **7b** as a white solid, 270 mg (54%), R_f 0.85 (solvent A).

d-Uridylyl-(3′–5′)-thymidine (8b).—The preceding fully protected dinucleoside monosphosphate (**7b**, 20 mg) was dissolved in 50% ethanol (2.5 ml), diluted with an equal volume of pyridine, cooled to 0°, and treated with cold (0°) 2 *N* sodium hydroxide solution (5 ml). After standing at 0° for 5 min, the solution was neutralized with Dowex 50W-X8 resin (pyridinium form). The solution was filtered, concentrated, and chromatographed on Whatman No. 3MM (solvent C). Elution of the zone R_f 0.85 gave the dinucleoside monophosphate 5′-BPTr-d-UpT (**9b**), 16.7 mg (94%).

This dinucleoside monophosphate (4 mg) was dissolved in 40% acetic acid (10 ml) containing zinc dust. After standing at room temperature overnight the solution was filtered, evaporated, and chromatographed on paper (solvent A). The main zone had R_f 0.50 and on elution gave d-UpT (**8b**), λ_{max} 263 mμ, 50 OD_{260} units (74%).

d-5′-(p-Hydroxytrityl)uridylyl-(3′–5′)-thymidine (5′-(p-HOTr)-dUpT, 10b).—5′-BPTr-d-UpT (**9b**, 4 mg) was dissolved in 20% acetic acid (10 ml), the solution treated with zinc dust (500 mg), and the mixture shaken for 1 hr at room temperature. The mixture was filtered, concentrated, and chromatographed. Work-up of the zone at R_f 0.69 (solvent A) gave 5′-(p-HOTr)-dUpT, **10b**, 35 OD_{260} units (50%).

When 10 OD_{260} units of 5′-(p-HOTr)-dUpT were dissolved in 90% formic acid (1 ml) for 10 min or 20% acetic acid (1 ml) for 4 hr, and the solutions were chromatographed on Whatman No. 1 (solvent A), the unprotected dinucleoside monophosphate d-UpT (**8b**) was formed in both cases, R_f 0.48, 8.1 OD_{260} units (85%) and 7.8 OD_{260} units (82%), respectively.

5′-(p-Bromophenacyloxytrityl)uridine 2′,3′-Cyclic Phosphate.—Uridine 2′,3′-cyclic phosphate (350 mg, 0.9 mmol) was dissolved in a mixture of dimethylformamide (10 ml) and pyridine (1 ml) and treated with *p*-bromophenacyloxytrityl chloride (490 mg, 1.0 mmol). The mixture was stirred at room temperature for 2 days and then treated with water (2 ml); the solution was evaporated to dryness and azeotroped with small portions of dry pyridine. The gummy residue was dissolved in pyridine (5 ml) and precipitated with dry ether (200 ml) at 0°. The white precipitate was filtered and dried *in vacuo* to give 5′-BPTr-U>p, 650 mg (86%), R_f 0.77 (solvent A).

5′-(p-Bromophenacycloxytrityl)uridine 3′-Phosphate.—The above compound (650 mg, 0.78 mmol) was taken up in dimethylformamide (8.0 ml) and 2.5 *M* ammonium acetate buffer (3.5 ml) and incubated at 37° for 24 hr with pancreatic ribonuclease (Bovine) (11 mg). The pH of the solution was maintained between 7.5 and 7.6 by addition of 1.0 *M* ammonium hydroxide from a microsyringe. The solution was diluted with 1% aqueous ammonia until turbidity developed and then extracted with ethyl acetate (two 65-ml portions). The aqueous phase was saturated with sodium sulfate and extracted with *n*-butyl alcohol (four 65-ml portions). The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* in the presence of added pyridine, the residue taken up in 5% pyridine, and the solution passed through a column of Dowex 50W-X8 (pyridinium, 4 × 19 cm). The eluate was evaporated and rendered anhydrous by repeated evaporations of dry pyridine. The residue was taken up in dry pyridine (5 ml), precipitated with cold dry ether (200 ml), collected, and dried *in vacuo* to give 5′-BPTr-U-3′-p, 490 mg (74%), R_f 0.71 (solvent A).

2′-Acetyl-5′-(p-bromophenacyloxytrityl)uridine 3′-Phosphate (11).—The above compound (440 mg, 0.57 mmol) was acetylated by dissolving it in acetic anhydride (0.6 ml) in the presence of tetraethylammonium acetate (6.0 mmol). The mixture was stirred for 16 hr at room temperature and then treated with a mixture of methanol–pyridine, 4:1, for 10 min. The solution was evaporated and the residue taken up in a mixture of methanol–pyridine–water, 3:1:1 (50 ml), and the solution passed through a column of Dowex 50W-X8 (pyridinium) resin (2 × 18 cm). The eluate was concentrated, dried, and precipitated with pyridine–ether in the usual way to give **11** as a white powder, 500 mg (97%), R_f 0.79 (solvent A).

5′-(p-Bromophenacyloxytrityl)-2′-acetyluridylyl-(3′–5′)-2′,3′-dibenzoyluridine (5′-BPTr-U(OAc)pU(OBz)$_2$, 12).—Dibenzoyluridine (113 mg, 0.25 mmol), 5′-BPTr-U(OAc)-3′-p (**11**, 324 mg, 0.36 mmol), and anhydrous Dowex (pyridinium) resin (1.0 g) were azeotroped and then dissolved in dry pyridine (4 ml). A solution of dicyclohexylcarbodiimide (750 mg, 3.7 mmol) in dry pyridine (6 ml) was added and the mixture stirred at room temperature for 3.5 days. It was then treated with water (10 ml) for 2 hr, extracted with cyclohexane (three 20-ml portions), and stored overnight at room temperature. The solution was filtered, concentrated, and chromatographed on Whatman No. 3 MM (solvent A). The fully protected dimer was eluted as a zone R_f 0.83 and after drying precipitated from pyridine–ether as an off-white powder, 150 mg (47%).

5′-(p-Bromophenacyloxytrityl)uridylyl-(3′–5′)-uridine (5′-BPTr-UpU, 15).—The above fully protected dimer (27 mg) was treated with methanol saturated with ammonia at 0° for 16 hr. The solvent was removed *in vacuo* and the residue dissolved in pyridine and precipitated with ether to give **15**, 18 mg (83%).

Detritylation of the Dimers 5′-BPTr-U(OAc)pU(OBz)$_2$ (12) and 5′-BPTr-UpU (15).—Portions (2 mg) of the dinucleoside monophosphates **12** and **15** were treated with 10, 20, 40, 50, 60, and 80% acetic acid (0.4 ml) and zinc dust (4 mg) at room temperature. The progress of the reactions was followed by tlc (cellulose, solvent A) and by paper chromatography (Whatman No. 1, solvent A). In the case of **15** (5′-BPTr-UpU), R_f 0.73, detritylation was complete in under 1 hr with 20–80% acetic acid and in 4 hr with 10% acid, to give UpU (**16**), R_f 0.45. The detritylation of **12** (5′-BPTr-U(OAc)pU(OBz)$_2$), R_f 0.90, was also complete in under 1 hr with 20–80% acetic acid, to give U(OAc)pU(OBz)$_2$ (**13**), R_f 0.82 (36%), but in addition other side products were formed with R_f 0.76 (38%) and 0.86 (26%). Both products were trityl negative and showed the presence of uracil in their uv spectra.

A second sample of 5′-BPTr-U(OAc)pU(OBz)$_2$, prepared from U(OBz)$_2$ (75 mg, 0.17 mmol) and 5′-BPTr-U(OAc)-3′-p (100 mg, 0.11 mmol), was not isolated but treated directly with 90% formic acid for 10 min at room temperature. After rapid evaporation of the formic acid *in vacuo* the residue was chromatographed on Whatman No. 3 MM paper (solvent A) and the band at R_f 0.82 eluted to give **13**, U(OAc)pU(OBz)$_2$, 32 mg (32%). An aliquot of this dinucleoside monosphosphate was treated with methanol saturated with ammonia for 16 hr to give UpU which was identical with that prepared from **15**.

5′-(p-Bromophenacyloxytrityl)-2′-acetyluridylyl-(3′–5′)-2′-acetyluridylyl-(3′–5′)-2′,3′-dibenzoyluridine (5′-BPTr-U(OAc)-pU(OAc)pU(OBz)$_2$, 14).—The dinucleoside monophosphate **13** (U(OAc)pU(OBz)$_2$) (32 mg, 35 μmol), **11** (5′-BPTr-U(OAc)-3′-p) (74 mg, 82 μmol), and anhydrous Dowex resin (pyridinium) (10 mg) were dried by coevaporation of pyridine and treated with a solution in dry pyridine (5 ml) of dicyclohexylcarbodiimide (100 mg, 485 μmol). The mixture was stored at room temperature for 6 days and then treated with water (5 ml). After extraction with cyclohexane (three 10-ml portions) the aqueous phase was stored at 0° overnight, filtered, and evaporated to dryness. Chromatography (Whatman No. 3MM, solvent A) gave the product 14, R_f 0.84, 21 mg (34%).

5'-(p-Bromophenacyloxytrityl)uridylyl-(3'–5')-uridylyl-(3'–5')-uridine (5'-BPTr-UpUpU, 18).—The preceding trinucleoside diphosphate 14 (7 mg) was treated with concentrated ammonia (5 ml) for 15 hr. Preparative paper chromatography on Whatman No. 3MM paper (solvent A) gave 18 (5'-BPTr-UpUpU), R_f 0.63, 4.5 mg (83%).

Detritylation of 14, 5'-BPTr-U(OAc)pU(OAc)pU(OBz)₂, and 18, 5'-BPTr-UpUpU.—Portions (0.5 mg) of the trinucleoside diphosphates 14 and 18 were treated with 10, 20, and 40% acetic acid (0.2 ml) and zinc dust (2 mg) and the reactions followed by tlc (cellulose, solvent A).

The detritylation of 18, R_f 0.63, was complete in 1 hr with 20 and 40% acetic acid and zinc to give UpUpU, R_f 0.27. In the case of 14, R_f 0.84, the detritylation was also complete in under 1 hr with 20 and 40% acid to give 17, U(OAc)pU(OAc)pU$(OBz)_2$, R_f 0.43, but again side products were formed, R_f 0.49 and 0.53.

Treatment of 14, 5'-BPTr-U(OAc)pU(OAc)pU$(OBz)_2$ (30 OD_{260} units), with 90% formic acid (1 ml) at room temperature for 10 min, followed by evaporation and chromatography (Whatman No. 3MM, solvent A), gave 17, U(OAc)pU(OAc)pU$(OBz)_2$, 21 OD_{260} units, R_f 0.43. Treatment with concentrated ammonia for 16 hr gave UpUpU.

Registry No.—2f, 33608-41-2; 3f, 33608-42-3; 4a, 33531-85-0; 4b, 33608-43-4; 4c, 33531-86-1; 4d, 33531-87-2; 4e, 33531-88-3; 4f, 33531-89-4; 5a, 33531-90-7; 5b, 33531-91-8; 5c, 33531-92-9; 5d, 33531-93-0; 6a, 33531-94-1; 6b, 33531-95-2; 6c, 33531-96-3; 6d, 33531-97-4; 7a, 33531-98-5; 7b, 33531-99-6; 8a, 1969-54-6; 8b, 10300-41-1; 9b, 33532-02-4; 10a, 33532-03-5; 10b, 33532-04-6; 11, 33532-05-7; 12, 33532-06-8; 14, 33545-29-8; 15, 33608-44-5; 18, 33608-45-6; 5'-(p-bromophenacyloxytrityl)uridine 2',-3'-cyclic phosphate, 33532-07-9; 5'-(p-bromophenacyloxytrityl)uridine 3'-phospate, 33532-08-0.

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Partial Asymmetric Induction in the Ene Reaction

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Asymmetric induction in the ene reaction of (−)-menthyl glyoxylate with pent-1-ene has been studied. Optical yields were found to depend on temperature, solvent, and catalyst. The configuration of the new dissymmetric center in the obtained adducts changed with catalyst. In the presence of $SnCl_4$, BF_3, and $TiCl_4$ configuration *S* was induced, whereas with $AlCl_3$ center with configuration *R* was obtained. Postulation of an equilibrium between transition states derived from single- (s-) cisoid and transoid conformations of carbonyl groups of (−)-menthyl glyoxylate accounts for the results of asymmetric induction in the examined ene reaction.

Studies of partial asymmetric synthesis are of theoretical and preparative interest. On one hand they may be used as a tool to establish or relate configuration,[1] or, when configuration of the substrate and product is known, asymmetric induction may serve as a criterion of the assumed geometry of a transition state. On the other hand, high (70–100%) optical yields achieved for several reactions[2] open the possibility of applying asymmetric synthesis as a method for the preparation of optically active compounds with the desired absolute configuration. Though the area has been studied extensively with respect to both of these possibilities, little is known about asymmetric induction in the ene[3] reaction, for which so far only two examples have been examined.[4] In this paper we describe the results of the asymmetric induction in the ene condensation of pent-1-ene with (−)-menthyl glyoxylate in the presence of Lewis acid type catalyst.

Results

Data reported by Klimova, *et al.*,[5] indicate that butyl glyoxylate is an enophile of low reactivity. The thermal reaction (150°) with olefins gives poor yields; however, when catalyzed by Lewis acids it takes place readily at room temperature. Accordingly, we found that (−)-menthyl glyoxylate in the presence of 1 equiv of tin tetrachloride at room temperature reacted with pent-1-ene to afford in 87% yield the expected adduct, (−)-menthyl 2-hydroxy-4-heptenoate (**1**). Likewise high yields of adduct **1** were obtained with other Lewis acids ($AlCl_3$, BF_3, $TiCl_4$). The structure of **1** was confirmed by analysis, spectral data (ir, nmr), and chemical transformations shown in Scheme I.

Adduct **1** was comprised of two components[6] (vpc) which we assumed to be cis and trans isomers, since catalytic hydrogenation of the double bond of adduct **1** yielded dihydro derivative 2, giving only one peak in vpc, whereas methanolysis of **1** gave methyl ester **3** as a two-component mixture (vpc).

The optical yield of the ene reaction and the absolute configuration of the new dissymmetric center predominantly formed in adduct **1** were established by correlation of the latter with a compound of known specific rotation and absolute configuration, *i.e.*, methyl (−)-malate. To this end adduct **1** was subjected to ozonolysis, oxidative decomposition of the ozonide, and subsequent hydrolysis and methylation of malic acid with diazomethane (Scheme I). The methyl malate

(1) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 72.

(2) T. D. Inch, *Synthesis*, 466 (1970), and references cited therein.

(3) For the review, see H. M. R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

(4) R. K. Hill and M. Rabinowitz, *J. Amer. Chem. Soc.*, **86**, 965 (1964).

(5) (a) E. I. Klimova and Y. A. Arbuzow, *Dokl. Akad. Nauk SSSR*, **167**, 1060 (1966); *Chem. Abstr.*, **65**, 3736h (1966); (b) E. I. Klimova, E. G. Treshchova, and Y. A. Arbuzow, *Dokl. Akad. Nauk SSSR*, **180**, 865 (1968); *Chem. Abstr.*, **69**, 67173b (1968); (c) E. I. Klimova and Y. A. Arbuzow, *Dokl. Akad. Nauk SSSR*, **173**, 1332 (1967); *Chem. Abstr.*, **67**, 108156c (1967).

(6) In principle, adduct 1 is a four-component mixture: geometric isomers of two diastereoisomers. However, separation by vpc of isomers other than cis and trans in this case is rather unlikely, as follows from the vpc examination of the hydrogenation and methanolysis products.

TABLE I
EFFECT OF SOLVENT AND QUANTITY OF CATALYST ON OPTICAL YIELD

No.	Catalyst (equiv)	Solvent	Temp, °C	Specific rotation of methyl malate[a] c	$[\alpha]_{578}$	$[\alpha]_{546}$	$[\alpha]_{436}$	Optical yield, %	Configuration
1	$SnCl_4$ (0.12)	CH_2Cl_2	20	11.04	−1.18	−1.30	−1.90	13.3	S
2	$SnCl_4$ (0.25)	CH_2Cl_2	20	10.47	−1.32	−1.46	−2.07	14.7	S
3	$SnCl_4$ (0.50)	CH_2Cl_2	20	10.75	−1.38	−1.52	−2.16	15.4	S
4	$SnCl_4$ (1.00)	CH_2Cl_2	20	11.60	−1.28	−1.42	−2.01	14.3	S
5	$SnCl_4$ (1.00)	$C_6H_5CH_3$	20	7.57	−1.70	−1.93	−2.77	19.4	S
6	$SnCl_4$ (1.00)	CH_3NO_2	20	8.18	−1.97	−2.21	−3.24	22.5	S
7	$SnCl_4$ (1.00)	CH_3CN	20	4.65	−1.94	−2.11	−3.14	21.8	S

[a] Obtained from adducts 1.

TABLE II
EFFECT OF LEWIS ACID AND TEMPERATURE ON OPTICAL YIELD

No.	Catalyst (1 equiv)	Solvent	Temp, °C	Specific rotation of methyl malate[a] c	$[\alpha]_{578}$	$[\alpha]_{546}$	$[\alpha]_{436}$	Optical yield, %	Configuration
1	$SnCl_4$	CH_2Cl_2	20	11.60	−1.28	−1.42	−2.01	14.3	S
2	$SnCl_4$	CH_2Cl_2	−70	10.08	−2.01	−2.25	−3.15	22.2	S
3	$TiCl_4$	CH_2Cl_2	20	9.17	−1.09	−1.24	−1.79	12.5	S
4	$TiCl_4$	CH_2Cl_2	0	9.72	−1.23	−1.38	−1.96	13.9	S
5	$TiCl_4$	CH_2Cl_2	−20	8.59	−2.31	−2.55	−3.59	25.7	S
6	BF_3	CH_2Cl_2	10	6.27	−0.48	−0.56	−0.89	5.8	S
7	BF_3	CH_2Cl_2	−25	10.13	−0.69	−0.82	−1.24	8.3	S
8	$AlCl_3$	CH_2Cl_2	20	9.42	+0.70	+0.77	+0.98	7.5	R
9	$AlCl_3$	CH_2Cl_2	0	5.35	+0.93	+1.07	+1.42	10.4	R
10	$AlCl_2$	CH_2Cl_2	−15	11.17	+0.98	+1.10	+1.47	10.8	R
11	$AlCl_2$	CH_2Cl_2	−22	4.32	+0.58	+0.63	+0.72	6.0	R
12	$SnCl_4$	CH_3NO_2	0	8.06	−2.81	−3.10	−4.33	31.2	S
13	$SnCl_4$	CH_3CN	0	4.98	−2.01	−2.23	−3.17	22.5	S
14	None	None	160	10.05	+0.16	+0.18	+0.30	1.8	R

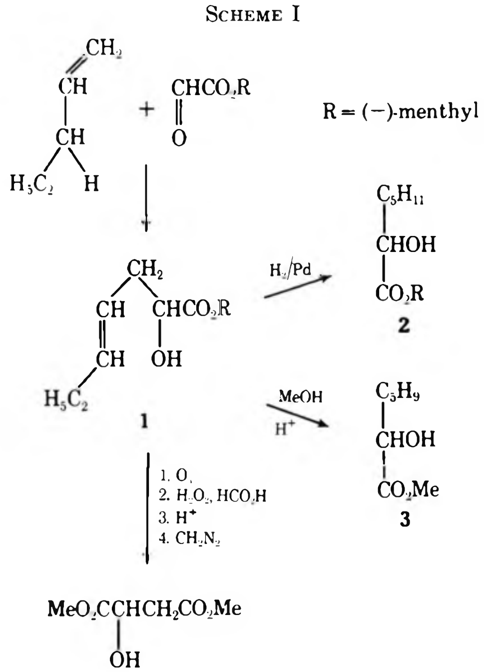
[a] Obtained from adducts 1.

thus obtained was purified by column chromatography on silica gel, and its purity was checked by tlc and vpc.

The ene reaction of (−)-menthyl glyoxylate with pent-1-ene was run at several temperatures with different catalysts and solvents. Optical yields and absolute configurations of adducts 1 are collected in Tables I and II.

Optical yields of examined ene reaction carried out with various amounts of $SnCl_4$ as catalyst (0.12–1.00 equiv) remained unchanged (Table I, entries 1–4). Therefore in the subsequent experiments equivalent amounts of catalyst were used. The solvent effected the optical yield of the reaction (Table I, entries 4–7). Replacement of dichloromethane by nitromethane, methyl cyanide, or toluene caused an increase in optical yields. This may be related to the higher dielectric constant and/or the ability of these solvents to form complexes with Lewis acids. However, the decisive influence on the asymmetric induction was the presence and nature of the catalyst. Lewis acids used ($SnCl_4$, BF_3, $AlCl_3$, $TiCl_4$) caused an increase in optical yields as compared with thermal condensation; moreover, the absolute configuration of the induced dissymmetric center depended on the nature of the catalyst (Table II). Optical yields increased[7] at lower temperatures. However in neither case did optical yields reach values which permit use of this ene reaction as a method for the synthesis of optically active α-hydroxy acids (after hydrolysis and hydrogenation of the double bond).

SCHEME I



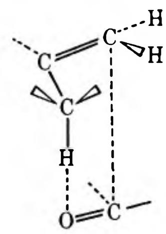
We have shown that adducts 1 could not be equilibrated under the conditions of ene reaction. The action of $AlCl_3$ or BF_3 on adduct 1 obtained with $SnCl_4$ as well as treatment with $SnCl_4$ of adduct 1 prepared in the presence of $AlCl_3$ failed to bring about any changes, either in the optical purity or ratio of cis–trans isomers.

Discussion

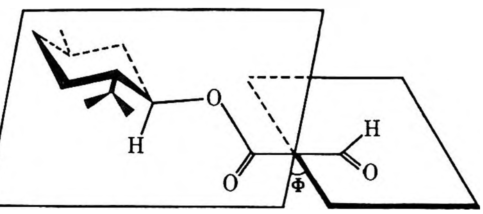
We assume that in the synchronous ene reaction the olefin approaches the aldehydic carbonyl group preferentially from the less shielded side and attains a transitional state geometry which maximizes the allylic

(7) With the exception of the reaction run in the presence of $AlCl_3$ (Table II, entries 8–11). In this case there appeared a maximum between 0 and −15°, optical yields being smaller at higher and lower temperatures.

resonance;[8] *i.e.*, the ruptured C–H bond takes position parallel to the π orbital of the double bond.[9]

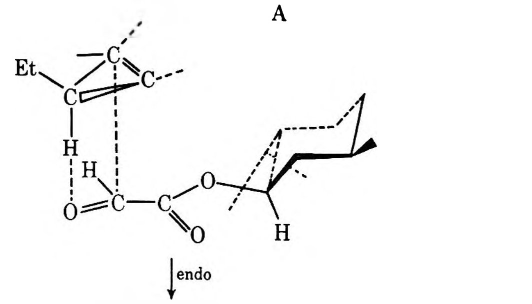


To choose the less hindered side of the aldehydic group it is necessary to consider the preferred conformation of (−)-menthyl glyoxylate, particularly the relative position of both carbonyl groups and the orientation of the (−)-menthyl residue relative to the ester group. According to previous studies[10] the alkyl α hydrogen of an ester is coplanar with the carboxyl group and faces the carbonyl oxygen. This was found for simple esters[10] and esters of α-keto acids[11] in the solid state and in solution alike. On the other hand, the angle between the carbonyl groups found for two keto esters amounted to 75° for ethyl *p*-bromophenylglyoxylate[11a] at 104° for (−)-menthyl *p*-bromophenylglyoxylate.[11b] Per analogy we ascribe to (−)-menthyl glyoxylate the conformation depicted below, where Φ is an dihedral angle approaching 90°.



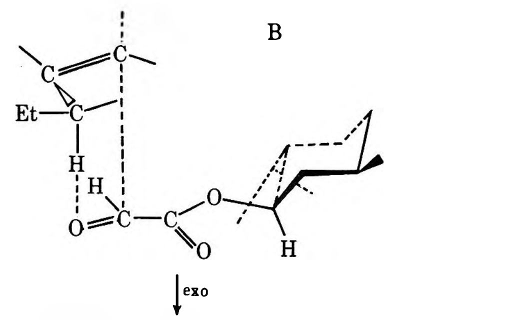
It has been noticed before[11b] that for such conformations steric hindrance of both sides of the aldehydic carbonyl group should be independent of the substituents of the alkoxyl residue; consequently, the asymmetric induction of the ene reaction would be negligible. On the other hand, to interpret the results of an asymmetric induction in the diene reaction of (−)-menthyl glyoxylate with 1-methoxybuta-1,3-diene, transition states based on conformations of (−)-menthyl glyoxylate with parallel and antiparallel orientation of carbonyl groups were postulated.[12] Analogously, to accommodate our results we assume that under the conditions of catalytic ene reaction, depending on the Lewis acid used, either antiparallel (s-transoid) or parallel (s-cisoid) conformation of the carbonyl groups of (−)-menthyl glyoxylate is induced.[13] From these conformations four transition states, A, B, C, and D, are derived which determine the direction of asymmetric induction. Transition states A and B, with s-cisoid orientation of the carbonyl groups correspond to endo and exo addition, respectively.

A



(−)-menthyl *cis*-2-(*S*)-hydroxy-4-heptenoate

B



(−)-menthyl *trans*-2-(*S*)-hydroxy-4-heptenoate

Both yield adduct **1** with configuration *S* of the newly formed dissymmetric center; *i.e.*, they predominate in the ene reaction catalyzed by $SnCl_4$, BF_3, and $TiCl_4$. The difference between endo and exo addition is reflected[14] in the formation of cis and trans iomers of **1**. According to Berson, *et al.*,[15] endo addition predominates in ene reaction, though not so decidedly as in diene synthesis.[16] Our results also indicate lack of positive preference of one mode of addition over another;[17] the proportion of the geometric isomers of adduct **1** varied in the range of 3:7 to 4:6, depending on both catalyst and temperature.

Likewise, transition states C and D derived from the s-transoid conformation of (−)-menthyl glyoxylate correspond to endo and exo addition, respectively, leading to geometric isomers of adduct **1**, with *R* configuration at the newly created dissymmetric center. Thus, they are favored in the ene reaction catalyzed by $AlCl_3$ (Table II, entries 8–11).

According to the postulated mechanism of the asymmetric ene synthesis the configuration and optical yield of the product depend on the equilibrium between four different transition states with s-cisoid (A and B) and s-transoid (C and D) conformations of the carbonyl groups. Factors which affect the relative rates of formation of products include solvent, temperature, and, most importantly, catalyst. We think that Lewis acids influence the equilibria between transition states

(8) Reference 3, p 575.

(9) Postulation of such a transition state well accommodated the results of the ene reaction between (*S*)- or (*R*)-3-phenylbut-1-ene and maleic anhydride.[4]

(10) (a) A. McL. Mathieson, *Tetrahedron Lett.*, 4137 (1965); (b) J. P. Jennings, W. Klyne, W. P. Mose, and P. M. Scopes, *Chem. Commun.*, 553 (1966); (c) J. P. Jennings, W. P. Mose, and P. M. Scopes, *J. Chem. Soc.*, 1273 (1967).

(11) (a) G. Oehme and A. Schellenberger, *Chem. Ber.*, **101**, 1499 (1968); (b) R. Parthasarathy, J. Ohrt, A. Horeau, J. P. Vigneron, and H. B. Kagan, *Tetrahedron*, **26**, 4705 (1970).

(12) (a) J. Jurczak, Ph.D. Dissertation, Institute of Organic Chemistry, Polish Academy of Sciences, 1970; (b) J. Jurczak and A. Zamojski, *Tetrahedron*, in press.

(13) s-Cisoid and s-transoid conformations are extreme cases used for the sake of simplicity. In fact, for our argument it is sufficient to postulate conformations with the dihedral angle between carbonyl groups much smaller and larger than 90°.

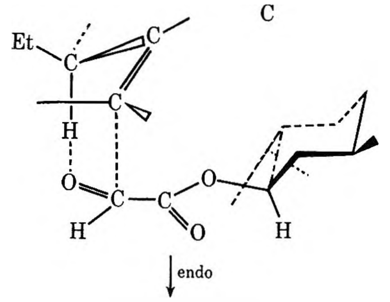
(14) We assume that owing to the steric hindrance pent-1-ene reacts in a conformation with the ethyl residue located outside the transition complex.

(15) J. A. Berson, R. G. Wall, and H. D. Perlmutter, *J. Amer. Chem. Soc.*, **88**, 187 (1966).

(16) For review see (a) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); (b) J. Sauer, *Angew. Chem.*, **79**, 76 (1967).

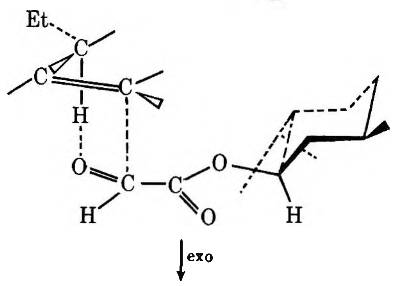
(17) This conclusion can be drawn without assignment of cis and trans configuration.

C



(−)-menthyl *cis*-2-(*R*)-hydroxy-4-heptenoate

D



(−)-menthyl *trans*-2-(*R*)-hydroxy-4-heptenoate

owing to their ability to form complexes with carbonyl groups.[18] On the other hand, the difference in steric shielding as related to the bulkiness of the substituents in the alkoxy residue is not decisive[19] for the direction of asymmetric induction.

Experimental Section

Boiling points refer to the air bath temperature and are uncorrected. Ir spectra were taken as liquid films using a Perkin-Elmer Model 137 spectrophotometer. Pmr spectra were obtained from a Varian HA-60/IL instrument in CCl_4 using TMS as internal standard. Optical rotations (°) were measured on a Perkin-Elmer 141 photopolarimeter at three wavelengths (436, 546, 578 nm) on *ca.* 10% methanolic solutions. Vapor phase chromatographic analyses were performed on a Willy Giede gas chromatograph 18.3.

Pent-1-ene[20] and (−)-menthyl glyoxylate hydrate[21] were prepared by known methods. The latter was dehydrated by distillation before use. A reference sample of methyl malate, $[\alpha]^{20}_{436}$ −13.88, $[\alpha]^{20}_{546}$ −9.94, $[\alpha]^{20}_{578}$ −9.00 (c 10.2, MeOH), was obtained by esterification with diazomethane of commercial malic acid. All condensations of (−)-menthyl glyoxylate with pent-1-ene and equilibrations of adduct 1 were carried out in an analogous manner.

(−)-Menthyl 2-Hydroxy-4-heptenoate (1). A. Catalytic Condensation.—To a stirred solution of 1.965 g (9.28 mmol) of (−)-menthyl glyoxylate in 10 ml of methylene chloride at 0° were added in succession solutions of 2.41 g (9.28 mmol) of tin tetrachloride and of 1.30 g (18.56 mmol) of pent-1-ene, each in 5 ml of methylene chloride. The reaction was stirred for 24 hr at 0°, and then 0.94 g (9.28 mmol) of triethylamine was added to neutralize the solution. The mixture was diluted with 100 ml of ether, washed with water, dried ($MgSO_4$), concentrated, and distilled, giving 2.26 g (87%) of 1, which solidified on standing, bp 110–115° (10^{-1} mm). Vpc analysis of 1 showed it to be 4:6 mixture: ir 3500 (OH), 1730 cm^{-1} (C═O); pmr δ 5.80–5.05 (m, 2, CH═CH), 4.72 (broad t, 1, *J* = 9.0 Hz, $-CO_2CH<$), 4.16 (t, 1, *J* = 5.5 Hz, CHOH), 2.83 (s, 1, OH), 2.42 (t, 2, *J* = 5.8 Hz, CH_2CHOH), 2.30–1.00 (m, 11), 0.97 (t, 3, *J* = 7.0 Hz, CH_2CH_3), 0.88 [d, 6, *J* = 7.0 Hz, $-CH(CH_3)_2$], 0.75 (d, 3, *J* = 7.0 Hz, $>CHCH_3$).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.03; H, 10.59.

B. Thermal Condensation.—A mixture of 2.12 g (10.0 mmol) of (−)-menthyl glyoxylate and 1.40 g (20.0 mmol) of pent-1-ene was heated in a sealed tube for 24 hr at 160°, then was chromatographed over 60 g of silica gel (mesh 200–300). Elution with benzene–ethyl acetate (9:1), evaporation of appropriate (tlc) fractions, and distillation afforded 0.65 g (23%) of product identical (tlc, ir, pmr) with the specimen obtained according to procedure A.

Attempted Equilibration of Adduct 1.—To a stirred solution of 1.41 g (10.0 mmol) of 1 (prepared using $SnCl_4$ as catalyst) in 10 ml of methylene chloride at −10° a solution of 1.33 g (10.0 mmol) of aluminum chloride in 10 ml of methylene chloride was added and the mixture was left for 48 hr at −10°; then 1.01 g (10.0 mmol) of triethylamine was added, and the reaction mixture was diluted with 100 ml of ether, washed with water, dried ($MgSO_4$), and evaporated to dryness. The optical purity and cis:trans ratio of the product was the same, within experimental error, as that of the starting material.

(−)-Menthyl 2-Hydroxyheptanoate (2).—A solution of 523 mg of adduct 1, $[\alpha]^{20}_{436}$ −107.16, $[\alpha]^{20}_{546}$ −64.85, $[\alpha]^{20}_{578}$ −57.29, $[\alpha]^{20}_{589}$ −55.09 (*c* 10.13, MeOH), in 10 ml of acetic acid was hydrogenated in the presence of 57 mg of platinum oxide. Removal of catalyst and solvent (at reduced pressure) afforded 505 mg of 2: bp 105–110° (10^{-4} mm); $[\alpha]^{20}_{436}$ −122.71, $[\alpha]^{20}_{546}$ −74.03, $[\alpha]^{20}_{578}$ −65.25, $[\alpha]^{20}_{589}$ −62.82 (*c* 10.38, MeOH); ir 3500 (OH), 1735 cm^{-1} (C═O); pmr δ 4.75 (broad t, 1, *J* = 9.0 Hz, $-CO_2CH<$), 4.05 (t, 1, *J* = 5.0 Hz, >CHOH), 3.35 (s, 1, OH), 2.20–0.70 (m, 29).

Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.70; H, 11.10.

Methyl 2-Hydroxy-4-heptenoate (3).—A solution of 665 mg (2.36 mmol) of adduct 1, $[\alpha]^{20}_{436}$ −107.16, $[\alpha]^{20}_{546}$ −64.85, $[\alpha]^{20}_{578}$ −57.29, $[\alpha]^{20}_{589}$ −55.09 (*c* 10.13, MeOH), and 54 mg (10.0 mmol) of sodium methoxide in 10 ml of anhydrous methanol was left overnight at room temperature; then the reaction mixture was brought to pH 2 with diluted hydrochloric acid and evaporated to dryness, the residue was dissolved in benzene, and inorganic salt was filtered off. The solvent was removed to give 650 mg of crude product, which was chromatographed over 20 g of silica gel (mesh 200–300). Elution with benzene–ethyl acetate (95:5) and evaporation of appropriate fractions (tlc) afforded 202 mg of (−)-menthol and 147 mg of ester 3: bp 65–70° (16 mm); $[\alpha]^{20}_{436}$ +5.32, $[\alpha]^{20}_{546}$ +2.84, $[\alpha]^{20}_{578}$ +2.48, $[\alpha]^{20}_{589}$ +2.45 (*c* 8.69, MeOH); ir 3500 (OH), 1735 cm^{-1} (C═O); pmr δ 5.80–5.05 (m, 2, CH═CH), 4.09 (t, 1, *J* = 5.5 Hz, >CHOH), 3.21 (s, 3, CO_2CH_3), 3.28 (s, 1, OH), 2.32 (t, 2, *J* = 5.5 Hz, CH_2CHOH), 2.20–1.80 (m, 2, CH_2CH_3), 0.95 (t, 3, *J* = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.54; H, 8.68.

Ozonolysis of Adduct 1.—A solution of 1.87 g (6.63 mmol) of 1, $[\alpha]^{20}_{436}$ −107.16, $[\alpha]^{20}_{546}$ −64.85, $[\alpha]^{20}_{578}$ −57.29, $[\alpha]^{20}_{589}$ −55.09 (*c* 10.13, MeOH), in 40 ml of methylene chloride was cooled in a Dry Ice–acetone bath and saturated with ozone until the blue color persisted; then the solvent was removed, 10 ml of formic acid and 10 ml of 30% hydrogen peroxide were added, the reaction mixture was heated on the steam bath for 40 min, and the solvents were evaporated under reduced pressure. To the amorphous residue 60 ml of 5% hydrochloric acid was added, and the mixture was heated on the steam bath for 60 min and then steam distilled until no more menthol passed over. The solution was taken to dryness *in vacuo*, and the residue was dissolved in 2 ml of methanol, treated with an excess of diazomethane in ether, and evaporated again. Chromatography over 20 g of silica gel (mesh 200–300) in benzene–ethyl acetate (9:1) afforded, after concentration and distillation, 650 mg (60%) of methyl malate: bp 83–85° (0.8 mm); $[\alpha]^{20}_{436}$ −2.01, $[\alpha]^{20}_{546}$ −1.42, $[\alpha]^{20}_{578}$ −1.28 (*c* 11.60, MeOH); identical with an authentic sample (tlc, vpc, ir, pmr).

Registry No.—*cis*-(*R*)-**1**, 33537-19-8; *trans*-(*R*)-**1**, 33495-66-8; *cis*-(*S*)-**1**, 33495-67-9; *trans*-(*S*)-**1**, 33495-68-0; (*R*)-**2**, 33537-20-1; (*S*)-**2**, 33495-69-1; *cis*-**3**, 33495-70-4; *trans*-**3**, 33537-21-2.

(18) H. F. Lappert, *J. Chem. Soc.*, 542 (1962).

(19) The presently postulated mechanism of asymmetric induction is substantially different from that adopted by Prelog[1] for addition of Grignard reagent to α-keto esters in which the direction and optical yield depended solely on the relative size of the substituents of the optically active ester group. It should be mentioned that Prelog's results can be interpreted in terms of our model of asymmetric induction providing one assumes prevalence of the s-cisoid orientation of carbonyl groups.

(20) (a) W. J. Bailey, J. J. Hewitt, and Ch. King, *J. Amer. Chem. Soc.*, **77**, 75 (1955); (b) W. J. Bailey and Ch. King, *ibid.*, **77**, 357 (1955).

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Stereochemistry of Free-Radical Recombination Reactions. The Cage Effect in Decomposition of S-(+)-*tert*-Butyl 2-Phenylperpropionate[1]

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Decomposition of *tert*-butyl 2-phenylperpropionate in cumene at 60° in the presence of butanethiol scavenger afforded a 10% yield of *tert*-butyl 1-phenylethyl ether. The cage effect, measured by use of the Koelsch radical, was 42%. The decomposition of optically active perester, *S*-(+)-*tert*-butyl 2-phenylperpropionate, in the presence of 0.5 *M* butanethiol gave *tert*-butyl 1-phenylethyl ether with 20% net retention of configuration. The absolute configuration and maximum rotation of the ether have been determined independently; (−)-ether is of *S* configuration. The principal result of this study is that the rate of 180° out-of-plane rotation of the 1-phenylethyl radical with respect to the *tert*-butoxyl radical within the solvent cage (Scheme I) is approximately 4.5 times as fast as the rate of the cage termination reactions (combination plus disproportionation).

Stereospecific radical reactions may be separated into several groups. One group is composed of reactions that are stereospecific because the radical can maintain configuration long enough to undergo an atom transfer or an electron transfer reaction before inverting. Examples of this type of stereospecific reaction are the reduction of 7-halo-7-fluoronorcaranes[2] and the reduction of 3-bromo-3-hexenes with sodium naphthalide.[3] Decomposition of *tert*-butyl 9-decalylpercarboxylate in the presence of a high concentration of oxygen[4] and decomposition of 9-decalylcarbinyl hypochlorite[5] may also be examples of this type, or may be of a different type in which the stereospecificity is associated with atom transfer to a (planar) radical at a faster rate than conformational changes elsewhere in the system. A third group is composed of reactions that are stereospecific because the radical has a reactive partner initially positioned in a stereospecific manner within the solvent cage; examples of this latter category are cyclic azo decomposition (pyrazolines[6] and tetrahydropyridazines[7]), cage combination,[8,9] cage disproportionation,[10] photobromination,[11] and probably a number of oxidation reactions[12a,b] and rearrangement reactions[12c] of ylides and carbanions. Stereospecificity in this class of reactions does not require that the radical maintain configuration. As has been pointed out for cage combination reactions,[9] the caged arrangement is asymmetric and may give rise to stereospecific products even for cages in which the radicals may be planar. Although cage combination reactions are limited in the information about radical structure, they permit certain insights into the nature of cage reactions.

Stereochemical studies of free radical cage reactions represent an approach to detailed information on the behavior of molecules in media over a wide range of viscosity. Two recent studies on azo decompositions[8,9] have elucidated the degree of freedom of a radical pair derived from an optically active azo compound. Homolytic perester decomposition may generate an alkyl radical, an alkoxyl radical, and a carbon dioxide molecule within the solvent cage.[13,14] Several important factors distinguish the cage resulting from perester decomposition from the cage resulting from azo compound decomposition. First, the perester cage contains an alkoxyl radical that is quite reactive as a hydrogen abstracting agent. Second, the alkoxyl radical and the alkyl radical are on atoms of different electronegativity and may be influenced by polar contributions.[13e,15] Third, a molecule of carbon dioxide rather than nitrogen initially separates the two radicals.

In this paper we describe the decomposition of *tert*-butyl 2-phenylperpropionate and provide information on the relative rates of the cage reactions.

Results

Products.—*tert*-Butyl 2-phenylperpropionate (**1**) decomposes in cumene to give a 1-phenylethyl radical, carbon dioxide, and a *tert*-butoxyl radical. The products in the absence of scavenger are given in Table I. The products are analogous to those formed in the decomposition of *tert*-butyl 2-phenylperisobutyrate.[14] The low accounting for the 1-phenylethyl groups (64%) is thought to result from polymerization of some of the styrene. Studies on the cage effect (see below) suggest that styrene is formed in 30% yield within the solvent cage.

Cage Effect.—The magnitude of the cage effect was determined by the "excess initiator" method[16] using the Koelsch radical.[17] In this method the rate

(1) Financial support from the Atomic Energy Commission [Contract No. AT(30-1)-905] is gratefully acknowledged.

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(6) See E. L. Allred and R. L. Smith, *J. Amer. Chem. Soc.*, **91**, 6766 (1969), and references cited therein.

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(14) F. E. Herkes, J. Friedman, and P. D. Bartlett, *Int. J. Chem. Kinetics*, **1**, 193 (1969).

(15) C. Walling, H. P. Waits, J. Milovanovic, and C. G. Pappiaonnou, *J. Amer. Chem. Soc.*, **92**, 4927 (1970).

(16) P. D. Bartlett and T. Funahashi, *ibid.*, **84**, 2596 (1962).

(17) (a) C. F. Koelsch, *ibid.*, **79**, 4439 (1957). (b) S. F. Nelsen and P. D. Bartlett, *ibid.*, **88**, 143 (1966). This paper compares the "excess scavenger" and "excess initiator" methods for determining the cage effect. Attempts

TABLE I

PRODUCTS FROM THE DECOMPOSITION OF *tert*-BUTYL 1-PHENYLPERPROPIONATE (1) IN CUMENE AT 60° IN THE ABSENCE OF SCAVENGER

Product	Yield, %[a]
$C_6H_5CH(CH_3)OC(CH_3)_3$	16
$C_6H_5CH{=}CH_2$	(5)
$C_6H_5C_2H_5$	5
$PhCH(CH_3)CH(CH_3)Ph$[b]	12
$PhC(CH_3)_2CH(CH_3)Ph$	14
$(CH_3)_3COH$	74
$PhC(CH_3)_2C(CH_3)_2Ph$	~10

[a] The total percentage of alkyl groups accounted for is 64%; the total percentage of *tert*-butyl groups accounted for is 90%. [b] Both meso and *dl* isomers were present in approximately 1:1 ratio.

of radical production is determined during the first 1–5% of the decomposition; the scavenging experiments thus could be carried out at lower temperatures than for the "excess scavenger" method,[18] and the problem of scavenged product instability was circumvented. The excess initiator method depends upon measuring the difference in the rate of initiator disappearance and the rate of radical production.

The rate of decomposition of *tert*-butyl 2-phenylperpropionate in cumene was determined by following the rate of disappearance of the carbonyl absorption in the infrared spectrum at 1770 cm^{-1}. A summary of the rate constants appears in Table II. The enthalpy

TABLE II

DECOMPOSITION OF *tert*-BUTYL 2-PHENYLPERPROPIONATE IN CUMENE

Temp, °C	k, sec^{-1}
40.7	7.60×10^{-6}
40.7	8.16×10^{-6}
60.1	8.38×10^{-5}
60.1	8.49×10^{-5}
80.1	8.10×10^{-4}

of activation for decomposition is 25.5 kcal/mol and the entropy of activation at 60° is −0.1 eu.

The rate of radical formation was followed by observing the decrease in the scavenger absorption[16] in the visible spectrum. The decrease in scavenger concentration with time was linear in all cases, affording the zero-order rate constants, λ. The cage effect, F, defined in the usual manner (eq 1), was calculated by eq 2, in which k_1 is the rate constant for decomposition

$$F = \left(\frac{k_{\text{combination}} + k_{\text{disproportionation}}}{k_{\text{combination}} + k_{\text{disproportionation}} + k_{\text{diffusion}}}\right)_{\text{cage}} \quad (1)$$

$$F = 1 - \frac{\lambda}{2k_1[\text{perester}]_0} \quad (2)$$

of the perester and in which the factor 2 appears in the denominator because of the maximum generation of two radicals for every perester molecule undergoing decomposition. The results are summarized in Table III. An estimate for the cage effect at 60° of 0.42 ± 0.03 was obtained by extrapolation of the data of Table III.[19]

to use the "excess scavenger" method failed, presumably because the scavenged products were unstable. (c) R. Kuhn and F. A. Neugebauer, *Monatsh. Chem.*, **95**, 3 (1964). (d) For evidence on the efficiency of the Koelsch radical as a scavenger for cumyl radical, see ref 17b.

(18) R. C. Lamb and J. G. Pacifici, *J. Amer. Chem. Soc.*, **86**, 914 (1964).

TABLE III

DETERMINATION OF CAGE EFFECT BY CONSUMPTION OF KOELSCH RADICAL[a] IN THE DECOMPOSITION OF *tert*-BUTYL 2-PHENYLPERPROPIONATE (1)[b] IN CUMENE

Temp, °C	$(\lambda/P_0) \times 10^6$,[c] sec^{-1}	$k_1 \times 10^6$,[d] sec^{-1}	Cage effect, F[e]
30.1	1.43	1.87[b]	0.62 ± 0.03
40.5	6.78	7.7	0.56 ± 0.03
48.3	20.4	21.0[f]	0.51 ± 0.03
60.1	97.8[g]	84.4	0.42

[a] Initial concentration, ~1 × 10^{-4} M (~1% of perester concentration). [b] Range of initial concentrations, 0.01–0.025 M. [c] Zero-order rate constant for disappearance of Koelsch radical = λ. [d] Rate of decomposition of perester (see Table II). [e] Calculated by eq 2. [f] Extrapolated; see Table II. [g] Extrapolated value from the data at 30.1, 40.5, and 48.3° by means of a linear plot of log (λ/P_0) *vs.* $1/T$.

The amount of *tert*-butyl 1-phenylethyl ether formed within the solvent cage was determined by decomposing the perester in the presence of varying concentrations of butanethiol. The yield of ether decreases with increasing butanethiol concentration until the concentration of butanethiol reaches 0.1 M and then remains constant at 10% (see Table IV). At concentrations

TABLE IV

DECOMPOSITION OF *tert*-BUTYL 2-PHENYLPERPROPIONATE[a] IN CUMENE IN THE PRESENCE OF BUTANETHIOL AT 60°

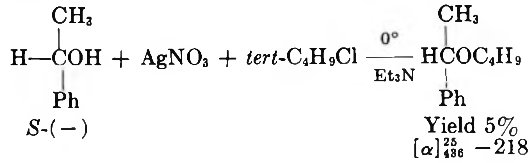
n-BuSH, M	Yield of ether, %
0	16.5
0.005	15.3
0.010	12.9
0.05	11.0
0.10	9.8
0.50	9.9

[a] Initial concentration, 0.025 M.

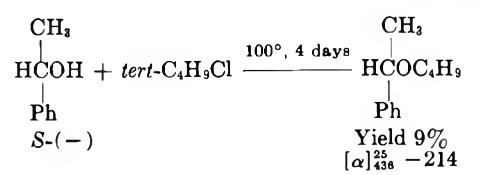
of butanethiol greater than 0.10 M it was assumed that all the radicals escaping the solvent cage were scavenged and did not give *tert*-butyl 1-phenylethyl ether.

Optically Active 1.—*S*-(+)-*tert*-Butyl 2-phenylperpropionate was prepared according to standard procedures from *S*-(+)-2-phenylpropionic acid. Reduction of the perester with potassium iodide and acetic acid afforded the starting acid with greater than 98% retention of optical activity.

S-(−)-*tert*-Butyl 1-phenylethyl ether was prepared from *S*-(−)-1-phenylethanol by the methods given in eq 3 and 4.



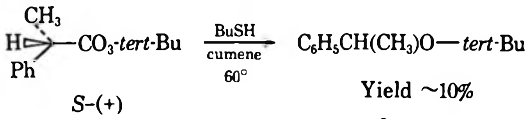
(3)



(4)

(19) A linear plot of log (λ/P_0) *vs.* $1/T$ was used for the extrapolation. For related problems, see *tert*-butyl 2-phenylperisobutyrate (ref 15) and azo decompositions [L. Herk, M. Feld, and M. Szwarc, *J. Amer. Chem. Soc.*, **83**, 2998 (1961)].

S-(+)-*tert*-Butyl 2-phenylperpropionate was decomposed in cumene in the presence of butanethiol (0.50 *M*) at 60°, *i.e.*, under conditions of complete scavenging of all radicals escaping the solvent cage (see above). After ten half-lives *tert*-butyl 1-phenylethyl ether was isolated. The degree of retention of optical activity in the ether from three different experiments is given in eq 5.



(5)

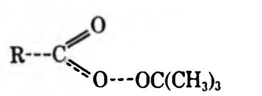
Yield ~10%

S-(−)[a]	R-(+)
60.3	39.7
60.9	39.1
59.9	40.1

[a] Corresponds to retention of configuration in this reaction.

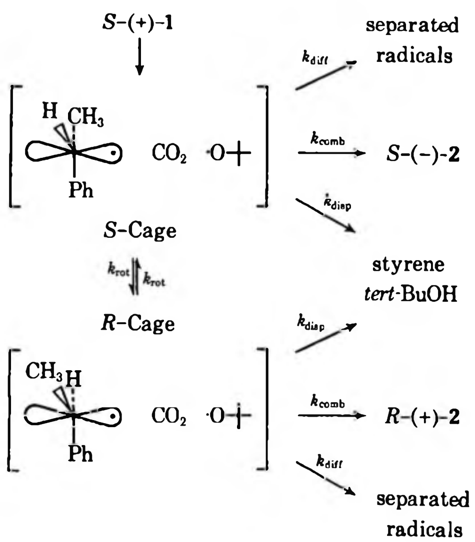
Discussion

Several lines of evidence (isotope effects,[13c] effect of viscosity[13d] and pressure[13e] on rate, and activation parameter comparisons[13a]) from a number of peresters are suggestive that the rate-determining step for decomposition of *tert*-butyl 2-phenylperpropionate (**1**) will involve two-bond cleavage affording 1-phenylethyl radical, carbon dioxide, and *tert*-butoxyl radical. The probable geometry for the transition state is one in which the incipient alkyl and alkoxyl radicals are trans to one another with respect to the developing carbon–oxygen double bond, giving rise to a caged pair of radicals initially separated by a molecule of carbon dioxide. The subsequent reactions—cage combination



and disproportionation, rotation, and diffusion—are dependent on the relative rates of diffusive displacements of the radicals, carbon dioxide, and the surrounding solvent molecules. Interpretation of the results of the decomposition of optically active perester **1** is based on Scheme I. The situation is closely analogous to the decomposition of *S*-(−)-1,1′-diphenyl-1-methylazomethane.[8]

SCHEME I



In the analysis of Scheme I, the rate constants for diffusion (k_{diff}), combination (k_{comb}),[20] and disproportionation (k_{disp})[20] are assumed to be the same for both cages. The rate constant, k_{rot}, refers to a 180° out-of-plane rotation of the 1-phenylethyl radical relative to the *tert*-butoxyl radical, and is also assumed to be the same for both cages.

By the usual steady-state approximation (working with $-d[R_{cage}]/dt \cong 0$, Scheme I, and with $d[R\text{-}\mathbf{2}]/dt$ and $d[S\text{-}\mathbf{2}]/dt$), the optical activity of the ether cage product may be expressed in terms of the rate constants (eq 6). By use of the definition of eq 7, eq 6 may be reexpressed as eq 8. In terms of this analysis, the mole

$$\frac{S\text{-}2 - R\text{-}2}{R\text{-}2} = \frac{k_{diff} + k_{comb} + k_{disp}}{k_{rot}} \tag{6}$$

mf 2 = mole fraction of ether formed in the cage =

$$\frac{k_{comb}}{(k_{diff} + k_{comb} + k_{disp})} \tag{7}$$

$$\frac{k_{comb}}{k_{rot}} = \frac{S\text{-}2 - R\text{-}2}{R\text{-}2}\ (\text{mf } 2) \tag{8}$$

fraction of ether formed in the original solvent cages (*i.e.*, the yield of ether under scavenging conditions) and the optical activity of this ether provide a measure of the ratio of k_{comb}/k_{rot}. One sees that this value is not dependent on the value of the cage effect[21] or on the amount of cage recombination.

By means of eq 1, eq 9, and the value for F at 60° of 0.42 (Table III), the relative values of the rate constants may be estimated.[22] (The relative value for k_{disp} is thus obtained as the difference between total

$$\frac{k_{comb}}{k_{comb} + k_{disp}} = \frac{0.1}{0.42} \tag{9}$$

cage reaction and the amount of cage ether.) These values are summarized in Table V along with values from some related studies of azo decompositions. The ratio of disproportionation to combination is considerably greater with perester **1** than with the second and third entries of Table V. The implication that disproportionation is faster for an alkyl–alkoxyl radical pair than for an alkyl–alkyl pair is not surprising based on the knowledge that hydrogen abstraction by an alkoxyl radical is generally faster than abstraction by an alkyl radical.

A question of primary interest in this study and in the azo cases of Table V is the extent of randomization of positions of the radicals in the cage prior to termination. The closest measure of this by experiments of the type presented here and in the azo studies would appear to be the rate of "turnover" of 1-phenylethyl radical (k_{rot}) relative to the rate of the termination reactions in the cage ($k_{comb} + k_{disp}$). The rates of these termination reactions are a function of the diffusive displacement of the CO_2 from between the two caged

(20) Note that k_{comb} and k_{disp} are not the usual second-order termination constants but are first-order rate constants for the conversion of the radical pair cages of Scheme I to the combination and disproportionation products.

(21) Errors in the cage effect are not thought to be large; however, determination of the cage effect, F, involves two extrapolations (see Results section).

(22) The equations of Kopecky (ref 9) could have been applied directly to obtain the relative k's; a modified treatment is used here to emphasize the simple relationship shown in eq 8.

TABLE V
RELATIVE RATES (HORIZONTAL COMPARISON)

Compd	k_{comb}	k_{disp}	k_{rot}	k_{diff}	$k_{rot}{}^{a}/k_{cage\ reaction}$	Retention of configuration, %
S-(+)-1[b]	1	3.2	19	5.8	4.5	21
Azobis-1-phenylethane[c]	1	0.14	15	2.4	12	20.5
S-(−)-1,1′-Diphenyl-1-methylazomethane[d]	1	0.1	10–17	2–3	~12	10–17
Azobis-2-phenyl-3-methylbutane[e]	1		Very small			>95
3,6-Dimethyl-3,6-diethyl-1,2-pyridazine[f]	1		0.02			98

[a] $k_{cage\ reaction} \equiv k_{combination} + k_{disproportionation}$. [b] This work, 60° in cumene, cage effect 0.47. [c] Reference 8, 105° in benzene, cage effect 0.32. [d] Reference 9, 100° in several solvents, cage effect ~0.3. [e] P. D. Bartlett and J. M. McBride, *Pure Appl. Chem.*, **15**, 89 (1967); photolysis in frozen benzene (−196°). [f] Reference 7.

radicals, plus any further energy requirements in the interactions of these two radicals. The principal conclusion from this study, and from the acyclic azo cases of Table V (second and third entries), is that considerable randomination of the positions of the radicals occurs in the cage prior to termination. The value of k_{rot}/k_{cage} reaction for the perester case is approximately 4.5; the corresponding values for the azo cases are approximately 12.

Differences in the radicals involved, in the intervening molecule (CO_2 *vs.* N_2), in solvent, and in temperature render further comparisons at this point of limited value. One might comment, however, on the apparent similarity in the ratio of k_{rot}/k_{comb} for the perester and the azo cases in contrast to the difference in the ratio of $k_{rot}/(k_{comb} + k_{disp})$ indicated above. The higher value of k_{rot}/k_{comb} for the perester is a consequence of the large amount of disproportionation in the cage. The major barrier to the cage reactions in this case may be associated with diffusion of the carbon dioxide from between the two radicals. This carries the implication that the *sum* of k_{comb} plus k_{disp} would be constant here; *i.e.*, had disproportionation been less important, combination would have been more important. Under these circumstances the degree of retention of configuration in the cage ether and the ratio of k_{rot}/k_{cage} reaction could be the same as reported in Table V, even though the ratio of k_{rot}/k_{comb} were smaller.

Experimental Section

2-Phenylpropionic acid was prepared by the method of Eliel and Freeman,[23] bp 145–150° (10 mm), n^{25}D 1.5218 [lit.[23] bp 144–147° (11 mm), n^{25}D 1.5213].

S-(+)-**2-Phenylpropionic Acid**.—2-Phenylpropionic acid was resolved with strychnine according to the procedure of Arcus and Kenyon[24] with the modification that the salt was dissolved in an excess of 75% ethanol–water and then the excess solvent was removed under vacuum. This method was superior to heating the solvent to dissolve the salt, because heating led to slow decomposition of the salt.

2-Phenylpropanoyl chloride was prepared from 2-phenylpropionic acid and thionyl chloride (by the method of Greene),[25] bp 50° (0.15 mm) [lit.[25] bp 93–94° (11 mm)].

S-(+)-*tert*-**Butyl 2-phenylperpropionate** was prepared by a modification of a literature procedure.[13a] S-(+)-2-Phenylpropanoyl chloride (17.0 g) in an equal volume of ether was added very slowly to a solution of *tert*-butyl hydroperoxide (22 ml) in 20 ml of pyridine and 15 ml of ether cooled in an ice–acetone bath. The reaction was stirred for 4 hr at 0°. Saturated aqueous sodium chloride was added to the reaction mixture and the aqueous layer was extracted three times with ether. The ethereal layer was washed with three portions of 10% aqueous sulfuric acid and with saturated aqueous sodium bicarbonate and dried ($MgSO_4$). The ether was removed under reduced pressure. The remaining *tert*-butyl hydroperoxide was partially removed by trap-to-trap distillation.

A 1.429-g sample of perester ([α]^{25}D +23.44°) was dissolved in 50 ml of ether and washed with 100 ml of cold 5% aqueous KOH. The ether solution was dried ($MgSO_4$) and the ether was removed at room temperature. Nmr analysis of the perester showed less than 1% *tert*-butyl hydroperoxide and [α]^{25}D +24.98°. Thus the washing with cold 5% aqueous potassium hydroxide did not racemize the perester. The remainder of the perester was dissolved in 300 ml of ether, washed with three 300-ml portions of cold 5% aqueous KOH and once with saturated aqueous NaCl, and dried ($MgSO_4$). The ether was removed under vacuum at room temperature and the nmr analysis of the perester showed only trace amounts of *tert*-butyl hydroperoxide.

The S-(+)-*tert*-butyl 2-phenylperpropionate could be recrystallized at low temperature from pentane. Approximately 2 g of perester was dissolved in 10 ml of pentane in a centrifuge tube and cooled to −78°. The first crystallization gave a very fine precipitate which after three or four more recrystallizations gave long needles which melted below room temperature. Racemic mixtures of *tert*-butyl 2-phenylperpropionate were much more difficult to recrystallize and did not give a nicely crystalline product. The data for the pure *tert*-butyl 2-phenylperpropionate were n^{25}D 1.4868, [α]^{25}D 25.5° (*c* 11.60 in $CHCl_3$). The optical purity of the starting S-(+)-2-phenylpropionic acid was 96.8%; therefore the rotation for optically pure perester is [α]^{25}D 26.3°: ir (CCl_4) 3060 (w), 3025 (w), 2980 (s), 2930 (m), 1770 (s), 1600 (w), 1485 (w), 1390 (w), 1370 (m), 1190 (m), 1120 (m), 1080 (m), 1050 (m), 850 (m), 750 (m), 720 (w), and 695 cm^{-1} (m); nmr (CCl_4) 1.12 (9 H, s), 1.45 (3 H, d, J = 7 Hz), 3.65 (1 H, q, J = 7 Hz), 7.25 (5 H, s); $[\alpha]^{25}_{578}$ 27.8, $[\alpha]^{25}_{546}$ 32.6, $[\alpha]^{25}_{436}$ 66.0, $[\alpha]^{52}_{365}$ 121.8°.

S-(−)-**1-Phenylethanol**.—1-Phenylethyl hydrogen phthalate was prepared by the method of Houssa and Kenyon,[26] mp 106–108° (lit.[26] mp 107–108°). Brucine (52 g, 0.132 mol) was dissolved in a warm solution of racemic 1-phenylethyl hydrogen phthalate (35.6 g, 0.137 mol) in 200 ml of acetone. The solution was placed in the freezer (−27°) and allowed to crystallize overnight. The supernatant liquid was decanted from the crystals and the crystals were redissolved in methyl acetate. Heating the methyl acetate solution to speed solution of the salt led to a gradual decomposition of the salt; thus the salt was dissolved by vigorously stirring the suspension at room temperature and then placing the solution in the freezer. After three recrystallizations the salt was decomposed with 10% hydrochloric acid. The phthalate obtained was hydrolyzed in 5 *N* sodium hydroxide on a steam bath for 1 hr. The reaction mixture was extracted with ether and the ethereal layer was washed with saturated aqueous NaCl and dried ($MgSO_4$). The ether was removed and the alcohol was distilled, bp 70° (2.5 mm), to

(23) E. L. Eliel and J. P. Freeman, *J. Amer. Chem. Soc.*, **74**, 923 (1952); H. D. Kay and H. S. Raper, *Biochem. J.*, **16**, 469 (1922).

(24) C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939); H. I. Bernstein and F. C. Whitmore, *J. Amer. Chem. Soc.*, **61**, 1324 (1939).

(25) F. D. Greene, *ibid.*, **77**, 4869 (1955).

(26) A. J. H. Houssa and J. Kenyon, *J. Chem. Soc.*, 2260 (1930).

give 5 g of alcohol, $[\alpha]^{25}_{436}$ −8.165° (9.00% optically pure), n^{25}D 1.5251 (lit.[22] n^{25}D 1.5267).

S-(−)-*tert*-**Butyl 1-Phenylethyl Ether. Method A.**—Powdered silver nitrate (3.74 g, 0.212 mol) was added in small amounts to a solution of *S*-(−)-1-phenylethanol (1.29 g, 0.0106 mol, 9.00% optically active) and *tert*-butyl chloride (1.96 g, 0.0202 mol) in 2.14 g of triethylamine cooled to 0°. After the addition was complete, the reaction mixture was filtered and diluted with ether. The ether layer was washed with 10% aqueous HCl and saturated aqueous sodium bicarbonate and dried ($MgSO_4$). The solvent was removed and the product was chromatographed on alumina (I) using ether–hexane (1:9) as the eluent. The product was found in the first three fractions (approximately 150 ml). The solvent was removed and the product was collected by vpc (SE-30 at 100°) to give 0.100 g (5%): $[\alpha]^{25}_{436}$ −19.6° (*c* 5.01, ethanol) which corresponds to a rotation of $[\alpha]^{25}_{436}$ −218° for the optically pure *S*-(−)-1-phenylethyl *tert*-butyl ether; nmr (CCl_4) δ 1.13 (9 H, s), 1.31 (3 H, d, *J* = 7 Hz), 4.62 (1 H, q, *J* = 7 Hz), 7.35 (5 H, broad s). *Anal.* Calcd: C, 80.85; H 10.18. Found: C, 80.74; H, 10.27.

Method B.—A mixture of *S*-(−)-1-phenylethanol (1.6287 g, 13.3 mmol, 9.06% optically active), 2.46 g (26.6 mmol) of *tert*-butyl chloride, and 3.22 g (26.6 mmol) of 2,4,6-trimethylpyridine was degassed and sealed in Pyrex tubes. The tubes were then placed in a steam cone (110°) for 4 days. The tubes were opened and the reaction mixture was separated by vpc (SE-30, 100°) to give 0.213 g (9% yield) of *S*-(−)-*tert*-butyl 1-phenylethyl ether, $[\alpha]^{25}_{436}$ −19.05° (*c* 10.65 ethanol). The polarimeter sample was then recollected from vpc (SE-30, 100°) to give a sample with a rotation of $[\alpha]^{25}_{436}$ −19.36° which corresponds to a rotation of $[\alpha]^{25}_{436}$ −214° for optically pure ether. The rotations from method A and B were averaged to give $[\alpha]^{25}_{436}$ −216°.

Cage Yield of *tert*-Butyl 1-Phenylethyl Ether.—Pyrex test tubes with solutions of perester and butanethiol in cumene or benzene as solvent were degassed, sealed, and placed in a constant-temperature bath at 60° for 45 hr (30 half-lives). The tubes were opened and 1,2-dichlorobenzene was added as an internal standard for vpc analysis. The results are summarized in Table IV.

Decomposition of *S*-(+)-*tert*-Butyl 2-Phenylperpropionate in Cumene.—A 5.0-ml aliquot of perester in cumene (0.11 *M*) and 5.0 ml of butanethiol solution in cumene (1.0 *M*) were placed in each of ten tubes. The tubes were degassed (three freeze–thaw cycles), sealed, and placed in a constant-temperature bath at 60° for 24 hr (16 half-lives). The tubes were opened and trap-to-trap distilled; teflon spinning band distillation removed some of the solvent. The residual solution was then passed through the gc (SE-30 at 100°) and collected, followed by gc on Carbowax 20M from which the products were collected and identified by comparison with authentic samples.

Decomposition of *tert*-Butyl 2-Phenylperpropionate in Cumene in the Presence of Excess Koelsch's Radical.—A decomposition mixture 1.85×10^{-3} *M* in Koelsch's radical[17c] and 0.93×10^{-3} *M* in perester was placed in a Pyrex uv cell; the mixture was degassed and sealed. The decomposition was carried out at 60° and followed at 860 nm using a Beckman DU-I. The rate of disappearance of Koelsch's radical was not first order, indicated greater than 100% efficiency, and gave scavenged products which were not stable to the reaction conditions.

Decomposition of *tert*-Butyl 2-Phenylperpropionate in the Presence of 1–2% Koelsch's Radical.[17c]—A decomposition mixture 0.0147 *M* in perester and 3.4×10^{-4} *M* in Koelsch's radical (2.3%) was degassed and sealed in a Pyrex uv cell. The sample was given a preliminary warm-up at 41.6° for 2 min and then placed in the sample cavity of the DU-I, which was thermostated at 40.7°. The decomposition was followed to the complete disappearance of the Koelsch's radical. The disappearance of Koelsch's radical was zero order. The decomposition at 30.1 and 48.3° was executed in the same manner as the above.

Kinetics of the Perester Decomposition.—A solution of perester (0.0652 g/10 ml of cumene, 0.0239 *M*) was placed in seven sample tubes and decomposed at 60.10°. The tubes were removed from the bath and quenched at 0°. The tubes were then stored in the freezer (−27°) until the completion of the run, at which time all the samples were analyzed by ir at the carbonyl absorption (ν_{max} 1770 cm^{-1}, ε 56 M^{-1} mm^{-1}, *b* = 0.50 mm). The decomposition at 80.50° was carried out in exactly the same manner as that given above. In the decompositions at 40°, the samples were analyzed when the tube was removed from the bath because long storage of the decomposition samples led to erratic results. The infrared spectrophotometer was a Perkin-Elmer 237B; a normal slit width and slow scan speed were used. Due to the difficulty in maintaining the pen at the ν_{max}, the 1765–1790 cm^{-1} region of the spectrum was scanned twice for each sample and the absorbances were averaged. The plots of the logarithm of the perester concentration *vs.* time were linear for at least two to three half-lives. Infinity points taken after ten half-lives showed no detectable carbonyl absorption. The results are summarized in Table III.

Hydrolysis of *R*-(−)-2-Phenylpropanoyl Chloride.—*R*-(−)-2-Phenylpropanoyl chloride prepared from *R*-(−)-2-phenylpropionic acid, $[\alpha]^{26}$D −48.5° ($CHCl_3$), was hydrolyzed with 20% aqueous KOH at 0°. The reaction mixture was extracted with ether and the aqueous layer was acidified with 10% aqueous HCl. The acid was then extracted into ether; the ether layer was washed with saturated aqueous NaCl and dried ($MgSO_4$). The ether was removed under vacuum and the acid was distilled (short path) to give *R*-(−)-2-phenylpropionic acid, n^{25}D 1.5213, $[\alpha]^{25}$D −49.9°.

Reduction of *R*-(−)-*tert*-Butyl 2-Phenylperpropionate.—*R*-(−)-*tert*-Butyl 2-phenylperpropionate prepared from *R*-(−)-2-phenylpropanoyl chloride (from 53.8% optically pure acid) was treated with potassium iodide, 2-propanol, acetic acid, and acetic anhydride at room temperature for 2 days. The iodine produced was consumed with aqueous sodium thiosulfate and the acids were extracted into ether. The acids were then extracted into saturated aqueous sodium bicarbonate which was washed with ether and then neutralized with 10% aqueous HCl. The acidified aqueous solution was then extracted with ether. The ether layer was dried ($MgSO_4$) and the ether and some of the acetic acid were removed under vacuum. After two short-path distillations the rotation of the *R*-(−)-2-phenylpropionic acid showed 98% retention of the initial optical activity.

Registry No.—1, 3377-90-0; *S*-(+)-**1,** 33122-25-7; *S*-(−)-1-phenylethanol, 1445-91-6; *S*-(−)-*tert*-butyl-1-phenylethyl ether, 33069-10-2; *R*-(−)-2-phenylpropionic acid, 7782-26-5.

Steroids and Related Natural Products. 66. Structural Modification of the Triterpene A Ring[1,2]

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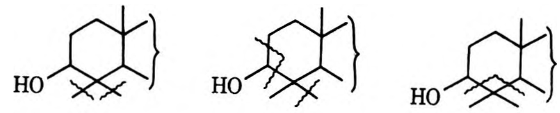
A new synthetic procedure has been developed for conversion of tetracyclic triterpenes to 14α-methyl or 4,14α-dimethyl steroids. Transformation of lanosterol to 3-oxo-14α-methylcholest-4-ene was used for illustration.

Naturally occurring steroids usually lack substituents at the C-4 position, but their biogenetic precursors usually possess a 4,4-dimethyl-substituted A ring.[3] A variety of new and potentially useful steroids can, in principle, be obtained by deletion of the 4,4-dimethyl substituents from the increasing number of readily available tetracyclic triterpenes. Therefore, it is important to have a selection of practical methods for reconstruction of the triterpene 3β-hydroxy-4,4-dimethyl system.

The classic procedure[4] for terpene → steroid transformation has been used, for example, for preparing 14α-methyl steroids[5] which might arise from a defect in the normal biosynthesis of cholesterol from squalene *via* lanosterol.[6,7] One of the early attempts to improve upon the method of Voser and colleagues for converting triterpene A rings to steroid 3-oxo-4-ene systems involved oxidizing the enol acetate of 3-oxo-14α-methyl-5α-A-norcholestane with perphthalic acid and adding methylmagnesium iodide to the rearranged product, 3-oxo-5-hydroxy-14α-methyl-5α-*A*-norcholestane, but the sequence proved impractical.[8] After our preliminary report of the present study,[9] three new methods for triterpene A-ring reconstruction were described. One has the advantage of not requiring a Grignard step,[10] another utilizes a "second-order" Beckmann cleavage,[11] and the third is based on the photochemical cleavage of a cyclopentyl nitrite.[12]

Discussion

Logical synthetic approaches to remove the 4,4-dimethyl substituents from the A ring of tetracyclic triterpenes would include a biosynthetic-type sequential elimination of the 30- and 31-methyl groups (i), or to expel either a 30- or 31-methyl group and then the

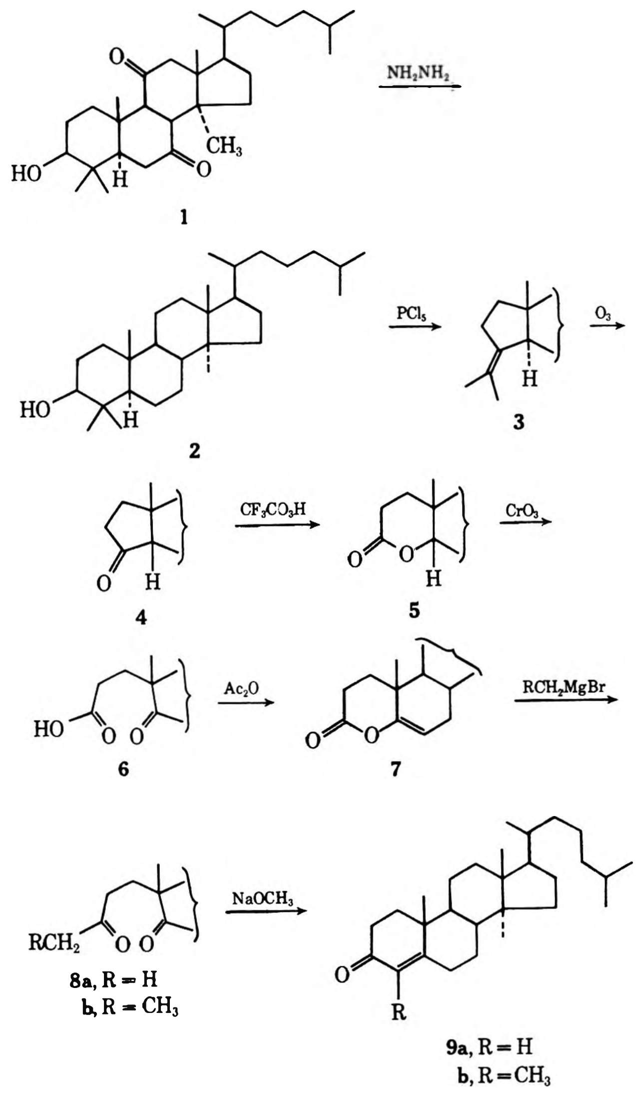


i ii iii

C-3 carbon (ii),[13] or to remove the isopropyl group (iii) followed by readdition of a carbon atom, as accomplished by Voser and colleagues.[4] A successful approach employing the initial two steps of the Voser method (iii) as applied to 3β-hydroxy-5α-lanostane (Scheme I) will be first discussed, and then preliminary

SCHEME I

CONVERSION OF TETRACYCLIC TRITERPENES TO STEROIDS



(1) For Part 65 refer to G. R. Pettit, P. Brown, F. Bruschweiler, and L. Houghton, *Chem. Commun.*, 1566 (1971).

(2) Abstracted in part from the dissertation of J. R. Dias, Arizona State University, 1970; NIH predoctoral fellow, 1968–1970.

(3) For example, see G. Ourisson, P. Crabbé, and O. Rodig, "Tetracyclic Triterpenes," E. Lederer, Ed., Holden-Day, San Francisco, Calif., 1964.

(4) W. Voser, H. Heusser, O. Jeger, and L. Ruzicka, *Helv. Chem. Acta*, **36**, 299 (1953).

(5) G. R. Pettit and P. Hofer, *ibid.*, **46**, 2142 (1963); *J. Chem. Soc.*, 4439 (1963).

(6) E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

(7) Since *in vivo* demethylation of the 14α-methyl group in lanosterol is activated by the 8,9 double bond, such a defect might arise from accidental reduction or premature isomerization of this double bond: P. Crabbé, *Rec. Chem. Progr.*, **20**, 180 (1959).

(8) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

(9) G. R. Pettit and J. R. Dias, *Can. J. Chem.*, **47**, 1091 (1969).

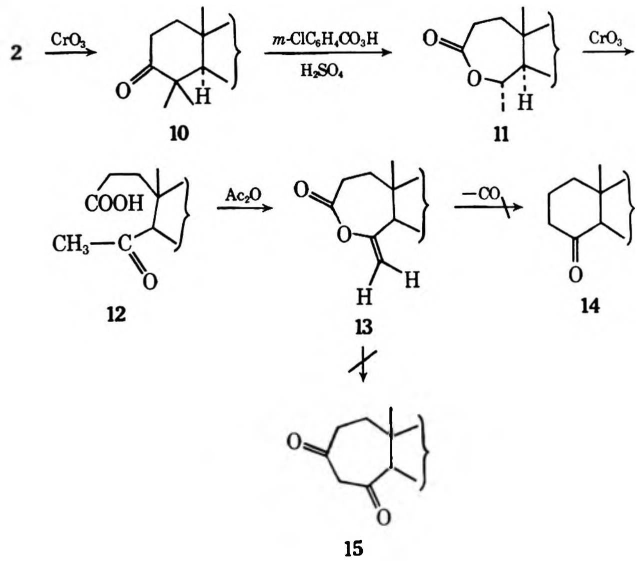
(10) R. Kazlauskas, J. Pinhey, J. Simes, and T. Watson, *Chem. Commun.*, 945 (1969).

(11) C. W. Shoppee, N. W. Hughes, R. E. Lack, and J. T. Pinhey, *J. Chem. Soc. C*, 1443 (1970).

(12) D. H. R. Barton and D. Kumari, *Justus Liebigs Ann. Chem.*, **737**, 108 (1970).

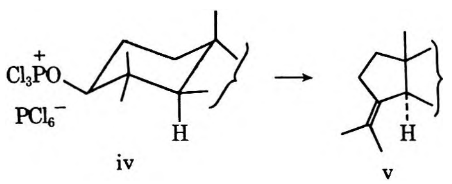
(13) The method used by the authors in footnote 10 embodies a combination of i and ii.

SCHEME II
ATTEMPTED CONVERSION OF TETRACYCLIC TRITERPENES TO STEROIDS



attempts to achieve this transformation *via* approach ii (Scheme II) will be described.

The key step in the Voser method for elimination of the 4,4-dimethyl groups utilizes a 1,3-Wagner–Meerwein rearrangement to transform the 3β-hydroxy-4,4-dimethyl system into an isopropylidene group (**2** to **3**). Stereoelectronic requirements make it imperative that the 3-hydroxy group has a β configuration so that the C–O bond is trans to the approaching 4,5 bond; otherwise, olefins resulting from hydrogen and methyl migrations are obtained (1,2-Nametkin rear-



rangement). When we allowed 1:1 mole ratios of phosphorus pentachloride to triterpene alcohol **2** to react (ice bath temperature, 1 hr, in benzene–toluene), only a 10% conversion of alcohol to olefin **3** occurred, whereas, with a 2:1 mole ratio, a 100% conversion was realized. Apparently the first mole of phosphorus pentachloride is rapidly consumed to form the tetrachlorophosphate of alcohol **2**, and the second mole forms a dimer ion pair, $PCl_6PCl_3{}^+O$-R, in which $PCl_3{}^+O$- is a better leaving group than PCl_4O- (iv → v).

Cleavage of the isopropylidene group by ozone (**3** to **4**) introduces a 3-oxo group adjacent to the 5α hydrogen. The strained trans A-nor B ring junction undergoes facile acid isomerization to the more stable cis A-nor B ring system concurrently with zinc–acetic acid reduction of the ozonide.[14a] The positive Cotton effect curve observed for ketone **4** unequivocally established the 5β configuration.[14b,c]

A method for Baeyer–Villiger oxidation of ketone **4** to lactone **5** was not realized using *m*-chloroperbenzoic acid, but was easily effected by pertrifluoroacetic acid.[15] Only minor amounts of 3-oxa-4-oxo-14α-methyl-5β-cholestane, an isomer of lactone **5**, were detected. As Baeyer–Villiger oxidation is well known to proceed with retention of configuration (of the migrating group), the lactones would be expected to bear cis A/B ring junctions. Prolonged contact with chromium trioxide in concentrated sulfuric acid or with excess Jones reagent in acetone was found most effective for transforming lactone **5** directly to keto acid **6**. Since the milder Jones reagent proved quite adequate for this oxidation, the former oxidizing system was not further investigated.[16] Isolation of keto acid **6** in crystalline form was difficult if lactone **5** was contaminated by the isomeric lactone, 3-oxa-4-oxo-14α-methyl-5β-cholestane.

Enol-lactone **7** was obtained by brief contact of keto acid **6** with an acetic anhydride–perchloric acid reagent.[17] The enol exhibited an ability in methanol (containing a trace of pyridine) to readily form the corresponding methyl ester.

Slowly adding a methyl or ethyl Grignard reagent to an ice-cold solution of enol-lactone **7** led to good yields of 1,5-diketone **8a** or **8b**, respectively. Without further purification, the ketone was cyclized using 1% sodium hydroxide to give enone **9a** or **9b**.[18] The experiments just summarized, leading to ketones **9a** and **9b**, complete (Scheme I) a new and useful reconstruction of the tetracyclic triterpene A ring to yield 3-oxo-4-ene-type steroids.

The unique loss (in 65% yields) of a 31-methyl group has been observed when perbenzoic acid promoted Baeyer–Villiger oxidation of 3-oxo-4,4-dimethyl-5α-cholestane was explored in the presence of mineral acid.[19] Our alternative approach to triterpene → steroid conversion was based on this interesting reaction. A 3:1 molar ratio of *m*-chloroperbenzoic acid to 3-oxo-5α-lanostane (**10**) in the presence of 2% sulfuric acid was found to consistently give 29% yields of 3-oxo-4-oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (**11**). Prolonged contact of lactone **11** with Jones reagent in acetone gave keto acid **12** in good yields, thereby further demonstrating the utility of this oxidizing system for direct conversion of lactones to keto acids. Brief contact of keto acid **12** with acetic anhydride–perchloric acid reagent gave enol-lactone **13** in which the double bond was exo, as demonstrated by the pair of doublets in a pmr spectrum at δ 5.0 and 4.6.

Since the thermodynamic favorability for transformation of enol-lactone **13** to ketone **14** or 1,3-diketone **15** was estimated to be −20 or −25 kcal, respectively, it was anticipated that either photolysis or thermolysis of enol-lactone **13** would effect one or both of these transformations. Further encouragement for transformation **13** to **14** was given by the observation of a $M^+ - 28$ peak in the mass spectrum of enol-lactone

(14) (a) J. F. Biellmann and G. Ourisson, *Bull. Soc. Chim. Fr.*, 348 (1960); (b) N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960); (c) G. R. Pettit, B. Green, and W. J. Bowyer, *ibid.*, **26**, 2870 (1961).

(15) W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.*, **77**, 2287 (1955).

(16) To our knowledge, this is the first example of one-step oxidation of a lactone directly to a keto acid.

(17) B. E. Edwards and P. Narasima Rao, *J. Org. Chem.*, **31**, 324 (1966).

(18) A new method for converting enol lactones to enones with dimethyl methylphosphonate and *n*-butyllithium has been reported: C. A. Henrick, E. Bohme, J. A. Edwards, and J. A. Fried, *J. Amer. Chem. Soc.*, **90**, 5926 (1968).

(19) J. S. E. Holker, W. R. Jones, and P. J. Ramm, *Chem. Commun.*, 435 (1965).

13. By comparison, no such fragment was observed in the mass spectrum of enol-lactone 7.

Photolysis of enol-lactone 13 in a quartz apparatus (carbon tetrachloride solution for 5 hr) gave a mixture with a distinct acid chloride odor. The product appeared to represent extensive chlorination of the steroid skeleton.[20]

Photolysis of enol-lactone 13 in tetrahydrofuran–ligroin (2:3) under nitrogen for 34 hr gave a yellow oil with a strong amine-like odor, and gave spectral data consistent with significant alteration of the olefin and ester functions. Such results combined with the consistently low yields of lactone 11[21] discouraged further exploration of this superficially plausible approach.

Experimental Section

All routine reagents and solvents were Baker analyzed, Mallinckrodt AR, or Matheson Coleman and Bell. Jones reagent corresponds to a solution of chromium trioxide (8 *N* or 2.67 *M*) in aqueous sulfuric acid (4 *M*).[22] Acetic anhydride–perchloric acid reagent was prepared by adding 72% perchloric acid (0.05 ml) to ethyl acetate (50 ml), and 10 ml of this solution was added to ethyl acetate (30 ml) containing acetic anhydride (4.8 ml). More ethyl acetate was added to reach a final volume of 50 ml.[17] The Grignard reagents (approximately 0.5 *M*) were prepared in ether under a nitrogen atmosphere. Organic solutions were dried over anhydrous sodium sulfate and concentrated on a rotating evaporator.

Activated alumina (basic and acid washed, Merck, Rahway) and silica gel (E. Merck, Darmstadt, Germany, 0.2–0.5 mm) were used for column chromatography. Silica gel HF_{254} (E. Merck) was used for analytical and preparative thin layer chromatography (tlc). The chromatograms were routinely prepared with benzene–ethyl acetate (5:1) and developed with iodine vapor or by heating with 2% ceric sulfate in 2 *N* sulfuric acid. The preparative thin layer plates were viewed under ultraviolet light.

Elemental microanalysis was performed by the laboratory of Dr. A. Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach Uber Engelskirchen, Fritz-Pregl-Strasse, West Germany. All samples submitted for analysis were colorless and exhibited a single spot on a tlc. Melting points were determined on a Kofler melting point apparatus. All spectra were recorded by J. R. D. or Miss K. Reimer as follows: infrared, Beckman IR-12 (potassium bromide or chloroform solution); rotatory dispersion (RD), Jasco (ORD/UV, in dioxane at room temperature); pmr, Varian A-60 (60 MHz, in deuteriochloroform, TMS internal standard). The mass spectra were determined (by E. Bebee and R. Scott) using an Atlas CH-4B (low resolution) or Atlas SM-1B (high resolution) instrument equipped with molecular beam inlet system.

3-Isopropylidene-14α-methyl-*A*-nor-5α-cholestane (3).[8]—To a cold (ice bath) solution of alcohol 2 (4.8 g, 0.011 mol) in benzene (700 ml)–toluene (250 ml) was added phosphorus pentachloride (4.8 g, 0.024 mol, in 80 ml of methylene chloride). After the clear, cold mixture (5–10°) was stirred for 55 min, saturated sodium carbonate (50 ml) and water (200 ml) were added, and stirring was continued for another 0.5 hr. The upper phase was evaporated to dryness. The yellow residue in carbon tetrachloride was chromatographed on a column of basic alumina (200 g) to yield upon elution with ligroin 2.82 g of needles: mp 110–113°; ν_{max} (0.1 *M* in $CHCl_3$) 2970, 1480, and 1390 K; pmr δ 2.2 (broad, 3 p, C-2 and C-5), 1.7 and 1.6 Hz (broad singlets 3p each, isopropylidene), 0.93 (s, 19-methyl), 0.83 (s, 14- and 18-methyls), and 0.77 (d, J = 7 Hz, C-21, C-26, and C-27 methyls).

(20) For another example of unanticipated chlorination by photolysis in carbon tetrachloride solution, see R. Breslow and S. Baldwin, *J. Amer. Chem. Soc.*, **92**, 733 (1970).

(21) More recently we learned that *m*-perchlorobenzoic acid is much less effective than perbenzoic acid: J. S. E. Holker, W. R. Jones, and P. J. Ramm, *J. Chem. Soc. C*, 357 (1969). Thus, the Holker procedure with perbenzoic acid is recommended for obtaining lactone **11**.

(22) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

3-Oxo-14α-methyl-*A*-nor-5β-cholestane (4).[8]—Olefin 3 (21.2 g) in chloroform (3.6 l.) was cooled to *ca.* −65° (Dry Ice–acetone bath). A slow stream of ozone in oxygen was passed through the reaction mixture until a deep blue color persisted for 30 min. Oxygen was passed into the solution until the blue color vanished. Zinc dust (20 g) and glacial acetic acid were added (800 ml), and the mixture was stirred 2 hr. The chloroform layer was washed with water (3 l. in two aliquots) and evaporated to dryness. The acetic-smelling, yellow oil was dissolved in benzene and chromatographed on a column of alumina (600 g of acid-washed grade). Elution with benzene–petroleum ether (1:4) yielded 10 g (50%) of colorless solid. Recrystallization from ethyl acetate gave an analytical sample: mp 126.5–127.5° (lath shaped crystals); ν_{max} (0.1 *M* in $CHCl_3$) 2970, 1740 (str C=O stretch), 1475, 1390, and 1240 K; pmr δ 2.2 (m, C-2 and C-5), 1.3 (s), 0.92 (s), 0.82 (s), and 0.72 (s); RD in chloroform (*c* 0.196), $[\alpha]_{589}$ +126°, $[\alpha]_{500}$ +175°, $[\alpha]$ +385°, $[\alpha]_{350}$ +740°, $[\alpha]_{314}$ +2430° (peak), $[\alpha]_{306}$ +1900° (shoulder), $[\alpha]_{292}$ 0.00°, $[\alpha]_{275}$ −1330° (trough), and $[\alpha]_{250}$ −4670°; mass spectrum 231 (100%), M^+ − 15 (1.5%), and M^+ 386 (9%).

Anal. Calcd for $C_{27}H_{46}O$ (386): C, 83.87; H, 11.99; O, 4.14. Found: C, 83.82; H, 11.75; O, 4.43.

3-Oxo-4-oxa-14α-methyl-5β-cholestane (5).—To ketone 4 (5.24 g, 0.0135 mol) in methylene chloride (*ca.* 30 ml) was added pertrifluoroacetic acid (13 ml from 8.47 ml of trifluoroacetic anhydride, 1.37 ml of 90% hydrogen peroxide, and 10.5 ml of methylene chloride).[15] After remaining in a refrigerator 24 hr, the amber mixture was heated at reflux for 2 min. Chloroform (50 ml) was added to the cooled mixture, and washing was performed with water (300 ml in three aliquots), 1 *M* sodium carbonate (50 ml), and saturated sodium chloride (25 ml). The residue on column chromatography through silica gel (100 g) and elution with benzene–ethyl acetate (5:1) yielded 4.24 g (78%) of solid. Recrystallization from methanol gave an analytical sample as plates: mp 172–177° (plates to needles at 163°); ν_{max} (0.1 *M* in $CHCl_3$) 2970, 1730 (str C=O stretch), 1470, 1380, and 1270 K (med C–O stretch); pmr δ 4.2 (1p, C-5 proton), 2.5 (quartet, 2p, C-2 protons), 1.0 (s, 19-methyl), 0.87 (d, J = 6 Hz, 21-, 26- and 27-methyls), and 0.82 (s, 14 α and 18-methyls); mass spectrum M^+ 402.

Anal. Calcd for $C_{27}H_{46}O_2$ (402): C, 80.54; H, 11.52; O, 7.95. Found: C, 80.53; H, 11.78; O, 8.20.

5-Oxo-14α-methyl-3,5-seco-*A*-norcholestane-3-carboxylic Acid (6).—To lactone 5 (0.33 g, 0.82 mmol) in aqueous acetone (50 ml containing 2 ml of water) was added Jones reagent (0.40 ml). After magnetically stirring for 12 hr 2-propanol (5.0 ml) was added to the yellow solution containing a green precipitate; the yellow color was discharged. The acetone was concentrated and the green residue extracted with ether (28 ml in four aliquots). The ethereal solution was extracted with 1 *N* potassium hydroxide (45 ml in five aliquots). To the cool basic solution of the potassium salt was added concentrated hydrochloric acid (5.0 ml): yield, 0.32 g of colorless solid. The solid was triturated with acetone (*ca.* 5 ml), and evaporation of the acetone yielded 0.31 g (91%) of needles, mp 115–120°. Recrystallization from ether–ligroin gave 0.23 g of needles, mp 121.4–122.8°, and 0.08 g of cruder material. The pure keto acid gave the following spectra: ν_{max} (KBr) 3400, (broad CO_2–H stretch, wk), 3100 (broad CO_2–H hydrogen-bonded stretch, med), 2970, 1710 (broad, str C=O stretch, shoulder at 1650), 1460, 1380, and 1225 K (med C–O stretch); pmr δ 10.0 (s, 1p, removed by D_2O), 2.3 (m, 4p, C-2 and C-5 protons), 1.1 (s, 19-methyl), 0.88 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.88 (s, 14 and 18 methyls); RD (*c* 0.521), $[\alpha]_{589}$ +53°, $[\alpha]_{500}$ +77°, $[\alpha]_{400}$ +135°, $[\alpha]_{350}$ +213°, $[\alpha]_{314}$ +380° (peak), $[\alpha]_{290}$ +246°, $[\alpha]_{271}$ +146° (trough), and $[\alpha]_{250}$ +295°; mass spectrum 346 (100%), M^+ − 18 (38%), M^+ − 15 (24%), and M^+ 418 (13%).

Anal. Calcd for $C_{27}H_{46}O_3$ (346): C, 77.46; H, 11.07; O, 11.46. Found: C, 77.54; H, 11.01; O, 11.34.

3-Oxo-4-oxa-14α-methylcholest-4-ene (7).—A solution of keto acid 6 (0.13 g) in acetic anhydride perchloric acid reagent (20 ml) was allowed to stand at room temperature for 5 min. Saturated sodium bicarbonate (20 ml) was added and stirring continued for 1.5 hr. The ethyl acetate phase was evaporated to dryness. The 0.13 g residue of yellow needles was dissolved in ethyl acetate and passed through Celite. Recrystallization from methanol afforded 74 mg of colorless needles, mp 124.2–125.2°. Preparative thin layer separation of mother liquor residue led to an additional 19 mg (total yield 74%). The following spectra were obtained for the pure product: ν_{max} (KBr) 2970, 1745 (str C=O stretch), 1675 (med C=C stretch), 1460, 1390, and 1260 K; pmr δ 5.3 (1p, C-5 protons), 2.3 (q, 2p, C-2 protons), 2.0 (m, 2p, C-7 protons), 1.2 (s, 19-methyl), 0.90 (d, J = 4 Hz, 21-, 26-, and 27-methyls), and 0.87 (s, 14α- and 18-methyls); λ_{max}^{EtOH} 205 (log ϵ 3.7); mass spectrum M^+ 400 (100%).

Anal. Calcd for $C_{27}H_{44}O_2$ (400): C, 80.94; H, 11.07; O, 7.99. Found: C, 81.22; H, 10.84; O, 7.94.

3-Oxo-14α-methylcholest-4-ene (9a).—Enol-lactone **7** (0.25 g) was dissolved in benzene (10 ml)–ether (10 ml) and cooled (ice salt bath). A clear solution of methylmagnesium iodide was slowly added to the stirred reaction mixture (under nitrogen). Progress of the reaction was monitored by tlc. After 3 hr, the tlc barely detected enol-lactone **7** but showed an intense lower R_f spot corresponding to the product. Hydrochloric acid (5 ml) and ether (10 ml) were added, and the ethereal phase was washed with saturated sodium bicarbonate (10 ml), sodium thiosulfate solution, water, and saturated sodium chloride. Solvent was evaporated and to the residue in methanol (20 ml) was added 10% sodium hydroxide (2.0 ml). After heating (steam bath) for 1.5 hr the methanolic solution was poured into water (40 ml), saturated sodium chloride (40 ml) was added, and the aqueous mixture was extracted with ether (50 ml in three aliquots). Evaporation of solvent gave a yellow solid which upon preparative thin layer chromatography (5:1 benzene–ethyl acetate), yielded 0.145 g (58%) of colorless plates: mp 113.5–115.0°;[8] λ_{max}^{EtOH} 242 (log ϵ 4.19); ν_{max} (0.1 M in $CHCl_3$) 2960, 1670 (conjugated C=O), 1620 (med C=C stretch), 1470, 1390, 1240, and 800 K; pmr δ 5.7 (s, 1p, C-4 proton), 2.3 (m, 4p, C-2 and C-6 protons), 1.2 (s, 3p, 19-methyl), 0.88 (d, J = 6 Hz, 21-, 26-, and 27-protons) and 0.87. (s, 14α- and 18-methyls); mass spectrum $M^+ - 15$ (34%) and M^+ 398 (100%).

Anal. Calcd for $C_{28}H_{46}O$ (398): C, 84.35; H, 11.63; O, 4.02. Found: C, 84.19; H, 11.83; O, 3.98.

3-Oxo-4,14α-dimethylcholest-4-ene (9b).—Ethylmagnesium bromide was slowly added to a solution of enol-lactone **7** (0.14 g) in benzene (5 ml)–ether (5 ml). The reaction mixture was cooled (ice–salt bath), stirred under nitrogen, and monitored by tlc. After 1.5 hr, hydrochloric acid (5 ml) was added and the mixture allowed to stand at room temperature overnight. Solvent was evaporated from the ethereal layer. Methanol (10 ml) and 10% aqueous sodium hydroxide (1 ml) was added to the solid residue and the solution was heated on a steam bath 2 hr. The reaction mixture was diluted with water (40 ml) and extracted with ether (40 ml in four aliquots). The combined ether extract was washed with saturated sodium chloride solution and evaporated, and the solid residue was subjected to preparative thin layer chromatography using benzene–ethyl acetate (5:1) as the mobile phase: yield 94 mg (65%) of prisms for elution of the higher R_f zone with ether; mp 120.5–124.0°; λ_{max}^{EtOH} 251 (log ϵ 4.19); ν_{max} (KBr) 2970, 1660 (conjugated C=O stretch), 1600 (wk C=C stretch), 1460, 1370, and 1300 K; pmr δ 2.5 (m, 4p, C-2 and C-6 protons), 1.8 (s, 3p, 4-methyl), 1.2 (s, 19-methyl), 0.88 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.87 (s, 14α- and 18-methyls); mass spectrum M^+ 412.3724 (100%) (Beynon calcd mass 412.3705) and $M^+ - 15$ (35%).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72; O, 3.88. Found: C, 84.37; H, 11.60; O, 4.03.

Elution of the lower R_f zone by ether led to 9 mg of needles, mp 198–202°, believed to be 3,3-diethyl-4-oxa-14α-methyl-5α-hydroxycholestane: ν_{max} (KBr) 3400 (broad), 2950, 1450, 1360, and 1015 K; mass spectrum 309 (100%), $M^+ - 32$ (16%) and $M^+ - 18$ (1.2%).

3-Oxo-5α-lanostane (10).—Jones reagent (23.0 ml) was added dropwise to alcohol **2** (20.0 g) dissolved in acetone (1.4 l.) containing enough ether (or tetrahydrofuran) to achieve solution. After standing for 10 min, 2-propanol (100 ml) was added to discharge the orange color. The green precipitate was collected and washed well with acetone. The acetone solution from the combined filtrates was concentrated and the residue in benzene was passed through basic alumina. The benzene solution was concentrated and the residue upon crystallization from ligroin afforded 10.3 g (98%) of colorless prisms: mp 131.5–132.0° (lit.[23] mp 127–128°); ν_{max} (KBr) 2970, 1700, 1455 (med), and 1370 K (med); pmr δ 2.4 (m, 2p, C-2), 1.1 (s, 19-, 31-, and 32-methyls), 0.87 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.82 (s, 14α- and 18-methyls); pmr (benzene) 2.3 (m) 1.1 (s, 19-methyl), 1.0 and 1.0 (s, 4α-and 4β-methyls), 0.90 (s), 0.87 (s), and 0.82 (s); RD in cyclohexane (c 0.56), $[\alpha]_{600}$ +18°, $[\alpha]_{589}$ +19°, $[\alpha]_{450}$ +36°, $[\alpha]_{380}$ +44° (hump), $[\alpha]_{350}$ +36°, $[\alpha]_{336}$ 0.0°, $[\alpha]_{324}$ + 17° (trough), $[\alpha]_{320}$ 0.0°, $[\alpha]_{300}$ +210°, and $[\alpha]_{280}$ +310°.[24]

3-Oxo-4-oxa-4α,14α-dimethyl-*A*-homo-5α-cholestane (11).—A cold (ice bath) solution prepared from ketone **10** (8.58 g, 0.02 mol), m-chloroperbenzoic acid (15.2 g, 0.06 M, 75% assay), chloroform (50 ml), glacial acetic acid (50 ml), and concentrated sulfuric acid (2 ml) was allowed to stand at room temperature in the dark for 5 days.[21] The amber solution was decanted from the precipitated m-chlorobenzoic acid and added to water (350 ml)–ether (100 ml). The aqueous layer was separated and extracted with ether (100 ml in three aliquots). The combined ether extract was washed with 1.5 M sodium hydrogen sulfite (900 ml in five aliquots) and saturated sodium bicarbonate (400 ml in four aliquots) which removed most of the brown color, and the emulsion was eliminated by filtration. The yellow etheral solution was dried and concentrated to dryness. Recrystallization of the yellow residue from ethyl acetate yielded 2.5 g (29%) of colorless needles: mp 185.5–186.2°; ν_{max} (0.1 M in $CHCl_3$) 2970 and 1730 K; pmr δ 4.5 (m, 1p, 4β-H), 2.6 (m, (m, 2p, C-2), 1.3 (d, J = 6.5 Hz, 4α-methyl) 1.0 (s, 19-methyl), 0.92 (s), and 0.80 (s); RD in chloroform (c 1.75), $[\alpha]_{650}$ +12°, $[\alpha]_{589}$ +15°, $[\alpha]_{500}$ +24°, $[\alpha]_{400}$ +42°, $[\alpha]_{300}$ +92°, $[\alpha]_{264}$ +114° (peak), $[\alpha]_{250}$ +71°, and $[\alpha]_{240}$ 0.0°; mass spectrum M^+ 430 (100%).

Anal. Calcd for $C_{29}H_{50}O_2$ (430): C, 80.87; H, 11.70; O, 7.43. Found: C, 80.68; H, 11.83; O, 7.57.

4-Oxo-4,14α-dimethyl-3,4-seco-5α-cholestane-3-carboxylic Acid (12).—A solution of lactone **11** (0.12 g) in acetone (26 ml)–water (1 ml)–Jones' reagent (0.35 ml) was stirred for 15 hr. To the yellow mixture was added 2-propanol (5 ml). The green precipitate was collected and washed well with hot acetone and the filtrate evaporated to dryness. The residue was purified by preparative thin layer chromatography using benzene–ethyl acetate (5:1) as the mobile phase. Elution of the uppermost band with ether yielded 34 mg (27%) of recovered lactone as needles, mg 185.0–186.5°, and elution of the lower band with ether yielded 92 mg (72%) of keto acid as needles: mp 157.5–160.5°; ν_{max} (KBr) 3450 (broad shoulder appears at 3250) 2970, 1730 (str ketone C=O stretch), 1690 (str acid C=O stretch), and 1170 (med C–O stretch) K; pmr δ 9.3 (broad, 1p, removed by D_2O), 2.3 (m, 3p, C-2 and C-5), 2.2 (s, 3p, 4α-methyl), 1.1 (s, 19-methyl), 0.87 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.82 (s, 14α- and 18-methyls); mass spectrum 345 (100%), $M^+ - 18$ (82%), $M^+ - 15$ (88%) and M^+ 446 (59%).

Anal. Calcd for $C_{29}H_{50}O_3$ (446): C, 77.97; H, 11.28; O, 10.74. Found: C, 77.80; H, 11.28; O, 10.91.

3-Oxo-4-oxa-4a-methylidene-14α-methyl-*A*-homo-5α-cholestane (13).—After 15 min a solution of keto acid **12** (80 mg) in acetic anhydride–perchloric acid regent (10 ml) was treated and stirred with 1 M sodium carbonate solution (20 ml) for 40 min. The organic phase was evaporated to dryness. Separation of the residue by preparative thin layer chromatography, using benzene–ethyl acetate (10:1) as the mobile phase, and elution of the upper band with ether yielded 40 mg (52%) of prisms: mp 152–156°; ν_{max} (KBr) 2930, 1735, 1630, and 880 (2,2-disubstituted vinyl group), and 1100 K; pmr δ 5.0 (d, J = 1.5 Hz, 1p, 4a H cis to the ester), 4.6 (d, J = 1.5 Hz, 1p, 4a H trans to the ester), 2.5 (m, 2p, C-2), 1.0 (s, 19-methyl), 0.87 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.82 (s, 14α- and 18-methyls); RD in chloroform (c 0.159), $[\alpha]_{589}$ +118°, $[\alpha]_{500}$ +190°, $[\alpha]_{400}$ +330°, $[\alpha]_{350}$ +510°, $[\alpha]_{300}$ + 910°, $[\alpha]_{250}$ +3320°, $[\alpha]_{236}$ +4660° (peak), $[\alpha]_{230}$ +4010°, and $[\alpha]_{224}$ +2330°; mass spectrum 206 (100%), $M^+ - 28$ (8%) and M^+ 428 (35%).

Anal. Calcd for $C_{29}H_{48}O_2$ (428): C, 81.25; H, 11.29; O, 7.46. Found: C, 81.15; H, 11.24; O, 7.61.

Registry No.—**3**, 21857-87-4; **4**, 21857-88-5; **5**, 21857-89-6; **6**, 21857-90-9; **7**, 21857-91-0; **9a**, 21857-92-1; **9b**, 33495-90-8; **10**, 4639-29-6; **11**, 31656-58-3; **12**, 33495-93-1; **13**, 33487-95-5.

(23) J. L. Simonson and W. C. J. Ross, "The Terpenes," Vol. IV, Cambridge University Press, New York, N. Y., 1957, p 68.

(24) C. Djerassi, O. Halpern, and B. Riniker, *J Amer. Chem. Soc.*, **80**, 4001 (1958).

General Methods of Alkaloid Synthesis. A New Approach to the Synthesis of the 5,10b-Ethanophenanthridine *Amaryllidaceae* Alkaloids. A Stereoselective Total Synthesis of *dl*-Elwesine (Dihydrocrinine)[1]

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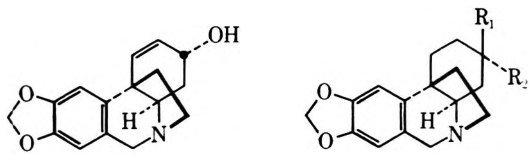
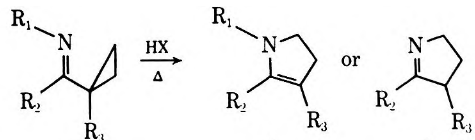
An efficient eight-stage stereoselective total synthesis of the *Amaryllidaceae* alkaloid elwesine (**2a**) and its C-3 epimer is portrayed. Key steps in this synthesis involved the methyl vinyl ketone annelation of a Δ^2-pyrroline to achieve the basic *cis*-octahydroindolone skeleton and the acid-catalyzed thermal rearrangement of cyclopropyl imines as a general device for the elaboration of the required Δ^2-pyrrolines.

The *Amaryllidaceae* family has been known for some time now to be a rich source of complex and intriguing alkaloids. The structural diversity which characterizes these interesting bases is quite remarkable and necessitates their classification into several skeletally homogeneous subgroups. One of these includes those alkaloids which incorporate the 5,10b-ethanophenanthridine nucleus and is usually referred to as the crinine group after the parent natural product **1**. A recent review[4] of these alkaloids lists 35 closely related members of this family, and from a careful inspection of their structures we conceived of a number of potentially general synthetic approaches which, perhaps with only minor modification, could be employed in the synthesis of selected members of this family.[5] We selected for our initial investigation elwesine (dihydrocrinine) **2a**, a minor alkaloid of *Galanthus elwesii* Hook. f.[6]



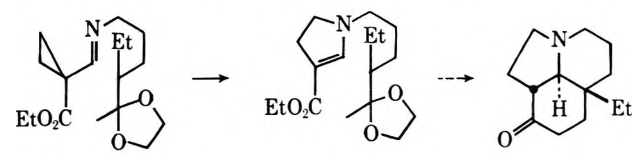
1 **2a**, $R_1 = H; R_2 = OH$ **b**, $R_1 = OH; R_2 = H$

The method of approach we decided to investigate first was a logical extension of two fundamental and increasingly important general principles of alkaloid synthesis which we, and others, have been developing. The first of these exploits, the acid-catalyzed, thermally induced rearrangement of cyclopropyl imines as a useful general approach to Δ^1- or Δ^2-pyrrolines (**3** → **4** or **5**), provided simple efficient syntheses of the pyridine alkaloids myosmine **6** and apoferrorosamine **7**[7] and constituted a key step in the synthesis of the hydrolulolidine *Aspidosperma* alkaloid intermediate **8**[8]



3 **4** **5**

6 **7**



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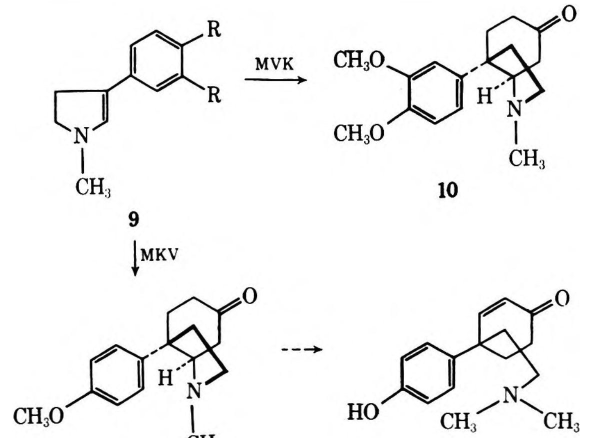
as well as the *Aizoaceae* alkaloid mesembrine **10**[9a,b] and the *Sceletium* base joubertiamine **11**.[10]

Also of importance in the synthesis of the latter two substances was the application of the methyl vinyl ketone (MVK) annelation to an endocyclic enamine (*e.g.*, **9** to **10**), a reaction which has also been employed



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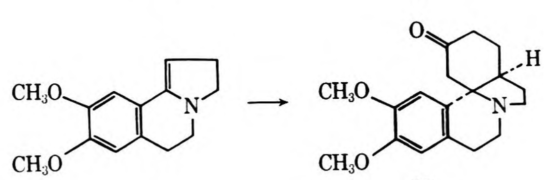

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(1) Preliminary communication: R. V. Stevens and L. E. DuPree, Jr., *Chem. Commun.*, 1585 (1970).

(2) A. P. Sloan Fellow, 1969–1971.

(3) National Science Foundation Predoctoral Fellow, 1968–present.

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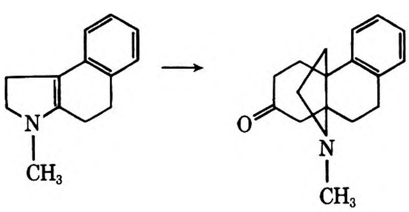
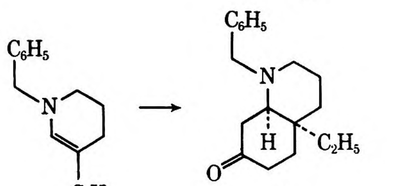
(9) (a) R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5580 (1968); (b) S. L. Keely, Jr., and F. C. Tahk, *ibid.*, **90**, 5584 (1968); (c) T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).

(10) R. V. Stevens and J. Lai, *J. Org. Chem.*, in press.

to advantage in the synthesis of the *Erythrina*[11] and hasubanan[12] skeletons, 12 and 13, respectively, as well as providing an alternative approach to the useful aspidospermine precursor **14**.[13] The rather similar



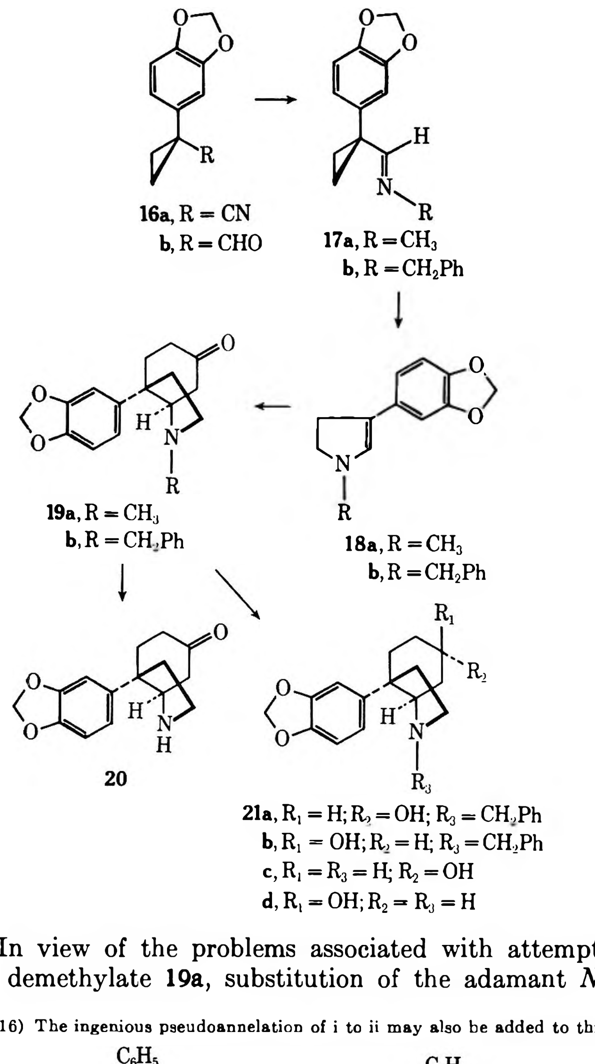
13



14

structural features of mesembrine (**10**) and various crinine-type alkaloids such as elwesine (**2a**) had, from the very beginning of our investigation,[14] captured our imagination and prompted additional study to more clearly define the utility of these two principles in the execution of alkaloid synthesis.

Thus, the now familiar approach to the synthesis of endocyclic enamines **18a** and **18b** was investigated and not found lacking. Lithium amide induced cyclopropanation of piperonyl cyanide with ethylene dibromide proceeded smoothly in glyme at room temperature in 65–75% yield. This result is in direct contrast to the employment of other strong bases such as sodium amide or sodium hydride, which gave at best very modest yields of **16a**, and is in agreement with our previous studies[9a] concerning the beneficial effect of generating the more covalent lithium salts in electronically destabilized carbanions of this type. Conversion of **16a** to the corresponding aldehyde **16b** was achieved in 75–85% yield by selective reduction with diisobutylaluminum hydride (DIBAL).[9b,13] Virtually complete conversion of **16b** to the *N*-methylimine **17a** was accomplished by exposure to a saturated benzene solution of methylamine in the presence of anhydrous magnesium sulfate. Rearrangement of this cyclopropyl imine **17a** to pyrroline **18a** was catalyzed by anhydrous HBr at 140–150°, providing another example of the utility of this process. By employing the same procedure developed previously in the synthesis of mesembrine[9a] (*cf.* **9** to **10**), a 42% yield of analytically pure *cis*-octahydroindole **19a** was obtained from the methyl vinyl ketone annelation of **18a**.[15] The identity of the highly diagnostic pmr spectrum of **19a** with that of mesembrine **10**[9a] in the significant aliphatic region confirmed the structural and stereochemical assignments. The cis stereochemistry observed in this annelation is in consonance with previously defined stereochemical arguments[9a] and is corroborated further by an increasing number of examples involving other structurally diverse endocyclic enamines (*cf.* **10–14**).[16] Attempts to demethylate **19a** to **20** by a variety of standard techniques were uniformly unsuccessful and in most instances were complicated by simple β elimination.[17] However, these results proved to be of value in the subsequent design and successful execution of the synthesis.



16a, R = CN; **b**, R = CHO

17a, R = CH_3; **b**, R = CH_2Ph

18a, R = CH_3; **b**, R = CH_2Ph

19a, R = CH_3; **b**, R = CH_2Ph

20

21a, R_1 = H; R_2 = OH; R_3 = CH_2Ph
b, R_1 = OH; R_2 = H; R_3 = CH_2Ph
c, R_1 = R_3 = H; R_2 = OH
d, R_1 = OH; R_2 = R_3 = H

In view of the problems associated with attempts to demethylate **19a**, substitution of the adamant *N*-

(11) R. V. Stevens and M. P. Wentland, *Chem. Commun.*, 1104 (1968).

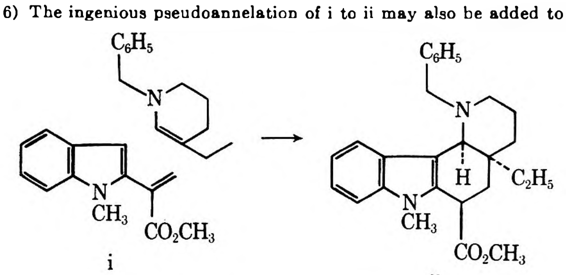
(12) D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, **35**, 4122 (1970); S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron*, **26**, 4729 (1970).

(13) R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *Chem. Commun.*, 1104 (1968).

(14) R. V. Stevens and M. C. Ellis, *Tetrahedron Lett.*, 5185 (1967).

(15) In view of subsequent difficulties encountered in attempts to demethylate **19a**, no attempt was made to maximize its yield or that of its precursor, pyrroline **18a**.

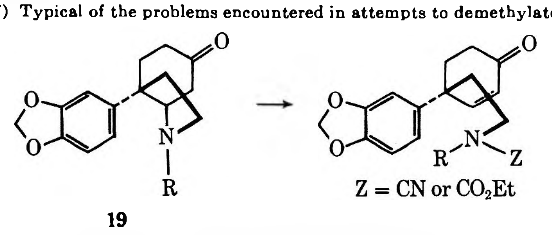
(16) The ingenious pseudoannelation of i to ii may also be added to this



i ii

ever-growing list: F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).

(17) Typical of the problems encountered in attempts to demethylate **19a**



19

Z = CN or CO_2Et

or debenzylate **19b** by a variety of methods is their fate upon exposure to cyanogen bromide or ethyl chloroformate. In each case simple β elimination predominated.

methyl function by the more labile benzyl group attracted our attention as a logical solution to this problem and required only a slight variation of the scheme and no compromise whatever in efficiency. Thus, aldehyde **16b** could be transformed to aldimine **17b** in 72–92% yield by simply stirring a benzene solution of the reactants (excess benzylamine) with anhydrous calcium chloride for 2–3 days. Considerable resinification accompanied the rearrangement of this aldimine when HBr was employed as the acidic catalyst. However, thermal rearrangement to pyrroline **18b** proceeded smoothly in 72–80% yield by employing ammonium chloride. We were rather surprised and annoyed to observe that the methyl vinyl ketone annelation of this intermediate produced only complex unstable mixtures containing little if any of the desired product, since the same procedure had been so successfully employed with other closely related substances. However, this frustration was only temporary when it was discovered that 56–67% yields of pure crystalline *cis*-octahydroindole **19b** could be secured by prior conversion of **18b** to its hydrochloride salt and admixture to a solution of methyl vinyl ketone in acetonitrile.[9c]

With the obtention of **19b** we were now in a position to affect its debenzylation. However, the facile β eliminations which plagued our efforts in the *N*-methyl series were no less conspicuous in the present case.[17] Presented with these difficulties, various alternatives were considered which involved modification of the menacing carbonyl function. Since this particular oxidation state is not that which is found in any of the naturally occurring crinine-type bases and elwesine (**2a**) in particular, the most obvious solution to this problem would be to reduce **19b** to the desired alcohol **21a**.[18]

Sodium borohydride reduction of **19b** yielded a 3:1 mixture of two epimeric alcohols which were readily separated by preparative layer chromatography. Catalytic debenzylation[19] of the major isomer (**21b**, *vide infra*, see discussion below) yielded **21d** (100%). Pictet–Spengler cyclization under carefully defined conditions[5c,21b] provided *dl*-3-*epi*-elwesine (**2b**)[20] in 65% yield.

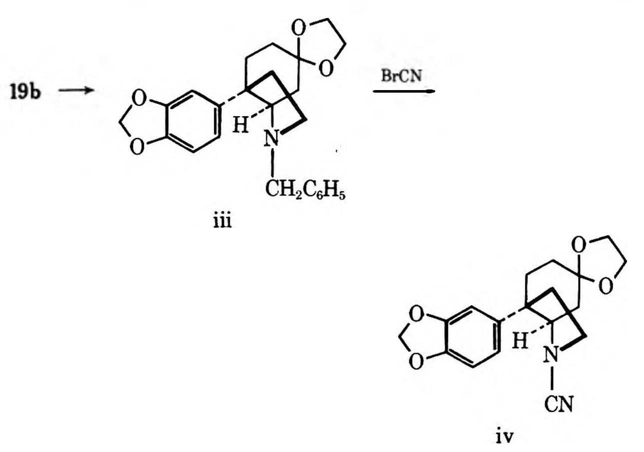
The unfavorable 3:1 product distribution of epimeric alcohols **21b** and **21a** obviously required adjustment if a truly effective synthesis of elwesine was to be achieved. This was accomplished by reducing ketone **19b** catalytically in isopropyl alcohol as solvent and 10% Pd/C catalyst. This provided a more than satisfactory ratio of 8:1 in favor of the desired alcohol **21a**. Subsequent debenzylation (100%) and Pictet–Spengler cyclization provided totally synthetic racemic elwesine **2a**[20] in 61% yield. Completion of this work establishes the validity and efficiency of the synthetic principles involved.

Spectral Data.—During the course of this investigation it became increasingly clear that we were dealing with a very subtle but important conformational equilibrium in our bicyclic intermediates **19** and **21**. The surprising revelation[21] that mesembrine (**10** = **22a**), both epimeric mesembranols (**21e** and **21f**), and their corresponding acetates prefer (in $CDCl_3$ or C_6H_6 solvent) a conformation in which the bulky aryl moiety occupies an axial configuration prompted a similar analysis in the present series. Our results are in consonance with these previous observations, and we present additional evidence which supports this striking conclusion.

The infrared (ir) spectrum of **21a** in tetrachloroethylene exhibits a free hydroxyl stretching absorption at 3620 cm^{-1} (sharp) and a broad hydrogen-bonded band at approximately 3500 cm^{-1} which disappears in solutions ≤ 0.025 *M*, thus demonstrating the intermolecular nature of this hydrogen bond. By contrast, **21b** has but one hydroxyl stretching band at 3325 cm^{-1} typical of a strongly hydrogen-bonded hydroxyl. Furthermore, this absorption persists and no free hydroxyl band appears at concentrations as low as 0.0083 *M*, a fact which strongly suggests intramolecular hydrogen bonding. Conclusive evidence to support this conclusion was obtained by the method of successive dilution.[22]

The ir spectra of **21c** and **21d** are very similar to those of their precursors **21a** and **21b**, respectively. Compound **21c** exhibits a sharp free OH stretching band at 3620 cm^{-1} and a broad absorption at 3360 cm^{-1}. This broad absorption can be attributed to a hydrogen-bonded hydroxyl and/or the NH stretching band of the secondary amine. Epimeric alcohol **21d**, however, shows only a broad band centered at 3340 cm^{-1}. No free OH band appears at concentrations as low as 0.0125 *M*. The successive dilution technique was not applied in this case, as the contribution of the NH band could not be determined. However, the data are consistent with intramolecular hydrogen bonding in compound **21d**. When coupled with the

(18) Alternatively, the marked tendency for these compounds to β eliminate could be suppressed by conversion of **19b** to the corresponding ketal iii.



iv

This was achieved with partially gratifying consequences, since exposure of this substance to cyanogen bromide finally resulted in removal of the benzyl function. However, subsequent transformation of iv into useful synthetic intermediates proved to be a rather more arducus task than we had envisaged.

(19) According to the procedure of G. Büchi, D. Coffen, K. Korsis, P. Sonnet, and F. Ziegler, *J. Amer. Chem. Soc.*, **88**, 3099 (1966).

(20) The structural and stereochemical assignments were confirmed by comparison of solution infrared spectra and tlc behavior with those of an authentic optically active specimen and by oxidation to the known racemic ketone, mp 171.5–174.5° (lit.[5e] mp 171–173°). We are most grateful to Professor W. C. Wildman for providing us with these authentic samples.

(21) (a) P. W. Jeffs, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, **91**, 3831 (1969); *cf.* P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, **35**, 3512 (1970). We are grateful to Professor Jeffs for communicating these results to us prior to their publication. (b) H. Taguchi, T. Oh-ishi, and H. Kugita, *Chem. Pharm. Bull.*, **18**, 299, 1008 (1970), and references cited therein.

(22) M. Tichy in "Organic Chemistry: Methods and Results," Vol. 5, 1965, p 115.

following pmr data this information provides conclusive evidence concerning the preferred conformations of each of these intermediates.

The assignment of specific resonances in the pmr spectra of these compounds to the conformationally diagnostic protons on C_6 and C_{7a} were made as follows. A one-proton triplet at δ 3.22 in the spectrum of ketone **22b** was readily assigned to the C_{7a} proton, since this is the only proton in the molecule capable of providing such a signal and is consistent with average chemical shift data for a methine located adjacent to an amine function.[23]

On reduction of ketone **22b** to the two epimeric alcohols **21a** and **21b**, a triplet attributable to the C_{7a} proton is no longer clearly visible, having become obscured by the methylene signals. However, new multiplets appear at δ 4.02 and 4.11 in the spectra of **21b** and **21a**, respectively, which integrate for one proton. Based on the fact that these signals appear on reduction of the ketone they were tentatively assigned to the C_6 protons. Unambiguous confirmation of these assignments was obtained by reduction of the ketone with $NaBD_4$, which provided the two epimeric alcohols **21h** and **21g** (*vide infra*, *cf.* also discussion above) in a 2:1 ratio. The pmr spectra of these compounds lacked the absorptions at δ 4.02 and 4.11, respectively, thus confirming the original assignment. After debenzylation the epimeric monodeuterated alcohols **21i** and **21j** also lacked absorptions at δ 4.00 and 3.97 found in the spectra of their nondeuterated partners **21c** and **21d** and made it possible to assign these peaks to the C_6 protons and additionally those at δ 3.67 and 3.71 to the C_{7a} protons (Table I).

TABLE I

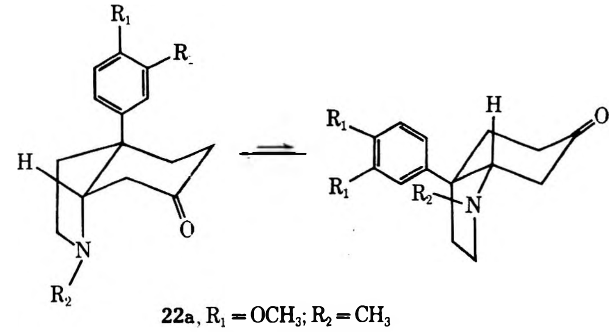
PERTINENT PMR DATA ($CDCl_3$)

Compd	C-6 hydrogen δ	C-6 hydrogen $W_{1/2}$, Hz	C-7a hydrogen δ	C-7a hydrogen J_{app} or $W_{1/2}$, Hz
19b			3.22	J_{app} = 3.5
21a	4.11	18	Obscured	
21b	4.02	8	Obscured	
21c	4.00	21	3.67	$W_{1/2}$ = 10
21d	3.97	8	3.71	$W_{1/2}$ = 7.8

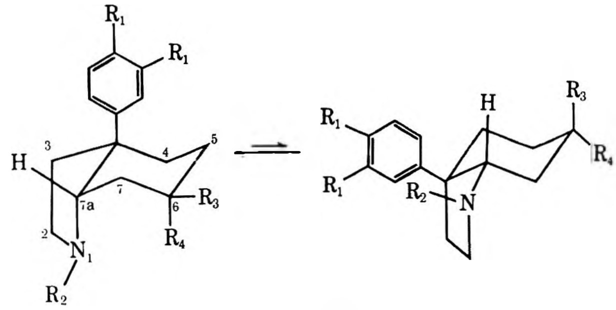
The employment of pmr spectroscopy to establish preferred ground state conformations is rather well established. Thus, the distinction between an axial and an equatorial alcohol in an epimeric pair can usually be made on the basis of relative chemical shift data and/or the half band width ($W_{1/2}$) properties of the methine hydrogen signal, especially when this signal is poorly resolved. Typically, an equatorial proton of this type exhibits a $W_{1/2} \cong$ 5–10 Hz, and an axial one a value of about 15–30 Hz.[21,24] The widths at half-height for the diagnostic hydrogens at C_6 and C_{7a} listed in Table I lead to only one possible conclusion: all of these substances, regardless of the nature of the substituent on nitrogen (*i.e.*, H, CH_3, $PhCH_2$), prefer the conformation in which the C_{7a} proton is equatorial and the adjacent aryl group is axial. The infrared data cited above are fully in accord with this conclusion.

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

(24) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).



22a, $R_1 = OCH_3$; $R_2 = CH_3$
b, R_1 = -OCH_2CH_2O-; $R_2 = CH_2Ph$
c, R_1 = -OCH_2CH_2O-; $R_2 = CH_3$



21a, R_1 = -OCH_2O-; R_2 = CH_2Ph; R_3 = OH; R_4 = H
b, R_1 = -OCH_2O-; R_2 = CH_2Ph; R_3 = H; R_4 = OH
c, R_1 = -OCH_2O-; R_2 = H; R_3 = OH; R_4 = H
d, R_1 = -OCH_2O-; R_2 = H; R_3 = H; R_4 = OH
e, R_1 = OCH_3; R_2 = CH_3; R_3 = OH; R_4 = H
f, R_1 = OCH_3; R_2 = CH_3; R_3 = H; R_4 = OH
g, R_1 = -OCH_2O-; R_2 = CH_2Ph; R_3 = OH; R_4 = D
h, R_1 = -OCH_2O-; R_2 = CH_2Ph; R_3 = D; R_4 = OH
i, R_1 = -OCH_2O-; R_2 = H; R_3 = OH; R_4 = D
j, R_1 = -OCH_2O-; R_2 = H; R_3 = D; R_4 = OH

Experimental Section[25]

1-(3,4-Methylenedioxyphenyl)cyclopropane Carbonitrile (16a).—The general method was as follows: *x* g of piperonyl cyanide, *x* g of $LiNH_2$, 2*x* ml of ethylene dibromide, and 10*x* ml of dry glyme were combined in a dry flask equipped with N_2 blanket and mechanical stirrer. The reaction may be followed by tlc or by a color change from an initial light tan to a chocolate brown upon completion. The glyme was evaporated *in vacuo*, H_2O was added cautiously to the residue, and the mixture was extracted three times with CH_2Cl_2 and dried over Na_2SO_4. Removal of the solvent left a dark oil which upon distillation provided reasonably pure product in 65–75% yield, bp 120° (0.2 mm). The distillate solidified upon standing. Two recrystallizations from petroleum ether (bp 30–60°) gave needles: mp 74.8–75.5° (sublimation at 80° (0.2 mm) is also a suitable method of purification); ir ($CHCl_3$) 2200 and 1040 cm^{-1}; pmr δ 1.44 (sym m, 4 H), 5.9 (s, 2 H), 6.7 (s, 3 H).

Anal. Calcd for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.66; H, 5.02; N, 7.33.

1-(3,4-Methylenedioxyphenyl)cyclopropane Carboxaldehyde (16b).—Nitrile **16a** (10 g, 0.054 mol) was dissolved in 100 ml of dry benzene in a flask equipped with a N_2 atmosphere, dropping funnel, and magnetic stirrer. A solution of 1.25 equiv of diisobutylaluminum hydride in toluene was added dropwise to the stirred solution and stirring was continued for an additional hour after addition was complete. The mixture was then cautiously poured into 5% aqueous H_2SO_4 (foaming!), the layers were separated, and the aqueous phase was extracted with ether. The organic phases were combined, dried ($MgSO_4$), and freed of solvent. The residual oil was dissolved in a minimum amount

(25) Infrared spectra were obtained on a Beckman IR-8 spectrometer. Pmr spectra were secured from a Varian A-56/60a spectrometer using tetramethylsilane as internal standard. Mass spectra were taken on a Consolidated Electrodynamics Corp. 21-110 high resolution spectrometer. Melting points and boiling points are uncorrected. Microanalyses were performed by the Elek Microanalytical Laboratory, Torrance, Calif. Preparative layer chromatography operations employed Brinkmann precoated 20 × 20 cm plates of silica gel F-254, 2 mm thick.

of hot cyclohexane from which the pure aldehyde crystallized upon cooling (75–85%): mp 62.5–63.5°; mp (2,4-DNP) 232–232.5°; ir (CCl_4) 1715 cm^{-1}; pmr (CCl_4) δ 1.24 (t, 2 H), 1.41 (t, 2 H), 5.88 (s, 2 H), 6.66 (s, 3 H), 9.3 (s, 1 H).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30. Found: C, 69.67; H, 5.46.

N-**Methylaldimine (17a).**—The procedure was essentially that described previously in the mesembrine synthesis:[9a] bp 105.5–106.5° (0.45 mm); ir (film) 1663 cm^{-1}; pmr ($CDCl_3$) δ 1.16 (sym m, 4 H), 3.2 (d, 3 H), 5.84 (s, 2 H), 6.68–6.8 (m, 3 H), 7.47 (q, 1 H).

Anal. Calcd for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; mol wt, 203.23. Found: C, 70.89; H, 6.46; mol wt, 203.

1-Methyl-3-(3,4-methylenedioxyphenyl)-2-pyrroline (18a).—Aldimine 17a (490 mg) and 25 mg of NH_4Cl were introduced into a small flask equipped with N_2 blanket and magnetic stirrer and heated to 140–150°. After 1 hr the imine band at 1663 cm^{-1} had completely disappeared and the orange oil was allowed to cool, whereupon the mass solidified. Extraction with several portions of hot hexane, filtration to remove residual NH_4Cl, and removal of the solvent provided a yellow solid which was conveniently purified by sublimation at 80° (0.4 mm), providing 293 mg (60%) of pure pyrroline. An analytical sample was recrystallized from hexane: mp 109–110°; ir ($CHCl_3$) 1612 and 1040 cm^{-1}; pmr ($CDCl_3$) δ 2.5–3.3 (m, 4 H), 2.63 (s, 3 H), 5.88 (s, 2 H), 6.26 (t, 1 H), 6.57–6.8 (m, 3 H).

Anal. Calcd for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; mol wt, 203.23. Found: C, 70.98; H, 6.69; mol wt, 203.

Amino Ketone 19a.—The procedure was essentially that described in the mesembrine synthesis.[9a] Except for methylenedioxy rather than the dimethoxy absorption, the pmr spectra of this material and those of *dl*-mesembrine (10) were virtually identical in the diagnostic aliphatic region.

N-**Benzylaldimine (17b).**—Aldehyde 16b (7.75 g, 0.048 mol) and 10 ml of benzylamine were dissolved in 50 ml of benzene, and 5 g of $CaCl_2$ was added to the stirred solution. After 12 hr no carbonyl absorption could be detected in the ir. The solution was filtered and freed of solvent, and the excess benzylamine was removed *in vacuo* at room temperature. Distillation provided a clear oil which solidified upon standing, bp 168–170° (0.1 mm) (72–92%). An analytical sample was obtained by sublimation at 110° (0.4 mm) providing needles: mp 67–67.5°; ir (film) 1655 cm^{-1}; pmr (CCl_4) δ 1.22 (m, 4 H), 4.5 (d, 2 H), 5.89 (s, 2 H), 6.7–6.85 (m, 3 H), 7.25 (s, 5 H), 7.9 (t, 1 H).

Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.40; H, 6.13; mol wt, 279.32. Found: C, 77.60; H, 6.11; mol wt, 279.

1-Benzyl-3-(3,4-methylenedioxyphenyl)-2-pyrroline (18b).—Aldimine 17b was heated with a catalytic amount of NH_4Cl at 135° under a N_2 atmosphere. The reaction was followed by observing the disappearance of C=N absorption. The resultant dark orange oil was extracted with boiling hexane which upon cooling precipitated the product (72–80°). Sublimation at 100° (0.3 mm) provided an analytical sample: mp 62.5–63°; ir [tetrachloroethylene (TCE)] 1618 and 1045 cm^{-1}; pmr (TCE) δ 2.5–3.4 (m, 4 H), 3.99 (s, 2 H), 5.51 (t, 1 H), 5.86 (s, 2 H), 6.56–6.76 (m, 3 H), 7.33 (s, 5 H).

Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.40; H, 6.13; mol wt, 279.32. Found: C, 77.52; H, 6.31; mol wt, 279.

Amino Ketone 19b.—The procedure was essentially that of Curphey.[9c] Pyrroline 18b was dissolved in dry ether and treated with anhydrous HCl gas, thus precipitating the salt. The ether was then removed *in vacuo*, the residue was dissolved in dry CH_3CN, and a slight excess of freshly distilled methyl vinyl ketone was added. The solution was then brought to reflux for 9 hr in a N_2 atmosphere. Upon cooling the reaction mixture was poured into dilute HCl, washed with ether to remove neutral materials, basified with KOH, and extracted three times with ether. The ether extracts were combined, washed with brine, dried over $MgSO_4$, and finally freed of solvent, leaving a white solid, mp 98–99.5° with softening at 94°. Recrystallization from cyclohexane–benzene provided reasonably pure product (56–67%). An analytical sample was secured by sublimation at 120° (0.2 mm) and melted at 98.5–101°: ir (TCE) 1725 cm^{-1}; pmr (TCE) δ 1.8–3.2 (m, 11 H), 2.98 (d, 1 H, J = 12 cps), 4.06 (d, 1 H, J = 12 cps), 5.85 (s, 2 H), 6.65–6.85 (m, 3 H), 7.12 (s, 5 H).

Anal. Calcd for $C_{22}H_{23}O_3N$: C, 75.62; H, 6.63; mol wt, 349.41. Found: C, 75.62; H, 6.85; mol wt, 349.

Sodium Borohydride Reduction of 19b. Synthesis of Amino Alcohols 21a and 21b.—Amino ketone 19b was reduced with excess sodium borohydride in EtOH solution. The epimeric alcohols were readily separated by preparative layer chromatography (1:1 $CHCl_3$–Et_2O).

Alcohol 21b was removed from the plate and triturated with Et_2O, which induced crystallization. Recrystallization from Et_2O gave transparent cubes: mp 105–106°; pmr ($CDCl_3$) δ 1.0–2.6 (m, 10 H), 2.8–3.3 (m, 2 H), 3.12 (d, 1 H, J = 12.5 cps), 3.96 (poorly resolved quintet, 1 H, J = 2 cps), 4.39 (d, 1 H, J = 12.5 cps), 5.86 (s, 2 H), 6.7–6.85 (m, 3 H), 7.25 (s, 5 H); mol wt, 351. A picrate, mp 229–231°, was analyzed.

Anal. Calcd for $C_{28}H_{28}O_{10}N_4$: C, 57.93; H, 4.86. Found: C, 58.28; H, 4.94.

Alcohol 21a was removed from the plate and it crystallized upon removal of the solvent. One recrystallization from ether provided an analytical sample: mp 135.5–136°; pmr ($CDCl_3$) δ 1.0–2.5 (m, 10 H), 2.7–3.2 (m, 2 H), 3.13 (d, 1 H, J = 13 cps), 3.8–4.35 (m, 1 H), 4.17 (d, 1 H, J = 13 cps), 5.87 (s, 2 H), 6.7–6.85 (m, 3 H), 7.25 (s, 5 H).

Anal. Calcd for $C_{22}H_{25}O_3N$: C, 75.19; H, 7.17; mol wt, 351.43. Found: C, 74.83; H, 7.21; mol wt, 351.

Catalytic Reduction of 19b. Stereoselective Synthesis of Amino Alcohol 21a.—The reduction of 2.38 g of the ketone was carried out in 200 ml of *i*-PrOH solution employing PtO_2 catalyst and an initial pressure of 42 psi in a Paar hydrogenator. After 48 hr the catalyst was removed and the filtrate was freed of solvent, leaving 2.3 g of a white residue (96%) whose tlc revealed that it was cleanly a mixture of the two epimeric alcohols 21a and 21b. These isomers were separated on a silica gel column eluting with 1:39 Et_2O–benzene mixture. The ratio of 21a to 21b was 8:1.

Debenzylation of 21b.—The method was essentially that of Büchi, *et al.*[19] The alcohol was dissolved in dry ether and the hydrochloride salt was precipitated with HCl gas. Excess HCl and solvent were then removed *in vacuo* and the dry salt was dissolved in MeOH. Hydrogenation at room temperature and 1 atm over 10% Pd/C catalyst was continued until hydrogen uptake ceased. Filtration and removal of the solvent gave essentially pure amine hydrochloride 21d (100%). One recrystallization from MeOH–THF gave a white powder, mp 246–251.5°, in a vacuum-sealed capillary. The free amine was recrystallized from benzene–Et_2O and sublimed at 110° (0.45 mm) to give an analytical sample, mp 179–180°, in a vacuum-sealed capillary: pmr of HCl salt (D_2O) δ 1.5–2.5 (m, 8 H), 3.2–3.8 (m, 2 H), 3.9–4.35 (m, 2 H), 4.61 (s, HDO), 5.94 (s, 2 H), 6.85–7.05 (m, 3 H).

Anal. Calcd for $C_{15}H_{18}O_3N$: C, 68.94; H, 7.33; mol wt, 261.30. Found: C, 68.59; H, 7.62; mol wt, 261.

Debenzylation of 21a.—The same procedure as above provided a quantitative yield of amine hydrochloride 21c which was recrystallized from MeOH–ether and dried *in vacuo* at 60°. The resultant white powder melted at 241.5–242° dec in a vacuum-sealed capillary, but the pmr spectrum revealed the presence of 0.25 mol of methanol of crystallization. The free amine could be recrystallized from benzene–Et_2O and sublimed at 90° (0.3 mm) to provide an amorphous powder: mp 154–156.5; pmr of HCl salt (D_2O) δ 1.4–2.6 (m, 8 H), 3.41 (s, 7 H, CH_3OH), 3.52 (broad t, 2 H), 4.05–4.45 (m, 2 H), 4.61 (HDO, s), 5.96 (s, 2 H), 6.9–7.1 (m, 3 H).

Anal. Calcd for $C_{15}H_{18}O_3N \cdot {}^1/_4CH_3OH$: C, 59.89; H, 6.92; mol wt, 261.30. Found: C, 59.78; H, 7.02; mol wt, 261.

dl-epi-**Elwesine (2b).**—The procedure was essentially that of Whitlock and Smith.[5c] The hydrochloride salt of 21d (234 mg) obtained in the debenzylation step was converted to the free amine and dissolved in 10 ml of 36% formalin and 10 ml of methanol. After 5 min 20 ml of 8 *N* HCl was added and the reaction was allowed to stand for 2 hr at room temperature. The mixture was then diluted with 25 ml of H_2O, extracted twice with 20-ml portions of ether to remove neutral materials, and basified with solid KOH. The resultant cloudy solution was then extracted with three 50-ml portions of $CHCl_3$, and the extracts were dried over K_2CO_3 and freed of solvent to give 275 mg of a white solid. Recrystallization from benzene–cyclohexane gave 139 mg (65%) of a white powder, which had mp 184–188°. Prolonged drying *in vacuo* at 60° (required to remove traces of benzene) raised the mp to 187–188.5° with softening at 185°. The solution ($CHCl_3$) ir spectrum of this substance was identical with that of an authentic sample[20] as was its behavior on tlc using a variety of solvents and solvent systems.

dl-Elwesine (Dihydrocrinine) **2a**.—Amine **21c** (234 mg) was freed from its hydrochloride salt by dissolution in water, addition of 3 *M* NaOH, and extraction of the precipitated free base with ether. The ether was removed and the free base was dissolved in 5 ml of MeOH to which 2.4 ml of 37% formalin was added. After 10 min of stirring at room temperature the mixture was poured into 80 ml of 6 *N* HCl and stirred overnight. The slightly yellow solution was treated with charcoal, neutralized with concentrated NH_4OH, and extracted three times with $CHCl_3$. The organic extracts were combined, washed with H_2O, and dried over Na_2SO_4. Removal of the solvent provided 130 mg (61%) of a white crystalline solid which was essentially pure elwesine. Recrystallization from MeOH and drying *in vacuo* provided crystals, mp 216–220°. The solution ir spectra ($CHCl_3$) of this substance and that of an authentic sample[20] of elwesine were identical, as was their behavior on tlc.

Registry No.—*dl*-**2a**, 33531-72-5; *dl*-**2b**, 32209-87-3; **16a**, 33522-14-4; **16b**, 33522-15-5; **16b** (2,4-D), 33522-16-6; **17a**, 33522-17-7; **17b**, 32042-34-5; **18a**, 33608-35-4; **18b**, 33522-19-9; **19b**, 32209-88-4; **21a**, 33531-75-8; **21b**, 33531-76-9; **21b** (picrate), 33531-77-0; **21c**, 33531-78-1; **21c** (HCl), 33531-79-2; **21d**, 32209-89-5; **21d** (HCl), 33531-81-6.

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The Synthesis of (±)-Guaiol and (±)-7-Epiguaiol

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The synthesis of guaiol was carried out in two stages. In the first stage methyl *cis*-4-methyl-1(9)-octalin-2-one 10-carboxylate (**1**) was converted *via* enol acetylation and reduction ($NaBH_4$ followed by mesylate formation and Li–NH_3 reduction) to *cis*-5-methyl-10-hydroxymethyl-1(9)-octalin (**5**). Ring contraction *via* ozonolysis of the corresponding benzyl ether and aldol cyclization of the resulting ketoaldehyde afforded *cis*-7-methyl-7a-benzyloxymethyl-2,4,5,6,7,7a-hexahydroindene 3-carboxaldehyde (**8**). This intermediate was subjected to deconjugation–reduction through treatment of the enolate with ethanolic sodium borohydride followed by hydrogenolysis of the derived mesylate with Li–NH_3–*tert*-BuOH to give *cis*-3,7-dimethyl-7a-hydroxymethyl-5,6,7,7a-tetrahydroindan (**11**). The corresponding mesylate derivative upon acetolysis afforded *cis*-6,10-dimethylbicyclo[5.3.0]dec-1(7)-en-3-yl acetate (**13**) stereoselectively. The second stage of the synthesis was concerned with the introduction of a 1-methyl-1-hydroxyethyl grouping at the 3 position of this acetate. This transformation was finally achieved through carbonation of the Grignard reagent derived from the corresponding bromide. The sequence afforded a 2:1 mixture of acids in which the 7-epi isomer **16b** predominated. Equilibration of the derived methyl esters gave a 1:1 mixture of cis and trans esters **17a** and **17b** which yielded (±)-guaiol (**18**) and (±)-7-epiguaiol in the same ratio upon treatment with methyllithium. These epimeric alcohols were separated by preparative gas chromatography and identified through comparison with authentic material.

A major problem of synthesis relating to hydroazulene natural products[2] is the rational control of stereochemistry. An examination of molecular models clearly indicates the inherent stereochemical ambiguities of synthetic approaches which allow equilibration of chiral centers on the hydroazulene ring system. Thus particular effort must be made to avoid reactions and intermediates where such equilibration might occur. An especially fruitful approach to substituted hydroazulenes utilizes as a key step the skeletal rearrangement of relatively rigid bicyclic systems under conditions such that epimerization does not take place.[3] Such schemes have employed cyclohexane rings to good advantage for the control of stereochemistry in the various bicyclic precursors. This report describes a partially successful approach of this type to the total synthesis of guaiol, the structural prototype and first recognized member of the guaiane family of sesquiterpenes.[4–6]

Our synthetic plan was based on the expected rearrangement of a bicyclo[4.3.0]nonyl derivative through a formal ring expansion of the six-membered ring facilitated by homoallylic participation. This type of reaction has been examined in some detail by Tadanier using C-19 functionalized Δ^5 steroids as substrates.[7] Applications to bicyclo[4.3.0]nonyl systems have recently been reported by us[8] and by Scanio.[9] Our previous studies indicated that the methanesulfonate **12** (Chart I) would be the intermediate of choice for a projected synthesis of guaiol along these lines.[8] Accordingly, the known *cis*-methyloctalonecarboxylic ester **1**[10] was subjected to deconjugation–reduction *via* treatment of the enol acetate **2**[11] with ethanolic sodium borohydride.[12] The resulting hydroxy ester **3** readily lactonized upon work-up unless care was taken to avoid heating. Further reduction was effected through treatment of the methanesulfonate derivative **4** with lithium–ammonia–*tert*-butyl alcohol to give the unsaturated alcohol **5**, which was protected as the benzyl ether **6**.

The requisite ring contraction of octalin **6** was achieved through ozonolysis and subsequent aldol cyclization of the intermediate ketoaldehyde **7**. Double-

(1) National Institutes of Health Predoctoral Fellow, Institute of General Medical Sciences (Fellowship 4 FOl GM38262), 1967–1970.

(2) *Cf.* P. de Mayo, "Mono and Sesquiterpenoids," Interscience, New York, N. Y., 1959, pp 244–262.

(3) *Cf.* J. A. Marshall and J. J. Partridge, *Tetrahedron*, **25**, 2159 (1969); C. H. Heathcock and R. Ratcliffe, *Chem. Commun.*, 994 (1968); M. Kato, H. Kosugi and A. Yoshikoshi, *ibid.*, 185 (1970).

(4) H. Minato, *Tetrahedron Lett.*, 280 (1961).

(5) For a recent nonstereoselective synthesis of guaiol, see G. L. Buchanan and G. A. R. Young, *Chem. Commun.*, 643 (1971).

(6) For a preliminary account of this work, see J. A. Marshall and A. E. Greene, *Tetrahedron Lett.*, 859 (1971); J. A. Marshall, A. E. Greene, and R. A. Ruden, *ibid.*, 855 (1971).

(7) J. Tadanier, *J. Org. Chem.*, **31**, 3204 (1966).

(8) J. A. Marshall and A. E. Greene, *ibid.*, **36**, 2035 (1971).

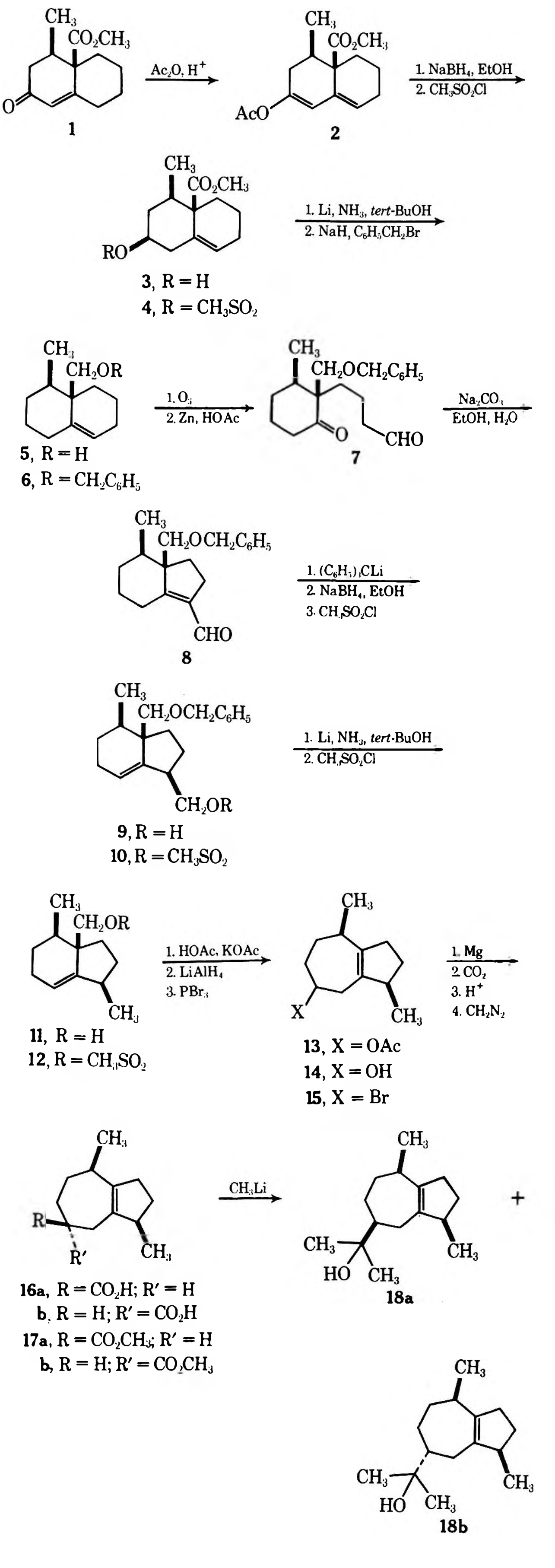
(9) C. J. V. Scanio and L. P. Hill, *Chem. Commun.*, 242 (1971).

(10) J. A. Marshall and T. M. Warne, Jr., *J. Org. Chem.*, **36**, 178 (1971).

(11) B. E. Edwards and P. N. Rao, *ibid.*, **31**, 324 (1966).

(12) W. G. Dauben and J. F. Eastham, *J. Amer. Chem. Soc.*, **73**, 4463 (1951).

Chart I



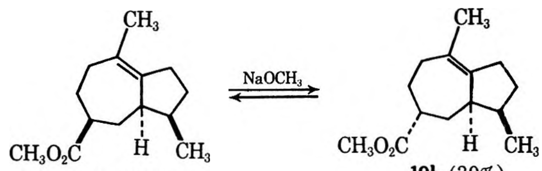
bond isomerization was achieved as before (*cf.* **1** → **3**) *via* deconjugation–reduction. In this case, however, enol acetylation of aldehyde **8** afforded appreciable amounts of by-products consisting largely of acylals. Accordingly, an alternative procedure was developed whereby aldehyde **8** was converted to its enolate using triphenylmethyllithium, and this enolate was allowed to protonate in aqueous ethanol containing a large excess of sodium borohydride to rapidly reduce the resulting β,γ-unsaturated aldehyde before conjugation or epimerization could take place.[8] In this manner a 2:1 mixture of alcohol **9** and its presumed double bond isomer was obtained. Separation of these isomers was unnecessary at this stage, since the unwanted allylic alcohol by-product was destroyed through reaction with methanesulfonyl chloride and pyridine, presumably by pyridinium salt formation, in the next step of the sequence. Mesylate **10** underwent hydrogenolysis of the methanesulfonoxy and benzyl groups in lithium–ammonia–*tert*-butyl alcohol to give the desired *cis*-dimethylbicyclo[4.3.0]nonylcarbinol **11**. The stereochemistry of this intermediate can be assigned on the basis of previous studies with keto ester **1**[10] and the expectation of stereoselective protonation of the enolate derived from aldehyde **8**.[8]

The methanesulfonate **12** was smoothly converted to the hydroazulenyl acetate **13** in refluxing acetic acid buffered with potassium acetate. At this point we were faced with the problem of replacing the acetoxyl grouping of acetate **13** by a 1-methyl-1-hydroxyethyl side chain with retention of stereochemistry. An earlier plan to prepare the related cyano derivative (**13**, X = CN) by conducting the solvolysis of mesylate **12** in liquid HCN had met with failure in a model study[8] and was therefore not pursued. In this previous study we were unable to prepare appropriate Grignard reagents from halides related to **15** and were consequently forced to devise a more circuitous route to the desired substituted hydroazulene. In the present work the onset of cooler and dryer weather encouraged us to reexamine the Grignard route.

To that end the alcohol **14** was converted with phosphorus tribromide in benzene to the bromide **15**. Successful initiation of the Grignard reaction was eventually achieved by adding a portion of the bromide **15** mixed with methyl iodide (neat) to crushed magnesium turnings. Once reaction had been initiated, the remainder of the bromide could be added in tetrahydrofuran solution. Carbonation followed by esterification of the resulting acidic material with diazomethane afforded at 2:1 mixture of esters **17b** and **17a** in 27% yield. The low overall yield of this sequence makes it difficult to draw valid conclusions regarding the stereochemistry of the carbonation reaction. In related cases this reaction was found to be highly stereoselective with retention of configuration.[13] Our isolation of a 2:1 mixture of acids **16b** and **16a** may therefore reflect the isomer composition of the organometallic derived from bromide **15**. We chose not to examine the addition of acetone to this Grignard reagent, a seemingly more direct route to guaiol (**18**), because of the reported low yields for a similar conversion.[13] Furthermore, since the ratio of carbonation products (2:1 **16b** to **16a**) was unfavorable we wished to study the equilibration of esters **17a** and **17b** with a view to increasing the proportion of the former isomer. In fact, this aim

(13) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968), and references cited therein.

could be accomplished by treating the aforementioned 1:2 mixture with methanolic sodium methoxide at reflux, whereupon a 1:1 mixture was secured. In an analogous compound, a 70:30 mixture of the related esters **19a** and **19b** (see below) was obtained upon equilibration.[3] These findings underscore the hazards of relying upon equilibration to control stereochemistry in hydroazulene ring systems.



19a (70%) **19b** (30%)

Treatment of the 1:1 ester mixture **17** with ethereal methyllithium afforded a comparable mixture of (±)-guaiol (**18a**) and (±)-7-*epi*-guaiol (**18b**), separated by preparative gas chromatography and identified through comparison with naturally derived material.[6]

Experimental Section[14]

Methyl *cis*-4-Methyl-*cis*-2-methanesulfonoxy-8-octalin-10-carboxylate (4).—A solution of 1.00 g of keto ester **1** (9:1 *cis*:*trans*)[10] in 85 ml of ethyl acetate containing 17 μl of 70% perchloric acid and 8.2 ml of acetic anhydride was allowed to stand at room temperature for 11 min.[11] The solution was washed with saturated sodium bicarbonate and the product was distilled, affording 1.13 g (95%) of enol acetate **2**: bp (bath temperature) 110° (0.03 mm); λ_{max}^{film} 3.32, 5.68, 5.80, 5.98, 6.13 mμ; $\delta_{TMS}^{CCl_4-CDCl_3}$ 5.79 (H-1), 5.56 (H-8 triplet, J = 4 Hz), 3.66 (OCH_3), 2.10 (CH_3CO), 1.08 ppm (CH_3 doublet, J = 6 Hz). Longer reaction times gave rise to an unidentified by-product while shorter reaction times led to varying amounts of recovered starting material.

The above enol acetate in 30 ml of ethanol was added dropwise to a stirred mixture of 5.3 g of sodium borohydride in 110 ml of ethanol and 16.5 ml of water at 0°.[12] After 30 min, the mixture was stored at 5° for 3 hr and then poured into cold 10% NaOH and extracted with ether–benzene. The entire process was carried out with cold solvents and the solvent was removed below room temperature in order to minimize lactonization of the hydroxy ester **3**. This procedure yielded 1.0 g of **3**: λ_{max}^{film} 2.90, 3.24, 5.80, 5.97 mμ; $\delta_{TMS}^{CCl_4}$ 5.50 (H-8), 4.63 (OCH_3), 0.95 ppm (CH_3 doublet, J = 6 Hz).

The above hydroxy ester in 6 ml of pyridine at 0° was treated with 1.0 ml of methanesulfonyl chloride. After 1 hr at 0° and 3 hr at room temperature, ice chips were added with external cooling and the product was isolated with ether, affording 0.96 g of semisolid material. Recrystallization from methanol at −77° afforded 0.61 g (45% overall) of mesylate **4**: mp 95–100°; λ_{max}^{KBr} 3.30, 5.81, 8.24, 8.58 mμ; $\delta_{TMS}^{CCl_4-CDCl_3}$ 5.65 (H-8), 4.65 (H-2), 3.68 (CH_3O), 3.00 (CH_3SO_3), 0.92 ppm (CH_3 doublet, J = 6 Hz). The analytical sample, mp 102–103°, was obtained after two additional recrystallizations.

Anal. Calcd for $C_{14}H_{22}O_5S$: C, 55.61; H, 7.33; S, 10.60. Found: C, 55.89; H, 7.10; S, 10.50.

***cis*-5-Methyl-10-hydroxymethyl-1(9)-octalin (5).**—To a solution of 5.81 g of lithium in 600 ml of ammonia at −78° was added 3.33 g of mesylate **4** in 50 ml of *tert*-butyl alcohol and 66 ml of tetrahydrofuran. After 1.25 hr at −78° and 2 hr at −33° (reflux) the solution was treated with ethanol to discharge the blue color and solid ammonium chloride was added to neutralize the alkoxides. The ammonia was allowed to evaporate through a mercury trap and the product was isolated with ether, affording 1.79 g (90%) of solid alcohol **5**: bp 100° (bath temperature) (0.1 mm); λ_{max}^{KBr} 3.01 mμ; $\delta_{TMS}^{CCl_4-CDCl_3}$ 5.55 (H-1 triplet, J = 3 Hz), 3.55 (CH_2 AB, J = 10 Hz $\Delta\nu_{AB}$ = 12 Hz), 0.85 ppm (CH_3 doublet, J = 3 Hz). The analytical sample, mp 41–46°, was prepared by sublimation [25° (0.04 mm)].

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.70; H, 11.20.

***cis*-5-Methyl-10-benzyloxymethyl-1(9)-octalin (6).**—A solution of 1.79 g of alcohol **5** in 90 ml of dioxane was added to pentane-washed NaH (from 0.96 g of 57% oil dispersion) and the mixture was stirred at reflux for 2 hr. The cooled solution was treated with 1.50 ml of benzyl bromide and the mixture was stirred at reflux for 15 hr. The product was isolated with ether and distilled, affording 2.51 g (94%) of benzyl ether **6**: bp 120° (bath temperature) (0.02 mm); $\delta_{TMS}^{CCl_4-CDCl_3}$ 7.20 (aromatic H's), 5.38 (H-1), 4.39 (benzylic H's), 3.48 (CH_2O), 0.93 ppm (CH_3 doublet, J = 3 Hz).

Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.34; H, 9.59.

***cis*-7-Methyl-7a-benzyloxymethyl-2,4,5,6,7,7a-hexahydroindene-3-carboxaldehyde (8).**—A solution of 0.63 g of olefin **6** in 27 ml of pentane was treated at −78° with a stream of ozonized oxygen with periodic centrifugation of the solid ozonide. The excess ozone was allowed to evaporate and the pentane was decanted from the solid ozonide. Acetic acid (4.65 ml) and zinc powder (1.16 g) were added at −78° and the mixture was allowed to reach room temperature with stirring. After 11 min, the mixture was filtered and the product was isolated with ether, affording 0.49 g of keto aldehyde **7**: λ_{max}^{film} 3.30, 3.68, 5.80, 5.87 mμ; $\delta_{TMS}^{CCl_4-CDCl_3}$ 9.67 (CHO triplet, J = 2 Hz), 7.20 (aromatic H's), 4.35 (benzylic H's), 3.42 (CH_2O–AB, J = 10 Hz, $\Delta\nu_{AB}$ = 16 Hz), 0.85 ppm (CH_3 doublet, J = 7 Hz).

A 1.48-g sample of the above material was stirred at reflux with 1.30 g of sodium carbonate in 10.6 ml of water and 224 ml of ethanol for 16 hr. The product was isolated with ether–benzene and chromatographed on silica gel to give 0.76 g (38% overall) of aldehyde **8**: λ_{max}^{film} 3.32, 3.67, 6.00 mμ; $\delta_{TMS}^{CCl_4-CDCl_3}$ 10.00 (CHO), 7.15 (aromatic H's), 4.33 (benzylic H's), 3.45 (CH_2O– AB, J = 9 Hz, $\Delta\nu_{AB}$ = 10 Hz), 0.95 ppm (CH_3 doublet, J = 5 Hz). The analytical sample, mp 53–54°, was prepared by crystallization from pentane.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.21; H, 8.65.

***cis*-3,7-Dimethyl-7a-hydroxymethyl-5,6,7,7a-tetrahydroindan (11).**—Triphenylmethyllithium was prepared from 9.5 ml of 1.5 *M* ethereal methyllithium and 3.85 g of triphenylmethane in 15 ml of 1,2-dimethoxyethane.[15] To this solution was added 1.06 g of aldehyde **8** in 20 ml of DME dropwise over 0.5 hr. After 1 hr this solution was added dropwise to a well-stirred solution of 50 g of sodium borohydride in 50 ml of water and 380 ml of ethanol. After 3.5 hr the solution was poured into 10% NaOH and the product was isolated with ether–benzene and chromatographed on silica gel, affording 0.68 g of alcohol **9**: λ_{max}^{film} 2.94, 3.30 mμ; $\delta_{TMS}^{CCl_4}$ 7.20 (aromatic H's), 5.50 (H-4), 4.33 (benzylic H's), 3.50–3.30 (CH_2OH), 3.25 (CH_2O–), 0.95 ppm (CH_3 doublet, J = 4 Hz). The integration indicated 66% of the desired alcohol **9**. The remaining 34% appeared to consist mainly of the isomeric allylic alcohol.

A 0.60-g sample of the above mixture in 5.5 ml of pyridine at 0° was treated with 1.1 ml of methanesulfonyl chloride. After 0.5 hr at 0° and 2 hr at room temperature, the mixture was cooled and added dropwise to 30 ml of pyridine containing 15 ml of water. Isolation with ether afforded 0.66 g of mesylate **10**: $\delta_{TMS}^{CCl_4-CDCl_3}$ 7.20 (aromatic H's), 5.55 (H-4), 4.36 (benzylic H's), 4.05 and 3.93 (doublets, J = 1.5 Hz), 3.25 (CH_2O–), 2.70 (CH_3SO_3), 0.95 ppm (CH_3 doublet, J = 4 Hz).

The above mesylate in 5.1 ml of *tert*-butyl alcohol and 2.5 ml of tetrahydrofuran was added dropwise to a stirred solution of 0.94 g of lithium in 75 ml of ammonia at −78°. After 1.5 hr at −78° and 1 hr at −33° (reflux) the solution was treated with ethanol dropwise to discharge the blue color and the ammonia was allowed to evaporate through a mercury trap. The product was isolated with ether and distilled, affording 0.26 g (44% overall) of alcohol **11**: bp 110° (bath temperature) (0.05 mm); λ_{max}^{film} 2.93 mμ; $\delta_{TMS}^{CCl_4-CDCl_3}$ 5.55 (H-4), 3.70–3.30 (CH_2OH), 1.15 (CH_3 doublet, J = 7 Hz), 1.00 ppm (CH_3 doublet, J = 3 Hz). The analytical sample was prepared by preparative layer chromatography (95:5 benzene–ether) on silica gel and distillation.

(14) Reactions were carried out under a nitrogen atmosphere. The isolation procedure involved adding the reaction mixture to water or saturated brine and extracting thoroughly with the specified solvent. Anhydrous magnesium sulfate or magnesium carbonate was used to dry the combined extracts and the solvent was removed on a rotary evaporator under reduced pressure. Microanalyses were preformed by Microtech Inc., Skokie, Ill.

(15) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.86; H, 11.38.

cis-**6,10-Dimethylbicyclo[5.3.0]dec-1(7)-en-3-yl Acetate (13).**—A solution of 0.16 g of alcohol 11 in 0.95 ml of pyridine was stirred at 0° and 0.4 ml of methanesulfonyl chloride was added dropwise. After 20 min at 0° the mixture was poured into a stirred solution of 6 ml of pyridine and 1 ml of water at 0°. The product was isolated with ether, affording 0.20 g of mesylate 12.

The above mesylate in 9.5 ml of a solution prepared from 25 ml of acetic acid, 0.5 ml of acetic anhydride, and 0.35 g of potassium carbonate[7] was stirred at reflux for 5.25 hr. The product was isolated with ether and distilled, affording 0.16 g of acetate 13: bp 100° (bath temperature) (0.05 mm) (80% pure by gas chromatographic analysis); λ_{max}^{film} 5.77, 8.06, mμ; $\delta_{TMS}^{CDCl_3}$ 4.75 (H-3), 2.30 and 2.20 (allylic H's), 1.03 and 0.91 ppm (CH_3 doublets, J = 6 Hz). The analytical sample was obtained by preparative layer chromatography (silica gel, benzene) and distillation.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.50; H, 9.83.

cis-**6,10-Dimethylbicyclo[5.3.0]dec-1(7)-en-3-ol (14).**—A solution of 158 mg of acetate 13 in 10 ml of ether was added dropwise with stirring to a solution of 0.20 g of lithium aluminum hydride in 100 ml of ether. The mixture was stirred for 8 hr, 0.4 ml of water and 0.32 ml of 10% NaOH were added, and stirring was continued for 1 hr. A small quantity of anhydrous magnesium sulfate was then added and the mixture was filtered, chromatographed on silica gel, and distilled, affording 82 mg of alcohol 14: bp 100° (bath temperature) (0.05 mm); λ_{max}^{film} 3.02 mμ; $\delta_{TMS}^{CCl_4-CDCl_3}$ 3.60 (CHOH), 2.30 and 2.18 (allylic H's), 1.00 and 0.98 ppm (CH_3 doublets, J = 7 Hz). The analytical sample was prepared by distillation.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.80; H, 11.22.

Methyl *cis*-**6,10-Dimethylbicyclo[5.3.0]dec-1(7)-ene 3-Carboxylate (17).**—A solution of 92 mg of alcohol 14 and 58 μl of phosphorous tribromide in 0.4 ml of benzene was heated at reflux for 4.5 hr.[13] Ice chips were added to the cooled solution and the product was isolated with benzene, affording 100 mg of bromide 15, bp 95° (bath temperature) (0.05 mm).

A 10-μl sample of the above bromide and 10 μl of methyl iodide were added under helium to 0.1 g of freshly crushed Mg turnings. After 1 min, the remainder of the bromide in 1 ml of tetrahydrofuran was added dropwise. The mixture was heated at 60° for 45 min, cooled to 10°, and diluted with 1 ml of tetrahydrofuran. Carbon dioxide was slowly bubbled into the solution for 5 min at 10° and 15 min at room temperature. Small chips of Dry Ice were added and the mixture was poured onto crushed Dry Ice. Ether and dilute sulfuric acid were added and the product was isolated with ether. Neutral impurities were removed by extracting with dilute sodium hydroxide, acidifying the basic extracts, and extracting the resulting acid fraction with ether, affording 25 mg of acid 16. Esterification with diazomethane afforded 28 mg (27%) of methyl ester 17: bp 100° (bath temperature) (0.1 mm); λ_{max}^{film} 5.75 mμ; $\delta_{TMS}^{CCl_4}$ 3.60 (OCH_3) and 1.2–0.8 ppm (CH_3's). The gas chromatogram showed peaks at 12.7 (55%, **17b**) and 13.6 min (25%, **17a**).[6] The analytical sample was obtained after preparative layer chromatography on silica gel and short path distillation.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.81; H, 9.93.

A combined sample of 86 mg of ester 17 (2:1 **17b** and **17a**) in 12 ml of 0.4 *M* methanolic sodium methoxide was heated at reflux for 40 hr. Acidic material was esterified with diazomethane and the combined ester sample was distilled, affording 48 mg of a 53:47 mixture of esters **17b** and **17a** according to gas chromatography.[6]

(±)-Guaiol (18a) and (±)-7-Epiguaiol (18b).—To 4 ml of 1.5 *M* ethereal methyllithium was added 26 mg of the above 1:1 ester mixture in 6 ml of ether. After 3.5 hr the mixture was poured onto ice and the product was isolated with ether, affording 26 mg of a 1:1 mixture of guaiol and 7-epiguaiol, bp 120° (bath temperature) (0.1 mm). The two epimers separated by preparative gas chromatography had the following properties. (1) (±)-Guaiol: mp 55–60°; λ_{max}^{KBr} 3.00, 6.90, 7.38, 7.67, 7.88, 8.04, 8.18, 8.30, 8.52, 8.70, 8.80, 10.05, 10.33, 10.81, 11.00, 11.38, 12.20 mμ; $\delta_{TMS}^{CDCl_3}$ 1.18 (CH_3's), 0.98 (CH_3 doublet, J = 7.5 Hz), 0.96 ppm (CH_3 doublet, J = 7 Hz). The spectral and chromatographic characteristics exactly matched those of natural guaiol.[6] (2) (±)-7-Epiguaiol: λ_{max}^{film} 2.97, 6.89, 7.32, 7.60, 8.85, 9.18, 10.36, 10.79, 11.12, 12.22 mμ; $\delta_{TMS}^{CDCl_3}$ 1.19 (CH_3's), 1.04 (CH_3 doublet, J = 7 Hz), 1.03 ppm (CH_3 doublet, J = 6 Hz). The spectral and chromatographic characteristics exactly matched those of material obtained from natural sources.[6]

Registry No.—**2**, 33536-32-2; **3**, 33536-33-3; **4**, 33536-34-4; **5**, 32667-68-8; **6**, 33536-36-6; **7**, 33536-37-7; **8**, 32667-69-9; **9**, 32667-70-2; **10**, 33536-40-2; **11**, 33536-41-3; **13**, 33536-42-4; **14**, 33536-43-5; **15**, 33536-44-6; **17a**, 33536-45-7; **17b**, 33536-46-8; **18a**, 33496-08-1; **18b**, 33536-48-0.

Acknowledgments.—We are indebted to the National Institutes of Health for their support of this work through a research grant (National Cancer Institute, 5 R01 CA 11089) and a predoctoral fellowship. A sample of Guaiacum Wood Oil was generously provided by Professor R. B. Bates.

Perhydroindan Derivatives. XIII. Selective Metalation of a 7-Methoxyhexahydrofluorene Derivative[1a]

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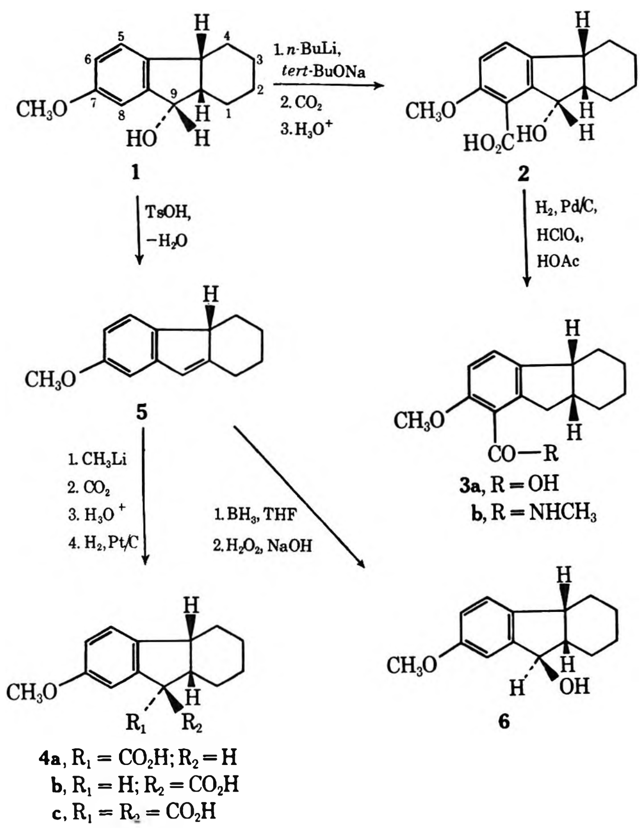
The regiospecific metalation of the methoxy acid 3a at C-9 has been accomplished by reaction of the corresponding *N*-methylamide with *n*-butyllithium. Carbonation of the organolithium intermediate has provided a useful synthetic route to the epimeric diacid derivatives 9 and 10. The applicability of the Birch reduction to the conversion of the methoxy acid 4a to either the enol ether 11 or the keto acid 12a has also been demonstrated.

In previous model studies with 7-methoxyhexahydrofluorene derivatives[2] we developed selective metalation procedures that allowed us to introduce carboxyl functions at either C-8 or C-9. The use of these methods to prepare acids **3a** and **4a** is illustrated in Scheme I. Also illustrated is the hydroboration of the intermediate olefin **5** from the less hindered side to form alcohol **6**, an epimer of the previously described alcohol **1**; this sequence confirms our earlier tentative assignment of stereochemistry to alcohol **1**.[2] Further reaction of the sodium salt of acid **4a** with *n*-BuLi formed a benzylic anion which reacted with carbon dioxide to form the 9,9-dicarboxylic acid **4c**; thermal decarboxylation of this

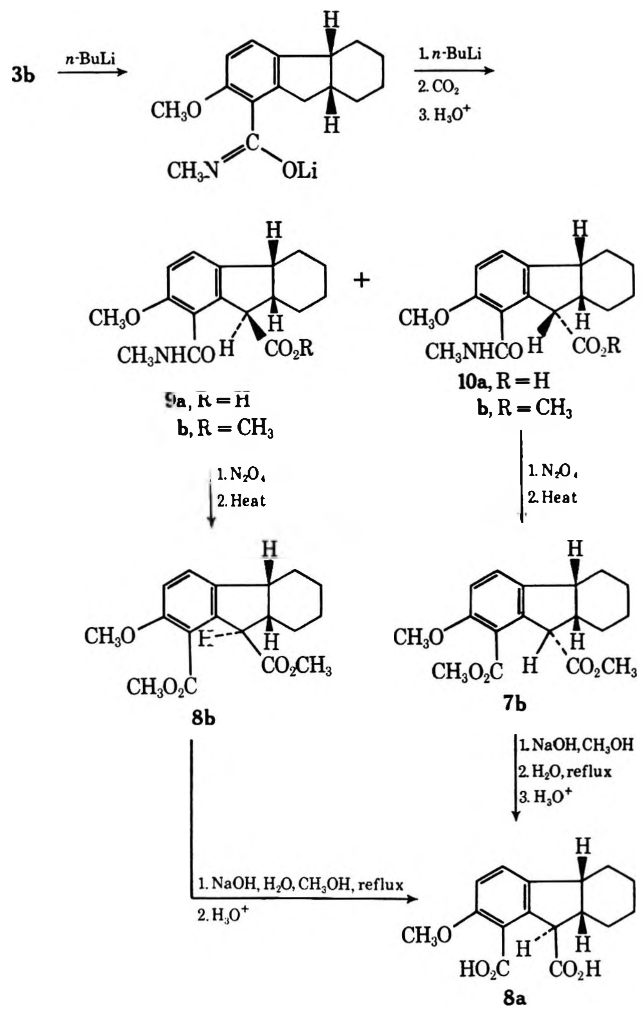
(1) (a) This research has been supported by Public Health Service Grant R01-CA-12634 from the National Cancer Institute. (b) Department of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332. (c) National Institutes of Health Predoctoral Fellow, 1968–1971.

(2) H. O. House, T. M. Bare, and W. E. Hanners, *J. Org. Chem.*, **34**, 2209 (1969).

SCHEME I

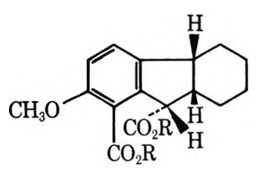


SCHEME II

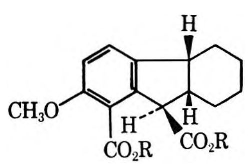


malonic acid derivative **4c** yielded a mixture of the epimeric acids **4a** and **4b**.

By the successive use of these two metalation procedures we had been able[2] to convert the alcohol **1** *via* the hydroxy acid **2** and the related olefin to the epimeric dicarboxylic acid derivatives **7** and **8**. However, the



7a, R = H
b, R = CH_3

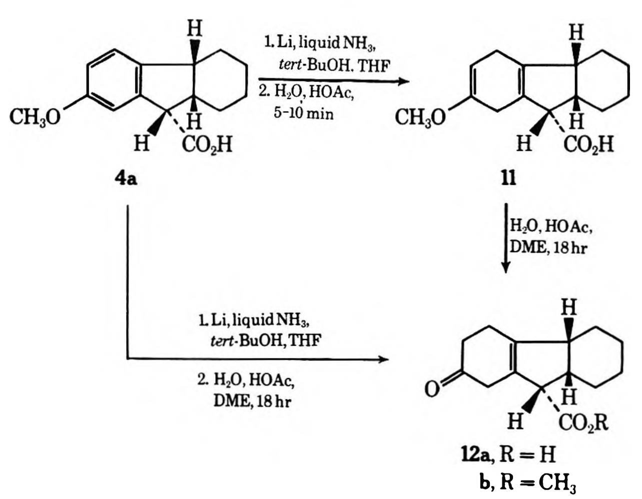


8a, R = H
b, R = CH_3

progress of other synthetic work created the need to introduce a second carboxyl function at the benzylic C-9 position in monoacid derivatives such as **3** which contain no additional activating group in the five-membered ring. We have used the compounds **3** as models to explore possible synthetic methods and have found the lithium salt of the *N*-methylamide **3b** to be very effective in directing further metalation at C-9.[3] This conversion to form the epimeric diacid derivatives **9** and **10** is illustrated in Scheme II. Reaction of the amide **9b** with N_2O_4 and subsequent thermal decomposition[4] produced the known[2] diester **8b**, which was further characterized by saponification to the crystalline diacid **8a**. Similarly, the amide **10b** was converted to the known[2] diester **7b**; base-catalyzed epimerization and hydrolysis converted **7b** to the same diacid **8a** which is known[2] to be more stable than its epimer **7a**.

We also examined briefly the Birch reduction[5,6] of the methoxy acid **4a** (Scheme III). When the crude reduction product was exposed only briefly to the aqueous acetic acid, the crystalline enol ether acid **11** could be isolated in good yield. However, prolonged exposure

SCHEME III



(3) The use of *N*-methylbenzamide as a directing group for ortho metalation has been described by W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

(4) E. White, *Org. Syn.*, **47**, 44 (1967).

(5) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, Part 2, Wiley-Interscience, New York, N. Y., 1963, pp 151–285.

(6) M. Smith, "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, pp 98–126.

of either the crude reduction product or the pure enol ether **11** to aqueous acetic acid resulted in hydrolysis of the enol ether to form the keto acid **12a**.

Experimental Section[7]

Preparation of the Hexahydrofluorene Derivatives 3.—The alcohol 1 was metalated and then carbonated to form the previously described[2] acid **2**, mp 134–135° (lit.[2] mp 136–137°). A solution of 3.00 g (11.5 mmol) of the hydroxy acid **2**, 0.25 ml of aqueous 70% $HClO_4$, and 10 ml of HOAc in 40 ml of tetrahydrofuran was hydrogenated at 1 atm and 25° over 300 mg of a 5% Pd/C catalyst. The absorption of H_2 (305 ml or 12.2 mmol) was complete in 5 min and the reaction mixture was filtered and concentrated. After a solution of the residue in Et_2O had been washed with H_2O, dried (Na_2SO_4), and concentrated, the residue crystallized from hexane as 2.78 g (99%) of the crude acid **3a**, mp 84–93°. Recrystallization from hexane–CH_2Cl_2 mixtures afforded the pure acid **3a** as white prisms: mp 93–94°; ir ($CHCl_3$), 3260 (associated OH) and 1730 cm^{-1} (carboxyl C=O); uv max (95% EtOH) 296 mμ (ϵ 2900); nmr ($CDCl_3$) δ 10.45 (1 H, broad, OH), 7.28 (1 H d, J = 8 Hz, aryl CH), 6.85 (1 H d, J = 8 Hz, aryl CH), 4.00 (3 H s, OCH_3), and 1.0–3.5 (12 H m, aliphatic CH); mass spectrum m/e (rel intensity) 246 (100, M$^+$), 228 (31), 203 (22), and 185 (33).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.96; H, 7.46.

A solution of 800 mg (3.25 mmol) of the acid **3a** in 5.0 ml of $SOCl_2$ was stirred at 25° for 15 hr and then concentrated under reduced pressure. A solution of the residual acid chloride in 10 ml of tetrahydrofuran was added to 40 ml of aqueous 40% CH_3NH_2. The crude product separated and was collected as 755 mg (89%) of a white solid, mp 166–169°. Recrystallization from MeOH afforded the pure amide **3b** as white needles: mp 168–169°; ir ($CHCl_3$) 3430 (NH), 1655 (amide C=O), and 1530 cm^{-1} (amide NH bending); uv max (95% EtOH) 289 mμ (ϵ 3140); nmr ($CDCl_3$) δ 7.15 (1 H d, J = 8 Hz, aryl CH), 6.75 (1 H d, J = 8 Hz, aryl CH), 7.0 (1 H broad, NH), 3.85 (3 H s, OCH_3), 2.7–3.2 (6 H m, CH_3N and benzylic CH), and 0.9–2.5 (9 H m, aliphatic CH); mass spectrum m/e (rel. intensity), 259 (100, M$^+$), 229 (22), 216 (43), 185 (50), 127 (68), and 126 (38).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.05; H, 8.06; N, 5.54.

Preparation of the Diacid 4c.—A sample of the acid **4a**, mp 185–187° (lit.[2] mp 186–187°), was prepared from olefin **5** by previously described procedures.[2] A mixture of 1.0 g (41 mmol) of NaH and 5.00 g (20.4 mmol) of the acid **4a** in 150 ml of tetrahydrofuran was stirred at 55° for 10 min. The resulting solution of the sodium salt was diluted with 250 ml of pentane and cooled in a Dry Ice bath. To the resulting cold suspension was added, dropwise and with stirring over 10 min, 55 ml of a hexane solution containing 88 mmol of n-BuLi. The mixture was warmed to 0° and the resulting orange solution was added, with vigorous stirring, to a slurry of 200 g of Dry Ice in 50 ml of tetrahydrofuran. The resulting mixture was concentrated under reduced pressure and a solution of the residue in 500 ml of H_2O was extracted with Et_2O, acidified (HCl), and again extracted with Et_2O. The acidic etheral extract was washed with H_2O, dried, and concentrated. Trituration of the residue with CH_2Cl_2 and with hexane left 5.13 g (87%) of the diacid **4c** as a white solid: mp 175–177° dec; ir (KBr pellet) 3000 (broad, associated OH) and 1705 cm^{-1} (carboxyl C=O); uv max (95% EtOH) 221 mμ (ϵ 9500), 284 (2920), and 290 (shoulder, 2680); nmr ($CDCl_3$ + pyridine-d_5) δ 13.3 (2 H, OH), 6.7–7.7 (3 H m, aryl CH), 3.75 (3 H s, OCH_3), and 0.9–3.6 (10 H m, aliphatic CH).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.45; H, 6.24.

A 1.00-g (3.44 mmol) sample of the diacid **4c** was heated to 185° for 5 min under a N_2 atmosphere, at which time decarboxylation appeared to be complete. The residue was crystallized from a CH_2Cl_2–hexane mixture to separate 0.55 g (65%) of the monoacid **4a** as white needles, mp 181–183°. Recrystallization gave the pure monoacid **4a**, mp 185–186°, which was identified with an authentic sample by a mixture melting point and comparison of ir spectra. The mother liquors from this crystallization were concentrated and then crystallized from hexane to separate 0.31 g (36%) of crude monoacid **4b** as white prisms, mp 108–120°. Fractional recrystallization from hexane separated 20 mg (3%) of the pure monoacid **4b**, mp 115–116° (lit.[2] mp 117.5–118.5°), identified with an authentic sample by a mixture melting point determination and comparison of ir spectra.

Preparation of the Alcohol 6.—A 1.00-g (4.58 mmol) sample of the alcohol 1 was dehydrated (TsOH in PhH)[2] to form 890 mg (97%) of the crude olefin **5**. A solution of this olefin **5** in 10 ml of tetrahydrofuran was treated with 4.6 ml of a tetrahydrofuran solution containing *ca.* 5 mmol of BH_3 and the resulting solution was stirred at 25° for 30 min. To the reaction solution were added 1.0 ml of H_2O, 2.0 ml of aqueous 15% NaOH, and 20 ml of aqueous 30% H_2O_2. The resulting solution was partitioned between H_2O and Et_2O and the ethereal layer was washed with aqueous NaCl, dried, and concentrated to leave 940 mg (94%) of the crude alcohol **6**, mp 92–94°. Recrystallization from hexane afforded the pure alcohol **6** as a white solid: mp 98–99°; ir (CCl_4), 3600 and 3450 cm^{-1} (broad) (unassociated and associated OH); uv max (95% EtOH) 217.5 mμ (ϵ 8000), 225 (shoulder, ϵ 7600), 281 (2840) and 287 (shoulder, 2520); nmr ($CDCl_3$) δ 6.7–7.4 (3 H m, aryl CH), 4.91 (1 H d, J = 6 Hz, benzylic CHO), 3.82 (3 H s, OCH_3), 2.9–3.3 (1 H m, benzylic CH), and 1.1–2.6 (10 H m, OH and aliphatic CH).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.05; H, 8.21.

Preparation of the Acid Derivatives 9 and 10.—To a cold (0°) suspension of 5.00 g (19.3 mmol) of the amide **3b** in 10 ml of hexane and 40 ml of tetrahydrofuran was added 32.1 ml of a hexane solution containing 51.3 mmol of n-BuLi. When 1 equiv of n-BuLi had been added the suspended amide **3b** dissolved to form a yellow solution which became red in color as more n-BuLi was added. The resulting solution was stirred at 0° for 1 hr, during which time a yellow precipitate separated. The resulting suspension was refluxed for 30 min. and then cooled and poured into a slurry of 300 g of Dry Ice in 300 ml of Et_2O. The resulting mixture was partitioned between H_2O and Et_2O. Concentration of the ether layer and crystallization of the residue separated 0.22 g (4%) of the starting amide, mp 160–164°. The aqueous layer was cooled in an ice bath and then acidified (HCl, pH 2) and mixed with Et_2O. The mixture was filtered to separate 2.84 g (48%) of the crude acid **10a**, mp 183–195°, which was relatively insoluble in Et_2O. Recrystallization from EtOH afforded the pure acid **10a** as white needles: mp 213–215°; ir (KBr pellet) 3420 (NH), 2940 (broad, associated OH), 1735 (carboxyl C=O with intramolecular H bonding), and 1625 cm^{-1} (amide C=O with intramolecular H bonding); uv max (95% EtOH) 295 mμ (ϵ 3340) with intense end absorption (ϵ 27,100 at 210 mμ); nmr (NaOD + D_2O) δ 7.26 (1 H d, J = 9 Hz, aryl CH), 6.95 (1 H d, J = 9 Hz, aryl CH), 3.8–4.4 (4 H m, benzylic CHCO including the CH_3O singlet at δ 3.86), and 1.0–3.5 (13 H m, aliphatic CH including the NCH_3 singlet at δ 2.91); mass spectrum m/e (rel intensity) 303 (0.5, M$^+$), 272 (29), 259 (100), 242 (24), 229 (43), 228 (32), 227 (22), 216 (48), 185 (67), 128 (21), and 115 (25).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.30; H, 6.97; N, 4.54.

A 560-mg (1.85 mmol) sample of the acid **10a** (mp 209–210°) was esterified with excess CH_2N_2 in an Et_2O–tetrahydrofuran mixture to yield 556 mg (95%) of the crude ester **10b**, mp 158–163°. Recrystallization from MeOH–H_2O afforded the ester **10b** as white needles: mp 158–163°; ir ($CHCl_3$), 3450 (NH), 1730 (conjugated ester C=O), and 1645 cm^{-1} (broad, amide C=O); nmr ($CDCl_3$) δ 6.7–7.3 (3 H m, NH and aryl CH), 4.41 (1 H d, J = 8 Hz, benzylic CHCO), 3.84 (3 H s, OCH_3), 3.63 (3 H s, OCH_3), and 0.7–3.4 [13 H m, aliphatic CH and NCH_3 doublet (J = 5 Hz) at δ 2.92].

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.98; H, 7.51; N, 4.25.

The ether-soluble fraction from the original carbonation reaction was washed with aqueous NaCl, dried, and concentrated to leave 2.14 g (37%) of the crude acid **9a**, mp 145–147°. Recrystallization from EtOH separated the pure acid **9a** as white

(7) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202, recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

needles: mp 152–153°; ir ($CHCl_3$) 3425 (NH), 2930 (broad, associated OH), 1735 (carboxyl C=O with intramolecular H bonding), and 1615 cm^{-1} (broad, amide C=O with intramolecular H bonding); uv max (95% EtOH) 298 mμ (ϵ 3430) with intense end absorption (ϵ 29,100 at 210 mμ); nmr ($CDCl_3$) δ 7.7 (1 H broad, OH or NH), 7.22 (1 H d, J = 9 Hz, aryl CH), 6.86 (1 H d, J = 9 Hz, aryl CH), 3.90 (3 H s, OCH_3), 3.00 (3 H d, J = 5 Hz, NCH_3), and 0.7–4.0 (12 H m, OH or NH and aliphatic CH); mass spectrum m/e (rel intensity), 303 (2, M$^+$), 259 (100), 216 (29), and 185 (36).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.24; H, 6.90; N, 4.53.

A 1.00-g (3.3 mmol) sample of the acid **9a** (mp 148–150°) was esterified with excess CH_2N_2 in an Et_2O–tetrahydrofuran mixture to yield 918 mg (87%) of the ester **9b**, mp 120–121°, as white plates from Et_2O–hexane. Recrystallization gave the pure ester **9b**: mp 124–125°; ir ($CHCl_3$) 3430 (NH), 1725 (conjugated ester C=O), 1645, 1655, and 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 6.7–7.4 (3 H m, aryl CH and NH), 4.17 (1 H d, J = 5 Hz, benzylic CHCO), 3.86 (3 H s, OCH_3), 3.67 (3 H s, OCH_3), 2.92 (3 H d, J = 5 Hz, NCH_3), and 1.0–3.4 (10 H m, aliphatic CH).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.15; H, 7.25; N, 4.14.

Attempts to effect equilibration of the esters **9b** or **10b** with NaOMe in MeOH or of the acids **9a** and **10a** with TsOH in PhH produced a crude product which appeared to be a cyclic imide, ir ($CHCl_3$) 1670 and 1710 cm^{-1}.

Birch Reduction of the Acid 4a.—To a mixture of 1.00 g of the acid **4a**, 30 ml of *tert*-BuOH, 40 ml of tetrahydrofuran, and 100 ml of redistilled liquid NH_3 was added 0.40 g (58 mg-atoms) of Li. After the resulting mixture had been stirred under reflux for 4 hr (during which time the blue color was discharged), an additional 0.40 g (58 mg-atom) of Li was added and stirring under reflux was continued for 3 hr. The mixture was treated successively with 30 ml of MeOH and 40 ml of H_2O and then the NH_3 was allowed to evaporate. After the mixture had been filtered and the residue had been washed with H_2O, the combined filtrates and washings were concentrated, and the residue was dissolved in 300 ml of H_2O and acidified with 13 ml of HOAc. The acid **11** which separated was collected as 0.93 g (92%) of white solid, mp 140–141° dec. Recrystallization from CH_2Cl_2–hexane separated 0.63 g (62%) of the pure acid **11** as white needles: mp 147–149° dec; ir ($CHCl_3$) 2920 (broad, associated OH), 1705 (carboxyl C=O), and 1662 cm^{-1} (enol ether C=C); uv (95% EtOH) end absorption (ϵ 3580 at 210 mμ); nmr ($CDCl_3$ + pyridine-d_5) δ 14.5 (1 H broad, OH), 4.66 (1 H m, vinyl CH), 3.49 (3 H s, OCH_3), and 0.8–3.9 (15 H m, aliphatic CH); mass spectrum, m/e (rel intensity), 204 (100), 177 (21), 162 (55), 161 (83), 123 (24), 91 (22), 83 (28), 81 (26), 79 (24), 73 (46), 55 (27), and 41 (33).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 8.09.

Preparation of the Keto Acid 12. A. From the Enol Ether 11.—A solution of 200 mg (0.81 mmol) of the enol ether **11** and 4.0 ml of aqueous 50% HOAc in 8.0 ml of 1,2-dimethoxyethane was allowed to stand at 25° for 18 hr and then concentrated under reduced pressure. The crude residue (229 mg) was recrystallized from acetone–hexane mixtures to separate 73 mg (29%) of the acid **12a** as white solid, mp 155–156°. The pure acid **12a** crystallized from PhH as white needles, mp 157–158°, identified with the subsequently described sample by comparison of ir spectra.

B. From the Aromatic Acid 4a.—The reduction of 20.0 g (81.5 mmol) of the acid **4a** with 16 g (2.3 g-atoms) of Li, 400 ml of *tert*-BuOH, 400 ml of tetrahydrofuran, and 800 ml of liquid NH_3 was performed as previously described. A solution of the crude product **11** and 350 ml of aqueous 50% HOAc in 450 ml of 1,2-dimethoxyethane was allowed to stand for 18 hr at 25° and then concentrated under reduced pressure. The crude product was partitioned between Et_2O and aqueous HOAc (5:2 v/v) and the ethereal layer was separated, washed with aqueous NaCl, dried (Na_2SO_4), and concentrated. A solution of the residue in 200 ml of toluene was again concentrated to remove water from the crude product **12a** (17.8 g or 94%, mp 105–150°). Recrystallization from CH_2Cl_2–hexane separated 12.9 g (68%) of the acid **12a**, mp 157–158°. This product crystallized from benzene as white needles: mp 157–158°; ir ($CHCl_3$) 2930 (broad, associated OH) and 1710 cm^{-1} (broad, C=O); uv max (95% EtOH) 282 mμ (ϵ 32) with intense end absorption (ϵ 3500 at 210 mμ); nmr ($CDCl_3$) δ 11.6 (1 H, broad, OH), 2.0–3.7 (9 H m, aliphatic CH), and 0.9–2.0 (8 H m, aliphatic CH); mass spectrum m/e (rel intensity), 234 (2, M$^+$), 162 (29), 119 (25), 91 (21), 78 (100), 77 (29), 53 (29), 52 (26), 51 (30), 50 (24), and 39 (38).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.88.

A 5.00-g (21.3 mmol) sample of the acid **12a** was esterified with excess ethereal CH_2N_2. The crude neutral product was obtained as 5.27 g of yellow liquid. A portion of the material was distilled in a short-path still (0.05 mm and 140° bath) to separate the partially purified ester **12b**: n^{27}_D 1.5222; ir (neat) 1740 (ester C=O) and 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.63 (3 H s, OCH_3), 2.0–3.6 (9 H m, aliphatic CH), and 1.0–2.0 (8 H m, aliphatic CH).

Conversion of the Amide Esters 9 and 10 to the Diesters 7 and 8. A. The More Stable Epimer 9b.—A solution of 830 mg (2.62 mmol) of the amide ester **9b** and 450 mg (5.5 mmol) of NaOAc in 21 ml of HOAc was cooled to the freezing point and then treated with 0.70 ml (*ca.* 11 mmol) of liquid N_2O_4. The resulting green suspension was stirred for 15 min and then partitioned between cold H_2O and CCl_4. After the organic layer had been washed with aqueous $NaHCO_3$ and with H_2O, it was dried (Na_2SO_4) and concentrated. A mixture of the residual yellow oil, 55 mg of anhydrous Na_2CO_3, and 100 ml of methylcyclohexane was refluxed with stirring for 36.5 hr and then cooled, diluted with Et_2O, and washed successively with aqueous 5% NaOH and with H_2O. The organic phase was dried and concentrated to leave 518 mg of the crude product as a brown liquid. The aqueous NaOH wash was acidified and extracted with EtOAc to separate 200 mg of crude acid product, which was esterified with excess ethereal CH_2N_2. The combined neutral products were distilled in a short-path still (0.15 mm and 160° bath) to separate 505 mg (64%) of the diester **8b** as a pale yellow liquid, which was identified with an authentic sample by comparison of ir and nmr spectra. For further characterization, a mixture of 446 mg (1.4 mmol) of the diester **8b**, 4.5 ml (9 mmol) of methanolic 2 *M* NaOMe, and 4.5 ml of H_2O was refluxed for 2 hr and then partitioned between H_2O and CH_2Cl_2. After the aqueous phase had been acidified and extracted with CH_2Cl_2, the organic extract was dried and concentrated. The residual crude product was recrystallized from CH_2Cl_2–PhH to separate 314 mg (77%) of the diacid **8a** as tan prisms, mp 189–190° dec. Recrystallization afforded the pure acid **8a** as white prisms, mp 189.5–191° dec, which was identified with an authentic sample (lit.[2] mp 190–191° dec) by a mixture melting point determination and by comparison of ir spectra.

B. The Less Stable Epimer 10b.—The same reaction procedure was used with 785 mg (2.48 mmol) of the amide ester **10b**, 427 mg (5.28 mmol) of NaOAc, 22 ml of HOAc, and 0.75 ml (*ca.* 12 mmol) of N_2O_4. The crude *n*-nitroso amide, a yellow liquid, and 85 mg of anhydrous Na_2CO_3 in 100 ml of methycyclohexane was refluxed with stirring for 51 hr and then subjected to the previously described isolation procedure. The crude neutral product (503 mg of orange liquid) was distilled in a short-path still (0.15 mm and 160° bath) to separate 377 mg (48%) of the diester **7b** as an orange liquid. The ir and nmr spectra of this product indicated the presence of the known[2] diester **7b** accompanied by small amounts of the more stable epimer **8b**. For further characterization, a solution of 377 mg (1.18 mmol) of the diester product and 8 mmol of NaOMe in 10 ml of MeOH was refluxed for 22 hr and then treated with 4 ml of H_2O and refluxed for an additional 2 hr. The reaction mixture was subjected to the previously described isolation procedure to separate 90 mg (27%) of the diacid **8a**, mp 179–188° dec. Recrystallization (acetone–hexane) afforded a sample of the pure diacid **8a**, mp 188–189° dec, which was identified with an authentic sample by a mixture melting point determination and by comparison of ir spectra.

Registry No.—**3a**, 33495-50-0; **3b**, 33495-51-1; **4a**, 19765-79-8; **4c**, 33495-53-3; **6**, 33495-54-4; **7b**, 33495-55-5; **8a**, 19765-82-3; **8b**, 19766-02-0; **9a**, 33495-58-8; **9b**, 33495-59-9; **10a**, 33495-60-2; **10b**, 33495-61-3; **11**, 33537-16-5; **12a**, 33495-62-4; **12b**, 33495-63-5.

Perhydroindan Derivatives. XIV. Derivatives of 6-Methoxyindene[1a]

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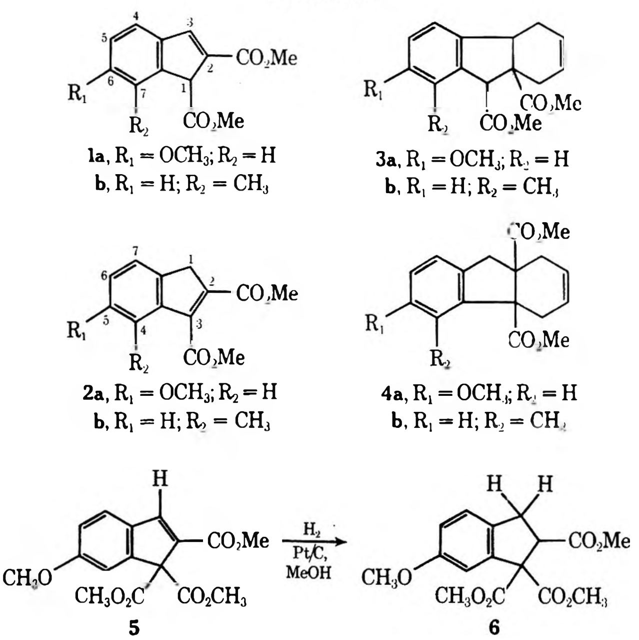
The isomeric 2-carbomethoxyindenes **16** and **17** have been synthesized and studied as dieneophiles in the Diels–Alder reaction to form tetrahydrofluorenes **26** and **27**. Although the indenes isomerize under the conditions of the Diels–Alder reaction, it was possible to prepare the desired 7-methoxytetrahydrofluorene derivative **26** in reasonable yield when the indene precursor **17** had a carbomethoxy substituent at C-7.

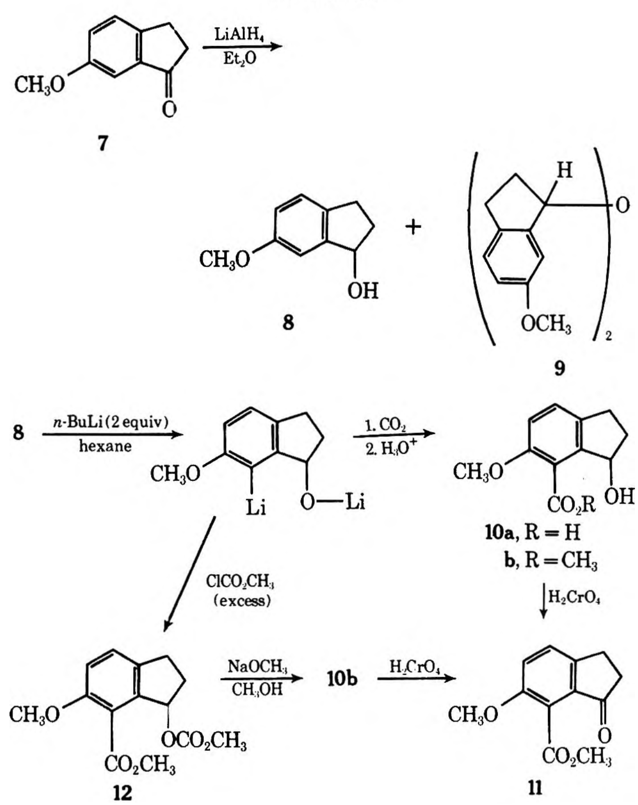
In seeking a preparative route to the tetrahydrofluorene derivatives **3**[2] (Scheme I) as potential precursors for the gibberellins, we found that, although the 7-methylindene derivative **1b** reacted with butadiene to form the expected Diels–Alder adduct **3b**,[2a] the 6-methoxyindene diester **1a** formed adduct **4a**, an isomer of the desired product **3a**.[2b] It was apparent that the starting indene **1a** was equilibrating with its double bond isomer **2a** under the rather vigorous conditions required for the Diels–Alder reaction. The formation of largely (if not exclusively) the adduct **4a** suggested that the indene **2a** was more stable than **1a**, that the indene **2a** was a more reactive dienophile than **1a**, or that some combination of these two factors determined the principal course of this reaction. An initial attempt to solve this problem by the preparation and use of the indene triester **5** (prepared from **1a** with NaH and $ClCO_2CH_3$) was not satisfactory because we were unable to isolate any pure adduct from reaction of butadiene with the sterically hindered triester **5**. Consequently, we have examined the use of various substituents to control the proportions of 6-methoxyindene derivatives and their double bond isomers which are present in reaction mixtures.

SCHEME I



The successful use of the indene **1b** to form the desired tetrahydrofluorene **3b** has been attributed[2] to the fact that isomerization of **1b** to the indene **2b** (the precursor of **4b**) would be opposed by a serious steric interaction between the two coplanar peri substituents (R_2 and CO_2CH_3) in **2b**.[3] Consequently, in our further study of 6-methoxyindene precursors for the tetrahydrofluorenes **3**, we elected to introduce a C-7 carbomethyl group into the indene; this substituent, which would be useful at a later stage in our synthetic scheme, was expected to favor the desired indene double bond isomer (*i.e.*, **1** rather than **2**) for the steric reason discussed above. To prepare an appropriate synthetic intermediate **11**, the procedures outlined in Scheme II were employed. This scheme, starting with the methoxyindanone **7**,[4] utilizes the selective ortho metalation[5] of the alcohol **8** to introduce the desired car-

SCHEME II



(1) (a) This research has been supported by Public Health Service Grant R01-CA-12634 from the National Cancer Institute. (b) Department of Chemistry, Georgia Institute of Technology, Atlanta, Ga. 30332. (c) National Institutes of Health Predoctoral Fellow, 1968–1971.

(2) (a) H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, *J. Org. Chem.*, **33**, 957 (1968); (b) H. O. House, J. K. Larson, and H. C. Müller, *ibid.*, **33**, 961 (1968).

(3) (a) In the absence of such a steric interaction, the two isomeric indenes are of about equal stability: D. G. Lindsay, B. J. McGreevy, and C. B. Reese, *Chem. Commun.*, 379 (1965). (b) When alkyl substituents are present at the 1 and 3 positions of indene, the favored double-bond isomer is the one with the smaller alkyl group at the double bond: J. Almy and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 4459 (1969).

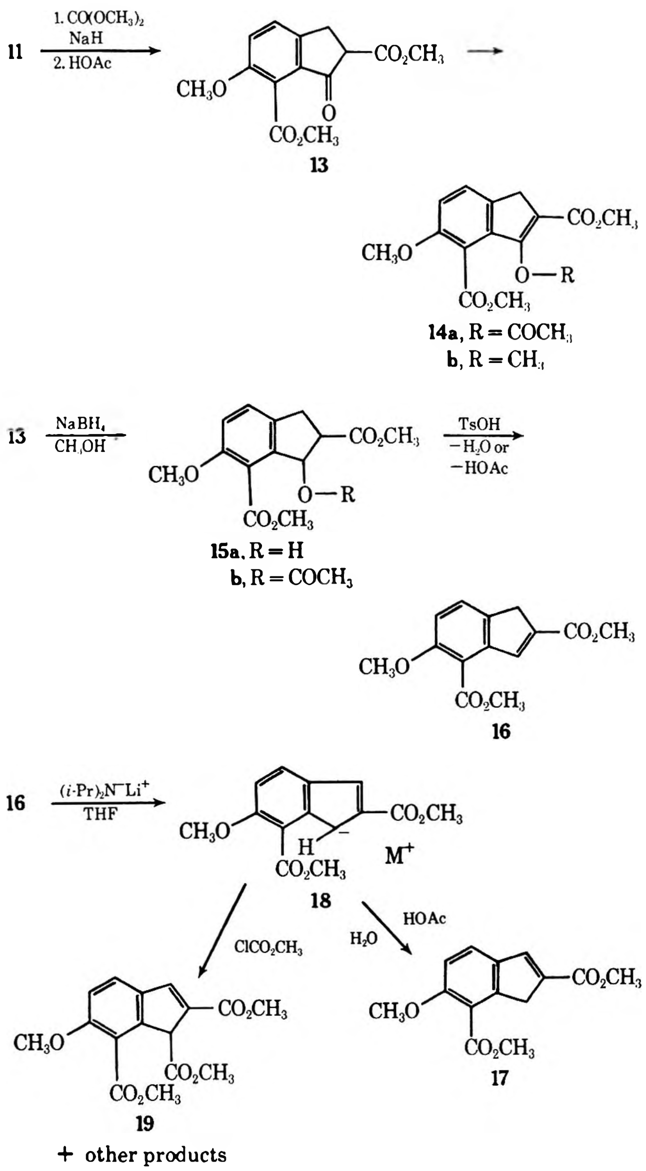
(4) H. O. House and C. B. Hudson, *J. Org. Chem.*, **35**, 647 (1970).

(5) See H. O. House, T. M. Bare, and W. E. Hanners, *J. Org. Chem.*, **34**, 2209 (1969), and references cited therein.

boxyl function at C-7. By formation of the crude diester **12** followed by alcoholysis and oxidation the indanol **8** was converted to the keto ester **11** in an overall yield of 58%.

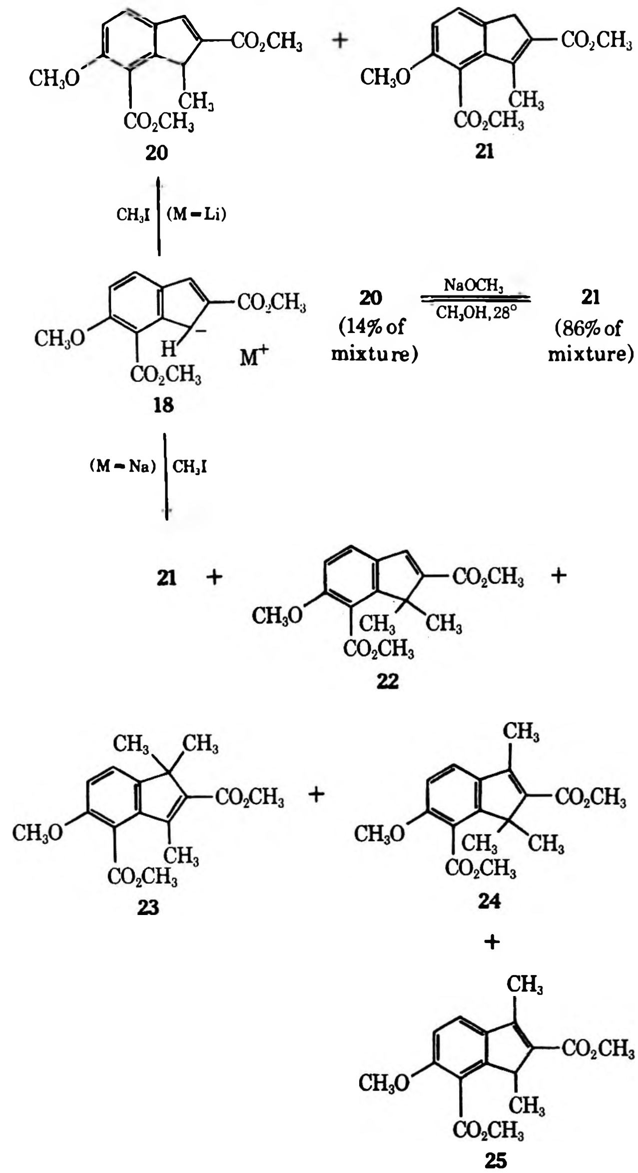
The further conversion of the keto ester **11** to the indenediester **16** is summarized in Scheme III. When the

SCHEME III



indenyl anion **18** (M = Li) formed from this ester **16** was protonated under kinetically controlled conditions, the major product (80–85% of the mixture) was the desired indene **17**. At equilibrium (25° in MeOH), the mixture of these two indenes contained 25% of **16** and 75% of **17**. Although we were able to obtain the triester **19**[6] from the anion **18** in poor yield, we have thus far been unsuccessful in forming a tricarboxylic acid derivative in high yield. Methylation (Scheme IV) of

SCHEME IV



the indenyl anion **18** (M = Li) produced the 1-methylindene **20**[6] which isomerized with great ease to the isomer **21**;[6] at equilibrium (28° in MeOH), the mixture contained 14% of **20** and 86% of **21**. This equilibrium composition is unexpected on steric grounds since the major component **21** possesses the same unfavorable steric interaction between coplanar CH_3 and CO_2CH_3 groups which is believed to destabilize the indene **2b** with respect to its isomer **1b**. It appears that the general tendency of indene isomers to be more stable with a substituent at the olefinic C-3 position rather than C-1[7,8] is sufficiently great to overcome the unfavorable steric interaction. Methylation of the sodium derivative of the indenyl anion **18** (M = Na) produced both the monomethyl product **21** and a series of di- and trimethylated products believed to possess structures

(6) The uv spectra of the isomeric indenes **16** [244 mμ (ε 15,600), 283 (14,300), 330 (6100)] and **17** [245 mμ (ε 8550), 307 (20,000)] differ sufficiently to allow us to assign structures to other derivatives that have one of these two chromophores.

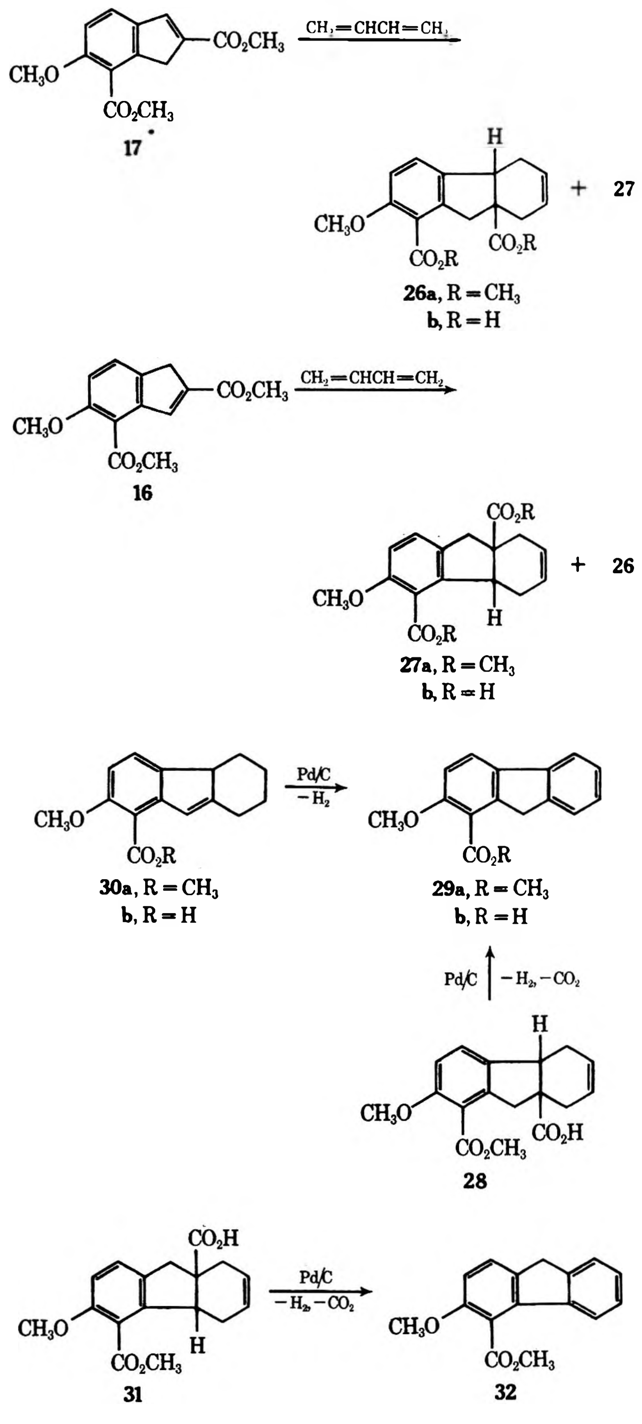
(7) For example, see (a) K. Bott, *Tetrahedron Lett.*, 4569 (1965); (b) O. Meth-Cohn and S. Gronowitz, *Chem. Commun.*, 81 (1966); (c) A. Melera, M. Claesen, and H. Vanderhaeghe, *J. Org. Chem.*, **29**, 3705 (1964); (d) R. C. Kerber and M. Hodos, *ibid.*, **33**, 1169 (1968).

(8) From studies of the equilibration of 1-methylindene and 3-methylindene, it is clear that the equilibrium mixture contains at least 90% of the 3-methyl isomer: H. Christol, F. Plenat, and C. F. Huebner, *Bull. Soc. Chim. Fr.*, 2640 (1964); A. M. Weidler and G. Bergson, *Acta Chem. Scand.*, **18**, 1487 (1964), and references cited therein.

22–25. Although we did not obtain sufficient amounts of these materials for complete characterization, it is pertinent to observe that the dimethyl product 25[6] does appear to exist predominantly as the indicated double bond isomer, which avoids the previously discussed steric interaction.

The foregoing data led us to select the indene 17 for study as a dienophile with butadiene. As illustrated in Scheme V, the conditions required to effect the Diels–Alder reaction were sufficiently vigorous to cause interconversion of the isomeric indenes 16 and 17.[9] When the reactions of each of the isomeric indenes 16 and 17

SCHEME V



(9) We presume that this interconversion is not a thermal process but, rather, was catalyzed by traces of either acidic or basic substances which were present in the reaction mixtures.

were performed on a small scale in sealed glass vessels, each of the double bond isomers 16 and 17 gave a slight excess of the expected tetrahydrofluorene 26a or 27a. However, in preparative scale reactions performed in an autoclave, equilibration of the indenes[9] clearly occurred more rapidly than the Diels–Alder reaction so that the same mixture of tetrahydrofluorenes 26a and 27a was obtained from either indene 16 or 17. Each of the adducts 26a and 27a appeared to be stable to the conditions of the Diels–Alder reaction.

The mixture of diesters 26a and 27a produced in this reaction could be separated effectively by saponification and fractional crystallization of the diacids 26b and 27b. Fortunately, the desired tetrahydrofluorene 26b was the less soluble and consequently the more easily isolated. Although the structures of the two tetrahydrofluorenes were tentatively assigned from the results of small-scale Diels–Alder reactions (17 → mainly 26a and 16 → mainly 27a), further verification of the structure for adducts 26 was clearly desirable. For this reason we dehydrogenated the crude monoester 28 (from 26b and 1 equiv of CH_2N_2) to form the fluorene ester 29a, which was also prepared by dehydrogenation of the known[5] tetrahydro ester 30a. The corresponding dehydrogenation–decarboxylation reaction applied to the crude isomeric monoester 31 (from 27b and 1 equiv of CH_2N_2) produced the previously unknown fluorene ester 32.

Experimental Section[10]

Preparation of the Triester 5.—To a suspension of 1.1 g (46 mmol) of NaH (previously washed with pentane) in 10 ml of 1,2-dimethoxyethane (DME) was added a solution of 2.6 g (10 mmol) of the diester 1a, mp 96–99° (lit.[2b] mp 97–98.5°). After the H_2 evolution (215 ml or 0.87 equiv) ceased, the pale green suspension was treated with 2.86 g (30 mmol) of $ClCO_2Me$ and the resulting mixture was refluxed for 5 hr. After the solution had been cooled and neutralized with 5 ml of HOAc, it was poured onto ice. The solid product was collected and combined with the benzene extract of the filtrate after the extract had been washed (aqueous $NaHCO_3$ and aqueous NaCl), dried, and concentrated. Crystallization from MeOH afforded 2.8 g (88%) of fractions of the crude triester, melting range 138–149.5°. Recrystallization (MeOH) separated 2.33 g (73%) of the triester 5 as tan needles, mp 149–150.5°. Sublimation at 140° (0.05 mm) afforded the pure triester 5 as white needles: mp 149–150°; ir (CCl_4) 1740 (unconjugated ester C=O) and 1720 cm^{-1} (conjugated ester C=O); nmr ($CDCl_3$) δ 6.3–7.8 (4 H m, aryl and vinyl CH), 3.85 (3 H s, OCH_3), 3.83 (3 H s, OCH_3), and 3.72 (6 H s, OCH_3); mass spectrum *m/e* (rel intensity) 320 (18, M^+), 57 (31), 56 (39), 55 (25), 44 (100), 43 (23), 41 (73), and 39 (29); uv (95% EtOH) 241 mμ (ϵ 13,400), 310 (13,700), and 323 (13,900); uv (95% EtOH with added 0.1 *M* aqueous NaOH) 240 mμ (ϵ 13,200), 310 (13,600), and 323 (13,700). For comparison the corresponding values for the starting diester 1a with an acidic H atom are uv (95% EtOH) 237 mμ (ϵ 11,500), 308 (16,200), and 318 (16,200); uv (95% EtOH with added EtOK) 260 mμ (sh, ϵ 14,900), 289 (23,200), and 340 (11,700). When this latter basic solution was acidified (aqueous HCl), it exhibited the same spectrum as the original diester 1a.

(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined with a Varian Model A-60, T-60, or HA-100 nmr spectrometer. The chemical shift values are expressed either in Hertz or δ values relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer) mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.89; H, 5.04.

Hydrogenation of the Triester 5.—A solution of 409 mg (1.28 mmol) of the unsaturated ester **5** in 45 ml of MeOH was hydrogenated at 45° and 1 atm over 45 mg of a 5% Pt/C catalyst. After an H_2 uptake of 47.7 ml (1.2 equiv), the reaction was stopped and the mixture was filtered and concentrated. Crystallization of the residual oil from a benzene–hexane mixture separated 275 mg (67%) of the triester **6** as tan prisms, mp 75–76°. Recrystallization from MeOH gave the pure triester **6** as colorless needles: mp 76–77°; ir ($CHCl_3$) 1740 cm^{-1} (ester C=O); uv (95% EtOH) 283 mμ (ε 3060); nmr ($CDCl_3$) δ 6.7–7.3 (3 H m, aryl CH), 3.77 (3 H s, OCH_3), 3.74 (3 H s, OCH_3), 3.66 (6 H s, OCH_3), with a multiplet centered at δ 4.08 (1 H, CH) and a broad doublet (both *J* values ~ 8 Hz) centered at 3.23 (2 H, benzylic CH_2); mass spectrum *m/e* (rel intensity), 322 (18, M^+), 263 (29), 262 (100), 212 (23), 211 (40), 168 (27), 154 (35), 78 (23), 56 (22), and 43 (28).

Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.53; H, 5.71.

6-Methoxy-1-indanol (8).—The methoxyindanone **7**[4] was reduced with ethereal $LiAlH_4$ to produce the alcohol **8** in 92–94% yield. The pure alcohol **8** crystallized from hexane as colorless plates, mp 46–47.5° (lit.[11] mp 47–48.5°), ir (CCl_4) 3590 and 3340 cm^{-1} (free and associated OH).

When a partially purified sample of this alcohol **8** was allowed to stand for several months, partial decomposition (presumably acid-catalyzed) of the sample was evident. Two recrystallizations (MeOH) of this crude product separated the dimeric ether **9** as white needles: mp 91.5–92°; ir (CCl_4) no OH or C=O in 3 or 6 μ regions; uv (95% EtOH) 283 mμ (ε 6560) and 288 (sh, 5950); nmr ($CDCl_3$) δ 6.6–7.3 (6 H m, aryl CH), 5.03 (2 H t, *J* = 6 Hz, > CHO), 3.68 (6 H s, OCH_3), and 1.8–3.4 (8 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 146 (100), 131 (50), 91 (17), and 77 (16).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.64; H, 6.93.

Preparation of the Hydroxy Acid 10.—A mixture of 26.4 g (0.161 mol) of the alcohol **8** and 31.0 g (0.323 mol) of freshly sublimed *tert*-BuONa in 500 ml of hexane was metalated with 0.323 mol of *n*-BuLi in 135 ml of hexane and the resulting mixture was carbonated with Dry Ice.[12] After acidification the acid **10a** (31.1 g, mp 159° dec) was collected; extraction of the aqueous filtrate with EtOAc separated an additional 7.95 g of the crude acid **10a**. From the various hexane and Et_2O solutions of neutral products, the unchanged alcohol **8** was recovered as 725 mg of colorless plates from hexane, mp 46–47.5°. The yield of acid **10a** based on unrecovered alcohol **8** was 89%. A pure sample of the acid **10a** was obtained as colorless prisms from EtOAc: the decomposition point varied within the range 150–151° to 160–161° (dependent on rate of heating); ir ($CHCl_3$) 3500 and 3240 (associated OH) and 1725 cm^{-1} (carboxyl C=O); uv (95% EtOH) 296 mμ (ε 3200); nmr (pyridine-d_5) δ 11.07 (1 H s, COOH, exchanged with D_2O), 7.42 (1 H d, *J* = 8.5 Hz, aryl CH), 7.09 (1 H d, *J* = 8.5 Hz, aryl CH), 5.96 (1 H m, >CHO), 3.84 (3 H s, OCH_3), and 2.2–3.3 (5 H m, aliphatic CH and OH, 1 H exchanged with D_2O).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.41; H, 5.78.

In a subsequent preparation[12] a solution of 192 mmol of *n*-BuLi in 120 ml of hexane was added, dropwise and with stirring, to a suspension of 15.68 g (96 mmol) of the alcohol **8** in 300 ml of hexane. The bright red mixture was stirred at 25° for 1 hr and then added to excess Dry Ice. After the usual isolation procedure, manipulation of the neutral fraction separated 4.18 g (26.5%) of the starting alcohol **8**, mp 45–47°. Acidification, filtration, and subsequent extraction (EtOAc) of the aqueous phase separated a total of 13.25 g (66.5% or 91% based on unrecovered alcohol **8**) of fractions of the acid **10a** with decomposition points in the range 157–158 to 160–161°.

After 8.43 g (40.5 mmol) of the acid **10a** had been esterified with excess ethereal CH_2N_2, the residual neutral product (9.19 g, mp 55–56°) was recrystallized (pentane) to give the pure ester **10b** as colorless rods: mp 55–55.5°; ir (CCl_4) 3590 and 3530 (free and associated OH), 1740 (w), and 1700 cm^{-1} (s) (ester C=O); uv (95% EtOH) 204 mμ (ε 26,400) and 292 (3400); nmr ($CDCl_3$) δ 7.22 (1 H d, *J* = 8.5 Hz, aryl CH), 6.82 (1 H d, *J* = 8.5 Hz, aryl CH), 5.21 (1 H m, CHO), 3.90 (3 H s, OCH_3), 3.78 (3 H s, OCH_3), and 2.0–3.3 (5 H m, OH and aliphatic CH); mass spectrum *m/e* (rel intensity) 222 (23, M^+), 194 (50), 189 (100), 173 (25), 162 (50), 161 (20), 115 (25), 105 (25), 104 (39), 103 (29), 91 (32), 77 (29), 63 (20), 51 (20), and 39 (20).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.96; H, 6.29.

Preparation of the Keto Ester 11.—To a cold (0°), stirred solution of 1.55 g (7.0 mmol) of the hydroxy ester **10b** in 15 ml of acetone was added 2.5 ml of acidic aqueous 2.67 *M* H_2CrO_4 reagent.[13] The excess oxidant was consumed with *i*-PrOH and the mixture was partitioned between H_2O and EtOAc. The organic layer was washed (aqueous NaCl), dried, and concentrated to leave the crude ketone **11** as 1.43 g (93%) of yellow solid, mp 125–126°. Recrystallization (acetone–hexane mixture) afforded the pure keto ester **11** as colorless prisms: mp 127–127.5°; ir ($CHCl_3$) 1735 (ester C=O) and 1715 cm^{-1} (C=O); uv (95% EtOH) 248 mμ (ε 7100) and 322 (4700); nmr ($CDCl_3$) δ 7.45 (1 H d, *J* = 8.5 Hz, aryl CH), 7.20 (1 H d, *J* = 8.5 Hz, aryl CH), 3.95 (3 H s, OCH_3), 3.85 (3 H s, OCH_3), and 2.5–3.2 (4 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 220 (38, M^+), 205 (38), 189 (100), 103 (26), 89 (22), 78 (21), and 77 (26).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.75; H, 5.47.

In subsequent experiments the hydroxy acid **10a** was esterified (CH_2N_2) and oxidized without isolation of the intermediate. Thus, 13.25 g of the acid **10a** was converted to 11.42 g (81.5%) of the keto ester **11**, mp 126–127°.

Preparation of the Diester 12.—After a mixture of 44 mmol of *n*-BuLi and 3.18 g (19.6 mmol) of the indanol **8** in 128 ml of hexane had been allowed to react for 4 hr at 25° as previously described, the mixture was added to a cold (0°), stirred solution of 9.5 ml (95 mmol) of $ClCO_2Me$ in 50 ml of hexane. The resulting white suspension was acidified (HOAc) and partitioned between Et_2O and aqueous $NaHCO_3$, and the ethereal layer was washed with aqueous NaCl and then dried and concentrated. After further concentration under reduced pressure (0.3 mm and 40–50° to remove methyl valerate), the residual orange liquid (4.95 g) contained (tlc, silica gel coating and a PhH–Et_2O eluent) the desired diester **12** and a more rapidly eluted impurity. A benzene solution of this crude product was filtered through Florisil and a 2.53-g aliquot of the resulting crude product was chromatographed on 400 g of silica gel (Davison No. 922) packed in a 3.8 × 50 cm column of nylon tubing. After the chromatogram had been developed with a hexane–Et_2O mixture (2.5:1 v/v), the column was scanned with a uv lamp and the sections containing the diester **12** were removed and washed with Et_2O. The diester **12** was obtained as a yellow oil which crystallized on standing in the cold. Recrystallization from cold Et_2O afforded the partially purified diester **12** as white needles, mp 41–42°, which rapidly discolored on standing: ir (CCl_4) 1750 cm^{-1} (broad, ester C=O); uv max (95% EtOH) 296 mμ (ε 3610) with intense end absorption (ε 31,500 at 204 mμ); nmr (CCl_4) δ 7.13 (1 H d, *J* = 8.2 Hz, aryl CH), 6.80 (1 H d, *J* = 8.2 Hz, aryl CH), 6.0–6.3 (1 H m, benzylic CHO), 1.8–3.2 (4 H m, aliphatic CH), and three 3 H singlets at δ 3.77, 3.73, and 3.70 (three OCH_3 groups); mass spectrum *m/e* (rel intensity) 280 (3, M^+), 204 (41), 189 (24), 173 (51), 172 (100), 115 (23), and 59 (45).

A solution of 1.08 g (3.99 mmol) of the diester **12** in 10 ml of MeOH was treated with 6 mmol of NaOMe in 6 ml of MeOH. After the resulting solution had been stirred at 25° for 3.5 hr, it was acidified (HOAc) and partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal layer was washed with aqueous NaCl, dried (Na_2SO_4), and concentrated to leave 0.9 g of orange liquid containing (tlc) primarily the hydroxy ester **10b**. Crystallization from pentane separated 573 mg (66%) of the hydroxy ester **10b**, mp 50–54.5°. Recrystallization gave the pure ester **10b**, mp 53–54.5°.

The most efficient preparative route to the keto ester **11** involved the successive conversion of the indanol **8** to the diester **12**, the hydroxy ester **10b**, and the ketone **11** without purification of intermediates. In a typical preparation 24.05 g (147 mmol) of the indanol **8** was metalated with *n*-BuLi and *tert*-BuOLi [from 14.6 g (154 mmol) of *tert*-BuOH and 510 mmol of *n*-BuLi], acylated with 80 ml (1.0 mol) of $ClCO_2CH_3$, transesterified with

(11) J. C. Winter, D. D. Godse, and P. K. Gessner, *J. Org. Chem.*, **30**, 3231 (1965).

(12) This carboxylation procedure was described previously.[5] In this study we have been able to achieve the same specificity without adding *tert*-BuONa. In this way the tedious purification of *tert*-BuONa is avoided.

(13) D. C. Kleinfelter and P. v. R. Schleyer, *Org. Syn.*, **42**, 79 (1962).

154 mmol of NaOMe in 177 ml of MeOH (containing 0.5 ml of HCO_2Me to remove any NaOH), and oxidized with 150 mmol of H_2CrO_4 in 300 ml of acidic aqueous acetone to give 29.5 g of the crude ketone **11** as a yellow solid. Recrystallization (CCl_4) separated 17.92 g of the keto ester **11** as tan prisms, mp 120–124.5°; 920 mg (3.9%) of 6-methoxyindanone **7** (mp 100–105°, needles from hexane) and 1.84 g of the keto ester, mp 120–124° (prisms from CCl_4), were recovered from the mother liquors. Thus, the overall yield of the keto ester **11** was 19.76 g (57.9% based on the indanol **8**).

Preparation of the Keto Diester 13.—A solution of 4.06 g (18.5 mmol) of the keto ester **11** in 30 ml of PhH was added, dropwise and with stirring over 1 hr, to a warm (55–60°) mixture of 1.20 g (50 mmol) of NaH , 9.9 g (110 mmol) of $(MeO)_2CO$, and 30 ml of PhH. After the resulting mixture had been stirred at 60° for 30 min, it was cooled, neutralized with 5 ml of HOAc, poured into ice water, and acidified with HCl to pH 2. The organic layer was separated, combined with the PhH extract of the aqueous phase, and then washed (aqueous $NaHCO_3$ and aqueous NaCl), dried, and concentrated. Crystallization of the residue from MeOH separated 4.125 g (80.5%) of a mixture of keto and enol forms of the keto diester **13** as orange prisms: mp 120–125°; the broad melting range was not altered by recrystallization; ir ($CHCl_3$) 1735 (br, ester C=O) and 1655 cm^{-1} (enol C=C); uv (95% EtOH), 217 mμ (ε 17,700), 251 (6400), 301 (6200), and 322 (br, 6600); nmr ($CDCl_3$) δ 10.2 (*ca.* 0.2 H br, enol OH), 6.8–7.2 (2 H m, aryl CH), a series of singlets at 3.88, 3.75, and 3.68 (total 9 H, OCH_3), and 3.0–4.6 (*ca.* 3 H m, aliphatic CH).

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.45; H, 5.09.

A mixture of 1.39 g (5.0 mmol) of the keto diester **13**, 3.0 ml of Ac_2O, and 10 ml of CCl_4 was treated with 1 drop of aqueous 70% $HClO_4$. The crystalline product began to separate from the resulting red solution after 1 min. After the mixture had been partitioned between aqueous $NaHCO_3$ and $CHCl_3$, the organic layer was dried and concentrated. Recrystallization of the solid residue (1.602 g) from MeOH separated the 1.417 g (89%) of the pure enol acetate **14a** as colorless prisms: mp 166–167°; ir ($CHCl_3$) 1790 (enol ester C=O), 1730 and 1710 cm^{-1} (ester C=O); uv (95% EtOH) 240 mμ (ε 12,600), 281 (17,100), and 322 (6050); nmr ($CDCl_3$) δ 7.44 (1 H d, J = 8.5 Hz, aryl CH), 6.98 (1 H d, J = 8.5 Hz, aryl CH), 3.94 (3 H s, OCH_3), 3.83 (3 H s, OCH_3), 3.78 (3 H s, OCH_3), 3.64 (2 H s, benzylic CH_2), and 2.33 (3 H s, $COCH_3$).

Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.98; H, 5.24.

A cold (0°) solution of 2.69 g (10.3 mmol) of the keto diester **13** in 15 ml of DME was treated with excess ethereal CH_2N_2 and allowed to stand at 0° for 2 hr. After the resulting mixture had been concentrated and diluted with hexane, the enol ether **14b** was collected as 2.91 g (96.5%) of crystalline fractions melting within the range 132–135.5°. Recrystallization from PhH afforded the pure enol ether **14b** as pale gray prisms: mp 135.5–136°; ir (CCl_4) 1745 and 1715 cm^{-1} (ester C=O); uv (95% EtOH), 222 mμ (ε 14,400), 285 (16,400), and 315 (sh, 9000); nmr ($CDCl_3$) δ 7.28 (1 H d, J = 8.4 Hz, aryl CH), 6.85 (1 H d, J = 8.4 Hz, aryl CH), 4.10 (3 H s, OCH_3), 3.90 (3 H s, OCH_3), 3.83 (3 H s, OCH_3), 3.78 (3 H s, OCH_3), and 3.50 (2 H s, benzylic CH_2); mass spectrum m/e (rel intensity) 292 (59, M^+), 262 (29), and 234 (100).

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.87; H, 5.56.

Preparation of the Indenes 16 and 17.—A suspension of 2.78 g (10 mmol) of the enolic keto ester **13** in cold (−50°), neutral MeOH was treated with 950 mg (25 mmol) of $NaBH_4$ and the resulting mixture was stirred successively at −50° for 15 min, −35° for 30 min, and −20° for 1 hr. The mixture was neutralized with 1.5 ml of HOAc and then partitioned between aqueous $NaHCO_3$ and EtOAc. After the organic solution had been washed (aqueous NaCl) and dried, concentration left the crude alcohol **15a** as a pale brown gum which partially crystallized on standing. A portion of this crude product from a comparable experiment was recrystallized from a PhH–hexane mixture to separate one pure stereoisomer of the alcohol **15a** as colorless needles: mp 158–159.5°; ir ($CHCl_3$) 3520 (br, OH), 1735, and 1705 cm^{-1} (sh) (ester C=O); uv (95% EtOH) 295 mμ (ε 4900); nmr ($CDCl_3$) δ 7.18 (1 H d, J = 8.5 Hz, aryl CH), 6.80 (1 H d, J = 8.5 Hz, aryl CH), 5.35 (1 H partially resolved multiplet, CHO), 3.95 (3 H s, OCH_3), 3.85 (3 H s, OCH_3), 3.78 (3 H s, OCH_3), and 3.0–3.6 (4 H m, aliphatic CH and OH).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.03; H, 5.82.

A solution of the crude alcohol **15a** described above and 203 mg of TsOH in 35 ml of PhH was refluxed with continuous separation of H_2O for 16 hr and then washed successively with aqueous $NaHCO_3$ and aqueous NaCl. After the resulting solution had been dried and concentrated, successive recrystallization of the neutral yellow solid from an acetone–hexane mixture and then from MeOH separated 2.113 g (80% based on the ketone **13**) of the indene **16** as fractions melting within the range 116–120.5°. Recrystallization (MeOH) afforded the pure indene **16** as yellow needles: mp 120–121°; ir ($CHCl_3$) 1735 (sh) and 1715 cm^{-1} (ester C=O); uv (95% EtOH) 244 mμ (ε 15,600), 283 (14,300), and 330 (6100); nmr ($CDCl_3$) δ 7.90 (1 H br, vinyl CH), 7.50 (1 H d, J = 8.5 Hz, aryl CH), 6.95 (1 H d, J = 8.5 Hz, aryl CH), 3.98 (3 H s, OCH_3), 3.90 (3 H s, OCH_3), 3.85 (3 H s, OCH_3), and 3.60 (2 H br, CH_2); mass spectrum m/e (rel intensity) 262 (38, M^+), 231 (38), 230 (100), 173 (21), and 43 (24).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.15; H, 5.47.

To a cold (−78°) solution of $(i\text{-Pr})_2NLi$ [from 3.2 mmol of n-BuLi and 400 mg (4.0 mmol) of $(i\text{-Pr})_2NH$] in 5 ml of THF was added a solution of 262 mg (1.0 mmol) of the indene **16** in 5 ml of THF. The resulting mixture, containing the red indenyl anion **18** partially in solution and partially as a suspension, was neutralized by passing a stream of CO_2 through the reaction mixture and then partitioned between Et_2O and aqueous Na_2CO_3. After the neutral Et_2O layer had been dried and concentrated, recrystallization of the residual solid (238 mg) from MeOH separated 219 mg (84%) of the indene **17** as yellow rods, mp 98–101°. Recrystallization (MeOH) gave the pure indene **17** as yellow rods: mp 100.5–101°; ir (CCl_4) 1735 (sh) and 1715 cm^{-1} (ester C=O); uv (95% EtOH) 245 mμ (ε 8550) and 307 (20,000); nmr ($CDCl_3$) δ 7.60 (br, 1 H, vinyl CH), 7.55 (1 H d, J = 8.5 Hz, aryl CH), 6.95 (1 H d, J = 8.5 Hz, aryl CH), 3.95 (3 H s, OCH_3), 3.90 (3 H s, OCH_3), 3.82 (3 H s, OCH_3), and 3.80 (2 H m, CH_2); mass spectrum m/e (rel intensity) 262 (43, M^+), 230 (45), 229 (100), 214 (24), 200 (23), 197 (20), 171 (34), 140 (20), 115 (33), 114 (24), 101 (24), and 44 (29).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.31; H, 5.48.

In subsequent mixtures of the indenes **16** and **17** obtained by equilibration the approximate compositions were determined by integration of the nmr vinyl CH peaks at δ 7.90 (for **16**) and 7.60 (for **17**). A solution of 105 mg (0.4 mmol) of the indene **16** and 0.04 mmol of NaOMe in 10 ml of MeOH was allowed to stand at 25° for 24 hr and then neutralized with HOAc. The recovered neutral product (100 mg) contained *ca.* 25% of **16** and 75% of **17**. When the sodium indenyl anion was generated from indene **16** (3.14 g or 12 mmol), NaH (480 mg or 20 mmol), and 0.2 ml of MeOH in 80 ml of THF and then neutralized with 1.5 ml of HOAc, the recovered neutral product (3.02 g) contained *ca.* 20% of **16** and 80% of **17**. Similarly, the lithium salt from 262 mg (1.0 mmol) of indene **16** and 1.2 mmol of $(i\text{-Pr})_2NLi$ in 30 ml of THF was neutralized with HOAc to give a neutral mixture (255 mg) containing *ca.* 18% **16** and 82% **17**. Reaction of 262 mg (1.0 mmol) of the indene **16** with 1.1 mmol of MeLi in 35 ml of cold (−50°) THF also produced the lithium salt of the red anion **18**. After this mixture had been neutralized with HOAc, the crude neutral product (263 mg) was chromatographed (SiO_2). The indene **17** (192 mg or 73%) was recovered from fractions eluted with 5% MeOAc in PhH. From the fractions eluted with 15% MeOAc in PhH, recrystallization (CH_2Cl_2–hexane) afforded 22 mg of yellow needles, mp 146–147°, with spectral properties suggesting that this unidentified material is a monoester monoketone: ir ($CHCl_3$) 1725 (ester C=O) and 1660 cm^{-1} (conjugated ketone C=O); uv (95% EtOH) 251 mμ (ε 6800) and 323 (21,800); nmr ($CDCl_3$) δ 7.5–7.6 (2 H m, vinyl CH and aryl CH), 7.00 (1 H d, J = 8.5 Hz), 3.97 (3 H s, OCH_3), 3.96 (3 H s, OCH_3), 3.80 (2 H d, J = 1.6 Hz, CH_2), and 2.42 (3 H s, $COCH_3$).

The most efficient preparative procedure for converting the keto diester **13** to the indene **16** involved the successive preparations of alcohol **15a**, acetate **15b**, and the olefin **16** without purification of intermediates. In a typical preparation, 18.2 g (65.6 mmol) of the ketone **13** was reduced with 6.50 g (187 mmol) of $NaBH_4$ in 300 ml of MeOH and then acidified (44 ml of HOAc). The crude alcohol **15a** (18.4 g of orange solid) was dissolved in 200 ml of cold (0°) CH_2Cl_2 containing 5.7 ml (71 mmol) of pyridine and treated with 5.3 ml (74 mmol) of AcCl. After the resulting solution had been stirred at 25° for 2.5 hr, it was washed successively with H_2O, aqueous 1 M HCl, and H_2O, and then dried and concentrated. An 18.8-g portion of the crude acetate **15b** (20.4 g of brown liquid) was distilled in a short-path still (0.15 mm and 95–105°) to separate 17.8 g of the crude acetate **15b** as a yellow liquid: ir (CCl_4) 1745 cm^{-1} (broad, ester C=O); uv max (95% EtOH) 295 mμ (ε 3400); nmr (CCl_4) δ 6.4–7.5 (3 H m, aryl CH and benzylic CHO), 2.9–4.0 (12 H m, three OCH_3 groups and aliphatic CH), and two singlets at 2.00 and 1.92 (3 H, CH_3CO of stereoisomeric acetates). A solution of this acetate **15b** in 250 ml of PhH containing 1.36 g (8.6 mmol) of p-toluenesulfonic acid was refluxed for 24 hr and then cooled and washed successively with aqueous Na_2CO_3 and aqueous NaCl. The aqueous phases were extracted with EtOAc and the combined organic layers were dried and concentrated. Recrystallization of the residual solid (12.7 g) from MeOH afforded 8.41 g (53% based on the ketone **13**) of the indene **16**, mp 118.5–120°.

Preparation of the Triester 19.—A cold (0°) solution of the lithium indenyl anion **18**, prepared from 633 mg (2.4 mmol) of the indene **16** and 3.0 mmol of $(i\text{-}Pr)_2NLi$ in 40 ml of THF, was treated with 470 mg (5.0 mmol) of $ClCO_2Me$. After 2 min the red color was discharged and the solution was neutralized (HOAc) and partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O solution was washed (aqueous NaCl), dried, and concentrated to leave 884 mg of orange liquid. Crystallization from MeOH separated 191 mg of the crude triester **19**, mp 152–160°. Recrystallization afforded 100 mg (17%) of the pure triester **19**, as pale yellow needles: mp 167–168°; ir ($CHCl_3$) 1740 and 1715 cm^{-1} (ester C=O); uv (95% EtOH) 238 mμ (ε 9600) and 308 (19,800); nmr ($CDCl_3$) δ 7.70 (1 H d, J = 1.6 Hz, vinyl CH), 7.50 (1 H d, J = 8.5 Hz, aryl CH), 6.95 (1 H d, J = 8.5 Hz, aryl CH), 4.90 (1 H d, J = 1.6 Hz, benzylic CH), and four 3 H singlets (OCH_3) at 3.95, 3.90, 3.83, and 3.65.

Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 60.16; H, 5.17.

Methylation of the Indenyl Anion 18. A. The Lithium Salt.—To a cold (−50°), stirred solution of $(i\text{-}Pr)_2NLi$ [prepared from 2.08 mmol of n-BuLi and 0.50 ml (3.5 mmol) of $(i\text{-}Pr)_2NH$] in 50 ml of THF was added a solution of 524 mg (2.0 mmol) of the indene **16** in 10 ml of THF. The resulting red solution was stirred at −20° for 10 min and then warmed to 0°, and 5 ml of CH_3I was added dropwise and with stirring during 15 min. The resulting mixture was neutralized (2.0 ml of HOAc) and then partitioned between H_2O and Et_2O. After the Et_2O layer had been washed (aqueous NaCl) and dried, concentration left a yellow oil which was *immediately* crystallized from MeOH. The indene **20** separated as 245 mg (44.5%) of yellow prisms, mp 99–104°. The melting range, which may be the result of the equilibration **20** → **21** during the melting point determination, was not improved by recrystallization: ir (CCl_4) 1740 and 1715 cm^{-1} (ester C=O); uv (95% EtOH) 243 mμ (ε 8700) and 308 (20,800); nmr (CCl_4) δ 7.2–7.5 (2 H m, vinyl CH and aryl CH), 6.85 (1 H d, J = 8.5 Hz, aryl CH), 3.87 (3 H s, OCH_3), 3.83 (3 H s, OCH_3), 3.74 (3 H s, OCH_3), 3.4–3.9 (1 H m, benzylic CH), and 1.25 (3 H d, J = 7.5 Hz, CH_3C); mass spectrum m/e (rel intensity) 276 (12, M^+), 244 (16), 185 (18), 58 (43), 44 (30), and 43 (100).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.03; H, 5.81.

A solution of the mother liquors from this separation in 6 ml of MeOH was treated with 0.07 mmol of NaOMe. After the solution had been allowed to stand for 16 hr at 28°, it was neutralized with HOAc and the neutral material was recovered in the usual manner. Recrystallization of the crude residual solid (268 mg) from MeOH separated 175 mg (32%) of fractions of the indene **21** melting within the range 125–130.5°. Recrystallization afforded the pure indene **21** as colorless prisms: mp 130–130.5°;[14] ir (CCl_4) 1740 and 1715 cm^{-1} (ester C=O); uv (95% EtOH) 219 mμ (ε 12,800), 241 (12,500), 282 (16,500), and 317 (6300); nmr (CCl_4) δ 7.28 (1 H d, J = 8.5 Hz, aryl CH), 6.77 (1 H d, J = 8.5 Hz, aryl CH), 3.82 (3 H s, OCH_3), 3.78 (3 H s, OCH_3), 3.72 (3 H s, OCH_3), 3.50 (2 H m, benzylic CH_2), and 2.40 (3 H t, J = 2.4 Hz, vinyl CH_3); mass spectrum m/e (rel intensity) 276 (3, M^+), 116 (5), 91 (7), 58 (44), 44 (24), 43 (100), and 42 (12).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.02; H, 5.95.

In a comparable methylation reaction starting with 262 mg (1.0 mmol) of the indene **16** where the crude product was distilled in a short-path still (0.1 mm and 170° bath) before crystallization, the product separated after one recrystallization (139 mg, mp 118–119°) contained (nmr analysis) about equal amounts of the methylindenes **20** and **21**. After equilibration of the mixture with NaOMe the pure indene **21** was isolated, mp 130–130.5°.[14] Attempts to analyze mixtures of the methylindenes **20** and **21** by glpc (silicone 710 column) also resulted in partial or complete equilibration of the double bond isomers either in the injection port or on the glpc column. Therefore the compositions of mixtures of the two methylindenes were estimated by integrating the areas under the nmr peaks at δ 2.40 (from **21**) and 1.25 (from **20**). To study the equilibration of the indenes **20** and **21** a solution of 126 mg (0.45 mmol) of the indene **20** in 8 ml of MeOH containing 0.06 mmol of NaOMe was allowed to stand for 16 hr at 28° and then neutralized and the crude neutral product (119 mg) was separated in the usual way. This neutral material contained (nmr analysis) ca. 14% of **20** and 86% of **21**. Recrystallization of this material from MeOH separated 47 mg of the pure indene **21**.

B. The Sodium Salt.—A mixture of 262 mg (1 mmol) of the indene **16**, 257 mg (10.7 mmol) of NaH, 0.5 ml of MeOH, and 35 ml of THF was stirred at 0° for 10 min, at which time H_2 evolution had ceased. The resulting red solution was added, dropwise with stirring, to a cold (0°) solution of 5 ml of CH_3I in 10 ml of THF. After the mixture had been neutralized (HOAc), it was partitioned between H_2O and Et_2O, and the Et_2O layer was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. A solution of the brown, semisolid residue (280 mg) in an Et_2O-PhH mixture was filtered through a column of silica gel and the filtrate was concentrated and distilled in a short path still (0.1 mm and 160° bath). The liquid distillate (258 mg) contained (glpc, silicone 710) four components: ca. 24% of a component thought to be the dimethylindene **22** (retention time 48.8 min), ca. 5% of a component thought to be the trimethylindene **23** (42.0 min), ca. 36% of the trimethylindene **24** (63.5 min), and ca. 35% of the dimethylindene **25** (73.6 min). A collected (glpc) sample of the first eluted component thought to be **22** was recrystallized from MeOH to give colorless prisms, mp 84.5–85°, with the following spectral properties: ir (CCl_4) 1735 and 1710 cm^{-1} (ester C=O); uv (95% EtOH) 235 mμ (ε 8500) and 310 (19,500); nmr (CCl_4) δ 7.2–7.4 (2 H m, vinyl and aryl CH), 6.80 (1 H d, J = 8.5 Hz, aryl CH), 3.88 (3 H s, OCH_3), 3.85 (3 H s, OCH_3), 3.75 (3 H s, OCH_3), and 1.40 (6 H s, CH_3C); mass spectrum m/e (rel intensity) 290 (59, M^+), 259 (36), 258 (36), 232 (26), 231 (100), 230 (41), 199 (58), 177 (34), 77 (24), 73 (24), 58 (25), 44 (20), and 43 (66).

A collected sample of the component eluted second which would appear to be the trimethylindine **23** exhibited the following abundant mass spectral peaks: m/e (rel intensity) 304 (41, M^+), 255 (33), 242 (68), and 213 (100).

A collected sample of the component eluted third crystallized from methanol as pale yellow prisms, mp 123–124°, and is believed to be the trimethylindene **24**: ir (CCl_4) 1740 and 1705 cm^{-1} (ester C=O); uv (95% EtOH) 230 mμ (ε 8600) and 310 (20,800); nmr (CCl_4) δ 7.35 (1 H d, J = 8.5 Hz, aryl CH), 6.85 (1 H d, J = 8.5 Hz, aryl CH), 3.90 (3 H s, OCH_3), 3.88 (3 H s, OCH_3), 3.78 (3 H s, OCH_3), 2.40 (3 H s, vinyl CH_3C), and 1.40 (6 H s, CH_3C).

The component eluted last crystallized from MeOH as yellow prisms, mp 107–108°, believed to be the dimethylindene **25**: ir (CCl_4) 1740 and 1705 cm^{-1} (ester C=O); uv (95% EtOH) 240 mμ (sh, ε 9100) and 308 (21,300); nmr (CCl_4) δ 7.35 (1 H d, J = 8.5 Hz, aryl CH), 6.85 (1 H d, J = 8.5 Hz, aryl CH), 3.90 (3 H s, OCH_3), 3.87 (3 H s, OCH_3), 3.77 (3 H s, OCH_3), 3.6–3.8 (1 H m, benzylic CH), 2.42 (3 H d, J = 2.0 Hz, vinyl CH_3C), and 1.25 (3 H d, J = 7.0 Hz, CH_3C).

In a second similar methylation of the sodium indenyl anion **18**, the crude distilled product contained (glpc, silicone 710) the four previously described components, namely materials thought to be **22** (36.5 min), **23** (42.0 min), **24** (46.0 min), **25** (53.7 min, the major component present), and also the methylindene **21** (57.8 min). Crystallization of this sample from MeOH separated a small amount of the monomethyl derivative **21**, mp 130–130.5°, which was identified with the previously described sample by a mixture melting point determination.

Diels–Alder Reactions with the Indene Diesters 16 and 17.—A sealed glass tube containing a solution of 45 mg (0.17 mmol) of the indene **16**, 5 mg of diphenyl sulfide (as an inhibitor), and 1.5 ml (ca. 17 mmol) of liquid butadiene in 1.0 ml of toluene was heated to 185–195° for 41 hr. The resulting solution was cooled,

(14) In certain cases this material separated in a different crystal modification which melted at 119–120°, resolidified, and remelted at 128–129°.

mixed with 10 mg of phenanthrene (an internal standard), and partitioned between petroleum ether (bp 30–60°) and acetonitrile. The acetonitrile layer (in which the polymerized butadiene was insoluble) was concentrated for analysis. Analysis (glpc, silicone no. 710 on Chromosorb P) indicated the presence of phenanthrene (8.4 min), 53% of the indenes **16** and **17** (26.1 min, not resolved), 23% of the adduct **27a** (38.6 min), and 8% of the adduct **26a** (47.8 min).

An analogous experiment was performed by heating a solution of 46 mg (0.18 mmol) of an indene mixture containing (uv analysis) 17% of **16**, 83% of **17**, 5 mg of diphenyl sulfide, and 1.5 ml. (*ca.* 17 mmol) of liquid butadiene in 1.0 ml of toluene to 185–195° for 41 hr. Application of the previously described isolation and analytical procedures indicated the presence of phenanthrene, 39% of the indenes **16** and **17** (not resolved), 11% of the adduct **27a**, and 18% of the adduct **26a**.

A collected (glpc) sample of the ester **26a** (51 mg) was dissolved in a mixture of 0.8 ml of toluene and 1.0 ml of liquid butadiene and the solution was heated to 180–195° in a sealed tube for 109 hr. Use of the previously described isolation and analysis procedures indicated that the ester **26a** was recovered unchanged and none of the isomeric ester **27a** was detected.

Samples of each of the esters **26a** and **27a** were collected (glpc) for partial characterization. The diester **26a** was obtained as a colorless liquid: ir (CCl_4) 1735 cm^{-1} (broad, ester C=O); uv max (95% EtOH) 301 mμ (ε 2700); nmr (CCl_4) δ 7.06 (1 H d, J = 9 Hz, aryl CH), 6.70 (1 H d, J = 9 Hz, aryl CH), 5.5–5.9 (2 H m, vinyl CH), 3.5–3.8 (1 H m, benzylic CH), 3.83 (3 H s, OCH_3), 3.80 (3 H s, OCH_3), 3.68 (3 H s, OCH_3), 3.16. (1 H d, J = 15 Hz, part of benzylic CH_2), 2.89 (1 H, d, J = 15 Hz, part of benzylic CH_2), and 1.6–2.8 (4 H m, allylic CH_2); mass spectrum m/e (rel intensity) 316 (17, M^+), 285 (24), 284 (46), 262 (53), 230 (100), and 225 (26). A 200-mg (0.63 mmol) sample of the collected (glpc) diester **26a** was saponified with 1 ml of aqueous 15% NaOH in 10 ml of refluxing MeOH for 9.5 hr. The resulting mixture was partitioned between H_2O and Et_2O and the aqueous phase was acidified and extractd with EtOAc. After this organic extract had been dried and concentrated the residual brown solid (205 mg) was fractionally crystallized ($CHCl_3$) and the mother liquors were chromatographed (silica gel, EtOAc–$CHCl_3$ eluent) to separate 78 mg of fractions of the crude diacid **26b** melting within the range 199–205° dec. Recrystallization ($CHCl_3$) afforded the pure diacid **26b** as white needles: mp 206–208° dec; ir ($CHCl_3$) 1735 (intramolecularly H-bonded carboxyl C=O) and 1700 cm^{-1} (carboxyl C=O); uv max (95% EtOH) 297 mμ (ε 2750); nmr (CD_3SOCD_3) δ 7.16 (1 H d, J = 9 Hz, aryl CH), 6.86 (1 H d, J = 9 Hz, aryl CH), 5.4–5.8 (2 H m, vinyl CH), 3.75 (3 H s, OCH_3), 3.4–3.8 (1 H m, benzylic CH), 3.20 (1 H d, J = 15 Hz, part of benzylic CH_2), 2.87 (1 H d, J = 15 Hz, part of benzylic CH_2), and 1.4–2.6 (4 H m, allylic CH_2); mass spectrum m/e (rel intensity), 288 (M^+, 11), 234 (61), 216 (100), 172 (28), 115 (24), 44 (22), and 39 (20).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.94; H, 5.61.

The diester **27a** was obtained as a colorless liquid: ir (CCl_4) 1735 cm^{-1} (broad, ester C=O); uv max (95% EtOH) 293 mμ (ε 3110); nmr (CCl_4) δ 7.03 (1 H d, J = 8 Hz, aryl CH), 6.58 (1 H, d, J = 8 Hz, aryl CH), 5.6–6.0 (2 H m, vinyl CH), 3.78 (3 H s, OCH_3), 3.70 (3 H s, OCH_3), 3.54 (3 H s, OCH_3), 3.7–4.0 (1 H m, benzylic CH), 3.21 (1 H d, J = 15 Hz, part of benzylic CH_2), 2.76 (1 H d, J = 15 Hz, part of benzylic CH_2), and 1.7–2.6 (4 H m, allylic CH_2); mass spectrum m/e (rel intensity) 316 (14, M^+), 285 (26), 284 (100), 230 (57), 225 (97), and 223 (20). A 220-mg (0.70 mmol) sample of the collected (glpc) diester **27a** was saponified with 2 ml of aqueous 15% NaOH in 10 ml of refluxing MeOH for 20 hr. The reaction mixture was subjected to the previously described isolation and purification procedures to separate the diacid **27b** as tan prisms from EtOAc–hexane: mp 193–194° dec; ir ($CHCl_3$) 1738 (intramolecularly H-bonded carboxyl C=O) and 1700 cm^{-1} (carboxyl C=O); uv max (95% EtOH) 292.5 mμ (ε 1930); nmr (CD_3SOCD_3) δ 7.18 (1 H d, J = 8 Hz, aryl CH), 6.81 (1 H d, J = 8 Hz, aryl CH), 5.6–5.9 (2 H m, vinyl CH), 3.74 (3 H s, OCH_3), and 1.6–3.8 (7 H m, allylic and benzylic CH); mass spectrum m/e (rel intensity) 288 (14, M^+), 270 (82), 242 (27), 234 (26), 225 (100), 224 (36), 216 (98), 172 (42), 165 (34), 152 (30), 115 (32), 77 (22), and 43 (34).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.42; H, 5.60.

Samples of each of the diacids **26b** and **27b** were esterified with excess ethereal CH_2N_2 to form the corresponding esters **26a** and **27a** which were identified with previously described samples by comparison of glpc retention times.

A solution of 8.30 g (31.7 mmol) of the indene **16**, 0.25 ml of diphenyl sulfide, and 40 ml of liquid butadiene in 65 ml of toluene was placed in a glass liner in a stainless steel autoclave and heated to 130–150° for 48 hr. At intervals after 48, 118, 160, 304, and 371 hr the autoclave was cooled and opened, and the low-boiling products formed from butadiene, which distilled out of the glass liner, were removed. Additional 50-ml quantities of liquid butadiene were added and heating was continued. Each time the autoclave was opened aliquots were removed for glpc analysis; after 118 hr the mixture contained 41% of the indenes **16** and **17**, 28% of the adduct **27a**, and 31% of the adduct **26a**. After 379 hr the mixture contained 11% of the indenes **16** and **17**, 38% of the adduct **27a**, and 51% of the adduct **26a**. The final reaction mixture was concentrated under reduced pressure and then extracted with six portions of boiling MeOH. The MeOH extract was concentrated and the residue was fractionally distilled in a short-path still. The products were contained in a 7.65-g fraction of yellow liquid collected at 165–175° (0.15 mm). Aliquots of this distillate were mixed with known weights of phenanthrene for glpc analysis; the calculated yields were 8% of the indenes **16** and **17**, 26% of the adduct **27a**, and 32% of the adduct **26a**.

This procedure was repeated with 12.45 g (47.5 mmol) of the indene **16**, 0.4 ml of diphenyl sulfide, 50 ml of liquid butadiene, and 100 ml of toluene. After reaction periods at 170–180° of 60, 126, 202.5, 268, and 308 hr, the lower boiling products were removed and additional 40-ml portions of liquid butadiene were added. Use of the previously described isolation procedure separated 11.52 g of yellow liquid, bp 165–175° (0.15 mm), which contained (glpc) 2% of the indenes **16** and **17**, 50% of adduct **27a**, and 48% of adduct **26a**. A 11.5-g (36.5 mmol) sample of this crude product was saponified with 50 ml of aqueous 15% NaOH in 250 ml of refluxing MeOH. The crude acidic product, 9.0 g of brown liquid separated in the usual way, was crystallized from PhH to separate 4.16 g of solid diacid. Fractional crystallization of this material from EtOAc separated 1.80 g (13.2%) of the diacid **26b** as tan prisms, mp 205–209.5° dec, and 1.10 g (8.2%) of the diacid **27b** as white prisms, mp 190–193° dec.

In another experiment, the crude acidic product (5.8 g of brown semisolid) obtained by saponification of 6.60 g of the crude mixture of Diels-Alder adducts **26a** and **27a** was chromatographed on silica gel ($CHCl_3$–EtOAc eluent) and the resulting tan solid was subjected to a series of fractional crystallizations from EtOAc and from $CHCl_3$–hexane. From the less soluble fractions we separated 474 mg of the acid **26b** as white prisms, mp 205.5–209° dec. An MeOH solution of the mother liquors was decolorized with carbon and then subjected to fractional recrystallization from EtOAc to separate a sample of the more soluble diacid **27b** as white prisms, mp 192–194° dec. Each of these diacids was identified with the previously described materials by a mixture melting point determination and by esterification (ethereal CH_2N_2) and subsequent glpc analysis.

From a comparable Diels-Alder reaction employing 6.69 g (25.2 mmol) of a mixture of indenes (*ca.* 83% of **17** and 17% of **16**), with 0.6 ml of diphenyl sulfide, a total of 170 ml of liquid butadiene, and 60 ml of toluene at 180–190° for 143 hr, the crude distilled product (6.62 g) contained (glpc) 27% of the indenes **16** and **17**, 30% of the adduct **27a**, and 43% of the adduct **26a**.

Dehydrogenation of the Tetrahydrofluorenes 30. A. Preparation of the Ester 29a.—A mixture of 446 mg (1.73 mmol) of the previously described[5] ester **30a** and 55 mg of 30% Pd/C catalyst was heated to 205–215° for 2.5 hr while a slow stream of N_2 was passed through the reaction mixture. The resulting mixture was extracted with a $CHCl_3$–MeOH mixture and the extract was filtered and concentrated to leave 395 mg of solid. Recrystallization from MeOH separated 162 mg (36%) of the fluorene ester **29a** as white needles: mp 95–97°; ir ($CHCl_3$), 1725 cm^{-1} (conjugated ester C=O); uv max (95% EtOH) 215 mμ (ε 17,500), 271 (16, 800), 279 (inflection, ε 13,900), and 321 mμ (ε 3360); nmr ($CDCl_3$) δ 6.8–7.9 (6 H m, aryl CH), 3.98 (5 H, OCH_3 and benzylic CH_2), and 3.92 (3 H s, OCH_3); mass spectrum m/e (rel intensity) 254 (60, M^-), 223 (36), 222 (100), 179 (23), 165 (53), 164 (62), 152 (41), and 151 (28).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.67; H, 5.41.

B. Preparation of the Acid 29b.—A mixture of 810 mg (3.28

mmol) of the known[6] acid **30b** and 200 mg of 30% Pd/C catalyst was heated to 175–190° for 1.75 hr while a slow stream of N_2 was passed through the reaction mixture. The resulting mixture was extracted with EtOAc and the extract was filtered through Celite and then extracted with aqueous $NaHCO_3$. After the aqueous solution had been acidified, it was extracted with EtOAc. The crude acid product (400 mg), obtained after drying and concentrating the final EtOAc extract, was fractionally crystallized from $CHCl_3$–hexane, to separate 83 mg (11%) of the crude fluorene acid **29b**, mp 172–176°. Recrystallization gave the pure acid **29b** as white prisms: mp 176–178°; ir ($CHCl_3$) 1735 cm^{-1} (intramolecularly H-bonded carboxyl C=O); uv max (95% EtOH) 213 mμ (ϵ 28,500), 271 (20,500), 281 (inflection, 16,000), and 319 (4500); nmr (CD_3SOCD_3 + $CDCl_3$) δ 6.9–8.0 (6 H m, aryl CH), 3.91 (2 H s, benzylic CH_2), and 3.78 (3 H s, OCH_3); mass spectrum m/e (rel intensity), 240 (62, M^+), 222 (100), 179 (30), 165 (33), 164 (78), 152 (47), and 151 (38).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.08; H, 5.03.

A sample of the acid **29b** was esterified with ethereal CH_2N_2 to form the ester **29a** as white needles from MeOH, mp 95–97°; this sample was identified with the previously described material by comparison of ir spectra.

Conversion of the Diacid 26b to the Fluorene 29a.—A solution of 720 mg (2.5 mmol) of the diacid **26b** in 20 ml of THF was treated with 27 ml of an Et_2O solution containing 2.5 mmol of CH_2N_2. The resulting solution was concentrated and the residue was partitioned between Et_2O and aqueous $NaHCO_3$. Concentration of the Et_2O phase left 150 mg (19%) of the crude diester **26a** (tlc analysis) as an orange liquid. After the aqueous phase had been acidified and extracted with EtOAc, the organic extract was washed (aqueous NaCl), dried (Na_2SO_4), and concentrated. Chromatography of the residue (619 mg of tan semisolid) on 20 g of silica gel separated 388 mg of the crude monoester **28** in fractions eluted with EtOAc–$CHCl_3$ (1:49 v/v). Later fractions from the chromatograph afforded 122 mg (17%) of the starting diacid **26b** as prisms from EtOAc, mp 207–208° dec. Recrystallization of the monoester separated 265 mg (35%) of the monoester **28** as white prisms: mp 142.5–144°; ir ($CHCl_3$) 1725 (ester C=O) and 1705 cm^{-1} (carboxyl C=O); uv max (95% EtOH and 95% EtOH containing excess NaOH)[15] 212 mμ (ϵ 18,100) and 299 (2850); nmr ($CDCl_3$) δ 11.8 (1 H s, CO_2H), 7.16 (1 H d, J = 9 Hz, aryl CH), 6.80 (1 H d, J = 9 Hz, aryl CH), 5.7 (2 H broad, vinyl CH), 3.88 (3 H s, OCH_3), 3.81 (3 H s, OCH_3), and 1.7–3.8 (7 H m, aliphatic CH); mass spectrum m/e (rel intensity) 302 (M^+, 13), 270 (25), 249 (46), 216 (100), 172 (24), and 115 (20).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 5.70. Found: C, 67.81; H, 5.93.

A mixture of 141 mg of the monoester **28** and 31 mg of 30% Pd/C catalyst was heated to 170–175° for 2.5 hr. After a $CHCl_3$ solution of the crude reaction mixture had been filtered, it was washed with aqueous $NaHCO_3$ to separate 70 mg of the crude starting monoester **28**, mp 136–138°. This material was combined with an additional 30 mg of monoester **28** and heated with 30 mg of 30% Pd/C catalyst to 165–172° for 12 hr. After following the previously described isolation procedure, the combined neutral fractions from the two reactions were sublimed (95° and 0.1 mm) to separate 45 mg (31%) of the crude fluorene **29a**, mp 87–88°. Recrystallization from aqueous MeOH afforded the pure ester **29a** as white needles, mp 98–99°, which was identified with the previously described sample by a mixture melting point determination and by comparison of ir spectra.

Conversion of the Diacid 27b to the Fluorene 32.—After a solution of 303 mg (1.05 mmol) of the diacid **27b** in 20 ml of EtOAc had been treated with 13.6 ml of an Et_2O solution containing 1.06 mmol of CH_2N_2, the reaction mixture was concentrated and partitioned between Et_2O and aqueous $NaHCO_3$. The crude diester **27a** separated amounted to 83 mg (25%). The aqueous phase was acidified and extracted with EtOAc and the organic extract was washed (aqueous NaCl), dried (Na_2SO_4), and concentrated. Chromatography of the residue (231 mg of colorless liquid) on 7.0 g of silica gel separated 151 mg of the crude monoester **31** in fractions eluted with EtOAc–$CHCl_3$ (3:97 v/v). Later chromatographic fractions contained 36 mg (12%) of the starting diacid **27b**, mp 190–192° dec. The crude monoester was crystallized from Et_2O–hexane to separate 92 mg (29%) of the monoester **31** as white needles: mp 161–163°; ir ($CHCl_3$) 1725 (ester C=O) and 1705 cm^{-1} (carboxyl C=O); uv max (95% ETOH and 95% EtOH containing excess NaOH)[15] 212 mμ (ϵ 16,700) and 294 (3150); nmr ($CDCl_3$) δ 11.8 (1 H, CO_2H), 7.17 (1 H d, J = 9 Hz, aryl CH), 6.70 (1 H d, J = 9 Hz, aryl CH), 5.8 (2 H broad, vinyl CH), 3.92 (3 H s, OCH_3), 3.79 (3 H s, OCH_3) and 1.7–3.7 (7 H m, aliphatic CH).

A mixture of 37 mg (0.12 mmol) of the monoester **31** and 14 mg of the 30% Pd/C catalyst was heated to 185° for 1.5 hr and then subjected to the previously described isolation procedure. The crude neutral product (15 mg) was recrystallized from MeOH, subjected to preparative thin layer chromotography, and again recrystallized from MeOH to separate 10 mg (33%) of the pure fluorene **32** as colorless prisms: mp 133–133.5°; ir ($CHCl_3$) 1725 cm^{-1} (ester C=O); uv max (95% EtOH), 235 mμ (ϵ 10,600), 262 (10,200), 269 (10,000), 304 (infl, 6600), and 314 (7600); nmr ($CDCl_3$) δ 7.1–7.7 (5 H m, aryl CH), 6.78 (1 H d, J = 9 Hz, aryl CH), 4.02 (3 H s, OCH_3), 3.86 (3 H s, OCH_3), 3.79 (2 H s, benzylic CH); mass spectrum m/e (rel intensity) 254 (M^+, 100), 223 (31), 222 (65), 195 (81), 180 (23), 166 (41), 165 (68), 164 (60), 152 (56), 151 (25), 83 (28), 73 (35), 71 (35), 69 (45), 60 (37), 57 (80), and 55 (55); high-resolution mass measurement, m/e 254.09287 (calcd for $C_{16}H_{14}O_3$: m/e 254.09429).

Registry No.—**1a,** 15378-00-4; **5,** 33521-56-1; **6,** 33521-57-2; **7,** 13623-25-1; **8,** 3469-09-8; **9,** 33521-60-7; **10a,** 33521-61-8; **10b,** 33521-62-9; **11,** 33521-63-0; **12,** 33521-64-1; **13,** 33521-65-2; **14a,** 33521-66-3; **14b,** 33521-67-4; **15a,** 33521-68-5; **15b,** 33521-69-6; **16,** 33521-70-9; **17,** 33521-71-0; **19,** 33608-26-3; **20,** 33521-72-1; **21,** 33521-73-2; **22,** 33521-74-3; **23,** 33521-75-4; **24,** 33521-76-5; **25,** 33521-77-6; **26a,** 33536-19-5; **26b,** 33536-20-8; **27a,** 33536-21-9; **27b,** 33536-22-0; **28,** 33536-23-1; **29a,** 33521-78-7; **29b,** 33521-79-8; **32,** 33521-80-1.

(15) The lack of change in the uv spectrum of the sample with added base indicates that the aromatic carboxyl function has been esterified. The corresponding addition of NaOH to an EtOH solution of the diacid **26b** caused the longer wavelength maximum to shift from 297 to 287 mμ.

The Extent of Bond Formation in the Transition State for Alkylation at Nitrogen and at Carbon[1a]

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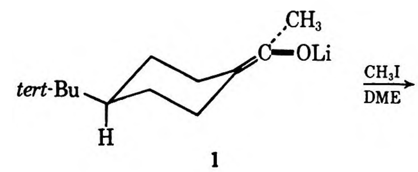
Chlorine isotope effects (k_{35}/k_{37}) in reactions of methyl chloride with 4-*tert*-butyl-1-ethylpiperidine, triethylamine, and the lithium salt of 4-*tert*-butylcyclohexanecarbonitrile in 1,2-dimethoxyethane solution at 25° are identical (1.0064) within experimental precision (0.0001) but considerably smaller than with sodium iodide (1.0086), indicating an "early" transition state for the amines and the enolate, with nearly the same small degree of bond formation at their transition states. Stereochemical differences between piperidines and enolates are therefore interpreted by consideration of relative steric strain in transition states for axial *vs.* equatorial alkylation, at relatively long but similar N–C and C–C distances.

An important aspect of stereospecific synthesis is the ability to predict (and if possible control) the stereochemical path by which an alkyl group is introduced into an organic molecule. Explorations of this problem include numerous stereochemical studies of the N-alkylation of tertiary amines[2] and, especially, of the C-alkylation of enolate anions.[3] Equations A–E illustrate a different stereochemical preference in the N-[4] and C-alkylation[5] of similarly constituted compounds: methylation of either of the enolate anions **1** or **4** produces predominantly the product **2** or **5** with an equatorial methyl group while methylation of the amines **7** and **10** yields mainly products **9** and **11** in which an axial methyl group has been introduced.[6]

With more complex piperidine derivatives which offer steric hindrance to an axial approach of the alkylating agent to the usual[7] chair conformation of the piperidine ring, this stereochemical path may not be observed.[2] For example, alkylation of the bicyclic amine **13** (and related substances) is believed to form primarily the stereoisomer **14**.[8]



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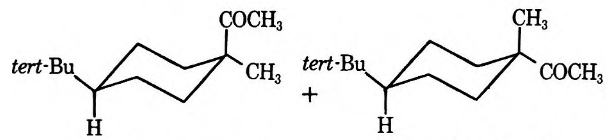
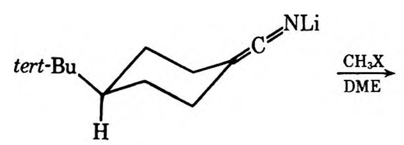


(A)

2 (85% of product)[5d] **3** (15% of product)[5d]



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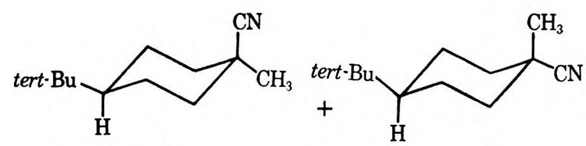


(B)

5 **6**

Methylating agent	Product composition, % **5**	**6**
CH_3Cl	81	19
CH_3I	72	28
$(CH_3)_3O^+BF_4^-$	~42	~58

(1) (a) Supported in part by research grants from the National Institutes of Health (Grant R01-CA-10933 and Grant R01-GM-03711), the National Science Foundation, and by the Atomic Energy Commission under Contract No. AT(30-1)-905. (b) National Institutes of Health Predoctoral Fellow, 1965–1967. (c) National Science Foundation Predoctoral Fellow, 1965–1968.

(2) For recent reviews of the stereochemistry of N-alkylation, see (a) J. McKenna, *Top. Stereochem.*, **5**, 275 (1970); (b) A. T. Bottini, *Selec. Org. Transform.*, **1**, 89 (1970); (c) R. A. Y. Jones, A. R. Katritzky, and P. G. Mente, *J. Chem. Soc. B*, 1210 (1970).

(3) For recent reviews of the stereochemistry of C-alkylation, see (a) J. M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963); (b) H. O. House, *ibid.*, **28**, 99 (1967); (c) L. Velluz, J. Valls, and G. Nominé, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965); (d) L. Velluz, J. Valls, and J. Mathieu, *ibid.*, **6**, 778 (1967); (e) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., in press.

(4) (a) H. O. House, P. P. Wickham, and H. C. Müller, *J. Amer. Chem. Soc.*, **84**, 3139 (1962); (b) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); (c) H. O. House and C. G. Pitt, *ibid.*, **31**, 1062 (1966); (d) H. O. House and B. A. Tefertiller, *ibid.*, **31**, 1068 (1966); (e) H. O. House, B. A. Tefertiller, and C. G. Pitt, *ibid.*, **31**, 1073 (1966).

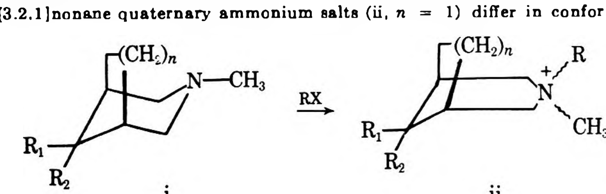
(5) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965); H. O. House and C. J. Blankley, *ibid.*, **32**, 1741 (1967); (c) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *ibid.*, **33**, 935 (1968); (d) H. O. House and T. M. Bare, *ibid.*, **33**, 943 (1968).

(6) A number of types of experimental evidence support the view that alkylation of unhindered *N*-alkylpiperidines occurs with predominant introduction of the new alkyl group from an axial direction. See ref 2 and 4c.

(7) F. G. Riddell, *Quart. Rev. Chem. Soc.*, **21**, 364 (1967).

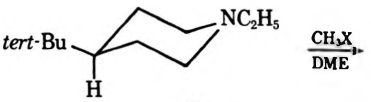
(8) We have provided rigorous experimental proof for the stereochemistry of alkylation of several 3-azabicyclo[3.3.1]nonane derivatives with methyl bromoacetate and the analogous stereochemistry has been assigned to the salts **14** and **15** and the related C-9 hydroxy derivatives by an empirical correlation of nmr chemical shift data among three pairs of compounds. Although the populations in solution of the various possible conformers of these quaternary ammonium salts are not known, our experiments involving facile lactone formation and, especially, intramolecular aldol condensation required that the chair–boat conformations indicated in structures **14** and **15** are readily attained and the nmr spectrum of the methiodide of 3-methyl-3-azabicyclo[3.3.1]nonane suggests an analogous conformation for this salt. See R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.*, **No. 15**, 356 (1965).

In our studies of the alkylation of other bicylic compounds of the type i (n = 1, 2, and 3, R_1 and R_2 = H and OH or = O), we noted[4c,d] that the above empirical nmr relationship suggested that all of the compounds underwent preferential alkylation in the same direction. This assignment was tentative and was predicated on the assumption that the principal solution conformations of all the quaternary ammonium salts were the same. McKenna and coworkers have subsequently argued that the 3-azabicyclo[3.2.1]nonane quaternary ammonium salts (ii, n = 1) differ in conforma-



i ii

tion from the other series (ii, n = 2 or 3) and, consequently, the stereochemical assignments should be reversed. See ref 2a and D. R. Brown, R. Lygo, J. McKenna, and B. G. Hutley, *J. Chem. Soc. B*, 1184 (1967). Until definitive experimental data (X-ray crystallographic analysis or chemical correlation) are available, we see no compelling basis for making stereochemical assignments to the salts ii (n = 1).



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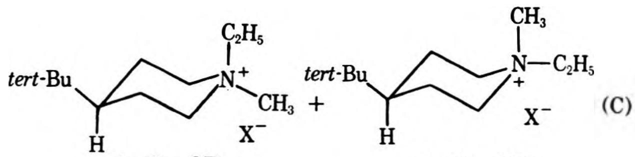
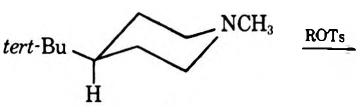


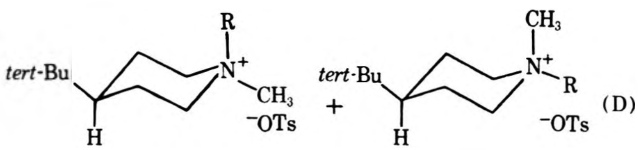
8a, X = OTs
b, X = I
c, X = Cl

9a, X = OTs
b, X = I
c, X = Cl

Methylating agent	Product composition, % 8	9
CH_3Cl	27	73
CH_3I	18	82
CH_3OTs	17	83

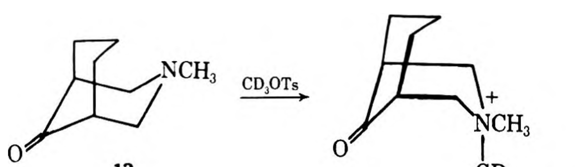


10



11 12

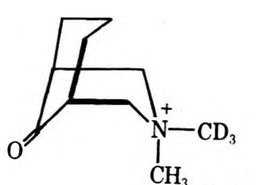
Alkylating agent	Product composition, % 11	12
CD_3OTs, acetone	87[4e]	13[4e]
C_2H_5OTs, DME	75	25
C_2H_5OTs, acetone	83[4e]	17[4e]



13

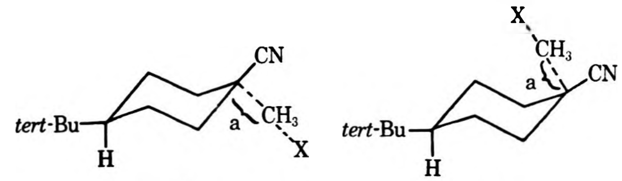
14 (82% of product)[4e]

(E)

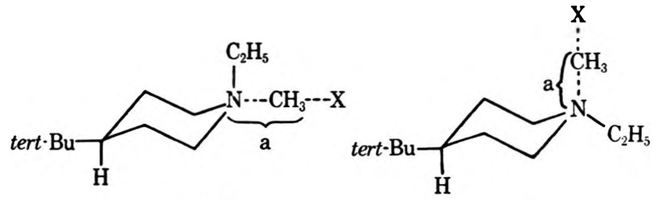


15 (18% of product)[4e]

We previously considered[5d] two general explanations for the different stereochemical results obtained from the N-alkylation of piperidine derivatives (mainly axial alkylation, eq C and D) and the C-alkylation of structurally similar enolates (mainly equatorial alkylation, eq A and B). Either the extent of bond formation between the nucleophile and the entering alkyl group (bond a in structures 16 and 17) is very different at the

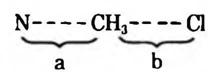


16a 16b



17a 17b

transition state in the two cases[9] or the direction of attack by the entering alkyl group is different in the two cases. Since other data obtained with enolates[5] suggested a reactantlike transition state for the C-alkylation reactions, we favored the second explanation. We now wish to present experimental evidence for an early, reactantlike transition state in both the C-alkylation of the enolate 4 and the N-alkylation of the tertiary amine 5. This evidence was obtained by measuring the heavy-atom isotope effect observed when each of several nucleophiles (N:) (see Table I) was allowed to react with excess CH_3Cl. These experiments, which measure the relative rates of reaction of CH_3–^{35}Cl and CH_3–^{37}Cl with each N:, provide a measure of the extent of C–Cl bond breaking in the transition state (structure 18). The maximum isotope effect if the



18

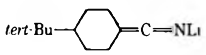
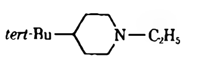
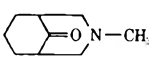
C–Cl bond were completely broken at the transition state is calculated to be $k_{35}/k_{37} = 1.017$.[10] We assume that throughout the process of nucleophilic bimolecular substitution at a methyl halide the small charge at the methyl group will not change appreciably and, consequently, the total bond order at carbon will remain approximately constant from methyl chloride through the transition state 18 to form the product. Given this assumption, if we can estimate the extent of C–Cl bond breaking in the transition state (bond b in 18), we can also estimate the extent of formation of the new bond to the neculeophile (bond a in 18). As previously noted, we would expect a chlorine isotope effect (k_{35}/k_{37}) of about 1.017 if the C–Cl bond were completely broken at the transition state and a value approximately one-half as large (1.009) if the bond to chlorine were only half broken (and bonding to the nucleophile were half completed). Although, in principle, the actual value could be obtained by measuring the chlorine isotope effect (k_{35}/k_{37}) in the symmetrical transition state which would be attained by displacement at methyl chloride with chloride ion composed of a third chlorine isotope, this ideal experiment is difficult to perform. However,

(9) For other uses of this argument to explain alkylation stereochemistry, see (a) A. T. Bottini, B. F. Dowden, and R. L. Van Etten, J. Amer. Chem. Soc., 87, 3250 (1965); (b) A. T. Bottini and M. K. O'Rell, Tetrahedron Lett., No. 6, 423, 429 (1967); (c) M. E. Kuehne and J. A. Nelson, J. Org. Chem., 35, 161 (1970); M. E. Kuehne, ibid., 35, 171 (1970).

(10) Two-atom model at 298°K, CH_3 treated as a point mass of 15 amu, 3.4 mdyn/Å force constant for C–Cl bond, bending neglected.

TABLE I

CHLORINE ISOTOPE EFFECT (k_{35}/k_{37}) IN THE REACTION OF METHYL CHLORIDE WITH NUCLEOPHILES IN 1,2-DIMETHOXYETHANE SOLUTION

Nucleophile, N:	Reaction conditions	Isotope effect, k_{35}/k_{37}
 4	0.17 *M* 4, 1.0 *M* CH_3Cl, 25°, 2.5 min	1.0063 ± 0.0002 (four runs)
 7	0.50 *M* 7, 2.0 *M* CH_3Cl, 25°, 24 hr	1.0064 ± 0.0002 (four runs)
 13	0.50 *M* 13, 2.0 *M* CH_3Cl, 25–30°, 60 days	1.0072 ± 0.0004 (two runs)
$(C_2H_5)_3N$ 19	0.20 *M* 19, 2.0 *M* CH_3Cl, 25°, k_2 = 4.1×10^{-5} M^{-1} sec^{-1}	1.0064 ± 0.0001 (five runs)
NaI	0.20 *M* NaI, 2.0 *M* CH_3Cl, 25°	1.0086 ± 0.0001 (three runs)

a related experiment, the displacement at methyl chloride with iodide ion, was readily effected (Table I) and provides a reasonable approximation of the chlorine isotope effect (k_{35}/k_{37} = 1.0086) to be expected in a symmetrical transition state.

With this calibration point in hand we can offer at least a qualitative[11] estimate of the extent of new bond formation at the transition state between methyl chloride and the other nucleophiles studied (Table I). The most striking result for all these nucleophiles is the fact that for either carbon or nitrogen nucleophiles, bond formation at the transition state has progressed significantly less than half way. Furthermore, with the two structurally similar nucleophiles, the enolate 4 and the amine 7, the extent of bond formation is the same within the limits of our experiment. Such results are very difficult to reconcile with any explanation for alkylation stereochemistry that requires substantially different degrees of bond formation at the transition state.

For this reason we believe that the different stereochemical results obtained by alkylating either the enolate anions such as 1 and 4 or amines such as 7 and 10 are best explained by reactantlike transition states such as 16 and 17. An axial attack (*i.e.*, **16b**) of the alkylating agent perpendicular to the planar enolate system will clearly be impeded sterically more than an axial attack (*i.e.*, **17b**) on a tetrahedral amine system because of the differing direction of approach of the alkyl halide.

The steric environment for attack of an alkylating agent perpendicular to a planar enolate system (structures 16) is analogous to that discussed in the hydride reduction of cyclohexylidenecyanoacetate derivatives.[13] Specifically, if the CH_3–nucleophile bond (bond a in 16) is relatively short, steric interference will be greatest between the entering methyl group and the axial hydrogen atoms at C-2 and C-6 and transition state **16a** will be destabilized. However, when the forming bond is relatively long (*e.g.*, 2.0 Å), steric interference between the entering alkyl group and axial hydrogen atoms at C-3 and C-5 predominates and the transition state **16b** is expected to be less stable. Thus, the stereochemical results observed on alkylation of the enolates 1 and 4 (**16a** more stable than **16b**) are also in accord with an early, reactantlike transition state with a relatively long bond between the nucleophile and the entering alkyl group.

In the alkylation of the piperidine derivatives 7 and 10, it seems most probable that in transition states 17 the nitrogen atom retains approximately the same tetrahedral geometry which is present in the starting amines and the final quaternary salt products. Further, it seems most probable that the entering pentacoordinate methyl group in these transition stages has an effective steric bulk at least as large as a fully bonded, tetrahedral methyl group. Since the stereochemical results of this alkylation require the transition state **17b** (axial alkylation) to be more stable than **17a**, these considerations also indicate that bonding of nitrogen to the entering alkyl group is relatively incomplete and the forming bond (bond a in 17) is relatively long. If one assumes the entry of a planar CH_3 group from an axial direction to an *undeformed* chair piperidine ring, then calculation of nonbonded hydrogen–hydrogen repulsion energies[14] suggests that the forming nitrogen–methyl bond is no shorter than 2.0 Å. However, appropriate deformation of the piperidine ring will relieve the principal nonbonded hydrogen–hydrogen interaction between the entering methyl group and the axial hydrogen atoms at C-3 and C-5 so that the 2.0-Å value is not necessarily the minimum value for the forming nitrogen–methyl bond at the transition state.

The chlorine isotope effects observed (Table I) suggest that the degree of bond formation in the transition states for N- and C-methylation is not very responsive to changes in the environment of the attacking nucleophile and, consequently, generalizations about effect of reactant structure on transition-state structure[15,16] are not particularly useful for predicting the stereochemical outcome of structural changes in the nucleophile being alkylated.

Seemingly, these rules could be more useful in predictions of the stereochemical outcome of changes in the leaving group of the alkylating agent, since the rules

(11) There is no particular reason to suppose that the relationship between the isotope effect and the extent of bond breaking will be linear. In fact, measurements of sulfur isotope effects have been interpreted as not being a linear function of the extent of bond breaking.[12]

(12) A. M. Katz and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **91**, 4472 (1969).

(13) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965).

(14) (a) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955); (b) H. E. Simmons and J. K. Williams, *ibid.*, **86**, 3222 (1964).

(15) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(16) (a) C. G. Swain and E. R. Thornton, *ibid.*, **84**, 817 (1962); (b) E. R. Thornton, *ibid.*, **89**, 2915 (1967).

concur in their prediction that the better the leaving group, the more reactantlike will be the transition state and, consequently, the less bonding between the nucleophile and the alkylating agent at the transition state. The very limited comparison of CH_3Cl *vs.* CH_3I or CH_3OTs made in this study would appear to support such an idea, since the use of the less reactive CH_3Cl (predicted to give increased nucleophilic bonding at the transition state) results in a more stereospecific alkylation (less axial product) of the enolate **5** and a less stereospecific alkylation (less axial product) of the amine **7**. Although use of the very reactive alkylating agent trimethyloxonium tetrafluoroborate would also seem to fit this prediction by giving very little stereospecificity in the alkylation of the enolate **4**, we have observed the opposite result in the alkylation of a different enolate with this alkylating agent.[5a] Also, the alkylation of various piperidine derivatives with triethyloxonium tetrafluoroborate was observed to be less stereospecific than alkylation with C_2H_5I,[17] a result opposite to what might be predicted. In addition, no substantial change in alkylation stereochemistry was observed when *N*-methyl-d_3-nortropine was alkylated with either CH_3Cl or CH_3I.[18] In view of such results, it clearly is desirable to obtain more compelling experimental evidence before placing reliance upon arguments concerned with the extent of bonding in the transition state to explain stereochemical changes that result when the leaving group in the alkylating agent is changed.

Experimental Section[19]

Preparation of Starting Materials.—4-*tert*-Butyl-1-ethylpiperidine [**7**, bp 72.5–74° (8 mm), $n^{27}D$ 1.4526] and 4-*tert*-butyl-1-methylpiperidine [**10**, bp 59.5–60.5° (8 mm), $n^{25}D$ 1.4504] were prepared as previously described.[4e] The preparation and characterization of the 4-*tert*-butylcyclohexanecarbonitrile (mixture of stereoisomers) and the stereoisomeric methyl derivatives **5** and **6** was described previously.[5d] To a solution of 858.4 mg (5.07 mmol) of the *N*-ethyl amine **7** in 7.5 ml of 1,2-dimethoxyethane (hereafter DME) was added 1.867 g (10.0 mmol) of methyl *p*-toluenesulfonate so that the initial concentrations after mixing were 0.5 *M* in the amine **7** and 1.0 *M* in the alkylating agent. This solution, from which the amine salt began to precipitate almost immediately, was stirred at 25° for 6 hr and then filtered. The collected mixture of amine salts (1.745 g or 97.2%, mp 190–198°) contained (nmr analysis) 83% of the axial methyl salt **9a** and 17% of the equatorial methyl salt **8a**. Fractional recrystallization from $CHCl_3$–ether mixtures separated the pure (nmr analysis) axial methyl salt **9a** as white plates, mp 207–208° (lit.[4e] mp 201–202°), with spectroscopic properties corresponding to those previously reported.[4e]

Similarly, a solution of 5.71 g (3.67 mmol) of the *N*-methyl amine **10** and 8.01 g (40 mmol) of ethyl *p*-toluenesulfonate in 40 ml of DME was stirred at room temperature for 16 hr and then concentrated under reduced pressure. Trituration of the residue with ether separated 7.186 g (55.1%) of a mixture of amine salts, mp 154–158.5°, containing (nmr analysis) 25% of the axial methyl isomer **9a** and 75% of the equatorial methyl isomer **8a**. Fractional recrystallization from an ethyl acetate–methanol mixture separated the pure (nmr analysis) equatorial methyl salt **8a** as white plates, mp 163–164° (lit.[4e] mp 158–159°), with spectroscopic properties corresponding to those previously reported.[4e]

In $CDCl_3$ solution the *N*-methyl nmr peaks for the axial methyl (**9a**) and equatorial methyl (**8a**) salts are located at δ 2.92 and 3.10, respectively. In D_2O solution,[4e] the two *N*-methyl nmr signals (δ 2.84 for the axial methyl salt **9a** and δ 2.92 for the equatorial methyl salt **8a**) are less well separated but the peak attributable to the axial methyl group remains at higher field.[20]

In order to analyze mixtures of the salts **8a** and **9a**, the nmr spectra of chloroform solutions of a series of known mixtures of the pure salts were measured to establish the validity of equating the heights of the *N*-methyl peaks at δ 2.92 (for **9a**) and 3.10 (for **8a**) to the proportions of the two isomers present.

Gaseous CH_3Cl (Matheson) was passed over $CaSO_4$ before use. Triethylamine (Eastman pure) was dried over $CaSO_4$ (Drierite), then distilled from several pellets of KOH through a 16-cm Vigreux column, bp 89.0° (766 mm) [lit.[21] bp 88.8–89.0° (760 mm)], $n^{25}D$ 1.3982 (lit.[22] $n^{20}D$ 1.40032). It was stored under dry N_2 and used within a week of distillation.

1,2-Dimethoxyethane (DME, Eastman White Label, 75 ml) was dried over $CaSO_4$ (Drierite) for several days, then filtered. About 1 g of $LiAlH_4$ (Metal Hydrides) was added and the mixture was stirred for 1 hr. The liquid was distilled through a 16-cm Vigreux column, bp 84.2° (754 mm), $n^{34}D$ 1.3730 [lit.[23] bp 84.7–84.8° (760 mm), $n^{20}D$ 1.37965]. This material was stored under dry N_2, but was always used within 2 days of distillation. Both of the common peroxide tests[24,25] were negative for the purified DME. A more sensitive test can be conducted by dissolving several large crystals of NaI in a few milliliters of DME; an orange color indicates the presence of peroxides. Freshly distilled DME gave a negative test by this method.

All inorganic materials were reagent grade used without further purification. Water was laboratory-distilled water redistilled from alkaline $KMnO_4$ in an aged Pyrex still. $CaSO_4$ was Drierite. Prepurified N_2 gas (Airco) was passed over Ascarite (NaOH on asbestos) and $CaSO_4$.

Alkylation of the *N*-Ethyl Amine 7. A. With Methyl Iodide.—To a solution of 862.5 mg (5.09 mmol) of the amine **7** in 8.4 ml of DME was added 1.392 g (9.83 mmol) of CH_3I so that the initial concentrations were 0.5 *M* in amine and 1.0 *M* in CH_3I. The resulting solution, from which a precipitate began to form almost immediately, was stirred at 25° for 6 hr and then filtered. After the residue had been washed with ether, the mixture of iodides **8b** and **9b** amounted to 1.564 g (98.3%), mp 208.5–210° dec. A sample of this mixture of salts was recrystallized from a methanol–ethyl acetate mixture to separate a mixture of salts **8b** and **9b** as white needles: mp 209–210° dec; nmr ($CDCl_3$) δ 3.42 (singlet, CH_3N of the equatorial methyl salt **8b**, *ca.* 25% of 3 H), 3.24 (singlet, CH_3N of the axial methyl salt **9b**, *ca.* 75% of 3 H), 3.5–4.2 (6 H multiplet, CH_2N), 1.1–2.2 (8 H multiplet, aliphatic CH), and 0.93 [9 H singlet, $(CH_3)_3C$]. In D_2O solution, the CH_2N nmr multiplet is shifted to the region δ 3.1–3.7 and the *N*-methyl signals are located at δ 3.01 (*ca.* 25% of 3 H) and 2.96 (*ca.* 75% of 3 H).

Anal. Calcd for $C_{12}H_{26}IN$: C, 46.30; H, 8.42; N, 4.50; I, 40.77. Found: C, 46.33; H, 8.14; N, 4.49; I, 40.60.

To determine the composition of the initially isolated mixture of iodide salts **8b** and **9b**, the mixture was converted to the corresponding *p*-toluenesulfonate salts **8a** and **9a**. To a solution of 204.8 mg (0.659 mmol) of the mixture of iodides **8b** and **9b** in 3.0 ml of acetonitrile was added a solution of 196.2 mg (0.703 mmol) of silver *p*-toluenesulfonate in 4 ml of CH_3CN. The resulting mixture, from which AgI separated immediately, was stirred for 1 hr at 25° and then filtered through Celite. The filtrate was concentrated under reduced pressure to leave 232.3 mg (99.1%) of a mixture of the *p*-toluenesulfonate salts which contained (nmr analysis) 82% of the axial methyl isomer **9a** and 18% of the equatorial methyl isomer **8a**.

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(17) D. R. Brown, J. McKenna, and J. M. McKenna, *Chem. Commun.* **No. 5**, 186 (1969).

(18) (a) G. Fodor, J. D. Medina, and N. Mandava, *Chem. Commun.*, **No. 10**, 581 (1968); (b) For the latest revision in the stereochemical assignments of the tropane quaternary ammonium salts with leading references to earlier assignments, see G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, **93**, 403 (1971); P. Benci, C. H. Stam, and C. H. MacGillavry, *Tetrahedron Lett.*, **No. 3**, 243 (1971).

(19) General comments of footnote 9 of ref 5d apply.

(20) For an example where the positions of the two peaks interchange when the solvent is changed from deuteriochloroform to deuterium oxide, see ref 9b. For other examples where the relative spacing of the *N*-methyl signals changes with solvent, see ref 4a.

(21) W. Herz and E. Neukirch, *Z. Phys. Chem. (Leipzig)*, **104**, 439 (1923).

(22) J. W. Brühl, *Justus Liebigs Ann. Chem.*, **200**, 186 (1879).

(23) M. H. Palomaa and I. Honkanen, *Chem. Ber.*, **70**, 2203 (1937).

(24) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 287.

(25) A. I. Vogel, "Practical Organic Chemistry," 3rd. ed, Wiley, New York, N. Y., 1957, p 163.

To verify further the fact that the axial methyl nmr signal was located at higher field in both the iodide (**9b**) and *p*-toluenesulfonate (**9a**) salts, a warm solution of 175.8 mg (0.494 mmol) of the *p*-toluenesulfonate salts (containing *ca.* 80% of **9a** and *ca.* 20% of **8a**) in 5 ml of ethanol was added to a warm solution of 111.9 mg (0.260 mmol) of BaI_2 in 5 ml of ethanol. The resulting mixture, from which a precipitate separated immediately, was stirred for 10 min and then filtered. The filtrate was concentrated and the residual solid (157.7 mg) was taken up in $CHCl_3$, filtered, and diluted with ether. The mixture of iodides **8b** and **9b**, 136.5 mg (88.7%), mp 207.5–209° dec, which separated was identified with the previously described mixture of iodides obtained from the alkylation experiment by comparison of infrared and nmr spectra. In particular, the nmr singlets ($CDCl_3$) at δ 3.42 and 3.24 have peak heights in the ratio 1:4.

B. With Methyl Chloride.—In a flask fitted with a Dry Ice condenser were placed a solution of 1 g (20 mmol) of CH_3Cl in 8.0 ml of DME and 851.1 mg (5.02 mmol) of the amine **7** (initial concentrations 0.5 *M* in the amine **7** and 2 *M* in CH_3Cl). The resulting solution was stirred at 25° for 24 hr, during which time a mixture of the chloride salts **8c** and **9c** separated. Filtration separated 274.6 mg (24.8%) of the mixture of chlorides **8c** and **9c** as white plates, mp 261° dec. A portion of this mixture was dissolved in $CHCl_3$ and reprecipitated by the addition of ether to give the mixture of salts **8c** and **9c** as a white solid: mp 260° dec; nmr ($CDCl_3$) δ 3.5–4.2 (6 H multiplet, CH_2N), 3.47 (singlet, equatorial methyl salt **8c** CH_3N, *ca.* 30% of 3 H), 3.24 (singlet, axial methyl salt **9c**, CH_3N, *ca.* 70% of 3 H), 1.1–2.2 (8 H multiplet, aliphatic CH), and 0.93 [9 H singlet, $(CH_3)_3C$].

Anal. Calcd for $C_{12}H_{26}ClN$: C, 65.57; H, 11.92; N, 6.37; Cl, 16.13. Found: C, 65.32; H, 12.19; N, 6.14; Cl, 16.36.

A solution of 81.9 mg (0.372 mmol) of the initially separated mixture of chloride salts in 2 ml of CH_3CN was treated with a solution of 106.7 mg (0.382 mmol) of silver *p*-toluenesulfonate as previously described to yield 127.6 mg (96.8%) of a mixture of *p*-toluenesulfonate salts which contained (nmr analysis) 73% of the axial methyl isomer **9a** and 27% of the equatorial methyl isomer **8a**. In a duplicate experiment, the initially formed mixture of chloride salts, obtained in 24.1% yield, contained (nmr analysis) *ca.* 70% of the isomer **9c** and *ca.* 30% of the isomer **8c**. This material was converted in 96.8% yield to a mixture of *p*-toluenesulfonic acid salts which contained (nmr analysis) 73% of the axial methyl isomer **9a** and 27% of the equatorial methyl isomer **8a**.

To verify the fact that the axial methyl nmr signal of the chloride salt **9c** is at higher field than the methyl signal of the stereoisomeric salt **8c**, a refluxing solution of 218.9 mg (0.821 mmol) of $SrCl_2$ in 18 ml of ethanol plus sufficient water to effect complete solution was treated with a warm solution of 530.5 mg (1.49 mmol) of a mixture of *p*-toluenesulfonate salts (83% of **9a** and 17% of **8a**) in 9 ml of ethanol. The resulting mixture, from which a white precipitate separated immediately, was stirred for 10 min and then cooled and filtered. The filtrate was concentrated under reduced pressure and the residual solid was taken up in $CHCl_3$, filtered, and diluted with ether. The mixture of chlorides **8c** and **9c** separated as 326.8 mg (99.7%) of white solid, mp 238° dec, which was identified with the previous sample by comparison of infrared and nmr spectra. The nmr singlets ($CDCl_3$) at δ 3.45 and 3.23 have peak heights in the ratio 1:4.

Alkylation of the Nitrile Anion 4. A. With Methyl Iodide.—A cold (0°) solution of 1.20 mmol of methyllithium and 188 mg of biphenyl (an internal standard) in 2.8 ml of DME was treated with 87.5 mg (1.20 mmol) of diethylamine and the solution of lithium diethylamide was stirred at 0° for 5 min. The cooling bath was removed, 206.6 mg (1.25 mmol) of 4-*tert*-butylcyclohexanecarbonitrile was added, and the resulting solution was stirred for 5 min. The solution of the lithium salt **4** was added, dropwise and with vigorous stirring over a 1-min period at 25°, to a solution of 1.002 g (7.07 mmol) of CH_3I in 3.7 ml of DME (the initial concentrations after mixing were 0.17 *M* in the lithium salt **4** and 1 *M* in CH_3I). The resulting solution was stirred at 25° for 1.5 min and then quenched by the addition of dilute aqueous HCl. The ethereal extract of the reaction mixture was washed with aqueous $NaHCO_3$, dried, and concentrated by distillation of the bulk of the ether through a 40-cm Vigreux column. The residual liquid was analyzed by glpc, using LAC-728 (diethylene glycol succinate) on Chromosorb P, employing equipment that had been calibrated as decribed elsewhere.[5d] The monoalkylated product (calculated yield 91%) was composed of 28% of the axial methyl isomer **6** and 72% of the equatorial methyl isomer **5**. In a duplicate experiment, the monoalkylated product (yield 96%) contained 29% of **6** and 71% of **5**.

B. With Methyl Chloride.—A solution of the lithium salt **4** was prepared as previously described from 1.20 mmol of methyllithium, 1.22 mmol of diethylamine, 1.26 mmol of the nitrile, and 173.1 mg of biphenyl in 2.8 ml of DME. This solution was added, dropwise and with stirring at 25° over a 1-min period, to a solution of 0.36 g (7.13 mmol) of CH_3Cl in 3.7 ml of DME (the initial concentrations after mixing were 0.17 *M* in the lithium salt **4** and 1 *M* in CH_3Cl). After the resulting solution had been stirred at 25° for 1.5 min it was quenched by the addition of dilute aqueous nitric acid and then extracted with four portions of hexane. After the organic extract had been dried and concentrated, the residual liquid contained the unalkylated nitrile and the monoalkylated product (yield 92%) composed of 20% of the axial methyl isomer **6** and 80% of the equatorial methyl isomer **5**. The aqueous phase from the alkylation reaction was diluted with water to 100 ml and aliquots were titrated by the Volhard procedure. The calculated yield of chloride ion was 1.125 mmol or 102% of the amount of monoalkylated product. Three additional runs were performed at 25° utilizing as initial concentrations of reactants 0.085 *M* lithium salt **4** and 1 *M* CH_3Cl. The aqueous phases were separated as described above for analysis of the chloride ion. The calculated yields of monoalkylated products were in the range 82–96% and the compositions were 19–20% of the axial methyl isomer **6** and 80–81% of the equatorial isomer **5**.

C. With Trimethyloxonium Fluoroborate.—A solution of the lithium salt **4** from 1.20 mmol of methyllithium, 1.36 mmol of diethylamine, 1.24 mmol of the nitrile, 182.5 mg of biphenyl, and 2.8 ml of DME was added, dropwise and with stirring at 25°, to a *suspension* of 955.9 mg (7.24 mmol) of trimethyloxonium fluoroborate[26] in 3.7 ml of DME (initial concentration 0.17 *M* in the lithium salt **4**). After the mixture had been stirred at 25° for 0.75 hr, dilute aqueous HCl was added and the previously described isolation and analysis procedures were followed. The monoalkylated products (yield 24%)[27] contained 40% of the axial methyl isomer **6** and 60% of the equatorial methyl isomer **5**. In an additional run, the monoalkylated product (yield 28%) contained 45% of **6** and 55% of **5**. Collected (glpc) samples of the monoalkylated products **5** and **6** were identified with previously described samples by comparison of ir spectra and glpc retention times.

Methylation of the Amino Ketone 13.—A mixture of 533 mg (3.47 mmol) of the amino ketone **13**,[4a,28] 2 g (*ca.* 40 mmol) of CH_3Cl, and 1 ml of DME was heated to 85–90° in a sealed tube for 4.5 days. A solution of the resulting crystalline mass in methanol was concentrated to separate 618 mg (87.3%) of the crude salt as tan crystals, mp 237° dec. A methanol solution of the crude product was decolorized with charcoal and then crystallized from a methanol–ethyl acetate mixture to separate 583 mg (82.4% of the methochloride of amine **13** as hygroscopic white plates: mp 239° dec; ir (KBr pellet) 1718 and 1731 cm^{-1} (C=O split by Fermi resonance with vibrations from bridgehead C–H bonds);[29] nmr (D_2O) δ 4.08 and 3.97 (4 H, two center peaks from a partially resolved AB pattern, $-CH_2N^+$), 3.37 (3 H singlet, CH_3N^+, 3.08 (3 H singlet, CH_3N^+), 2.7–3.4 (2 H multiplet, bridgehead CH), and 1.4–2.6 (6 H multiplet, aliphatic CH).

Anal. Calcd for $C_{10}H_{18}ClNO$: C, 58.96; H, 8.90; Cl, 17.41; N, 6.88. Found: C, 58.91; H, 8.86; Cl, 17.27; N, 7.15.

In subsequent experiments, mixtures of 763–769 mg (4.98–5.02 mmol) of the amino ketone **13** and 1 g (*ca.* 20 mmol) of CH_3Cl were diluted to a total volume of 10 ml with DME and then allowed to stand at 25–30° in sealed tubes for 2 months. Filtration of the resulting solutions separated 63.1–70.9 mg (6.2–6.9%) of the quaternary salt as white plates, mp 239° dec. Two additional runs were made with 764–770 mg (4.98–5.03 mmol) of the amine **13** and 2 g (*ca.* 40 mmol) of CH_3Cl diluted to a total volume of 10 ml of DME. In these cases, the solutions were

(26) This oxonium salt was prepared by the procedure of H. Meerwein, *Org. Syn.*, **46**, 120 (1966). As noted elsewhere,[5c] it is probable that the methyl groups of this oxonium salt have equilibrated, at least in part, with the *O*-methyl groups of the solvent, DME.

(27) When these reactions were run further toward completion by use of longer reaction times, other unidentified by-products were formed in significant amounts. We, therefore, ran the reaction only to the fraction of completion described to avoid the possibility that the composition of the monoalkylated product might be altered by subsequent side reactions.

(28) H. O. House and W. M. Bryant, III, *J. Org. Chem.*, **30**, 3634 (1965).

(29) H. O. House and H. C. Müller, *ibid.*, **27**, 4436 (1962).

heated to 75–80° in sealed tubes for 7 days. The quaternary salt, isolated as usual, amounted to 533–534 mg (52%), mp 244° dec.

Measurement of Chlorine Isotope Effects.—Chlorine isotope effects for the reactions with CH_3Cl are given in Table I. All errors are standard deviations of the mean. With triethylamine (**19**), runs ranging from 4.2 to 10.8% reaction (amount of CH_3Cl converted to NaCl, controlled by the amount of amine present) were carried out to demonstrate that the isotope effect did not change with this variable. The insoluble product was allowed to remain in the reaction mixture for varying lengths of time to show that the isotope effect did not vary due to exchange of ionic and covalent chloride. The fact that the isotope effect showed no trend with time is evidence that such exchange does not occur. Chlorine isotope effects have been reported previously for other reactions.[30]

Reaction tubes were made from 12-mm-o.d., medium-wall Pyrex tubing 23 cm long, sealed at one end. The tubes were boiled in 70% HNO_3, rinsed, boiled, and rinsed again in distilled water, oven dried at 120° for at least 1 day, and stored over $CaSO_4$ (Drierite) in desiccators until used. A slight constriction for sealing was made about 3 cm from the open end. A file mark at the 1-ml level was made on each tube. The tube was capped with an 11-mm no-air stopper. After flushing with dry N_2 by means of needles inserted in the stopper, the tube was cooled in a Dry Ice–ethanol bath. CH_3Cl was introduced by a long needle and condensed into the tube up to the 1-ml mark (0.991 g,[31] 20 mmol). Pure DME was then added by syringe, the final total volume (after addition of amine) being 10 ml. The liquid amines were weighed into the reaction tubes by difference from syringes. The amount of amine was varied according to the desired per cent reaction (4.2–10.8%). Alternatively, NaI (Mallinckrodt reagent) sufficient for 8.6% reaction was weighed out, then quickly poured into the tube while the no-air stopper was momentarily removed; NaI is soluble in the DME. The tube was sealed at the constriction. At zero time the tube and its contents were warmed quickly to reaction temperature by immersing the tube in a stream of running tap water and shaking vigorously. The tube was then thermostatted at 25.00 ± 0.05°. After the reaction was complete, the tube was cooled in Dry Ice–ethanol, scored, and cracked open. The insoluble product was collected on a small Büchner funnel. There was no ionic chloride in the filtrate. The organic products were hygroscopic, white, crystalline solids. The product was dissolved in 5 ml of 0.4 *M* KNO_3 solution and acidified with two drops of concentrated HNO_3, and the AgCl was precipitated with 0.4 *M* $AgNO_3$–0.4 *M* KNO_3 solution, gravity filtered, and dried for 2 hr at 120°. The AgCl was cooled, crushed to a powder, and converted to CH_3Cl by the method previously described.[30] This CH_3Cl was called the product sample. CH_3Cl from the tank was used as the reactant sample.

Relative isotopic compositions of the CH_3Cl samples were determined with a Consolidated Engineering Corp. Model 21-201 isotope ratio mass spectrometer. This instrument had been modified by replacing the preamplifiers and amplifiers with two Cary 401 vibrating reed electrometers. The original voltage divider was replaced by a four-dial General Radio Co. type 1454-AH decade voltage divider. The electrometers were operated on the positive current mode using 4×10^{10} Ω input resistors (specially installed). The *m/e* 52 peak was focused on the small plate 2 (large plate 1 then collects ions of *m/e* 51–47) with amplifier 2 on the 30-V scale and amplifier 1 on the 3-V scale. The signal from amplifier 1 was switched onto the voltage divider and thus used to balance the signal from amplifier 2. When the signal on amplifier 2 was reduced nearly to zero, the recorder was used to read the residual small voltage. The damping circuit on preamplifier 2 was engaged at this point to reduce the noise level. The last dial on the voltage divider was switched from one number to the next and back again across the zero voltage line. The experimental signal ratio to six figures could then be determined from the recorder traces.[32] As the last dial of the voltage divider was switched, the voltage approached its new value exponentially. The fifth and sixth decimal figures were obtained by measuring vertical displacements on the recording relative to the zero voltage line, for the ascending and descending exponentials successively. This procedure was repeated until six values of the ratio were obtained for a sample. The average of these numbers (called a "value" for a sample) was used for subsequent calculations. The values themselves are dependent on the circuitry of the instrument and are not direct measures of the isotopic composition.

Calculation of the isotope effect[32] involves division of the signal ratio value for the reactant sample by that for the product sample. These samples were measured one after the other, so that the measurement for, say, the product (reactant) sample was bracketed by two measurements for the reactant (product) sample. If the two values for the bracketing sample were very different, no calculations were performed. If the values were close, their average was calculated and used to compute the initial ratio (reactant value over product value). The initial ratio was used to calculate the isotope effect. The calculation of R_R, the ratio of rates (k_{35}/k_{37}) corrected for % reaction, was simplified by use of the approximation

$$R_R \cong R_I\,[1 + (f/2)(R_I - 1)]$$

$$\text{where } R_R = \frac{\log (1 - R_I f)}{\log (1 - f)}$$

R_I = initial ratio (reactant value/product value)
f = fraction of CH_3Cl converted to NaCl

The R_R finally obtained from three signal ratio values was called a "measurement" of the isotope effect. Several measurements of the isotope effect were made for each product sample for a run. These measurements were averaged to give an isotope effect for that run. The observed values for 44 independent runs are recorded elsewhere,[32] with chronological run number, ratios for reactant sample, pruduct sample, and reactant sample again, each with its standard deviation, and R_I for each run.

Registry No.—**4**, 33209-52-8; **7**, 7576-03-6; **8a**, 33209-54-0; **8b**, 33209-55-1; **8c**, 33209-56-2; **9a**, 33209-57-3; **9b**, 33209-58-4; **9c**, 33209-59-5; **10**, 7576-02-5; **13**, 4146-35-4; **13** (methochloride), 33209-62-0; **19**, 121-44-8; NaI, 7681-82-5; chloromethane, 74-87-3; 1,2-dimethoxyethane, 110-71-4.

(30) R. M. Bartholomew, F. Brown, and M. Lounsbury, *Can. J. Chem.*, **32**, 979 (1955); J. W. Hill and A. Fry, *J. Amer. Chem. Soc.*, **84**, 2763 (1962); E. P. Grimsrud and J. W. Taylor, *ibid.*, **92**, 739 (1970).

(31) C. Vincent and Delachanal, *Bull. Soc. Chim. Fr.*, **31**, 12 (1879).

(32) N. D. Hershey, "Chlorine Isotope Effects as Probes for Transition-State Structure," Ph.D. Thesis in Chemistry, M. I. T., Jan 1971, pp 3, 14–62. Further details on experimental procedure may be found here and also in B. S. Magid, Ph.D. Thesis in Chemistry, M. I. T., June 1964, pp 9, 25–28, 34, and 62–67, and M. H. O'Leary, Ph.D. Thesis in Chemistry, M. I. T., May 1966, pp 53, 54, 60, 78, 79, 99, 104, and 105.

The Synthesis of Some Diphenyl and Triphenyl Derivatives of Anthracene and Naphthalene[1]

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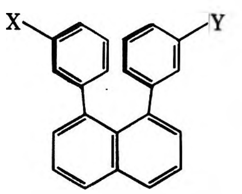
Coupling reactions of lithium diphenylcuprate and appropriate aryl halides have been developed to provide efficient syntheses of 1,8-diphenylnaphthalene (**1d**), 1-iodo-8-phenylnaphthalene (**3**). 1-phenyl-9,10-anthraquinone (**13**), and 1,8-diphenyl-9,10-anthraquinone (**15**). Appropriate transformations of the anthraquinones **13** and **15** yielded 1,8-diphenylanthracene (**22**), 1,9-diphenylanthracene (**25**), and 1,8,9-triphenylanthracene (**26**). The spectroscopic properties of all these phenylated anthracenes and naphthalenes are consistent with the existence of these molecules in conformations with the phenyl rings parallel to one another and perpendicular to the plane of the anthracene or naphthalene ring.

Earlier publications[3-8] have described preparative routes to anthracene and naphthalene derivatives which contain at least two aryl substituents at adjacent peri positions. Particularly in the naphthalene series, it has been common to obtain these substances by constructing alicyclic intermediates with the necessary carbon skeleton. Aromatization has then been accomplished by a combination of dehydration and/or dehydrogenation steps. These synthetic pathways have provided a sufficient variety of 1,8-diarylnaphthalene derivatives to show (uv, nmr, and dipole moment measurements)[3b,c] that in solution these molecules exist primarily in the conformation illustrated in structure **1** with the aryl rings approximately parallel to one another and approximately perpendicular to the plane of the naphthalene nucleus. In derivatives (*e.g.*, **1a**)



1a, X = H; Y = $C(CH_3)_2OH$
b, X = Y = CO_2CH_3
c, X = Y = CO_2H
d, X = Y = H

with meta-substituted aryl rings, the energy barrier to rotation of the substituted ring ($\Delta G^{\ddagger}$ = 16 kcal/mol at 25°) is sufficiently low that it is not practical to separate cis and trans isomers of structures such as **1b** or **1c** at room temperature. A complete X-ray crystallographic analysis of the parent hydrocarbon, 1,8-diphenylnaphthalene (**1d**),[9] has shown this molecule to have the dimensions and packing pattern in the crystal illustrated in Figure 1. Both previous X-ray crystallographic measurements with other naphthalene derivatives[8,10] and various speculations and calculations concerning similar compounds[6b,11] suggest that this hydrocarbon should be deformed to alleviate the nonbonding interaction between the two phenyl rings. It will be seen in Figure 1 that this relief of strain is distributed among deformation of the naphthalene ring, a splaying out of the two phenyl rings, and a rotation of the phenyl rings so that the approximately parallel planes of the two phenyls are at an angle of approximately 70° to the plane of the naphthalene ring. As a result the meta positions and, especially, the para positions of the phenyl rings are relatively distant from one another and our earlier failure to convert the diacid **1c** to a cyclic anhydride[3b] is understandable.

To pursue further the chemical and physical properties of the aryl-substituted naphthalenes and anthracenes, we sought more direct synthetic routes to these substances. Although the Ullmann coupling of 1,8-diiodonaphthalene (**2**) and iodobenzene in the presence of copper powder did not provide a useful route to 1,8-diphenylnaphthalene,[12] coupling of the diiodide **2** with performed organocopper(I) derivatives[12,13] was more effective. Thus, a small-scale reaction of the diiodide **2** with a reagent preformed from phenyllithium and copper(I) bromide led to the formation of 1,8-diphenylnaphthalene (**1d**) in 47% yield.[13] However, in our subsequent attempts to use this process for the synthesis of the diphenylnaphthalene **1d** the reaction proved very capricious, sometimes producing the hydrocarbon **1d** but more frequently yielding the known monophenyl iodide **3**.[14] After considerable experimentation, we found that the course of the reaction was critically dependent on the proportions of phenyllithium and copper(I) bromide used to prepare the copper reagent. When the reagent was prepared by reaction of 2 mol of phenyllithium with slightly more

(1) This research has been supported by Public Health Service Grant No. R01-CA-12634 from the National Cancer Institute.

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(3) (a) H. O. House, R. W. Magin, and H. W. Thompson, *J. Org. Chem.* **28**, 2403 (1963); (b) H. O. House and R. W. Bashe, II, *ibid.*, **30**, 2942 (1965); **32**, 784 (1967); (c) H. O. House, W. J. Campbell, and M. Gall, *ibid.*, **35**, 1815 (1970).

(4) (a) A. S. Bailey, G. A. Dale, A. J. Shuttleworth, and D. P. Weizmann, *J. Chem. Soc.*, 5110 (1964); (b) A. S. Bailey and A. J. Shuttleworth, *ibid.*, *C*, 1115 (1968).

(5) S. C. Dickerman, D. deSouza, and P. Wolf, *J. Org. Chem.*, **30**, 1981 (1965).

(6) (a) E. D. Bergmann, S. Blumberg, P. Bracha, and S. Epstein, *Tetrahedron*, **20**, 195 (1964); (b) M. Rabinovitz, I. Agranat, and E. D. Bergmann, *Tetrahedron Lett.*, 4133 (1965).

(7) (a) C. Dufraisse and Y. Lepage, *C. R. Acad. Sci.*, **258**, 1507, 5447 (1964); (b) Y. Lepage and O. Pouchot, *Bull. Soc. Chim. Fr.*, 2342 (1965).

(8) For a review, see V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(9) A. S. Parkes and R. A. Ogilvie, unpublished work. The details are available in the Ph.D. dissertation of R. A. Ogilvie, Massachusetts Institute of Technology, 1971.

(10) M. B. Jameson and B. R. Penfold, *J. Chem. Soc.*, 528 (1965).

(11) A. I. Kitaigorodsky and V. G. Dashevsky, *Tetrahedron*, **24**, 5917 (1968).

(12) R. W. Bashe, II, Ph.D. Dissertation, Massachusetts Institute of Technology, 1966.

(13) See G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969), and references cited therein.

(14) W. A. Henderson, Jr., R. Lopresti, and A. Zweig, *ibid.*, **91**, 6049 (1969). We are grateful to Dr. Henderson for providing us with a sample of their material for comparison with our product.

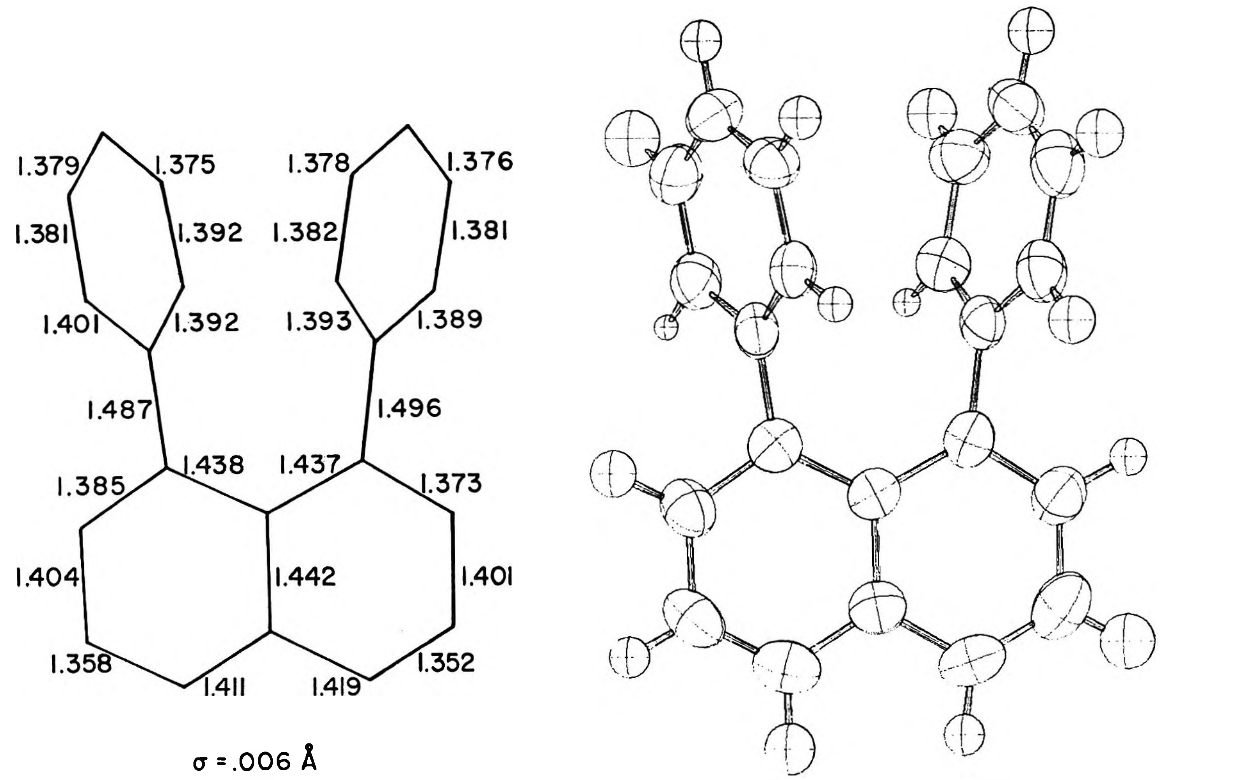
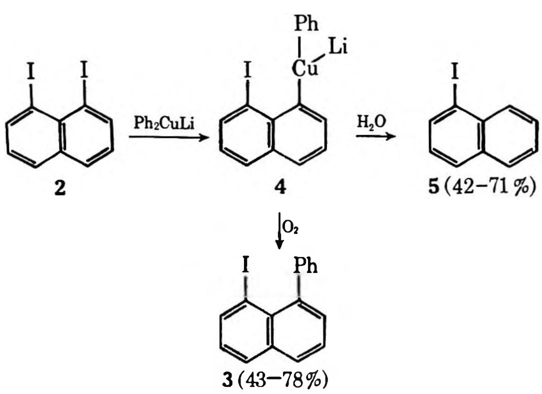


Figure 1.—Bond lengths and a perspective view perpendicular to the naphthalene ring of 1,8-diphenylnaphthalene as determined by X-ray cystallography (ref 9).

than 1 mol of copper(I) bromide, a solution containing only a reagent having the stoichiometry Ph_2CuLi was obtained. As indicated in Scheme I, an excess of this

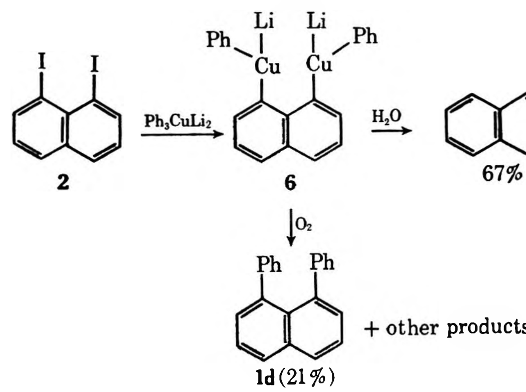
Scheme I



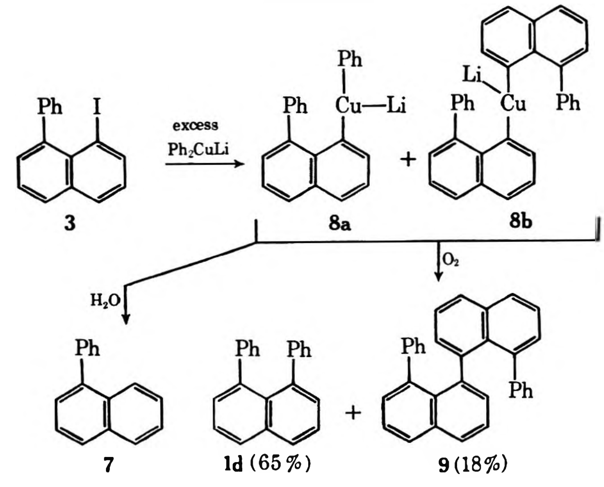
reagent reacted rapidly at only one position of the diiodide 2 to form an intermediate cuprate with the stoichiometry implied in structure 4. As expected,[13] hydrolysis of this intermediate formed 1-iodonaphthalene (5) and oxidation yielded mainly the monophenyl monoiodide 3. However, if even a slight excess of phenyllithium was present a more reactive species was apparently generated which reacted further with the monocuprate 4. Scheme II illustrates the results of treating the diiodide 2 with a copper reagent having the apparent stoichiometry Ph_3CuLi_2 (from 3 mol of PhLi and 1 mol of CuBr). In this case a biscuprate species such as 6 was apparently formed, since hydrolysis yielded mainly naphthalene whereas oxidation produced the diphenyl derivative **1d** and other higher molecular weight materials.

The highest overall yields of the diphenylnaphthalene **1d** were obtained from the diiodide 2 by a two-stage process in which the intermediate monophenyl iodide 3 Scheme III) was isolated and then treated with

Scheme II



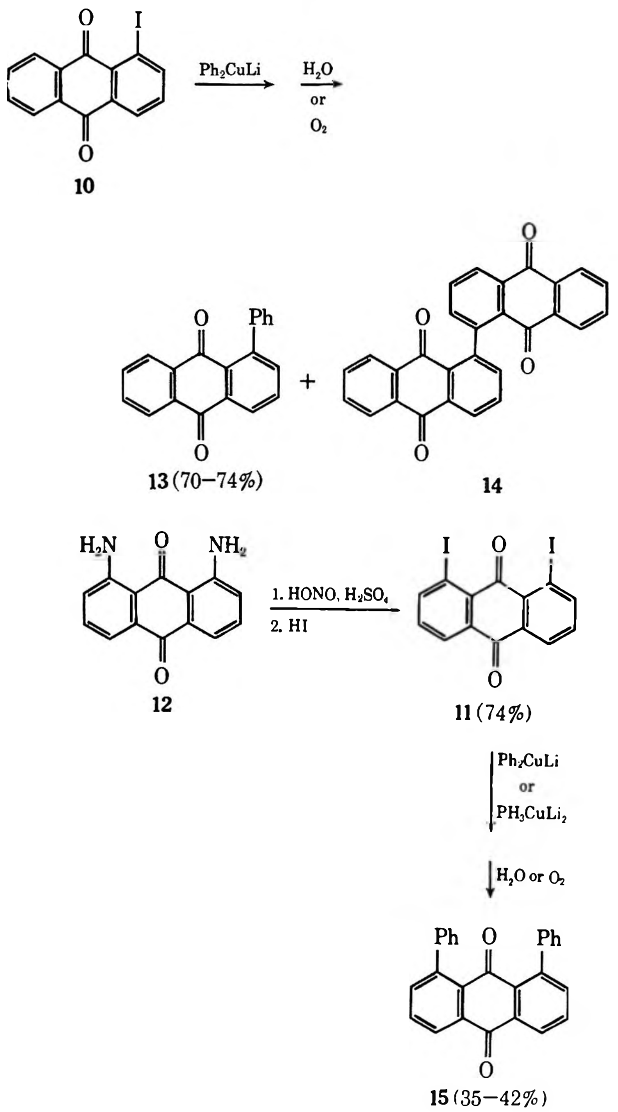
Scheme III



excess lithium diphenylcuprate. Oxidation of the intermediate mixture of cuprates **8** produced the hydrocarbons **1d** and **9**. When equimolar amounts of the cuprate and the iodide **3** were used, an unusually high percentage of the symmetrical coupling product **9** was produced. This suggests that formation of the symmetrical cuprate intermediate **8b** may be favored by a special type of stabilization involving coordination of the metal with the adjacent phenyl rings. The nature of the cuprate **8b** is under investigation and will be reported elsewhere.

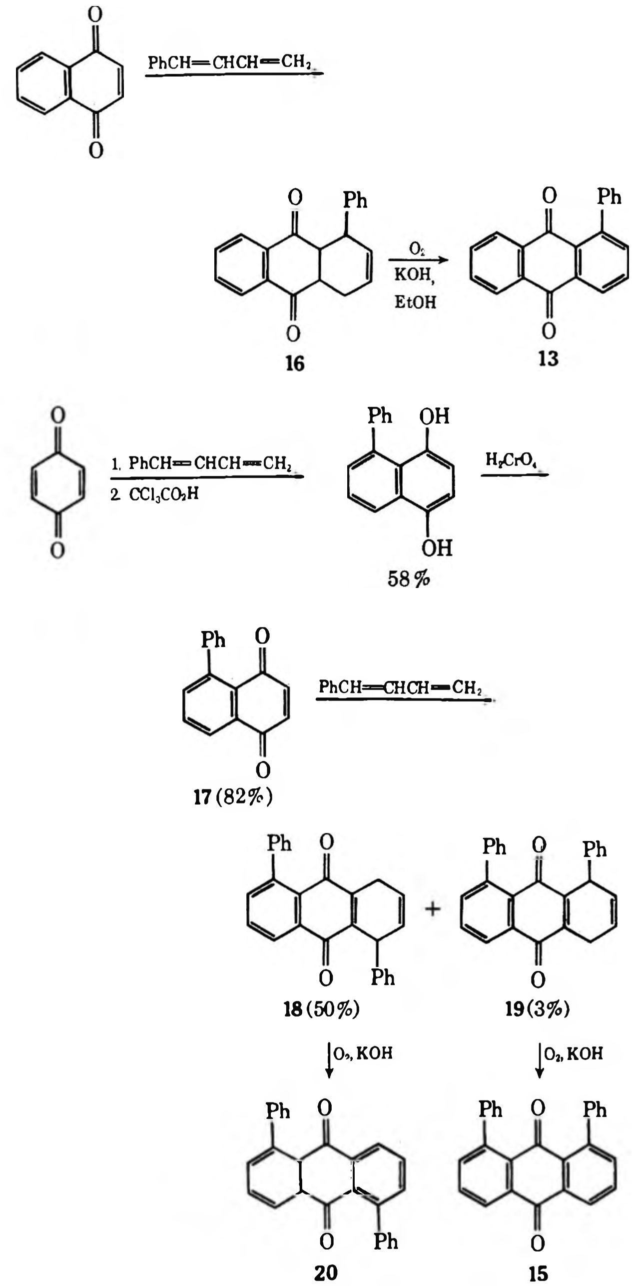
With this background, we were led to explore syntheses of various phenylated anthracenes which were based on the reaction of lithium diphenylcuprate with iodoquinones **10** and **11** (Scheme IV). As indicated,

SCHEME IV



the diiodoquinone **11** was readily available from the corresponding diamine **12**. The phenylquinones **13** and **15** were obtained much more easily by this procedure than by the alternative Diels–Alder procedure summarized in Scheme V. The reactions of the iodoquinones **10** and **11** with lithium diphenylcuprate or dilithium triphenylcuprate differed from the reactions with the iodonaphthalenes in that halogen–metal exchange was much faster (complete in less than 30 sec at 0°) and C–C bond formation occurred relatively

SCHEME V



rapidly even when no oxidant was added to the reaction mixture prior to hydrolysis. Although these coupling reactions might be supposed to follow a pathway analogous to the conjugate addition of cuprates to α,β-unsaturated carbonyl compounds,[15] we found that reaction of the diiodoquinone **11** with Ph_3CuLi_2 for 25–30 sec at 0° followed by hydrolysis without prior oxidation yielded a mixture containing primarily 9,10-anthraquinone (42%) accompanied by smaller amounts of the phenylquinone **13** (9%) and the diphenylquinone **15** (14%). Use of the same reaction conditions with oxidation *before* hydrolysis produced the diphenylquinone **15** in 42% yield. Therefore, we believe that these iodoquinone coupling reactions follow a path analogous to other aryl iodides[13] in which initial metal–halogen exchange (possibly preceded by electron transfer) forms a diaryl (or triaryl) cuprate. Subse-

(15) (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (b) H. O. House and W. L. Fischer, Jr., *ibid.*, **33**, 949 (1968).

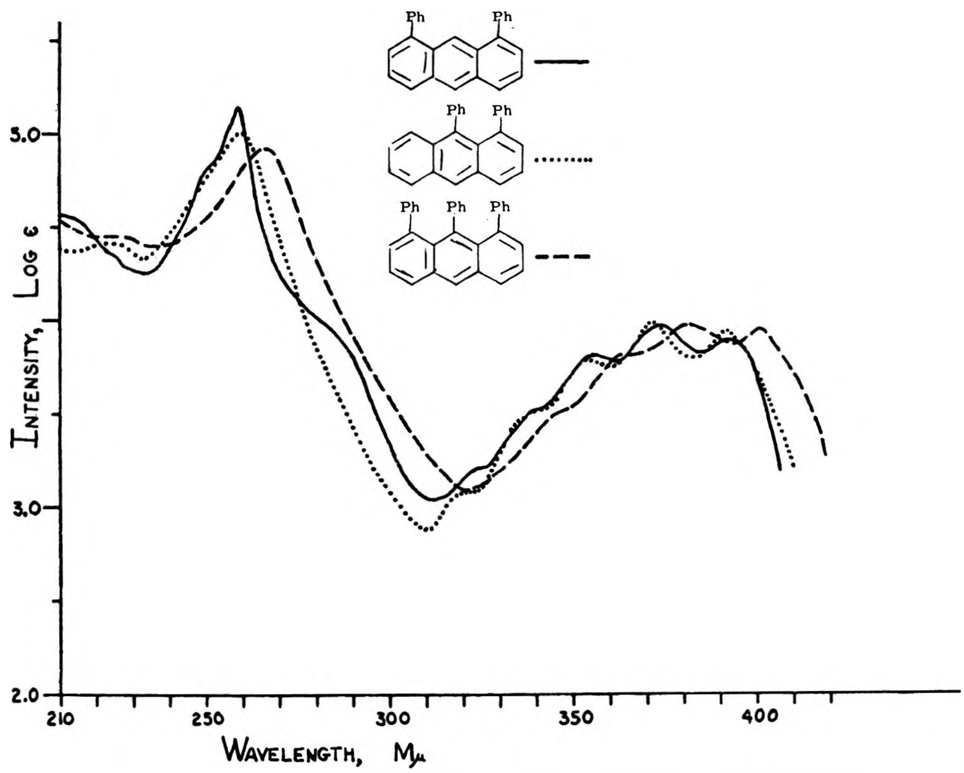


Figure 2.—The electronic spectra of the phenylated anthracenes 22, 25, and 26 determined in 95% EtOH.

quent oxidation of this cuprate intermediate, either by added oxygen or by one of the quinones present in the reaction mixture, leads to formation of the new C–C bond.

The reaction scheme VI, devised and used previously to prepare compounds 21, 23, and 25,[5] was equally useful for the new compounds 22, 24, and 26 and for the conversion of anthrone to the known 9-phenylanthracene (27).

The electronic and nmr spectra of the diphenylanthracenes 22 and 25 and the triphenylanthracene 26 are compared in Figures 2 and 3. As had been observed for 1-phenylnaphthalene and the 1,8-diphenyl derivative 1d, the electronic spectra (Figure 2) of the anthracenes 22, 25, and 26 resemble closely the spectra of anthracene and the monophenyl derivatives 21 and 27, the principal differences being a shift of the low-intensity peaks in the region 300–400 mμ to slightly longer wavelengths. These shifts in peak positions are related primarily to the number of phenyl substituents present, and no special effect on the electronic spectrum arises from having two phenyl groups on adjacent peri positions. The similarity among these electronic spectra is consistent with the idea that each of these molecules exists in a conformation with the phenyl groups approximately perpendicular to the anthracene ring so that π-orbital overlap between the aromatic rings is slight. Comparison of the nmr spectra (Figure 3) reveals that the 1,8-diphenylanthracene (22), like the monophenyl compounds 21 and 27, has no nmr absorption at higher field than δ 7.0. In the 1,9-diphenyl compound, the resonance for the two presumably parallel phenyl rings is shifted above δ 7.0. In the triphenyl derivative 26, the resonance for all the phenyl rings is shifted above δ 7.0 and the phenyl substituent at C-9 with adjacent parallel phenyl substituents on each side is shifted upfield to δ 6.36.

The polarographic reduction potentials for the various naphthalene, anthraquinone, and anthracene derivatives prepared in this study were measured and are summarized in Table IV. Although further studies will be required to characterize the species being produced, each of the materials exhibits two reduction waves which probably correspond to the successive reduction of each compound to a radical anion and to a dianion.[16] In general, the half-wave potentials for the hydrocarbons became less negative by about 0.05–0.1 V for each phenyl substituent added. The only unusual case was the triphenyl derivative 26; in this case the half-wave potential for the first reduction step had the value expected but the value for the second wave was significantly less negative than the above generalization would predict. We do not yet know whether this result is explained by relief of strain in the presumably nonplanar anthracene ring of the dianion or by a rapid further reaction of the dianion in this case. We hope to resolve this question with cyclic voltammetry and product studies which are in progress.

Experimental Section[17]

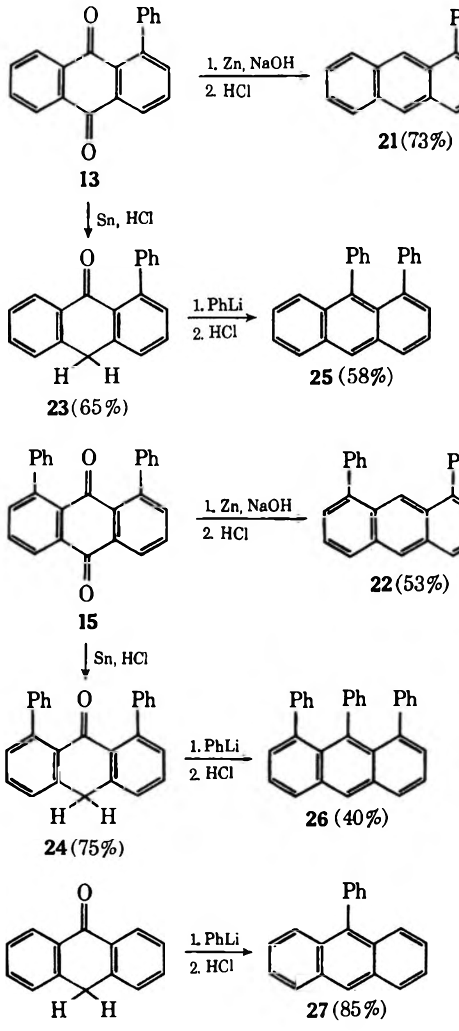
1,8-Diiodonaphthalene (2).—By use of a modification of the procedure described by Shechter and coworkers[18] in which pure 1,8-diaminonaphthalene in aqueous 4.1 *M* H_2SO_4 was diazotized

(16) For related studies, see (a) L. H. Klemm, C. D. Lind, and J. T. Spence, *J. Org. Chem.*, **25**, 611 (1960); (b) A. J. Bard, K. S. V. Santhanam, J. T. Maloy, J. Phelps, and L. O. Wheeler, *Discuss. Faraday Soc.*, 167 (1968).

(17) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shifts are expressed in δ values relative to a tetramethylsilane internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

(18) B. Bossenbroek, D. C. Sanders, H. M. Curry, and H. Shechter, *J. Amer. Chem. Soc.*, **91**, 371 (1969).

SCHEME VI



at −10° rather than at 5°, we obtained the pure diiodide 2 in 55% yield. In agreement with these workers, our efforts to obtain the diiodide 2 by stepwise diazotization[19] of the diamine resulted in low yields. The following procedure was found most satisfactory for preparation of the diiodide 2. Technical grade (Aldrich) 1,8-diaminonaphthalene (100 g) was distilled from 5 g of zinc dust, and the distillate [bp 183–187° (4–5 mm)] was crystallized from hexane to separate 83.8 g (0.53 mol) of the pure diamine as white needles, mp 63–65.5°. A suspension of this diamine salt in 975 ml of aqueous 6.9 M H_2SO_4 was cooled to −20° and then a solution of 108 g (1.59 mol) of $NaNO_2$ in *ca.* 400 ml of H_2O was added, dropwise and with stirring, while the temperature of the mixture was kept at −15 to −20°. As soon as the addition was complete a solution of 538 g (3.24 mol) of KI in *ca.* 450 ml of H_2O was added, dropwise and with stirring. During this addition the reaction mixture was kept at −15 to −20° and additional portions of concentrated H_2SO_4 were added as needed to keep the reaction mixture from freezing. The resulting mixture was warmed to 80°, rapidly and with stirring, and then cooled to 20° and made alkaline by the addition of solid NaOH. The mixture was filtered and the black solid residue was collected, pulverized, and extracted with several portions of boiling Et_2O (total volume 3 l.). The ethereal solution was washed successively with aqueous 10% HCl, saturated aqueous $Na_2S_2O_3$, and dilute aqueous NaOH and then dried and concentrated. The residual brown solid (147.6 g) was recrystallized from hexane to separate 126.6 g (63%) of the pure diiodide 2 as tan prisms, mp 108.5–110° (lit.[18] mp 109°), as well as 10.0 g (5%) of less pure fractions melting within the range 102.5–108.5°; ir ($CHCl_3$), no absorption attributable to OH or C=O in the 3- or 6-μ region; uv max (95% EtOH) 237 mμ (ϵ 47,000), 299 (6900), 311 (8000), and 325 (6200); nmr ($CDCl_3$) δ 8.38 (2 H, d of d, J = 7.5 and 1.3 Hz), 7.79 (2 H, d of d, J = 7.5 and 1.3 Hz), and

(19) R. Scholl, C. Seer, and R. Weitzenböck, *Ber.*, **43**, 2202 (1910).

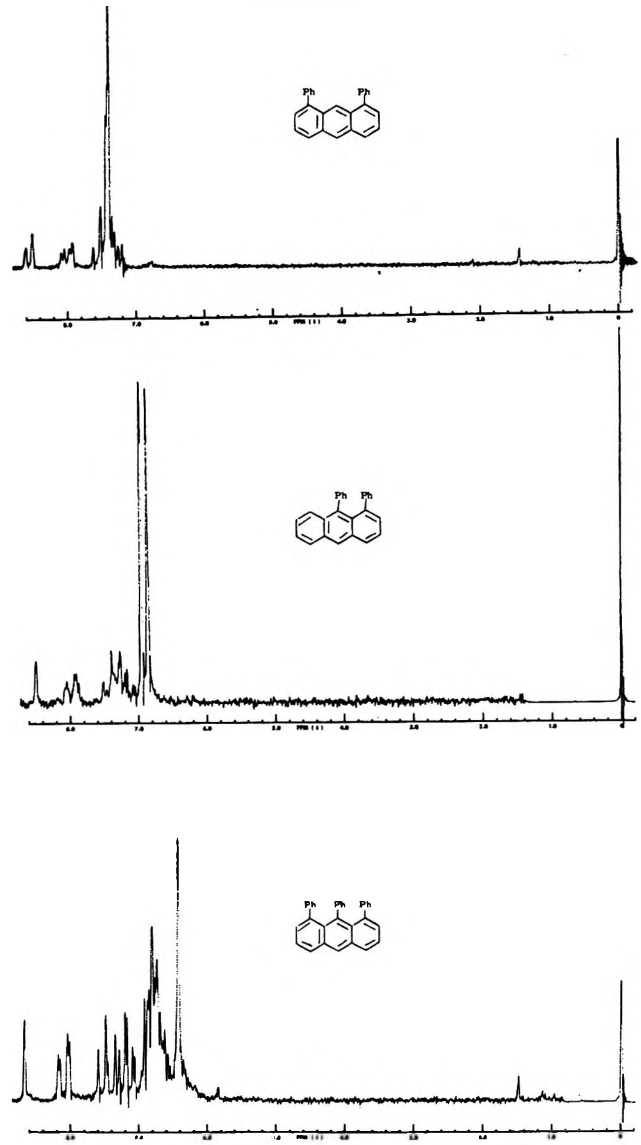


Figure 3.—The nmr spectra of the phenylated anthracenes **22**, **25**, and **26** determined in $CDCl_3$.

7.03 (2 H t, J = 7.5 Hz); mass spectrum m/e (rel intensity) 380 (54, M^+), 253 (38), and 126 (100).

1-Iodo-8-phenylnaphthalene (3).—A cold (0°) solution of lithium diphenylcuprate,[13] prepared from 3.78 g (26.3 mmol) of CuBr and 52.7 mmol of phenyllithium in 60 ml of Et_2O, was added over 2.5 min to a cold (−5°), stirred suspension of 5.00 g (13.2 mmol) of the diiodide 2 in 70 ml of Et_2O. The resulting solution was stirred in an ice bath for 3 min and then a stream of oxygen was passed over the surface of the liquid, with vigorous stirring and cooling, for 20 min. The resulting black colored mixture was partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl and the ethereal phase was dried and concentrated. The residue was chromatographed on 170 g of silica gel with hexane as an eluent. After separation of the early fractions containing iodobenzene and biphenyl, the crude iodide 3 was eluted as 2.43 g of pale yellow liquid. Crystallization from hexane afforded 1.847 g (43%) of the iodide 3 as pale yellow needles, mp 63–65°. Recrystallization narrowed the melting range to 64–65° (lit.[14] mp 65–65.5°); ir (CCl_4) no absorption attributable to OH or CO functions in the 3- or 6-μ regions; uv max (95% EtOH) 214 mμ (ϵ 38,000), 232 (38,000), and 301 (9700); nmr ($CDCl_3$) δ 6.6–8.3 (multiplet, aryl CH); mass spectrum m/e (rel intensity) 330 (50, M^+), 203 (100), 202 (62), 102 (26), and 101 (34). This material was identified with an authentic sample[14] by comparison of ir spectra, glpc retention times, and a mixture melting point.

To establish the optimum conditions for this coupling reaction a number of small-scale experiments were performed. In one representative set of experiments a cold (0°) solution of 2.00

mmol of $LiPh_2Cu$ in 10 ml of Et_2O was treated with a solution of 380 mg (1.00 mmol) of the diiodide **2** and 114 mg of bibenzyl (an internal standard) in 10 ml of ether. The resulting solutions were either stirred at 0° or refluxed and aliquots were removed periodically. The aliquots were either hydrolyzed directly with an aqueous solution of NH_3 and NH_4Cl or they were first stirred at 0° under an oxygen atmosphere and then hydrolyzed. In each case the final ethereal solution remaining after hydrolysis was dried and analyzed by glpc. The glpc analysis (silicone gum, SE-52, on Chromosorb P) was started at 100° with a programmed temperature rise of 5°/min. Under these conditions the retention times and the various components were iodobenzene, 5.0 min; naphthalene, 8.2 min; biphenyl, 12.2 min; bibenzyl, 15.0 min; 1-iodonaphthalene (**5**), 17.5 min; 1-phenylnaphthalene (**7**), 22.2 min; 1-iodo-8-phenylnaphthalene (**3**), 29.0 min; 1,8-diphenylnaphthalene (**1d**), 31.0 min. The glpc equipment was calibrated with known mixtures of authentic samples. The results of these analyses are summarized in Table I.

TABLE I

REACTION OF 0.1 *M* $LiPh_2Cu$ WITH 0.05 *M* 1,8-DIIODONAPHTHALENE (**2**) IN ETHER SOLUTION

Temp, °C	Reaction time, min	Isolation procedure[a]	Product yields, % **5**	**3**	**1d**
0	1	H_2O	71	33	
		O_2, H_2O		66	4
0	10	H_2O	69	31	
		O_2, H_2O		78	
0	180	H_2O	59	5	
		O_2, H_2O		69	4
Reflux	1	O_2		55	4
Reflux	30	O_2		3	10
Reflux	180	O_2			6
		H_2O			3

[a] Aliquots of the reaction mixture were either hydrolyzed (H_2O) or oxidized with oxygen and then hydrolyzed (O_2, H_2O).

In a similar set of experiments a cold (3–6°) solution of 2.00 g (5.37 mmol) of the diiodide **2** and 393 mg of bibenzyl in 35 ml of ether was treated with 10 ml of an Et_2O solution containing 5.4 mmol of $LiPh_2Cu$ and stirred for 1 min. After aliquots had been removed for the previously described hydrolysis or oxidation and glpc analysis, an additional 10-ml portion of $LiPh_2Cu$ (5.4 mmol) in Et_2O was added and the processes were repeated. The results of these experiments are summarized in Table II.

TABLE II

REACTION OF 0.06–0.12 *M* 1,8-DIIODONAPHTHALENE (**2**) WITH 0.12–0.72 *M* $LiPh_2Cu$ AT 3–6° IN ETHER SOLUTION

$LiPh_2Cu$, equiv	Reaction time, min	Isolation procedure[a]	Product yields, % **2**	**5**	**3**	**3** + **5**	**7**	**1d**	**1d** + **7**
1.0	1	O_2, H_2O	59	7	31	38	2		2
		H_2O	43	16	25	41			
2.0	4	O_2, H_2O		7	63	70		4	4
		H_2O		42	36	78	3	1	4
3.0	7	O_2, H_2O		7	71	78	5	15	20
		H_2O		47	23	70	11	5	16
4.0	10	O_2, H_2O			66	66		21	21
		H_2O		55	14	69	17	6	23
5.0	13	O_2, H_2O		5	59	64	4	25	29
		H_2O		50	13	63	22	7	29
6.0	16	O_2, H_2O		5	44	59	6	28	34
		H_2O		52	6	58	23	6	29
6.0	20[b]	O_2, H_2O		3	41	44	5	27	32

[a] Aliquots of the reaction mixture were either hydrolyzed (H_2O) or oxidized and then hydrolyzed (O_2, H_2O). [b] The entire remaining reaction mixture was oxidized and then hydrolyzed.

In another set of experiments a cold (0°) solution of 500 mg (1.32 mmol) of the diiodide **2** and a weighed amount of bibenzyl (*ca.* 100 mg) in 4.5 or 5.5 ml of Et_2O was treated with a solution of either 1.97 mmol of $LiPh_2Cu$ in 5.5 ml of Et_2O (from 3.95 mmol of PhLi and 292 mg or 2.02 mmol of CuBr) or 3.94 mmol of Li_2Ph_3Cu in 14.5 ml of Et_2O (from 576 mg or 3.94 mmol of CuBr and 11.82 mmol of PhLi). After the resulting solution had been stirred at 0° for 2.0 min, 2.0-ml aliquots were removed for the previously described hydrolysis or oxidation and glpc analysis. The remaining mixture from the reaction with $LiPh_2Cu$ was treated with an additional 1.24 mmol of PhLi and then stirred for 2.0 min at 0°. Aliquots were either hydrolyzed or oxidized and then subjected to glpc analysis. The results of these experiments are summarized in Table III.

TABLE III

REACTION OF 0.07–0.13 *M* 1,8-DIIODONAPHTHALENE (**2**) WITH EITHER $LiPh_2Cu$ OR Li_2Ph_3Cu FOR 2 MIN AT 0° IN ETHER SOLUTION

Cuprate (concn, *M*)	Isolation procedure[a]	Product yields, % **3**	**5**	**7**	**1d**	Naphthalene
$LiPh_2Cu$	H_2O	9	62	2	1	5
(0.2)	O_2, H_2O	60		1	3	
$LiPh_2Cu$ (0.2)	H_2O			3		67
+ PhLi (0.2)	O_2, H_2O				21	
Li_2Ph_3Cu	H_2O	1		8	1	68
(0.2)	O_2, H_2O				27	1

[a] Aliquots of the reaction mixtures were either hydrolyzed (H_2O) or oxidized with oxygen and then hydrolyzed (O_2, H_2O).

Reaction of the Iodide 3 with Lithium Diphenylcuprate.—To a cold (−2 to −5°) solution of 90.9 mmol of $LiPh_2Cu$ in 250 ml of Et_2O was added, dropwise and with stirring over 3 min, a solution of 5.00 g (15.2 mmol) of the iodide **3** in 50 ml of Et_2O. The resulting mixture was stirred in an ice bath for 3 min and then oxidized by passing oxygen over the surface of the cold solution, with vigorous stirring, for 30 min. After the reaction mixture had been partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl, the ethereal phase was dried and concentrated. Chromatography on silica gel separated 2.959 g (69.8%) of the crude diphenylnaphthalene **1d** (eluted with hexane) which was recrystallized from hexane to afford 2.77 g (65.4%) of pure 1,8-diphenylnaphthalene (**1d**) as white needles, mp 149.5–151° (lit.[3a] mp 149–150°). A later fraction (0.818 g), eluted with mixtures of Et_2O and hexane, was recrystallized from hexane to separate 0.525 g (18%) of the dinaphthyl derivative **9** as white prisms: mp 210.5–212°; ir ($CHCl_3$) no OH or C=O absorption in the 3- and 6-μ regions; uv max (95% EtOH) 221 mμ (ϵ 58,000), 248 (shoulder, 29,000), 285 (11,000), and 315 (12,000); nmr ($CDCl_3$) δ 6.8–7.7 (12 H m, naphthyl CH) and 6.0–6.8 (10 H m, phenyl CH); mass spectrum *m/e* (rel intensity) 406 (100, M^+), 405 (21), and 215 (16).

Anal. Calcd for $C_{32}H_{22}$: C, 94.54; H, 5.46. Found: C, 94.56; H, 5.40.

To obtain an authentic sample of the dinaphthyl derivative **9**, a mixture of 300 mg (0.91 mmol) of the iodide **3** and 225 mg of copper bronze was heated to 150–180° with stirring for 19 hr. The resulting mixture was cooled and extracted with ether. The crude extract was chromatographed on silica gel to separate 141.8 mg of crude solid (eluted with Et_2O–hexane mixtures) which was recrystallized from hexane to separate 56.6 mg (31%) of the binaphthyl **9**, mp 210–212.5°. This product was identified with the previously described sample by a mixture melting point determination and by comparison of ir, uv, and nmr spectra.

In a subsequent experiment, a cold (0°) solution of 0.76 mmol of $LiPh_2Cu$ in 2.0 ml of Et_2O was added to a cold (0°) solution of 500 mg (1.52 mmol) of the iodide **3** in 0.5 ml of Et_2O. The resulting solution was stirred while oxygen was passed over the surface for 5 min and the reaction mixture was subjected to the usual isolation procedure. Crystallization of the crude organic product from hexane separated 121 mg (39%) of the dinaphthyl **9**, mp 210–211°. Chromatography on silica gel separated an additional 18 mg of the dimer **9**, mp 209–210° (total yield 139 mg or 45%). Analysis (tlc, silica gel coating) of the remaining mother liquors suggested that a small amount of 1,8-diphenylnaphthalene (**1d**) was also present.

5-Phenyl-1,4-naphthoquinone (17).—Following a published procedure,[20] *trans*-1-phenyl-1,3-butadiene was obtained as a colorless liquid: bp 61–63° (3 mm); $n^{23}D$ 1.6064 [lit.[20] bp 78–81°

(20) O. Grummitt and E. I. Becker, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 771.

(8 mm); $n^{25}D$ 1.607–1.608]; ir (CCl_4) 1630 (C=C), 945 (trans CH=CH), and 895 cm^{-1} ($C=CH_2$); nmr (CCl_4) δ 7.0–7.5 (5 H m, aryl CH), 6.0–6.8 (3 H m, vinyl CH), and 5.0–5.5 (2 H m, vinyl CH).

A solution of 5.00 g (38 mmol) of the diene and 4.50 g (42 mmol) of *p*-benzoquinone in 50 ml of PhH was refluxed for 8.5 hr. The reaction mixture was treated[21b] with a solution of 0.1 g of CCl_3CO_2H in 3 ml of PhH and refluxing was continued for 4 hr. The resulting solution was concentrated under reduced pressure and the residue was triturated with CH_2Cl_2 to leave 5.21 g (58%) of the crude hydroquinone, mp 157–163°. Recrystallization from an EtOAc–hexane mixture afforded the pure 5-phenyl-1,4-dihydroxynaphthalene as colorless prisms: mp 169.5–171° (lit.[21] mp 170°); ir (Nujol mull) 3250 cm^{-1} (broad, associated OH); uv max (95% EtOH) 215 mμ (shoulder, ϵ 17,500) and 295 (3900); nmr (CD_3COCD_3) δ 7.0–8.0 (7 H m, 5 aryl CH and 2 OH, exchanged with D_2O), 6.4–6.8 (2 H m, aryl CH), 5.7–6.2 (2 H m, vinyl CH), 4.6–5.0 (1 H m, benzylic CH), and 3.3–3.8 (2 H m, allylic CH_2); mass spectrum *m/e* (rel intensity) 238 (M^+, 35), 165 (40), 160 (69), 152 (30), 147 (83), 131 (54), 115 (74), 105 (37), 103 (42), 91 (51), 77 (100), 63 (34), 55 (82), 51 (77), and 39 (42).

A solution of 5.00 g (21 mmol) of this hydroquinone in 22.5 ml of HOAc was treated with a solution of 14 g of $Na_2Cr_2O_7$ and 0.7 ml of H_2SO_4 in 9 ml of H_2O and the resulting solution was heated on a steam bath with stirring for 10 min. The reaction mixture was cooled and poured into ice water. Filtration separated 4.13 g (82%) of the naphthoquinone **17** as an orange solid, mp 167–171°. Recrystallization from MeOH separated the pure quinone **17** as orange plates: mp 169.5–170°; ir (CCl_4) 1675 cm^{-1} (conjugated C=O); uv max (95% EtOH) 246 mμ (ϵ 22,000) and 352 (2420); nmr ($CDCl_3$) δ 8.16 (1 H, d of d, J = 6.8 and 2.0 Hz, aryl CH), 7.0–7.9 (7 H m, aryl CH), and 6.6–7.0 (2 H m, CH of quinone); mass spectrum *m/e* (rel intensity) 234 (M^+, 63), 233 (100), 205 (16), 152 (11), and 76 (12).

Anal. Calcd for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found: C, 81.91; H, 4.09.

Reaction of the Naphthoquinone 17 with 1-Phenylbutadiene.—A solution of 3.00 g (12.8 mmol) of the naphthoquinone **17** and 2.00 g (15.4 mmol) of the 1-phenylbutadiene in 40 ml of PhH was refluxed for 104 hr. On standing at 25° the reaction mixture deposited 3.055 g of crude solid, mp *ca.* 215–330°, followed by 130 mg of solid, mp 156–160°. Recrystallization of the higher melting solid from $CHCl_3$–MeOH afforded 2.302 g (50%) of the dihydroquinone **18** as yellow plates, mp 228–229° (softens) and 356–358° (completely melts). We presume that this melting behavior arises from a partial or complete conversion of the dihydroquinone **18** to the quinone **20** during the melting point determination. The dihydroquinone has the following properties: ir ($CHCl_3$) 1660, 1655 (shoulder) (conjugated C=O), and 1625 cm^{-1} (C=C); uv max (95% EtOH) 249 mμ (ϵ 24,000) and 348 (3230); nmr ($CDCl_3$) δ 8.10 (1 H, d of d, J = 2.4 and 7.2 Hz, aryl CH at C-8), 7.0–7.8 (12 H m, aryl CH), 5.7–6.2 (2 H m, vinyl CH), 4.6–5.0 (1 H m, benzylic CH), and 2.9–3.5 (2 H m, allylic CH_2); mass spectrum *m/e* (rel intensity), 362 (49, M^+), 228 (28), 226 (41), 181 (33), 153 (38), 152 (100), 151 (45), 77 (68), and 51 (51).

Anal. Calcd for $C_{26}H_{18}O_2$: C, 86.16; H, 5.01. Found: C, 86.26; H, 4.90.

The mother liquors from crystallization of **18** and the lower melting solid from the initial crystallization were each crystallized from hexane to separate 140 mg (3%) of the dihydroquinone **19** as yellow needles: mp 160–161°; ir ($CHCl_3$) 1665, 1655 (shoulder) (conjugated C=O), and 1630 cm^{-1} (C=C); uv max (95% EtOH) 248 mμ (ϵ 22,200) and 353 (2020); nmr ($CDCl_3$), δ 8.03 (1 H d of d, J = 2.4 and 6.8 Hz, aryl CH at C-6), 6.6–7.8 (12 H m, aryl CH), 5.6–6.3 (2 H m, vinyl CH), 4.5–5.0 (1 H m, benzylic CH), and 3.2–3.5 (2 H m, allylic CH); mass spectrum *m/e* (rel intensity) 362 (100, M^+), 360 (43), 359 (58), and 344 (23).

Anal. Calcd for $C_{26}H_{18}O_2$: C, 86.16; H, 5.01. Found: C, 85.99; H, 5.28.

A solution of 597 mg (1.7 mmol) of the dihydroquinone **18** and 3.0 g of KOH in 30 ml of EtOH and 30 ml of PhH was refluxed for 3 hr, during which time a slow stream of O_2 was passed through the solution. The resulting mixture was cooled, diluted with H_2O, and filtered to separate 392 mg (66%) of the quinone **20** as yellow crystals: mp 352–355° (lit. mp 345°,[21b] 355°[21a]); ir (KBr pellet) 1675 cm^{-1} (conjugated C=O); uv max ($CHCl_3$) 256 mμ (ϵ 40,500), 270 (inflection, 21,800), and 347 (4680); mass spectrum *m/e* (rel intensity) 360 (68, M^+), 359 (100), 358 (38), and 179 (45).

A solution of 44 mg (1.2 mmol) of the hydroquinone **19** and 0.1 g of KOH in 15 ml of EtOH was refluxed for 5 hr while a slow stream of O_2 was passed through the solution. The solution was cooled, filtered (to separate some quinone **15**), concentrated, and partitioned between CH_2Cl_2 and H_2O. The organic phase was dried and concentrated. The combined residues from filtration and extraction were recrystallized from EtOH to separate 25 mg (57%) of the quinone **15** as yellow needles, mp 197.5–199.5°. Recrystallization raised the melting point to 199.5–201°; this product was identified with a subsequently described sample of the quinone **15** by a mixture melting point determination and by comparison of ir spectra.

1-Iodo-9,10-anthraquinone (10).—1-Aminoanthraquinone (20 g, 90 mmol) was converted to 16.4 g of the crude iodo derivative **10**, mp 195–199°, as previously described.[22] Sublimation (175–185° and 3 mm) afforded the pure iodoquinone **10** as orange needles: mp 204.5–205.5° (lit.[22] mp 204–205°; ir ($CHCl_3$) 1680 cm^{-1} (C=O); uv max (95% EtOH) 213 mμ (ϵ 22,200), 254 (32,300), and 363 (4750); uv max ($CHCl_3$) 257 (ϵ 31,900) and 367 (ϵ 3730); nmr ($CDCl_3$) δ 8.1–8.6 (4 H m, aryl CH), 7.7–8.1 (2 H m, aryl CH), and 7.40 (1 H t, J = 7.2 Hz, aryl CH); mass spectrum *m/e* (rel intensity) 334 (19, M^+), 179 (31), 151 (100), 150 (52), 76 (37), 75 (20), 74 (43), and 50 (34).

1-Phenyl-9,10-anthraquinone (13). A. Coupling with Lithium Diphenylcuprate.—To a solution of $LiPh_2Cu$, from 867 mg (6.04 mmol) of CuBr and 12.0 mmol of PhLi in 30 ml of Et_2O, was added a solution of 499 mg (1.49 mmol) of 1-iodoanthraquinone (**10**) in 30 ml of tetrahydrofuran. The resulting red solution was stirred for 20 min and the O_2 was passed over the surface of the solution with stirring for an additional 20 min. The yellow-brown reaction mixture was partitioned between Et_2O and aqueous NH_4Cl and NH_3 and the organic phase was separated, dried, and concentrated. Trituration of the residue with hexane left 230 mg (54%) of the phenylquinone **13**, mp 178.5–179.5°. Recrystallization from isopropyl alcohol separated the pure quinone **13** as yellow needles: mp 179.9–180.5° (lit.[21a] mp 177°); ir ($CHCl_3$) 1675 cm^{-1} (C=O); uv max (95% EtOH) 254 mμ (ϵ 46,400), 272 (shoulder, 17,600), and 335 (4520) with intense end absorption (ϵ 32,900 at 210 mμ); uv max ($CHCl_3$) 256 mμ (ϵ 45,800), 274 (shoulder, 18,500), and 335 (4760); nmr ($CDCl_3$) δ 7.0–8.6 (multiplet, aryl CH); mass spectrum *m/e* (rel intensity) 284 (52, M^+), 283 (100), 226 (18), and 113 (17). Chromatography of the mother liquors on silica gel (deactivated with water) separated an additional 81 mg (total yield 74%) of the 1-phenylquinone **13** in fractions eluted with CH_2Cl_2. From a similar reaction, employing 4.12 g (12.3 mmol) of the iodide **10** and 49.5 mmol of $LiPh_2Cu$ in a mixture of 225 ml of tetrahydrofuran and 90 ml of Et_2O the yield of the 1-phenylquinone was 880 mg (25%) and 1.43 g of an insoluble by-product, 1,1′-dianthraquinone (**14**), was obtained. Recrystallization from PhBr afforded the pure dimer **14** as yellow needles: mp 436–438° (lit.[23] mp 435–435.5°); ir (KBr pellet) 1660 cm^{-1} (C=O); uv max ($CHCl_3$) 254 mμ (ϵ 68,700), 276 (shoulder, 37,300), and 343 (7960). An authentic sample of this dimer was prepared[23] by reaction of 1.50 g (4.5 mmol) of the iodide **10** and 590 mg of copper powder in 3 ml of refluxing $PhNO_2$ for 3 hr. The dimer **14** was separated as 352 mg (38%) of tan solid, mp 436–438°, which was identified with the previously described sample by a mixture melting point determination and comparison of ir spectra. In subsequent small-scale coupling reactions with the iodide **10** and $LiPh_2Cu$, the isolation of the pure 1-phenylquinone **13** in *ca.* 70% yield was found to be facilitated when the original reaction was not subject to oxidation (with O_2) before hydrolysis. Apparently the 1-phenylquinone **13** is formed in the reaction mixture without oxidation.

B. Use of a Diels–Alder Reaction.—A mixture of 3.43 g (21.7 mmol) of 1,4-naphthoquinone and 4.00 g (30.8 mmol) of 1-phenylbutadiene was heated to 170–180° for 5 hr and then cooled and triturated with MeOH. The residual crude 1-phenylquinone **13**, mp 173–175°, amounted to 1.65 g (27%). Recrystallization (*i*-PrOH) afforded the pure quinone, mp 177.5–

(21) (a) C. Weizmann, E. Bergmann, and L. Haskelberg, *J. Chem. Soc.*, 391 (1939); (b) E. A. Braude, J. S. Fawcett, and A. A. Webb, *ibid.*, 1049 (1954).

(22) A. E. Goldstein, *J. Amer. Chem. Soc.*, **61**, 1600 (1939).

(23) F. Ullmann and W. Minajeff, *Ber.*, **45**, 687 (1912).

178.5°, which was identified with the previously described material by a mixture melting point determination. The MeOH mother liquors from the separation deposited 3.38 g of the crude 1,4-dihydroquinone **16**, mp 110–138°. Recrystallization from isopropyl alcohol separated a sample of the pure dihydroquinone **16**: mp 139–140° (lit.[21b] mp 139°); ir ($CHCl_3$) 1665 cm^{-1} (C=O); uv max (95% EtOH) 247 mμ (ε 19,500), 264 (shoulder, 11,600), and 334 (3280); uv max ($CHCl_3$) 251 mμ (ε 18,400), 264 (shoulder, 12,700), and 335 (3140), nmr ($CDCl_3$) δ 7.4–8.2 (4 H m, aryl CH), 7.0–7.4 (5 H m, aryl CH), 5.94 (2 H, two center lines of AB pattern, vinyl CH), 4.6–5.0 (1 H m, benzylic CH), and 3.2–3.5 (2 H m, allylic CH_2); mass spectrum m/e (rel intensity) 286 (100, M^+), 284 (30), 283 (55), 268 (30), 257 (30), 209 (22), 181 (24), 152 (36), 77 (40), and 76 (24).

A solution of 2.325 g of this dihydroquinone **16** and 1.0 g of KOH in 200 ml of refluxing EtOH was oxidized by passing O_2 through the solution for 1.5 hr. The solution was cooled and diluted with H_2O to precipitate 1.648 g of the crude quinone **13**, mp 174–177°.

1-Phenylanthracene (21).—A mixture of 739 mg (26 mmol) of the 1-phenylquinone **13**, 4.0 g of Zn dust (activated with 20 mg of $CuSO_4$[24]), 40 ml of aqueous 30% NaOH, 5 ml of concentrated aqueous NH_3, and 20 ml of EtOH was refluxed with stirring for 58 hr and then cooled and partitioned between H_2O and CH_2Cl_2. The organic layer was separated and concentrated and a solution of the residue in 100 ml of isopropyl alcohol was treated with 2 ml of concentrated aqueous HCl and heated to boiling. The hot solution was filtered, concentrated, and then washed with water to leave a residue which was chromatographed on silica gel. The fractions eluted with benzene were recrystallized from MeOH to separate 479 mg (73%) of the anthracene **21** as pale yellow needles, mp 108–112°. Recrystallization from hexane gave the pure hydrocarbon **21**: mp 114–115° (lit.[5] mp 116–117°); ir (CCl_4) no OH or C=O absorption in the 3- and 6-μ regions; uv max (95% EtOH), 255 mμ (ε 141,000), 347 (6240), 365 (8420), and 384 (7630); nmr ($CDCl_3$) δ 8.42, 8.48 (two 1 H s, aryl CH at C-9 and C-10), and 7.1–8.1 (12 H m, aryl CH); mass spectrum m/e (rel intensity) 254 (100, M^+), 253 (51), 252 (42), 126 (28), and 113 (17).

1-Phenyl-9-anthrone (23).—Reduction of 1.276 g (4.49 mmol) of the 1-phenylquinone **13** with 1.624 g of granular Sn and 9 ml of concentrated aqueous HCl in 30 ml of HOAc as previously described[5] yielded 776 mg (65%) of the crude anthrone **23**, mp 188–195°. Successive recrystallization from PhH and from $CHCl_3$ separated the pure anthrone **23** as colorless needles: mp 194–195.5° (lit.[5] mp 196–197.5°); ir ($CHCl_3$) 1665 cm^{-1} (C=O); uv max (95% EtOH) 262.5 mμ (ε 19,000) and 310 (4620) with intense end absorption (ε 23,500 at 210 mμ); nmr ($CDCl_3$) δ 8.0–8.3 (1 H m, aryl CH at C-8), 7.0–7.7 (11 H m, aryl CH), and 4.40 (2 H s, benzylic CH_2); mass spectrum m/e (rel intensity) 270 (74, M^+), 269 (100), 268 (29), 239 (26), and 134 (23).

1,9-Diphenylanthracene (25).—Following a known procedure,[5] 245 mg (0.91 mmol) of the anthrone **23** was converted to 174 mg (58%) of crude diphenylanthracene **25**, mp 179–185°. Recrystallization from hexane afforded the pure hydrocarbon **25** as pale yellow needles: mp 184.5–185° (lit.[5] mp 183.5–184°); ir ($CHCl_3$) no OH or C=O absorption in the 3- and 6-μ regions; uv max (95% EtOH) 224 mμ (ε 25,500), 260 (101,000), 338 (shoulder, 3050), 354 (6100), 371 (9550), and 392 (8700); nmr ($CDCl_3$) δ 8.53 (1 H s, aryl CH at C-10), 7.8–8.2 (2 H m, aryl CH), 7.1–7.6 (5 H m, aryl CH), 6.95 (5 H s, phenyl CH), and 6.88 (5 H s, phenyl CH); mass spectrum m/e (rel intensity) 330 (70, M^+), 253 (88), 252 (100), and 250 (33).

1,8-Diiodo-9,10-anthraquinone (11).—Following previously described procedures,[25] a mixture of 60.0 g (217 mmol) of 1,8-dichloro-9,10-anthraquinone, 111.0 g (650 mmol) of *p*-toluenesulfonamide, 48 g of KOAc, 3.0 g of $Cu(OAc)_2$, and 600 ml of $PhNO_2$ was refluxed with stirring for 5 hr. The resulting solution was cooled to separate 37.0 g of the crude bissulfonamide, mp 266–269°. After removal of the $PhNO_2$ from the mother liquor by steam distillation, an additional 31.7 g (total yield 68.7 g or 58%) of the bissulfonamide, mp 259–268°, was obtained. Recrystallization from benzene afforded the pure bissulfonamide as yellow needles: mp 269.5–270.5° (lit.[25] mp 264–264.5°); ir ($CHCl_3$) 3170 (broad, associated NH), 1674 and 1622 cm^{-1} (C=O); uv max (95% EtOH) 230 mμ (ε 46,000), 261 (28,400), and 432 (9120); nmr ($CDCl_3$) δ 11.82 (2 H s, NH), 7.0–8.3 (14 H m, aryl CH), and 2.37 (6 H s, aryl CH_3). A solution of 37.0 g (67.7 mmol) of the bissulfonamide in 200 ml of concentrated H_2SO_4 was heated on a steam bath for 1 hr and then poured onto ice and neutralized with NaOH. The resulting precipitate was triturated with H_2O to leave 15.38 g (95%) of the diamine **12** as a red solid, mp 265–268°. Recrystallization from benzene afforded the pure diamine **12** as maroon needles: mp 269–270.5° (lit.[25] mp 262–264°); ir (KBr pellet) 3440 and 3300 (NH) and 1591 cm^{-1} (C=O); uv max (95% EtOH) 233 mμ (ε 46,100), 278 (13,900), 310 (5950), and 513 (10,700); nmr (pyridine-d_5 at 79°) δ 7.3–8.7 (8 H m, aryl CH and two NH) and 4.15 (2 H broad, NH); mass spectrum m/e (rel intensity), 238 (100, M^+), 209 (21), 183 (29), 182 (33), 181 (31), 154 (56), 127 (32), 91 (41), 77 (37), 65 (36), 64 (34), 63 (42), 52 (27), and 39 (33).

To a cold (−15°) mixture prepared from 12.24 g (51.5 mmol) of the diamine **12**, 55 ml of concentrated H_2SO_4, 72 ml of H_2O, and 160 g of ice was added, dropwise with stirring and cooling, a solution of 18.0 g of $NaNO_2$ in 78 ml of H_2O. The resulting mixture (an orange slurry) was stirred at −15° for 30 min and then a solution of 72 g of KI in 96 ml of water was added, dropwise with stirring and cooling. The resulting mixture was warmed to 80° and then cooled and made basic with NaOH. The solid product was collected and washed successively with aqueous 10% HCl, saturated aqueous $Na_2S_2O_3$, and aqueous $NaHCO_3$. The residual brown solid (26.44 g, mp 270–276°) was chromatographed on silica with PhH as the eluent to separate 16.66 g (74%) of the diiodide **11** as red-orange needles: mp 282–283°; ir (KBr pellet), 1675 and 1660 cm^{-1} (shoulder) (C=O); uv max (95% EtOH) 224 mμ (ε 31,100), 261 (25,800), and 367 (4940); uv max ($CHCl_3$) 263 mμ (ε 25,800) and 371 (4930); mass spectrum m/e (rel intensity) 460 (100, M^+), 368 (23), 305 (23), 149 (42), 75 (48), and 74 (20).

Anal. Calcd for $C_{14}H_6I_2O_2$: C, 36.54; H, 1.31; I, 55.17. Found: C, 36.53; H, 1.49; I, 55.22.

1,8-Diphenyl-9,10-anthraquinone (15).—A solution of 2.003 g (4.35 mmol) of the diiodide **11** in 650 ml of THF was cooled to 0° and then a solution of Li_2Ph_3Cu (from 3.75 g or 26.2 mmol of CuBr and 77.9 mmol of PhLi) in 129 ml of Et_2O was added rapidly (15 sec) with stirring. The resulting solution was stirred for 10 sec and then O_2 was bubbled through the solution with stirring for 7 min. The resulting mixture was partitioned between Et_2O and aqueous NH_4Cl and NH_3. The crude organic product was chromatographed on silica gel and the fractions (eluted with CH_2Cl_2) contained 657 mg (42%) of the diphenyl quinone **15**, mp 196–200°. This material was recrystallized from isopropyl alcohol to separate the quinone **15** as 610 mg of pale yellow needles: mp 200–201°; ir ($CHCl_3$) 1680 (shoulder) and 1672 cm^{-1} (C=O); uv max (95% EtOH) 218 mμ (ε 33,700), 253.5 (40,600), and 349 (4700); uv max ($CHCl_3$) 255 mμ (ε 40,500) and 349 (4340); nmr ($CDCl_3$) δ 8.1–8.4 (2 H m, aryl CH at C-4 and C-5), 7.4–7.8 (4 H m, aryl CH), and 7.29 (10 H s, phenyl CH); mass spectrum m/e (rel intensity), 360 (67, M^+), 359 (100), 302 (22), 300 (25), 283 (30), 151 (22), and 150 (20).

Anal. Calcd for $C_{26}H_{16}O_2$: C, 86.65; H, 4.48. Found: C, 86.52; H, 4.70.

The reaction was repeated with 1.003 g (2.18 mmol) of the diiodide **11** in 340 ml of THF and 16 ml of an Et_2O solution containing Li_2Ph_3Cu (from 1.25 g or 8.72 mmol of CuBr and 26 mmol of PhLi). After a reaction time of 30 sec at 0° the reaction mixture was partitioned between Et_2O and aqueous NH_4Cl and NH_3 without prior treatment with O_2. The Et_2O layer was concentrated and the residue was dissolved in CH_2Cl_2, at which time 57 mg of 9,10-anthraquinone, mp 284–286°, separated. The CH_2Cl_2 solution was chromatographed on silica gel employing CH_2Cl_2 and CH_2Cl_2–Et_2O mixtures as the eluents to separate 112 mg (14%) of the diphenylquinone **15** (mp 197–200°), 56 mg (9%) of the crude phenylquinone **13** (mp 170–178°), and 135 mg (total yield 192 mg or 42%) of 9,10-anthraquinone (mp 283–287°). Recrystallization of the crude phenylquinone **13** from isopropyl alcohol raised the melting point to 178–179.5°. The samples of 9,10-anthraquinone and the phenylquinone **13** were identified with authentic samples by mixture melting point determinations and comparison of ir spectra. In another experiment the reaction of 1.001 g (2.18 mmol) of the diiodide **11** and $LiPh_2Cu$ (from 2.50 g or 17.5 mmol of CuBr and 35.1 mmol of PhLi) in 87 ml of Et_2O for 30 min at 25° followed by hydrolysis (without prior oxi-

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dation) yielded 272 mg (35%) of the diphenylquinone **15**, mp 200–201°.

1,8-Diphenylanthracene (22).—A mixture of 275.7 mg (0.766 mmol) of the diphenylquinone **15**, 1.5 g of Zn powder (activated with 8 mg of $CuSO_4$),[24] 16 ml of aqueous 30% NaOH, 2 ml of concentrated aqueous NH_3, and 20 ml of EtOH was refluxed with stirring for 52 hr and then cooled and extracted successively with CH_2Cl_2 and hexane. The combined organic extracts were dried and concentrated and a solution of the residue in 300 ml of isopropyl alcohol was treated with 3 ml of concentrated aqueous HCl and then heated to boiling. The hot solution was filtered and cooled to separate 222 mg of crude product, mp 178–180°. Concentration of the mother liquor left an additional 82 mg of crude product. The chromatography of the crude product on silica gel separated 134 mg (53%) of the diphenylanthracene **22**, mp 190–192°. Recrystallization from hexane afforded the pure hydrocarbon **22** as white needles: mp 191.5–193°; ir (KBr pellet) no OH or C=O absorption in the 3- or 6-μ region; uv max (95% EtOH) 211 mμ (ϵ 36,900), 251 (shoulder, 65,400), 259 (127,000), 356 (6500), 374 (9440), and 394 (7850); nmr ($CDCl_3$) δ 8.55 and 8.46 (two 1 H singlets, aryl CH at C-9 and C-10), 7.97 (2 H, d of d, J = 7.2 and 2.4 Hz, aryl CH at C-4 and C-8), and 7.1–7.7 (14 H m, aryl CH); mass spectrum m/e (rel intensity) 330 (100, M^+) and 252 (14).

Anal. Calcd for $C_{26}H_{18}$: C, 94.51; H, 5.49. Found: C, 94.70; H, 5.47.

1,8-Diphenyl-9-anthrone (24).—A mixture of 697.1 mg (1.94 mmol) of the diphenylquinone **15**, 504 mg of granular Sn, and 13.5 ml of HOAc was heated under reflux with stirring for 2 hr, during which time 3.3 ml of concentrated aqueous HCl was added dropwise to the mixture. The resulting mixture was partitioned between H_2O and CH_2Cl_2 and the organic layer was separated and concentrated. Recrystallization of the residue from hexane separated 500 mg (75%) of the anthrone **24** as white needles, mp 166–167.5°. Recrystallization from hexane raised the melting point to 167.5–168.5°: ir (CCl_4) 1680 cm^{-1} (C=O); uv max (95% EtOH) 234 mμ (ϵ 25,600), 283 (12,100), and 311 (shoulder, 6030) with intense end absorption (ϵ 45,300 at 210 mμ); nmr ($CDCl_3$) δ 7.1–7.6 (16 H m, aryl CH) and 4.26 (2 H s, benzylic CH_2); mass spectrum m/e (rel intensity) 346 (66, M^+), 345 (100), 344 (20), 268 (20), and 239 (21).

Anal. Calcd for $C_{26}H_{18}O$: C, 90.14; H, 5.24. Found: C, 90.14; H, 5.28.

1,8,9-Triphenylanthracene (26).—A solution of 605 mg (1.74 mmol) of the anthrone **24** in 77 ml of PhH was treated with 32.5 ml of an Et_2O solution containing 34.8 mmol of PhLi. The resulting mixture, from which a yellow precipitate settled, was stirred at 25° for 2 hr and then acidified with aqueous 10% HCl. The resulting mixture was refluxed for 30 min and then cooled and extracted with PhH. After the organic extracts had been washed with H_2O and concentrated, the residue (242 mg) was chromatographed on 50 g of silica gel. The early fractions, eluted with PhH, contained 395 mg (56%) of the crude triphenylanthracene **26**, mp 225–230°. Recrystallization from hexane separated 323 mg of the pure anthracene **26** as yellow prisms: mp 230–231°; ir ($CHCl_3$) no OH or C=O absorption in the 3- and 6-μ regions; uv max (95% EtOH) 227 mμ (shoulder, ϵ 28,300), 266 (82,700), 363 (6460), 381 (10,480), and 401 (8940); nmr ($CDCl_3$) δ 8.62 (1 H s, aryl CH at C-10), 8.02 (2 H, d of d, J = 7.0 and 1.6 Hz, aryl CH at C-4 and C-5), 6.4–7.6 (14 H m, aryl CH), and 6.36 (5 H partially resolved multiplet, CH for phenyl group at C-9); mass spectrum m/e (rel intensity) 406 (100, M^+), 329 (65), 328 (28), 327 (20), and 326 (22).

Anal. Calcd for $C_{32}H_{22}$: C, 94.54; H, 5.46. Found: C, 94.61; H, 5.44.

Later fractions from the chromatographic separation, eluted with PhH and with PhH-CH_2Cl_2 mixtures, contained 216 mg (36% recovery) of the crude starting anthrone **24**, mp 157–163°, which was identified with an authentic sample by a mixture melting point determination and by comparison of ir spectra.

9-Phenylanthracene (27).—To a solution of 503 mg (2.59 mmol) of 9-anthrone in 120 ml of PhH was added 23 ml of an Et_2O solution containing 25 mmol of PhLi. The resulting mixture was stirred for 2 hr at 25° and then acidified with aqueous 10% HCl. This mixture was refluxed for 30 min and then cooled and extracted with PhH. The combined organic solutions were washed with H_2O and concentrated. Recrystallization of the residue (782 mg) from hexane separated 542 mg (83%) of the crude anthracene **27**, mp 148–156°. Recrystallization from EtOH afforded the pure phenylanthracene **27** as pale yellow plates: mp 156–157° (lit. mp 155–157°,[26] 151–152°[5]); uv max (95% EtOH) 255 mμ (ϵ 140,000), 331 (3800), 347 (7100), 365 (10,500), and 385 (10,100); nmr (CCl_4), δ 8.39 (1 H s, aryl CH at C-10) and 7.0–8.2 (13 H m, aryl CH); mass spectrum, m/e (rel intensity) 254 (100, M^+), 253 (40), 252 (39), and 126 (15).

Polarographic Reduction of the Naphthalene and Anthracene Derivatives.—These measurements were obtained at 25° with a Heath polarograph (Model EU-402V) employing either a 0.30 M or a 0.50 M solution of n-$Bu_4N^+BF_4^-$ in $(CH_3)_2NCHO$ as the solvent and supporting electrolyte.[27] The reference, a saturated calomel electrode, made contact with the solution through intermediate salt bridges containing aqueous 1 M $NaNO_3$ and 0.5 M $Et_4N^+BF_4^-$ in $(CH_3)_2NCHO$. The $E_{1/2}$ values (*vs.* sce) and the αn values, obtained from plots of E *vs.* log $[i/(i_d - i)]$, are presented in Table IV.

TABLE IV
POLAROGRAPHIC REDUCTION POTENTIALS FOR THE NAPHTHALENE AND ANTHRACENE DERIVATIVES IN $(CH_3)_2NCHO$ CONTAINING 0.30 M OR 0.50 M n-Bu_4NBF_4

Compd	First wave		Second wave	
(concn, $M \times 10^3$)	$E_{1/2}$ *vs.* sce, V	αn value	$E_{1/2}$ *vs.* sce, V	αn value
Naphthalene (15.2)	−2.49[a]	0.90		
7 (9.2–13.7)	−2.37[b]	0.87	−2.61	1.3
1d (3.5)[c]	−2.23	0.98	−2.50	1.2
9 (7.1)	−2.27	0.94	−2.56	1.0
Anthraquinone (8.3)	−0.82	0.99	−1.50	0.95
13 (3.4)	−0.85	1.2	−1.54	1.1
15 (4.5)	−0.92	0.93	−1.62	0.91
Anthracene (8.9)	−1.93[d]	0.98	−2.48	0.94
21 (3.5)[e]	−1.86[f]	0.98	−2.35	1.1
27 (7.8)	−1.87[g]	0.99	−2.43	0.93
22 (3.2)	−1.84	0.94	−2.34	1.1
25 (1.9)[h]	−1.83[i]	0.92	−2.21	1.0
26 (2.7)	−1.83	0.90	−2.05	1.2

[a] Reported −2.46 V.[16a] [b] Reported −2.40 V.[16a] [c] A wave was also observed at −2.78 V (αn = 1.5). [d] Reported −1.96 V,[16a] −1.92 V.[16b] [e] A wave was also observed at −2.70 V (αn = 1.2). [f] Reported −1.89 V,[16a] −1.88 V.[16b] [g] Reported −1.92 V,[16a] −1.86 V.[16b] [h] A wave was also observed at −2.69 V (αn = 1.1.). [i] Reported −1.85 V.[16b]

Registry No.—**1d**, 1038-67-1; **2**, 1730-04-7; **3**, 25308-69-4; **7**, 605-02-7; **9**, 33522-22-4; **10**, 3485-80-1; **11**, 30877-00-0; **12**, 129-42-0; **13**, 1714-14-3; **14**, 914-20-5; **15**, 33522-27-9; **16**, 33522-28-0; **17**, 33522-29-1; **17** (dihydroxy derivative), 33522-30-4; **18**, 33522-31-5; **19**, 33522-32-6; **20**, 33522-33-7; **21**, 1714-09-6; **22**, 33522-35-9; **23**, 1714-15-4; **24**, 33522-37-1; **25**, 1714-19-8; **26**, 33522-39-3; **27**, 602-55-1; $LiPh_2Cu$, 23402-69-9; Li_2Ph_3Cu, 33520-60-4; *trans*-1-phenyl-1,3-butadiene, 16939-57-4; bissulfonamide, mp 266–269°, 33522-40-6.

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Alkyldihydroaryllithiums. V. Alkylation of 10-Alkyl-9,10-dihydroanthracenyllithiums with Alkyl Iodides

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The structural assignments for *cis*- and *trans*-9-isopropyl-10-methyl-9,10-dihydroanthracene (DHA = dihydroanthracene) have been determined by means of nmr nuclear Overhauser enhancement (NOE) experiments. These hydrocarbons may be formed stereoselectively by reaction of the appropriate 9-lithio-10-alkyl-9,10-DHA with an alkyl iodide. NOE experiments on *cis*- and *trans*-9-isopropyl-10-methyl-9,10-DHAs confirm the structural assignments made previously in this laboratory.

The reaction of 9-lithio-10-alkyl-9,10-dihydroanthracenes (1) with alkyl halides is reported to produce stereospecifically *cis*-9,10-dialkyl-9,10-dihydroanthracenes (DHA = dihydroanthracene) when **1** is prepared by the addition of alkyllithium reagents to anthracene.[2] This report differs from one of our earlier observations that 9-lithio-10-isopropyl-9,10-DHA reacts with isopropyl iodide to give a mixture of *trans*- and *cis*-9,10-diisopropyl-9,10-DHAs.[3] The predominant product was assigned trans stereochemistry based on carbon–deuterium ir stretching absorptions and nmr coupling constants for the isopropyl methinyl meso hydrogens. It is important to resolve this difference in stereochemical assignments because it implies that the reaction of **1** with alkyl halides not only is nonstereospecific, but also nonstereoselective.

The difference between the two earlier reports may be that the intermediates, **1**, were generated by two different methods (method A, addition of RLi reagent to anthracene, and method B, lithiation of a 9-alkyl-9,10-DHA). We decided to compare the product ratios secured by the two methods and also to study the effect of reversing the order of introducing the alkyl groups.

It is significant that the two different methods for preparing carbanions **1** both produced the same *cis*-9-methyl-10-ethyl-9,10-DHA after treatment of 9-lithio-10-ethyl-9,10-DHA with methyl halide.[2,4,5]

Results

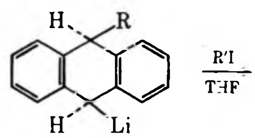
Treatment of 9-methyl-9,10-DHA with 1 equiv of *n*-butyllithium in dry THF followed by reaction with isopropyl iodide produced a 59:41 mixture of isomeric 9-isopropyl-10-methyl-9,10-DHAs. (See eq 1 in Table I.) Conversely, metalation of 9-isopropyl-9,10-DHA with *n*-butyllithium in dry THF, followed by reaction with methyl iodide, gave a 90:10 mixture of the 66 and 77° mp isomers. (See eq 2.)

The addition of isopropyllithium to anthracene in dry THF according to method A was followed by reaction with methyl iodide to produce a 90:10 mixture of the same isomers as were secured by method B. See Table II.

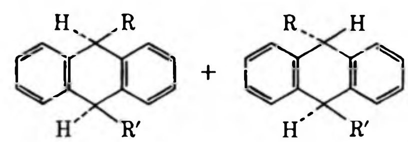
Cis stereochemistry has been assigned to the 9-isopropyl-10-methyl-9,10-DHA isomer of mp 66° by virtue of its method of preparation.[2] Among stereoisomeric 9,10-dialkyl-9,10-DHAs, cis stereochemistry was assigned to the higher melting point isomer for the dimethyl,[5] diethyl,[5] and methyl ethyl[3,5] homologs. Examination of Table II shows that isopropyllithium addition to anthracene followed by methyl iodide alkylation gives predominantly the 66° mp compound as reported earlier.[2] However, 10% of its stereoisomer was also obtained, indicating that dialkylation of anthracene *via* method B in THF is a stereoselective rather than a stereospecific reaction. The fact that this compound had a higher melting point than its stereoisomer was not in harmony with previous structural assignments of lower homologs. Fortunately, an unambiguous stereochemistry assignment can be made with the aid of nuclear Overhauser enhancements of the C-9 and C-10 proton signals, as was shown recently for 9-alkyl-9,10-DHAs.[6] Equally fortunate was the conclusion from these NOE experiments that the

TABLE I

REACTIONS OF 9-LITHIO-10-ALKYL-9,10-DHA WITH ALKYL IODIDES[a]



1



2 3

	R	R'	cis,[b] %	trans,[c] %
(1)	CH_3–	$(CH_3)_2CH$–	41 ± 2.0	59 ± 2.0
(2)	$(CH_3)_2CH$–	CH_3–	90 ± 1.5	10 ± 1.5

[a] Percentages determined by vapor phase chromatography (H_2 flame ionization) and checked by electronic integration of pmr signals for **2** and **3** in crude reaction mixtures for eq 1. [b] Mp 66°. [c] Mp 76–77°.

TABLE II

ALKYLLITHIUM ADDITIONS TO ANTHRACENE

RLi	+	R'I	→	9-isopropyl-10-methyl-9,10-DHA cis, %	trans, %
$(CH_3)_2CHLi$		CH_3I		90 ± 1.5	10 ± 1.5
CH_3Li		$(CH_3)_2CHI$		40 ± 1.0	60 ± 1.0

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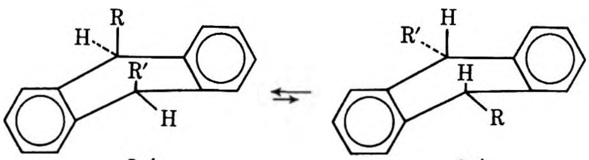
(6) A. W. Brinkman, M. Gordon, R. G. Harvey, P. W. Rabideau, J. B. Stothers, and A. L. Ternay, Jr., *ibid.*, **92**, 5912 (1970).

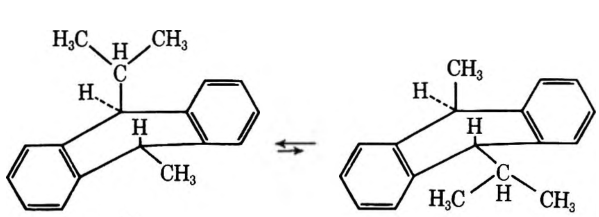
66° mp compound is the cis isomer and the higher melting point material (77°) is the trans isomer.

Nuclear Overhauser Enhancements.—There is general agreement that the central ring of 9,10-dihydroanthracene has a shallow boat conformation.[5] Furthermore, it has been clearly demonstrated that 9-alkyl-9,10-DHAs with bulky alkyl groups prefer the conformation in which the alkyl group is quasiaxial rather than quasiequatorial.[5,6] In a *cis*-9,10-dialkyl-9,10-DHA the preferred conformation would be expected to have both of the alkyl groups quasiaxial rather than quasiequatorial (*i.e.*, **2a′** rather than **2e′**). A *trans*-



2a′ **2e′**

9,10-dialkyl-9,10-DHA necessarily must have one of the alkyl groups quasiaxial and the other quasiequatorial. If, as in *trans*-9-isopropyl-10-methyl-9,10-DHA, one of the alkyl groups is large and the other small, then that conformational isomer having the larger alkyl group oriented quasiaxial would be expected to predominate as in **3** rather than **4**. The corollary to the



3 **4**

foregoing is that the meso hydrogens in a *cis*-9,10-dialkyl-9,10-DHA would both be quasiequatorial (He′) while the trans isomer would have the meso hydrogen of the carbon bearing the bulky alkyl group in a quasiequatorial orientation ($H_{e'}$) and its counterpart would be quasiaxial ($H_{a'}$).

The pmr spectra for these two meso hydrogens are easy to distinguish because they possess different chemical shifts and different spin–spin splitting patterns. Both of these effects are traceable to differences between the isopropyl and methyl groups. In practice the simple, first-order low-field quartet and higher field doublet are broadened because of the long range spin–spin interactions with the peri aryl hydrogens (allylic coupling) and because of homoallylic coupling ($H–C_9–C{=}C–C_{10}–H$) between the meso protons themselves.

Spin decoupling of the peri aryl hydrogens (at C_1, C_3, C_4, C_8) is expected to produce a nuclear Overhauser enhancement (NOE) of the meso hydrogen intensities which is larger for $H_{e'}$ than for $H_{a'}$ at C_9 or C_{10} because the former are located closer to the peri aryl hydrogens than are the latter. Therefore, the *cis*-9,10-dialkyl-9,10-DHA would be expected to show intensity enhancements of both the C_9 doublet and the C_{10} quartet while the trans isomer should exhibit enhancement only for the C_9 doublet upon spin decoupling of the peri hydrogens. Examination of NOE results in Table III for the benzylic hydrogens of the 9-isopropyl-10-methyl-9,10-DHA isomers leads to the conclusion that the lower melting point isomer possesses cis stereochemistry.[7] For comparison purposes, data for the known[4,8] *cis*- and *trans*-9-ethyl-10-methyl-9,10-DHAs are included in Table III.

TABLE III[a]
NOE RESULTS FOR BENZYLIC PROTONS IN 2 AND 3

Mp, °C	R-C_9	R-C_{10}	C_9-H	C_{10}-H
66	$(CH_3)_2CH$–	CH_3–	+8.53	+6.78
77	$(CH_3)_2CH$–	CH_3–	+15.3	−0.88
cis (mp 108)	CH_3CH_2–	CH_3–	+16.8	+14.3
trans (mp 33)	CH_3CH_2–	CH_3–	+10.3	+4.1

[a] An average of six integrations was performed for each meso H signal.

Symmetrically dialkylated 9,10-DHAs such as *cis*- and *trans*-9,10-DHAs would not be so amenable to study by NOE as a pair of unsymmetrical stereoisomers because both meso hydrogens (in both isomers) have the same chemical shift. Nevertheless, the cis isomer would be expected to show a larger NOE effect than the trans compound because the latter has half of its meso hydrogens a′ and half e′ while the cis compound populates predominantly one conformer in which both meso hydrogens are oriented e′.

Authentic *cis*-9,10-diisopropyl-9,10-DHA, mp 99.5–105° (lit.[3] mp 109–110°), was prepared as described previously and exhibited a nuclear Overhauser enhancement of 11.8% for the meso hydrogens, while the value for the trans isomer of mp 76–77° was 3.9%.[9]

Long Range Coupling Constants.—Measurement of the long range homoallylic coupling constants ($H–C_9–C{=}C–C_{10}–H$) was expected to provide confirmation for the stereochemical assignments, since it had been shown that $J_{a'e'} > J_{e'e'}$ in monoalkyl-9,10-DHAs with values of 1.0–1.3 and 0.40–0.70 Hz, respectively.[6] This expectation was realized when the lower melting point (66°) stereoisomer yielded a homoallylic $J_{H_9,H_{10}} = 0.60$ Hz, while the higher melting point (77°) isomer had $J_{H_9,H_{10}} = 1.3$ Hz.

Discussion

The most startling observation to be made about the data in Tables I and II is that reaction of 9-lithio-10-isopropyl-9,10-DHA with excess methyl iodide gives predominantly *cis*-9-isopropyl-10-methyl-9,10-DHA (**2**) while a comparable reaction with isopropyl iodide produces chiefly *trans*-9,10-diisopropyl-9,10-DHA. Whatever the mechanism for reaction of anthryl carbanions like **1** with alkyl iodides, the formation of both *cis*- and *trans*-9,10-dialkyl-9,10-DHAs in unequal amounts suggests that the intermediate **1** also exists in cis and trans stereoisomeric forms. The reason for this conclusion is based upon the accepted view "that lithium salts like **1** in THF are contact ion pairs."

(7) This conclusion agrees with the structure assignment of Harvey and Davis[2] but does not follow the pattern of lower homologs wherein the cis isomer was found to be of higher melting point and lower solubility.[5]

(8) Recently an X-ray crystal structure has been completed for the cis compound by Dr. R. H. Stanford, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, Calif. It confirms the stereochemical assignments reached earlier by stereospecific synthesis.[3]

(9) These NOE results provide additional evidence that earlier stereochemistry assignments are correct[3] and that the 9,10-diisopropyl-9,10-DHA obtained from alkylation of dilithioanthracene with isopropyl chloride by R. G. Harvey and L. Arzadon[10] is the trans isomer.

(10) R. G. Harvey and L. Arzadon, *Tetrahedron*, **25**, 4887 (1969).

Consequently, the lithium atom must be oriented either cis or trans to the C_{10} alkyl group.

The fact that the isomer ratios in Table I are the same as those in Table II indicates that *cis*-**1** interconverts with *trans*-**1** because the same equilibrium mixture is obtained by two completely different methods. Additional support for the proposed interconversion of *cis*-**1** and *trans*-**1** may be found in the absolute values for the ratios of **2**:**3** (which are 9:1 and 2:3). If the quenching process involved a delocalized carbanion with some planarity of C_9 with the aromatic rings, then approach of the alkyl iodide from either side of the molecule would give 1:1 ratios of **2** and **3** without regard for the size of the alkyl group at C_{10}. The observed difference in ratios is better understood in terms of the potential existence of two conformational isomers for *cis*-**1** and also two for *trans*-**1**, summarized in Table IV. Clearly,

Table IV

Summary of Configurations and Conformations[a]

	Conformer A		Conformer B	
	R	Li	R	Li
cis	a′	a′	e′	e′
trans	a′	e′	e′	a′

[a] a′ = quasiaxial orientation; e′ = quasiequatorial

the steric requirements of the isopropyl group would be expected to influence not only the conformer population but also the equilibrium position of the two configurational isomers. When **1** possesses an isopropyl group at C_{10} the cis configuration will predominate over the trans to a much greater extent than it does when a methyl group is at C_{10}. This analysis finds support in an earlier estimate of the conformational populations for 9-methyl-9,10-DHA based on nmr chemical shifts which concluded that 25% of the molecules had the methyl group oriented quasiequatorial.[6] The literature also contains spectroscopic evidence from uv and visible studies on the lithium salts of 10-alkyl derivatives of DHA[11] which is completely in harmony with the existence of two forms for the 10-alkyl derivative but only one absorption for the lithium salt of DHA.

The most plausible explanation of the difference between methyl iodide and isopropyl iodide reaction with **1** is that they may be reacting by two different mechanisms. One possibility is simple S_N2 displacement. An alternate sequence is halogen–metal exchange to form 9-iodo-10-alkyl-9,10-DHAs and alkyllithiums. Rapid coupling of such benzylic iodo compounds with the alkyllithiums would give the products. Precedent for this latter pathway has been reported in recent literature.[12]

The NOE experiments on *cis*- and *trans*-9,10-diisopropyl-9,10-DHAs provide additional experimental evidence for our earlier conclusion[3] that quasiequatorial hydrogens are more shielded than quasiaxial hydrogens in symmetrically dialkylated 9,10-DHAs.

Experimental Section

Nmr Spectra.—NOE measurements were obtained on sealed, vacuum-degassed solutions in deuteriochloroform. Concentrations ranged from 170 to 175 mg/ml. The spectra were obtained on a Varian Associates HA-100 spectrometer operated in the frequency sweep mode. A H-P, V-4315 frequency counter permitted measurement of the line positions within ±0.01 ppm for the chemical shifts.

Gas chromatography was run on a Hewlett-Packard Model 5754 B instrument equipped with a hydrogen flame ionization detector and Disc integrator. A 6 ft × 1/8 in. column of 10% SE-30 on Chromosorb W (DMCS) was used.

Materials.—Ethyllithium (1.2 *M* in benzene), *n*-butyllithium (2.4 *M* in hexane), and isopropyllithium (1.9 *M* in pentane) were secured from Alfa Inorganics. Analysis was accomplished by titration with *sec*-butyl alcohol using phenanthroline indicator.[13] Anthracene and 9-methyl-9,10-DHA were purified and prepared as described previously.[4] 9,10-Dihydroanthracene (Aldrich, 95+ %) was recrystallized from ethanol using decolorizing carbon. It was dried *in vacuo* for 24 hr. Tetrahydrofuran (99.5+ %, Aldrich) was dried by refluxing with lithium aluminum hydride followed by distillation. It was stored at reflux over Na–benzophenone, and was freshly distilled immediately before use. Isopropyl iodide was prepared from isopropyl alcohol according to the literature procedure.[14]

9-Isopropyl-9,10-DHA.—To a solution of DHA (10 g, 0.055 mol) in THF (250 ml) at −60° was added *n*-butyllithium (23 ml, 0.0552 mol). The stirred solution was warmed to 5° during 0.5 hr, cooled to −30°, and treated with an excess of isopropyl iodide. Water (10 ml) was added followed by NaCl. After separation of phases, THF was removed with the rotary evaporator and the resulting oil was crystallized from ethanol using a low-temperature bath to yield 9.0 g (73%) of hydrocarbon, mp 30–33° (lit. mp 28–29°). The 100-MHz pmr spectrum showed δ 7.180 (s, 8 H), 4.120 and 3.790 (C_{10} H_aH_b, J_{ab} = 19 Hz), 3.595 (d, C_9H_9, J = 7.0 Hz), 1.86 [m, $-CH(CH_3)_2$], and 0.798 [d, $-CH(CH_3)_2$]; uv λ_{max} 252.5 mμ (ε 4122), 265 (985), 272 (1.053).

Preparation of *trans*-9-Isopropyl-10-methyl-9,10-DHA.—To 10 g of 9-methyl-9,10-DHA (0.052 mol) in 250 ml of THF at −60° was added 21.5 ml of 2.4 *M* *n*-butyllithium (0.052 mol). The temperature was permitted to rise to 0° with magnetic stirring during 30 min. After cooling to −30°, excess isopropyl iodide was added quickly and stirring was continued for 1 hr. Water (25 ml) was added, phases were separated, and THF was removed *in vacuo* to give an oil. Gas chromatography showed the presence of *cis*- and *trans*-9-isopropyl-10-methyl-9,10-DHAs (**2** and **3**) together with starting material. By means of column chromatography over alumina (100 g oven-dried at 120°), 1.48 g of **2** and **3** in hexane was separated with the isomer of longer gas chromatographic retention time being eluted in the earlier column chromatography fractions. After recrystallization from ethanol this isomer had mp 68–70°.

In an identical run, the oil obtained after removal of THF was dissolved in ethanol and seeded with a crystal of the higher melting stereoisomer. The resulting crystals, 6.0 g (47%), mp 68–70°, were recrystallized twice from ethanol, yielding white needles, mp 76–77°.

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.36; H, 8.76.

Nmr ($CDCl_3$) had δ 0.865 [d, 6, J = 7.0 Hz, $(CH_3)_2CH-$], 1.731 [d, 3, J = 7.3 Hz, $(CH_3)C_{10}H$], 1.77 [m, 1, $(CH_3)_2CH-$)], 3.454 (d, 1, J = 9.6 Hz, C_9H), 3.984 (q, 1, J = 7.7 Hz, $C_{10}H$), 7.12, 7.15, 7.17, 7.21, 7.27 [m, 8, aromatic H]; uv λ 258 mμ (ε 567), shoulder 264.3 (773), 271.5 (794).

Preparation of *cis*-9-Isopropyl-10-methyl-9,10-DHA.—To 10 g of anthracene (0.053 mol) in 250 ml of THF at −60° was added 45 ml of 1.25 *M* isopropyllithium (0.056 mol). The reaction mixture was maintained at −60° for 30 min, after which an excess of methyl iodide was added quickly. Water was added, phases were separated, the THF layer was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The oil was crystallized from ethanol, yielding white crystals, 6.05 g (46%). After recrystallization from ethanol the compound had mp 65–66° (lit.[2] mp 65.5–66.5°).

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.13; H, 8.65.

Nmr ($CDCl_3$) had δ 0.916 [d, 6, J = 6.9 Hz, $(CH_3)_2CH-$], 1.59 [d, 3, J = 7.7 Hz, $(CH_3C_{10}H)$], 1.72 [m, 1, $(CH_3)_2CH-$], 3.489 (d, 1, J = 8.8 Hz, C_9H), 4.043 (q, 1, J = 7.7 Hz, $C_{10}H$), 7.16 (m, 8, aromatic H).

These chemical shifts agree well with the literature[2] values.

(11) D. Nicholls and M. Szwarc, *Proc. Roy. Soc., Ser. A*, **301**, 223 (1969).

(12) R. M. Magid and S. E. Wilson, *Tetrahedron Lett.*, 4925 (1969).

(13) S. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(14) A. I. Vogel, "Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 285.

However, three of the four coupling constants differ substantially from those reported previously.[2] Uv had λ 258 mμ shoulder, 265.5 (ε 1026), 272.5 (1036).

cis-**9,10-Diisopropyl-9,10-DHA.**—To 9-isopropyl-9,10-DHA (1.25 g, 5.6 mmol) in dry THF (50 ml) at −60° was added *n*-butyllithium (6.0 mmol). The reaction mixture was stirred at 0° for 1 hr and the reaction was terminated by the rapid addition of excess isopropyl iodide. After separation of salts with water and removal of ether solvents, an nmr spectrum indicated the presence of 12.5% *cis*- and 87.5% *trans*-9,10-diisopropyl-9,10-DHA by integration of the benzylic hydrogen doublets at δ 3.78 (J = 5.0 Hz for the trans isomer) and 3.27 (J = 9.5 Hz for the cis compound). See earlier literature.[3]

After chromatography over dry basic alumina (hexane), 0.85 g of trans-9,10-diisopropyl-9,10-DHA (57%), mp 73–74°, was obtained after recrystallization from ethanol (lit.[3] mp 76–77°); uv 257 mμ (shoulder), 265 (ε 647), 272 (588).

In later fractions the cis isomer appeared predominantly as an oil which crystallized upon trituration with ethanol to yield 60 mg of *cis*-9,10-diisopropyl-9,10-DHA (4%, mp 99.5–105°), lit.[3] mp 109–110°; uv λ 258 mμ (ε 822), 265 (1084), 272 (1221).

Methyllithium Addition to Anthracene.—Anthracene (0.5 g, 2.8 mmol) in 50 ml of THF was mixed with excess methyllithium (14 mmol) in ether. After refluxing for 4 hr, excess isopropyl iodide was added quickly. After 1 hr stirring, salts were separated with water and gas chromatography showed the presence of five components. The ratio of *cis*- and *trans*-9-isopropyl-10-methyl-9,10-DHA was 40:60 ± 1 as determined by vpc. Unchanged anthracene was recovered.

trans-**9-Ethyl-10-methyl-9,10-DHA.**[15]—Lithium (0.15 g)-ammonia (300 ml) reduction of 9-ethyl-10-methylanthracene (2 g) in THF (120 ml) for 3.5 hr was followed by addition of ethanol (10 ml) and H_2O (10 ml). Solvents were evaporated and the oil obtained from ether–water treatment was recrystallized from absolute ethanol to give 1.3 g of white needles (65%), mp 33–34°.

Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.73; H, 8.25; C, 91.75; H, 8.38.

Uv had λ 212.2 mμ (ε 19,480), 264.5 (1140), 271.8 (1067); nmr δ 0.887 (t, 3, CH_3CH_2–, J = 7.0 Hz), 1.71 (d, 3, $CH_3C_{10}H$, J = 6.7 Hz), 3.80 (t, 1, C_9HCH_2–, J = 7.5 Hz), 3.99 (q, 1, $C_{10}HCH_3$, J = 6.7 Hz), 7.22 (m, 8, aromatic).

These chemical shifts and coupling constants do not agree well with those published previously.[5] This sample was purified by recrystallization before nmr spectroscopy and spectra were obtained on an HA-100 instrument better suited for careful determination of coupling constants. There is no doubt, however, of the identity of this material with that described previously.[6]

(15) We thank Mr. Isaac Angres (NSF undergraduate participant) for running this experiment.

Registry No.—*cis*-2, 21438-93-7; *trans*-2, 33608-27-4; 9-isopropyl-9,10-dihydroanthracene, 17573-50-1; *trans*-9,10-diisopropyl-9,10-dihydroanthracene, 25340-82-3; *cis*-9,10-diisopropyl-9,10-dihydroanthracene, 24316-21-0; *trans*-9-ethyl-10-methyl-9,10-dihydroanthracene, 23660-35-7.

Acknowledgment.—This investigation was supported in part by Undergraduate Science Education Program Grants GY-5723 and GY-7540, National Science Foundation.

The Synthesis of 9,10-Cyclobutenophenanthrene from 9,10-Dimethylene-9,10-dihydrophenanthrene

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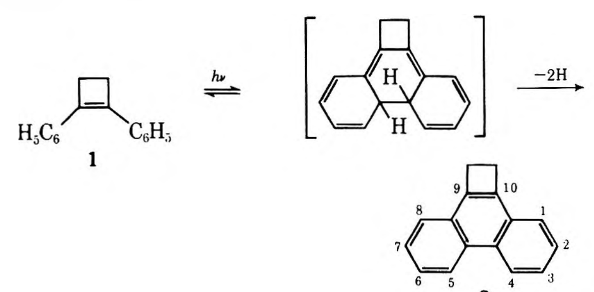
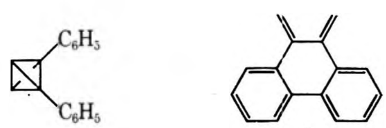
9,10-Dimethylene-9,10-dihydrophenanthrene (4) has been prepared from trimethyl(10-methyl-9-phenanthrylmethyl)ammonium chloride (6) and characterized by its physical data and the formation of an adduct with maleic anhydride. Irradiation of compound 4 yielded 9,10-cyclobutenophenanthrene (2), the proof of structure of which is discussed.

Our interest in 9,10-cyclobutenophenanthrene (2) was first aroused during a study of the photochemistry of 1,2-diphenylcyclobutene (1), in which it is a possible product (eq 1).[2] We were stimulated to the synthesis



1 2 (1)

of 2 by the subsequent report by Masamune and Kato of diphenyltetrahedrane (3).[3] This report drew our attention because of our interest in 3 and because the physical properties attributed to 3 by Masamune and Kato appeared to match better the predicted proper-



3 4

ties of 2.[4] We wish now to report the full synthesis and characterization of 2.

During the progress of this synthesis, we were able to demonstrate the intermediacy of 9,10-dimethylene-9,10-dihydrophenanthrene (4). Previously, this compound had been reported as a reactive intermediate and its presence was inferred only by trapping with various dienophiles.[5] The instability of 4 with respect to dimerization and polymerization prevented our complete characterization of it; however, we were able to obtain its ultraviolet spectrum in dilute solution. The direct observation of 4 in the ultraviolet is to our knowledge the first such observation of an *o*-quinodi-

(1) Author to whom inquires should be addressed.

(2) E. H. White and J. P. Anhalt, *Tetrahedron Lett.*, 3927 (1965).

(3) (a) S. Masamune and M. Kato, *J. Amer. Chem. Soc.*, **87**, 4190 (1965); (b) S. Masamune and M. Kato, *ibid.*, **88**, 610 (1966).

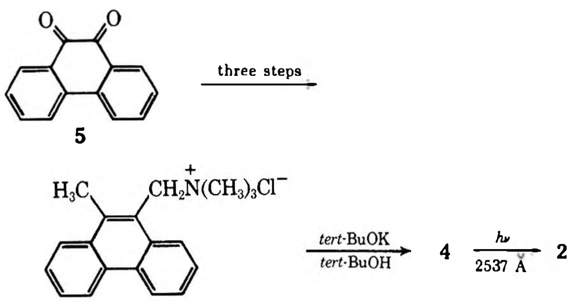
(4) E. H. White, G. E. Maier, R. Graeve, U. Zirngibl, and E. W. Friend, *ibid.*, **88**, 611 (1966).

(5) (a) I. T. Millar and K. V. Wilson, *J. Chem. Soc.*, 2121 (1964); (b) J. K. Stille and R. T. Foster, *J. Org. Chem.*, **28**, 2708 (1963); (c) P. D. Gardner and H. S. Sarrafizadeh R., *J. Amer. Chem. Soc.*, **82**, 4287 (1960).

methane not substituted in the terminal methylene positions.[6]

9,10-Cyclobutenophenanthrene (2).—The synthesis of 2 was achieved in five steps starting with the readily available 9,10-phenanthroquinone (**5**). The conversion of **5** to trimethyl(10-methyl-9-phenanthrylmethyl)-ammonium chloride (**6**) was effected by known procedures.[5] This intermediate was purified as the monohydrate.

The conversion of the monohydrate of **6** to cyclobutenophenanthrene (2) was straightforward (eq 2).

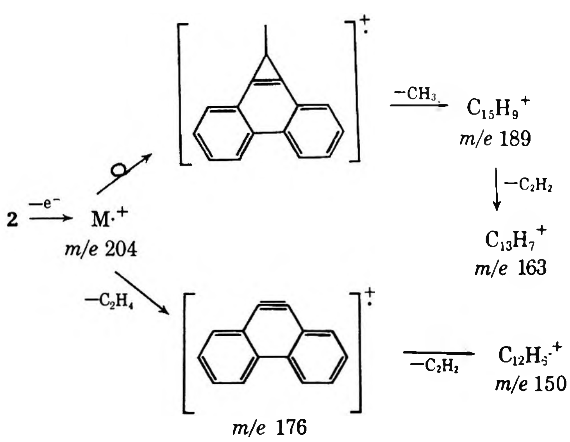


(2)

It was found that best yields are obtained when dry *tert*-butyl alcohol is used, and when both steps in the reaction are carefully monitored (see Experimental Section). Early irradiation of **6** before elimination is completed appeared to give more complicated reaction mixtures. In addition, compound **2** is photodecomposed by prolonged irradiation.

The physical data found for the product are completely consistent with the assigned structure of 2. In particular (see Experimental Section for other data) the ultraviolet spectrum of 2 [$\lambda_{max}^{n\text{-hexane}}$ 255 mμ (log ϵ 4.83)] is very similar to that of 9,10-dimethylphenanthrene and clearly indicates a phenanthrene chromophore.[4]

The mass spectrum of 2 shows apparent successive losses of 15, 13, 13, and 13 mass units. The pattern of fragmentation may be explained by two parallel processes (eq 3).



(3)

The nmr spectrum is consistent in detail with structure 2. The methylenic protons of 2 at δ 3.35 are shifted 0.70 ppm downfield from the methyl protons of 9,10-dimethylphenanthrene; this shift is consistent with the presence of a fused cyclobutane ring (Table I).

TABLE I

POSITION OF BENZYLIC PROTONS AS A FUNCTION OF RING SIZE IN BENZOCYCLOALKENES

	Benzylic protons, δ
o-Xylene[a]	2.23
Tetralin[a]	2.76
Indan[a]	2.91
Benzocyclobutene[b,c]	3.14
9,10-Dimethylphenanthrene[c]	2.65
Cyclobutenophenanthrene[c]	3.35

[a] N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalogue," Vol. II, Varian Associates, Palo Alto, Calif., 1963. In chloroform-d_1. [b] G. Fraenkel, Y. Asahi, M. J. Mitchell, and M. P. Cava, *Tetrahedron*, **20**, 1179 (1964). [c] In carbon tetrachloride.

Furthermore, the increased downfield shifts of the 1,8 protons in 9,10-substituted phenanthrenes[7a] (van der Waals deshielding)[7b] are not observed in 2 (Table II), a

TABLE II

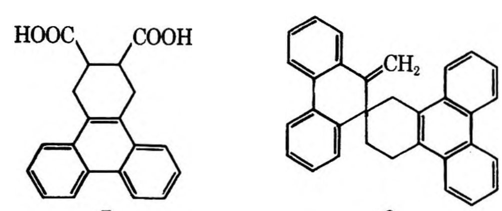
POSITION OF RING PROTONS AS A FUNCTION OF SUBSTITUTION IN PHENANTHRENES[a]

	Ring protons, δ[b]		
	2,3,6,7	1,8	4,5
Phenanthrene	7.51	7.74	8.56
9,10-Dideuterio-2,7-dimethylphenanthrene[c]	7.3	7.6	8.4
9,10-Cyclobutenophenanthrene (2)	7.45	7.65	8.60
9,10-Dimethylphenanthrene	7.47	7.98	8.57
9-Methoxymethyl-10-methylphenanthrene	7.61	8.15	8.67

[a] Spectra, except where noted, were obtained in carbon tetrachloride using a Varian Associates HA-100 spectrometer. [b] Centers of multiplets in most cases. Positional assignments are made in accord with assignments given in ref 7 for phenanthrenes. [c] L. A. Paquette, *J. Amer. Chem. Soc.*, **86**, 4085 (1964); no conditions given.

result, presumably, of the smaller size of the cyclobutane ring relative to two methyls.

9,10-Dimethylene-9,10-dihydrophenanthrene (4).—The intermediacy of quinodimethane 4 in the synthesis of compound 2 (eq 2) was demonstrated by trapping it with maleic anhydride (in experiments without irradiation). The nearly quantitative yield of 1,2,3,4-tetrahydro-2,3-triphenylene-*cis*-dicarboxylic acid (**7**)[5b] isolated after hydrolysis indicates that almost complete conversion of **6** to **4** had occurred (Table III). The small amount of dimer **8**[5c] found may have formed after addition of maleic anhydride. The formation of **8**



7 **8**

was not evident in ultraviolet spectra of reaction mixtures immediately after being quenched with acetic acid; however, it is not certain that such a small quantity would be detected. When the addition of maleic anhydride to **4** was delayed, dimerization of the

(6) G. Quinkert, M. Finke, J. Palmowski, and W-W Wiersdorff, *Mol. Photochem.*, **1**, 433 (1969), and G. Quinkert, *Photochem. Photobiol.*, **7**, 783 (1968), have observed diphenyl- and tetraphenyl-*o*-xylylene at low temperature.

(7) (a) P. M. Bavin, K. D. Bartle, and J. A. S. Smith, *Tetrahedron*, **21**, 1087 (1965); (b) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 183.

TABLE III

PRODUCT YIELDS FOR THE REACTION OF 9,10-DIMETHYLENE-9,10-DIHYDROPHENANTHRENE (4) WITH MALEIC ANHYDRIDE

		Yields					
		Compd 7			Compd 8		
Aliquot	Time of addn of maleic anhydride, hr[a]	mg	mmol	%[b]	mg	mmol	%[b]
A_1	0.1	29.0	0.091	91.0	0.7	0.0017	3.4
A_2	0.1	29.0	0.093	93.0	0.5	0.0012	2.4
B	8.0	12.3	0.038	38.0	10.3	0.025	50.0
C	103.0	2.8	0.0087	8.7	17.1	0.042	84.0

[a] After ultraviolet spectra indicated complete conversion to 4. [b] Based on 0.100 mmol of 6.

TABLE IV

ULTRAVIOLET SPECTRA OF MODEL 2,3-DIPHENYL-1,3-DIENES

	λ_{max}, mμ (log ε)
9,10-Dimethylene-9,10-dihydrophenanthrene (4)	216 sh (4.56), 244 (4.42), 260 sh (4.25), 300 (3.79)[a]
2,3-Diphenylbutadiene[c]	243 (4.26), 280 sh (3.22), 287 sh (2.70)[b]
2,3-Diphenyl-1,3-cyclooctadiene[c]	247 (4.41), 295 sh (3.00)[b]

[a] In *tert*-butyl alcohol. [b] In cyclohexane. [c] A. C. Cope and D. S. Smith, *J. Amer. Chem. Soc.*, **74**, 5136 (1952).

unstable **4** did occur to yield compound **8**. The yields of **7** and **8** as a function of time (Table III) indicate that quinodimethane **4** has a half-life of about 8 hr at room temperature at a concentration of 10^{-3} *M* in *tert*-butyl alcohol.

Comparison of the ultraviolet spectrum of the quinodimethane with model systems (Table IV) indicates that the spectrum is consistent with structure **4**. Since the quinodimethane **4** could not be isolated, concentration of solutions of **4** leading to dimer **8** and polymer, the ε values we report are approximate and are calculated by assuming the concentration of **4** to be the same as the initial concentration of **6**. This assumption is justified since high yields (93%) of the maleic anhydride adduct **7** were obtained (Table III). Furthermore, the ultraviolet spectra of solutions of **4** briefly irradiated with a 4-W germicidal lamp were interpretable as the sum of just the two components **2** and **4** (see Experimental Section). Since the reactant **6** and known products **2** and **8** have greater extinction coefficients at the position of maxima for **4**, the presence of small amounts of these compounds would lead to an increase in the calculated ε values for **4**. The absence of these compounds in the reaction mixture after apparent complete conversion of **6** to **4** is evident from the constant ε values obtained for **4** over a range in concentrations from 2.0×10^{-5} to 5.3×10^{-4} *M*.

Each of the model compounds in Table IV shows some evidence of long wavelength absorption between 280 and 300 mμ. The presence of a well-defined maximum at 300 mμ in **4** may be the expression of a relatively rigid structure compared to the model compounds.

Experimental Section

Melting points, except where noted, were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were preformed by either Mr. Joseph Walters in this department or Galbraith Laboratories, Inc., Knoxville, Tenn.

Infrared spectra were determined on Perkin-Elmer Model 337 or 521 infrared spectrometers and were calibrated against known absorption bands of polystyrene. Ultraviolet spectra were determined on a Cary Model 14 spectrometer. Proton magnetic resonance spectra (nmr) were determined on Varian Associates A-60 or HA-100 spectrometers using tetramethylsilane as an internal standard for nonaqueous solutions and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for aqueous solutions. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6 mass spectrometer.

Thin layer chromatography (tlc) was performed on Eastman chromatogram sheets containing a fluorescent indicator. Visualization was with 2537-Å light.

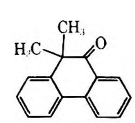
9-Chloromethyl-10-methylphenanthrene.—9-Chloromethyl-10-methylphenanthrene was prepared by a modification of the method of Millar and Wilson.[5a] To a suspension of 9,10-dimethyl-9,10-dihydroxy-9,10-dihydrophenanthrene[8] (10.58 g, 44.0 mmol) in ether (60 ml), thionyl chloride (12.7 ml, 21.0 g, 0.18 mol) was added with stirring. The reaction mixture was protected from atmospheric moisture with a drying tube. After stirring for 1.5 hr the mixture was heated to reflux for 5.5 hr at which time the reaction mixture became homogeneous. Reflux was allowed to continue for 2 hr, after which time the ether was allowed to distill off until stirring became impossible and hydrogen chloride evolution commenced. The mixture was then placed under aspirator vacuum and heated on a steam bath until hydrogen chloride evolution ceased (1 hr). Ethyl acetate (100 ml) was added and the mixture was heated to reflux overnight. The nearly homogeneous hot solution was filtered and allowed to cool to give 4.25 g of 9-chloromethyl-10-methylphenanthrene (17.7 mmol, 40%): mp 152.5–154° (lit.[5c] 155–156°); ir (KBr) 1254, 780, 760, and 720 cm^{-1}. The ethyl acetate mother liquor was evaporated to dryness on a rotary evaporator and the residue was dissolved in hot benzene. Addition of an equal volume of isooctane gave nicely shaped, slightly colored crystals of 9-chloromethyl-10-methylphenanthrene (1.40 g, 5.8 mmol, 13%), mp 146–148.5°. Tlc of each batch on silica gel (benzene–hexane, 1:2) gave a single spot of R_f 0.48.

The benzene–isooctane mother liquor on evaporation gave a crystalline mass (4.52 g) which on tlc on silica gel (benzene–hexane, 1:2) gave two spots of R_f 0.27 and 0.48. This material was chromatographed on silica gel (100 g) using a benzene–hexane mixture (1:2) as eluent. The fractions containing the slow-moving material were evaporated to crystalline solids and combined. Recrystallization from hexane gave 2.45 g (10.6 mmol, 24%) of 10,10-dimethyl-9(10*H*)-phenanthrone (i), mp 72.0–73.5° (lit.[9] 75°).[10] The infrared spectrum (KBr) was identical with that reported in the literature for i[12] with prominent bands at

(8) 9,10-Dimethyl-9,10-dihydroxy-9,10-dihydrophenanthrene was prepared by the addition of 9,10-phenanthraquinone to a solution of methylmagnesium iodide in ether according to the method of Gardner and Sarrafizadeh.[5c] The product after recrystallization from benzene melted at 162.5–163.8° (lit.[5c] 163–164°).

(9) T. Zincke and W. Tropp, *Justus Liebigs Ann. Chem.*, **362**, 242 (1908).

(10) The production of i had not previously been reported in the synthesis of 9-chloromethyl-10-methylphenanthrene by this method.[11] The occurrence here may have been due to the somewhat more vigorous conditions employed.



i

(11) S. Hauptmann, *Chem. Ber.*, **93**, 2604 (1960).

(12) A. Schönberg and G. Schütz, *ibid.*, **95**, 2386 (1962).

1675, 982, 783, 756, and 732 cm^{-1}; uv (hexane) 238 mμ (log ε 4.39), 248 (4.33), 267 (3.99), 276 (4.05), 292 sh (3.74), and 320 (3.50); nmr (CCl_4) δ 7.92 (m, 3.2 H), 7.38 (m, 5.2 H), and 1.50 (s, 6.0 H). The fraction containing the faster moving material gave a crystalline solid after evaporation. Tlc on silica gel (benzene–hexane, 1:2) of this material was identical with that of 9-chloromethyl-10-methylphenanthrene.

Trimethyl(10-methyl-9-phenanthrylmethyl)ammonium Chloride Monohydrate (6).—The procedure of Millar and Wilson[5a] for the synthesis of trimethyl(10-methyl-9-phenanthrylmethyl)ammonium chloride (6) was followed. Complications attend the synthesis, and thus our procedure is described in detail. Trimethylamine generated by stirring the corresponding hydrochloride (9.6 g, 0.10 mol) with barium oxide (26 g, 0.27 mol) was bubbled into a stirred suspension of 9-chloromethyl-10-methylphenanthrene (3.000 g, 12.45 mmol) in a mixture of chloroform (210 ml) and absolute methanol (70 ml). After stirring for 1.5 hr at room temperature, the reaction mixture was heated to reflux for 1.0 hr at which time the solution was homogeneous. The reaction mixture was allowed to cool with stirring for an additional 3 hr. Tlc on silica gel (benzene–hexane, 1:2) showed the presence of considerable starting material. Additional trimethylamine generated by adding dropwise a solution of the hydrochloride (14.4 g, 0.150 mol) in water (50 ml) to a huge excess of sodium hydroxide (200 g) was bubbled through the reaction mixture for 1.0 hr at room temperature. Tlc under the same conditions no longer showed starting material; however, a new spot at R_f 0.18 was present in addition to the expected spot at the origin corresponding to the title quarternary chloride. The reaction mixture was then heated to reflux for 2.0 hr, after which time the tlc was unchanged. The solvents were removed from the reaction mixture on a rotary evaporator and the resulting solid was placed under high vacuum overnight. The solid was then dissolved in absolute ethanol and the solution was filtered. Addition of ether to the filtrate gave 1.958 g of material which gave only a very faint spot of R_f 0.20 in addition to the spot at the origin. The nmr ($CDCl_3$) of this material showed a doublet at δ 2.93 (J = 5 Hz) attributable to trimethylamine hydrochloride.[13] The only other peaks in the spectrum were attributable to the quaternary chloride 6 at δ 8.72 (m, 3.0 H), 8.17 (m, 1.2 H), 7.70 (m, 3.7 H), 5.82 [broad doublet (unresolved AB quartet), 1.7 H, CH_2], 3.50 (s, 9.0 H), and 3.02 (s, 3.6 H). Integration of this spectrum indicated 9.0% (31 mol %) of trimethylamine hydrochloride was present. When the spectrum was taken using deuterium oxide as solvent the doublet attributed to trimethylamine hydrochloride coalesced to a singlet at δ 3.17,[14] which also indicated the presence of about 9% of trimethylamine hydrochloride. The presence of trimethylamine hydrochloride was further confirmed by weak infrared bands (Nujol) at 2515, 2470, and 987 cm^{-1}. The quaternary chloride 6 readily formed a chloroform insoluble hydrate. The impure quaternary chloride 6 was crystallized twice from water to give 1.103 g (3.47 mmol, 28%) of analytically pure trimethyl(10-methyl-9-phenanthrylmethyl)ammonium chloride monohydrate (6): uv max (*tert*-butyl alcohol) 224 mμ (log ε 3.38), 250 (4.63), 257 (4.69), 272 sh (4.11), 278 sh (3.99), 292 (3.96), 303 (3.93), 334 (2.53), 340 sh (2.26), and 350 (2.26); ir (Nujol) 3430, 3350, 875, and 760 cm^{-1}; nmr (D_2O) δ 8.21 (m, 2.0 H), 7.91 (m, 1.9 H), 7.68 (m, 3.8 H), 4.82 [broad doublet (unresolved AB quartet), 1.7 H], 2.98 (s, 8.9 H), and 2.52 (s, 3.1 H).

Anal. Calcd for $C_{19}H_{22}NCl \cdot H_2O$: C, 71.80; H, 7.61; N, 4.41. Found: C, 71.81; H, 7.36; N, 4.22.

The mother liquor from the initial precipitation of the quaternary ammonium chloride with ether was evaporated to a crystalline solid (1.638 g) which gave a principal spot on tlc on silica gel (benzene–hexane, 1:2) of R_f 0.20. This material was dissolved in carbon tetrachloride (10 ml) and filtered. The clear solution was then evaporated to give a crystalline solid which was recrystallized from ethanol to give 0.598 g (2.54 mmol, 20%) of 9-methoxymethyl-10-methylphenanthrene: mp 108.7–111.0° (lit.[5c] 113–114°); ir (KBr) 1099, 953, 755, and 720 cm^{-1}; nmr ($CDCl_3$) δ 8.67 (m, 2.2 H), 8.15 (m, 2.2 H), 7.61 (m, 4.0 H), 4.96 (s, 2.0 H), 3.48 (s, 2.8 H), and 2.76 (s, 3.0 H).

9,10-Dimethylene-9,10-dihydrophenanthrene (4).—A freshly prepared solution of potassium *tert*-butoxide (0.10 ml of 0.37 M, 37 μmol) was added to 5 ml of a 5.25 × 10^{-4} M solution of 6 (2.63 μmol) in *tert*-butyl alcohol. The solution was mixed well and then placed in an ultraviolet cell of 0.5-mm path length. The disappearance of the fine structure and maxima characteristic of 6 and the appearance of maxima at 244 and 300 mμ (characteristic of 4) were observed. After 21 min there was no longer any evidence of 6, and the maxima at 244 and 300 mμ showed no further decrease in intensity (the decrease results from the low extinction of 4 relative to 6 in this region). After an additional 8 min the spectrum was unchanged. The ultraviolet spectrum of this solution showed max (log ε) 216 sh (4.56), 244 (4.42), 260 sh (4.25), and 300 mμ (3.79).

A portion of this reaction solution was diluted with *tert*-butyl alcohol to 3.17 × 10^{-5} M and placed in a 1-cm path length cell. After irradiation for 2 min with a 4-W germicidal lamp, the ultraviolet spectrum showed maxima at positions identical with 9,10-cyclobutenophenanthrene (2). The intensities corresponded to a mixture comprised of 56% 2 (1.76 × 10^{-5} M) and 44% 4 (1.41 × 10^{-5} M). Further irradiation caused a net decrease in the concentration of 2.

Adduct of 9,10-Dimethylene-9,10-dihydrophenanthrene with Maleic Anhydride.—Trimethyl(10-methyl-9-phenanthrylmethyl)ammonium chloride monohydrate (159 mg, 0.500 mmol) was dissolved in *tert*-butyl alcohol (500 ml, Baker Analyzed) and protected from atmospheric moisture by a drying tube. A freshly prepared solution of potassium *tert*-butoxide (27 ml of 0.34 M, 7.5 mmol) was then injected. After stirring for 2 min, a sample was withdrawn and placed in an ultraviolet cell of 0.5-mm path length. The reaction was followed in the ultraviolet until no further decrease in the maximum at 244 mμ was observed. This occurred 14 min after addition of the potassium *tert*-butoxide. Glacial acetic acid (0.50 ml, 817 mmol) was then added to give approximately a pH of 7.0. The reaction was allowed to stir an additional 4 min, after which time four 100-ml aliquots were withdrawn. After the addition of potassium *tert*-butoxide (20 min), maleic anhydride (1.1 g, 11 mmol) was added to each of two of the aliquots (A_1 and A_2). Upon addition of the maleic anhydride, a cloudy precipitate formed and the solution turned pink. After 8 hr at room temperature, the same amount of maleic anhydride was again added to A_1 and A_2 (to ensure complete reaction) as well as to a third aliquot (B). After an additional 8 hr, A_1 and A_2 were worked up as described below and additional maleic anhydride was added to B. This aliquot was worked up after an additional 8 hr. The fourth aliquot (C) was treated exactly the same as the first three with addition of maleic anhydride commencing 103 hr after maleic anhydride was added to A_1 and A_2.

After the addition of maleic anhydride (16 hr), each aliquot was concentrated on a rotary evaporator until only a few milliliters of *tert*-butyl alcohol remained. A solution of potassium hydroxide (5 g) in water (100 ml) was then added and the mixture was heated to 80–90° for 2.5 hr. Upon cooling, the mixture was vacuum filtered through Whatman No. 50 filter paper and the precipitate was washed well with water and dried *in vacuo*. The clear filtrate was then acidified with 1 N hydrochloric acid. The precipitate was collected by vacuum filtration through a medium grade sintered glass filter and washed well with water followed by drying *in vacuo*. The base-insoluble precipitates each melted at 234–237° dec (Kofler). The literature values for 2-methylene-3,4,5,6-dibenzo-3′,4′-(9,10-phenanthro)spirobicyclohexane (8) are 228.5–229° and 252–253° depending on the solvent for crystallization.[15] The infrared (KBr and CS_2), ultraviolet (ethanol), and nmr ($CDCl_3$) spectra of the combined base-insoluble product were identical with those of 8 prepared by the method of Stille and Foster.[16] The tlc on silica gel (benzene–hexane, 1:2) showed a large spot at R_f 0.38 identical with 8 and barely perceptible spots at R_f 0.19 and at the origin. A portion of this product after recrystallization from ethanol gave an ir (KBr) identical with the spectrum of the crude product and melted at 245–247° dec. A second portion recrystallized from cyclohexane melted at 229–231° dec. The ir (KBr) of this sample showed a strong band at 913 cm^{-1} characteristic of the lower melting form of 8.[5b] Tlc on

(13) A nearly saturated solution of trimethylamine hydrochloride in $CDCl_3$ gave a singlet at δ 2.95; however, a dilute solution gave a doublet at δ 2.88 (J = 5 Hz).

(14) The nmr (D_2O) of trimethylamine hydrochloride gave a singlet at δ 2.91. Addition of trimethyl(10-methyl-9-phenanthrylmethyl)ammonium chloride (<50 mol %) shifted this peak to δ 3.07.

(15) The lower melting form was obtained by crystallization from cyclohexane by Stille and Foster.[5b] The higher melting form was obtained by crystallization from ethanol.[5b,c]

(16) Gardner and Sarrafizadeh[5c] report uv max (EtOH) 245 mμ (log ε 4.44), 256 (4.46), and 272 (4.44) for 8. In our hands, compound 8 prepared by the method of Stille and Foster[5b] gave uv max (EtOH) 215 mμ (log ε 4.72), 225 (4.71), 247 (4.81), 256 (4.81), 268 (4.46), 272 (4.45), 278 (4.39), 287 (4.32), 300 (4.19), 336 (2.83), 342 (2.63), and 351 (2.85).

silica gel (benzene–hexane, 1:2) of both forms and 8 prepared by the method of Stille and Foster[5b] gave a single spot of R_f 0.43.

The acid-precipitated material sublimed readily upon melting. Material from the first two aliquots melted at 280–290° dec (Kofler). Due to the small amount of sample, only the melting point of the sublimate could be determined for the second two aliquots. In each case, the sublimed material melted at 305–308°. The values reported for 1,2,3,4-tetrahydro-2,3-triphenylene-*cis*-dicarboxylic acid (7) are 279–282° dec (sublimate, 308–313°).[5b] Recrystallization from an ethyl acetate–ethanol mixture (1:1) gave crystals which melted at 282–284° dec: ir (KBr) 1690 cm^{-1} [lit.[5b] (Nujol mull) 1698 cm^{-1} (C=O str)]; uv max (EtOH) 349 mμ (log ε 2.90), 333 (2.76), 298 (4.05), 286 (4.03), 278 (4.15), 272 (4.19), 255 (4.79, lit.[5b] 4.78), 247 (4.70), 224 (4.37), and 215 (4.47). A small sample of this material was sublimed in an 8-mm glass tube sealed at 20 mm and heated to 275–300° to give very nice needles. The ir (KBr) was identical with that of Stille's 1,2,3,4-tetrahydro-2,3-triphenylene-*cis*-dicarboxylic anhydride.[17] The yields of 7 and 8 for each aliquot are summarized in Table III.

9,10-Cyclobutenophenanthrene (2).—Trimethyl(10-methyl-9-phenanthrylmethyl)ammonium chloride monohydrate (239 mg, 0.75 mmol) and *tert*-butyl alcohol (Baker Analyzed, 1.0 l.) were placed in a 1.0-l. quartz round-bottom flask with a single 24–40 ₸ joint. To the other member of this joint was attached a coarse porosity gas dispersion tube and a section of 8-mm-o.d. glass tubing. The 8-mm tubing was closed with a rubber septum through which a long stainless steel needle was inserted. This needle normally functioned to allow the nitrogen being bubbled through the reaction solution to escape; however, the tip could be inserted below the surface of the liquid for the withdrawing of aliquots. The flask also contained a magnetic stir bar.

The solution of 6 was then flushed for 8 hr with nitrogen (Airco Prepurified) dried by passage through a glass coil immersed in a Dry Ice–ethanol bath. During this period, a solution of potassium *tert*-butoxide in *tert*-butyl alcohol was prepared under argon and diluted with *tert*-butyl alcohol to 0.76 *N* as determined by titration with hydrochloric acid. The clear, colorless solution of potassium *tert*-butoxide (14.0 ml, 10.6 mmol) was injected below the surface of the nitrogen flushed solution of quaternary chloride over a 5-min period. An aliquot was withdrawn and placed in an ultraviolet cell of 0.5-mm path length. The formation of 9,10-dimethylene-9,10-dihydrophenanthrene (4) in this aliquot was monitored in the ultraviolet until no further change (decrease) in the maximum at 244 mμ was observed (20 min). Irradiation was begun using a Rayonet photochemical reactor[18] equipped with 2537-Å lamps. The photolysis was followed in the ultraviolet by periodically withdrawing aliquots. The concentration of cyclobutenophenanthrene appeared to reach a maximum after 25 min of irradiation; irradiation was stopped after a total of 30 min. Glacial acetic acid (1.0 ml, 17.4 mmol) was added to the cloudy reaction mixture to give a neutral solution. The *tert*-butyl alcohol was then removed on a rotary evaporator at 40–50° to give a white solid which was dried at 5×10^{-3} Torr overnight. This solid was stirred with a mixture of hexane (100 ml) and water (100 ml). The mixture was then filtered to give an amorphous solid (67.0 mg) which did not melt below 290°; however, it appeared to decompose slowly above 200°. This material did not contain any cyclobutenophenanthrene by tlc on silica gel (benzene–hexane, 1:2).

The hexane solution on tlc on silica gel (benzene–hexane, 1:2) gave a major spot at R_f 0.58 corresponding to cyclobutenophenanthrene. A minor spot at the origin as well as extremely light spots at R_f 0.47 and 0.27 were present. Evaporation of the hexane solution gave a semicrystalline mass. Attempted recrystallization of this material from ethanol–water mixtures kept under nitrogen gave solid products which on tlc showed that decomposition had occurred. From the tlc of the combined solids, cyclobutenophenanthrene was now estimated to constitute only one-half of the total. The combined solids were chromatographed on 12 g of silica gel using cyclohexane as eluent. The fractions were collected under argon and yielded 23 mg (0.113 mmol, 15%) of cyclobutenophenanthrene, mp (Kofler) 135–137° (lit.[4] 130–131°). Recrystallization from hexane gave an analytical sample: mp 135.5–136° (Kofler); ir (KBr) 2955, 1204, 948, 942, 744, and 721 cm^{-1}; uv max[19] (EtOH) 220 mμ (log ε 4.33), 247 (4.70), 255 (4.80), 270 (4.23), 279 (4.06), 289 (4.01), 301 (4.14), 324 (2.83), 339 (3.10), and 357 (3.23); uv max (*n*-hexane) 220 mμ (log ε 4.37), 247 (4.73), 255 (4.83), 270 (4.27), 278 (4.10), 288 (4.04), 301 (4.20), 324 (2.70), 332 (2.67), 339 (3.06), 343 (2.75), 348 (2.74), 352 (2.73), and 357 (3.34); fluorescence max[20] (diethyl ether, 340-mμ excitation) 362 mμ (rel intensity 1.29), 382 (1.55), and 398 sh (1.00); nmr (CCl_4) δ 8.60 (m, 2.1 H), 7.65 (m, 2.0 H), 7.45 (m, 4.0 H), and 3.35 (s, 4.0 H); mass spectrum (70 eV) *m/e* (rel intensity) 204 (100), 203 (67), 202 (48), 201 (12), 200 (11), 189 (7.5), 176 (6.0), 163 (2.6), 150 (3.5), 102 (6.7), 101.5 (6.2), 101 (25), 100.5 (4.6), 100 (8.4), 89 (7.4), 88 (9.3), and 76 (5.7).

Anal. Calcd for $C_{16}H_{12}$: C, 94.08; H, 5.92; mol wt, 204. Found: C, 94.03; H, 5.94; mol wt, 215 (Mechrolab osmometer in chloroform); 204 (mass spectrum).

Unsuccessful Approach to the Synthesis of 9,10-Cyclobutenophenanthrene (2).—Trimethyl(10-methyl-9-phenanthrylmethyl)ammonium chloride monohydrate (108 mg, 0.34 mmol) dissolved in ethanol (10 ml) was converted to trimethyl(10-methyl-9-phenanthrylmethyl)ammonium hydroxide by passage through a column of Amberlite IRA-400 (OH) resin according to the method of Millar and Wilson.[5a] The solution was diluted to 225 ml with additional ethanol and then placed in a cylindrical quartz vessel (5 × 18 cm). The solution was stirred and flushed with nitrogen (Airco Prepurified) for 30 min. So far, the procedure was performed in a refrigerated room at 5°. Tlc on silica gel (benzene–hexane, 1:2) showed a single spot at the origin. The reaction solution was then irradiated with stirring in a Rayonet photochemical reactor[18] at 2537 Å at 35°. The reaction was followed by tlc on silica gel (benzene–hexane, 1:2). Irradiation was stopped after 30 min. Tlc showed the absence of starting material. Spots were present at R_f 0.048, 0.25, 0.41, and 0.56. The spot at R_f 0.56 corresponded in position to both 9,10-dimethylphenanthrene and 9,10-cyclobutenophenanthrene. The reaction solution contained a fine precipitate and gave a strong odor of trimethylamine. The precipitate (27 mg) was separated by filtration. The solution was evaporated to dryness at 25° on a rotary evaporator. This residue was chromatographed on a preparative tlc plate (20 × 20 cm) prepared with 30 g of alumina using a benzene–hexane (1:2) mixture for development. During this chromatography, the products were protected from oxygen by an argon atmosphere. Five bands of material were evident; however, only the two apparently major bands were extracted and the material was identified. One band (R_f 0.51–0.67) gave 7.0 mg (0.034 mmol, 10%) of dimethylphenanthrene, mp (Kofler) 138.5–141° (lit.[10] 139°). The ir [(KBr) 1602, 1580, 1435, and 749 cm^{-1}], uv (Et_2O), and mass spectrum [(70 eV) *m/e* (rel intensity) 206 (100) and 191 (97)] were identical with those of authentic 9,10-dimethylphenanthrene. The second band (R_f 0.23–0.32) gave 2.0 mg (8 μmol, 2.4%) of 9-ethoxymethyl-10-methylphenanthrene: mp (Kofler) 96.0–97.2° (lit.[5c] 91–92°); uv max (EtOH) 224 mμ (log ε 4.25), 248 (4.56), 255 (4.63), 272 (4.04), 278 (3.94), 287 (3.83), 299 (3.83), 333, and 350; ir (KBr) 1120, 1097, 1010, and 755 cm^{-1}; nmr (CCl_4) δ 8.59 (m, 2.1 H), 8.09 (m, 2.1 H), 7.50 (m, 3.8 H), 4.94 (s, 1.9 H), 3.57 (q, 2.1 H, J = 7 Hz), 2.74 (s, 3.0 H), and 1.19 (t, 3.4, H, J = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 250 (0.76), 206 (14), 204 (13), 191 (15), and 44 (100).

Registry No.—2, 33482-75-6; 4, 33537-23-4; 6, 33482-76-7; 7, 33495-80-6; 8, 33482-77-8; 9-methoxymethyl-10-methylphenanthrene, 33482-78-9; 9-ethoxymethyl-10-methylphenanthrene, 33482-79-0.

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(17) We wish to thank Professor Stille for a generous sample of this material.

(18) The Southern New England Ultraviolet Co., Middletown, Conn.

(19) The low-intensity absorptions (log ε less than 2.80) between 320 and 360 mμ are not reported for the ethanol spectrum because of the low solubility of cyclobutenophenanthrene (2) in this solvent.

(20) Fluorescence spectrum and molecular weight (osmometer) as reported by E. W. Friend, Dissertation, The Johns Hopkins University, 1967.

Thermolysis of 5,5-Dimethyl-1,3-cyclohexadiene. Evidence for Rearrangement *via* [1,5] Sigmatropic Methyl Migration[1]

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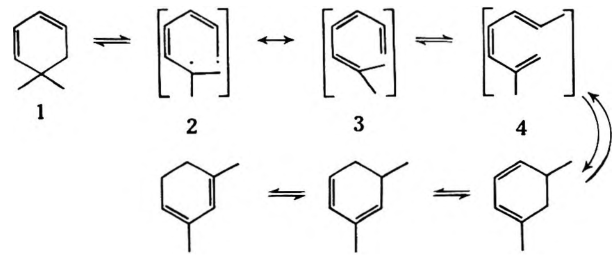
Thermolysis of 5,5-dimethyl-1,3-cyclohexadiene at temperatures ranging from 300 to 475° yields mixtures composed of toluene, 1,5-dimethyl-1,3-cyclohexadiene, 2,6-dimethyl-1,3-cyclohexadiene, 1,3-dimethyl-1,3-cyclohexadiene, and *m*-xylene. The distributions of dienes and their relative rates of appearance are consistent with an initial slow [1,5] sigmatropic migration of a methyl group, followed by rapid [1,5] sigmatropic migration of hydrogen. Toluene and *m*-xylene are formed by elimination of methane or hydrogen from either the starting material or any of the intermediate dienes, respectively.

Thermal [1,5] sigmatropic migration of hydrogen in cyclic dienes and trienes is well known and has been studied extensively.[2] However, [1,5] migration of groups of greater complexity than hydrogen or deuterium has not attracted the same attention until recently.[3] De Haan and Kloosterziel[4,5] and Herndon and Manion[6] have interpreted the thermal migration of a methyl group in the thermolysis of 1,5,5-trimethylcyclopentadiene in terms of a rate-determining [1,5] sigmatropic methyl shift. Boekelheide and coworkers[7,8] have observed apparent [1,5] alkyl migration in the *trans*-15,16-dialkyldihydropyrenes for methyl, ethyl, and *n*-propyl substituents. Similarly, Maier and coworkers[9] have interpreted the low-temperature (60°) thermolysis of 1,6-dimethyl-2,5-diphenyl-3,4-diazabicyclo[4.4.0]deca-2,4,7,9-tetraene also as occurring *via* [1,5] methyl migration as the initial step. Finally Millet, *et al.*,[10] have been able to obtain relative migratory aptitudes in substituted indenes by kinetic studies and found that hydrogen migrates faster than phenyl which in turn migrates faster than methyl, a result that is substantiated in part by Shen, *et al.*[11]

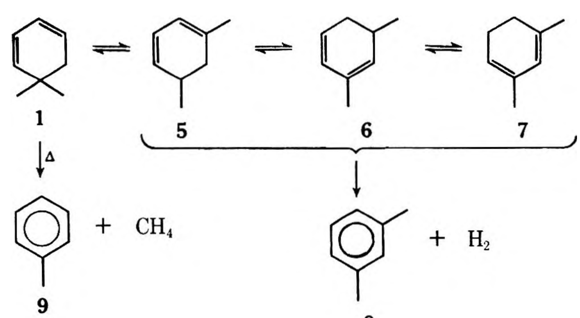
Previous to the present study, Pines and Kozlowski[12] had reported a 500° thermolysis of 5,5-dimethyl-1,3-cyclohexadiene (**1**) in which there occurred an apparent methyl migration, as well as many other reactions. Their product distributions were interpreted in terms of a biallyl–biradical mechanism proceeding through two intermediate trienes, ring closure, and further isomerization. Toluene and *m*-xylene as well as various methyl-methylenecyclohexenes were also reported products. However, no trienes were detected in the reaction products. Therefore, we were hopeful that by carrying out the thermolysis of **1** at various temperatures and times, followed by rapid quenching, that we could


1 2 3 4 7 6 5

obtain direct experimental evidence for the intermediates actually involved in the apparent rearrangement and thus distinguish between the biallyl–biradical and sigmatropic pathways.

5,5-Dimethyl-1,3-cyclohexadiene (**1**) was thermolyzed over a wide temperature range (167–475°) under both flow and static conditions. Static runs were in sealed tubes in thermostatically controlled baths, while flow experiments were conducted utilizing techniques described previously.[13] In both cases, glpc analyses were performed immediately following low-temperature quenching. Results of the flow experiments are presented in Table I, while those from the static runs are found in Table II.

It can easily be seen from the results in Table I that the first detectable product in the thermolysis at 300° is 1,5-dimethyl-1,3-cyclohexadiene (**5**), the product one would expect from initial [1,5] methyl migration in **1**. At higher temperatures, operating under faster conversion rates,[14] the appearance of **6** and **7** as well as **8** and **9** lead us to postulate the following reaction scheme.



1 5 6 7 9 8

The formation of **8** and **9** complicates the mechanistic interpretations of these thermolyses. Aromatization of cyclic dienes *via* elimination of either methane or hydrogen at high temperatures is well known[12,15] and

(1) (a) Partial support of this research under an Undergraduate Research Participation Grant (National Science Foundation) is gratefully acknowledged. (b) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif.

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(6) W. Herndon and J. Manion, *J. Org. Chem.*, **33**, 4504 (1968).

(7) V. Boekelheide and E. Sturm, *J. Amer. Chem. Soc.*, **91**, 902 (1969).

(8) V. Boekelheide and T. Hylton, *ibid.*, **92**, 3669 (1970).

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(11) K. Shen, W. McEwen, and A. Wolf, *Tetrahedron Lett.* 827 (1969).

(12) H. Pines and R. Kozlowski, *J. Amer. Chem. Soc.*, **78**, 3776 (1956).

(13) C. Spangler and N. Johnson, *J. Org. Chem.*, **34**, 1444 (1969).

(14) At all temperatures flow rates are set such that the residence time in the heated zone is not more than *ca.* 10 sec.

(15) H. Pines and C. Chen, *J. Amer. Chem. Soc.*, **81**, 928 (1959).

TABLE I
THERMOLYSIS OF 5,5-DIMETHYL-1,3-CYCLOHEXADIENE (1) UNDER FLOW CONDITIONS

Temp, °C	% recovery	% of total product[a] 1	5	6	7	8	9
300	95	99.9	0.1	0.0	0.0	0.0	0.0
350	88	99.7	0.3	0.0	0.0	0.0	0.0
400	88	93.7	0.5	0.8	3.7	0.2	1.1
450	75	63.0	4.7	4.6	17.5	6.5	3.7
475	75	39.0	7.7	6.4	26.7	11.5	8.6

[a] Per cent composition of degassed liquid product; methane and hydrogen were not determined quantitatively. Below 300° 1 was recovered unchanged in almost quantitative yield.

TABLE II
THERMOLYSIS OF 5,5-DIMETHYL-1,3-CYCLOHEXADIENE UNDER STATIC CONDITIONS

Temp, °C[a]	Time, min	% of total products[b,c] 1	5	6	7	8	9
290	30	74.2	2.0	0.1	0.5	0.0	23.2
290	60	60.5	2.8	0.2	0.5	0.5	35.4
320	30	66.3	2.8	0.5	0.1	0.4	29.8
320	60	35.8	4.6	0.6	0.4	2.5	56.2
350	30	18.4	7.2	0.4	0.2	7.5	66.1
350	60	10.1	6.6	0.3	0.6	11.3	71.0

[a] Bath temperatures ±2° over the course of the reaction. [b] Per cent composition of degassed liquid product as in Table I. [c] At 250° for 90 min, there was no apparent reaction.

essentially irreversible under the conditions of our experiments. This fact is evident when one compares the static *vs.* the flow results. Toluene is the major product in all static results, wherein products have an opportunity to undergo equilibration. Thus it would appear that the methyl migration is reversible, as well as [1,5] hydrogen migration in our system. One can also extrapolate the static results to completetion, and at elevated temperatures it is likely that the final products would consist mainly of toluene and *m*-xylene.

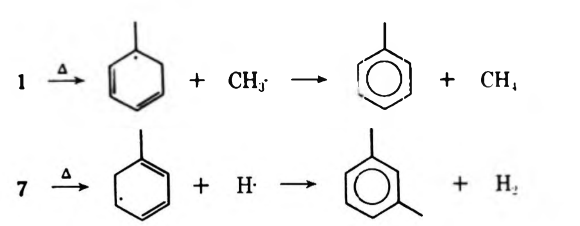
We believe that the above results indicate that sigmatropic migrations account for the thermolytic behavior of 1 as opposed to the biallyl–biradical mechanism proposed several years ago by Pines, *et al.*,[12,15] and which we indicated previously. We can find no evidence for the trienic intermediates 3 and 4 necessary to the latter mechanism. In order to establish that they are indeed not involved in the rearrangement of 1, the following was carried out: (1) 4 was prepared separately and was shown to be easily detectable under the conditions of our isolation and analysis techniques, and (2) 4 was thermolyzed over the temperature range 375–425° to demonstrate that sufficient quantities survive to be detected in the thermolysis product. When mixed with either 1 or with the thermolysis products, 4 is easily separated and quantitatively detected by glpc. The results of the thermolysis of 4 are shown in Table III.

It can be seen from these results that significant quantities of both geometric isomers of 4 do survive thermolysis. In addition, the product distributions are dissimilar in their relative make-up, particularly in the formation of the exocyclic methylenecyclohexene structures. No evidence could be found for reversible formation of 3 at any of the above temperatures. This observation is important in that our static experiments indicate that all transformations should be reversible. We feel that the above establishes the fact that 4 was not present in any of our thermolysis samples from 1, both static and flow.

Another aspect of the biallyl–biradical mechanism that we cannot accept without direct evidence is the conversion of 3 to 4. Presumably, this occurs *via* a thermal [1,7] shift of hydrogen. In order for this shift to be allowed, it must take place antarafacially, presumably *via* a spiral conformation. Such transitions are known,[16–18] but are primarily limited to examples such as the vitamin D_2–precalciferol and similar transformations. We are not aware of any [1,7] shifts occurring in simple acyclic trienic systems. In order to test the ease of such a transformation, we thermolyzed 1,3,5-octatriene (11) in a manner similar to that of 1, in the temperature range 375–425°. In no case did we observe the formation of even trace quantities of 2,4,6-octatriene. The only products from this thermolysis are the various ethyl-1,3-cyclohexadienes. We have previously demonstrated that this transformation is facile if acid catalyzed.[19] We can only conclude from this that a thermal [1,7] sigmatropic hydrogen migration is a highly unlikely process in this temperature range, and that the postulated transformation of 3 to 4 is similarly unlikely.

It can be argued that the absence of trienic products at any stage of these reactions does not prove that a sigmatropic process is therefore operative. We do, however, feel that most of the evidence does point in this direction and our reasoning can be outlined as follows: (1) the first *new*[20] product to appear in the early stages of the reaction is 5, which would result from a [1,5] sigmatropic methyl migration; (2) at progressively higher temperatures in the flow studies, 6 and 7 appear, which one would predict for an increased rate for the same residence time;[14] (3) 7 eventually becomes the major product at higher temperatures than one would predict on the basis of relative diene stabilities. At first glance it might seem that the static studies do not show the same results; however, we feel that they do provide evidence for the reversibility of all migrations, both methyl and hydrogen. Thus the thermolysis of 1 under conditions approaching equilibrium yields progressingly greater quantities of toluene and *m*-xylene, both with respect to time and temperature.

It can be argued also that some reaction may proceed *via* a free radical pathway. Indeed, this pathway is probably responsible for the aromatization products, as first postulated by Pines.[12,15]



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(19) C. Spangler and R. Feldt, *Chem. Commun.*, 709 (1968).
(20) The authors recognize that [1,5] hydrogen migration probably occurs much more rapidly and at a lower temperature, but that this migration is degenerate for 1 and undetectable without some suitable tracer (deuterium substitution).

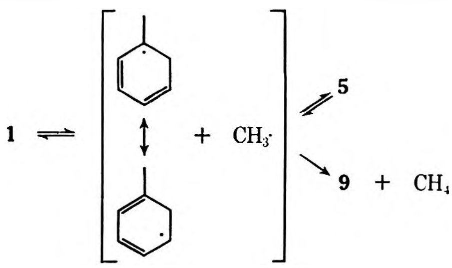
TABLE III

THERMOLYSIS OF 2-METHYL-1,3,5-HEPTATRIENE (4)[a] UNDER FLOW CONDITIONS

Temp, °C	% Recovery	% of total product[b] t,t-4	c,t-4	5	6	7	8	10[c]
375	82	66.5	4.1	2.3	Trace	18.7	Trace	6.1
400	82	54.5	3.8	3.2	Trace	28.9	0.6	8.2
425	84	11.7	1.0	13.3	5.7	36.3	10.8	19.2

[a] Initial composition: 84.8% *t,t;* 15.2% *c,t.* [b] Per cent composition of degassed liquid product as in Tables I and II. [c] Compound **10** is a mixture of 5-methyl-3-methylenecyclohexene and 1-methyl-3-methylenecyclohexene, the latter predominating, which could not be totally resolved by glpc.

However, we do not believe that this can explain both the flow and static experiments. If the original methyl migration occurred by a reversible free radical recombination mechanism, then one would expect other alkyl-1,3-cyclohexadiene systems to undergo similar reaction. However, in our previous studies[13,21] on the high-temperature generation and isomerization of methyl-1,3-cyclohexadienes, we found no trace of such contribution.[22] On this basis we conclude that the initial [1,5] methyl migration, commencing at 300°, and subsequent [1,5] hydrogen migrations are sigmatropic in nature and separate from the aromatization reactions.



Experimental Section[23]

5,5-Dimethyl-1,3-cyclohexadiene (1).—4,4-Dimethyl-2-cyclohexenone (12) was prepared by base-catalyzed condensation of methyl vinyl ketone and isobutyraldehyde essentially by the method of Eliel and Lukach.[24]

p-Toluenesulfonylhydrazide[25] (78.6 g, 0.42 mol) and 4,4-dimethyl-2-cyclohexenone (50.0 g, 0.40 mol) were mixed with sufficient THF to yield a homogeneous solution. Two drops of concentrated HCl were added and the resulting yellow solution was refluxed for 6 hr, during which time product began precipitating from solution. Cooling and filtration of the resulting mixture yielded a pale yellow solid. Addition of water to the filtrate yielded additional product (113 g, 97% crude yield, mp 194–198°). Recrystallization of the combined impure product from EtOH–water yielded 4,4-dimethyl-2-cyclohexenone tosylhydrazone (98.0 g, 83%), mp 197–199°.

The tosylhydrazone (131 g, 0.45 mol) in 450 ml of anhydrous ether was treated with 1 mol of methyllithium[26] in ether solution essentially by the method of Dauben, *et al.*,[27] yielding 1: bp 25–26° (20 mm) (20 g, 41%); $n^{25}D$ 1.4550; λ_{max} (isooctane) 257 nm (ϵ 4300); nmr τ 4.1–4.6 (m, 4 H, vinyl), 7.8–8.0 (m, 2 H, allylic), 9.0 (s, 6 H, methyl) [lit.[12] bp 111–114°; $n^{20}D$ 1.4558; λ_{max} (EtOH) 258 nm].

Thermolysis of 5,5-Dimethyl-1,3-cyclohexadiene (1). A.—1 (5 g) was added dropwise at a rate of 0.25 ml/min through a 22-mm Pyrex tube packed to a depth of 26 cm with $^1/_{16}$-in. Pyrex helices and externally heated with a Lindberg Hevi-Duty split-tube furnace. A pressure of 20–25 mm was maintained in the system to facilitate rapid removal of the product from the column. The product was trapped in a flask immersed in a Dry Ice–acetone bath and subsequently warmed to room temperature and analyzed immediately by glpc. Gas evolution (a mixture of hydrogen and methane) was complete prior to analysis except for a small quantity of dissolved methane.

B.—Samples of 1 (0.5 ml) were sealed in 8-mm heavy-wall tubes previously washed in distilled water. The samples were degassed and sealed under vacuum in the usual manner. Heating was accomplished by either oil bath (<200°) or air bath (>200°). Temperature control was ±0.1 and ±2°, respectively. Tubes were removed after a specified time interval, quenched rapidly to room temperature, broken, degassed, and analyzed by glpc.

Analysis of Products.—The thermolysis samples both from the flow and static studies were submitted to glpc analysis. Each peak emanating from the chromatograph was trapped in two different ways in V tubes immersed in cooling baths: (1) in isooctane for uv analysis and (2) in $CDCl_3$ for nmr analysis. Structural assignments were made as follows.

Compound **5**: λ_{max} (isooctane) 260 nm (ϵ *ca.* 4000); nmr τ 4.2 (very broad s, 3 H, vinyl), 7.8–8.3 (m, 3 H, allylic), 8.5 (s, 3 H, $=CCH_3$), 9.0 (d, J = 7 Hz, 3 H, methyl).

Compound **6**: λ_{max} (isooctane) 262 nm (ϵ *ca.* 4000); nmr τ 4.2–4.5 (m, 2 H, vinyl), 4.6 (m, 1 H, vinyl), 7.7–8.5 (m, 3 H, allylic), 8.2 (s, 3 H, $=CCH_3$), 9.0 (d, J = 6 Hz, 3 H, methyl).

Compound **7**: λ_{max} (isooctane) 263 nm (ϵ *ca.* 4000); nmr τ 4.4–4.5 (broad s, 1 H, vinyl), 4.5–4.7 (broad s, 1 H, vinyl), 7.6–8.0 (m, 4 H, allylic), 8.1–8.4 (m, 6 H, 2 $=CCH_3$).

Compounds **8** and **9**: Both **8** and **9** had identical uv and nmr spectra compared to those of authentic *m*-xylene and toluene. Glpc retention times were also identical with those of authentic samples. Although we were unable to totally resolve 5-methyl-3-methylenecyclohexene and 1-methyl-3-methylenecyclohexene, comparison of their crude uv spectra to published[28,29] examples easily identified them (λ_{max} 233 and 235 nm, respectively).

The similar nmr spectra of **5** and **6** were resolved by comparison of the vinyl multiplet splittings with those of authentic 1-methyl-1,3-cyclohexadiene and 2-methyl-1,3-cyclohexadiene. We have found this method to be most reliable in the assignment of positional isomerism in both the 1,3-cyclohexadiene and 1,3,5-hexatriene systems.

1,5-Octadien-4-ol (13).—2-Pentenal (63.0 g, 0.72 mol) dissolved in 200 ml of anhydrous ether was added to an ether solution of allylmagnesium bromide prepared from allyl bromide (145 g, 1.2 mol), magnesium turnings (73 g, 3.0 g-atoms), and 500 ml of ether. Hydrolysis and isolation was carried out in the usual manner, yielding **13** as a colorless liquid (75 g, 83%): bp 66–67° (10 mm); $n^{23}D$ 1.4523; nmr τ 9.0 (t, 3 H, J = 7.5 Hz, methyl), 8.12 (s, 1 H, OH), 7.5–8.2 (m, 4 H, allylic), 5.89 (q, 1 H, J = 6.0 Hz, methine), 3.75–5.15 (broad m, 5 H, vinyl).

Benzyldimethyl-4-(1,5-octadienyl)ammonium Bromide.—1,5-Octadien-4-ol (75 g, 0.69 mol) in 200 ml of anhydrous ether was added dropwise to phosphorus tribromide (81 g, 0.30 mol) over

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(22) One of the referees has suggested that Pines and Chen[15] report reversible skeletal isomerization of ethylcyclohexadiene to 1,2- and 1,4-dimethylcyclohexadienes, and that this supports the biallyl-biradical mechanism. On the contrary, we think this supports a reversible free-radical contribution to the mechanism, especially since this occurs *only* at 450° and higher. Our migrations, on the other hand, begin to develop at 300°, a highly significant difference.

(23) Gas–liquid partition chromatography (glpc) was performed with an Aerograph Model 202-1B dual column instrument equipped with a Hewlett-Packard Model 3370A electronic integrator for peak area measurement; dual 15-ft 15% TCEP on 60/80 mesh Chromosorb W columns were utilized for all analyses. Ultraviolet spectra were obtained with a Cary Model 14, nmr spectra with a Varian A60-A using TMS as an internal standard ($CDCl_3$). All spectra were consistent with the assigned structures, and satisfactory C and H analyses were obtained for all compounds.

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(29) A. Thomas and M. Stoll, *Chem. Ind. (London)*, 1491 (1963).

a 2-hr period with ice-bath cooling. The product mixture was then allowed to stand overnight at room temperature. The mixture was hydrolyzed by adding to a mixture of ice and water, and the resulting mixture was neutralized with saturated sodium carbonate solution. The organic product was extracted with ether, washed with water, and finally dried with anhydrous magnesium sulfate. The ether was removed under reduced pressure, yielding crude 4-bromo-1,5-octadiene (14) as a yellow, lachrymatory, unstable liquid (99 g, 87% crude yield).

Crude 4-bromo-1,5-octadiene (99 g, 0.52 mol), *N,N*-dimethylbenzylamine (94.5 g, 0.70 mol), and toluene (800 ml) were mixed and allowed to stand overnight at room temperature. The mixture was then heated on a steam cone for 8 hr to complete formation of the quaternary salt, which was then removed by filtration as a crude brown semisolid (126 g, 75%). A small portion was recrystallized from EtOH-EtOAc, mp 141-142°. The remainder of the crude product was dissolved in 600 ml of water, and the aqueous solution was extracted several times with ether to remove suspended organic impurities. The aqueous solution of the salt was then heated to boiling to remove any dissolved ether, yielding a clear yellow solution of benzyldimethyl-4-(1,5-octadienyl)ammonium bromide (15).

1,3,5-Octatriene (11).—The above aqueous solution of 15 was added dropwise to a solution of sodium hydroxide (128 g in 800 ml of water) which was undergoing distillation. The organic product was extracted from the distillate with ether, and the ether solution was washed several times with 3 *N* HCl, followed by several water washings. The ether solution was dried with anhydrous magnesium sulfate, filtered, and distilled at reduced pressure, yielding 11 (12 g, 28%): bp 52-53° (23 mm); $n^{23}D$ 1.5200; λ_{max}^{iso} 274, 263, 254 nm ($\epsilon \times 10^{-4}$ 3.10, 3.90. 290) [lit.[30] $n^{26}D$ 1.5170; λ_{max} 274, 264, 254 nm ($\epsilon_{max} \times 10^{-4}$ 2.72, 3.46, 2.76)]; nmr τ 9.0 (t, 3 H, J = 7 Hz, methyl), 7.6-8.2 (q, 2 H, J = 7 Hz, allylic methylene), 2.8-5.2 (m, 7 H, vinyl). Glpc analysis indicated a mixture of geometric isomers composed of 68% trans,trans- and 32% cis,trans configurations.

2-Methyl-1,3,5-heptatriene (4).—*trans*-2-Methyl-1,5-heptadien-4-ol[31] (141 g, 1.12 mol) in 200 ml of anhydrous ether was allowed to react with phosphorus tribromide (120 g, 0.42 mol) in a manner similar to that described above for 4-bromo-1,5-octadiene, yielding 4-bromo-2-methyl-1,5-heptadiene (187 g, 99%) as a crude lachrymatory liquid. The crude bromide (0.99 mol), in 100 ml of DMSO, was added dropwise to a solution of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1.05 mol) and the reaction mixture was worked up as we have recently described.[32] 2-Methyl-1,3,5-heptatriene (4) (32 g, 30%) was obtained as a mixture of geometric isomers composed of 85% *trans,trans*- and 15% *cis,trans*-4: bp 68-70° (25 mm); $n^{25}D$ 1.5263; λ_{max} 272, 262, 252 nm ($\epsilon \times 10^{-4}$ 3.84, 4.68, 3.48); nmr τ 8.0-8.3 (m, 6 H, 2 CH_3C=), 5.05 (s, 2 H, CH_2=), 3.6-4.6 (m, 4 H, CH=CH) (lit.[32] identical with those above).

Thermolysis of 1,3,5-Octatriene, a Typical Run.—1,3,5-Octatriene (2.0 g) was thermolyzed in a manner identical with that described for 1. At 425° 1.9 g of product was obtained (95% recovery) and submitted to glpc analysis, yielding the following product distribution: 5-ethyl-1,3-cyclohexadiene, 18.6%; 1-ethyl-1,3-cyclohexadiene, 26.2%; *trans,trans*-11, 55.0%; *cis,trans*-11, 0.2%. No other products were detected. Assignment of structure to the thermolysis products was accomplished by comparison of uv, nmr, and glpc retention times to those of authentic samples.

Thermolysis of 2-Methyl-1,3,5-heptatriene, a Typical Run.—2-Methyl-1,3,5-heptatriene (5.0 g) was thermolyzed in a manner identical to that described for 1. The results are tabulated in Table III. At 425° 4.2 g of product was obtained (84% recovery) and submitted to glpc analysis.

Registry No.—1, 33482-80-3; *trans,trans*-4, 17679-94-6; *cis,trans*-4, 18304-16-0; 5, 1453-17-4; 6, 2050-32-0; 7, 4573-05-1; *trans,trans*-11, 33580-04-0; *cis,-trans*-11, 33580-05-1; 12, 1073-13-8; 12 tosylhydrazone, 21195-63-1; 13, 33580-07-3; 15, 33580-08-4.

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Reactions of Dienamines and Dienol Ethers

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The bicyclic morpholine dienamines I and II derived from 4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone and the corresponding 4a-methyl compound reacted on the nitrogen-substituted double bond with a nitrile oxide, an acyl azide, diethyl diazodicarboxylate, and the methylene-donating reagent methylene iodide and diethylzinc. The latter reagent reacted preferentially at the alternative double bond of the corresponding enol ether. Reactions of the dienamines with a sulfonimide occurred at both double bonds while phenylsulfene was regiospecific for the terminal double bond of the activated dienamine systems.

Conjugated dienes, which are substituted by electron-donating or -withdrawing substituents can be expected to react at more than one position. Prediction of a specific preferred reaction site should be governed by considerations of location of maximum charge density in the ground state of the diene, optimum electronic stabilization in the reaction transition state, as well as steric barriers at either reaction stage. Since these factors may or may not act in the same direction and will be differently weighted for different reactions, one would anticipate variations in the preferred position of attack on conjugated dienes. Indeed, lacking suitable analogies, one may find it difficult to predict a preferred reaction site with strong conviction for a given diene and reagent. The present study was undertaken to extend information on such reactions.

It has previously been found that fluorination of dienamine derivatives[1-6] of Δ^4-3-keto steroids leads to 4-fluoro products, whereas the corresponding enol ether[6,7] and enol acetate[8,9] derivatives gave predominantly 6-fluoro products. Halogenation of dienol ethers with *N*-halosuccinimides also led to substitution

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(3) S. Nakanishi, R. L. Morgan, and E. V. Jensen, *Chem. Ind. (London)*, 1136 (1960).

(4) D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *Chem. Commun.*, 804 (1968).

(5) S. Nakanishi, *Steroids*, 2, 765 (1963).

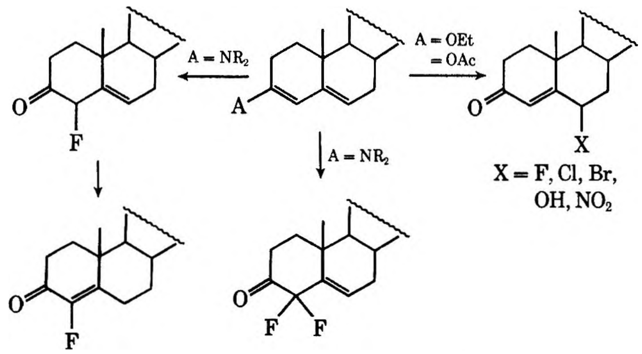
(6) J. Magerlein, J. E. Pike, R. W. Jackson, G. E. Vanderberg, and F. Kagan, *J. Org. Chem.*, 29, 2982 (1964).

(7) S. Nakanishi, K. Morita and E. Jensen, *J. Amer. Chem. Soc.*, 81, 5259 (1959).

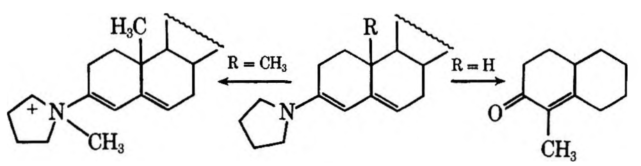
(8) Y. Osawa and M. Neeman, *J. Org. Chem.*, 32, 3055 (1967).

(9) H. J. Ringold, E. Batres A. Bowers, J. Edwards, and J. Zderic, *J. Amer. Chem. Soc.*, 81, 3485 (1959).

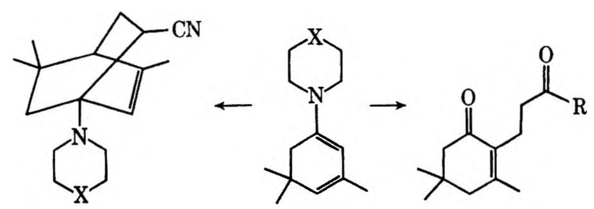
at the terminal double bond.[9] This position of substitution was again found in hydroxylations of dienol ethers[10] and dienol acetates[11] with monoperphthalic[10] and *m*-chloroperbenzoic[11] acids, as well as in an enol acetate nitration with fuming nitric acid.[12]



While methylation of the pyrrolidine enamine derivative of testosterone has been reported to take place on nitrogen,[13] carbon methylation was achieved in a corresponding octalone derivative[14,15] where steric shielding by an angular methyl group is not present. In this example alkylation was found at the double bond nearest the nitrogen. This position of reaction was also realized on alkylations with 3-methoxybenzyl bromide,[16] 1,3-dichloro-2-butene,[18] ethyl acrylate,[19] acryloyl chloride,[20] methyl vinyl sulfone,[21] and dichlorocarbene (with ring expansion).[22]

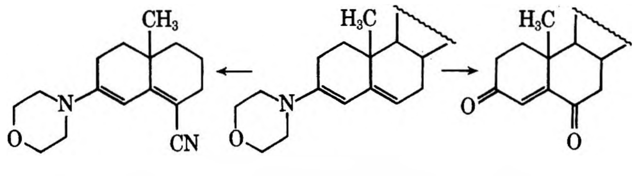


On the other hand, analogous dienol ethers were found to react with tetrabromomethane or bromotrichloromethane to give dihalomethylene substitution at the end of the activated diene system.[23] Additions of α,β-unsaturated nitriles,[24] esters,[24] and ketones,[24,25] and of diketene[26] to endocyclic cisoid dienamines provided examples of additions β to the amine nitrogen

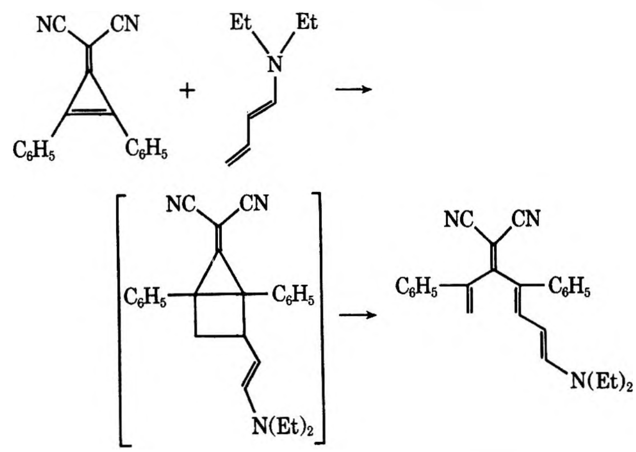


as well as the Diels–Alder products also observed with acyclic dienamines.[27–31]

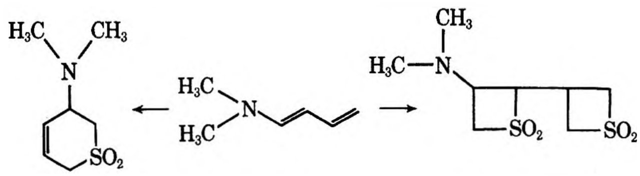
In contrast to the foregoing dienamine reactions it was found that cyanogen chloride[32] and oxygen with copper[33] react at the terminal double bond of dienamine derivatives of β-octalone systems.



Cycloaddition of 1,2-diphenyl-3-dicyanomethylenecyclopropane[34] to the terminal double bond of 1-diethylaminobutadiene led to a cyclobutane intermediate which opened to a cross-conjugated tetraene.



The formation of double adducts and a Diels–Alder product from sulfene and 1-dimethylaminobutadiene suggest preferred initial reaction at the terminal end of the diene system for this reaction as well.[35,36]



Disubstitution of dienamines was also found with the Vilsmeier reagent.[37] However, here an initial attack

(10) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).
(11) D. N. Kirk and J. M. Wiles, *Chem. Commun.*, 518 (1970).
(12) A. Bowers, L. C. Ibanez, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 3707 (1959).
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(14) G. Stork and G. Birnbaum, *Tetrahedron Lett.*, 313 (1961).
(15) M. Julia, S. Julia, and C. Jeanmart, *C. R. Acad. Sci., Ser. C.*, **251**, 249 (1960).
(16) U. K. Pandit, K. DeJonge, K. Erhart, and H. O. Huisman, *Tetrahedron Lett.*, 1207 (1969). The high yield of carbon alkylation in this example, analogous to the above testosterone enamine methylation, is likely due to rearrangement of an initial *N*-benzyl product at the temperature of refluxing dimethylformamide.[17]
(17) M. E. Kuehne and T. Garbacik, *J. Org. Chem.*, **35**, 1555 (1970).
(18) L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, and P. Dufay, *Tetrahedron Lett.*, 127 (1961).
(19) A. A. Brizzolara, Ph.D. Thesis, Columbia University, 1960.
(20) H. F. Firrell and P. W. Hickmott, *J. Chem. Soc. C*, 2320 (1968).
(21) D. Bertin and J. Perronet, *Bull. Soc. Chim. Fr.*, 1422 (1968).
(22) U. Pandit and S. de Graaf, *Chem. Commun.*, 381 (1970).
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(24) H. Nozaki, T. Yamagute, S. Ueda, and K. Kondo, *ibid.*, **24**, 1445 (1968).
(25) A. J. Birch, E. G. Hutchinson, and G. S. Rao, *Chem. Commun.*, 657 (1970).
(26) B. B. Millward, *J. Chem. Soc.*, 26 (1960).
(27) H. Leotte, *Rev. Port. Quim.*, **7**, 214 (1965); *Chem. Abstr.*, **65**, 13647 (1966).
(28) G. Opitz and H. Holtmann, *Justus Liebigs Ann. Chem.*, **684**, 79 (1965).
(29) S. Hünig and K. Kahanek, *Chem. Ber.*, **90**, 238 (1957).
(30) J. Ciabattoni and G. A. Berchtold, *J. Amer. Chem. Soc.*, **87**, 1404 (1965).
(31) J. Ciabattoni and G. A. Berchtold, *J. Org. Chem.*, **31**, 1336 (1966).
(32) M. E. Kuehne and J. A. Nelson, *ibid.*, **35**, 161 (1970).
(33) V. Van Rheenen, *Chem. Commun.*, 314 (1969).
(34) J. Ciabattoni and E. C. Nathon, *J. Amer. Chem. Soc.*, **89**, 3081 (1967).
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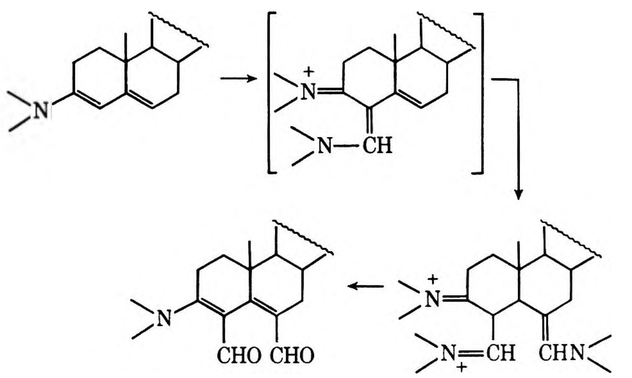
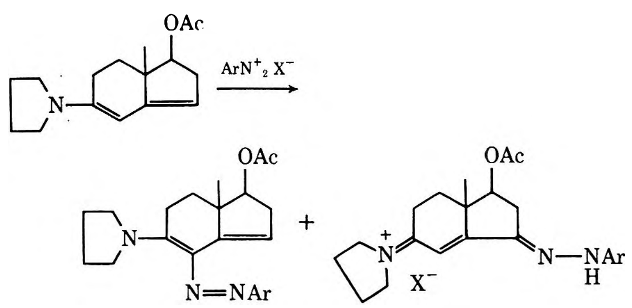
(36) L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967).
(37) R. Sciaky, U. Pallini, and A. Consonni, *Gazz. Chim. Ital.*, **96**, 1284 (1966).

on the nitrogen-substituted double bond can give rise to a new enamine which may then react with a second equivalent of the acylating agent. Diformylation of methylenecyclohexane at the methylene carbon in a Vilsmeier reaction[38] can be formulated as the analogous reaction of an initially formed dienamine.



In contrast, dienol ether derivatives of Δ^4-3-keto steroids[39,40] gave terminal acylation products (at C-6) in Vilsmeier reactions while the dienol acetate derivative of a 19-nor compound and its parent enone[41] led to equal acylation at both double bonds (C-4 and C-6).[42]

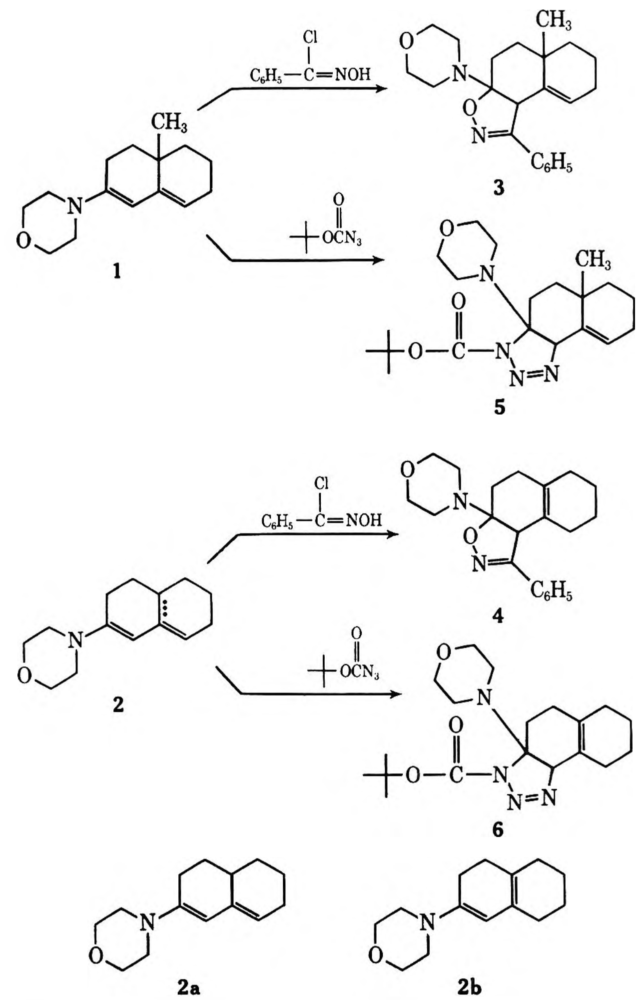
Terminal coupling of dienamines with aryldiazonium salts was found in dimethylformamide or water, while the use of dichloromethane or chloroform as solvent led to a mixture of α and γ coupling products.[43,44]



1,3-Dipolar Reactions.—The morpholine enamine derivatives of 10-methyl-$\Delta^{1(9)}$-2-octalone (1) and $\Delta^{1(9)}$-2-octalone (2) reacted with benzonitrile oxide, which was generated from the chloroxime by loss of hydrogen chloride, to give the aminoisoxazolines **3** and **4**. A nuclear magnetic resonance spectrum of **3** displayed a singlet at δ 3.8 for the isoxazoline proton and a triplet at δ 5.8 for the vinyl proton. Thus reaction at the amine substituted double bond of **1** was indicated. Lack of vinyl proton resonance in **4** again showed the same regiospecificity and indicated preferential reaction of the homoannular dienamine isomer **2b** in the mixture which contained predominantly the heteroannular dienamine isomer **2a**.

Similarly, *tert*-butyl azidoformate reacted with the

SCHEME I



dienamines **1** and **2** to give analogous adducts **5** and **6** (Scheme I). These products showed broad nmr signals at δ 4.8 and 4.6 for the heterocyclic protons and a broad vinyl signal at δ 5.5 for **5** but not for **6**.

Orientation of the 1,3-dipolar additions in **3** and **4** can be assigned from a comparison of chemical shifts of the heterocyclic protons in the two heterocyclic series and is consistent with other additions of nitrile oxides to enamines.[45] Direction of the acyl azide additions was assigned in analogy to other reactions of acyl and aryl azides with enamines.[46,47]

Attempts to obtain 1,3-dipolar additions of the preceding two 1,3-dipolar reagents to the ethyl enol ether and enol acetate derivatives of $\Delta^{1(9)}$-2-octalone and 10-methyl-$\Delta^{1(9)}$-octalone failed and led only to the isolation of 4,5-diphenylfuroxan when the nitrile oxide was used.

Methinylation Reaction.—The addition of diethylzinc and diiodomethane[48,49] to the dienamines **1** and **2** gave aminocyclopropane products **7** and **8** which showed cyclopropane protons at δ 0.2–1.0 and coupled vinyl proton signals at δ 5.4 in their nmr spectra. With a 50% excess of the carbenoid reagent only the monoaddition products to the nitrogen-substituted

(38) C. Jutz and W. Müller, *Chem. Ber.*, **100**, 1536 (1967).

(39) D. Burn, G. Cooley, M. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. Kirk, A. P. Leftwick, V. Petrow, and D. M. Williamson, *Tetrahedron*, **20**, 597 (1964).

(40) R. Sciaky, U. Pallini, and B. Patelli, *Gazz. Chim. Ital.*, **96**, 1268 (1964).

(41) R. Sciaky and F. Mancini, *Tetrahedron Lett.*, 137 (1965).

(42) Acylation at C-4 could be due to the homoannular diene in reaction of the 19-nor compounds.

(43) M. J. M. Pollmann, H. R. Reus, U. K. Pendit, and H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, **89**, 929 (1970).

(44) U. K. Pandit, M. J. M. Pollmann, and H. O. Huisman, *Chem. Commun.*, 527 (1969).

(45) M. E. Kuehne, S. J. Weaver, and P. Franz, *J. Org. Chem.*, **29**, 1582 (1964).

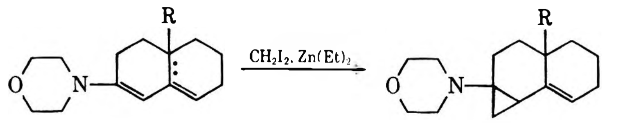
(46) Y. K. Kim and M. Munk, *J. Amer. Chem. Soc.*, **86**, 2213 (1964).

(47) E. Fanghaenel, *Z. Chem.*, **3**, 309 (1963).

(48) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).

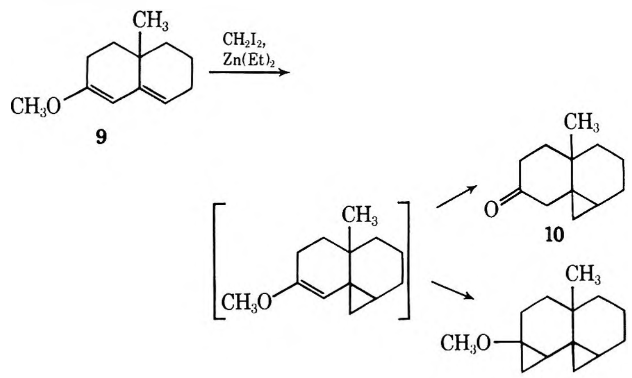
(49) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, 3495 (1968).

double bond were isolated. The reaction also appears to be stereospecific, at least in the addition to dienamine **1**, since there only one methyl signal could be detected in the total reaction product.



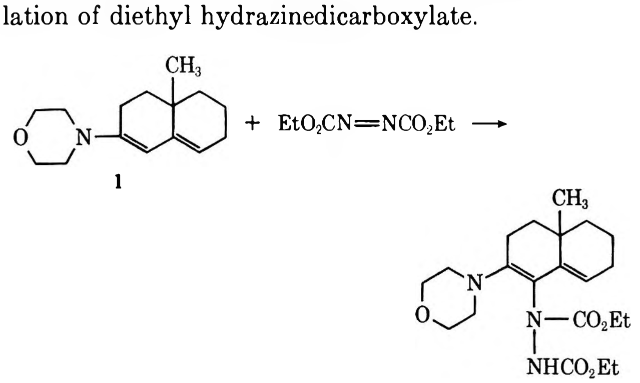
1, R = CH_3
2, R = H
7, R = CH_3
8, R = H

In contrast to these reactions, it was found that methylene groups were added preferentially to the terminal double bond of the methyldienol ether derivative **9** of 10-methyl-$\Delta^{1(9)}$-2-octalone. Thus the ketonic cyclopropane **10** and the dicyclopropane **11** were formed with a 50% excess of the methylene generating reagent. The dienol acetate derivative of the parent octalone was recovered unchanged under the same reaction conditions.



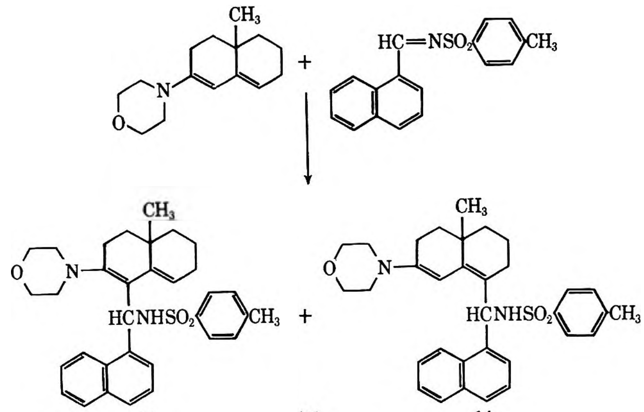
9
10
11

Reaction with Diethyl Azodicarboxylate.—The nitrogen-substituted double bond was also found to be substituted on addition of diethyl azodicarboxylate to the dienamine **1**. The nmr spectrum of the product **12** displayed a coupled vinyl proton. Addition of this reagent to the corresponding methyl dienol ether, however, resulted in reduction of the azo group and isolation of diethyl hydrazinedicarboxylate.



12

Reaction with 1-Naphthal-*p*-toluenesulfonimide.—In contrast to the foregoing dienamine reactions which were regiospecific for the nitrogen-substituted double bond, the reaction of **1** with a toluenesulfonimide[50] led to about equal addition to both double bonds. The product structures **13** and **14** could be assigned from observation of respective coupled and uncoupled vinyl protons, deuterium exchangeable sulfonamide protons, and conversion of the benzylic doublets to singlets on hydrogen–deuterium exchange. In product **13** the NH proton signal was quite diffuse, presumably because of hydrogen bonding to the morpholine nitrogen.



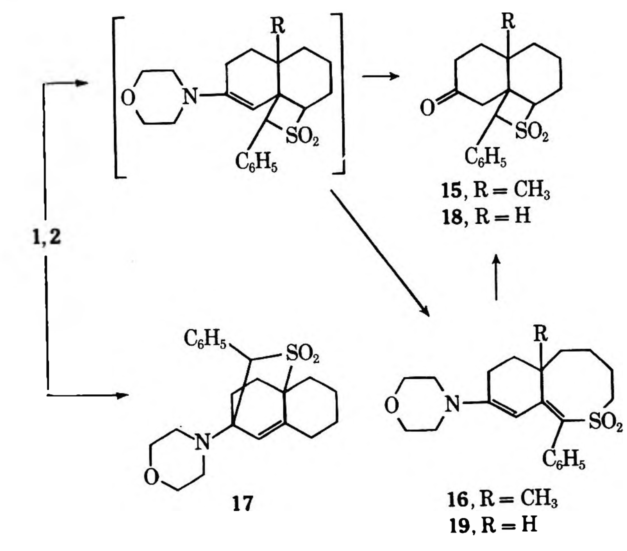
13 1:1 **14**

Reactions with Phenylsulfene.—The addition of benzylsulfonyl chloride to a mixture of the dienamine **1** and triethylamine resulted only in products of reaction at the end of the activated diene system. Thus hydrolytic work-up gave the tricyclic keto sulfone **15** and the ring expanded sulfone **16**. Heating of the reaction mixture in the absence of water and work-up resulted in the exclusive formation of **16** from the intermediate tricyclic enamine. On heating of **16** with aqueous acetic acid, the tricyclic keto sulfone **15** was formed. This interesting ring contraction may occur at the α,β-unsaturated imonium salt or the corresponding enone stage of the hydrolysis.

When benzyl sulfonyl chloride was added to the dienamine **2**, analogous products **18** and **19** were formed, as well as the bridged sulfone **17**, as major product.

Decreased medium basicity, which should allow direct sulfonation by the acid chloride, rather than initial sulfene generation, did not alter the course of these reactions. Thus identical products were obtained with or without triethylamine.

Attempts to add phenylsulfene to the enol ether derivative **9** of 10-methyl-$\Delta^{9(1)}$-2-octalone resulted only in the formation of stilbene in 46% yield. Stilbene was also formed from benzenesulfonyl chloride and triethylamine in petroleum ether.



15, R = CH_3
18, R = H
17
16, R = CH_3
19, R = H

(50) G. Kresze and R. Albrecht, *Angew. Chem.*, **74**, 781 (1962).

Experimental Section

Nmr spectra were recorded on a Varian A-60 instrument, ir spectra on a Perkin-Elmer 21 instrument, and uv spectra on a Perkin-Elmer 202 instrument. Melting points are corrected.

The preparations of 4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone, bp 78° (0.1 mm), 2,4-dinitrophenylhydrazone mp 171–172°, and its 4a-methyl analog, bp 100° (0.1 mm), semicarbazone mp 204–205, were carried out according to the method of Ross and Levine.[51] Conversion to the respective enamine derivatives **1**, bp 122–125° (0.6 mm), 67% yield, and **2**, bp 118–120° (0.5 mm), 62% yield, was achieved by azeotropic removal of water.[52] Compound **2** showed a 60:40 ratio of heteroannular to homoannular diene (nmr H-1 5.20 (s), H-8 5.30 (m) *vs.* H-1 (4.72), respectively). Using a procedure similar to one described,[53] 2-methoxy-3,4,4a,5,6,7-hexahydro-4a-methylnaphthalene (**9**) was obtained by solution of the parent octalone, 8.0 g (0.049 mol), and a few crystals of *p*-toluenesulfonic acid in 20 ml of a 3:1 mixture of methanol and dioxane. After 3 hr at room temperature 1.0 ml of triethylamine was added, the mixture concentrated under vacuum, and the enol ether distilled to give 6.50 g (71% yield): bp 78–80° (0.35 mm); ν_{max}^{neat} 1660 and 1620 cm^{-1}; nmr (neat) δ 0.83 (s, 3 H), 3.33 (s, 3 H), 4.97 (s, 1 H), and 5.05 (t, 1 H).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.56; H, 10.05.

Reactions of 2-(*N*-Morpholino)-3,4,4a,5,6,7-hexahydro-4a-methylnaphthalene (1) and 2-(*N*-Morpholino)-3,4,4a,5,6,7-hexahydronaphthalene (2) with Benzonitrile Oxide to 3 and 4.—A solution of 400 mg (2.58 mmol) of phenylhydroxamoyl chloride[54] in 10 ml of anhydrous benzene was added to 1.80 g (7.80 mmol) of the dienamine **1** or 1.70 g (7.80 mmol) of the dienamine **2**, in 10 ml of benzene, at 0°, under a nitrogen atmosphere. After 2 hr at 0° and 48 hr at room temperature, the solid amine hydrochlorides were filtered and the filtrates concentrated under vacuum. Addition of a little methanol and water, extraction with dichloromethane, concentration, and trituration with petroleum ether (bp 30–60°) gave 183 mg (20% yield) of **3**, mp 163–165°, and 330 mg (38% yield) of **4**, mp 185–188°. The products were recrystallized from methanol. **3** had mp 166–167°; ν_{max}^{KBr} 1460, 1440, and 1115 cm^{-1}; λ_{max}^{EtOH} 220 and 265 mμ; nmr ($CDCl_3$) δ 0.80 (s, 3 H), 2.67 (t, 4 H), 3.60 (t, 4 H), 3.80 (s, 1 H), 5.80 (t, 1 H), and 7.20–7.80 (m, 5 H).

Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.85; H, 7.98; N, 8.14. Found: C, 74.95; H, 8.01; N, 7.95.

4 had mp 193–194°; ν_{max}^{KBr} 1440 and 1115 cm^{-1}; λ_{max}^{EtOH} 220 and 260 mμ; nmr ($CDCl_3$) δ 2.70 (t, 4 H), 3.57 (t, 4 H), 3.73 (s, 1 H), and 7.20–7.80 (m, 5 H).

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.50; H, 7.74; N, 8.27 Found: C, 74.21; H, 7.64; N, 8.41.

Reactions of Enamines 1 and 2 with *tert*-Butyl Azidoformate to 5 and 6.—A mixture of 651 mg (2.79 mmol) of dienamine **1** and 400 mg (3.80 mmol) of *tert*-butyl azidoformate was stored at room temperature, in the dark, under nitrogen, without solvent, for 56 hr. Trituration with pentane gave 240 mg (23% yield) of **5**, mp 123–126°. Recrystallization from pentane gave needles: mp 129–130°; ν_{max}^{KBr} 1708 cm^{-1}; λ_{max}^{EtOH} 250 mμ; nmr ($CDCl_3$) δ 1.20 (s, 3 H), 1.60 (s, 9 H), 2.50 (t, 4 H), 3.70 (t, 4 H), 4.82 (broad, 1 H), and 5.52 (broad, 1 H).

Anal. Calcd for $C_{20}H_{32}N_4O_3$: C, 63.80; H, 8.57; N, 14.88. Found: C, 64.05; H, 8.53; N, 14.90.

Using the same procedure with 1.07 g (4.88 mmol) of dienamine **2** and 700 mg (6.65 mmol) of *tert*-butyl azidoformate gave 797 mg (45% yield) of **6**, mp 104–106. Recrystallization from pentane gave needles: mp 105–106°; ν_{max}^{KBr} 1702 cm^{-1}; λ_{max}^{EtOH} 250 mμ; nmr ($CDCl_3$) δ 1.52 (s, 9 H), 2.50 (t, 4 H), 3.60 (t, 4 H), and 4.50 (broad, 1 H).

Anal. Calcd for $C_{19}H_{30}N_4O_3$: C, 62.95; H, 8.34; N, 15.46. Found: C, 63.25; H, 8.46; N, 15.69.

Reactions of Dienamines 1 and 2 with Diiodomethane and Diethylzinc to 7 and 8.—To a solution of 500 mg (2.14 mmol) of the dienamine **1** in 20 ml of benzene was added 0.5 ml of diethylzinc at 0°, under nitrogen. A solution of 0.25 ml (3.10 mmol) of diiodomethane in 10 ml of benzene was then added over 30 min. After an additional 0.5 hr at room temperature the reaction mixture was quenched with 50 ml of cold 25% ammonium hydroxide solution and extracted with two 50-ml portions of benzene. Concentration of the magnesium sulfate dried extracts and distillation at 75–78° (0.006 mm) gave 180 mg (34% yield) of **7**, mp 88–89°, which was recrystallized from petroleum ether without change of melting point: nmr ($CDCl_3$) δ 0.20–1.00 (m, 2 H), 1.00 (s, 3 H), 2.60 (t, 4 H), 3.55 (t, 4 H), and 5.40 (t, 1 H). The crude undistilled product showed only one methyl singlet at δ 1.00 as well.

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19. Found: C, 77.31; H, 10.26.

Reaction of the dienamine **2** under the same conditions and on the same scale gave 180 mg (34% yield) of **8**, as a colorless oil: bp 75–80° (0.007 mm); nmr ($CDCl_3$) δ 0.40–1.00 (m, 2 H), 2.60 (t, 4 H), 3.50 (t, 4 H), and 5.40 (m, 1 H).

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.45; H, 9.79; N, 6.22.

Reaction of 2-Methoxy-3,4,4a,5,6,7-hexahydro-4a-methylnaphthalene (9) with Diiodomethane and Diethylzinc to 10 and 11.—Following the preceding reaction procedure for the dienamines, but with a 12-hr reaction time, 500 mg (2.81 mmol) of the dienol ether **9** was converted to 230 mg (45% yield) of an oily product which gave an nmr spectrum with two methyl singlets of equal intensity at δ 1.10 and 0.94. Preparative plate chromatography on silica gel, with benzene, afforded two products. The faster moving ketone **10**, bp 45° (0.5 mm), was contaminated by olefinic material and showed ν_{max}^{neat} 1705 cm^{-1}; nmr (CCl_4) δ 0.2–0.9 (m, 3 H), 1.10 (s, 3 H), and 4.75 (d or unresolved q, <1 H).

The slower moving dicyclopropane **11**, bp 40–44° (0.01 mm), showed nmr (CCl_4) δ 0.00–0.86 (m, 6 H), 0.94 (s, 3 H), and 3.17 (s, 3 H).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.20; H, 10.50.

Reaction of Enamine 1 with Diethyl Azodicarboxylate to 12.—A solution of 274 mg (1.57 mmol) of diethyl azodicarboxylate in 10 ml of anhydrous tetrahydrofuran was added at 0°, under nitrogen, to 400 mg (1.71 mmol) of dienamine **1** during 20 min. After 2 hr at 0° and 24 hr at room temperature (reaction mixture changed from orange to pale yellow), the solution was concentrated under vacuum and chromatographed on 20 g of Florisil eluting with 5% ethyl acetate in benzene. The first 150 ml of eluent produced 270 mg (42% yield) of crystalline **12** after trituration with petroleum ether. The product, recrystallized from hexane, showed mp 113–115°; ν_{max}^{KBr} 3350, 1750, and 1690 cm^{-1}; λ_{max}^{EtOH} 278 mμ; nmr ($CDCl_3$) δ 1.01 (s, 3 H), 1.1–1.8 (m, 12 H), 2.20 (m, 4 H), 2.70 (t, 4 H), 3.70 (t, 4 H), 4.00–4.30 (m, 4 H), 6.30 (m, 1 H), and 7.67 (s, 1 H).

Anal. Calcd for $C_{21}H_{33}N_3O_5$: C, 61.89; H, 8.16; N, 10.31. Found: C, 61.63; H, 8.41; N, 10.01.

Reaction of Enamine 1 with 1-Naphthal-*p*-toluenesulfonimide to 13 and 14.—A benzene solution of 400 mg (1.71 mmol) of the dienamine **1** and 400 mg (1.30 mmol) of 1 naphthal-*p*-toluenesulfonimide[55] was refluxed under nitrogen for 24 hr and concentrated under vacuum. Trituration with an ether-cyclohexane mixture gave 570 mg (81%) of a mixture of **13** and **14**. The nmr spectrum of this product showed two aromatic methyl singlets at δ 2.37 and 2.40 of about equal intensity. Recrystallization from ethanol gave **13**: mp 171–172°; ν_{max}^{KBr} 3200, 1612, and 1587 cm^{-1}; λ_{max}^{EtOH} 233 and 298 mμ; nmr ($CDCl_3$) δ 0.97 (s, 3 H), 2.37 (s, 3 H), 3.10 (t, 4 H), 3.80 (t, 4 H), 5.50 (d, 1 H), 5.95 (s, 1 H), 6.45 (d, 1 H), and 7.00–8.00 (m, 11 H). Addition of one drop of D_2O resulted in loss of the signal at δ 5.50 (NH) and collapse of the signal at δ 6.45 (adjacent CH) to a broad singlet.

Anal. Calcd for $C_{33}H_{38}N_2O_3S$: C, 73.00; H, 7.05; N, 5.16; S, 5.90. Found: C, 72.91; H, 7.12; N, 5.08; S, 5.79.

Crystallization of the mother liquor material from methanol gave **14**: mp 164–165°; ν_{max}^{KBr} 3200, 1612, and 1587 cm^{-1}; λ_{max}^{EtOH} 240 and 290 mμ; nmr ($CDCl_3$) δ 0.97 (s, 3 H), 2.40 (s, 3 H), 2.90 (t, 4 H), 3.70 (t, 4 H), 5.00 (m, 1 H), 5.60 (b, 1 H), 6.45 (d, 1 H), and 7.00–8.00 (m, 11 H). Addition of one drop of D_2O changed the δ 6.45 signal to a singlet.

Anal. Calcd for $C_{33}H_{38}N_2O_3S$: C, 73.00; H, 7.05; N, 5.16; S, 5.90. Found: C, 72.83; H, 7.05; N, 5.03.

Reactions of Enamines 1 and 2 with Phenylsulfene. (a) Dienamine 1.—A solution of 500 mg (2.80 mmol) of benzylsul-

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fonyl chloride in 10 ml of dichloromethane was added to a solution of 620 mg (2.70 mmol) of the dienamine 1 and 1.0 ml of triethylamine in 20 ml of dichloromethane at −15°, under nitrogen. After 2 hr at −15° and 12 hr at room temperature, the mixture was extracted with 5% hydrochloric acid, dried over magnesium sulfate, filtered, and concentrated under vacuum. Addition of 1:1 ether–ethyl acetate caused crystallization of products 15 and 16. The white solid 15, 100 mg (13% yield), mp 242–244°, was recrystallized from ethyl acetate and methanol to mp 244–246°: ν_{max}^{KBr} 1700 cm^{-1}; λ_{max}^{EtOH} 225 mμ; nmr ($CDCl_3$) δ 1.10 (s, 3 H), 4.00 (m, 1 H), 5.50 (s, 1 H), and 7.30–7.70 (m, 5 H).

Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.92; H, 6.96; S, 10.06. Found: C, 67.82; H, 7.05; S, 10.33.

The yellow crystals of 16 were recrystallized from ethanol to give 200 mg (22% yield): mp 169–170°; ν_{max}^{KBr} 1570 cm^{-1}; λ_{max}^{EtOH} 226 and 393 mμ; nmr ($CDCl_3$) δ 1.04 (s, 3 H), 3.10 (t, 4 H), 3.65 (t, 4 H), 4.20 (m, 2 H), 6.22 (s, 1 H), and 7.30 (s, 5 H).

Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.62; S, 8.28. Found: C, 68.18; H, 7.55; N, 3.65; S, 8.35.

An intermediate tricyclic enamine could be seen in the initial reaction product by ν_{max}^{neat} 1660 cm^{-1}. This absorption band was lost on hydrolysis or on heating. When the total reaction product mixture was heated for 2 hr at 80°, the ir spectrum changed to that of the ring expanded dienamine 16. A solution of 50 mg of 16 in 30% aqueous acetic acid was heated at reflux for 1 hr. Extraction with dichloromethane and washing with aqueous sodium carbonate gave a crude product with ν_{max}^{film} 1660 and 1700 cm^{-1}. Trituration with ethyl acetate gave 25 mg (60% yield) of the ketone 15.

(b) **Dienamine 2.**—This reaction was carried out without triethylamine. A solution of 880 mg (4.63 mmol) of benzylsulfonyl chloride in 10 ml of dichloromethane was added to 2.00 g (9.16 mmol) of dienamine 2 in 50 ml of dichloromethane at −20°, under nitrogen, during 1 hr. After 2 hr at this temperature and 10 hr at room temperature, the mixture was extracted with water; the organic phase was dried over magnesium sulfate and concentrated. Trituration with ethyl acetate gave three products: The bridged sulfone 17, 350 mg (20% yield), mp 142–143°, was recrystallized from ethyl acetate and cyclohexane to mp 149–150°: ν_{max}^{KBr} 1450 cm^{-1}; λ_{max}^{EtOH} 215 mμ; nmr ($CDCl_3$) δ 1.5–2.9 (m, 16 H), 3.33 (m, 4 H), 4.52 (s, 1 H), 4.85 (s, 1 H), and 7.20–7.60 (m, 5 H).

Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.27; H, 7.29; N, 3.75; S, 8.58. Found: C, 67.27; H, 7.48; N, 3.84; S, 8.98.

The keto sulfone 18, 100 mg (7% yield), was recrystallized from ethanol to mp 232–233°: ν_{max}^{KBr} 1705 cm^{-1}; λ_{max}^{EtOH} 225 mμ; nmr ($CDCl_3$) δ 4.15 (m, 1 H), 5.10 (s, 1 H), and 7.40 (s, 5 H).

Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.07; H, 6.62; S, 10.53. Found: C, 66.88; H, 6.51; S, 10.36.

The dienamine sulfone 19, 80 mg (4% yield), was recrystallized from ethyl acetate and showed ν_{max}^{KBr} 1575 cm^{-1}: nmr ($CDCl_3$) δ 3.15 (t, 4 H), 3.80 (t, 4 H), 4.30 (t, 2 H), 6.40 (s, 1 H), and 7.40–7.48 (d, 5 H).

Reaction of Phenylsulfene with Dienol Ether 9.—The reaction was carried out as described for method a used with the dienamines. Only *trans*-stilbene, mp 123° (46% yield), and recovered dienol ether 9 were isolated.

Registry No.—**1,** 23088-12-2; **2a,** 23088-05-3; **2b,** 23088-06-4; **3,** 33527-50-3; **4,** 33527-51-4; **5,** 33527-52-5; **6,** 33527-53-6; **7,** 33527-54-7; **8,** 33527-55-8; **9,** 33527-56-9; **10,** 33527-57-0; **11,** 33527-58-1; **12,** 33527-59-2; **13,** 33527-60-5; **14,** 33527-61-6; **15,** 33527-62-7; **16,** 33527-63-8; **17,** 33527-64-9; **18,** 33527-65-0; **19,** 33527-66-1; *trans*-stilbene, 103-30-0.

Organic Fluorine Compounds. XXXIII.[1] Electrophilic Additions to Fluoro Olefins in Superacids

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A series of fluoro olefins (I–X) were studied in the superacid systems, SbF_5–HF–SO_2ClF, SbF_5–HSO_3F–SO_2ClF, or in HSO_3F at low temperature. Eight of the fluoro olefins (I–VIII) reacted with the acid systems to give the corresponding fluoride or fluorosulfonate addition products. A preparative method for preparation of α-fluoroethyl and α,α-difluoroethyl fluorosulfate in 90–95% yield was developed. No long-lived fluorocarbenium ion[2] intermediates were observed, even in these very low nucleophilicity acid systems, as they react rapidly with gegenions to give the observed covalent fluorides or fluorosulfates. Two of the fluoro olefins (IX and X) were found to be inert even in superacids. 1,1,1-Trihaloethanes, CH_3CX_3 (X = F and Cl), reacted with SbF_5–SO_2ClF at −80° to give the first stable methyldihalocarbenium ion, $CH_3C^+X_2$ (X = F and Cl).

Due to the high electronegativity of fluorine the replacement of hydrogen by fluorine in ethylene results in the withdrawal of electron density from the π-electron system. Consequently, most of the ionic reactions of fluoro olefins are due to nucleophilic attack. The ionic reactions of fluoro olefins have been reviewed by Chambers and Hobbs.[3] They concluded that electrophilic attack on fluoro olefins may only be achieved in the presence of strong Lewis acid catalyst. However, no direct evidence was provided for this assumption. With techniques developed in our laboratories for study of stable carbenium ions in superacids and for their low-temperature nuclear magnetic resonance spectroscopic study, we attempted the protonation of a series of fluoro olefins hoping to study their protolytic behaviors and thus directly observe, if possible, the related fluorocarbenium ion and to evaluate the possibility of ionic polymerization of fluoro olefins in superacids.

(1) Part XXXII: G. A. Olah and Gh. Mateescu, *J. Amer. Chem. Soc.*, **93**, 781 (1971).

(2) For a discussion of the general concept of carbocations and differentiation of trivalent carbenium ion from penta- (or tetra-) coordinated carbonium ions, see G. A. Olah, *ibid.*, **94**, 808 (1972).

(3) R. D. Chambers and R. H. Mobbs in "Advances in Fluorine Chemistry," Vol. 4, M. Stacey, J. C. Tatlow, and A. G. Sharpe," Ed., Butterworths, London, 1965.

Results

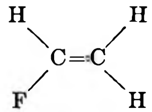
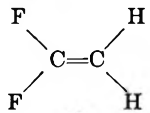
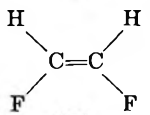
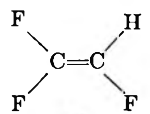
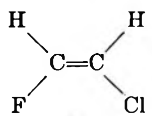
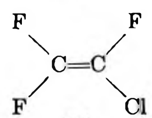
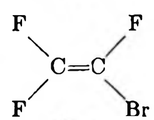
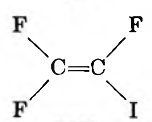
Ten fluoro olefins ($R_1R_2C{=}CR_3R_4$) were selected for our studies (I–X). Two different superacid media with variable ratio of SbF_5–HF and SbF_5–HSO_3F in

$R_1R_2C{=}CR_3R_4$

I, $R_1 = R_2 = R_3 = H$; $R_4 = F$
II, $R_1 = R_2 = H$; $R_3 = R_4 = F$
III, $R_1 = R_3 = H$; $R_2 = R_4 = F$
IV, $R_1 = R_2 = R_3 = F$; $R_4 = H$
V, $R_1 = R_3 = H$; $R_2 = Cl$; $R_4 = F$
VI, $R_1 = R_2 = R_3 = F$; $R_4 = Cl$
VII, $R_1 = R_2 = R_3 = F$; $R_4 = Br$
VIII, $R_1 = R_2 = R_3 = F$; $R_4 = I$
IX, $R_1 = R_2 = R_3 = R_4 = F$
X, $R_1 = R_2 = R_3 = F$; $R_4 = CF_3$

Table I

Proton and Fluorine Nmr Data of Fluoride and Fluorosulfate Addition Products of Fluoro Olefins

Fluoro olefin	Super acid system	Addition product	Pmr parameters[a]	^{19}F nmr parameters[b]
 I	SbF_5:HF (1:4)–SO_2ClF	CH_3CHF_2	1.78 (3 H, dt, J_{HF} = 21, J_{H-H} = 4 Hz) 5.90 (1 H, tq, J_{HF} = 57, J_{H-H} = 4 Hz)	+111.1 (2 F, dq, J_{HF} = 57, J_{HF} = 21 Hz)
	HSO_3F–SO_2ClF	$CH_3CHFOSO_2F$	1.84 (3 H, dd, J_{HF} = 21, J_{H-H} = 4 Hz) 6.42 (1 H, dq, J_{HF} = 56, J_{H-H} = 4 Hz)	+118.7 (1 F, ddq, J_{HF} = 56, J_{HF} = 21, J_{FF} = 10 Hz) −42.0 (1 F, d, J_{FF} = 10 Hz)
 II	SbF_5:HF (1:4)–SO_2ClF	CH_3CF_3	2.01 (3 H, q, J_{HF} = 14 Hz)	+62.0 (3 F, q, J_{HF} = 14 Hz)
	HSO_3F–SO_2ClF	$CH_3CF_2OSO_2F$	2.17 (3 H, t, J_{HF} = 14.5 Hz)	+64.6 (2 F, dq, J_{HF} = 14.5, J_{FF} = 9 Hz) −45.0 (1 F, t, J_{FF} = 9 Hz)
 III	SbF_5:HF (1:4)–SO_2ClF	CH_2F+CHF_2	4.84 (2 H, dtd, J_{HF} = 45, J_{HF} = 14, J_{HH} = 3.5 Hz) 5.31 (1 H, tdt, J_{HF} = 53, J_{HF} = 9.5, J_{HH} = 3.5 Hz)	+243.6 (1 F, ttd, J_{HF} = 45, J_{HF} = 9.5, J_{FF} = 1.7 Hz) +132.4 (2 F, ddt, J_{HF} = 54, J_{HF} = 14 Hz, J_{FF} = 17 Hz)
	SbF_5:HSO_3F (1:4)–SO_2ClF	$CH_2FCHFOSO_2F$	4.98 (2 H, ddd, J_{HF} = 47, J_{HF} = 14, J_{HH} = 3.5 Hz) 7.78 (1 H, ddt, J_{HF} = 54, J_{HF} = 10, J_{HH} = 3.5 Hz)	+241.9 (1 F, tdd, J_{HF} = 47, J_{HF} = 10, J_{FF} = 19 Hz) +139.0 (1 F, m, −45.5 (1 F, d, J_{FF} = 8 Hz)
 IV	SbF_5:HF (1:1)–SO_2ClF	CF_3CH_2F	4.50 (2 H, dq, J_{HF} = 46, J_{HF} = 8.5 Hz)	+242.8 (1 F, tq, J_{HF} = 46, J_{FF} = 15 Hz) +80.8 (3 F, qu, (dt), J_{HF} = 8.5, J_{FF} = 15 Hz)
	SbF_5:HSO_3F (1:1)–SO_2ClF	$CFH_2CF_2OSO_2F$	9.46 (2 H, dt, J_{HF} = 45, J_{HF} = 8.5 Hz)	+239.6 (1 F, tt, J_{HF} = 45, J_{FF} = 16.5 Hz) +83.6 (2 F, sex, J_{HF} = 8.5, J_{FF} = 16.5, J_{FF} = 9 Hz) −47.1 (1 F, t, J_{FF} = 9 Hz)
 V	SbF_5:HF (1:4)–SO_2ClF	CH_2ClCHF_2	3.82 (2 H, td, J_{HF} = 14, J_{HH} = 4 Hz) 6.11 (1 H, tt, J_{HF} = 56, J_{HH} = 4 Hz)	+86.5 (2 F, dt, J_{HF} = 56 Hz, J_{HF} = 14 Hz)
	SbF_5:HSO_3F (1:4)–SO_2ClF	$CH_2ClCHFOSO_2F$	4.27 (2 H, dd, J_{HF} = 13, J_{HH} = 4 Hz) 6.81 (1 H, dt, J_{HF} = 54, J_{HH} = 4 Hz)	+128.1 (1 F, dtd, J_{HF} = 54, J_{HF} = 13, J_{FF} = 8 Hz) −42.9 (1 F, d, J_{FF} = 8 Hz)
 VI	SbF_5:HF (1:1)–SO_2ClF	CF_3CHFCl	6.61 (1 H, dq, J_{HF} = 47, J_{HF} = 4 Hz)	157.9 (1 F, dq, J_{HF} = 47, J_{FF} = 11 Hz) 101.2 (3 F, dd, J_{HF} = 4, J_{FF} = 11 Hz)
	SbF_5:HSO_3F (1:4)–SO_2ClF	CF_3CHFCl		
 VII	SbF_5:HF (1:1)–SO_2ClF	CF_3CHFBr	6.91 (1 H, dq, J_{HF} = 47, J_{HF} = 5 Hz)	+162.2 (1 F, dq, J_{HF} = 47, J_{FF} = 13.5 Hz) +81.8 (3 F, dd, J_{HF} = 5, J_{FF} = 13.5 Hz)
	SBF_5:HSO_3F (1:1)–SO_2ClF	CF_3CHFBr		
 VIII	SbF_5:HF (1:4)–SO_2ClF	CF_3CHFI	7.31 (1 H, dq, J_{HF} = 45, J_{HF} = 4.4 Hz)	+166.9 (1 F, dq, J_{HF} = 46, J_{FF} = 16.5 Hz) −78.8 (3 F, dd, J_{HF} = 5.5, J_{FF} = 16.5 Hz)
	SbF_5:HSO_3F (1:4)–SO_2ClF	CF_3CHFI		

[a] Proton chemical shifts are referred to external capillary TMS in parts per million, d = doublet, t = triplet, q = quartet, qu = quintet, and sex = sextet. [b] Fluorine chemical shifts are referred to external capillary $CFCl_3$ in parts per million.

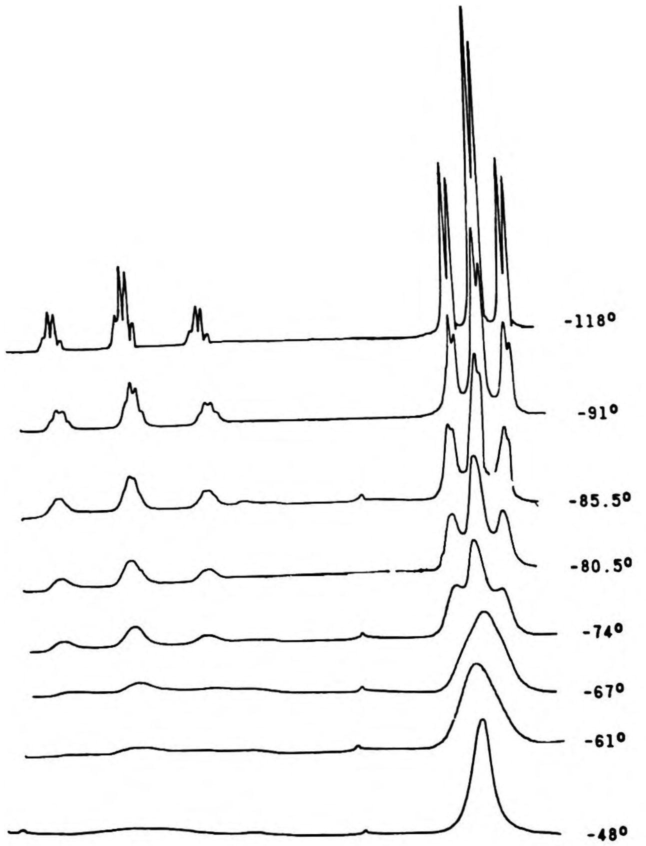


Figure 1a.—Temperature-dependent pmr spectra of fluorine exchange reaction in CH_3CHF_2–SbF_5–SO_2ClF system.

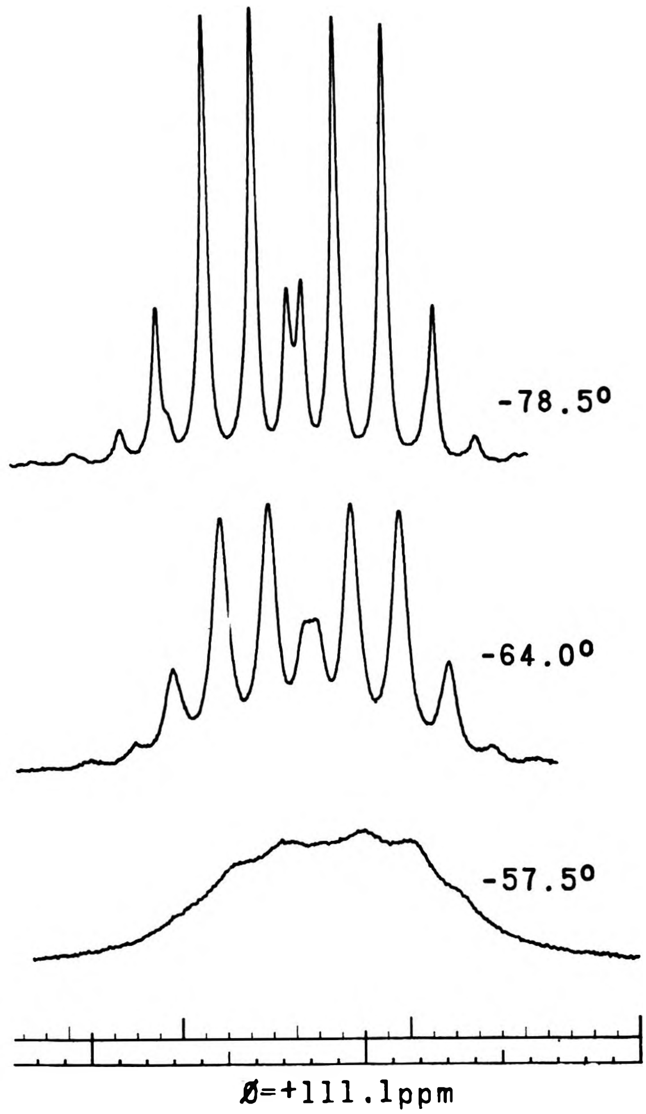


Figure 1b.—Temperature-dependent [19]F nmr spectra of fluorine exchange reaction in CH_3CHF_2–SbF_5–SO_2ClF system.

SO_2ClF or SO_2 were used. The results are summarized in Table I.

Vinyl Fluoride (I).—A solution of I in SO_2ClF reacted smoothly with fluorosulfuric acid at −78° to give α-fluoroethyl fluorosulfate, $CH_3CHFOSO_2F$. Alternatively, when I was bubbled into neat fluorosulfuric acid (until saturated) at −78°, $CH_3CHFOSO_2F$ was formed quantitatively as revealed by nmr spectra. A preparative yield of 95% was achieved by isolating the product by vacuum distillation, bp 33° (35 mm). Distillation at atmospheric pressure (bp 92–93°) gave a low yield due to decomposition to 1,1-difluoroethane (see subsequent discussion). In the pmr spectrum of $CH_3CHFOSO_2F$, the methyl group appears as a pair of doublets at δ 1.84 (3 H, J_{HF} = 21, J_{HH} = 4 Hz). The ^{19}F nmr spectrum of $CH_3CHFOSO_2F$ in HSO_3F–SO_2ClF showed a doublet at ϕ −42.0 (J_{FF} = 10 Hz) and a multiplet at ϕ 118.7. The low-field doublet is assigned to $-SO_2F$ and the multiplet to CH_3CHF. The latter is a A_3BMX system and should give a total of 16 lines (first-order spectrum). However, three lines coincide and only 13 lines are observed.

When I was dissolved in SbF_5–HSO_3F (1/4 *M/M*) –SO_2ClF at 78°, two products were obtained. The more predominant one is $CH_3CHFOSO_2F$, with 1,1-difluoroethane formed as the minor product. The chemical shifts and coupling constants in both the ^{1}H and ^{19}F nmr spectra of the solution corresponding to 1,1-difluoroethane were consistent with the spectral parameters of an authentic sample. When the temperature of the solution was raised to −20°, the intensity of both ^{1}H and ^{19}F signals of 1,1-difluoroethane increased substantially and the gaseous product obtained by distilling the reaction mixture at atmospheric pressure was exclusively 1,1-difluoroethane. This indicates that $CH_3CHFOSO_2F$ undergoes cleavage of SO_3 to give 1,1-difluoroethane. Further, when I was treated with SbF_5–HSO_3F (1/1 *M/M*)–SO_2ClF at −78° it gave 1,1-difluoroethane as a major product, and the concentration of the fluorosulfate was substantially decreased.

The reaction of I with SbF_5–HF–SO_2ClF is more complicated and the reaction conditions are very critical. The observed ^{1}H and ^{19}F nmr spectra are entirely dependent on the ratio of I, SbF_5, and HF. I reacted with a catalytic amount of SbF_5 in HF–SO_2ClF gave exclusively the HF addition product, *i.e.*, CH_3CHF_2. However, when the concentration of SbF_5 was increased

$$CH_2{=}CHF + HF\text{–}SO_2ClF \xrightarrow[SbF_5]{\text{catalytic}} CH_3\overset{+}{C}HF \underset{SbF_5}{\overset{HF}{\rightleftharpoons}} CH_3CHF_2$$

to about 5 mol % of I and HF kept at a concentration four times that of I, both the ^{1}H and ^{19}F nmr spectra became temperature dependent (Figure 1). When the mole ratio of SbF_5 to I was 10 mol %, the pmr spectrum of the solution showed a high-field doublet at δ 1.78 (3 H, J_{HH} = 4 Hz) and a low-field quartet at δ 6.20 (1 H, J_{HH} = 4 Hz). The ^{19}F nmr resonance of either I or CH_3CHF_2 is absent. Both the temperature dependent

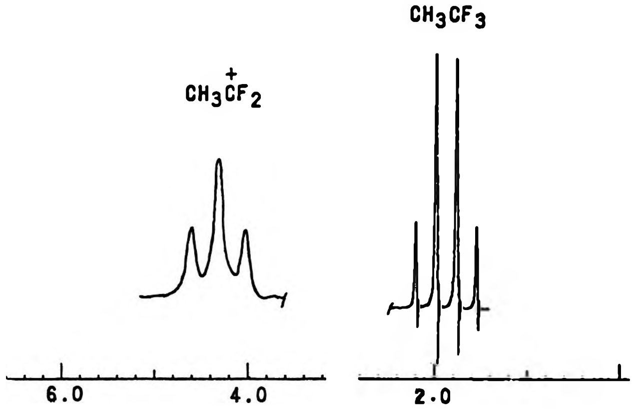
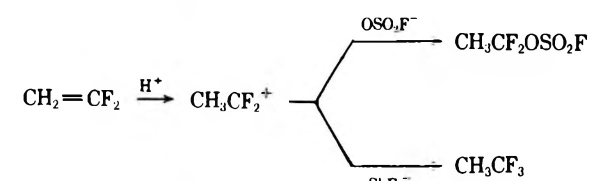


Figure 2a.—Pmr spectra of methyldifluorocarbenium ion and 1,1,1-trifluoroethane.

nmr spectra and the absence of proton–fluorine coupling indicate that CH_3CHF_2 exchanges its fluorines with $CH_3\overset{+}{C}HF$ or SbF_5.

Furthermore, when 1,1-difluoroethane was ionized in SbF_5–SO_2ClF, with an excess of SbF_5 present, the pmr spectrum of the solution displayed a doublet at δ 4.32 (3 H, J_{HH} = 1.8 Hz) and a quartet at δ 10.47 (1 H, J_{HH} = 1.8 Hz). These two resonances disappeared when the temperature was raised above $-40°$. Polymer was found in the nmr tube. On the other hand, when CH_3CHF_2 was added gradually at $-78°$ to the above solution mixture, the two resonances became shielded and the coupling constants were increased. The shielding and the increasing coupling constant were proportional to the amount of CH_3CHF_2 added. The same results (shielding of the two resonances and increasing of coupling constant) were obtained when HF was added to the solution mixture instead of CH_3CHF_2. The nature of the exchange reaction will be discussed subsequently.

Vinylidene Fluoride (II).—Reaction of II in HSO_3F–SO_2ClF at $-60°$ led to the formation of α,α-difluoroethyl fluorosulfonate, $CH_3CF_2OSO_2F$. Isolated product in a preparative run was obtained in 90% yield, bp 25° (30 mm). Distillation at atmospheric pressure (bp 67–68°) gave only a low yield due to decomposition to 1,1,1-trifluoroethane. When II was treated with SbF_5–HSO_3F (1/10 M/M)–SO_2ClF, both the ^1H and ^{19}F nmr spectra indicated that $CH_3CF_2OSO_2F$ was formed as a major product, with CH_3CF_3 as the minor product. When SbF_5HSO_3F (1/4 M/M) –SO_2ClF acid system was used, $CH_3CF_2OSO_2F$ was not found and CH_3CF_3 was formed as the only product.



II reacted with HF at $-50°$ in the presence of a catalytic amount of SbF_5 to give CH_3CF_3 quantitatively. The solution showed only a pmr quartet at δ 2.0 (3 H, J_{HF} = 14 Hz) and a ^{19}F nmr quartet at ϕ 62.0 (3 F, J_{HF} = 14 Hz). Pure CH_3CF_3 could be obtained by careful distillation of the solution. Protonation of II with SbF_5–HF (1/4 M/M) –SO_2ClF did not produce the difluoromethylcarbenium ion, $CH_3\overset{+}{C}F_2$, and again gave CH_3CF_3 as the major product. However, $CH_3\overset{+}{C}F_2$ was obtained by the treatment of CH_3CF_3 with SbF_5–SO_2ClF at $-80°$. The ion shows a pmr triplet at δ 4.50 (3 H, J_{HF} = 17 Hz) and a ^{19}F nmr quartet at ϕ -96.4 (2 F, J_{HF} = 17 Hz) (Figure 2).

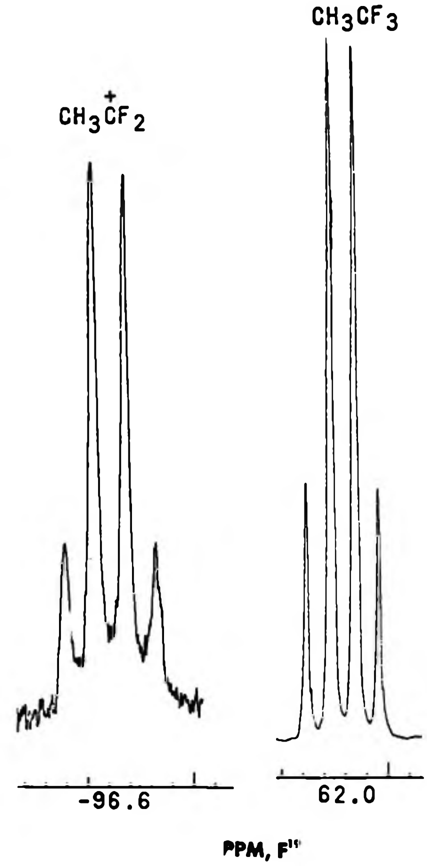


Figure 2b.—^{19}F nmr spectra of methyldifluorocarbenium ion and 1,1,1-trifluoroethane.

Similarly, when 1,1,1-trichloroethane was treated with SbF_5–SO_2ClF solution at $-78°$, the methyldichlorocarbenium ion, $CH_3\overset{+}{C}Cl_2$, was formed. It was evidenced by the substantial deshielding of the observed pmr resonance, singlet at δ 4.60 (1.70 ppm deshielded from the precursor, CH_3CCl_3). $CH_3\overset{+}{C}X_2$ (X = F and Cl) are the first directly observed alkyldihalocarbenium ions.

1,2-Difluoroethylene (III).—Protonation of III with neat HF or HSO_3F–SO_2 did not occur at $-20°$. When III was bubbled through a solution of SbF_5–HF (1/4 M/M) –SO_2ClF, both ^1H and ^{19}F nmr spectra of the resulting solution indicated that CHF_2CH_2F was the only product formed.

When III was treated with SbF_5–HSO_3F (1/4 M/M)–SO_2ClF it gave 1,2-difluoroethyl fluorosulfate, $CH_2FCHFOSO_2F$, which was stable at $-20°$. When the reaction mixture was distilled at atmospheric pressure, cleavage occurred and CH_2FCHF_2 was obtained. When III reacted with SbF_5–HSO_3F (1/1 M/M) –SO_2ClF at $-78°$, instead of giving $CH_2FCHFOSO_2F$, CH_2FCHF_2 was formed almost exclusively. When CH_2FCHF_2 was treated with SbF_5–SO_2ClF it showed no sign of reacting. This is expected since both $CH_2F\overset{+}{C}HF$ and $CHF_2\overset{+}{C}H_2$ would be extremely unstable.

Trifluoroethylene (IV) did not react with fluorosulfuric acid or hydrogen fluoride in SO_2ClF solution at $-20°$. However, when IV was treated with SbF_5-HF (1/4 M/M) in SO_2ClF at $-78°$, the resulting solution showed that CF_3CH_2F was formed as the only product. IV also reacted smoothly with SbF_5–HSO_3F (1/4 M/M) -SO_2ClF or SO_2 at $-78°$. The pmr spectrum of the solution at $-80°$ showed a doublet of triplets at δ 4.96 (J_{HF} = 45.0 and 8.5 Hz). The ^{19}F nmr spectrum showed a high-field triplet of triplets at ϕ 239.6 (1 F, J_{HF} = 45.0, J_{FF} = 16.5 Hz), a sextet at ϕ 83.6 (2 F, J_{HF} = 8.5, J_{FF} = 16.5 and 9.0 Hz), and a deshielded triplet at ϕ -47.1 (1 F, J_{FF} = 9.0 Hz). These data are only consistent with $CH_2FCF_2OSO_2F$. 1,1,2-Trifluoroethyl fluorosulfate is not stable at higher temperature and cleaves at $-50°$ to give CH_2FCF_3, which can be recovered from the distillate in high yield as the condensed gas. When IV was treated with SbF_5–HSO_3F (1/1 M/M) in SO_2ClF, only CH_2FCF_3 was found even at $-78°$.

CH_2FCF_3 is not ionized in SbF_5–SO_2ClF solution. This indicates that ions $CF_3\overset{+}{C}H_2$ and $CH_2F\overset{+}{C}F_2$ are unstable.

1-Chloro-2-fluoroethylene (V).—The behavior of V is similar to that of III in the super acid systems studied. CH_2ClCHF_2 was obtained when V was treated with SbF_5–HF (1/4 M/M) -SO_2ClF or SO_2. 1-Fluoro-2-chloroethyl fluorosulfonate, $CH_2ClCHFOSO_2F$, was obtained when V was treated with SbF_5–HSO_3F (1/4 M/M) -SO_2ClF or SO_2. The structure was confirmed by both pmr and ^{19}F nmr, respectively. As with III, V gave only CH_2ClCHF_2 when it was treated with SbF_4–HSO_3F (1/1 M/M) -SO_2ClF at $-78°$. V does not react with fluorosulfuric acid or hydrogen fluoride in SO_2ClF solution at $-20°$.

Highly pure CH_2ClCHF_2 could be obtained from the distillation of the V–SbF_5–HF (1/4 M/M) -SO_2ClF or V–SbF_5–HSO_3F (1/4 M/M) -SO_2ClF systems. A yet unidentified by-product was found in small amount when CH_2ClCHF_2 was allowed to stay in contact with SbF_5–SO_2ClF at $-80°$ for prolonged periods of time.

Trifluorochloroethylene (VI) reacted either with SbF_5–HF (1/1 M/M) -SO_2ClF or SbF_5–HSO_3F (1/4 M/M) -SO_2ClF at $-20°$ to give CF_3CHFCl exclusively. VI did not react either with HSO_3F–SO_2ClF or SbF_5–HF (1/4 M/M) -SO_2ClF. Similarly, **trifluorobromoethylene** (VII) reacted either with SbF_5–HF (1/1 M/M) -SO_2ClF or SbF_5–HSO_3F (1/1 M/M) -SO_2ClF at $-10°$ to give CF_3CHFBr exclusively. Again the pmr spectrum showed a doublet of quartets at δ 6.9 (1 H, J_{HF} = 47.0 and 5.0 Hz). The ^{19}F nmr spectrum of the same solution showed a one-fluorine doublet of quartets at ϕ 162.2 (J_{HF} = 47.0 Hz, J_{FF} = 13.5 Hz) and a three-fluorine doublet of doublets at ϕ 81.8 (J_{HF} = 5.0 Hz, J_{FF} = 13.5 Hz). VII did not react either with HSO_3F–SO_2ClF or SbF_5–HF (1/4 M/M) -SO_2ClF at $-15°$. However, it reacted very slowly with SbF_5–HSO_3F (1/4 M/M) -SO_2ClF at $-10°$ to yield CF_3CHFBr.

When **trifluoroiodoethylene** (VIII) was treated either with SbF_5–HSO_3F (1/4 M/M) -SO_2ClF or SbF_5–HF (1/4 M/M) -SO_2ClF at $-30°$ for 1 hr, the solution showed in its pmr spectrum a doublet of quartets at δ 7.31 (J_{HF} = 46.0 and 5.5 Hz). The ^{19}F nmr spectrum of the same solution revealed a doublet of quartets at ϕ 166.9 (1 F, J_{HF} = 46.0, J_{FF} = 16.5 Hz) and a doublet of doublets at ϕ 78.8 (3 F, J_{HF} = 5.5 Hz, J_{FF} = 16.5 Hz). Thus the product formed is CF_3CHFI.

Tetrafluoroethylene (IX) and hexafluoropropene (X) did not react either with SbF_5–HF (1/1 M/M) -SO_2ClF or SbF_5–HSO_3F (1/1 M/M) -SO_2ClF at $-5°$. The solution did not show any proton resonance except the acid proton peak. The ^{19}F nmr spectra showed fluorine signals corresponding only to the unreacted starting materials.

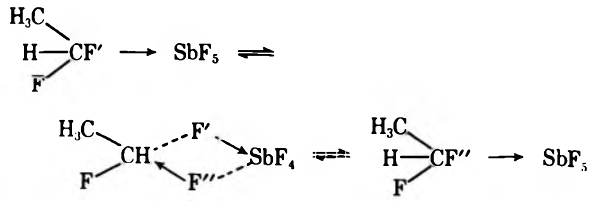
Discussion

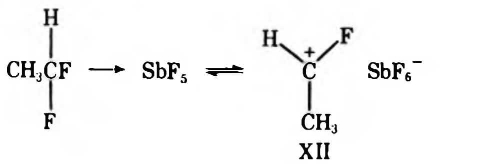
In all the investigated cases protonation of fluoro olefins in superacids did not give stable long-lived fluorocarbenium ions. However, results obtained indicate primary protonation according to the extended Markovnikov rule. Back-donation from the unshared fluorine electron pairs stabilizes the intermediate ions but they are still not sufficiently stable and are rapidly quenched by fluoride or fluorosulfate ions from the solvent systems. The ease of protolytic attack on the fluoro olefins was found to decrease with increasing fluorine substitution.

I and II showed similar chemical behavior toward the super acid systems at low temperature. Both I and II reacted with HF or HSO_3F in the presence of SbF_5 in SO_2ClF to give the HF or HSO_3F addition products. This indicates that electrophilic attack does occur and intermediate fluorocarbenium ions are formed. However, $CH_3\overset{+}{C}HF$ and $CH_3\overset{+}{C}F_2$ are not stable even in the low nucleophilic system and react rapidly with the counterions to form the addition products. In fact, $CH_3\overset{+}{C}HF$ was never directly observed (by nmr spectroscopy) even when ionization of CH_3CHF_2 was attempted with SbF_5–SO_2ClF. The reason for the instability of $CH_3\overset{+}{C}HF$ is that the monofluorocarbenium ion would be stabilized by only one fluorine atom (*via* back-donation of the lone-pair electrons to the electron-deficient carbon).[4] The pmr spectrum of CH_3CHF_2–SbF_5–SO_2ClF solution ($-80°$) displays a doublet at δ 4.32 (3 H, J_{HH} = 1.8 Hz) and a quartet at δ 10.47 (1 H, J_{HH} = 1.8 Hz), indicating that the carbenium ion $CH_3\overset{+}{C}HF$ exchanges fluorine with the solvent system (SbF_5–SO_2ClF). The possible mechanisms by which fluorine can be exchanged intramolecularly should be similar to those of methyl fluoride–antimony pentafluoride complex[5] and are shown by eq 1 and 2. Equation 1 represents a SNi process in which the transition state XI of the intramolecular nucleophilic displacement is shown by the substitution of F′ by F″. The second process for fluorine exchange is formation of an intermediate intimate ion-pair complex XII (eq 2) in very low concentration, in rapid equilibrium with $CH_3CHF_2 \rightarrow SbF_5$ and its subsequent collapse allowing front-side exchange (analogous to SN1 substitution). The two mechanisms represent limiting cases and any

(4) One of the referees questioned that it is difficult to understand that ion $CH_3\overset{+}{C}HF$ is less stable than ion $CH_3\overset{+}{C}F_2$. We have separately studied the carbon-13 nmr of halocarbenium ion and found that halogen back-donation is related to the stability of halocarbenium ions. See G. A. Olah, Y. K. Mo, and Y. Halpern, *J. Amer. Chem. Soc.*, in press. Thus, direct experimental evidence was obtained to substantiate observed differing stabilities.

(5) G. A. Olah, J. R. DeMember, R. H. Schlosberg, and Y. Halpern, *J. Amer. Chem. Soc.*, **91**, 2113 (1969); **94**, 156 (1972).


(1)
XI

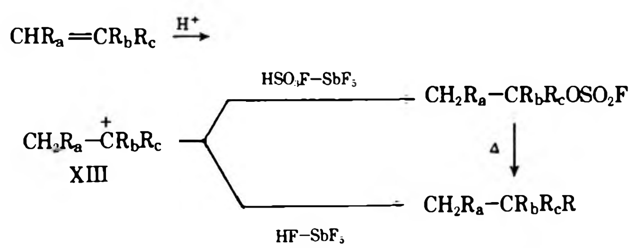

(2)
XII

degree of intermediate character between XI and XII should be possible.

The increase in shielding of the resonance and of coupling constants when either HF or CH_3CHF_2 was added to the solution indicates that a change of the nature of the transition state is possible. It is also possible that intermolecular fluorine exchange may occur. The roles of HF and CH_3CHF_2 in this exchange reaction will be fully discussed elsewhere.[6]

In the 1,1,1-trifluoroethane–SbF_5–SO_2ClF system, the first direct observation of an alkyldifluorocarbenium ion, *i.e.*, that of the methyldifluorocarbenium ion, was accomplished by nmr spectroscopy. The fluorine chemical shift of $CH_3\overset{+}{C}F_2$ (ϕ -96.4) is 87.9 ppm more shielded than that of $(CH_3)_2\overset{+}{C}F$, indicating that back-donation of fluorine lone-pair electrons is twice as much in $(CH_3)_2\overset{+}{C}F$.[7] Pmr spectra of the ion also agree with this observation, since the methyl resonance of $CH_3\overset{+}{C}F_2$ is only 0.31 ppm deshielded from the methyl resonance of $(CH_3)_2\overset{+}{C}F$.

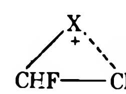
Fluoro olefins III, IV, and V reacted with superacids in a similar fashion. Protonation occurred only when the reactions were carried out in the presence of high concentration of SbF_5 in HF–SO_2ClF or HSO_3F–SO_2ClF (*i.e.*, in the stronger super acids). The π bonds in III, IV, and V are inductively deactivated by the increasing number of fluorine atoms; therefore protonation takes place only in the strongest acid systems. Furthermore, the carbenium ions (XIII) formed by protonation in super acids are destabilized by the fluorine or chlorine atom (R_a) adjacent to electron-deficient carbon. In fact, XIII was never observed as a stable long-lived



cation either upon protonation of fluoro olefins III, IV, and V or upon ionization of CH_2FCHF_2, CH_2FCF_3, and CH_2ClCHF_2 by SbF_5–SO_2ClF, even at $-20°$. The intermediate formed ions were rapidly quenched by the fluoride (fluorosulfonate) ion from the solution, leading to the Markovnikov addition products. However, the fluorosulfates (XIII–OSO_2F) were not stable at higher temperature, since $-OSO_2F$ is a good leaving group and exchanges readily to give the corresponding thermodynamically more stable fluorides (XIII–F).

The trifluorohaloethylenes (VI, VII, and VIII) when treated either with SbF_5–HF–SO_2ClF or SbF_5–HSO_3F–SO_2ClF gave similar HF addition products, $CHFXCF_3$ (X = Cl, Br, and I). As the reactions occurred only at higher temperature (from -30 to $-15°$), no fluorosulfate addition products ($CHFXCF_2OSO_2F$) were observed when the reaction was carried out in SbF_5–HSO_3F–SO_2ClF. This behavior is again caused by the substantial deactivation of the π bond by the four halogen atoms and the extreme instability of the corresponding carbenium ions, $CHFX\overset{+}{C}F_2$. In systems containing FSO_3H, fluorosulfates, $CHFXCF_2OSO_2F$ may be formed in the first step, but readily cleave to the corresponding fluorides.

The three trifluorohaloethylenes studied showed similar reactivity toward the superacid systems. Protolytic attack takes place again according to the extended Markovnikov's rule forming the more stable carbenium ion ($CHFX\overset{+}{C}F_2$), as the halogen atoms (Cl, Br, and I) can also stabilize the carbenium ion by neighboring group participation.[8] The alternative car-



benium ion ($CHF_2\overset{+}{C}FX$) could not be stabilized in a similar way, as neighboring fluorine is unable to participate.

Neighboring halogen atom participation is important, as can be seen from the observed inertness of IX and X toward superacids. Although fluorine inductively has greater electron-withdrawing power than other halogens atoms, the π-electron donor system (*i.e.*, the basicity of the double bond) in $CF_2{=}CFX$ and $CF_2{=}CF_2$ or $CF_2{=}CFCF_3$ would be expected to be more or less the same. The difference in reactivity of $CF_2{=}CFX$ and IX or X indicates that neighboring halogens indeed play a significant role in influencing the protonation of fluoro olefins, through their ability to stabilize the carbenium ion intermediates.

Experimental Section

Materials.—All fluoro olefins used were commercially available in high purity from Peninsular Chemical Research Inc. Antimony pentafluoride (Allied Chemical Co.) was purified first by removing HF by refluxing while passing a stream of dry nitrogen through it and then distilling twice (bp 161–164°). Fluorosulfuric acid (Allied Chemical Co.) was also twice distilled after removing HF.

Nmr Spectra.—A Varian Associates Model A56/60A nmr spectrometer equipped with a variable-temperature probe was used for all spectra. Both ^{19}F and ^{1}H coupling constant are believed accurate to ± 0.1 Hz. Unless otherwise indicated, all proton chemical shifts (δ) are in SO_2ClF solvent from external (capillary) TMS. ^{19}F chemical shifts (ϕ) in SO_2ClF solvent are from external CCl_3F.

(6) G. A. Olah, Y. K. Mo, and Y. Halpern, *J. Amer. Chem. Soc.*, in press.

(7) G. A. Olah, R. D. Chambers, and M. B. Comisarow, *ibid.*, **89**, 1268 (1967).

(8) B. Capon, *Quart. Rev.* (*London*), **18**, 45 (1964).

General Procedure of Reaction of Fluoro Olefins with Superacids.—Superacid solutions were prepared by dissolving SbF_5-HSO_3F (1/1 mol/mol) in an equal volume of sulfuryl chlorofluoride (Allied Chemical Co.) and cooling to −78°. Fluoro olefins were then introduced into the above solution also at −78°. The acid was always in slight excess over the fluoro olefins. Covalent fluorides were ionized in a solution prepared of antimony pentafluoride in sulfuryl chlorofluoride (1/1.5 v/v) at −78°.

α-Fluoroethyl and α,α-difluoroethyl fluorosulfates were prepared by introducing I and II into neat fluorosulfuric acid at −78°, respectively, until the solutions were saturated. The pure fluorosulfates were obtained by vacuum distillation. Yields are generally high (90–95%) and the fluorosulfates have the following boiling points: $CH_3CHFOSO_2F$, bp 33° (35 mm); $CH_3F_2OSO_2F$, bp 25° (30 mm). Spectral properties (^1H and ^{19}F nmr) and analytical data are in accordance with structures.

Registry No.—I, 75-02-5; II, 75-38-7; III, 1691-13-0; IV, 359-11-5; V, 460-16-2; VI, 79-38-9; VII, 598-73-2; VIII, 359-37-5; IX, 116-14-3; X, 116-15-4; α-fluoroethyl fluorosulfate, 33515-40-1; α,α-difluoroethyl fluorosulfonate, 460-95-7.

Acknowledgment.—Support of our work by the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

The Mechanism of Benzophenone Reduction with the 2-Norbornyl Grignard Reagent

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The reduction of 0.5 equiv of benzophenone with a Grignard reagent from 2-*exo*-chloro-3-*exo*-deuterionorbornane is characterized by deuterium transfer. Carbonation of the unreacted Grignard reagent produces *endo*-norbornane-2-carboxylic acid. These results show that the benzophenone reduction occurs preferentially by a cis-exo eliminative transfer of D and MgCl.

In connection with our work on chiral Grignard reagents,[1-4] it was desirable to know more about the detailed mechanism of ketone reductions with some bicyclic Grignard reagents. A suitable system for a study of the type required appeared to be the reduction of benzophenone with a Grignard reagent from deuterium labeled 2-chloronorbornane.

Recent studies have revealed that the norbornyl Grignard reagent is a relatively slowly equilibrating mixture of epimers.[5-8] On the basis of nmr evidence, Krieghoff and Cowan[6] concluded that either *exo*- or *endo*-chloronorbornane gave an ethereal solution consisting, at equilibrium, of about a 54:46 mixture of endo–exo epimers of the Grignard reagent. Hill[5] similarly concluded that in THF norbornylmagnesium chloride was a 50:50 mixture of epimers. Jensen and Nakamaye[7] prepared norbornylmagnesium bromide in ether and using nmr found it to be a 59:41 mixture of endo–exo isomers. Carbonation of the equilibrium mixture gave a mixture of the epimeric acids, 56–60% the endo isomer. When the equilibrated Grignard reagent was allowed to react with 0.5 equiv of benzophenone at 0°, the nmr signal due to the exo isomer disappeared and the benzophenone was converted to the bromomagnesium salt of benzhydrol. Rapid carbonation of the unreacted Grignard reagent gave almost exclusively *endo*-2-norbornanecarboxylic acid. It was observed that the *endo*-norbornylmagnesium bromide remaining after reaction with benzophenone reequilibrated to the original equilibrium composition if allowed to stand for 1 day at room temperature. These workers also examined the Grignard reagent from norbornyl chloride and found it to be a 57:43 mixture of endo–exo isomers; the behavior toward benzophenone paralleled that of the Grignard reagent from norbornyl bromide.

Davies and Roberts[8] confirmed the results of Jensen and Nakamaye and found that *endo*-norbornylmagnesium bromide did not reequilibrate at 0° over a 3-hr period; at −78° the reagent was still about 95% the endo isomer after 5 days. They also observed that the reduction of benzophenone with equilibrated reagent did not take place at −15°, although an intense red-brown color (presumably due to a Grignard reagent–ketone complex) was produced at this temperature.

The experiments of Jensen and Nakamaye make it clear that the *exo*-norbornyl Grignard reagent reduces benzophenone much more rapidly than the endo isomer. These experiments do not, however, allow one to completely define the stereochemistry of the reduction process. We wanted to know the stereoselectivity associated with the transfer of hydrogen from C-3 of the Grignard reagent. In other words, does the reduction of benzophenone involve transfer of the exo magnesium and the exo hydrogen, the exo magnesium and the endo hydrogen, or a combination of these alternatives? The following experiments led to an answer to this question.

Addition of gaseous DCl to a pentane solution of norbornene[9] at −78° gave 2-*exo*-chloronorbornane in 81% yield. The amount, location, and orientation of deuterium in the chloride had to be rigorously determined (see below). Stille and coworkers treated 2,3-dideuterionorbornene with HCl in pentane at −78° and obtained approximately a 50:50 mixture of *endo*-

(1) J. D. Morrison and R. W. Ridgway, *J. Amer. Chem. Soc.*, **91**, 4601 (1969).

(2) J. D. Morrison, D. L. Black, and R. W. Ridgway, *Tetrahedron Lett.*, 985 (1968).

(3) (a) J. D. Morrison A. Tomash, and R. W. Ridgway, *ibid.*, 565 (1969); (b) J. D. Morrison and R. W. Ridgway, *ibid.*, 569 (1969).

(4) For a review of asymmetric reduction using chiral Grignard reagents, see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, Chapter 5.

(5) E. A. Hill, *J. Org. Chem.*, **31**, 20 (1966).

(6) N. G. Krieghoff and D. O. Cowan, *J. Amer. Chem. Soc.*, **88**, 1322 (1966).

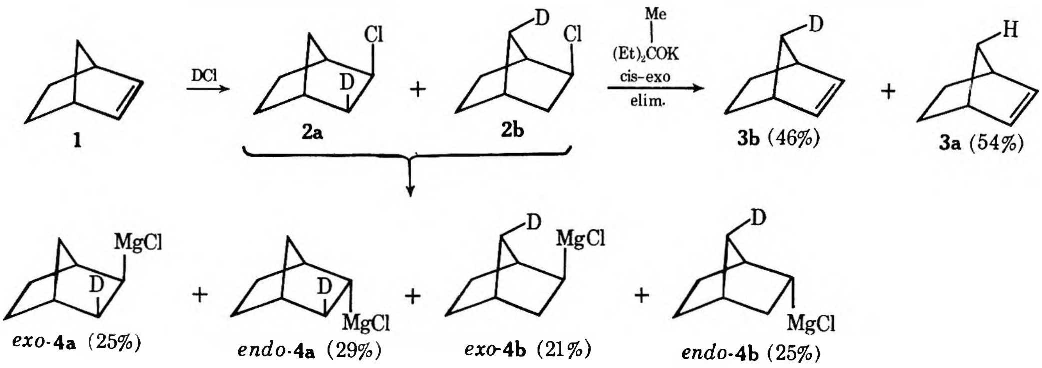
(7) (a) F. R. Jensen and K. L. Nakamaye, *ibid.*, **88**, 3437 (1966); (b) K. L. Nakamaye, Ph.D. Thesis, University of California, Berkeley, 1967.

(8) A. G. Davies and B. P. Roberts, *J. Chem. Soc. B*, 317 (1969).

(9) L Schmerling, *J. Amer. Chem. Soc.*, **68**, 195 (1946).

SCHEME I

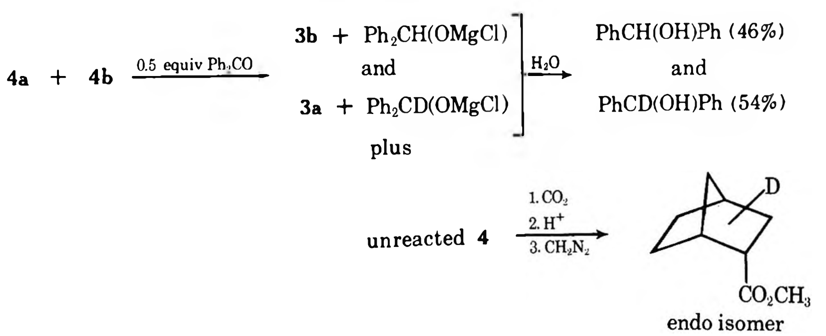
COMPOSITION OF THE GRIGNARD REAGENT FROM MONODEUTERIO-*exo*-NORBORNYL CHLORIDE[a]



[a] The approximate percentage of each isomer is calculated on the assumption that the chloromagnesium exo-endo ratio is the same (47:53)[6,7] for both the 3-exo and 7-syn deuterated isomers.

SCHEME II

REACTION OF THE GRIGNARD REAGENT 4 WITH 0.5 EQUIV OF BENZOPHENONE FOLLOWED BY CARBONATION OF THE UNREACTED 4



2,3-dideuterio-2-*exo*-chloronorbornane and 2-*exo*-chloronorbornanes with scrambled deuterium; the distribution of deuterium in the latter was not determined.[10] From a similar reaction in chloroform at $-78°$, Brown and McIvor[11] obtained norbornyl chloride which was, on the basis of a 220-MHz nmr analysis, about 55% 2-*exo*-chloro-3-*exo*-deuterionorbornane (**2a**) and 45% 2-*exo*-chloro-7-*syn*-deuterionorbornane (**2b**). It was concluded that there was less than 2%, if any, of a 5-deuterio isomer produced. Brown and Liu[12] reported that at $-78°$ in methylene chloride DCl addition to norbornene produced about 60% of **2a**, 34% of **2b**, and 6% of a 2-*exo*-chloro-5-*exo*-deuterio isomer.

Our *exo*-norbornyl chloride from DCl addition in pentane at $-78°$ contained one deuterium per molecule.[13] The amount of the 3-*exo*-deuterio isomer present was determined in the following way. Treatment of a sample of **2** with the potassium salt of 3-methyl-3-pentanol gave norbornene containing 46% of one deuterium per molecule (Scheme I). Since this elimination is known to proceed in a cis–exo manner,[10,12] 54% of one deuterium per molecule must have been present at the 3-exo position in the norbornyl chloride; *i.e.*, there was 54% deuterium and 46% hydrogen at the 3-exo position. A 220-MHz nmr spectrum of our chloride was virtually identical with that of the chloride prepared by Brown and McIvor,[11] a finding in excellent agreement with the conclusion from the above experiment and evidence that about 46% of the deuterium was at the 7-syn position in our *exo*-norbornyl chloride. For our purposes it is only important to know that about 54% of the deuterium is 3-exo, the exact distribution of the remainder is not critical, so long as none of it is 3-endo. The absence of 3-*endo*-deuterium was confirmed by the 220-MHz nmr spectrum.

Having established the composition of the chloride to be as shown in Scheme I,[14] the Grignard reagent was prepared and titrated to determine the exact amount present,[15] and then the equilibrated reagent was allowed to react with 0.5 equiv of benzophenone in ether at 0° (Scheme II). After the addition of the benzophenone (20 min) the reaction mixture was filtered, under nitrogen pressure, through a fritted glass filter into a flask cooled to $-78°$. The filtered solution was carbonated, thus converting the unreacted Grignard reagent to norbornane-2-carboxylic acid which was, in turn, converted to the methyl ester with diazomethane[16] (Scheme II). Glpc analysis of the methyl norbornane-2-carboxylate revealed the

(10) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *J. Amer. Chem. Soc.*, **88**, 4922 (1966).

(11) J. M. Brown and M. C. McIvor, *Chem. Commun.*, 238 (1969).

(12) H. C. Brown and K. Liu, *J. Amer. Chem. Soc.*, **89**, 3900 (1967).

(13) Deuterium analysis by Josef Nemeth, Urbana, Ill.; supported by mass spectrometric and 220-MHz nmr analysis. We thank Dr. Peter Kleinhomer for the nmr work.

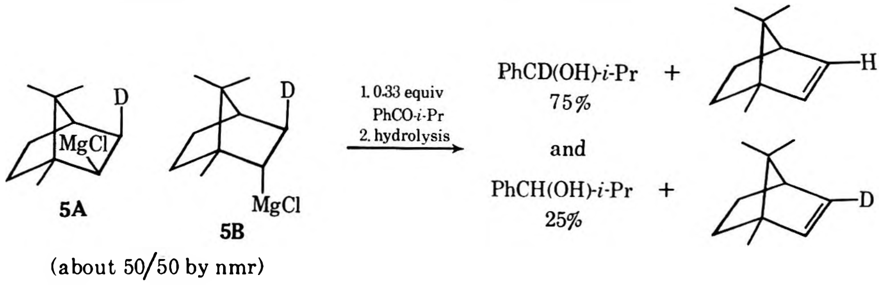
(14) In Scheme I only one enantiomer of each isomer is shown, but the *exo*-norbornyl chloride was, of course, racemic. The other enantiomer is omitted for clarity of illustration.

(15) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967). We have found that this method is much more accurate than acid-base titration.

(16) The carbonation and esterification sequences were carried out following the directions and observing the precautions of Nakamaye.[7b] Numerous control experiments confirmed the reliability of the method and the analytical procedure.

SCHEME III

REDUCTION OF ONE-THIRD EQUIVALENT OF PHENYL ISOPROPYL KETONE WITH THE ISOBORNYL (5a)/BORNYL (5b) GRIGNARD REAGENT[a]



[a] Reference 17.

presence of only the endo isomer. The precipitate from the Grignard reaction was hydrolyzed to yield benzhydrol. The benzhydrol contained 54% of one deuterium per molecule.

These experiments indicate that when an equilibrated Grignard reagent from norbornyl chloride is allowed to react with 0.5 equiv of benzophenone, reduction of the benzophenone occurs, in a formal sense, *via* a cis–exo eliminative transfer of H and MgCl. Within the limits of experimental error this is the exclusive mode of reduction under the conditions of this experiment.

After this work was completed it was reported[17] that the Grignard reagent (**5**) from α-*exo*-deuterioisobornyl chloride reduces phenyl isopropyl ketone with preferential transfer of deuterium. With **5** cis–exo eliminative transfer of "DMgCl" was judged to be preferred over cis–endo transfer of "MHgCl" by a factor of 3:1 (Scheme III). In the present work with the norbornyl system no cis–endo transfer was observed. Less preference for a cis–exo reduction mode in the isobornyl–bornyl Grignard system is probably a reflection of the influence of *gem*-dimethyl substitution in the C-7 bridge which reduces the energy difference between exo and endo transfer. In the absence of this influence there is, within the limit of detection, exclusive eliminative transfer of "DMgCl" from the exo direction when the exo and endo reagents (**4a**) compete for a limited amount of benzophenone. With the available information, however, one cannot exclude the possibility that the structure of the ketone is also a factor in determining the stereoselectivity of the eliminative transfer process.

Experimental Section

Deuterio-*exo*-norbornyl Chloride (2a + 2b).—Deuterium chloride, generated by the dropwise addition of phosphorus trichloride (9.15 g, 0.67 mol, distilled before use) to deuterium oxide (40 g, 2.0 mol, 99.8% deuterated), was passed into a well-stirred solution of norbornene (70.6 g, 0.75 mol) in pentane (250 ml, purified by percolation through a silica gel column) at −78°. After all the phosphorus chloride had been added to the D_2O, the mixture was heated until DCl was no longer evolved.

The reaction mixture was allowed to come to room temperature overnight. It was then washed with 0.1 *M* sodium bicarbonate solution (until neutral to litmus) and two 50-ml portions of water before drying ($MgSO_4$). The pentane solution was then filtered, combined with a pentane wash of the magnesium sulfate, and concentrated by distillation at atmospheric pressure. The residual oil was distilled through a Vigreux column and gave **2** as a colorless liquid, bp 49° (12 mm), 80 g (81% yield). Observed in the infrared spectrum of this liquid were characteristic norbornyl C–H stretching absorptions at 2865 and 2960 cm^{-1} and a C–D stretching absorption at 2180 cm^{-1}. The purity of the sample was established by glpc analysis on a 3-ft Pyrex column of 20% Carbowax 20M on Chromosorb W (acid washed) at 125° and 7 psi (retention time, 1.9 min). The sample was analyzed for deuterium content by mass spectrometric, 220-MHz nmr and falling drop methods,[13] which indicated 1 deuterium per molecule. The 220-MHz nmr spectrum was virtually identical with that reported by Brown and McIvor.[11]

Preparation of the Grignard Reagent (4) from Monodeuterated *exo*-2-Chloronorbornane.—Magnesium (2.4 g, 0.1 mol) was placed into a dry, 250-ml round-bottomed, three-necked flask equipped with dry condenser and magnetic stirrer. The flask was then flamed under dry nitrogen and allowed to cool. Dry ether (30 ml) and monodeuterated *exo*-2-chloronorbornane (about 30% of the total amount; *i.e.*, 30% of 13.1 g, 0.1 mol) were placed in the flask and allowed to stand undisturbed for 0.75 hr after which time a cloudiness appeared. The mixture was then stirred, and the reaction began. The remainder of the chloride, as the neat liquid, was added dropwise to the reaction mixture. Once the reaction ceased, dry ether (40 ml) was added to the mixture, and the reagent was refluxed under nitrogen for 2 hr. The solution was then pumped through a fritted glass filter into a dry, 250-ml, round-bottomed, three-necked flask filled with nitrogen. Titration of an aliquot of the filtered reagent with 1 *M* 2-butanol in xylene[15] indicated that the Grignard reagent had been produced in 96% yield.

Reaction of Benzophenone with the Grignard Reagent (4) from Monodeuterated *exo*-2-Chloronorbornane.—The flask containing the Grignard reagent was equipped with a dry condenser and a magnetic stirrer. Benzophenone (8 g, 0.044 mol) dissolved in sodium-dried ether (40-ml) was added to the flask containing the filtered Grignard reagent cooled to 0°. The reaction was characterized by the immediate appearance of a red color which faded as a white precipitate formed. After the addition of benzophenone (20 min), the reaction mixture was filtered through a fritted glass filter into a dry, 500-ml, round-bottomed, three-necked flask filled with nitrogen and cooled to −78°. An ether wash of the solid remaining behind was also pumped into the flask.

The solid diphenylmethoxymagnesium chloride on the fritted glass filter was hydrolyzed with saturated ammonium chloride solution. The resulting mixture was extracted several times with ether, and the combined extracts were dried ($MgSO_4$). The ether solution was filtered, combined with an ether wash of the magnesium sulfate, and concentrated by distillation at atmospheric pressure. A white solid (4.05 g) melting at 65–66° crystallized from a solution of the residual oil in petroleum ether (lit.[18] for benzhydrol, 69°).

A C–D stretching absorption at 2240 cm^{-1} and an OH absorption were observed in the infrared spectrum of the solid (Nujol and halocarbon mulls). Glpc analysis of an ether solution of the solid indicated the presence of a small amount of benzophenone. Deuterium content of the benzhydrol as determined by mass spectral analysis was 0.54 deuterium atom per molecule, the same as that determined by nmr using the phenyl protons as an internal integration reference. Comparison of the nmr spec-

(17) J. F. Fauvarque, *C. R. Acad. Sci., Ser. C*, 1053 (1971).

(18) "Heilbron's Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p 1286.

tra of benzophenone and benzhydrol showed that the aromatic protons of the former absorb further downfield than those of the latter, so that the presence of a small amount of benzophenone in the sample would not interfere with the deuterium analysis.

Carbonation of the Remaining Grignard Reagent.—The carbonation was begun 20 min after the reaction of the Grignard reagent with 0.5 equiv of benzophenone. Crushed Dry Ice contained in a 250-ml erlenmeyer flask was slowly added through Gooch tubing to the unconsumed Grignard reagent contained in a round-bottomed flask equipped with condenser and mechanical stirrer. Once all the Dry Ice had been added, the reaction mixture was allowed to attain room temperature overnight.

The mixture was then treated with 6 *N* hydrochloric acid until two clear layers separated. The aqueous layer was extracted several times with ether, and the extracts were combined with the organic layer. The yield of norbornyl acid was 62% of the theoretical amount as determined by titration of an aliquot of the ethereal solution in 65% methanol with standard sodium hydroxide solution to a phenolphthalein end point. The solution of norbornyl acid was then extracted with three 50-ml portions of 2 *N* sodium hydroxide solution and one 50-ml portion of water. The combined base extracts were held for the methylation step.

Reaction of Norbornyl Acid with Diazomethane.—Diazomethane was prepared from Diazald (21.5 g, 0.1 mol).[19]

Just prior to the reaction with diazomethane, the norbornyl acid was liberated from the sodium salt by acidification and extraction with ether. Esterification was accomplished by the dropwise addition of the dried norbornyl acid solution to diazomethane at 0°. The mixture was allowed to stand until nitrogen was no longer evolved and was then treated with 3 *M* sulfuric acid until the disappearance of the yellow color. The two layers were separated, and the aqueous layer was extracted several times with ether. The extracts were combined with the organic layer, washed with two 50-ml portions of 0.05 *M* sodium carbonate solution, and then dried ($MgSO_4$). The ethereal solution was then filtered, combined with an ether wash of the magnesium sulfate, and concentrated by distillation at atmospheric pressure. Analysis of the residual oil by glpc gave one peak, with a retention time of 9.5 min. Glpc analysis was carried out using a 6 ft × 0.25 in., 15% Apiezon L on Chromosorb W-HP, 80–100 mesh column coupled to a 6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W-HP, 80–100 mesh column, 210°, 120 ml/min He flow rate. An authentic sample of the methyl ester of *endo*-norbornane-2-carboxylic acid gave one peak with the same retention time, whereas a mixture of the endo and exo isomers gave a second peak at 12.0 min. Analysis of the oil was repeated using a 10 ft × 0.25 in. column of 25% castorwax on 60–80 Chromosorb P at 120° and 60 ml/min. One peak was observed at 73 min, the retention time of the endo isomer under these conditions.

(19) Th. J. de Boer and H. J. Backer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 943.

Dehydrohalogenation of Monodeuterated *exo*-2-Chloronorbornane.—Potassium (3 g, 0.075 mol) was slowly introduced under nitrogen into a dry flask containing 3-methyl-3-pentanol (51 g, 0.5 mol) and equipped with condenser and magnetic stirrer. As the concentration of potassium alkoxide increased, the solution acquired a reddish-brown hue, and the reaction became less vigorous. Completion of reaction was effected by heating.

Monodeuterated *exo*-2-chloronorbornane (6.6 g, 0.05 mol) was added all at once to the solution of potassium alkoxide, and the mixture was refluxed under nitrogen for 1 hr. Refluxing was then continued for a total of 17 hr while sweeping continuously with nitrogen. The norbornene (0.6 g) which formed was scraped from the inner surface of the condenser and from the tube leading into a trap cooled with a Dry Ice–isopropyl alcohol mixture.

Glpc analysis of an ether solution of the collected norbornene indicated the presence of less than 1% 3-methyl-3-pentanol. The sample was analyzed for deuterium content by low voltage mass spectroscopy, 0.46 deuterium atoms per molecule.

Registry No.—**2a**, 33495-71-5; **2b**, 33495-72-6; *exo*-**4a**, 33495-73-7; *endo*-**4a**, 33495-74-8; *exo*-**4b**, 33495-75-9; *endo*-**4b**, 33495-76-0; benzophenone, 119-61-9.

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The Nucleophilic Reactivity of Peroxy Anions[1]

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We report rate data on the reactivity of several peroxy anions with the anions of bromoacetic acid, α-bromo-*p*-toluic acid, *p*-cyanobenzoic acid, *p*-nitrophenylsulfuric acid, and with *p*-nitrophenylacetate and 2,4-dinitrochlorobenzene. The magnitude of the α effect, as measured by the ratio log (k_{HOO^-}/k_{HO^-}), appears to be linearly correlated with the magnitude of the product $|\alpha\beta|$ of the coefficients of the Edwards equation (the oxibase scale): $\log k/k_0 = \alpha E_n + \beta H$.

Edwards and Pearson[3] recognized a class of nucleophiles which showed exceptionally high reactivity toward a variety of substrates relative to their basicity toward hydrogen. This class is structurally characterized by an unshared pair of electrons on the atom adjacent or α to the nucleophilic atom. This rate enhancement is known as the α effect. Both uncharged nucleophiles such as hydrazine and hydroxylamine as well as anionic nucleophiles such as the peroxy anions exhibit this effect but to varying degrees toward various substrates. There have been a number of recent discussions of the α effect.[4] In this study, we have examined the reactivity of the anions of hydrogen peroxide, methyl hydroperoxide, *tert*-butyl hydroperoxide, and several peroxycarboxylic acids toward several substrates with a view toward defining more precisely the factors influencing the magnitude of the α effect.

(1) Presented in part at the 156th National Meeting of the American Chemical Society, Sept 1968, ORGN 70.

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Table I

Reactions of Nucleophiles with α-Bromo-p-toluic Acid at 25°[a]

Nucleophile	pK_a'	pH range	Nucleophile concn, M	Substrate concn, M	k_2, M^{-1} min^{-1}
p-Methoxyperoxybenzoic acid	7.8	9.04–9.36[b]	$3.5–6.5 \times 10^{-3}$	4.9×10^{-4}	3.8 ± 0.1
m-Chloroperoxybenzoic acid	7.4	9.04–9.36[b]	$3.05–6.05 \times 10^{-3}$	4.9×10^{-4}	4.0 ± 0.3
p-Nitroperoxybenzoic acid	7.1	9.04–9.36[b]	$2.47–4.26 \times 10^{-3}$	4.9×10^{-4}	4.0 ± 0.3
Peroxyacetic acid	8.2	9.95[b]	$5.6–11.4 \times 10^{-3}$	5×10^{-4}	1.5 ± 0.1
HOO^-	11.37	10.98–11.42[c]	$3.13–6.05 \times 10^{-2}$	$9.4–10.7 \times 10^{-4}$	2.1 ± 0.2[d]
$MeOO^-$	11.08	11.07–11.36[c]	$4.7–6.7 \times 10^{-2}$	$9.6–9.9 \times 10^{-4}$	1.8 ± 0.1
tert-$BuOO^-$	12.46	11.78–12.14[c]	$8.85–9.17 \times 10^{-2}$	1.02×10^{-3}	1.5 ± 0.2
HO^-	15.74	12.66–13.43[c]		1.1×10^{-3}	0.16 ± 0.01[e]
H_2O	−1.74		55.5	1.1×10^{-3}	4.3×10^{-6}

[a] EDTA (2×10^{-4} M) was present in all runs. The ionic strength was made up to 1.0 with KCl or $NaClO_4$. [b] Carbonate buffer. The blank correction, due largely to the buffer, was in the range 25–30%. [c] pH adjusted with NaOH. [d] Activation parameters for the temperature range 10–30°: $\Delta H^\ddagger = 15$ kcal mol^{-1}; $\Delta S^\ddagger = -15$ cal mol^{-1} deg^{-1}. [e] Activation parameters for the temperature range 15–40°: $\Delta H^\ddagger = 18$ kcal mol^{-1}; $\Delta S^\ddagger = -9$ cal mol^{-1} deg^{-1}.

Table II

The Reaction of Nucleophiles with Bromoacetic Acid at 40°[a]

Nucleophile	pK_a'	pH range	Nucleophile range, M	10^2k_2, M^{-1} min^{-1}
HO^-	15.27		0.1–0.3	2.2 ± 0.05
HOO^-	11.18	12.5–12.6[b]	$1–4 \times 10^{-2}$	28 ± 0.3
tert-$BuOO^-$	12.22	12.6[b]	$5–20 \times 10^{-3}$	10 ± 0.2
m-Chloroperoxybenzoic acid	7.6	10.3–10.5[c]	$1.5–4 \times 10^{-2}$	6.7 ± 0.05
$CH_3CO_3^-$	8.2	10.5[c]	$2–3.2 \times 10^{-2}$	9.1 ± 0.1

[a] EDTA (2×10^{-4} M) was present in all runs. The ionic strength was made up to 0.55 with KNO_3. Substrate was 5×10^{-4} M. [b] pH adjusted with NaOH. [c] Carbonate buffer. The blank correction was in the range of 1%.

Results and Discussion

Saturated Carbon.—Our results for displacement at tetrahedral carbon are given in Tables I and II. We have used two substrates, α-bromo-p-toluic acid and bromoacetic acid, and find for both that the ratio k_{HOO^-}/k_{HO^-} in water is about 13. This ratio is to be compared with the value of 35 for the reaction with benzyl bromide in 50% acetone–water as solvent.[5] Tables I and II show that the relative rate with which the aromatic and aliphatic peroxycarboxylic acid anions attack the substrate is dependent upon the substrate; the anion of peroxyacetic acid is more reactive than the anion of m-chloroperoxybenzoic acid when the substrate is bromoacetic acid, whereas this relative rate is reversed for the aromatic substrate, α-bromo-p-toluic acid. We attribute this phenomenon to an interaction of the aromatic rings (ref 4h, p 415). The order of reactivity for bromoacetic acid follows the basicity order with the exception of tert-butyl hydroperoxide. tert-Butyl hydroperoxide is generally less reactive than expected for its basicity and this can be reasonably attributed to steric factors. A significant exception in the literature is in the reaction with tetranitromethane, but in this case Sager and Hoffsommer[6] have demonstrated that the attack is at the outer oxygen atom where steric effects are minimized. The Brønsted slope for a reaction of this type is small.[4e] In fact, the rate constants for the three substituted peroxybenzoic acids with α-bromo-p-toluic acid are essentially identical although their acidities vary by about a factor of five.

Carbonyl Carbon.—Table III gives our results for the reaction with p-nitrophenylacetate. This substrate was chosen for a comparative study of the reaction of peroxyanions with carbonyl carbon because of the extensive previous work on this compound.[7] Our data coincide reasonably well with the literature data when allowance is made for the differences in the pK_a values used.

Tetrahedral Sulfur.—Table IV presents our data for p-nitrophenyl sulfate. Benkovic and Benkovic[8] find $k_{HO^-} = 3 \times 10^{-6}$ and $k_{H_2O} = 2.7 \times 10^{-9}$ M^{-1} min^{-1} at 35°. The very large value for k_{HOO^-}/k_{HO^-} compared with k_{MeOO^-}/k_{HO^-} is notable in view of the relatively small value of the Brønsted slope (0.2).[8] We feel that this is attributable either to a relatively large contribution to stabilization of the transition state by hydrogen bonding in the case of the anion of hydrogen peroxide, or, as has been argued for attack at tetrahedral phosphorus,[9] due to an increased dependence on steric factors relative to carbonyl carbon.

Nitrile Carbon.—We have reported recently[10] a study of the kinetics of the reaction of hydrogen peroxide with the nitrile, p-cyanobenzoic acid, together with labeling experiments using $H^{18}O^{18}OH$. We report here values for k_{HOO^-}/k_{HO^-} of 900–1200 depending on temperature (Table V). Wiberg's value[11] for this ratio varies from about 20,000 to 66,000, depending on the nitrile used. The value of 66,000 has been widely quoted as an extreme example of the α effect. We can compare our data for p-cyanobenzoic acid in water with Wiberg's data for benzonitrile in 50% aqueous acetone, since the σ constant for p-COO^-

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TABLE III

REACTIONS OF NUCLEOPHILES WITH p-NITROPHENYLACETATE[a]

Nucleophile	Temp, °C	$10^{-3}k_2$, M^{-1} min^{-1}
HOO^- [b]	25	68 ± 3[c]
HOO^-	30	75 ± 3
HOO^-	35	93.5 ± 3
HOO^-	40	107.5 ± 5
HOO^-	45	115 ± 2
CH_3OO^- [d]	25	19 ± 0.6[e]
CH_3OO^-	44.5	50 ± 4
$(CH_3)_3COO^-$ [f]	25	4.6 ± 0.2[g]
$(CH_3)_3COO^-$	35	6.8 ± 0.5
$(CH_3)_3COO^-$	45	8.9 ± 0.5
MCPB[h]	8	1.7 ± 0.05[i]
MCPB	15	2.6 ± 0.05
MCPB	20	3.5 ± 0.05
HO^- [j]	20	0.715 ± 0.02[k]
HO^-	25	0.88 ± 0.04
HO^-	32	1.26 ± 0.15
HO^-	40	1.79 ± 0.2

[a] EDTA (1×10^{-3} M) was present in all cases. The ionic strength was made up to 1.0 with KCl. Runs in the vicinity of pH 7 were conducted in phosphate buffer. We find k_2 for HPO_4^{2-} at 25° = 1×10^{-2} M^{-1} min^{-1}. Runs in the vicinity of pH 9.5 were conducted in carbonate buffer. See footnote j. [b] The nucleophile concentration range was 5×10^{-3} to 1.7×10^{-2} M (uncorrected for the fraction ionized). Substrate concentration was 1×10^{-3} M. The pH range was 6.7–7.0. [c] $\Delta H^{\ddagger}$ = 5 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -28 cal mol^{-1} deg^{-1}. [d] The nucleophile concentration range was 1.6×10^{-2} to 7.0×10^{-2} M (uncorrected for the fraction ionized). Substrate concentration was 1×10^{-3} M. The pH range was 6.3–7.0. [e] $\Delta H^{\ddagger}$ = 8.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -20 cal mol^{-1} deg^{-1}. [f] The nucleophile concentration range was 1.5×10^{-2} to 7.0×10^{-2} M (uncorrected for the fraction ionized). Substrate concentration was 1×10^{-3} M. The pH range was 7.3–7.8. [g] $\Delta H^{\ddagger}$ = 6 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -31 cal mol^{-1} deg^{-1}. [h] MCPB is m-chloroperoxybenzoic acid. The nucleophile concentration range was 8×10^{-5} to 1.6×10^{-4} M. Substrate concentration was 2 to 2.5×10^{-5} M. The pH range was 9.4–9.5. [i] $\Delta H^{\ddagger}$ = 9 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -17 cal mol^{-1} deg^{-1}. [j] Runs were made at constant pH values (9.4–9.7) for each temperature at five carbonate buffer concentrations (0.266, 0.20, 0.133, 0.067, and 0.033 M). Extrapolation to [B] = 0 gave k_{HO^-} for that temperature. $k_{CO_3^{2-}}$ values follow: 20°, 0.514; 25°, 0.81; 32°, 1.5; 40°, 2.75 (M^{-1} min^{-1}). Substrate concentration was 1×10^{-4} M. [k] $\Delta H^{\ddagger}$ = 8 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -26 cal mol^{-1} deg^{-1}. Tommila and Hinshelwood[7b] give $\Delta H^{\ddagger}$ = 10 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -19.5 cal mol^{-1} deg^{-1} for the reaction in 60% aqueous acetone.

is close to zero.[12] The data of Table V show that the difference between Wiberg's ratio and ours at 50° arises approximately equally from differences in k_{HO^-} and in k_{HOO^-}. Our value for k_{HO^-} is larger than Wiberg's by a factor of 6.7, while our value for k_{HOO^-} is smaller by a factor of 10.7. These differences may arise from at least three factors: solvent effects on SN2 displacement reactions may be large;[13] methods for calculating the necessary pK_a' values were different; there is a possible complication in 50% acetone from the formation of species such as 2,2-bis(hydroperoxy)propane.[14]

Aromatic Carbon.—Bigi and Pietra[15] report only a small α effect for the reaction of methoxylamine and of hydrazine[16] with 2,4-dinitrochlorobenzene. In view of the distinction between anionic and nonanionic α nucleophiles pointed out by Aubort and Hudson,[4b] we have examined the reaction of the anion of hydrogen

(12) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(13) A. J. Parker, *Advan. Phys. Org. Chem.*, **5**, 173 (1967).
(14) J. Hine and R. W. Redding, *J. Org. Chem.*, **35**, 2769 (1970).
(15) G. Bigi and F. Pietra, *J. Chem. Soc. B*, 44 (1971).
(16) J. F. Bunnett and G. T. Davis, *J. Amer. Chem., Soc.*, **80**, 4337 (1958).

TABLE IV

REACTIONS OF NUCLEOPHILES WITH p-NITROPHENYL SULFATE AT 50°[a]

Nucleophile	10^5k_2, M^{-1} min^{-1}
HOO^- [b]	200 ± 20
CH_3OO^- [c]	65 ± 5
$(CH_3)_3COO^-$ [d]	52 ± 2
HO^- [e]	1.6 ± 0.2

[a] EDTA (1×10^{-3} M) was present in all runs. The ionic strength was made up to 1.0 with KCl. [b] Runs were made in 0.825 M NaOH containing 1×10^{-3} M substrate and from 6×10^{-2} to 1.2×10^{-1} M total hydrogen peroxide. [c] Runs were made in 0.838 M NaOH containing 8×10^{-4} to 3.2×10^{-3} M substrate and from 1.2×10^{-1} to 2.4×10^{-1} M methyl hydroperoxide. [d] Runs were made in 0.839 M NaOH containing 8×10^{-4} to 3.2×10^{-3} M substrate and 1.5×10^{-1} M $tert$-butylhydroperoxide. [e] NaOH concentration was varied from 0.25 to 1.04 M.

TABLE V

THE REACTION OF p-CYANOBENZOIC ACID WITH HOO^- AND HO^-

Nucleophile	Temp, °C	k_2, M^{-1} min^{-1}
HO^-	50	0.045[a]
HO^-	45	0.031
HO^-	35	0.013
HO^-	25	0.0055
HOO^-	60	75[b]
HOO^-	50	41
HOO^-	40	22.5
HOO^-	25	6.5

[a] Solutions were 6×10^{-5} M in nitrile and 0.01–1.0 M in NaOH. μ = 1.0. $\Delta H^{\ddagger}$ = 15 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -25 cal deg^{-1} mol^{-1}. [b] Runs with hydrogen peroxide were in phosphate buffer in the pH range 6.7–7.4, μ = 0.25. An increase in the ionic strength to 1.0 decreased the rate constant by about 10%. The runs at 25 and 40° were 5×10^{-3} M in H_2O_2, 5×10^{-2} M in nitrile, and 5×10^{-5} M in EDTA. The runs at 50 and 60° were 0.1 M in H_2O_2, 0.05 M in nitrile, and 1×10^{-3} M in EDTA. The error in the rate constants is of the order of 5%. We have reported[10] a rate constant of about 1 M^{-1} min^{-1} for the reaction at 25° at pH values of 10 and above. We think that under these conditions the second step in the process becomes rate limiting because of a reduction in the concentration of the un-ionized peroxycarboximidic acid. $\Delta H^{\ddagger}$ = 13 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -19 cal deg^{-1} mol^{-1}.

peroxide with this substrate. We find k_{HOO^-} = 40 M^{-1} min^{-1} under the following conditions: 25°, [substrate] = 5×10^{-5} M, [H_2O_2] = 4.9–5.4 $\times 10^{-3}$ M, [EDTA] = 5×10^{-5} M, [NaOH] = 0.05–0.138 M, in 60% dioxane as solvent. The reaction was followed spectrophotometrically at 406 mμ, where 2,4-dinitrophenol has an extinction coefficient of 12,300 in this solvent. Bunnett and Davis[16] report that k_{HO^-} at 25° in this solvent is 0.066 M^{-1}min^{-1}. We confirm this value. Our value for k_{HOO^-} is 20 M^{-1} min^{-1} after the statistical correction and the ratio k_{HOO^-}/k_{HO^-} is thus 300. This represents a large α effect on the basis of this ratio, although the displacement of the point for HOO^- from the line defined by a series of primary n-alkylamines[15] is not large.

pK_a' Values for the Hydroperoxides.—Table VI compares our pK_a' values with literature values, corrected in each case to 25° and an ionic strength of 1.0. Since the reported values differ by as much as 0.2 pK units, we may expect that rate constants based on these ionization constants to differ by as much as a factor of 1.6.

Polarizability.—Ingold[4i] has suggested that there is a special factor of inhomogeneous polarizability associated with α nucleophiles which is important for

Table VI

pK_a' Values of Hydroperoxides in Water, 25°, μ = 1.0[a]

Hydroperoxide	E. & U.[b]	E. & M.[c]	S. & H.[d]	This study	ΔH_{ion}
	pK_a'				
HOOH	11.25	11.2	11.25	11.37[e]	8.9,[d] 7.0[e]
CH_3OOH		11.1		11.08[e]	6.5[e]
CH_3CH_2OOH		11.4	11.05		5.0[d]
i-C_3H_7OOH		11.7	11.45		7.5[d]
$(CH_3)_3COOH$		12.4	12.25	12.45[e]	7.1,[e] 6.4[d]

[a] Values from references *b*, *c*, and *d* are corrected to μ = 1.0, 25° using the ionic strength correction term given by Evans and Uri,[b] $-0.5\,\mu^{1/2} + 0.08\,\mu$, and the ΔH_{ion} values given in the table. [b] M. G. Evans and N. Uri, *Trans. Faraday Soc.*, **45**, 224 (1949). [c] A. J. Everett and G. J. Minkoff, *ibid.*, **49**, 410 (1953). [d] W. F. Sager and J. C. Hoffsommer, *J. Phys. Chem.*, **73**, 4155 (1969). [e] This study: μ = 1.0 with KCl at 25°. Our values at higher temperatures follow: HOOH at 39°, 11.15; MeOOH at 39°, 10.89; *tert*-BuOOH at 44.5°, 12.15. See also W. H. Richardson and V. F. Hodge, *J. Org. Chem.*, **35**, 4012 (1970), who find ΔpK for HOOH and *tert*-BuOOH in 40% methanol = 1.25, in good agreement with the Δ values in water.

their reactivity. Since even inhomogeneous polarizability should provide a component of extra polarizability in the average direction, we have measured approximate values (±5%)[17] for the molar refractions of the anions of hydrogen peroxide and of methyl hydroperoxide at 25°, 589 mμ. We find the following increases in $[R]_D$ for the anions as compared with the undissociated species: H_2O, 1.05;[18] H_2O_2, 0.86; MeOOH, 0.93 (cc mol^{-1}). We do not therefore observe any extraordinary polarizability of these anions within the error limits of our measurements. See also ref 4j.

α-Effect Correlations.—Ibne-Rasa and Edwards[19] first suggested that the α effect might arise from ground-state destabilization due to electrostatic repulsion between the adjacent electron pairs on the reacting atom and the α atom. These arguments have been refined recently.[4a,b,i] In particular, Aubort and Hudson[4b] have proposed that "a positive α effect is produced by a decrease in the overlap integral of orbitals containing lone pairs of electrons in the course of a chemical reaction" and that the magnitude of the effect is governed by the conformation of the nucleophile. They further suggest that it is only the anionic α nucleophiles such as ROO^-, ClO^-, RSS^-, and certain *N*-methylhydroxamic acids whose α effect is due to p_π–p_π overlap. These α nucleophiles should therefore exhibit enhanced reactivity toward all substrates in contrast to nucleophiles such as hydrazine and hydroxylamine, whose special reactivity they attribute to other causes. One must make clear one's definition of the α effect. Edwards and Pearson[3] spoke of the enhanced reactivity of α nucleophiles as a reactivity which could not be accounted for by basicity and polarizability, *i.e.*, those nucleophiles whose reactivity deviated from the line defined by the Edwards equation:[20] $\log k/k_0 = \alpha E_n + \beta H$. Others have, in effect, redefined the α effect as situations in which the rate ratio k_{HOO^-}/k_{HO^-} is large (a definition which may suffer from abnormally low values for k_{HO^-}), or as cases in which the reactivity

Table VII

Substrate	$\lvert\alpha\beta\rvert$	k_{HOO^-}/k_{HO^-} [a]
Ethyl acetate	0[b]	10^{-4} [b]
Bromoacetic acid	0.023[b]	13[f]
α-Bromo-*p*-toluic acid	(0.005)[c]	13[f]
p-Nitrophenyl methylphosphonate	0.26[d]	50[g]
p-Nitrophenylacetate	0.32[b]	77[f]
2,4-Dinitrochlorobenzene	0.52[e]	300[h]

[a] The ratios are temperature dependent. See Tables I–V. [b] Data of Klopman, *et al.*,[4a] α = 0, β = 0.8 (ethyl acetate); α = 2.1, β = −0.011 (bromoacetate); α = 0.7, β = 0.46 (*p*-nitrophenylacetate). [c] Data of Klopman, *et al.*,[4a] for benzyl bromide, α = 2.5, β = 0.002. [d] Data of Behrman, *et al.*,[9] using the points at 60° for N_2H_4, NH_2O^-, pyridine, PhO^-, and HO^-. α = 1.5, β = 0.17. [e] References 15 and 16 using the points for PhS^-, $PhNH_2$, N_2H_4, NH_3, and HO^-. k_{H_2O} was estimated as $7.8 \times 10^{-12}\ M^{-1}$, sec^{-1}, 40° from the data of J. Murto, *Acta Chem. Scand.*, **18**, 1043 (1964), for 2,4-dinitrofluorobenzene on the assumption that k_{HO^-}/k_{H_2O} for the two substrates and for the temperature range 25–40° do not differ significantly. α = 3.5, β = 0.15. [f] Our data, see Tables I–III. [g] Data of Behrman, *et al.*,[6] 30°. [h] Our data in 60% dioxane–water. Note Added in Proof.—J. E. Dixon and T. C. Bruice [*J. Amer. Chem. Soc.*, **93**, 6592 (1971)] have reported that k_{HOO^-}/k_{HO^-} for 2,4-dinitrochlorobenzene in water at 30° is 3.9×10^4. We have redetermined our data for this substrate in water at 25° with the other conditions substantially the same as those used for 60% dioxane (this table). We find $k_{HO^-} = 8.5 \times 10^{-3}\ M^{-1}\ min^{-1}$ and $k_{HOO^-} = 6.35\ M^{-1}\ min^{-1}$ (statistically corrected). Our ratio in water is thus 750. We do not know how to account for this large discrepancy. We have considered the possibility of the fast formation of the 2,4-dinitrophenyl peroxide anion followed by the slow formation of the phenoxide, but we exclude this since we observe no rapid formation of chloride ions. We have also considered the fast formation of an intermediate of the cyclohexadienone type [L. G. Cannell, *ibid.*, **79**, 2927, 2932 (1957)] which we also exclude since we observe no rapid change in the spectra of reaction mixtures in the region around 280 nm.

cannot be accounted for by basicity alone, *i.e.*, as a deviation from a Brønsted plot. For the case of HOO^-, we find an enhanced reactivity for all substrates whichever of these bases we use.[21] This is not true for hydrazine and hydroxylamine. Gregory and Bruice[4e] find no enhanced reactivity for hydrazine, hydroxylamine, or methoxylamine in reactions with methyl iodide as measured by displacement from a Brønsted plot of primary amines. This is consistent with the ideas of Aubort and Hudson[4b] as already discussed. On the other hand, Pearson, *et al.*,[22a] find $k_{N_2H_4}/k_{NH_3} \cong 10$ toward methyl iodide as a substrate and Klopman, *et al.*,[4a] view evidence of this sort as an indication of an α effect. Klopman, *et al.*,[4a] have reexamined the application of the Edwards equation to the prediction of enhanced reactivity of α nucleophiles. They have made the qualitative suggestion that in order for the α nucleophile to exhibit enhanced reactivity with a particular substrate, the ratio of the Edwards coefficients, α/β, must be large and at the same time, β must be sizable. In examining their data and our own results, we have observed what appears to be a quantitative correlation, namely that a plot of log (k_{HOO^-}/k_{HO^-}) *vs.* $\lvert\alpha\beta\rvert$ is linear. The data we have used for this correlation are shown in Table VII.[22b] The oxibase

(17) Judged from the correspondence between our value for H_2O_2 and those given by W. C. Schumb, C. N. Satterfield, and R. L. Wentworth, "Hydrogen Peroxide," Reinhold, New York, N. Y., 1955, p 271.

(18) R. J. W. LeFèvre, *Advan. Phys. Org. Chem.*, **3**, 23 (1965).

(19) K. M. Ibne-Rasa and J. O. Edwards, *J. Amer. Chem. Soc.*, **84**, 763 (1962).

(20) J. O. Edwards, *ibid.*, **76**, 1540 (1954). See also K. M. Ibne-Rasa, *J. Chem. Educ.*, **44**, 89 (1967). Also known as the oxibase scale.

(21) We have used our value for the molar refraction of HOO^-, 6.7 cc mol^{-1}, to calculate 1.76 V as the E_n value for HOO^-. See J. O. Edwards, *J. Amer. Chem. Soc.*, **78**, 1819 (1956), and K. M. Ibne-Rasa, *J. Chem. Educ.*, **44**, 89 (1967).

(22) (a) R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, **90**, 319 (1968). (b) A reviewer has suggested that coupling between the αE and βH terms would give rise to a cross term with the coefficient $\alpha\beta$. See the discussion in J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, pp 139–146.

scale plots were each drawn so as to include the point for HO^-. There is considerable scatter in the plots and so somewhat different values for α and β could have been used. Nevertheless, we feel that the trend toward the correlation we have used is there. This observation is consistent with the view[4a] that both the αE_n and the βH terms in the Edwards oxibase scale equation are important for the existence of α nucleophilicity. We note that our data show an increase in the ratio k_{HOO^-}/k_{HO^-} in the progression from sp^3 to sp^2 to sp carbon. This is, in part, fortuitous, since ethyl acetate is not attacked at a significant rate by HOO^-.[23]

Experimental Section

Substrates and Nucleophiles.—α-Bromo-*p*-toluic acid was prepared from α-chloro-*p*-tolunitrile (Matheson Coleman and Bell) by a modification of the method of Exner and Jonas.[24] Excess HBr was removed from the crude product under vacuum rather than by reprecipitation from 10% sodium carbonate solution, since this latter procedure in our hands yielded only α-hydroxy-*p*-toluic acid. The yield of α-bromo-*p*-toluic acid, mp 230–231° (corrected), was *ca.* 100%. *Anal.* Calcd: Br, 37.19. Found: Br, 37.40 (Galbraith Laboratories).

Bromoacetic acid and *p*-nitrophenyl acetate were Eastman products. The latter was recrystallized from hexane, mp 77–78° (corrected).

p-Nitrophenyl sulfate was obtained from the Sigma Chemical Co. It contained about 1% free *p*-nitrophenol and was used without recrystallization.

p-Cyanobenzoic acid (Aldrich Chemical Co.) was recrystallized twice from deionized water following an initial purification by extraction of an impurity with ether from aqueous buffer, pH 6.5, and treatment with charcoal.

tert-Butyl hydroperoxide (Matheson, Coleman, and Bell) was distilled under vacuum before use. Methyl hydroperoxide was prepared by a modification[9] of the original procedure of Rieche and Hitz.[25] *p*-Nitroperoxybenzoic acid and *p*-methoxyperoxybenzoic acid were prepared by the method of Vilkas.[26] *m*-Chloroperoxybenzoic acid and peroxyacetic acid were obtained from the Aldrich Chemical Co. and the FMC Corp., respectively.

Kinetics.—Second-order rate constants were obtained either by division of the corrected k_0 values by the calculated concentration of the anionic nucleophile and by the concentration of the substrate or by division of the corrected k_ψ values by the calculated concentration of the anionic nucleophile. The reported second-order rate constants for hydrogen peroxide have been divided by two for the statistical correction.

The reactions of bromoacetic acid and of α-bromo-*p*-toluic acid with nucleophiles were followed by measurement of the increase in bromide ion concentration with time. For the reactions with the hydroperoxides and with hydroxide ion, reaction aliquots were quenched with acetic acid and then titrated with standard silver nitrate solutions. The end point was detected using an Orion bromide-specific electrode. The bromide electrode was found to respond erratically in the presence of peroxycarboxylic acids. Therefore, for these nucleophiles, the peroxy acids were first rapidly[27] reduced by a cold 0.01 *M* methionine–acetic acid mixture followed by the silver nitrate titration at room temperature.

The reactions of *p*-nitrophenyl acetate and of *p*-nitrophenyl sulfate were followed by measurement of the rate of increase of *p*-nitrophenoxide ion concentration at 407 mμ using a Perkin-Elmer model 202 recording spectrophotometer equipped with a thermostatted cell compartment. Both zero- and first-order-conditions were used. Division of the pseudo-first-order rate constant by the nucleophile concentration gave second-order constants in good agreement with those obtained by the pseudo-zero-order technique. When necessary, suitable corrections were made for the buffer rate and the water rate. The concentration of *p*-nitrophenoxide anion was calculated for a particular pH and temperature using the value $pK_a' = 7.15$ at 25°,[28] and an experimentally determined heat of ionization at $\mu = 1.0$ of 3300 cal/mol in the range 25–54°. This value was determined by measurement of the absorbance of a solution of *p*-nitrophenol at constant pH as a function of temperature.

The reaction of *p*-cyanobenzoic acid with hydroxide ions was followed by the decrease in the absorbance at 235 mμ. The ratio of the extinction coefficients $\epsilon_{nitrile}/\epsilon_{amide}$ at this wavelength is 1.23. The reaction of *p*-cyanobenzoic acid with hydrogen peroxide was followed by measurement of the decrease in hydrogen peroxide concentration. When stoichiometric concentrations of nitrile and hydrogen peroxide were used, plots of $2/[H_2O_2]$ *vs.* time were linear. The slope of this plot is $2k_{HOO^-}K_a/[H^+]$. k_{HOO^-} values calculated from these plots agreed well with values derived from pseudo-first-order plots with $[H_2O_2]$ limiting.

For nucleophiles ionizing in the pH range of the experiment, the concentration of the anion was calculated from the pK'_a values given in the Tables. pK'_a values for the peroxycarboxylic acids at an ionic strength of 1.0 (KCl) were measured potentiometrically. The values are consistent with those given by Goodman, *et al.*[29]

pK'_a Values for the Hydroperoxides. A. *tert*-Butyl Hydroperoxide.—A Beckman Research pH meter equipped with a 0–14 Corning combination electrode was used. The system was standardized at pH 10.0, 25° (borate buffer) and at pH 12.45, 25° (saturated calcium hydroxide).[30] The absorbancy of 0.01505 *M* *tert*-butyl hydroperoxide was measured at 270 mμ after the addition of various amounts of sodium hydroxide solutions. The ionic strength was maintained at 1 by the addition of KCl. The molar absorbancy of *tert*-butyl hydroperoxide anion at 270 mμ was 61.7 cm^{-1} and that of the un-ionized molecule 6.85 cm^{-1}. The pH and the absorbance of the solutions at 270 mμ were then measured at four pH values, at both 25 and 44°.

B. Hydrogen Peroxide and Methyl Hydroperoxide.—The pK_a' values for these peroxides were determined potentiometrically at an ionic strength of 1.0 (KCl) using the same setup as described for *tert*-butyl hydroperoxide. Eight to ten additions of sodium hydroxide solution were made, after which the pH was determined at both 25 and 39°. pK_a' values were calculated, making corrections for the hydroxide ion concentration as outlined by Albert and Serjeant.[28] K_w values at $\mu = 1.0$ are 1×10^{-14} at 25° and 2.8×10^{-14} at 39°.[31]

Activation Parameters.—Apparent E_a values were obtained from slopes of the plots of the apparent second-order rate constants against the reciprocal of temperature. For the hydroperoxides, the apparent second-order rate constants were calculated using the pK_a' values for 25°. Actual E_a values were obtained by subtraction of the heats of ionization for the hydroperoxides from the apparent E_a. We estimate that the values for E_a and hence for $\Delta H^\ddagger$ are no better than ±1 kcal/mol and that the $\Delta S^\ddagger$ values are no better than ±3 cal mol^{-1} deg^{-1}.

Registry No.—α-Bromo-*p*-toluic acid, 6232-88-8; bromoacetic acid, 79-08-3; *p*-nitrophenyl acetate, 830-03-5; *p*-nitrophenyl sulfate, 1080-04-2; *p*-cyanobenzoic acid, 619-65-8.

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Conformational Analysis. LXXXI. γ-Piperidone and Related Compounds[1-3]

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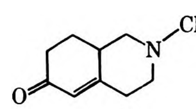
The conformations of N-methyl-γ-piperidone and N-acetyl-γ-piperidone have been studied by means of Z value correlations with n → π* spectra, by dipole moments, and by infrared methods. It is concluded that earlier interpretations of the Z value correlations are incorrect. All of the molecules examined appear to have the ring in an ordinary chair conformation.

The study of conformational analysis was originally developed from a consideration of cyclohexane rings,[5] and only during the last several years has there been an appreciable amount of work done on heterocyclic rings.[6] The piperidine ring, in particular, has been the subject of a substantial number of recent papers. The equilibrium between the chair and boat forms in this system has not yet been measured directly but is doubtlessly similar to that in cyclohexane. Much discussion has appeared in the literature concerning the orientational preference of a substituent on the nitrogen in piperidine, and not all of the experimental work is in agreement. For example, Lambert has indicated, from a study of the chemical shifts of the α protons in the nmr spectrum, that the proton on nitrogen in piperidine must be largely axial, and the data which he cites in support of this viewpoint seem quite convincing.[7] On the other hand, from a study of the band shapes of the C–H stretching vibrations in the infrared spectrum (a method utilized much earlier by Larnaudie[8]) Katritzky has found that the hydrogen on nitrogen in piperidine is mainly equatorial.[9] These data also seem to be quite convincing. Additional data of various kinds are equally inconsistent.[10-20] Katritzky has said[20] that, while some people believe the hydrogen is equatorial, and some believe it is axial, others have "hedged their winning bets." We feel that one should believe only that which experiment or theory tells us to be true. As the results of new experiments and theories become available, one should really be prepared to modify one's earlier viewpoint if the facts indicate such a modification is in order. Our current feeling is that the answer to this particular problem cannot be said to be known beyond doubt.

Boat forms in six-membered rings were for a long time of great interest, because they seem to be nonexistent, or at least very rare.[5] The first ring which appeared to have a boat conformation was uncovered by Barton in 1957, and this paper[21] was followed by a flurry of work directed at a study of boat and supposed boat forms.[22] An unusual example of the boat form in a piperidine-type ring system was proposed by Kosower (he referred to the structure as a "folded form").[23] He found that the transition energy or wavelength for the π → π* transition of compound I was quite sensitive to the Z value of the solvent (the polarity) in which the measurement was made; in fact, there was a linear relationship between the two. However, in compound II, the relationship was much less pronounced, indeed, apparently nonexistent. The transition energies varied over a range of about 2 kcal/mol, but this variation seemed to be independent of the Z value of the solvent. Kosower therefore suggested that, while I was normal (a half-chair–chair conformation), compound II had the piperidine ring in a folded (boat) form, the acetyl group interacting with the conjugated carbonyl system to produce the unexpected observed result.



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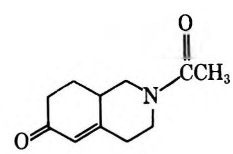
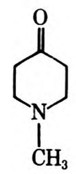
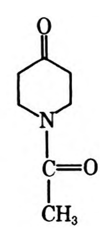


II

In the present work a study of 1-methyl-4-piperidone (III) and the corresponding acetyl derivative IV was undertaken. Whatever forces were acting in com-



III



IV

(1) Paper LXXX: N. L. Allinger and M. T. Tribble, *Tetrahedron*, in press.

(2) Taken from the thesis submitted to Wayne State University, Oct 1962, by S. P. J. in partial fulfillment of the requirements for the M.S. Degree.

(3) This work was supported by Grant GP 15263 from the National Science Foundation.

(4) Correpondence should be directed to this author at the University of Georgia.

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pounds I and II and whatever conformational situations developed, there should be analogous forces and conformations in compounds III and IV, and these were more amenable to study. In this case the spectroscopic transitions accessible were n → π*.

Results

To ascertain that the system under examination (III and IV) was indeed similar to that studied by Kosower, we first looked at the transition energies for the n → π* transitions as a function of the *Z* value of the solvent and, indeed, found trends analogous to those reported for π → π* transitions in the more complicated case. These data are given in Tables I and II and summarized in Figure 1. Thus, compound

TABLE I

UV SPECTRAL DATA FOR 1-METHYL-4-PIPERIDONE[a]

Z value	Solvent	λ_{max}, mμ	ε	E_T (n → π*), kcal mol^{-1}
60.1	Isooctane	294.0	18	97.3
62.3	Dioxane	296.5	18	96.5
64.2	Methylene chloride	300[c]		95.2
71.3	Acetonitrile	301[c]		95.0
86.9[b]	50% dioxane	329.5	8	87.7
94.6[b]	25% dioxane	332.0	8	86.1
96.7[b]	Water	333.0	6	85.9

[a] Concentrations approximately 10^{-2} *M*. [b] *Z* values were determined taking cyclohexanone as standard, others were taken from literature: E. M. Kosower, *J. Amer. Chem. Soc.*, **80**, 3253 (1958). [c] Because of strong end absorption, these absorptions appear only as shoulders, and the position of the maximum is poorly defined.

TABLE II

UV SPECTRAL DATA FOR 1-ACETYL-4-PIPERIDONE[a]

Z value	Solvent	λ_{max}, mμ	ε	E_T (n → π*), kcal mol^{-1}
62.3	Dioxane	282.5	49	101.2
64.2	Methylene	287.0		99.7
71.3	Acetonitrile	284.5	43	100.5
76.3	2-Propanol	286.5	42	99.8
79.6	Ethanol	288.5	33	99.1
96.7	Water	284.5	37	100.5

[a] Concentrations approximately 10^{-2} *M*.

III shows a transition energy which varies in an essentially linear manner over a range of about 8 kcal/mol with variation in *Z*. On the other hand, compound IV shows a much smaller variation in the transition energy with *Z*, about 2 kcal/mol, and there is no apparent correlation between *Z* and the transition energy in the latter case. Following Kosower, the interpretation would be that III exists in a normal chair form, while IV exists in the boat form (IVb) shown. The torsional arrangement about the carbonyl C–N bond in IVb is, as noted by Kosower, quite unfavorable. The other forces acting, especially the electrostatic attraction, would have to be sufficient to overcome the poor torsional arrangements, both here and with the eclipsing of the ethane type in the ring.

There are a good many physical techniques that can be used in studying conformations. The present study is concerned primarily with dipole moment measure-

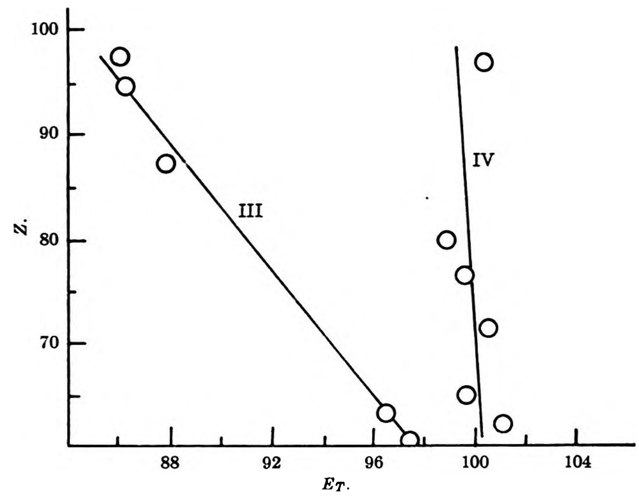
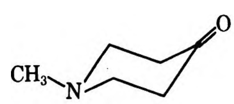
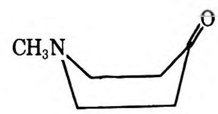


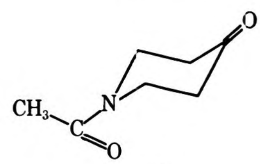
Figure 1.—The dependence of the n → π* transition energy on *Z* for compounds III and IV.



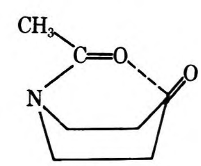
IIIc



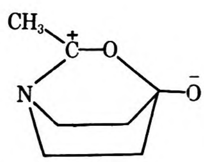
IIIb



IVc



IVb



IVct

ments, supplemented by an examination of the infrared spectra of the compounds. Finally, we want to rationalize the observed facts in terms of current theory.

The dipole moments were studied, based on the model compounds cyclohexanone (3.06 D), *N*-methylpiperidine (0.95 D), and *N*-acylpiperidine (3.99 D). At the time this work was done it was not clear that the methyl group on nitrogen was equatorial, it having been suggested by LeFevre[10] that the methyl of *N*-methylpiperidine was approximately equally axial and equatorial. Subsequently, additional work has indicated that the methyl is mainly equatorial, although the quantitative amount is still open to discussion. At any rate, using a Drieding model as a model and measuring the angles between the dipoles, it was concluded that the chair form of equatorial methylpiperidone (IIIc) should have a dipole moment of 2.90 D. The axial methyl piperidone should have a dipole moment of 2.39 D, and the boat form (IIIb) shown for the compound would have a moment of 3.94 D. This moment would be reduced if the molecule went into a twist conformation. The experimental value found for compound III was 2.91 D. The agreement for the equatorial methyl chair conformation is fortuitously good, and there could be present a sub-

TABLE III

DIPOLE MOMENTS IN BENZENE SOLUTION AT 25°

	α	β	ϵ_1	d_1	P_{2_∞}	μ
1-Methyl-4-piperidone	11.481	0.088	2.2745	0.87361	204.5	2.090 ± 0.03 D
N-Methylpiperidine	0.901	0.101	2.2760	0.87355	50.19	0.954 ± 0.04 D
N-Acetylpiperidine	21.597	0.215	2.2758	0.87362	353.7	3.941 ± 0.03 D
N-Acetyl-4-piperidone	12.511	0.434	2.2742	0.87348	218.7	2.987 ± 0.02 D

stantial amount of the axial methyl and perhaps a small amount of the boat or a larger amount of the twist form. However, the most simple interpretation is that the compound exists primarily in the conformation with an equatorial methyl in the chair form.

For the *N*-acyl compound, a rough approximation is to assume that the moment of the amido group lies along the C–O double bond. Actually, it must lie slightly from the nitrogen toward the oxygen, but, using our first approximation, it is calculated that the chair form of the ring with an equatorial acyl group and a planar ring nitrogen would have a moment of 3.59 D. The deviation of the moment from the C=O axis is 20° in formamide[24] away from the nitrogen. Using the same geometry here, the moment is calculated to be 2.51 rather than 3.59 D. The boat form shown (IVb) has a calculated moment of 4.85 D.

The results shown in Table III were obtained in benzene solution at 25°. The experimental dipole moment of *N*-acetyl-γ-piperidone was 2.99 D. This is consistent with a chair form but is clearly far too small to correspond to a boat form or any large amount of boat form in the equilibrium mixture. The reason for suggesting that compound IV might have a stable boat conformation was because of a possible electrostatic interaction between the carbonyl groups in that arrangement. Such an interaction would amount to a charge transfer, which would augment the dipole moment even further. If the charge transfer were complete (as in IVct), the dipole moment would be approximately 20 D. The dipole moment data are quite inconsistent with any such formulation.

A study of the infrared spectra of these compounds was also carried out. Compound III shows the ketone C=O stretching frequency at 1724 cm^{-1}, whereas the corresponding absorption of IV is at 1730 cm^{-1}. Any sizable electrostatic interaction such as in IVct would greatly reduce the frequency of the acetyl compound, relative to that of the methyl compound, and this is not observed. The frequency is in fact higher. If we consider that the carbonyl group consists primarily of two resonance forms

$$>C=O \longleftrightarrow >\overset{+}{C}-\overset{-}{O}$$

then the inductive effect of the acetyl would tend to make the double-bonded form more important than the singly bonded form, which would raise the stretching frequency. This is what is observed, although the effect is pretty small. However the evidence is quite inconsistent with a conformation such as IVb, being maintained by electrostatic forces.

The amide carbonyl frequency in 1-acetylpiperidine is observed at 1650 cm^{-1}, while in the corresponding 4-piperidone, the frequency is 1664 cm^{-1}. The inductive effect of the carbonyl on the acetyl should lead to this increase in frequency, just as the inductive effect of the acetyl on the carbonyl led to an increase in the double bond stretching frequency. Thus the observed frequency shift is compatible with a chair form. On the other hand, the electrostatic interaction between the carbonyls should lead to a decrease in frequency. However, in compound IVb, the π orbital of the amide carbonyl is orthogonal to that of the lone pair on nitrogen, and this also should lead to a substantially increased carbonyl frequency. Whether this effect is smaller or larger than the electrostatic effect mentioned is not obvious; so it is not clear what one would predict for the carbonyl frequency of the acetyl group in compound IVb.

Conclusions

In compound III, the dipole moment data indicate that the predominant conformation is the simple chair form with an equatorial methyl. Smaller amounts of other conformations cannot be excluded, but there is no evidence for them.

Compound IV cannot exist in the boat form analogous to that proposed by Kosower to any large extent. The simple chair conformation with an approximately planar nitrogen is consistent with the available data.

The correlation between the transition energies of the n → π^* transitions and the polarity of the solvent as measured by the *Z* value is pretty good in the case of the *N*-methyl compound. The points lie near to a straight line of moderate slope. It may be noted that the sign of the slope of the line is opposite to that usually observed[23] for n → π^* transition, however. The correlation is not very good in the case of the *N*-acetyl compound. The slope of the line is nearly infinite, indicating only a small random effect of the *Z* value of the solvent on E_T. The ring conformation seems to have nothing to do with the correlation between E_T and *Z*, however. There is no evidence for the ring being anything other than a simple chair in any case. The reason for the lack of a systematic effect of the *Z* value of the solvent on the transition energy is not clear. The scatter of the points can be attributed to the fact that the *Z* value, which is determined by the effect of the solvent on E_T in a specific molecule,[24] does not exactly account for the effect of solvent on E_T in structurally different molecules because of the specificity of solvation on a molecular scale. The nearly infinite slope of the line (Figure 1) in the case of compound IV shows that solvation is equally important in the n → π^* excited state and in the ground state. Why this is true in IV, but not in III, is not obvious. It is conceivable that the molecules of IV do not form solutions that are at all ideal, even at low concentrations, but instead tend to dimerize or clump together, particularly in less polar solvents.

(24) R. J. Kurland and E. B. Wilson, Jr., *J. Chem. Phys.*, **27**, 585 (1957).

Experimental Section

1-Methyl-4-piperidone (III).—Methyldi(β-carbethoxyethyl)-amine was prepared by the Michael addition of methylamine to ethyl acrylate, 78% yield, bp 117–119° (0.5 mm) [lit.[25] reports bp 118–119° (0.5 mm)]. The latter underwent a Dieckmann condensation with potassium *tert*-butoxide to give the cyclic β-keto ester, which upon hydrolysis and decarboxylation yielded 1-methyl-4-piperidone, bp 67–79° (19 mm), $n^{24}D$ 1.4580 [lit.[26] reports mp 56–58° (11 mm), $n^{25}D$ 1.4580, yield 58%].

1-Acetyl-4-piperidone.—A Michael addition of ammonia to ethyl acrylate gave di(β-carbethoxyethyl)amine, bp 154–164° (1.5 mm) [lit.[27] bp 150–164° (1–2 mm)]. The *N*-benzoyl derivative was prepared and had bp 192–197° (0.4 mm), $n^{24}D$ 1.5020 [lit.[27] bp 192–194° (0.4 mm), $n^{25}D$ 1.5040]. The Dieckmann reaction was then carried out with the aid of sodium and furnished 1-benzoyl-3-carbethoxy-4-piperidone, mp 59–60° (lit.[27] mp 54–56°).

4-Piperidone hydrochloride was prepared by hydrolysis of the previous compound by refluxing with 6 *N* hydrochloric acid until carbon dioxide evolution ceased. The solution was filtered to remove the benzoic acid, and the product was taken up in ether. The ether solution was evaporated to dryness and the product was decolorized with charcoal and crystallized from ethanol–ether. It was then taken up in acetic acid–sodium acetate and acetylated with acetic anhydride, bp 135–136° (0.3 mm), $n^{25}D$ 1.5016 [lit.[28] reports bp 124–128° (0.2 mm), $n^{25}D$ 1.5023].

Dipole Moments.—The apparatus and method[29] and the details of the computations[30] have all been described previously, no allowance for atomic polarization being made in line with earlier conclusions.[31]

Registry No.—III, 1445-73-4; IV, 32161-06-1; *N*-methylpiperidine, 626-67-5; *N*-acetylpiperidine, 618-42-8.

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(26) E. A. Prill and S. M. McElvain, *ibid.*, **55**, 1233 (1933).
(27) S. M. McElvain and G. Stork, *ibid.*, **68**, 1049 (1946).
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(29) N. L. Allinger, M. A. DaRooge, H. M. Blatter, and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961).
(30) N. L. Allinger and J. Allinger, *ibid.*, **24**, 1613 (1959).
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Notes

Friedel–Crafts Acylation of 10-Methylphenothiazine

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Received July 21, 1970

As part of the preparation of a compound containing the 3-(10-methylphenothiazinyl) group, it was necessary to use a Friedel–Crafts acylation in one of the synthetic steps. Although hundreds of phenothiazine compounds have been reported we were unable to find a high-yield procedure for the Friedel–Crafts acylation of 10-methylphenothiazine.

The literature reports that *N*-alkylphenothiazine is 3,7 directing and *N*-acylphenothiazine is 2,8 directing in Friedel–Crafts acylation.[1–6] Both mono- and disubstituted products are formed but were not separated in the reported crude yields. Acylation takes place with higher yields with *N*-acylphenothiazine than with *N*-alkylphenothiazine.

For example, when 1 mol of 10-methylphenothiazine was acylated with 1 mol of acetyl chloride in carbon disulfide with aluminum chloride, the crude yield of 3-acetyl product was 25% (reported as the hydrate) with 42.5% utilization of 10-methylphenothiazine.[1] In a recent attempt to duplicate the reaction, the major product found was the 3,7-diacetyl derivative.[2] With 2.5 mol of acetic anhydride, the yield of 3,7-diacetyl product was 39%.[3]

Acylation of 10-acetylphenothiazine with 1 mol of β-carbomethoxypropionyl chloride in carbon disulfide with aluminum chloride gave 58% of crude 2-acylated product.[5] A 94% yield of the 2-acetyl product was obtained using 1 mol of acetic anhydride,[6] while the 2,8-diacetyl derivative was obtained in 52% yield using 4 mol of acetyl chloride.[3]

Results and Discussion

In this laboratory, it was found that the aluminum chloride–carbon disulfide system gave rather poor yields of monosubstituted product in the acylation of 10-methylphenothiazine with β-carbomethoxypropionyl chloride. The effect of solvent and catalyst on the reaction was therefore investigated; the results are summarized in Tables I and II and Chart I.

The 3 position of the substituent is assigned by analogy to related cases[1,3,7] and the nmr spectra. The chemical shift of the aromatic protons in **4** (τ 2.18, 2.27, 3.14 for a_1, a_2, and b) agree well with those calculated for a 3-acyl-, 5-alkylthio-, 6 dialkylamino-substituted benzene (τ 2.19, 2.22, 3.34), using a recent table of aromatic chemical shifts,[8] but not for the corresponding 2-acyl derivative (τ 2.70, 2.72, 2.77).

Product **5** presumably arises by acylation of a second mole of phenothiazine by the monosubstituted product, leading to the tertiary alcohol which dehydrates to **5**. Compound **5** gave a single peak in thin

(1) A. Burger and A. C. Schmalz, *J. Org. Chem.*, **19**, 1841 (1954).
(2) E. Gipstein, W. A. Hewett, and O. U. Need, *J. Polym. Sci., Part A-1*, **8**, 3285 (1970).
(3) G. Cauquil and E. Casadevall, *Bull. Soc. Chim. Fr.*, 1061 (1955).
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(5) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Amer. Chem. Soc.*, **68**, 2673 (1946).
(6) G. Cauquil and A. Casadevall, *Bull. Soc. Chim. Fr.*, 768 (1955).
(7) G. A. Olah, Ed., "Friedel-Crafts and Related Reactions," Vol. III Part I, Interscience, New York, N. Y., 1964, p 99.
(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, p 202.

Table I

Friedel–Crafts Reactions. Yields of Products As a Function of Catalyst, Solvent, and Reaction Conditions

Mol of catalyst[a]	Solvent	Time, hr	Temp, °C	Recovered mol of 1	3	4	5	Yield of 3,[f] %
0.1 H_2SO_4	*c*	3.5	70		0.00			
0.1 H_2SO_4	CS_2	3.5	40		0.00			
2 $AlCl_3$	*c*	3.5	70		<0.05[b]	>0.10[b]	>0.10[b]	
2 $AlCl_3$	CS_2	3.5	40		<0.05[b]	>0.10[b]	>0.10[b]	
0.7 $AlCl_3$	$CHCl_3$	0.6	64	0.41	0.06	0.21	0.14	10
0.3 $AlCl_3$	$CHCl_3$	1.4	45	0.60	0.08	0.15	0.03	20
0.5 $ZnCl_2$	*c*	1.5	75	0.00	0.16			16
0.5 $ZnCl_2$	CS_2	4.0	46	0.82	0.07	0.02	0.02	39
2 $ZnCl_2$	CS_2	4.0	48	0.71	0.14	0.03	0.02	49
0.4 $ZnCl_2$	*d*	1.0	95		Tars			0
0.4 $ZnCl_2$	*e*	0.5	82	0.44	0.37	0.10	0.03	66
0.4 $ZnCl_2$	$CHCl_3$	4.5	63	0.55	0.36	0.02	0.01	80

[a] Based on 1 mol of 1 plus 1 mol of 2. [b] Estimated from thin layer chromatography. [c] Nitrobenzene. [d] *sym*-Tetrachloroethane. [e] *sym*-Dichloroethane. [f] Yield of 3 based on 10-methylphenothiazine reacted.

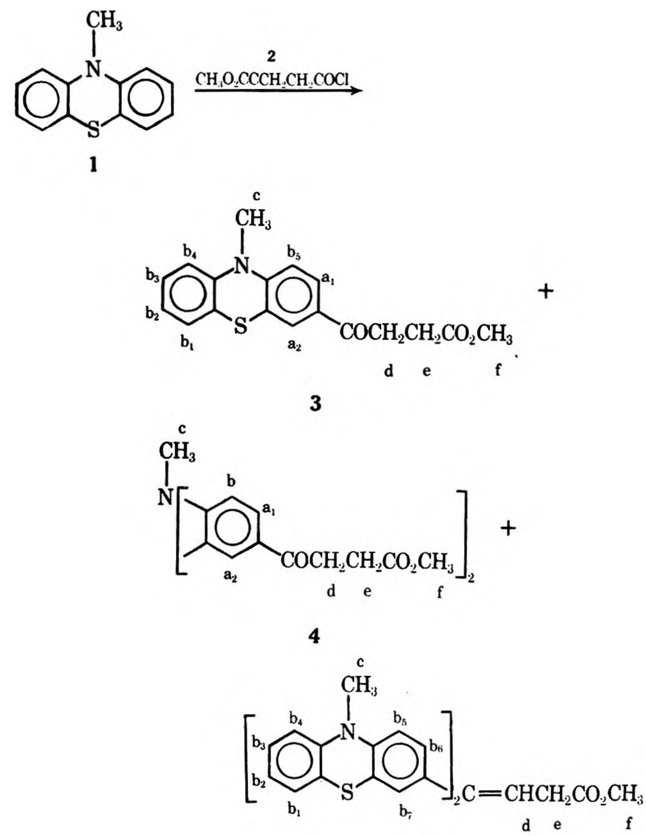
Table II

Nmr Spectra of Compounds

Compd	H	Area	τ, ppm	J, cps
3	a_1	2	2.19 (d)[a]	8.5, 2.0
	a_2		2.28 (s)[b]	
	b_{1-5}	5	2.60–3.30 (m)	
	c	3	6.60 (s)	
	d	2	6.78 (t)	6.0
	e	2	7.25 (t)	6.0
	f	3	6.29 (s)	
4	a_1	4	2.18 (d)[a]	9.0, 2.0
	a_2		2.27 (s)[b]	
	b	2	3.14 (d)	8.5
	c	3	6.56 (s)	
	d	4	6.76 (t)	6.0
	e	4	7.25 (t)	6.0
	f	6	6.28 (s)	
5	b_{1-7}	14	2.66–3.42 (m)	
	c	2	6.71 (s)	
		4	6.67 (s)	
	d	1	3.90 (t)	7.5
	e	2	6.88 (d)	7.5
	f	3	6.30 (s)	

[a] Ortho and meta splitting. [b] Meta splitting not visible because of overlap.

Chart I



layer chromatography; analysis and nmr confirmed the gross structure assignment and mechanism of formation. However, the glassy nature of 5 and the presence of two NCH_3 peaks in the nmr spectrum which did not coalesce or move together up to 90° indicate that this product is not a single compound. The nmr data suggest the possibility of conformational isomers with a high energy barrier to rotation, but this is not proven.

Catalysts and Solvents.—Sulfuric acid does not act as a catalyst for the acylation. With aluminum chloride the solution became red immediately; this is probably a reaction of the catalyst with the electron donor, 10-methylphenothiazine, to form an oxidized complex.[9] Also, there was much black tar, indicating further side reactions on the monoacylated and vinyl products. Yields improved with lower aluminum chloride levels, and by use of chloroform instead of carbon disulfide or nitrobenzene. With $AlCl_3$, 4 is produced in better yield than 3, and in many cases 5 is also present in higher yield than 3.

Zinc chloride is insoluble in all the solvents used. In nitrobenzene or carbon disulfide, black tars formed on the surface of the catalyst, and the reaction rate is therefore reduced considerably by blockage of the surface. The initial product, 3, insoluble in these solvents, remained on the surface of the zinc chloride and thus was available for further reactions which eventually produced tars. In chlorinated solvents, however, the reaction product, 3, was dissolved from the zinc chloride surface, and the zinc chloride stayed clean and active. This also led to a better yield, since the amount of side reaction was reduced. At 95° (run 10) only tars were obtained; the reaction proceeded too far. With $ZnCl_2$ catalyst, the relative amounts of products formed were vastly different from reactions in which $AlCl_3$ was

(9) Y. Sato, M. Kinoshita, M. Sano, and H. Akamatu, *Bull. Chem. Soc. Jap.*, **42**, 548 (1969).

used. The monoacylated product, 3, predominated. This indicates that $ZnCl_2$ is operating by a somewhat different mechanism than $AlCl_3$.

In general it seems that aluminum chloride is too active a complexing agent with 10-methylphenothiazine. While complexed with 10-methylphenothiazine, aluminum chloride probably prevents acylation; therefore acylation tends to take place on uncomplexed material. As the monoacylated product is less basic than 10-methylphenothiazine, it tends to be uncomplexed and is therefore preferentially acylated. This leads to multiple acylations and correspondingly poor yields of monoacylated product. Also, complexed 3 can acylate starting material to produce 5 and is removed by that path as well. In the case of 10-acylphenothiazine, the acyl group reduced the electron-donating properties of the phenothiazine and therefore reduces the strength of the complex with aluminum chloride. This can account for the better acylation yields for this compound reported in the literature.

Acylation apparently takes place on the surface of the insoluble zinc chloride. However, solvents such as chloroform can remove the acylated product and reduce secondary reactions. Another factor in favor of zinc chloride is that it is too weak a Lewis acid to complex irreversibly with the products. While this lowers reaction rates, they now tend to be related to the reactivity of the starting materials. Since the acid chloride and 10-methylphenothiazine are the most reactive materials present, formation of 3 is favored.

Experimental Section

10-Methylphenothiazine.—A method was used which is more convenient but similar in principle to those methods in the literature.[1,10] In this case, the strong base for removing the N proton from phenothiazine was made and used immediately in the same reaction vessel. Sodium (23 g, 1 g-atom) was added slowly in small pieces to 500 ml of dimethyl sulfoxide[11,12] under nitrogen with cooling to below 40° and stirring. After all of the metal had reacted, 100 g (0.5 mol) of phenothiazine was added slowly to maintain a temperature of 40°. Methyl iodide (142 g, 1 mol) was then added dropwise at 40°. The product was precipitated in water, filtered, and dried. The crude material, 107 g, was then chromatographed on a 1 × 30 in. silica gel column. The material eluted with benzene was recrystallized twice from ethanol-acetone (4:1), yield 91 g (86%), mp 97-100° (lit.[13] mp 99.5°).

Typical Procedure for Friedel-Crafts Reaction.—Chloroform was washed with water, and then dried over anhydrous calcium sulfate. Dry chloroform (700 ml), 85 g (0.4 mol) of 10-methylphenothiazine, and 60 g (0.4 mol) of β-carbomethoxypropionyl chloride[14] were mixed. Anhydrous zinc chloride (22 g, 0.16 mol) was added and the flask was heated to reflux at 63° with stirring for 4.5 hr. Formation of products was followed by thin layer chromatography in order to optimize the amount of monoacylated product. The reaction was quenched by cooling and addition of ice. After washing with water, the chloroform solution was evaporated. The products were dissolved in a minimum amount of benzene and chromatographed on a 1 × 28 in. silica gel column. Elution solvents were first benzene, then chloroform, then ethyl acetate. The eluted solvent was divided into 100-ml portions, which were evaporated separately. Separation of compounds was checked by tlc, and fractions containing two components were rechromatographed.

Unreacted 10-methylphenothiazine was eluted in the first 300 ml of benzene. There was a slight overlap with compound 5. After rechromatographing, recovered 1 weighed 47 g (0.218 mol).

Methyl 4,4-Bis(10-methyl-3-phenothiazinyl)butene-3-oate (5) (Probable Assignment).—Compound 5 was eluted with benzene in the 300-1000-ml fractions. The fractions which overlapped with 1 were rechromatographed on silica gel with benzene. In drying, an amorphous, glassy solid, 5, was obtained which had a single peak in tlc, weight 2.18 g (0.0042 mol).

Anal. Calcd for $C_{31}H_{26}N_2S_2O_2$: C, 71.4; H, 4.97; N, 5.36. Found: C, 71.36; H, 5.00; N, 5.56.

Methyl 4-(10-Methyl-3-phenothiazinyl)-4-oxobutanoate (3).—Elution of the column with 800 ml of 50:50 chloroform-benzene and 500 ml of $CHCl_3$ and solvent evaporation then produced 3, crude yield 47 g (0.145 mol). 3 was first recrystallized from cyclohexane-benzene (2:1) and then from methanol-acetone (2:1), mp 113-116° (half width on a Du Pont 900 DTA at 20°/min).

Anal. Calcd for $C_{18}H_{17}SNO_3$: C, 66.1; H, 5.20; N, 4.28. Found: C, 66.07; H, 5.21; N, 4.41.

Dimethyl 4,4'-(10-Methyl-3,7-phenothiazinylene)di(4-oxobutanoate) (4).—Further elution of the column with 800 ml of chloroform eluted a yellow band of 4 in substantially pure form. It was recrystallized from 50:50 methanol-acetone, weight 2.36 g (0.0054 mol), mp 142-145°.

Anal. Calcd for $C_{23}H_{23}NO_6S$: C, 62.6; H, 5.21; N, 3.17. Found: C, 62.46; H, 5.22; N, 3.24.

Registry No.—1, 1207-72-3; 3, 33214-29-8; 4, 33214-30-1; 5, 33214-31-2; $AlCl_3$, 7446-70-0; $ZnCl_2$, 7646-85-7.

Acknowledgment.—We wish to thank the NSF for partial support of this work.

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(11) A. Ledwith and N. McFarlane, *Proc. Chem. Soc.*, 108 (1964).
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The Reaction of 4- and 5-Acetyloxazoles with Malononitrile

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Ring opening of oxazoles with nucleophilic reagents such as ammonia,[1-4] hydroxide,[5] and 2,4-dinitrophenylhydrazine[6] has been reported. We now wish to report the facile ring opening and subsequent recyclization of 4- and 5-acetyloxazoles with the nucleophile, malononitrile, in the presence of a base.

When 4-acetyl-2,5-dimethyloxazole[7] (1, R = CH_3) is allowed to react with 1 mol of malononitrile in the presence of potassium acetate, a small yield of the expected dicyanovinyl condensation product (2, R = CH_3) can be isolated. However, when 1 or 2 mol of malononitrile reacts with the acetyloxazole in the presence of sodium hydroxide, 2 is not obtained, but a different,

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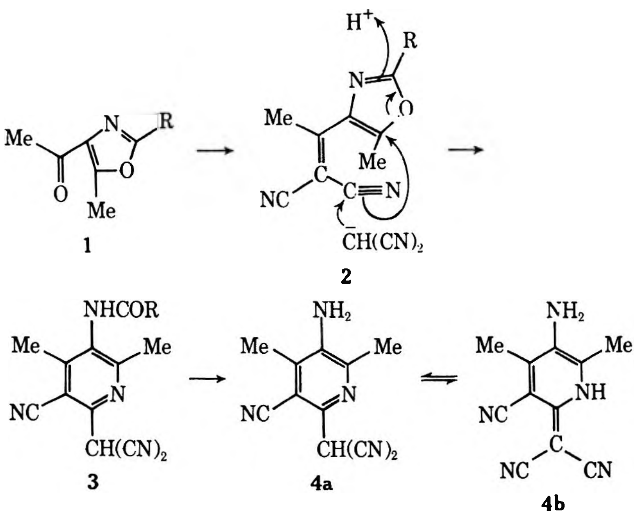
(2) G. Theilig, *ibid.*, **86**, 96 (1953).
(3) J. W. Cornforth and H. T. Huang, *J. Chem. Soc.*, 1960 (1948).
(4) A. Dornow and H. Hell, *Chem. Ber.*, **93**, 1998 (1960).
(5) J. W. Cornforth, *et al.*, *J. Chem. Soc.*, 1549 (1949).
(6) M. Ionescu and C. Makkay, *Stud. Univ. Babes-Bolyai, Ser. Chem.*, 121 (1966).
(7) A. Treibs and W. Sutter, *Chem. Ber.*, **84**, 96 (1951).

red, crystalline compound, $C_{11}H_9N_5$, precipitates. This red product also results by treating the dicyanovinyl derivative **2** (R = CH_3) with 1 mol of malononitrile.

On the basis of the spectroscopic and analytical evidence we assign structure **4** to the red compound and consider the mechanism shown in Scheme I as a

SCHEME I



possible route of formation. The infrared spectrum (KBr) showed the presence of at least two nitrile groups (peaks at ~2205 cm^{-1}). Several strong bands in the region 3160–3360 cm^{-1} suggested the presence of a primary amino group. Strong peaks were observed at 1640, 1590 (pyridine ring),[8] 1510, 1415, 1370 and 1385 (methyl groups), and 1270 and 1205 cm^{-1} (CN stretch[9]). The mass spectrum indicated the presence of a very stable molecular ion of *m/e* 211 and M^{2+} 105.5. Loss of $-CH_3$ (M − 15 = 196), HCN (M − 27 = 184), and $CH(CN)_2$ (M − 65 = 146) were prominent features. The loss of the $CH(CN)_2$ fragment in the mass spectrum of **2** was an extremely unfavorable process. The nmr spectrum (in pyridine-d_5) indicated the presence of two methyl groups at δ 2.14 and 2.85.

Under the conditions employed (aqueous ethanol and NaOH at 100°) it is likely that the second molecule of malononitrile had attacked the carbon of the nitrile in **2** yielding **3**. This type of addition is well known with malononitrile and has been shown to occur in the condensation with *o*-hydroxyacetophenone,[10] with 2,4-diketones,[11,12] and with the enamines[13] under basic conditions.

The conversion of **2** to **3** is probably best envisaged as attack by the second molecule of malononitrile on one of the nitrile groups, followed by concerted opening of the oxazole ring. This step would be favored by resonance stabilization of the pyridine ring so formed. When the carbonyl group is blocked, *e.g.*, by toluenesulfonylhydrazide, the reaction does not proceed at all, suggesting that formation of the dicyano vinyl derivative **2** is a necessary initial step before opening of the oxazole ring can occur.

Compound **4** is expected to be tautomeric[10,12,13] (**4a** ⇌ **4b**). While we have not attempted to measure the position of this tautomeric equilibrium, the strong fluorescence and intense color of the product indicates[12,14,15] that **4b** is a significant contributor. Reversible protonation results in an intense blue color and quenching of the fluorescence.

The reaction between 1 mol of malononitrile and either 5-acetyl-4-methyloxazole[4] (**5**, R = H) or 5-acetyl-2,4-dimethyloxazole[4] (**5**, R = CH_3) in the presence of catalytic amounts of KAc gave the expected dicyanovinyl condensation product **6** in low yield. With 1 or 2 mol of malononitrile in the presence of aqueous sodium hydroxide **6** was not isolated but the same yellow crystalline compound was obtained with either **5** (R = H) or **5** (R = CH_3). The liberation of ammonia was also observed during this reaction.

Elemental analysis and the mass spectrum (*m/e* 212) of the yellow material coresponded to $C_{11}H_8N_4O$. The infrared spectrum (KBr) indicated the presence of a primary amino group (ν_{NH} = 3150 and 3300 cm^{-1}). Strong bands at 2218 and 2225 cm^{-1} indicated the presence of at least two nitrile groups, while the presence of *C*-methyl groups was suggested by absorptions at 1375 and 1388 cm^{-1}. Medium-to-strong absorptions were observed at 1660, 1585, 1595, 1540, 1325, and 1030 cm^{-1}. A strong band at 1680 cm^{-1} suggested the presence of carbonyl group conjugated with amino function (*i.e.*, an amide carbonyl).

Confirmation of the presence of a primary amino group was provided by Purdie methylation (CH_3I–Ag_2O) of the yellow compound. The product, mp 194–195°, analysis and mass spectrum (*m/e* 240) corresponding to $C_{13}H_{12}N_4O$, lacked the prominent ir absorptions in the region 3150–3300 cm^{-1}, but a strong peak at 1412 cm^{-1} indicated the presence of an $N(CH_3)_2$ group.

It is worthy of note that in the dimethylated compound the closely spaced bands at 1585 and 1595 cm^{-1} and also the band at 1470 cm^{-1} are absent, while the two spectra are otherwise remarkably similar.

The nmr spectrum of the yellow compound showed (in DMSO-d_6) a broad signal at δ 9.10, which disappeared on deuterium exchange with DCl–D_2O, and also was absent in the spectrum of the dimethylamino derivative. Two methyl resonances were prominent at δ 2.19 and 2.15 in both the yellow compound and in its dimethyl derivative. In the latter the $N(CH_3)_2$ resonance was observed as a singlet (with the correct integral) at δ 3.04. Consideration of the available spectroscopic and chemical data leads us to suggest structure **10** for the yellow product.

The formation of **7** (see Scheme II) by nucleophilic attack of $CH(CN)_2$ on C_5 of either **5** or **6** is considered likely because it is flanked by two strongly electron-withdrawing groups. Ring closure **7** → **8** is possibly favored by the relative proximity of the vinyl nitrile and dicyanomethide anion obtained by proton loss from the dicyanomethyl group under the alkaline conditions employed.

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(9) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964.
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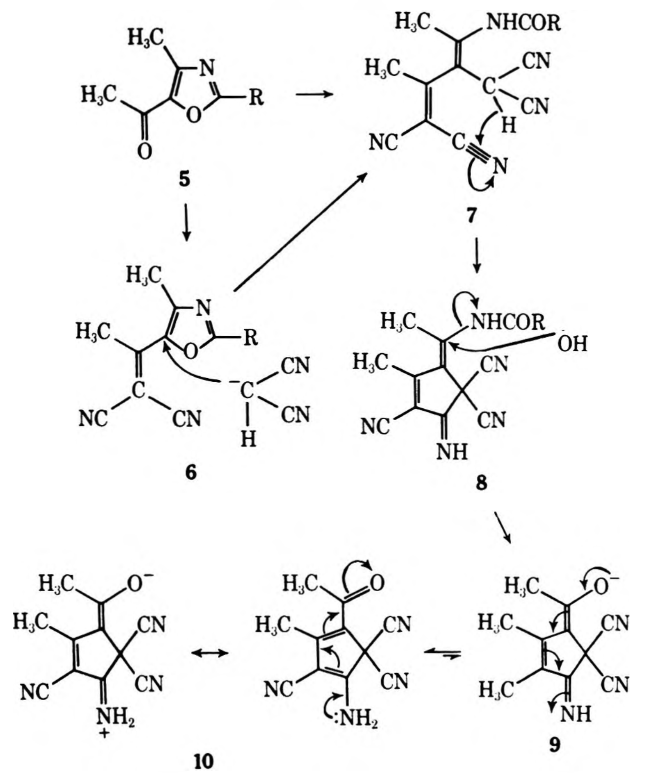
SCHEME II



Nucleophilic displacement of NHCOR by $^{-}$OH is in agreement with the finding that the yellow compound can be derived from either **5** (R = H) or **5** (R = Me).

Experimental Section

Microanalyses were performed by the Australian Microanalytical Service, CSIRO, Melbourne. The nmr spectra were recorded on a Varian Associates A-60D instrument; ir spectra were recorded on a Perkin-Elmer 225 spectrometer. Mass spectra were recorded by courtesy of Dr. G. Wunderlich, CSIRO Division of Organic Chemistry, Melbourne.

4-Acetyl-2,5-dimethyloxazole (1, R = CH_3) was prepared according to the procedure of Treibs and Sutter,[7] mp 49.0–49.5° (lit.[7] mp 49°).

2,5-Dimethyl-4-(β,β-dicyano-α-methylvinyl)oxazole (2, R = CH_3).—4-Acetyl-2,5-dimethyloxazole (0.35 g, 0.0025 mol), malononitrile (0.165 g, 0.0025 mol), and dry potassium acetate (0.01 g) were refluxed in dry benzene (20 ml) for 44 hr. Removal of the solvent *in vacuo* afforded a brown oil which was chromatographed on an aluminum oxide (BDH) column using benzene–petroleum spirit (bp 60–80) (1:1) as elutent. Unreacted 4-acetyl-2,5-dimethyloxazole (0.15 g) and 2 (R = CH_3) (0.1 g), mp 130–131°, were obtained as colorless needles: ir 2240 (CN), 1621 cm^{-1} (C=N); mass spectrum M^+ 187, 187 → 91 [loss of $(CN)_2C{=}C(CH_3)_2$].

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.17; H, 4.81; N, 22.46. Found: C, 64.30; H, 4.80; N, 22.34.

3-Amino-5-cyano-6-(dicyanomethyl)-2,4-dimethylpyridine (4).—To 4-acetyl-2,5-dimethyloxazole (0.7 g, 0.005 mol) in ethanol (10 ml) and aqueous sodium hydroxide (3 ml, 2 *N*) was added malononitrile (0.66 g, 0.01 mol) in water (10 ml). The resulting red solution was heated on a steam bath for 20 min, cooled in ice, filtered, and washed with water. 3-Amino-5-cyano-6-(dicyanomethyl)-2,4-dimethylpyridine (4) (0.32 g, 33%) crystallized from aqueous DMF (1:1) as red needles, mp >300° dec.

Anal. Calcd for $C_{11}H_9N_5$: C, 62.56; H, 4.26; N, 33.17. Found: C, 62.34; H, 4.25; N, 33.65.

Reaction of 2,5-Dimethyl-4-(β,β-dicyano-α-methylvinyl)oxazole with Malononitrile.—2,5-Dimethyl-4-(β,β-dicyano-α-methylvinyl)oxazole (0.09 g, 0.0001 mol) in ethanol (5 ml) and aqueous sodium hydroxide (1 ml, 2 *N*) were treated at 25° with malononitrile (0.007 g, 0.0001 mol) in water (1 ml). After heating the red solution on a steam bath for 20 min, the solvent was removed, water (2 ml) was added, and the precipitate was collected, washed with water, and recrystallized from aqueous DMF (1:5) to yield material (0.01 g) identical (mass spectrum, ir) with **4**.

5-Acetyl-4-methyloxazole (5, R = H).—This was prepared according to the method of Dornow and Hell,[4] bp 68–74° (10–12 mm) [lit.[4] bp 74–75° (15 mm)].

5-Acetyl-2,4-dimethyloxazole (5, R = CH_3) was prepared according to the procedure of Dornow and Hell[4] as colorless needles from petroleum spirit (bp 60–80°), mp 58–59° (lit.[4] mp 61°).

Anal. Calcd for $C_7H_9NO_2$: C, 60.48; H, 6.53; N, 10.08. Found: C, 60.52; H, 6.61; N, 10.31.

2,4-Dimethyl-5-(β,β-dicyano-α-methylvinyl)oxazole (6, R = CH_3).—5-Acetyl-2,4-dimethyloxazole[4] (1.39 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol), dry potassium acetate (0.01 g), and dry benzene (25 ml) were refluxed for 26 hr with water removal (Dean and Stark apparatus). Removal of the solvent *in vacuo* followed by addition of water (20 ml) to the residue and extraction with ethyl acetate gave after drying ($MgSO_4$) and evaporation of the solvent a brown oil. This was dissolved in benzene (10 ml) and petroleum spirit (bp 40–60°) was added dropwise to turbidity. After 5 days at 0° the crystals that deposited were collected, washed with petroleum spirit (bp 40–60°), and recrystallized twice (charcoal) from water to afford 6 (R = CH_3) (0.2 g) as colorless needles: mp 88–89°; ir 2200 cm^{-1} (CN); nmr δ 2.55 (s, 6, 2 CH_3), 2.46 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.22; H, 4.85; N, 22.47. Found: C, 64.28; H, 4.80; N, 22.29.

2-Acetyl-5-amino-4-cyano-1,1-dicyano-3-methylcyclopentadiene (10).—5-Acetyl-4-methyl- or 5-acetyl-2,4-dimethyloxazole (5) (0.01 mol) in ethanol (25 ml) and aqueous sodium hydroxide (5 ml, 2 *N*) was treated at 20° with malononitrile (0.02 mol) in water (5 ml). The red solution was heated on a steam bath for 15 min (NH_3 evolved), cooled to 20°, and neutralized with hydrochloric acid (12 *N*), water (100 ml) was added, and the yellow precipitate was collected and washed with water and then aqueous alcohol (1:1). **10** (60%) crystallized from aqueous DMF (1:3) as yellow needles, mp = 300° dec.

Anal. Calcd for $C_{11}H_8N_4O$: C, 62.26; H, 3.77; N, 26.41. Found: C, 62.48; H, 4.04; N, 26.17.

2-Acetyl-4-cyano-1,1-dicyano-5-dimethylamino-3-methylcyclopentadiene.—The yellow compound **10** (0.1 g), silver oxide (0.1 g), and methyl iodide (30 ml) were vigorously shaken in a stoppered flask at 20° for 16 hr. The red solution was filtered, the volume of the filtrate reduced *in vacuo* by two-thirds, and the red precipitate collected and washed with aqueous alcohol (2:1). The dimethylamino derivative of **10** crystallized from aqueous acetone (1:8) as red needles (0.1 g, 88%), mp 194–195°.

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 65.05, H, 5.04; N, 23.35. Found: C, 65.18; H, 5.29; N, 23.21.

Registry No.—**1**, 23000-12-6; **2** (R = Me), 33303-94-5; **4**, 33223-92-6; **5** (R = H), 23012-19-3; **5** (R = Me), 23012-25-1; **6** (R = Me), 33223-95-9; **10**, 33223-96-0; **10** dimethylamino derivative, 33223-97-1; malononitrile, 109-77-3.

Reactions of Triphenylarsonium and Triphenylphosphonium Phenacylides with 1-*p*-Nitrobenzoylaziridine

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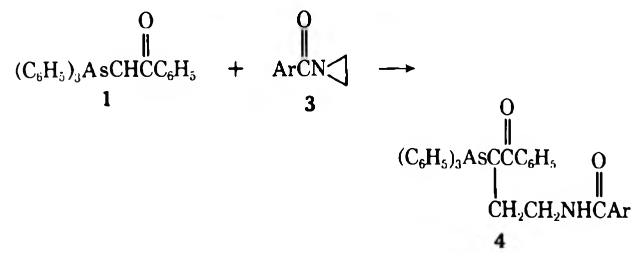
The chemistry of triphenylarsonium phenacylide (1) has recently been investigated and compared with that of triphenylphosphonium phenacylide (2).[1] It was observed that 1 and 2 showed the same sensitivity to hydrolysis and oxidation, and both gave O-alkylated

(1) A. W. Johnson and H. Schubert, *J. Org. Chem.*, **35**, 2678 (1970).

products exclusively when treated with ethyl iodide.[1-3] However, on heating in toluene, 1 gave a high yield of *trans*-1,2,3-tribenzoylcyclopropane, while 2 was recovered unchanged when it was subjected to the same experimental conditions. We now report the reactions of 1 and 2 and some of their analogs with 1-*p*-nitrobenzoylaziridine (3). Seemingly, the carbanionic centers of both 1 and 2 attack the aziridinyl carbon of 3 to form similar ring-opened intermediates. These intermediates, however, decompose to give different reaction products.

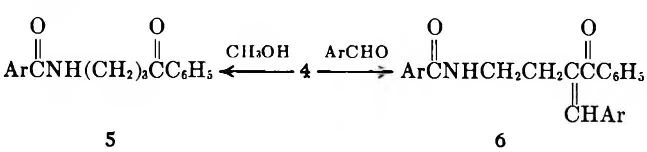
We have found that the reaction of equimolar amounts of 1 and 3 in refluxing toluene gives *N*-(γ-benzoyl-γ-triphenylarsenanylpropyl)-*p*-nitrobenzamide (4) in 41% yield.



Ar = *p*-$O_2NC_6H_4$–

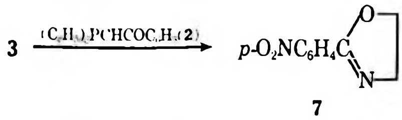
The structure of the new ylide is indicated by its infrared spectrum and by its chemical reactions. The infrared spectrum of 4 shows a carbonyl stretching frequency at 1550 cm^{-1} (as expected for a phenacyl group participating in extensive charge delocalization) and stretching frequencies at 1670 and 3130 cm^{-1} for the amido carbonyl and amido hydrogen groups, respectively.

Compound 4 is easily hydrolyzed in warm aqueous methanol to *N*-(γ-benzoylpropyl)-*p*-nitrobenzamide (5). The mass spectrum of 5 shows the molecular ion at *m/e* 312 and important mass fragments at *m/e* 207, 193, 162, and 150, indicative of successive cleavages α and β to the carbonyl group and at the amidocarbonyl linkage. Compound 4 also undergoes the Wittig reaction with *p*-nitrobenzaldehyde in refluxing toluene to give a 65% yield of *N*-(γ-benzoyl-γ-*p*-nitrobenzylidenepropyl)-*p*-nitrobenzamide (6).



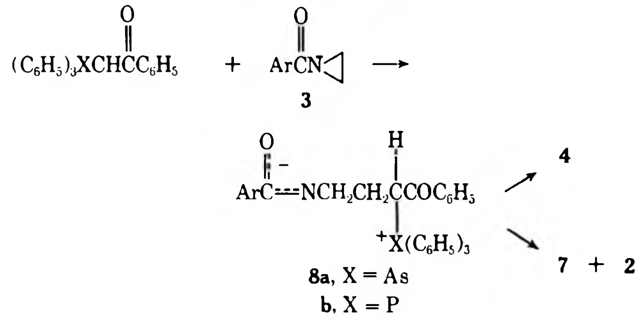
Ar = *p*-$O_2NC_6H_4$–

In contrast to the reaction of 1 with 3, triphenylphosphonium phenacylide (2) catalyzes the isomerization of 3 to 2-*p*-nitrophenyl-2-oxazoline (7). As little as 0.1 equiv of 2 (relative to 3) causes complete isomerization of 3 within a few hours in refluxing toluene. Control runs of 3 in refluxing toluene resulted in complete recovery of 3.

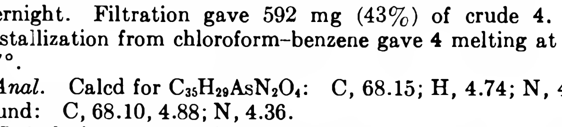


Triphenylphosphonium-*p*-nitrophenacylide and triphenylphosphonium-*p*-methoxyphenacylide also catalyze the isomerization of 3 to 7.

Both the reactions of 1 and 2 with 3 can be explained by a mechanism involving an initial nucleophilic attack of the carbanionic centers of 1 and 2 on the aziridinyl carbon of 3 to give intermediates 8a and 8b, respectively.



In the case of the arsonium intermediate 8a, proton transfer takes place to form the arsenic ylide 4, whereas in the case of the phosphonium intermediate 8b, displacement of the ylide 2 by the negatively charged benzamido moiety forms the oxazoline 7. Although the rearrangement of 1-aroylaziridines into 2-aryl-2-oxazolines by various nucleophiles such as iodide ion or trialkylamines is a well-known reaction, it is not clear why the triphenylphosphonium phenacylides catalyze the rearrangement of 3 to 7, while the corresponding triphenylarsonium phenacylide reacts with 3 to give 4. Furthermore, reaction of 3 with carbethoxymethylenetriphenylphosphorane (9) gives the ylide 10,[4] a result analogous to the reaction of 1 with 3. However, it is interesting to note that reaction of 3 with carbethoxyethylidinetriphenylphosphorane does form a small quantity of the oxazoline 7 (8%) along with the major product 1-(*p*-nitrobenzoyl)-2-ethoxy-3-methyl-2-pyrroline.[4]



Experimental Section

Reaction of 1 with 3.—To a solution of 430 mg (2.24 mmol) of 3 in 30 ml of dry toluene was added 1.00 g (2.35 mmol) of 1. The reaction mixture was refluxed for 2 hr and then allowed to stand overnight. Filtration gave 592 mg (43%) of crude 4. Recrystallization from chloroform–benzene gave 4 melting at 195–197°.

Anal. Calcd for $C_{35}H_{29}AsN_2O_4$: C, 68.15; H, 4.74; N, 4.54. Found: C, 68.10, 4.88; N, 4.36.

Hydrolysis of 4.—A mixture of 300 mg (0.49 mmol) of 4, 6 ml of methanol, and 2 ml of water was refluxed for 1 hr. The reaction mixture was cooled and filtered to give 103 mg (67%) of 5. Recrystallization from methanol gave 5 melting at 161–163°.

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.28; H, 5.31; N, 9.03.

Conversion of 4 to 6.—A mixture of 300 mg (0.49 mmol) of 4 and 75 mg (0.49 mmol) of *p*-nitrobenzaldehyde in 13 ml of dry toluene was refluxed for 1 hr. The solvent was evaporated and the residual oil was slurried in a small quantity of absolute ethanol. The crude 6 that precipitated was filtered (140 mg, 64%) and recrystallized from absolute ethanol, mp 179–181°.

(2) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

(3) F. Ramirez, R. B. Mitra, and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 5763 (1960).

(4) H. W. Heine, G. B. Lowrie, and K. C. Irving, *J. Org. Chem.*, **35**, 444 (1970).

Anal. Calcd for $C_{24}H_{19}N_3O_6$: C, 64.70; H, 4.29; N, 9.43. Found: C, 64.90; H, 4.66; N, 9.26.

Isomerization of 3 to 7.—A mixture of 190 mg (0.49 mmol) of **2** and 96 mg (0.50 mmol) of **3** in 10 ml of dry toluene was refluxed for 4 hr. The solvent was evaporated and the residue was extracted twice with 15-ml portions of hot petroleum ether (bp 65–75°). Evaporation of the pooled extracts gave 89 mg (92%) of **7**. The petroleum ether insoluble residue was shown to be **2**. The isomerization of **3** also occurred in high yield using 20 mg of **2** and 96 mg of **3**. Essentially the same results were obtained when triphenylphosphonium-*p*-nitro- and triphenylphosphonium-*p*-methoxyphenacylides[5] were substituted for **2**.

Registry No.—**1** (charged form), 24904-06-1; **1** (uncharged form), 20691-73-0; **2**, 859-65-4; **3**, 19614-29-0; **4** (charged form), 33406-31-4; **4** (uncharged form), 33406-30-3; **5**, 33406-32-5; **6**, 33406-33-6.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We also thank Professor Charles C. Sweeley for the mass spectrum of *N*-(γ-benzoylpropyl)-*p*-nitrobenzamide.

(5) S. Fliszar, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta*, **46**, 1580 (1963).

Rearrangements, Pyrolysis, and Photolysis of Trimethylcyclopropenyl Azide[1]

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Allylic rearrangements of azides exhibit relatively few of the characteristics associated with ion-pair mechanisms. Alkyl substitution and changes in solvent polarity have minor effects on the reaction rates.[2] Concerted [3,3] sigmatropic shift would appear to be a more appropriate description of the reaction. We wish to report here the allylic rearrangement of trimethylcyclopropenyl azide (I), a system which might be expected to favor the ion-pair mechanism.

The azide I was readily prepared from the known trimethylcyclopropenyl fluoroborate and sodium azide. The nmr spectrum of I in methylene chloride showed only one transition at 1.80 ppm (TMS) at room temperature. At lower temperature the line broadened, and at −79° two sharp transitions were observed at 1.36 and 2.09 ppm with relative intensities of 1:2, respectively. The activation parameters of the apparent allylic rearrangement were extracted from a complete nmr line shape analysis[3] from spectra recorded between −61 and −9°. A least-squares analysis of the data gave activation parameters of $\Delta H^{\ddagger} = 7.5 \pm 0.6$ kcal/mol and $\Delta S^{\ddagger} = -19 \pm 4$ eu. These values should be compared with $\Delta H^{\ddagger} = 20$ kcal/mol and $\Delta S^{\ddagger} = -10$ eu obtained for α,α-dimethylallyl azide.[2] The significantly lower enthalpy of activation in the cyclopropenyl system indicated at least partial ionic character of the reaction path.

(1) Supported by NSF Grant GP-18719X.

(2) A. Gagneux, S. Winstein, and W. G. Young, *J. Amer. Chem. Soc.*, **82**, 5956 (1960).

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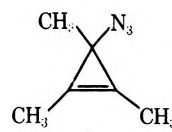
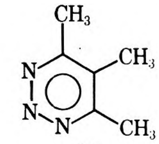


I



II

The solvent dependence of the reaction rate lends support for this hypothesis. Table I shows the activation energies estimated from the coalescence point of the methyl resonances in I in various solvents. Since no line shape analyses were made in those cases, the numbers were obtained by assuming identical preexponential factors in all solvents. This factor was determined from the data for methylene chloride. With the exception of chloroform, which shows an unusually fast rate, the general trend is as expected for an ionic pathway.

TABLE I

Solvent	Coalescence temp, °C	E_a
$CHCl_3$	−56	7.2
CH_3OH	−48	7.4
CH_2Cl_2	−33	7.9
CH_3COCH_3	−20	8.4
CCl_4	+35	10.2

Competing with the allylic shift, although with much slower rate, is the rearrangement of I to 4,5,6-trimethyl-*v*-triazine (II), a transformation which had been observed previously for triphenylcyclopropenyl azide.[4] Photolysis of either the azide I or the triazine II gave 2-butyne and acetonitrile in almost quantitative yield. The same products were formed on pyrolysis of I (300°) and II (*ca.* 500°). We were unable to observe any species intermediate between either I or II and the fragmentation products even at photolysis at low temperature (−50°). Trimethylcyclopropenylnitrene and trimethylazatetrahedrane are possible intermediates in these reactions.

Experimental Section

Trimethyl-3-azidocyclopropene (I).—A 1.41-g (8.4 mmol) sample of trimethylcyclopropenyl fluoroborate[5] and 0.59 g (9.2 mmol) of sodium azide were dissolved in 100 ml of water. The aqueous solution was stirred in an ice bath for 3 min and was then extracted with three 50-ml portions of methylene chloride. Vacuum fractionation (30–40° at 0.7–0.2 Torr) gave 1.10 g of material. On the basis of an nmr integral, this material was 67% I (0.74 g, 6.0 mmol, 71% yield) and 33% methylene chloride. This purity was sufficient for most of our studies.

Further purification by vacuum fractionation (−78°, 8 μ) removed most of the methylene chloride, allowing I to be prepared with greater than 99% purity (by nmr): nmr ($CDCl_3$) δ 1.82 (s), (CH_2Cl_2) δ 1.80 (s) [−79°, δ 2.09 (s, 2), 1.36 (s, 1)]; ir (neat) 2980, 2960, 2930, and 2860 (m, $-CH_3$), 2490 (w), 2090 (s, $-N_3$), 1859 and 1849 (w), 1438 (s), 1379 (m), 1279 (m), 1248 (s), 1083 (s), and 862 cm^{-1} (m); uv max (95% EtOH) 308 mμ (ε 71), end absorption.

4,5,6-Trimethyl-*v*-triazine (II).—A 0.50-g (3.0 mmol) sample of trimethylcyclopropenyl fluoroborate and 0.19 g (3.0 mmol) of sodium azide were treated as above. The methylene chloride extracts however, were dried over sodium sulfate and allowed to stand in the dark at room temperature for 2 days. The solvent was stripped off, and the residue was crystallized from 50:50

(4) E. A. Chandross and G. Smolinsky, *Tetrahedron Lett.*, **No. 13**, 19 (1960).

(5) G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *J. Amer. Chem. Soc.*, **90**, 173 (1968).

carbon tetrachloride–methylene chloride, giving 0.11 g (0.90 mmol, 30% yield) of II: mp 146–147°; nmr ($CDCl_3$) δ 2.66 (s, 2), 2.32 (s, 1); ir (KBr) 3000 (w), 1548 (s), 1433 (w), 1399 (m), 1386 (s), 1366 (s), 1241 (w), 1137 (w), 1102 (w), 1033 (m), 991 (s), 898 (w), 769 (w), and 668 cm^{-1} (s); uv max (95% EtOH) 278 mμ (ε 610), 217 (4300), end absorption; mass spectrum (70 eV) 123.0794 (calcd for $C_6H_9N_3^+$: 123.0796). *Anal.* Calcd for $C_6H_9N_3$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.29; H, 7.49; N, 33.96.

Photolyses of I and II were carried out in benzene and methylene chloride solutions in nmr tubes in the probe of a Varian HR-60 spectrometer. At ambient temperatures and with the probe cooled to −56° (cooled only for methylene chloride solution), irradiation (1000-W mercury lamp) of I gave material with an nmr spectrum identical with that of a mixture of 2-butyne and acetonitrile. The irradiations of I and II by medium pressure mercury arc also gave 2-butyne and acetonitrile, identified by identical nmr spectra and vpc retention times.

Pyrolyses of I and II were carried out in a flow system. At 300° I gave a mixture of II, 2-butyne, and acetonitrile. At the same temperature, II did not react. At higher temperaturs (*ca.* 500°), II also gave 2-butyne and acetonitrile. Products were identified by nmr and vpc as above.

Rate measurements on I were made in a Varian A-60A spectrometer equipped with a V-6040 variable temperature controller. Temperatures were determined by measuring the separation between the methyl and hydroxyl resonances in a separate methanol sample.[6] The methanol sample was used to determine the temperature before each sample spectrum. At least 15 min were allowed for thermal equilibration each time a tube was placed in the probe and each time the probe temperature was changed. Half-widths were measured and compared with computer-calculated values.[3] A linear least squares treatment gave the indicated activation parameters.

Registry No.—I, 33209-84-6; II, 33209-85-7.

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An Investigation of the Rate of Hydrolysis of 1-Phenylethyl Phenylphosphinate as a Function of pH[1]

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During our investigation of the solvolysis of a variety of phosphinate esters, we examined the mode of reaction of 1-phenylethyl phenylphosphinate (1) as a function of pH. The rate of reaction of 1 was found to be very sensitive to the addition of hydroxide ion. In order to determine the molecularity of the reaction, the rate of reaction of 1 as a function of pH was studied (Table I). The rates were measured in the presence of 0.10 *M* $NaClO_4$ to minimize salt effects.

The pH–rate profile for the solvolysis of 1 is shown in Figure 1. The interesting aspects of the curve are that between pH 4 and 6 there is a plateau and above pH 9 a linear plot with a slope of 1 is observed. The entire curve is reproduced very well by eq 1 where $k_1 = 1.58 \times 10^{-4}$ sec^{-1} and $k_2 = 2.63 \times 10^2$ M^{-1} sec^{-1}.

$$\text{rate} = k_1[1] + k_2[1][OH] \quad (1)$$

The comparison of the rates of hydrolysis of phos-

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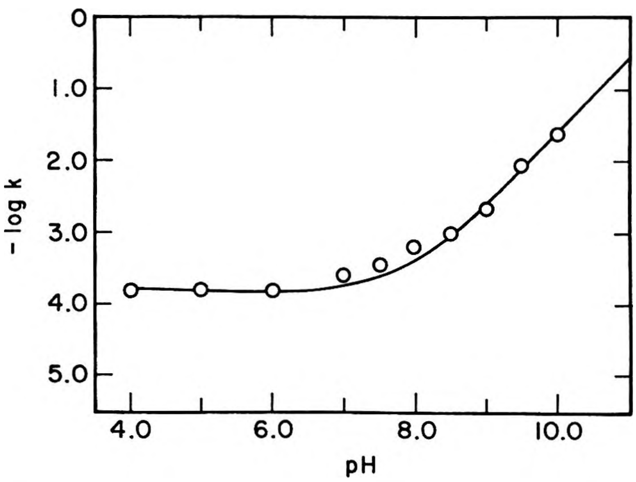

Figure 1.—pH–rate profile for the hydrolysis of 1-phenylethyl phenylphosphinate.

TABLE I

THE RATE OF REACTION OF 1 IN 30% ETHANOL–WATER (0.1 *M* $NaClO_4$) AT 45°

pH	Rate	Log *k*	Rel rate
4.0	1.60×10^{-4}	−3.796	1
5.0	1.55×10^{-4}	−3.809	1
6.0	1.58×10^{-4}	−3.801	1
7.0	2.46×10^{-4}	−3.609	1.6
7.5	3.48×10^{-4}	−3.458	2.2
8.0	6.42×10^{-4}	−3.192	4.1
8.5	8.05×10^{-4}	−3.094	5.1
9.0	2.06×10^{-3}	−2.686	13
9.5	9.06×10^{-3}	−2.043	57
10.0	2.44×10^{-2}	−1.613	154

phonates,[2] $(RO)_2P(O)H$, and phosphinates,[3] $(RO)C_2H_5$-P(O)H, which contain a P–H bond, has led to the conclusion that the enhanced rates of highly branched esters such as R = *tert*-butyl were attributable to the incursion of an SN1 mechanism. Since the 1-phenylethyl ester should be of the same order of reactivity and form a carbonium ion of the same stability as the *tert*-butyl group, the probable mechanism occurring in the plateau region of the curve is formation of a carbonium ion by an SN1 mechanism. In order to substantiate the SN1 nature of the reaction, the rates of solvolysis of 1-(*m*-chlorophenyl)ethyl phenylphosphinate ($k_1 = 9.45 \times 10^{-6}$ sec^{-1}), 1-(*p*-methylphenyl)ethyl phenylphosphinate ($k_1 = 8.28 \times 10^{-3}$ sec^{-1}), and the parent (1) ($k_1 = 2.95 \times 10^{-4}$ sec^{-1}) were measured in the acidic region in 30% ethanol–water (v/v) at 45.0°. The Hammett plot of the rate constants *vs.* Brown's σ^+ values gives a good correlation with a ρ of −4.25. This indicates that substantial positive charge is developed in the transition state and that the reaction in the acidic region does indeed follow a carbonium ion mechanism.

Recent investigations of alkaline hydrolysis have shown that phosphates,[4,5] phosphonates,[4] and phosphinates[6] hydrolyze by exclusive attack of the hydrox-

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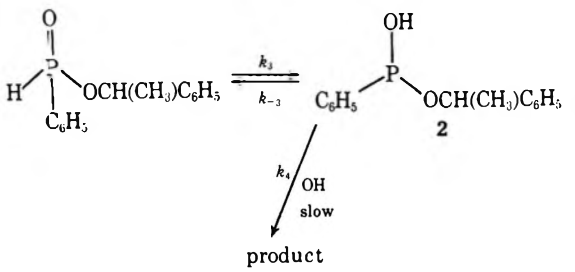
(5) P. W. C. Barnard, C. A. Bunton, D. R. Llewelly, K. G. Aldham, B. A. Silner, and C. A. Vernon *Chem. Ind. (London)*, 760 (1955).

(6) P. Haake, C. E. Diebert, and R. S. Marmor, *Tetrahedron Lett.*, 5247 (1968).

ide ion at phosphorus. By analogy to these and other studies the mechanism that is occurring in the basic region (above pH 9) is attack of hydroxide ion with the probable formation of a pentacoordinate intermediate (the formation of this intermediate has not been unambiguously established in the alkaline hydrolysis of noncyclic phosphorus compounds).

The high rate of reaction of **1** may be simply a more rapid rate due to the phosphorus atom being more liable to attack because of the lack of steric hindrance to the approaching hydroxide ion. A more attractive possibility is that the bimolecular reaction may be occurring through a trivalent species (eq 2) (*e.g.*, **2**). This mechanism implies that trivalent phosphorus esters would have an unusually fast rate of hydrolysis when compared to pentavalent compounds. This is substantiated by the rapid rate of hydrolysis of triethylphosphite (TEP) ($k_{10°}$ = 5.77 × 10^{-3} sec^{-1}).[7] Comparison of the rate ratio of TEO to diethyl phosphonate



(2)

(DEP)[3] at 80° shows that the hydrolysis of the trivalent species is unusually fast (TEP/DEP = 4670). Assuming k_4 for **2** to be very similar to the rate of hydrolysis of TEP (4.3 sec^{-1} at 80°), the value of k_3/k_{-3} would then be approximately 2 × 10^{-5}. This is in agreement with physical observations that the trivalent species could not be detected by spectral techniques.[8]

Acid-catalyzed exchange of the hydrogen bound to phosphorus and the oxidation of dialkyl phosphonates has been found to occur through the phosphite form (trivalent species).[9-12] In these reactions the rate-determining step was found to be the formation of the trivalent species.

Thus the trivalent species is a very attractive intermediate in the alkaline hydrolysis of phosphinate esters containing a P–H bond. Further evidence will be needed to definitely establish this hypothesis.

Experimental Section[13]

Preparation of Materials. A. 1-Phenylethyl Phenylphosphinate.—*N,N'*-Dicyclohexylcarbodiimide (5.00 g, 0.0242 mol, Aldrich) was added to a refluxing solution of phenylphosphinic acid (3.44 g, 0.0242 mol, Aldrich) in 200 ml of anhydrous benzene. After refluxing for 30 min, 1-phenylethanol (2.96 g, 0.0242 mol) was added dropwise and the mixture was refluxed for 30 min. The solution was cooled to room temperature and *N,N'*-dicyclohexylurea was removed by filtration. The benzene was removed on a rotary evaporator. The colorless oil was dissolved in 100 ml of diethyl ether and a small amount of solid material was removed by filtration. Removal of the ether on the rotary evaporator yielded 5.90 g (99%) of 1-phenylethyl phenylphosphinate as a colorless oil. The nmr spectrum[14] of the ester in chloroform-*d* showed bands at δ 7.3 (m, 10 H), 7.30 and 7.60 (2d, 1 H, J_{P-H} = 566 and 564 Hz), 1.55 and 1.63 (2 d, 3 H), and 5.60 (m, 1 H).

Anal. Calcd for $C_{14}H_{15}O_2P$: C, 68.35; H, 6.12; P, 12.58. Found: C, 68.18; H, 6.05; P, 12.46.

B. 1-(*p*-Methylphenyl)ethyl Phenylphosphinate.—1-(*p*-Methylphenyl)ethyl phenylphosphinate was synthesized in the same manner from 3.0 g (0.145 mol) of 1-(*m*-chlorophenyl)-ethanol to yield 6.06 g (96%) of the desired product. The infrared spectrum of the neat ester showed bands at 2370 (w), 1230 (s), 1125 (s), 955 (s), and 822 cm^{-1} (m). The nmr spectrum[14] of the ester in chloroform-*d* showed bands at δ 7.4 (m, 5 H), 7.18 (s, 4 H), 7.3 and 6.6 (2d, 1 H, J_{P-H} = 570 and 577 Hz), 1.48 and 1.61 (2d, 3 H, $CHCH_3$), 5.5 (m, 1 H), and 2.15 and 2.22 (2s, 3 H).

C. 1-(*m*-Chlorophenyl)ethyl Phenylphosphinate.—1-(*m*-Chlorophenyl)ethyl phenylphosphinate was synthesized in the same manner from 3.3 g (0.024 mol) of 1-(*p*-methylphenyl)-ethanol to yield 4.00 g (97%) of the desired product. The nmr spectrum[14] of the ester in chloroform-*d* showed bands at δ 7.5 (m, 9 H), 7.4 and 7.6 (2d, 1 H, J_{P-H} = 570 and 577 Hz), 1.62 and 1.72 (2d, 3 H) and 5.5 (m, 1 H).

Kinetic Methods.—Rates were measured by standard techniques (pH-Stat method) using a Radiometer automatic titration apparatus which consisted of a TTT 1c automatic titrator, a ABU 1c autoburette (with a 2.5-ml burette), a TTA 3c titrator assembly, and a 2c recorder.

Registry No.—**1**, 33521-92-5; 1-(*p*-methylphenyl)-ethyl phenylphosphinate, 33521-93-6; 1-(*m*-chlorophenyl)ethyl phenylphosphinate, 33521-94-7.

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(11) Z. Luz and B. L. Silver, *ibid.*, **83**, 4518 (1961).
(12) Z. Luz and B. L. Silver, *ibid.*, **84**, 1095 (1962).
(13) Analysis is by the Microanalytical Laboratory of the Department of Chemistry, University of California.
(14) The additional multiplicity in the nmr spectra is due to the presence of two diasteroisomers.

Spectrophotometric Determination of the Second Dissociation Constants of the Aminoisoquinolines

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The first protonation of nitrogen heterocycles containing amino substituents on the ring has been shown to occur at the ring nitrogen and not at the substituent amino group.[1-4] Albert[5] has compiled a large number of ionization constants corresponding to this first and second protonation as determined by various workers. In previous work done in this laboratory, we have updated or determined the second pK_a' values for the isomeric aminopyridines and aminoquinolines.[6] It is of interest to investigate the relative basicity of the primary amino group for the isomeric aminoisoquinolines (in terms of pK_a') by ultraviolet spectroscopy and compare their values to those obtained from the above pyridine and quinoline compounds. The second pK_a' values for the aminoisoquinolines along with the temperature at which they were determined are given in Table I.

(1) J. L. Irvin and E. M. Irvin, *J. Amer. Chem. Soc.*, **69**, 1091 (1947).
(2) D. P. Craig and L. N. Short, *J. Chem. Soc.*, 419 (1945).
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(4) J. C. Craig, Jr., and D. E. Pearson, *J. Heterocycl. Chem.*, **5**, 531 (1968).
(5) A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, pp 73–78.
(6) E. V. Brown and A. C. Plasz, *J. Heterocycl. Chem.*, **7**, 335 (1970).

Table I

Second Dissociation Constants of Aminoisoquinolines

Compd	Registry no.	First pK_a'	Second pK_a'	Spread[a]	Concn, *M*	Temp, °C	Analytical wavelength, mμ
Isoquinoline		5.40[c]				20	
1-Aminoisoquinoline	1532-84-9	7.62[c]	−9.59	0.10	4×10^{-5}	23.4 ± 0.5	236
3-Aminoisoquinoline	25475-67-6	5.05[b]	−4.20	0.06	1×10^{-4}	23.5 ± 0.5	391
4-Aminoisoquinoline	23687-25-4	6.28[b]	−2.29	0.05	4×10^{-5}	25.0 ± 1.0	248
5-Aminoisoquinoline	1125-60-6	5.59[b]	1.07	0.06	2×10^{-5}	25.0 ± 1.0	257
6-Aminoisoquinoline	23687-26-5	7.17[b]	−0.59	0.07	4×10^{-5}	25.0 ± 0.5	263
7-Aminoisoquinoline	23707-37-1	6.20[b]	1.13	0.06	2×10^{-5}	24.5 ± 0.5	254
8-Aminoisoquinoline	23687-27-6	6.06[b]	0.18	0.06	2×10^{-5}	25.0 ± 1.0	247

[a] The spread may not exceed ±0.06 units for pK_a' values above zero and ±0.10 for values below zero.[7] [b] A. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 2240 (1948). [c] A. R Osborn, K. Schofield, and L. N. Short, *ibid.*, 4191 (1956).

Table II

Ultraviolet Spectra of Aminoisoquinolines[a]

Compd	Solvent	pH or H_0	Species[b]	λ_{max}, mμ	Log ϵ_{max}
1-Aminoisoquinoline	95% Ethanol[e]		N	239, 300, 331	4.25, 3.81, 3.70
	NaOH–H_2O	~12	N	246, 290, 324	4.10, 3.81, 3.56
	H_2SO_4–H_2O	−4.00	M	236, 270, 281, 327, 337	4.37, 3.79, 3.83, 3.81, 3.70
	H_2SO_4–H_2O	−10.37[c]	D	236, 268, 279, 324, 335	4.44, 3.66, 3.66, 3.77, 3.74
3-Aminoisoquinoline	NaOH–H_2O	~12	N	229, 268, 277, 287 351	4.03, 3.08, 3.11, 2.96, 2.85
	Na_3BO_3–H_2O[d]	9.21	N	231, 269, 278, 288, 353	4.74, 3.67, 3.73, 3.58, 3.42
	H_2SO_4–H_2O	0.00	M	237, 277, 296, 391	4.79, 3.59, 3.28, 3.63
	H_2SO_4–H_2O	−8.00	D	237, 275, 339	4.67, 3.36, 3.63
4-Aminoisoquinoline	95% Ethanol[e]		N	246, 250, 338	4.04, 4.03, 3.79
	0.01 *N* NaOH[e]	~12	N	238, 308, 332	4.08, 3.64, 3.75
	Na_3BO_3–H_2O[d]	9.21	N	210, 240, 248, 310, 332	4.68, 4.10, 3.94, 3.64, 3.74
	0.01 *N* HCl[e]	~2	M	216, 230, 317, 357	4.48, 3.63, 3.54, 3.92
	Glycine–HCl[d]	3.28	M	217, 238, 262, 316, 354	4.50, 4.07, 3.59, 3.55, 3.94
	H_2SO_4–H_2O	1.00	M	248, 284, 353	4.07, 3.38, 3.34
	H_2SO_4–H_2O	−9.98	D	233, 274, 335	4.66, 3.43, 3.69
5-Aminoisoquinoline	95% Ethanol[e]		N	228, 238, 336	4.23, 4.27, 3.79
	0.01 *N* NaOH[e]	~12	N	238, 327	4.27, 3.70
	Na_3BO_3–H_2O	9.21	N	205, 238, 332	4.48, 4.22, 3.70
	0.01 *N* HCl[e]	~2	M	226, 258, 336, 380	4.23, 4.11, 3.54, 3.50
	Glycine–HCl[d]	3.07	M	208, 259, 340, 378	4.56, 4.18, 3.53, 3.53
	H_2SO_4–H_2O	3.00	M	257, 356	4.18, 3.54
	H_2SO_4–H_2O	−9.98	D	224, 259, 331	4.70, 3.30, 3.70
6-Aminoisoquinoline	NaOH–H_2O	~12	N	238, 297, 323	4.66, 3.98, 3.44
	Na_3BO_3–H_2O[d]	9.21	N	234, 239, 296, 304, 326	4.60, 4.61, 3.83, 3.84, 3.47
	$NaC_2H_3O_2$–$HC_2H_3O_2$[d]	4.27	M	231, 238, 266, 337, 352	4.43, 4.34, 4.32, 4.01, 4.03
	H_2SO_4–H_2O	3.00	M	230, 263, 333, 348	4.45, 4.33, 4.04, 4.06
	H_2SO_4–H_2O	−4.00	D	223, 263, 320, 328	4.71, 3.54, 3.65, 3.69
7-Aminoisoquinoline	NaOH–H_2O	~12	N	230, 271, 279, 345	4.60, 3.91, 3.85, 3.38
	Na_3BO_3–H_2O[d]	9.21	N	231, 273, 349	4.56, 3.90, 3.40
	Glycine–HCl[d]	3.22	M	218, 254, 289, 385	4.14, 4.58, 3.82, 3.35
	H_2SO_4–H_2O	3.60	M	254, 283, 385	4.63, 4.03, 3.48
	H_2SO_4–H_2O	−2.00	D	233, 263, 307, 328	4.65, 3.50, 3.65, 3.66
8-Aminoisoquinoline	NaOH–H_2O	~12	N	222, 238, 342	4.33, 4.18, 3.67
	Na_3BO_3–H_2O[d]	9.21	N	207, 224, 307, 345	4.61, 4.36, 3.51, 3.68
	Glycine–HCl[d]	3.05	M	209, 250, 325, 417	4.54, 4.26, 3.41, 3.66
	H_2SO_4–H_2O	3.00	M	247, 323	4.13, 3.48
	H_2SO_4–H_2O	−4.00	D	227, 257, 327	4.69, 4.32, 3.74

[a] The absorption peaks pertaining to this work were recorded between 220 and 400 mμ. [b] N = neutral molecule, M = monocation, D = dication. [c] The dication may not be 100% isolated at this H_0 value. Albert states that a species is considered isolated when the spectrum changes 1% or less in one pH unit. From −10.20 to −10.37 the maximum change in the spectrum is 3.6%. [d] See footnote *c*, Table I. [e] Reference 3.

The method selected for these determinations was that used by Albert for the determination of the second dissociation constant of 3-aminopyridine[7-9] and which we previously used.[6]

It can be seen that the second pK_a' value of 1-aminoisoquinoline is in the same general area of those of 2-aminopyridine (pK_a' = −8.1) and 2-aminoquinoline (pK_a' = −9.08).[6] This is probably due to the close proximity of the two positive charges on the molecule and some interaction with the peri hydrogen atom. In the case of 3-aminoisoquinoline where there exists two adjacent positive charges, however, the second pK_a' is considerably less than would be expected for an amino substituent α to the ring nitrogen. At first glance, the value obtained for the second pK_a' of 4-aminoisoquinoline is larger than that for a β-amino group, *e.g.*, 3-aminoquinoline (pK_a' = −0.40),[6] but it may be pointed out that this value is in the general area of 3-aminopyridine (pK_a' = −1.5).[6]

In the cases of the 6- and 8-aminoisoquinoline and 5- and 7-aminoquinoline, the pK_a' value should be less than those found for 5- and 7-aminoisoquinoline and 6-aminoquinoline owing to the second protonation of the additional ionic resonance forms described by Albert.[5]

The ultraviolet spectra of the 1-, 4-, and 5-aminoisoquinolines in 0.10 *N* hydrochloric acid have been recorded by Ewing and Steck.[3] It seems that they were not concerned with pure electronic species, for they have a mixture of mono- and dications in the 5 isomer. The ultraviolet spectra of all the pure mono- and dicationic species of the aminoisoquinolines were determined in sulfuric acid of accurately known pH and H_0 values. The results, as well as those of other workers, are recorded in Table II.

The effect on the ultraviolet spectra of monoprotonation of the isomeric aminoisoquinolines has been described previously.[10] Upon diprotonation, 1-, 6-, and 8-aminoisoquinoline undergo small changes in all the absorption bands. Large hypsochromic shifts occur of the long wavelength band for 3-, 4-, and 5-aminoisoquinolines. 7-Aminoisoquinoline is partly anomalous in that it exhibits large shifts in all the ultraviolet absorption bands. The data in Table II for all of the isomers of the aminoisoquinolines show that the spectra of all their dications resemble those of the isoquinolinium ion, which is to be expected since the same phenomena occur with the aminoquinolines.[6]

Experimental Section

The experimental procedure used was that of Brown and Plasz[6] except for 1-aminoisoquinoline. A stock solution of this amine was prepared by weighing out 0.0721 g (0.0005 mol) of the solid and dissolving it in 500 ml of Baker Analyzed sulfuric acid. It was then diluted to the proper H_0 by the addition of water and/or sulfuric acid and the pK_a' value was determined as above.

The preparation and purification of the aminoisoquinolines is described below.

1-Aminoisoquinoline.—This compound was purified by vacuum sublimation at 85°, mp 120–121° (lit.[11] 122–123°).

3-Aminoisoquinoline.—This compound was purified by vacuum sublimation at 140°, mp 175–176° (lit.[12] 178°).

4-Aminoisoquinoline.—This compound was recrystallized twice from benzene, mp 107–108° (lit.[13] 108.5°).

5-Aminoisoquinoline.—This amine was recrystallized from benzene–hexane, vacuum sublimed at 105–110°, and recrystallized again from benzene–hexane, mp 129° (lit.[13] 128–129°).

6-Aminoisoquinoline.—6-Acetamidoisoquinoline (0.1 g) was refluxed with 10 ml of 20% sodium hydroxide in water for 1 hr. After cooling, the amine was crystallized, removed by filtration, and sublimed under vacuum at 190°, mp 217–217.5° (lit.[14] 217–218°).

7-Aminoisoquinoline.—This compound was prepared by the method of Osborn and Schofield.[10] Purification was accomplished by recrystallization from benzene and sublimation under vacuum at 160°, mp 203–204° (lit.[10] 204°).

8-Aminosoquinoline.—This compound was purified by vacuum sublimation at 100° followed by recrystallization from heptane, mp 173–174° (lit.[15] 173–174°).

(7) A. Albert and E. P. Serjeant, "Ionization Constants, of Acids and Bases," Wiley, New York, N. Y., 1962.

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The Effect of Solvent and Cation on the Isomer Ratio of the Enolates of 3-Methylcyclohexanone[1a]

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If the enolization of an unsymmetrical ketone is carried out in the presence of excess ketone, the enolate mixture is thermodynamically controlled, whereas, if it is carried out with excess base, the mixture is kinetically controlled. The difference between kinetic and thermodynamic control has been demonstrated with a number of different ketones.[2-5] House and Kramer[6] have shown that the enolate mixture can be quenched with acetic anhydride to produce a mixture of enol acetates in the same isomer ratio as that of the original enolates.

This paper reports studies of the equilibrium and kinetic control of the enolization of 3-methylcyclohexanone and of the effect of changing the solvent or cation on the equilibrium mixture.

The preparation of the mixture of lithium enolates followed the procedure described by Huff[7] and was essentially similar to that previously described by other authors.[6] In a flame-dried apparatus, under nitrogen pressure, triphenyl methane was dissolved in the appropriate solvent, and to this a solution of phenyllithium in diethyl ether was added. 3-Methylcyclohexanone was then added with a syringe, and, after an appropriate length of time, the enolate mixture was quenched with excess acetic anhydride. In the case of equilibrium control, the ketone was in excess and the enolate mixture was stirred for over 18 hr before being

(1) (a) Supported in part by a National Science Foundation grant. (b) To whom correspondence is to be addressed: Chemistry Department, University College, London.

(2) D. Caine and B. J. L. Huff, *Tetrahedron Lett.*, **No. 39**, 4695 (1966).

(3) D. Caine, *J. Org. Chem.*, **29**, 1868 (1964).

(4) H. O. House and B. M. Trost, *ibid.*, **30**, 2502 (1965).

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(6) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963).

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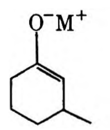
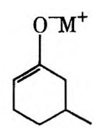
quenched. In the case of kinetic control, the trityllithium was about 20% in excess. The excess acetic anhydride was removed, the enol acetates were extracted with pentane, and the solution was distilled under vacuum. All the material which boiled below 150° at about 40 mm was collected and subjected to vapor phase chromatography. A 10 ft × 3/4 in. copper tube packed with Carbowax on firebrick (9% Carbowax) was used. The column was operated at 150°. The two peaks due to the enol acetate of 3-methylcyclohexanone were collected and identified on the basis of their nmr spectra. In particular, the vinyl proton peak for the Δ^1 isomer was a doublet, and for the Δ^6 isomer it was a triplet.



Δ^1



Δ^6

The two vpc peaks are clearly separated, but are right next to each other. Retention times were not determined; however, a peak due to 3-methylcyclohexanone was identified from the vpc of the pure ketone, and the Δ^1 peak always appeared at 1.52 and the Δ^6 peak at 1.64, the time that the 3-methylcyclohexanone peak appeared. The areas under the two peaks were assumed to be proportional to the amounts of Δ^1 and Δ^6 isomers.

Tritylsodium and tritylpotassium were prepared directly from the metal and triphenylmethane, in the appropriate solvent, according to the method of House and Kramer.[8] Otherwise, the procedure was the same as that with trityllithium. Each experiment was performed in duplicate, and in no case was disagreement greater than 2%.

The solvents which were used were monoglyme (1,2-dimethoxyethane), diglyme [1,2-bis (2-methoxyethoxy)-ethane], triglyme [bis-2-(2-methoxyethoxy)ethyl ether], and tetrahydrofuran. Attempts to carry out the experiment in diethyl ether were unsuccessful. The enolization of 3-methylcyclohexanone in monoglyme, with trityllithium as the attacking agent, led to 18% Δ^1 isomer and 82% Δ^6 isomer under kinetic control, which is probably indicative of partial blockage by the methyl group of the approaching base. Equilibrium control was studied under a variety of conditions and the results are summarized in Table I.

TABLE I

Solvent	Cation	Δ^1, %	Δ^6, %
Monoglyme	Li^+	46	54
Monoglyme	Na^+	43	57
Monoglyme	K^+	48	52
Diglyme	Li^+	47	53
Diglyme	Na^+	26	74
Triglyme	Li^+	47	53
Tetrahydrofuran	Li^+	42	58

Under equilibrium conditions, the enolization of 3-methylcyclohexanone leads to a nearly 50:50 mixture of Δ^1 and Δ^6 isomers in all cases but one. In every case, the Δ^6 isomer is favored over the Δ^1 isomer.

As far as the lithium enolates are concerned, it apparently makes little or no difference whether the solvent is monoglyme, diglyme, or triglyme. On the other hand, there appears to be a significant difference for the sodium enolates. This may be a reflection of variations in cation–solvent interactions. The small lithium cation is perhaps equally as well solvated by any of the glymes. With tetrahydrofuran, for which the carbon chain is pulled out of the way of the oxygen, the equilibrium is shifted towards the Δ^6 isomer to a greater extent than with the glyme solvents. Indeed, in a situation in which the coordinating ability of the glyme molecule is eliminated, Agami and Prevost[9] have found that monoglyme is actually a better base than diglyme toward forming a hydrogen bond with chloroform. Zakharkin[10] and coworkers reported that Mg^{2+} is more strongly solvated by monoglyme than by diglyme. It should be pointed out, however, that other authors[11] have interpreted their results in terms of increased Li–glyme interaction in going up the glyme series. The nature of the anion may be significant. The studies reported in this paper involved an enolate anion which should bond to lithium *via* an oxygen, whereas the studies by Chan and Smid[11] involved the fluorenyl anion separated from the cation by a glyme molecule. With the larger sodium ion, it may be possible for the glyme molecule to wrap itself around the cation, and hence diglyme may interact to a considerably greater extent than monoglyme with Na^+. That is, the Na^+–diglyme system may involve solvent-separated ion pairs, whereas the other systems reported here may involve contact ion pairs. Perhaps, since the oxygen–sodium bond is weaker than the oxygen–lithium bond, the diglyme molecule is able to insert itself between cation and anion in the former case, but not in the latter. There is agreement among authors[11–13] that glyme–Na^+ interaction increases as the glyme series is ascended.

Registry No.—3-Methylcyclohexanone Δ^1-enol, 33521-81-2; 3-methylcyclohexanone Δ^6-enol, 33521-82-3.

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(11) L. L. Chan and J. Smid, *J. Amer. Chem. Soc.*, **89**, 4547 (1967).

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Mechanism of the Formation of 1,8,*exo*-9,11,11-Pentachloropentacyclo-[6.2.1.1^3,6^.0^2,7^.0^4,10^]dodecan-5-one in the Photolysis of Endrin

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Endrin (1) reportedly photolyzes to 2[1,2] and two isomers, 3 and 4.[3] Although proposed previously,[1] 2

(1) M. Fujita, A. Ishii, and Y. Sakagami, *J. Hyg. Chem.*, **15**, 9 (1969).

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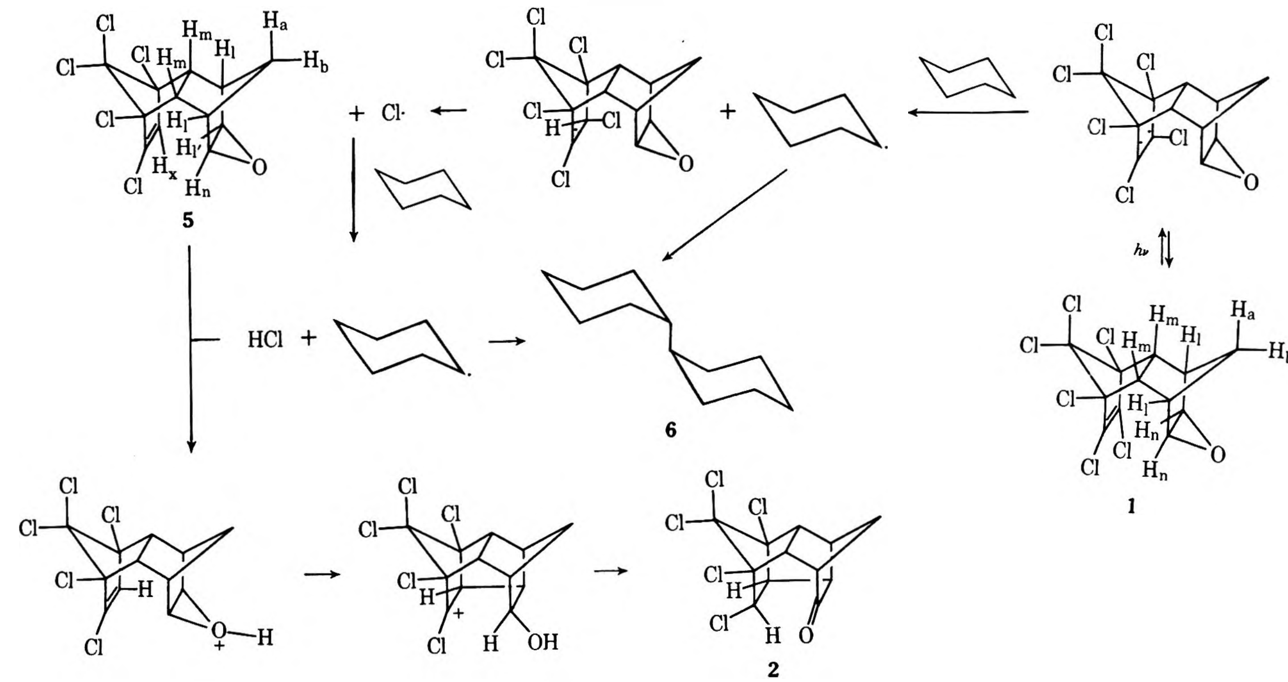
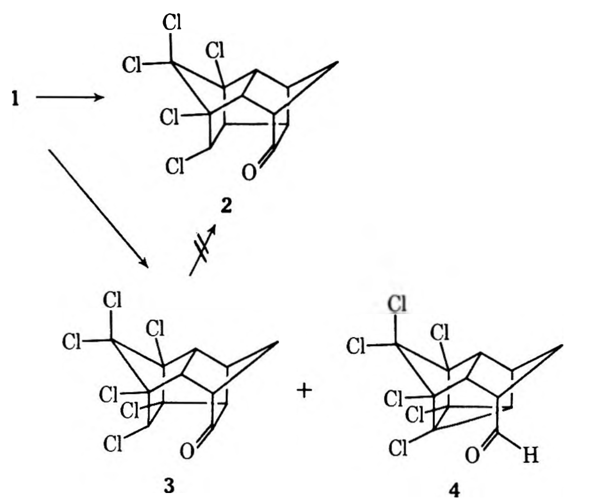
(3) J. D. Rosen and D. J. Sutherland, *Bull Environ. Contam. Toxicol.*, **2**, 1 (1967).

SCHEME I



does not arise from **3**.[2] We now report experiments that bear on the mechanism of the conversion of **1** to **2**.



Isomer **3** is the major product of either thermal[4] or acid-catalyzed[5] rearrangement of **1**, but its formation could also be suitably explained photochemically *via* intramolecular H abstraction involving a six-membered transition state. However, since such an intramolecular H abstraction does not easily provide **2** from **1**, an alternate route involving the formation of an intermediate was explored. Base was added to take up the HCl produced in order to retard any effect of acid catalysis. When a heterogenous mixture of sodium hydroxide and **1** in cyclohexane was well stirred during the photolysis, only one photoproduct was formed as followed by nmr, ir, and tlc. No chemical shifts at δ 4.6 and 5.0, characteristic of compounds **2** and **3**, or any aldehydic resonances were observed in the nmr spectra. No hydroxyl or carbonyl bands were observed in the ir spectra. The photoproduct (**5**) was stable under the reaction conditions in the presence of **1**. The photolysis was followed for 16 hr with no appearance of compounds **2**, **3**, or **4**.

Bicyclohexyl (**6**) was found as a secondary product of the photolysis of **1** as identified by tlc, nmr, ir, and mass spectroscopy. Time studies using nmr as an analytical tool showed that bicyclohexyl was formed in a ratio of 1:1 with **5**.

Attempted separation of **5** from the concentrated reaction mixture by column chromatography through silica gel or Florisil gave over 90% rearrangement of **5** to **2**. A Florisil column prewashed with an alkaline solution still afforded 22% rearrangement of **5** to **2**. Heating **5** quickly to over 200° in a capillary tube gave nearly quantitative conversion to **2**; a trace component having an identical R_f value with that of 1,8,9,11,11-pentachlorohexacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{4,10}.0^{5,9}]dodecan-5-ol was observed in the tlc.

On the basis of the data presented, it appears that the major route for the formation of **2** is *via* acid catalysis of **5**. The overall mechanism shown in Scheme I for the formation of **2** in the photolysis of **1** in cyclohexane is proposed.

Experimental Section[6]

Photolysis of 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,-6,7,8,8a-octahydro-1,4-*endo*,*endo*-5,8-dimethanonaphthalene (1) (Endrin).—After stirring for 2 hr, a mixture of 25.0 g of Endrin and 2.65 g of NaOH pellets in 300 ml of pesticide grade cyclohexane[7] was irradiated in a distilled-water-cooled quartz immersion well (ambient temperature 29°) with a Hanovia 450-W mercury arc lamp equipped with a Vycor filter for 12 hr. Nmr

(4) D. D. Phillips, G. E. Pollard, and S. B. Soloway, *J. Agr. Food Chem.*, **10**, 217 (1962).

(5) C. W. Bird, R. C. Cookson, and E. Crundwell, *J. Chem. Soc.*, 4809 (1961).

(6) Infrared spectra were obtained with a Perkin-Elmer Model 21 double-beam recording spectrophotometer in CCl_4 solutions against a CCl_4 blank. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer using pesticide grade cyclohexane. Nmr spectra were determined on a Varian Associates Model A-60A spectrophotometer with tetramethylsilane as an internal standard. Mass spectral data were obtained using a Hitachi RMU-6 mass spectrometer at an ionization voltage of 70 eV. Elemental analysis was determined by Dr. C. S. Yeh, Purdue University.

(7) Endrin, twice recrystallized from EtOH–H_2O gave uv max (cyclohexane) 222 nm (ϵ 4150).

analysis showed approximately 40% conversion of 1 to 5.[8] After concentration a representative sample, 0.200 g, was spotted on a Kontes K-416000 Chromaflex tlc plate coated with silica gel PF-254 and developed with a 4:1 solution of pentane–ethyl ether to yield three clear spots (1, 5, and 6) with R_f values of 0.54, 0.45, ad 0.81, respectively. Structures 1 and 6 were proved by isolation of these materials from the tlc plate and comparison (ir, nmr, tlc, and mass spectra) with authentic materials.

1,2,4,10,10-Pentachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo*,*endo*-5,8-dimethanonaphthalene (5).—This material, recovered from the tlc plate, slowly crystallized on standing to give mp 204–207° dec, sealed tube; uv max (cyclohexane) 219 nm (ϵ 2850); ir (CCl_4) 6.30 μ (ClC=CH), 11.73 μ (epoxide); nmr ($CDCl_3$) δ 6.04 (s, 1, H_x), 3.46 (m, 1, H_n), 3.13 (m, 2, H_m), 2.93 (m, 3, H_l), 1.81 (t of d, 1, J = 1.7, 10.0 Hz, H_b), and 0.99 (d, 1, J = 10.0 Hz, H_a); mass spectrum (70 eV), m/e (rel intensity) parent 344 (6.2) five chlorine pattern, P − Cl 309 (49.4) four chlorine pattern, base P − C_5H_6ClO 227 (78.0) four chlorine pattern, 82 (63.0), and 81 (75.2). The fragmentation pattern of photoproduct 5 is remarkably similar to that of 1 as seen by the alignment of their molecular ions.

Anal. Calcd for $C_{12}H_9Cl_5O$: C, 41.60; H, 2.62; Cl, 51.18. Found: C, 41.44; H, 2.89; Cl, 51.40.

Registry No.—1, 72-20-8; 2, 33487-97-7; 5, 33487-96-6.

Acknowledgment.—This investigation was supported in part by the Celanese Corp., Standard Oil of Ohio, and the Purdue Research Foundation, and by generous samples of Endrin from the Shell Development Co.

(8) An initial solution containing 8.5 g of Endrin gave over 95% conversion of 1 to 5 in 4 hr.

Oxidation of Tetramethyl-1,3-cyclobutanedione under Baeyer–Villiger Conditions

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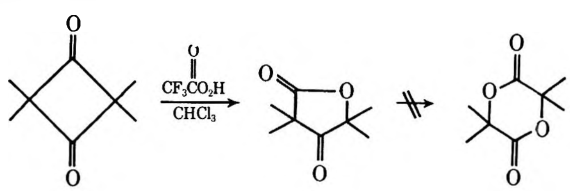
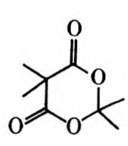
As part of a study on the acyloin reaction of lactones, we required large quantities of dilactones 1 and 2. A scan of the literature revealed only one laboratory synthesis of 1,[1] a vacuum pyrolysis of α-hydroxyisobutyric acid. The reported yield of 1 was 12% (10% in our hands).

It occurred to us that we might be able to synthesize 1 and/or 2 as a separable mixture by treating tetramethyl-1,3-cyclobutanedione (3) with 2 equiv of peracid (eq 1).



3 4 1 (1)

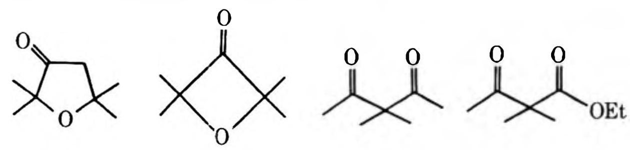


2

When this reaction was attempted using either monopermaleic acid[2a] or trifluoroperacetic acid[2b] in $CHCl_3$, only one product was formed. It was identified by its physical and spectral properties as 3,3,5,5-tetramethyl-2,4-furandione (4). When only 1 mol of peracid was used, 4 could be obtained in yields ranging from 95 to 75% depending on the scale of the reaction (0.1–to 1 mol).

Ketolactone 4 could not be further oxidized using either monopermaleic acid or trifluoroperacetic acid in chloroform even if the mixtures were heated for several days. In most cases good yields of 4 could be recovered. When the oxidation was run using monopermaleic acid in concentrated H_2SO_4–$CHCl_3$ (1:3), no oxidation products were observed but only 35% of 4 was recoverable. No attempt was made to isolate acidic products since if 1 were formed and subsequently hydrolyzed, α-hydroxyisobutyric acid would be formed and it, as noted, cannot be readily converted to 1.

As part of the same project, we also found we were not able to oxidize 2,2,5,5-tetramethyl-3-furanone (5a)[3] by any of the above procedures.



5a 5b 6 7

Boeseken and Jacobs[4] have shown that 2,2-dialkyl-1,3-dicarbonyl compounds 6 and 7 fail to undergo Baeyer–Villiger reaction. They speculated that the ketone carbonyls are too hindered to permit attack of the peracid. While this explanation might account for the lack of reaction of 4 and 5a, it does not account for the facile reaction of 3 or 5b[5] under similar conditions since their carbonyls are equally hindered to attack by the peracid. It seems apparent, however, that if the peracid can add to the carbonyl group of 3, relief of ring strain will be a driving force for product formation.

While we do not intend to pursue this approach to 1, the Baeyer–Villiger reaction on tetramethylcyclobutanedione appears to be an excellent and simple procedure for the synthesis of tetramethyltetronic acid (4), and probably of the other tetraalkylated derivatives of tetraonic acid, an important molecule in sugar chemistry.

Experimental Section

Melting points were taken on a Mel-temp apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrometer; nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Mass spectra were obtained on a Hitachi RMU6D mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3,3,5,5-Tetramethyl-2,4-furandione (4) from 3.—Maleic anhydride (1.0 mol) is added carefully to a stirred mixture of 34 g of 98% hydrogen peroxide (1 mol + 10%) in 760 ml of $CHCl_3$. The mixture is warmed gently until the maleic anhydride is all

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(2) (a) R. H. White and W. D. Emmons, *Tetrahedron*, **17**, 31 (1962); (b) W. F. Soger and A. Duckworth, *J. Amer. Chem. Soc.*, **77**, 188 (1955).

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(4) J. A. J. Boeseken and J. Jacobs, *Recl. Trav. Chim. Pays-Bas*, **55**, 804 (1936).

(5) J. K. Crandell and W. H. Machleder, *Tetrahedron Lett.*, 6037 (1966).

reacted. Dione **3**, 143.7 g (1.01 mol) in 250 ml of $CHCl_3$, is added to the mixture at such a rate as to maintain a gentle reflux. After allowing the mixture to cool to room temperature, the $CHCl_3$ is washed with saturated K_2CO_3 and H_2O, dried $CaCl_2$, filtered, and evaporated. The crude white solid residue is recrystallized from ether–petroleum ether giving 120.1 g (76.5% yield) of **4**: mp 37.5°; ir (CCl_4) 1796, 1750, 1375, 1360 cm^{-1}; nmr ($^{TMS}_{CCl_4}$) δ 1.29 (s, 6), 1.50 (s, 6); mass spectra (70 eV, rel intensity) *m/e* 156 (m^+, 4), 141 (2), 128 (20), 113 (20), 71 (10), 70 (100), 43 (23), 42 (62), 41 (25), 39 (51), metastable peak 25.4.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.79; H, 7.89.

Registry No.—**3**, 933-52-8; **4**, 4387-74-0.

Sigmatropic Chlorine Migration in 5-Chloro-5*H*-dibenzo[*a*,*d*]cycloheptenes

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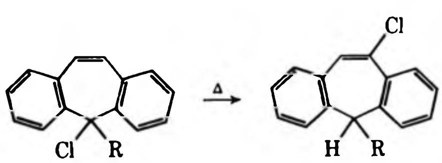
The scope of the thermal chlorine migration exemplified by the isomerization[1] of 5,5-dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1a**) to the 5,10 isomer **2a** has been examined. The intent was to uncover the driving force for the migration, since it was not clear why it should occur. When there is one hydrogen and one chlorine atom at position 5, no rearranged product is formed; only decomposition occurs upon heating. When one substituent is chlorine and the other is phenyl (**1c**) or 1-naphthyl (**1d**), the chlorine atom migrates to position 10 affording **2c** and **2d**, respectively. Thus, two large groups on carbon 5 appear necessary for migration to occur. This suggests that relief of crowding between the equatorial substituent on carbon 5 and the peri hydrogen atoms may be the reason for migration, since the rearranged product now has the smaller hydrogen atom in the sterically unfavorable equatorial position. Molecular models of these compounds confirm the presence of the suggested steric interactions.

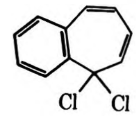


1 **2**

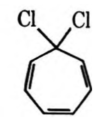
a, R = Cl
b, R = H
c, R = phenyl
d, R = 1-naphthyl

A comparison of the nmr spectra of the unrearranged (**1**) and rearranged (**2**) chlorides supports the hypothesis that crowding is relieved by migration. All chlorides with two large groups at carbon 5 (**1a**, **1c**, **1d**) have a two-proton multiplet downfield (τ 1.3–1.8) from the other aromatic protons. This absorption can be assigned to the protons on carbon 4 and carbon 6, which are very close to the equatorial substituent at position 5. This downfield shift of the aromatic protons is analogous to that observed for the peri hydrogen atom in 1-substituted naphthalenes.[2] When migration occurs, leaving a hydrogen atom to occupy the equatorial position (**2a**, **2c**, **2d**), this absorption disappears. The lowest resonance in these compounds is a one-proton multiplet at τ 2.0–2.2, which is assigned to the aromatic hydrogen peri to the vinyl chlorine atom.

Two gem-dichlorides void of the suggested steric interaction were pyrolyzed to see if migration would occur. Neither 5,5-dichloro-5*H*-benzocycloheptene (**3**) nor chlorotropylium chloride (**4**) gave thermally rearranged chlorides. Decomposition occurred in a



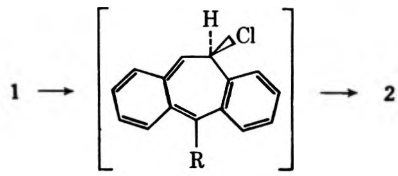
3



4

manner very similar to the behavior of 5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1b**), and led to unidentifiable material.

The original reaction path suggested[1] for this chlorine migration involved ionic intermediates. A better proposal appears to be a concerted 1,5-sigmatropic chlorine migration (**1** → **5**), followed by a 1,5-hydrogen shift (**5** → **2**). Both processes can occur in the allowed suprafacial manner in this ring system.



5

Experimental Section[3]

5-Chloro-5-phenyl-5*H*-dibenzo[*a*,*d*]cycloheptene (1c).—A solution of 8.2 g (0.029 mol) of 5-hydroxy-5-phenyl-5*H*-dibenzo[*a*,*d*]-cycloheptene[4] in 25 ml of thionyl chloride was heated at reflux for 1 hr. The solvent was removed leaving a white solid, mp 191–193°. An analytical sample was prepared by repeated recrystallization from ligroin (bp 63–75°): mp 201–203° dec (depends upon rate of heating); nmr τ 3.40 (s, 2, vinyl), 2.5–3.4 (m, 8, aromatic), 1.5–1.7 (m, 2, aromatic at C-4 and C-6).

Anal. Calcd for $C_{21}H_{15}Cl$: C, 83.3; H, 5.0; Cl, 11.7. Found: C, 83.3; H, 5.3; Cl, 11.4.

10-Chloro-5-phenyl-5*H*-dibenzo[*a*,*d*]cycloheptene (2c).—The crude chloride **1c** (from 10 g of the alcohol) was heated at 205° for 1 hr and recrystallized from ligroin (bp 63–75°): 6.5 g (74%); mp 114–116°; nmr τ 4.70 (s, 1, benzylic), 2.5–3.5 (m, 12, aromatic), 2.0–2.2 (m, 1, aromatic peri to Cl).

Anal. Calcd for $C_{21}H_{15}Cl$: C, 83.3; H, 5.0; Cl, 11.7. Found: C, 83.0; H, 4.8; Cl, 11.4.

5-Chloro-5-(1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (1d).—A solution of 10 g (0.030 mol) of 5-hydroxy-5-(1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene[5] in 50 ml of thionyl chloride was heated at reflux for 1 hr and concentrated, and the solid was recrystallized from methylcyclohexane: 2.75 g (25%); mp 171–172°; nmr τ 2.2–3.6 (m, 15, aromatic and vinyl), 1.3–1.6 (m, 2, aromatic at C-4 and C-6).

10-Chloro-5-(1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (2d).—A solution of 1.0 g (0.0028 mol) of **1d** in 20 ml of *o*-dichlorobenzene was heated at reflux for 45 min, concentrated, and chromatographed on Florisil. The benzene–ligroin (1:1) fraction gave a white solid, which was recrystallized from ligroin: 0.57 g

(1) J. J. Looker, *J. Org. Chem.*, **31**, 3599 (1966).

(2) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(3) Melting points and boiling points are uncorrected. The nmr spectra were measured on a Varian Associates A-60 instrument in deuteriochloroform, with TMS as an internal standard.

(4) W. Treibs and H. Klinkhammer, *Chem. Ber.*, **84**, 671 (1951).

(5) J. J. Looker, *J. Org. Chem.*, **36**, 1045 (1971).

(57%); mp 141–142°; nmr τ 4.00 (s, 1, benzylic), 2.2–3.3 (m, 15, aromatic and vinyl), 2.0–2.2 (m, 1, aromatic peri to Cl).

Anal. Calcd for $C_{25}H_{17}Cl$: C, 85.0; H, 4.9; Cl, 10.1. Found: C, 84.7; H, 4.9; Cl, 10.4.

5,5-Dichloro-5*H*-benzocycloheptene (3).—A solution of 4.5 g (0.029 mol) of 5*H*-benzocyclohepten-5-one[6] in 25 ml of dry methylene chloride was cooled in an ice bath while phosgene was passed in until 10 g (excess) had dissolved. The solution was left at room temperature under nitrogen overnight and the product was distilled: 5.6 g (92%); bp 105° (0.10 mm); nmr τ 4.9–5.0 (m, 1, vinyl), 3.9–4.1 (m, 2, vinyl), 3.1–3.2 (m, 1, vinyl), 2.4–2.8 (m, 3, aromatic), 2.0–2.2 (m, 1, aromatic). The dichloride should be kept in a freezer or under nitrogen because it decomposes when left at room temperature in air.

Anal. Calcd for $C_{11}H_8Cl_2$: C, 62.6; H, 3.8; Cl, 33.6. Found: C, 62.5; H, 3.6; Cl, 33.3.

The dichloride (1.0 g) was dissolved in 10 ml of 10% water in tetrahydrofuran, heated at reflux for 30 min, concentrated, and distilled (0.70 g, 95%). The nmr spectrum of the product was identical with that of 5*H*-benzocyclohepten-5-one.

Thermal Decomposition of Chlorides 1b,[7] 3, and 4.[8]—When each of these chlorides was heated at 180–200° for 10–30 min, black tars resulted. Chloroform extracts afforded poor nmr spectra with no benzylic proton absorption. Column chromatography of the extracts gave no identifiable materials. Similar results were obtained when the chlorides were heated at reflux in *o*-dichlorobenzene until decomposition occurred.

Registry No.—1c, 33482-70-1; 1d, 33482-71-2; 2c, 33482-72-3; 2d, 33482-73-4; 3, 33482-74-5.

(6) G. L. Buchanan and D. R. Lockhart, *J. Chem. Soc.*, 3586 (1969).

(7) G. Berti, *J. Org. Chem.*, **22**, 230 (1957).

(8) B. Föhlisch, P. Brügle, and D. Krockenberger, *Chem. Ber.*, **101**, 2717 (1968).

Enantiomeric Purity of 3-Phenyl-4,4-dimethyl-1-pentene. A Chemical Interrelation between the Maximum Rotations of α-*tert*-Butylphenylacetic Acid and β-*tert*-Butyl-β-phenylpropionic Acid

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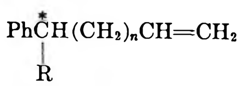
In the course of CD investigations of α olefins I,[1] we found it necessary to obtain optically active 3-phenyl-4,4-dimethyl-1-pentene (5) for which the relationship between optical purity and [α]D could be determined with a reasonable reliability by starting from optically active compounds used in the same synthesis. The

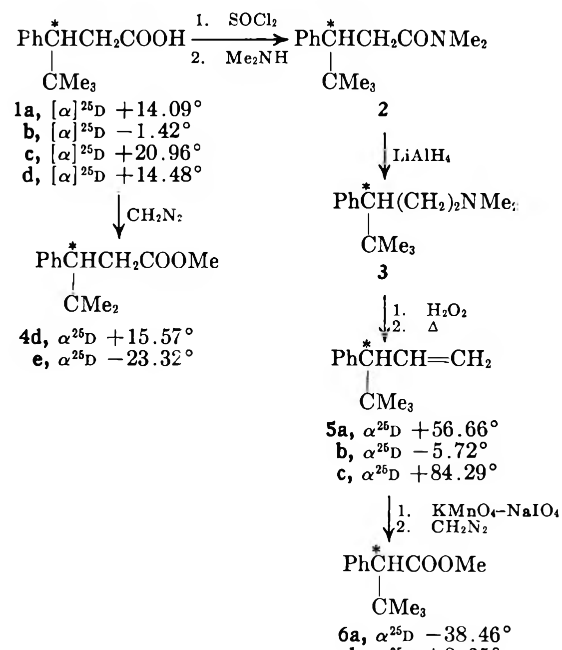


I, R = Me, Et, *i*-Pr, *tert*-Bu; *n* = 0, 1, 2

absolute configuration of α-*tert*-butylphenylacetic acid (7) and β-*tert*-butyl-β-phenylpropionic acid (1) has been recently determined[2-4] and the maximum rotations of 1 and 7 have been established from optical resolution criteria.[5,6]

In the present paper we report the synthesis of optically active 5 (Scheme I), the relationship between

Scheme I[a]



[a] All specific rotations are in $CHCl_3$ and all observed rotations are *l* = 1 dm, neat.

its optical purity and optical rotation (Scheme I), and some evidences of the reliability of the maximum rotations of 1 and 7 previously reported[5,6] and now interrelated by a chemical method (Schemes I and II).

(*S*)- and (*R*)-*N*,*N*-dimethyl-3-phenyl-4,4-dimethylpentylamine (3) were prepared[1] (80–90% yield), *via* 2, from the corresponding optically active β-phenyl-β-*tert*-butylpropionic acid (1) (Scheme I), in its turn obtained by resolution of the racemic acid[7] with brucine and cinchonidine.[5]

By pyrolysis of the amine 3 oxide at 120° (1.5 mm),[1,8] isomer-free (*S*)- and (*R*)-5 were recovered in high yield (86–88%) and high chemical purity (99%) (Scheme I). The olefin 5, $\alpha^{25}D$ +56.66°, was oxidized by permanganate–periodate reagent in 60% aqueous *tert*-butyl alcohol[9] to yield optically active α-*tert*-butylphenylacetic acid (7), converted by diazomethane into the methyl ester 6a, $\alpha^{25}D$ −38.46°.[10]

According to our experimental data the optical purity of 6a is 65.5% [based on $[\alpha]^{25}D$ max 62.9° ($CHCl_3$) for the optically pure acid 7][6] and that of 1a, used in the synthesis of 5 (Scheme I), is 63.4% [based on $[\alpha]^{25}D$ max 22.2° ($CHCl_3$) for optically pure acid 1].[5]

By assuming that the oxidative degradation of 5

(1) L. Lardicci, R. Menicagli, and P. Salvadori, *Gazz. Chim. Ital.*, **98**, 738 (1968).

(2) D. R. Clark and H. S. Mosher, *J. Org. Chem.*, **35**, 1114 (1970).

(3) J. Almy, R. T. Uyeda, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 6768 (1967).

(4) The configuration assigned to (+)-β-*tert*-butyl-β-phenylpropionic acid by Cram, *et al.*,[3] was confirmed and correctly designated *R* by Clark and Mosher.[2] In a subsequent paper by Almy and Cram [*ibid.*, **91**, 4460 (1969)] the correct configurational formulas were used but the wrong configurational rotation was assigned to this acid and several derivatives.

(5) J. Almy and D. J. Cram, *ibid.*, **91**, 4467 (1969).

(6) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2801 (1967).

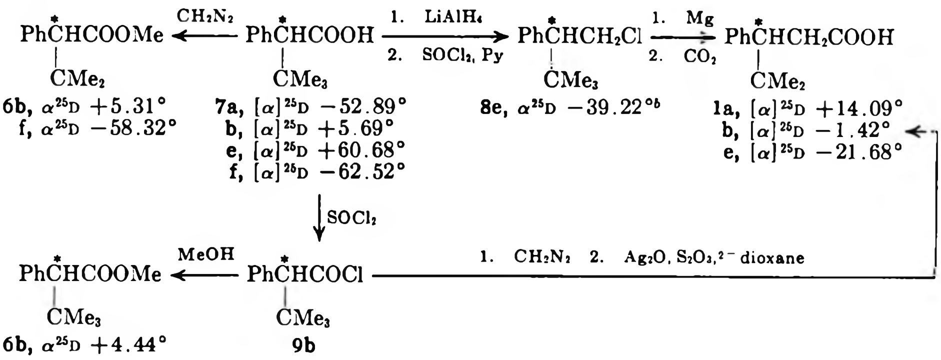
(7) C. F. Koelsch, *J. Amer. Chem. Soc.*, **65**, 1640 (1943).

(8) L. Lardicci, R. Menicagli, and P. Salvadori, *Chim. Ind.* (*Milan*), **52**, 83 (1970).

(9) E. Gil-Av and J. Shabtai, *J. Org. Chem.*, **29**, 261 (1964).

(10) Since the recovered crude acid 7 could be further resolved during the purification, we preferred to check its minimum optical purity by converting it into the methyl ester 6a, for which the relationship between optical purity and αD has been established in the present investigation.

SCHEME II[a]



[a] All specific rotations are in $CHCl_3$ and all observed rotations are l = 1 dm, neat. [b] *Via* tosylate.

occurs without appreciable racemization,[1,8,11] the maximum specific rotation of optically pure 3-phenyl-4,4-dimethyl-1-pentene lies therefore within the range 98–101° (at 25°) and earlier maximum rotations reported for the α-*tert*-butylphenylacetic acid[6] and for the β-*tert*-butyl-β-phenylpropionic acid[5] are substantially in a good agreement as indicated by the results of the Scheme I.[12]

The synthesis of optically active **5** had also been carried out by starting from (*S*)- and (*R*)-α-*tert*-butylphenylacetic acid (**7**) (Scheme II).[6]

The homologation of **7** to **1** was performed both by carbonation of the Grignard reagent prepared from the chloride **8**[1,2] and by Arndt–Eistert reaction[13] on the optically active acid **7b** (Scheme II).

Following the sequence recently reported by Clark and Mosher[2] and starting from **7a** (optical purity 84%),[6] a sample of **1a** (optical purity 63.4%)[5] was recovered (Scheme II).

Reaction of the acid chloride **9b** (from **7b**, optical purity 9%)[6] with diazomethane gave the corresponding crude diazo ketone; its rearrangement was effected in the usual fashion using silver thiosulfate in aqueous dioxane.[13] A sample of (*S*)-(−)-β-*tert*-butyl-β-phenylpropionic acid (**1b**), having $[\alpha]^{25}D$ −1.42° ($CHCl_3$) (optical purity 6.4%),[5] was recovered.

Using the rotations of methyl ester **6** obtained from (*S*)-(+)-α-*tert*-butylphenylacetic acid (**7b**) by treatment with diazomethane and by conversion to the acid chloride **9b** followed by treatment with methanol, it was possible to evaluate the maximum racemization in the formation and purification of **9b** (Scheme II). On this basis the acid chloride **9b**, used in the Arndt–Eistert reaction, is 7.5% optically pure.

While in the sequence **9b** → **1b** the observed 15% racemization is in agreement with that reported in the literature,[13] the reason for a 24.5% racemization in the sequence **7a** → **8a** → **1a** is not apparent since the homologation reaction *via* alcohol, chloride, Grignard, and carbonation of this reagent has been widely employed in similar cases[1,8,14] as a chemical process not affecting bonds to the asymmetric carbon atom.

However, a parallel investigation on the chemical and optical purity of several samples of optically active 3,3-dimethyl-2-phenyl-1-chlorobutane **8** (from the corresponding alcohol by treatment with thionyl chloride in dry pyridine)[2] showed that the optical rotation of the product from different experiments varied significantly.[15]

Indeed, a sample of (*S*)-(−)-3,3-dimethyl-2-phenyl-1-chlorobutane (**8e**) obtained from **7e**, optical purity 96.5%[6] (*via* alcohol, tosylate, and its treatment with lithium chloride in dimethylformamide),[16] was converted into the Grignard reagent which was carbonated to give (*S*)-(−)-β-*tert*-butyl-β-phenylpropionic acid (**1e**), the optical purity of which, evaluated through the methyl ester **4e** (Schemes I and II), is 97.5%.

The close agreement between the optical purity of (*S*)-(+)-α-*tert*-butylphenylacetic acid (**7e**) and of (*S*)-(−)-β-*tert*-butyl-β-phenylpropionic acid (**1e**) (Scheme II) confirms that (1) the sequence of homologation *via* Grignard reagent proceeds even in this case with a very high degree of retention of configuration but (2) the conversion of optically active 3,3-dimethyl-2-phenyl-1-butanol into the corresponding chloride **8**, upon treatment of the alcohol with thionyl chloride and pyridine,[2] occurs, at least in the conditions we have adopted, with a 25% racemization. Therefore the sequence **7a** → **8a** → **1a** is not suitable to establish the relationships between optical purities and optical rotations of the acids **1** and **7**.

Experimental Section[17]

(*R*)-(+)-*N*,*N*-Dimethyl-3-phenyl-4,4-dimethylpentanamide (2).—To an ether solution of 16.0 g (0.080 mol) of 1c, mp 94–95° (lit.[5] mp 94.5–95.0°), $[\alpha]^{25}D$ +20.96° (c 2.636, $CHCl_3$), was added 22.14 g (0.186 mol) of thionyl chloride and the mixture was left aside for 24 hr and then refluxed for 4 hr. The crude chloride, in ether, was cooled at −15° and an ether solution of 2 equiv of dimethylamine was added.[18] The reaction mixture was worked up as previously described[18] and the ether was removed to leave 17.0 g (91%) of crude amide 2c: mp 96–97°;

(11) D. D. Davis and G. G. Ansari, *J. Org. Chem.*, **35**, 4285 (1970).

(12) The little discrepancy (2–3%) between the minimum optical purity values of olefin **5** could fall within the range of the experimental errors either in the evaluation of minimum optical purity of the starting products (Scheme I) or in the assumed values for the maximum rotations of the acids **1** and **7**.

(13) K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, **78**, 1640 (1956).

(14) L. Lardicci and R. Menicagli, *Chim. Ind.* (*Milan*), **51**, 1387 (1969).

(15) The crude **8** recovered showed several glpc peaks and, in order to obtain isomers and impurities-free product, a difficult and tedious purification is to be carried out. Nevertheless, the optical rotations of chlorides **8**, of comparable chemical purity (≥97%), did not agree with those of the corresponding optically active acids **7**. At present the authors think, in agreement with the suggestions of referees, that some rearrangement takes place during the thionyl chloride reaction in the presence of pyridine. This may be responsible of the observed presence of isomers and impurities in the crude **8** and of the observed racemization, too (see sequence **7a** → **8a** → **1a**).

(16) A. Herdenberger, private communication.

(17) All boiling and melting points are uncorrected. Glpc analyses were performed on a C. Erba Fractovap Mod. GT instrument equipped with 2-m columns filled with 10% 1,4-butanediol succinate (BDS) on Chromosorb W 60–80 and N_2 as carrier gas. All rotations were taken on a Schmidt-Haensch polarimeter with sensitivity of ±0.005° in 1-dm tubes.

(18) N. L. Drake, C. M. Eaker, and W. Shenk, *J. Amer. Chem. Soc.*, **70**, 677 (1948).

$[\alpha]^{25}D$ +43.75° (*c* 3.440, benzene). A sample was crystallized once from *n*-heptane: mp 98–99°; $[\alpha]^{25}D$ +47.29° (*c* 3.478, benzene). In a similar manner from **1a**, $[\alpha]^{25}D$ +14.09° (*c* 2.344, $CHCl_3$), and **1b**, $[\alpha]^{25}D$ −1.42° (*c* 5.769, $CHCl_3$), was obtained **2a**, $[\alpha]^{25}D$ +29.41° (*c* 3.478, benzene), and **2b**, mp 107–108°, $[\alpha]^{25}D$ −2.93° (*c* 3.478, benzene), respectively. *Anal.* Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.68; H, 9.80; N, 6.13.

(*R*)-(+)-*N*,*N*-**Dimethyl-3-phenyl-4,4-dimethylpentylamine (3)**.—A solution of 15.5 g (0.066 mol) of crude **2c** in 230 ml of anhydrous ether was slowly added to a stirred suspension of 5.87 g (0.154 mol) of $LiAlH_4$ in 130 ml of ether. The resulting mixture was stirred at the reflux temperature for 26 hr and then it was worked up by a standard procedure[1] to give 13.0 g (90%) of **3c**: bp 84° (1.4 mm); $n^{25}D$ 1.4934–1.4936; $\alpha^{25}D$ +19.08° (neat); $[\alpha]^{25}D$ +18.65° (*c* 2.198, benzene). Runs **a** and **b** were carried out under identical conditions to give amines **3a** [bp 95° (2.3 mm), $\alpha^{25}D$ +12.84° (neat)] and **3b** [bp 79° (1 mm); $n^{25}D$ 1.4930–1.4931; $\alpha^{25}D$ +1.28° (neat)]. *Anal.* Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38. Found: C, 81.89; H, 11.45; N, 6.45.

(*R*)-(+)-**3-Phenyl-4,4-dimethyl-1-pentene (5)**.—The amine **3c** (12.5 g, 0.057 mol) was converted to its oxide[19] which was heated under 1.5 mm of pressure at a temperature of 120° until the decomposition was complete, 25 min. The distillate was worked up by the usual manner[19] and the crude alkene was distilled to give 8.5 g (86%) of **5c** [99% pure by glpc analysis (on 2-m Apiezon L column at 160°)]: bp 94° (15 mm); $n^{25}D$ 1.5032; $\alpha^{25}D$ +84.29° (neat). In run **a** the olefin was purified by preparative glpc (on 5-m 10% BDS column at 140°) to give pure **5a** (>99%): bp 97° (16 mm); $n^{25}D$ 1.5028; d_4^{25} 0.8808; $\alpha^{25}D$ +56.66° (neat); $[\alpha]^{25}D$ +64.33° (neat). Its ir spectrum showed no bands at 1625 and 980–960 cm^{-1}.[1] On a later run from **3b** was obtained **5b**: $n^{25}D$ 1.5029–1.5030; $[\alpha]^{25}D$ −6.49° (neat). *Anal.* Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.87; H, 10.16.

(*R*)-(+)-**2-Phenyl-3,3-dimethyl-1-butanol**.—To 25.2 g (0.664 mol) of $LiAlH_4$ in 326 ml of ether was added dropwise 70.0 g (0.364 mol) of **7a**, $[\alpha]^{25}D$ −52.89° (*c* 5.294, $CHCl_3$),[6] in 270 ml of dry ether. The mixture was refluxed 20 hr and then worked up by a standard procedure[1,2] to give 63.5 g (98%) of crude (*R*)-(+)-2-phenyl-3,3-dimethyl-1-butanol which was extracted continuously with pentane; from the resultant solution the carbinol (62.0 g), mp 96° [lit. mp of partially active material,[2] 75–90°], $[\alpha]^{25}D$ +2.00° (*c* 5.212, $CHCl_3$), was recovered. On a later run from **7e**, $[\alpha]^{25}D$ +60.68° (*c* 4.958, $CHCl_3$), was obtained (−)-carbinol: mp 97°; $[\alpha]^{25}D$ −2.31° (*c* 6.060, $CHCl_3$). In run **f** the acid **7**, $[\alpha]^{25}D$ −62.52° (*c* 4.958, $CHCl_3$), was reduced to give a product with mp 97°, $[\alpha]^{25}D$ +2.38° (*c* 5.988, $CHCl_3$).

(*R*)-(+)-**3-Phenyl-4,4-dimethylpentanoic Acid (1)**.—(*R*)-(+)-2-Phenyl-3,3-dimethyl-1-butanol, $[\alpha]^{25}D$ +2.00 ($CHCl_3$), was converted into **8a**, 88% pure (glpc).[2] The Grignard reagent from the above chloride was carbonated with Dry Ice. The reaction mixture was processed in the usual way[1] to give 9.5 g (57%) of crude **1a**, mp 108–110° (lit.[7] 114–116°). The acid was extracted continuously with pentane to yield 9.0 g of **1a**, $[\alpha]^{25}D$ +14.09° (*c* 2.344, $CHCl_3$); its methyl ester was shown to be 99% pure (glpc). On a later run from **8e** (98% pure), bp 79° (1.5 mm) [lit.[2] 79–82° (1 mm)], $n^{25}D$ 1.5153, $\alpha^{26}D$ −39.22° (neat) [obtained by reacting the tosylate of the carbinol, $[\alpha]^{25}D$ −2.31 ($CHCl_3$), with LiCl in dimethylformamide (62% yield)],[16] was prepared **1e**, mp 94–95°. This acid was converted, by diazomethane, to its methyl ester **4e**: bp 133° (13 mm); $n^{25}D$ 1.4953; $\alpha^{26}D$ −23.32° (neat).

(*S*)-(+)-**2-Phenyl-3,3-dimethylbutanoic Acid Methyl Ester (6)**.—To a solution of 2.13 g (0.011 mol) of **7f**, mp 142°, $[\alpha]^{25}D$ −62.52° (*c* 4.958, $CHCl_3$), in 15 ml of ether at 0° was added slowly and with shaking an ether solution of diazomethane. The excess of diazomethane and ether was removed under reduced pressure and distillation gave 2.0 g (88%) of **6f**: bp 122° (15 mm); $n^{25}D$ 1.4938; $\alpha^{25}D$ −58.32° (neat). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.02; H, 8.67.

(*R*)-(+)-**3-Phenyl-4,4-dimethylpentanoic Acid Methyl Ester (4)**.—By the method above described 2.04 g (0.0098 mol) of **1d**, mp 93–94°, $[\alpha]^{25}D$ +14.48° (*c* 2.624, $CHCl_3$), was converted to **4d** (82%): bp 139–140° (15 mm); $n^{25}D$ 1.4946; $\alpha^{25}D$ +15.57° (neat). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.50; H, 9.12.

(19) D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2137 (1952).

Arndt–Eistert Reaction on the (*S*)-2-Phenyl-3,3-dimethylbutanoic Acid (7).—The acid **7b** (73.0 g, 0.379 mol), $[\alpha]^{25}D$ +5.69° (*c* 5.443, $CHCl_3$), was converted to its chloride (**9b**) with the procedure above described for **1c**. A 3.5-g sample of distilled acid chloride was treated with absolute methanol.[13] Distillation gave 2.5 g (75%) of **6b**: $n^{26}D$ 1.4940; $\alpha^{25}D$ +4.44° (neat); $[\alpha]^{25}D$ +4.36° (*c* 5.150, MeOH). The residual chloride (75.0 g, 0.356 mol), bp 89° (2 mm), in 180 ml of ether was reacted with an ice-cold ether solution of diazomethane, prepared from 2.9 mol of *N*-nitrosomethylurea.[13] The crude diazo ketone, in 575 ml of purified dioxane, was subjected to the Wolff rearrangement in a solution of aqueous dioxane containing silver oxide and sodium thiosulfate.[13] The recovered acid was extracted continuously with pentane to give 53.1 g (72%) of **1b**: mp 116°; $[\alpha]^{25}D$ −1.42° (*c* 5.769, $CHCl_3$).

Oxidation of (*R*)-(+)-3-Phenyl-4,4-dimethyl-1-pentene (5).—The alkene **5a** (3.0 g, 0.017 mol), $[\alpha]^{25}D$ +64.33° (neat), was oxidized in 112 hr, by $KMnO_4$–$NaIO_4$ mixture in 60% aqueous *tert*-butyl alcohol, according to the procedure of Gil-Av and Shabtai.[9] The crude acid (83%) was esterified with diazomethane to give **6a**: $n^{26}D$ 1.4935; $\alpha^{25}D$ −38.46° (neat). In another experiment **5b**, $[\alpha]^{25}D$ −6.49° (neat), afforded **6b**: $n^{25}D$ 1.4940; $\alpha^{25}D$ +3.65° (neat).

Registry No.—**1**, 23406-59-9; **2**, 33124-15-1; **3**, 33124-16-2; **4**, 33124-17-3; **5**, 33124-18-4; **6**, 26164-17-0; **7**, 13490-71-6; (*R*)-(+)-2-phenyl-3,3-dimethyl-1-butanol, 33124-21-9.

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2-Carboxydeoxypicropodophyllin

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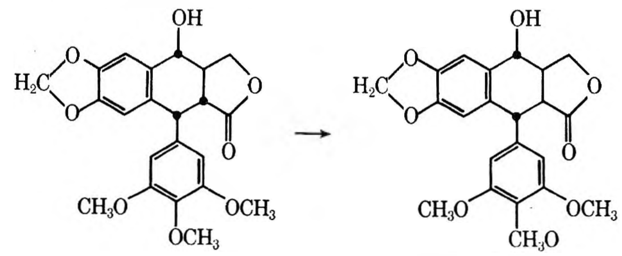
Podophyllotoxin (1) and also derivatives such as deoxypodophyllotoxin (3), which have the same con-



podophyllotoxin picropodophyllin

1 2

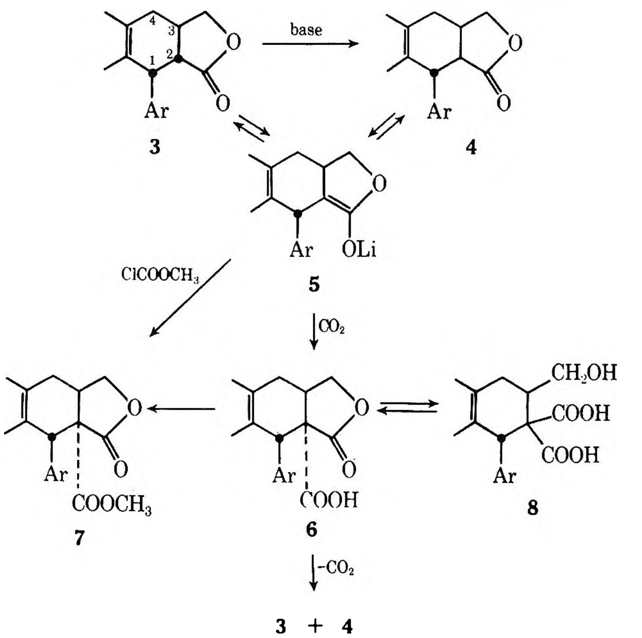
figurations at positions 1, 2, and 3,[1] are active cytotoxic agents and have been extensively investigated as cancer chemotherapeutic agents.[2] All of these podophyllo-

(1) J. L. Hartwell and A. N. Schrecker, *Progr. Chem. Org. Natur. Prod.*, **15**, 83 (1958).

(2) *Cf.* M. G. Kelly and J. L. Hartwell, *J. Nat. Cancer Inst.*, **14**, 967 (1954); H. Emmenegger, H. Stähelin, J. Rutschmann, J. Renz, and A. von Wartburg, *Arzneim.-Forsch.*, **11**, 327, 459 (1961); E. Schreier, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., 1966, Paper P-34. Two derivatives have actually received considerable clinical application, namely, *O,O*-benzylidenepodophyllotoxin-β-D-glucoside and podophyllic acid *N*-ethylhydrazide (*cf.* H. Lettré and S. Witte, "Experimentelle und Klinische Erfahrungen mit Podophyllinderivaten in der Tumortherapie," F. K. Schattauer-Verlag, Stuttgart, 1967).

toxin compounds epimerize easily by base-catalyzed removal of the proton at position 2.[1,3] The resulting products, now in the picropodophyllin (2) configuration, are virtually inert.[3] Since the cell probably utilizes this epimerization as a detoxication mechanism,[4] replacing the H at the 2 position with a group offering no opportunity for epimerization should block at least one mode of physiological deactivation and furnish a more persistent agent. With this in mind, we set out to prepare analogs substituted at position 2. The present paper reports the results of work aimed at attaching a carboxy group by carbonating the enolate from deoxypodophyllotoxin.

The starting material, 4-deoxypodophyllotoxin (3), although isolable from plant sources,[5,6] is more conveniently prepared by catalytic hydrogenolysis of podophyllotoxin (1).[7] Epimerization gave deoxypicropodophyllin (4).[6,7] Enolate 5, prepared by the action of triphenylmethyllithium (butyllithium could also be used) on either deoxypodophyllotoxin (3) or deoxypicropodophyllin (4) was carboxylated with carbon dioxide to produce 2-carboxydeoxypicropodophyllin (6). The corresponding methyl ester 7 was obtained either from the acid or by allowing the enolate to react with methyl chloroformate. Confirmation that the carboxyl group is on the 2 position, as anticipated, came from the fact that thermal decarboxylation of acid 6 produced a mixture of deoxypodophyllo-



toxin (3) and deoxypicropodophyllin (4). Since, under the decarboxylation conditions employed, the two products 3 and 4 failed to interconvert, they must be derived from some common intermediate stage, and if the carboxy group is placed on the 2 position as in 6, the enol[8] common to both products 3 and 4 serves in a straightforward way as this intermediate.

Assignment of the cis-fused (picropodophyllin) configuration to carboxylation product 6 rather than the trans-fused (podophyllotoxin) configuration rests on the observation that, when malonic acid 8 formed by saponifying the lactone ring of 6 is warmed, cyclization occurs to regenerate starting material 6. The other lactone product, although *a priori* possible, is not observed. All information on the relative stability of the cis lactone system, as in 6, *vs.* the corresponding trans lactone points to the former as energetically favored.[3] Since the transition state for lactonization of malonic acid 8 to a cis lactone would be expected to reflect this preference, the lactone product would be the cis-fused 2-carboxydeoxypicropodophyllin rather than the trans-fused 2-carboxydeoxypodophyllotoxin.

The lactone carbonyl infrared absorption offers no support for the cis assignment and, if anything, could be taken as favoring the opposite conclusion. Thus the lactone peak in carboxylation product 6 appears at 1770–1780 cm^{-1}, and the lactone absorption in the derived methyl ester 7 at 1787 cm^{-1}. These values fall closer to the 1780-cm^{-1} absorption peak for deoxypodophyllotoxin (3) than to the 1765-cm^{-1} peak for deoxypicropodophyllin (4). However, we tend to mistrust this kind of comparison. Local structural features not only can shift carbonyl absorption peaks but also, since several factors might be involved, do this in a way that is hard to predict.[9,10]

Questions remain on why carbonation furnishes none of the stereoisomeric 2-carboxydeoxypodophyllotoxin and on why the yield could not be brought over 40–50%. Factors that might operate to favor the cis picropodophyllin configuration over the trans podophyllotoxin configuration—a result contrary to what may be predicted on the basis of the planar enolate grouping[8]—have been discussed before.[11] Why the carbonation yields were not higher despite the elaborate precautions taken to exclude moisture and oxygen is a matter of speculation. Possibly carbonation on oxygen instead of carbon occurs to yield the enol half-ester of carbonic acid, which is stable enough to drain the supply of enolate 5 but not stable enough to isolate.

Experimental Section

General.—Melting points were taken in open capillary tubes and are uncorrected. Composition analyses were determined by Microanalytical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass., Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., and Scandinavian Microchemical Laboratory, Herlev, Denmark. Volatile solvents were generally removed in a rotary evaporator under water-pump vacuum at moderate temperatures. Nuclear magnetic resonance spectra were determined at 60 MHz. Thin layer chromatographic analyses were obtained with the help of commercial silica gel plates and films. Estimates indicate that, for samples in the

(3) See W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 3224 (1966).

(4) *Cf.* H. Emmenegger, H. Stähelin, J. Rutschmann, J. Renz, and A. von Wartburg, *Arzneim.-Forsch.*, **11**, 327 (1961); J. J. Kocsis, E. J. Walaszek, and E. M. K. Geiling, *Arch. Int. Pharmacodyn. Ther.*, **111**, 134 (1957); M. G. Kelly, J. Leiter, A. R. Bourke, and P. K. Smith, *Cancer Res.*, **11**, 263 (1951).

(5) K. Noguchi and M. Kawanami, *J. Pharm. Soc.* (*Jap.*), **60**, 629 (1940); *Chem. Abstr.*, **47**, 6386 (1953); H. Kofod and C. Jørgenson, *Acta Chem. Scand.*, **9**, 346 (1955); J. L. Hartwell and A. W. Schrecker, *J. Amer. Chem. Soc.*, **76**, 4034 (1954).

(6) J. L. Hartwell, A. W. Schrecker, and J. M. Johnson, *ibid.*, **75**, 2138 (1953).

(7) *Cf.* A. W Schrecker, M. M. Trail, and J. L. Hartwell, *J. Org. Chem.*, **21**, 292 (1956).

(8) *Cf.* J. Hine in "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 303.

(9) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958; "Advances in Infrared Group Frequencies," Methuen, London, 1968.

(10) Optical rotatory dispersion and circular dichroism curves were determined for the 2-carboxydeoxypicropodophyllin (6), but the results offered little help in deciding between the picropodophyllin and podophyllotoxin configurations: private communication from Professor W. Klyne, Westfield College, University of London.

(11) W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 4004 (1966).

order of 0.5 μg, 1–2% of extraneous material could be detected.

Reactions involving organometals and enolates were performed in clean glassware, dried carefully in a 100° oven, and often flamed while passing an inert gas through the apparatus. Air was vigorously excluded generally by using an atmosphere of oxygen-free nitrogen that had been bubbled first through a tower of concentrated sulfuric acid and then through calcium sulfate. The tetrahydrofuran and ether solvents were prepared routinely by condensing the vapors from a boiling mixture of solvent and lithium aluminum hydride directly into the reaction vessel. Solution transfers were made without opening the system to air, sometimes with the help of syringes that had just been flushed with pure nitrogen.

Deoxypodophyllotoxin (3) by Hydrogenolysis of Podophyllotoxin (1).—A mixture of 6.0 g of 10% palladium/carbon (Columbia Organic Chemicals) with 150 ml of acetic acid was stirred under hydrogen until no further hydrogen was absorbed. Podophyllotoxin (8.0 g; 19.3 mmol), mp 181–184° (lit.[1] 183–184°), was added, and the mixture was stirred at 95° under 2 atm of hydrogen for 5 hr, at which point the calculated volume of hydrogen had been absorbed. Continued stirring led to no further absorption. After catalyst and solvent had been removed, the residue was percolated through a small column of neutral alumina (<200 mesh) with the help of about 200 ml of methylene chloride. Solvent was removed in a low-actinic flask, and the residue, homogeneous according to thin layer chromatography (ether–methylene chloride, 6:1), was crystallized twice from methanol to give 5.6 g (73%) of deoxypodophyllotoxin (3), mp 166–168°. An additional 0.8 g obtained by reprocessing the mother liquors brought the yield to 83%: $[\alpha]_D$ −117° (c 1, $CHCl_3$); $[\alpha]_D$ −77.5° (*c* 0.5, C_2H_5OH); ir ($CHCl_3$) 1780, no absorption at 3700–3125 cm^{-1} [lit.[7] mp 168.4–169.4°; $[\alpha]_D$ −116.4° ($CHCl_3$)].

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.33; H, 5.53. Found: C, 66.43; H, 5.37.

Hydrogenolysis of podophyllotoxin to deoxypodophyllotoxin could also be performed effectively simply by bubbling hydrogen slowly through the hot, stirred mixture.

Deoxypicropodophyllin (4) by Epimerizing Deoxypodophyllotoxin (3).—The reaction was performed by boiling a mixture of deoxypodophyllotoxin (2.2 g, 5.5 mmol), 6.0 g (73 mmol) of anhydrous sodium acetate, and 50 ml of absolute ethanol for 18 hr.[6,7] Crystallized deoxypicropodophyllin, homogeneous according to thin layer chromatography, was obtained in 78% yield. Using ether–methylene chloride on a Camag silica gel plate, deoxypicropophyllin traveled with R_f 0.54, deoxypodophyllotoxin with R_f 0.75.

Appreciable quantities of deoxypicropodophyllin could also be recovered from the mixtures obtained in the carbonation experiments described below.

2-Carboxydeoxypicropodophyllin (6).—Tetrahydrofuran (*ca.* 300 ml) was condensed directly onto 35.0 g (0.14 mol) of pure dry triphenylmethane in an amber reaction vessel. A hexane solution of butyllithium (1.6 *N*) was injected in 10-ml portions to the swirled tetrahydrofuran solution until a total of 100 ml had been introduced (0.16 mol). Standardization of the resulting red solution of triphenylmethyllithium by titration against pure dry benzoic acid to the appearance of a red end point indicated an organometal content of 0.32 *M*. Samples were withdrawn by syringe, with the bottle always upright and with nitrogen used liberally. Prepared, stored, and utilized in this way, the triphenyllithium solution appeared to keep well.

Tetrahydrofuran (*ca.* 60 ml) was condensed directly onto 0.34 g (0.85 mmol) of deoxypicropodophyllin (4). Red triphenyllithium solution was then added dropwise from a syringe to the vigorously stirred solution. The reaction mixture, originally colorless, gradually became yellow to yellow-orange. The addition was interrupted when the red color from each drop of reagent took longer than 5 min to fade to orange; at this point 140% of the calculated amount had been introduced. The solution was transferred by syringe to a flask containing a large excess of solid carbon dioxide, which had been condensed at liquid nitrogen temperatures from specially dried commercial gas. The flask was then allowed to come to room temperature, and, when all the solid carbon dioxide had evaporated, solvent was removed *in vacuo* at temperatures no higher than 30°. Water (20 ml) was added, and the mixture was extracted with several portions of methylene chloride to remove triphenylmethane, triphenylcarbinol, deoxypicropodophyllin, and deoxypodophyllotoxin. The aqueous layer (pH 11) was cooled to 0° and acidified to pH 2 with 4 *N* hydrochloric acid to precipitate the desired product, which was separated by centrifugation, stirred with a small volume of cold water, and collected again. Crystallization of the solid from methanol or from methylene chloride–hexane afforded shining plates of 2-carboxydeoxypicropodophyllin (6) weighing 0.17 g (44%) and showing a single spot on thin layer chromatographic analysis (benzene–methanol, 3:1): mp (slow decomposition) >150°, or with rapid heating at 190–200° with foaming; $[\alpha]_D$ +143° (*c* 0.5, pyridine); ir (mineral oil mull) 3140 (OH), 1770–1780 (lactone carbonyl), 1725–1730 cm^{-1} (carboxy carbonyl).

Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01; $3CH_3O$, 21.04. Found: C, 62.24; H, 5.01; CH_3O, 21.10.

Many variations of this preparation were tried with little or no improvement in yield. Carbonation of the lithium enolate derived from deoxypodophyllotoxin (3) instead of deoxypicropodophyllin gave practically the same results. In one modification the enolate was prepared by adding butyllithium in hexane (1.3 *M* equiv) to a tetrahydrofuran solution of deoxypodophyllotoxin in the presence of a catalytic amount of triphenylmethane (0.1 *M* equiv) until the red color persisted; thereafter carbonation with a stream of dry carbon dioxide gas gave 2-carboxydeoxypicropodophyllin in about 28% yield. Even in the *absence* of triphenylmethane, butyllithium (1.2 molar equiv) produced the enolate, since subsequent carbonation with gaseous carbon dioxide led to the acid product in one experiment in 12% and in another in 22% yield. However, unidentified products were also detected here. A tetrahydrofuran solution of triphenylmethylsodium could be prepared (60–75% yield) by substituting tetrahydrofuran for ether in the published directions[12] for converting an ether solution of triphenylmethyl chloride with sodium amalgam to ethereal triphenylmethylsodium. The sodium enolate, obtained by titrating deoxypodophyllotoxin (3) with the dark red organometal solution (1.4 molar equiv) to a persistent red, was carbonated either with gaseous or solid carbon dioxide. 2-Carboxydeoxypicropodophyllin was obtained in 25–28% conversion.

In every run, thin layer chromatographic analysis of the products before fractionation revealed the presence not only of acid product 6 but also of triphenylmethane, triphenylmethyl alcohol, deoxypicropodophyllin, and deoxypodophyllotoxin.

Decarboxylation of 2-Carboxydeoxypicropodophyllin (6).—A 3-mg sample of the acid in a capillary tube was brought at 150° and maintained at this temperature for 6 min, after which time the sample melted with foaming. After another 2 min at 150°, the material in chloroform solution was spotted on a thin layer chromatography plate together with deoxypodophyllotoxin (3) and deoxypicropodophyllin (4). Development of the plate with carbon tetrachloride–ether (4:1) produced only two spots, one with R_f 0.50 corresponding to deoxypodophyllotoxin and one with R_f 0.32 corresponding to deoxypicropodophyllin.

In another similar decarboxylation, the infrared absorption curve of the product (KBr pellet) was found to correspond exactly with that observed for a pelleted mixture of deoxypodophyllotoxin and deoxypicropodophyllin, with the latter predominating. No carboxyl carbonyl absorption (1725 cm^{-1}) was evident.

Thin layer chromatographic analysis showed that heating samples of deoxypodophyllotoxin or of deoxypicropodophyllin for 0.5 hr, either alone or in the presence of a little hexanoic acid, failed to interconvert the epimers or to change them in any way.

Hydrolysis and Relactonization of 2-Carboxydeoxypicropodophyllin (6).—A solution of the acid (80 mg, 0.17 mmol) in 10 ml of 0.2 *N* sodium hydroxide solution was warmed at 50° for 1 hr. After the mixture was cooled to 0°, it was acidified to pH 2 with 1 *N* hydrochloric acid, and whatever solid formed was collected and dried over calcium sulfate *in vacuo*. This solid (31 mg), developed on a thin layer plate with benzene–methanol (3:1), developed a very faint spot (R_f 0.19) matching that obtained for 2-carboxydeoxypicropodophyllin and a dark spot (R_f 0.09) attributed to the desired dicarboxy acid 8. The neutralization equivalent of the solid (240) compared reasonably well with that calculated (230) for the expected diacid 8. The infrared absorption curve (mineral oil mull) showed a maximum at 3500 cm^{-1} (hydroxyl), which is absent in the curve for 2-carboxydeoxypicropodophyllin, and also showed only one carbonyl

(12) C. R. Renfrew and C. F. Hauser, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 607.

peak at 1720 cm^{-1} (COOH) as compared with the two peaks (1780 and 1725) for the starting lactone acid.

Relactonization was effected by boiling the heterogenous mixture of diacid **8** (10 mg) with 30 ml of benzene for 2 hr. The single spot (R_f 0.19) obtained when the relactonized material was developed on a plate showed that only 2-carboxydeoxypicropodophyllin had been formed. The infrared absorption spectrum (mineral oil mull) was identical with that of 2-carboxydeoxypicropodophyllin. Exposing the relactonized material dissolved in tetrahydrofuran to ethereal diazomethane produced 2-carbomethoxydeoxypicropodophyllin (see below), which ran side by side on a silica gel plate with authentic ester (R_f 0.42 using carbon tetrachloride–ether, 4:1). Removing all solvent left a solid residue, which when mixed with authentic ester (mp 190–191°) showed mp 187–190°. The infrared absorption curves of the two esters were identical.

Methyl Ester of 2-Carboxydeoxypicropodophyllin. a. From the Acid.—A solution of 2-carboxydeoxypicropodophyllin (0.20 g) in 15 ml of pure tetrahydrofuran was treated with excess ethereal diazomethane. After 15 min, volatiles were removed, and the residue (0.21 g; homogeneous according to thin layer chromatography) was crystallized from methylene chloride–hexane. The resulting 2-carbomethoxydeoxypicropodophyllin (**7**), mp 189.5–191°, weighed 0.17 g (84%): $[\alpha]D$ 110° (*c* 0.4, pyridine) or $[\alpha]D$ 83° (*c* 0.4, $CHCl_3$); ir (CCl_4) 1787 for lactone carbonyl and 1731 cm^{-1} for ester carbonyl; nmr ($CDCl_3$) resembles the curve for deoxypicropodophyllin with δ 6.80, 6.58, and 6.38 (aromatic H's), 5.88 (s, methylenedioxy H's), multiplets with close-lying chemical shifts (12, 4, CH_3O), multiplets for all other protons.

Anal. Calcd for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30; $4CH_3O$, 26.76. Found: C, 62.72, H, 5.29; CH_3O, 26.69.

b. From Enolate 5 with Methyl Chloroformate.—A 1 *M* butyllithium solution in hexane (0.84 ml, *ca.* 0.8 mmol) was added dropwise from a small graduated syringe sticking through a serum cap septum to a vigorously stirred solution of dry deoxypodophyllotoxin (**3**) (0.43 g, 1.1 mmol) and 0.26 g of triphenylmethane (1.1 mmol) in 20 ml of tetrahydrofuran that had just been distilled from calcium hydride. The resulting orange mixture was stirred further for 0.5 hr before dropwise injection of a solution of pure methyl chloroformate (0.13 g, 1.1 mmol) in 2 ml of dry tetrahydrofuran. After 1 hr, water was added, and the mixture was brought to pH 5.5 with a few drops of hydrochloric acid. The lower aqueous layer was extracted with ether, and the combined ether and hexane solutions were washed with water, dried, and stripped of volatiles. The residue was chromatographed through a 1-ft column of 60–100 mesh silica gel, with 50 ml of benzene serving to remove triphenylmethane and 100 ml of benzene–acetone (4:1) serving to remove product. The crude product was crystallized twice from methanol to give 0.28 g (56%) of 2-carbomethoxydeoxypicropodophyllin (**7**), mp 187–190°. This material showed a single spot on a Gelman silica gel strip (chloroform–ether, 4:1) with the same R_f as that from the methyl ester derived from acid **6** and spotted on the same plate; ir ($CHCl_3$) was identical with curve from the methylation product; the melting point was not depressed when the two esters were mixed.

Activity.—2-Carboxydeoxypicropodophyllin (**6**) was submitted to Cancer Chemotherapy National Service Center for screening. When tested against cell cultures of human epidermoid carcinoma of the nasopharynx,[13] a solution of the compound (NSC No. 92321) in dimethylformamide showed a confirmed ED_{50} toxicity (dose causing 50% growth inhibition) at less than 1.9 μg/ml, possible in the 0.2–0.5-μg/ml range.

Registry No.—**3**, 19186-35-7; **6**, 33369-69-6; **7**, 33369-70-9; **8**, 33369-71-0.

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(13) C. G. Smith, W. L. Lummis, and J. E. Grady, *Cancer Res.*, **19**, 843 (1959).

Enol Acetylation of Methyl 12-Oxopodocarp-13-en-19-oate and Methyl 12-Oxopodocarp-8(14)-en-19-oate

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The enol acetylation of alicyclic unsaturated ketones has been largely restricted to the steroid series[2] where interest has been focused on reagents which result in either thermodynamically or kinetically controlled[3,4] reaction products. In connection with a diterpenoid synthesis problem we wished to prepare a specific ring C acetoxy diene from methyl 12-oxopodocarp-13-en-19-oate[5,6] (**1**), and we report here the acetoxy dienes obtainable under both thermodynamically and kinetically controlled conditions.

Enol acetylation of **1** with isopropenyl acetate and toluenesulfonic acid[7] (kinetic control) gave only the 11,13-diene **2** and starting ketone. Acetic anhydride and *p*-toluenesulfonic acid enol acetylation gave 30% diene **2**, 50% 8(14),12-diene **3**, 5% nonconjugated diene **9**, and 5% methyl podocarpate **10**. To ensure that a true thermodynamic equilibrium was present, the 11,13-diene **2** was subjected to acetic anhydride–toluenesulfonic acid equilibration, and the same ratio of 3:5 for **2** to **3** was obtained. The product composition in all experiments was determined by integration of the vinylic signals at 5.40 and 5.87 ppm together with the C-20 methyl absorptions in the pmr spectra of the direct reaction mixtures (see Experimental Section).[8]

The thermodynamic ratio of 3:5 noted for **2** to **3** is unexpected on the basis of double bond stabilities[9] which should lead to an equilibrium ratio of 1:9. The discrepancy must arise from other factors, and previous authors[10] have pointed out the dominance of steric interactions in determining the enol acetate ratios observed for simple cyclic ketones. To probe

(1) Graduate Fellow of National Research Council of Canada.

(2) H. H. Inhoffen, *Chem. Ber.*, **69**, 2141 (1936); I. M. Heilbron, T. Kennedy, F. S. Spring, and G. Swain, *J. Chem. Soc.*, 869 (1938); L. F. Fieser and W.-Y. Huang, *J. Amer. Chem. Soc.*, **75**, 5356 (1953); L. Ruzicka and W. H. Fischer, *Helv. Chem. Acta*, **19**, 806 (1936); O. R. Rodig and G. Zanati, *J. Org. Chem.*, **32**, 1423 (1967); A. J. Liston and P. Toft, *ibid.*, **33**, 3109 (1968); P. Toft and A. J. Liston, *Tetrahedron*, **27**, 969 (1971).

(3) W. C. J. Ross, *J. Chem. Soc.*, 737 (1946); J. Libman and Y. Mazur, *Tetrahedron*, **25**, 1699 (1969).

(4) J. Champagne, H. Favre, D. Vocelle, and I. Zbikowski, *Can. J. Chem.*, **42**, 212 (1964); P. Toft and A. J. Liston, *Chem. Commun.*, 111 (1970).

(5) (a) R. H. Bible and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961); (b) R. A. Bell and M. B. Gravestock, *Can. J. Chem.*, **47**, 3661 (1969).

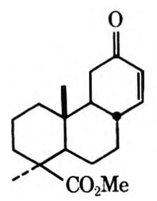
(6) The numbering system used here is that proposed by the IUPAC Committed on diterpene nomenclature, London, July 1968.

(7) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Amer. Chem. Soc.*, **74**, 3852 (1952).

(8) Chromatography of the dienes appeared to cause some degradation of diene **3** and the ratio of the dienes changed to 2:3 for **2** to **3**.

(9) J. D. Roberts and M. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1964, p 174.

(10) A. J. Liston, *J. Org. Chem.*, **31**, 2105 (1966); B. Berkoz, E. P. Chavez, and C. Djerassi, *J. Chem. Soc.*, 1323 (1962); H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).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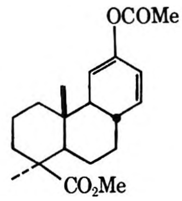
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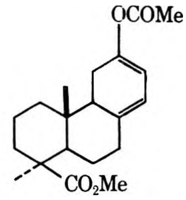
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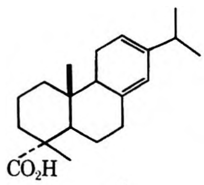
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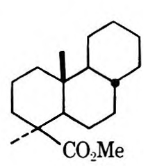
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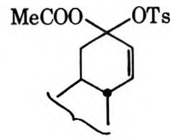
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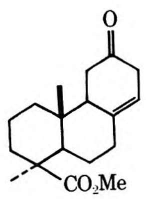
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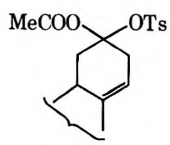
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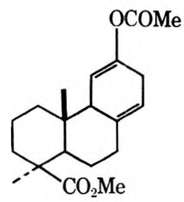
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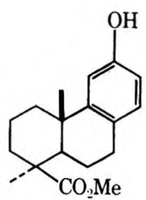
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this point further we examined the optical rotatory dispersion (ORD) curves[11] exhibited by 2 and 3 and found that 2 showed a plain, positive curve while 3 displayed an intense, negative Cotton effect (molecular amplitude 443). This latter Cotton effect is similar to that shown by levopimaric acid 4 (molecular amplitude 344)[12] and suggests that 3 possesses the same B/C folded conformation[13] which levopimaric acid is forced to adopt because of the interaction between the C-11 β-H and the C-20 CH_3 group.[14] The plain ORD curve of 2 is a result of the severe steric interaction between the C-1 β-H and the C-11 β-H which distorts ring C and allows the 11,13-diene to adopt a planar conformation. Application of the allylic axial bond chirality treatment[18] for this planar conformation then suggests a minimal Cotton effect. We can conclude then that the factors causing the thermodynamic ratio between the two dienes **2** and **3** are the result of a delicate balance between double bond stabilities and steric interactions.

The sole formation of **2** in the kinetically controlled experiments can be rationalized by the Mazur[19] intermediate acetoxy tosylate **6**. Here the rate of E2 elimination of the tosylate group toward C-11 will be greatly enhanced by the loss in steric compression energy between the C-11 and C-1 hydrogens, while loss of the C-8 proton occassions no such steric acceleration and is therefore negligibly slow. The results obtained for the kinetically controlled enol acetylation of the β,γ-unsaturated ketone **7**[5b] show a similar trend. Loss of the tosylate of intermediate **8** with elimination toward C-11 is again sterically accelerated and the nonconjugated diene **9** comprised 60% of the product. However, the increased acidity of the C-13 protons of **8** allows elimination toward C-13 to become competitive, and diene **3** was formed in 25% yield. The presence of 5% **9** in the thermodynamic enol acetylation mixture indicates that it is of comparable stability to the conjugated dienes **2** and **3**. Presumably the increased relative stability of **9** is a result of the relief of subtle steric interactions which are not directly apparent from molecular models.

(11) P. Crabbe. "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, Chapter 10.

(12) A. W. Burgstahler, H. Ziffer, and A. Weiss, *J. Amer. Chem. Soc.*, **83**, 4660 (1961).

(13) A. W. Burgstahler, I. Gawronski, T. F. Niemann, and B. A. Feinberg, *Chem. Commun.*, 121 (1971).

(14) An interesting feature of the folded conformation is the absence of any significant shielding effect of the 8(14),12-diene on the pmr absorption signal of the C-20 methyl. The observed signal at 0.78 ppm is similar to that recorded for methyl podocarpan-19-oate **5** (0.73 ppm).[15] Even one double bond in the 8(14) position has a strong shielding influence on the C-20 methyl, moving the signal into the 0.50–0.55-ppm region[5b,16] (*cf.* the nonconjugated diene **9** at 0.60 ppm). Either we must assume that the 12(13) double bond is deshielding the C-20 methyl by an amount sufficient to offset the shielding effect of the 8(14) double bond or we must conclude that the simple arithmetic addition of screening constants[17] of olefins is not a valid procedure for conjugated systems but rather the diene must be considered as a whole. No *ab initio* calculations are currently available to check this point.

(15) J. W. ApSimon, O. E. Edwards, and R. Howe, *Can. J. Chem.*, **40**, 630 (1962).

(16) A. Ahond, P. Carnero, and B. Gastambide, *Bull. Soc. Chim. Fr.*, 348 (1964).

(17) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day San Francisco, Calif., 1964, Chapter 2.

Experimental Section[20]

Methyl 12-Acetoxypodocarp-8(14),12-dien-19-oate (3).—*p*-Toluenesulfonic acid monohydrate, 80 mg, in 15 ml of acetic anhydride was heated to boiling in a flask fitted with a Dean-Stark trap until 5 ml of distillate was obtained. A solution of 240 mg (0.83 mmol) of methyl 12-oxopodocarp-13-en-19-oate (1) (mp 126–130°) in 10 ml of acetic anhydride was then added and distillation continued for 3.5 hr in such a manner that 10 ml of distillate was collected. The reflux ratio was controlled by a positive pressure of nitrogen. After cooling the reaction was worked up *via* hexane and, upon solvent evaporation, gave 280 mg (98%) of the mixture of acetoxy dienes as a light brown oil. Analysis of the pmr spectrum by integration of the vinyl and C-20 methyl absorptions showed the crude reaction mixture consisted of 10% unsaturated ketone **1**, 50% diene **3**, 30% diene **2**, 5% nonconjugated diene **9**, and 5% aromatized material, methyl podocarpate **10**. Chromatography on silica gel led to removal of aromatic material and starting ketone, and elution with 1% ethyl acetate–benzene gave the mixed acetoxy dienes **2** and **3** in the ratio 2:3. Solution in methanol and cooling to −20° yielded 80 mg (28%) of acetoxy diene **3** as colorless crystals. A second crystallization from methanol gave the analytical sample as clusters of needles: mp 96–97°; ir 1755 (acetate C=O), 1730 (ester C=O), 1680, 1630 cm^{-1} (diene); uv λ_{max} 257 mμ (sh) (ε 5200), 263.5 (7700), 282.5 (7800), 295 (sh) (5000); ORD (concn 0.10 mg/ml, CH_3OH) 22°, $[\Phi]_{650}$ 0°, $[\Phi]_{589}$ −1550°, $[\Phi]_{290}$ −21,300°, $[\Phi]_{232}$ +23,000°, $[\Phi]_{210}$ +15,600°, mol amplitude a = 443; pmr δ 0.78 (s, 3, C-20 CH_3), 1.19 (s, 3, C-18 CH_3),

(18) A. W. Burgstahler and R. C. Barkhurst, *J. Amer. Chem. Soc.*, **92**, 7601 (1970).

(19) J. Libman, M. Sprecher, and Y. Mazur, *Tetrahedron*, **25**, 1679 (1969).

(20) Melting points were determined on a Kofler micro hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 337 spectrometer in chloroform solution. Proton magnetic resonance spectra were recorded on a Varian Associates A-60 spectrometer in deuteriochloroform solution using tetramethylsilane as internal standard. Optical rotatory dispersion measurements were performed in methanol or cyclohexane solution on a JASCO ORD-UV-5 instrument. Ultraviolet spectra were obtained in methanol using a Cary 14 spectrometer. Carbon and hydrogen microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Unless otherwise stated the organic substrates were isolated by thorough extraction with hexane, followed by washing of the combined hexane solution with saturated sodium bicarbonate, water, and saturated brine, and drying over anhydrous sodium sulfate. The hexane was removed by evaporation at reduced pressure on a Buchi Rotavapur.

2.08 (s, 3, $OCOCH_3$), 3.58 (s, 3, $COOCH_3$), 5.40 ppm (q, 2, J_{AB} = 6.3 Hz, $\delta\nu_{AB}$ = 3.9 Hz).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.44.

Methyl 12-Acetoxypodocarp-11,13-dien-19-oate (2).—The procedure of Dauben, *et al.*, was used.[9] To a solution of 1.00 g (3.58 mmol) of unsaturated keton 1 (mp 126–130°) in 30 ml of isopropenyl acetate was added 0.300 g of *p*-toluenesulfonic acid monohydrate, and the mixture was heated at reflux under nitrogen, using the same apparatus and technique as above, for 4.5 hr. At the end of this period, 20 ml of distillate was obtained and, after cooling, the organic product was isolated *via* hexane extraction. Evaporation of the solvents gave 1.13 g (95%) of a light yellow oil, the pmr spectrum of which showed it to consist of 90% of acetoxy diene **2** and 10% of ketone **1**. There were no discernible absorptions of the acetoxy diene **3** present. Crystallization from dry hexane at 0° gave 0.80 g (70%) of **2** as colorless needles: mp 78–80°; ir 1760 (acetate C=O), 1730 (ester C=O), 1650, 1600 cm^{-1} (diene); uv λ_{max} 262 mμ (ϵ 3400); ORD (concn 0.1 mg/ml CH_3OH), 22°, $[\Phi]_{650}$ +1000°, $[\Phi]_{589}$ +1500°, $[\Phi]_{400}$ +1500°, $[\Phi]_{250}$ +7000°, $[\Phi]_{220}$ +12,600°; pmr δ 0.69 (s, 3, C-20 CH_3), 1.22 (s, 3, C-18 CH_3), 2.18 (s, 3, $OCOCH_3$), 3.77 (s, 3, $COOCH_3$), 5.70 (s, 2, $W_{1/2}$ = 4 Hz, C-13 and C-14 vinylic H), 5.87 ppm (d, 1, *J* = 1.0 Hz, C-11 H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.38.

When the pure acetoxy diene **2** was heated at reflux under nitrogen in acetic anhydride for 2 hr in the presenec of a crystal of *p*-toluenesulfonic acid and worked up *via* hexane, the thermodynamic mixture of 59% **3**, 36% **2**, and 5% **9** was obtained.

Methyl 12-Acetoxypodocarp-8(14),11-dien-19-oate (9).—To a solution of 100 mg (3.6 mmol) of methyl 12-oxopodocarp-8(14)-en-19-oate (**7**) in 5.0 ml of isopropenyl acetate was added 25 mg of *p*-toluenesulfonic acid monohydrate, and the mixture was heated at reflux under nitrogen in the same apparatus as above for 3 hr. At the end of this period 3.0 ml of distillate was obtained and, after cooling, the organic product was isolated *via* hexane. Evaporation of the solvents afforded 108 mg (94%) of oily crystals. The pmr spectrum of this showed the product to consist of 60% **9**, 25% **3**, and 15% methyl podocarpate **10**. Chromatographhy on Florisil removed the methyl podocarpate but did not achieve separation of **9** and **3**. Tlc on silica gel in a number of solvents was similarly unsuccessful. An enriched sample of **9** (containing 17% of **3** by integration of the C-20 CH_3 absorptions) was obtained by repeated crystallization from hexane and it showed ir 1760 (acetate C=O), 1730 (ester C=O), 1670 cm^{-1} (olefinic); uv (featureless except for absorption due to 17% of **3**); pmr δ 0.60 (s, 3, C-20 CH_3), 1.15 (s, 3, C-18 CH_3), 2.05 (s, 3, $OCOCH_3$), 2.5–2.85 (m, 2, C-14 allylic H), 3.58 (s, 3, $COOCH_3$), 5.35 ppm (m, 2, $W_{1/2}$ = 10 Hz, C-11 and C-14 H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.12; H, 8.67.

Registry No.—**1**, 24402-16-2; **2**, 33608-33-2; **3**, 33495-78-2; **7**, 24412-03-1; **9**, 33537-22-3.

Acknowledgment.—We gratefully acknowledge financial support from the National Research Council of Canada.

19-Hydroxy Steroids. III. Reactions with Lead Tetraacetate[1]

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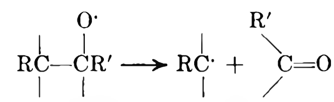
Department of Chemistry, University of Ottawa, Ottawa, Canada K1N 6N5

Received July 26, 1971

Since it was first reported[2] that treatment of secondary alcohols with lead tetraacetate could lead to cyclic ethers, this reaction has been used extensively to functionalize or to remove the methyl group at C-10 of certain steroids[3] in attempts to enhance the biological activity of such compounds and as a means of preparing estrogens[4] from androgens.

In addition to these important applications, the reaction *per se* has been extensively investigated and a number of generalizations[5] have been found to apply. One of these correlations relates to the limits of favorable internuclear distance (2.5–2.7 Å) between the oxyradical and the carbon atom from which hydrogen atoms can be abstracted intramolecularly. If more than one alkyl group is appropriately situated for hydrogen atom abstraction, it has been found that the reactivity of hydrogen atoms decreases in the order tertiary > secondary > primary. Hydrogen atoms attached to an oxygen-bearing carbon atom are more reactive than those attached to a carbon atom having another carbon atom as neighbor. More recently,[6] the effects of a methoxy group adjacent to the reacting hydroxy group have been evaluated.

Once an oxygen radical has been produced by oxidation with lead tetraacetate, fragmentation can also take place, as shown below. The amount of cleavage which occurs increases with the stability of the alkyl radical formed[5] but a number of other factors can also influence the course of this reaction.



While investigating approaches to the synthesis of cardiac-active steroids some model compounds containing a hydroxy group at C-19 were prepared. Following is a report of the course of the lead tetraacetate oxidation of one of these compounds in which it is shown that the reaction proceeds by intramolecular hydrogen abstraction.

Steroids with a double bond at C-5,C-6 are normally unaffected[7] in reactions with lead tetraacetate. However, Moriarty and Kapadia[8] have reported that the lead tetraacetate oxidation of 3β-acetoxycholest-5-en-19-ol (**1**) results in oxidative fragmentation, with loss of the hydroxymethyl group at C-10, yielding a product tentatively identified as 3β,6β-diacetoxy-19-norcholest-5(10)-ene (**2b**). The authors postulated a mechanism involving the concerted intramolecular transfer of an acetoxy group from the C-19 lead ester to C-6 which implies stereospecificity in the resulting C-6 acetoxy group. An analogous fragmentation reaction has also been observed[9] in the lead tetraacetate oxidation of the diethylene ketal of 19-hydroxyandrost-5-ene-3,17-dione.

The preparation of the 5α,6α- and 5β,6β-oxides (**3** and **4**) (Scheme I) from 3β-acetoxycholest-5-en-19-ol

(1) For part II, see P. Morand and M. Kaufman, *Can. J. Chem.*, **49**, 3185 (1971).

(2) G. Cainelli, M. Lj. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).

(3) See, for example, A. Bowers and E. Denot, *J. Amer. Chem. Soc.*, **82**, 4956 (1960); H. Immer, M. Lj. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 753 (1962); J. F. Bagli, P. Morand, and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963); M. E. Wolff, W. Ho, and R. Kwok, *Steroids*, **5**, 1 (1965).

(4) *Cf.* A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Amer. Chem. Soc.*, **84**, 3204 (1962); J. F. Bagli, P. Morand, K. Wiesner, and R. Gaudry, *Tetrahedron Lett.*, 387 (1964).

(5) K. Heusler and J. Kalvoda, *Angew. Chem.*, **76**, 518 (1964).

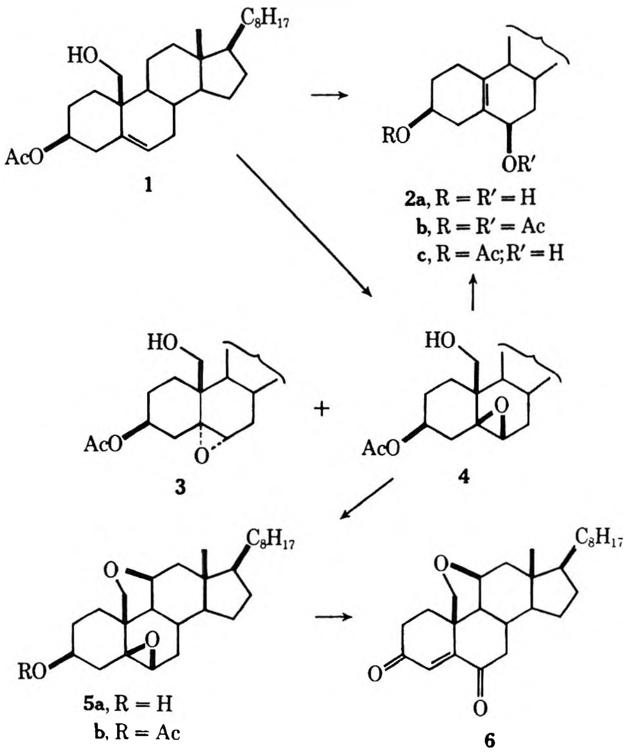
(6) P. Morand and M. Kaufman, *J. Org. Chem.*, **34**, 2175 (1969).

(7) *Cf.* G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **44**, 518 (1961).

(8) R. M. Moriarty and K. Kapadia, *Tetrahedron Lett.*, 1165 (1964).

(9) M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. Lj. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2682 (1962).

SCHEME I



(1) by treatment with perphthalic acid has been reported and the structures of these compounds have been established on the basis of physical[10] and chemical[1] evidence. It was subsequently observed that, when neutral alumina instead of Florisil was used as adsorbant to remove excess phthalic acid, the yield of the 5β,6β-oxide **4** decreased sharply and a third product could be isolated in 23% yield. That this substance was produced from the 5β,6β-oxide **4** was confirmed by treating the latter in a similar manner. The 5α,6α-oxide **3** was found to be stable under these conditions. The structure of this compound[11] is formulated as **2c** on the basis of the analytical and spectral data reported in the Experimental Section. On repeating the reaction reported by Moriarty and Kapadia[8] and hydrolyzing the product isolated, we obtained the diol **2a**, which was found to be identical in all respects with the diol obtained by hydrolysis of 3β-acetoxy-19-norcholest-5-(10)-en-6β-ol (**2c**) which was prepared in the manner described above. This therefore confirms the structure **2b** formulated by these authors and also provides support for their proposed mechanism.

We then proceeded to investigate the course of the reaction with lead tetraacetate in a C-19 steroidal alcohol in which the C-5,C-6 double bond was absent. Treatment of 3β-acetoxy-5,6β-oxido-5β-cholestan-19-ol (**4**) with this reagent led to the isolation (43%) of a substance identified as 3β-acetoxy-5,6β:11β,19-dioxido-5β-cholestane (**5b**). The empirical formula, $C_{29}H_{46}O_4$, for this compound was confirmed by elemental and mass spectral analyses. Examination of the nmr spectrum indicated that the 5β,6β-oxide group was intact. Signals for three protons attributable to the formation of an oxide ring were also observed. Since fragmentation apparently had not occurred in this reaction, the question remained as to which proton (C-2, C-4, C-8, or C-11) had been abstracted, as it is the alkyl group δ to the reacting alcohol that is normally involved[5] in the formation of such oxides. At C-2 and C-4, it is clearly the axial proton which would be abstracted, resulting in the formation of the β oxide in each case. Although the situation is not so clear-cut at C-11, it is most likely[12] that the β oxide would be formed since the isomeric α oxide would introduce considerably more strain into the molecule.

That the tertiary hydrogen atom at C-8 was not abstracted was established by examination of the nmr spectrum of **5b**. The integrated spectrum indicated five downfield protons whereas four would have been observed if the C-19 oxyradical had abstracted the δ hydrogen atom at C-8. Measurement of internuclear distances (Dreiding models) between the oxy radical and the relevant δ carbon atoms, C-2, C-4, and C-11, indicated a separation of 2.9 Å for the C-2 and C-4 positions and of 2.3 Å for the C-11 position. It is apparent, therefore, that the most likely hydrogen atom to be abstracted is one attached to C-11 since, by rotation of the oxy radical away from the C-11 atom, the critical distance[5] of 2.5–2.7 Å can be approached.

Confirmation that the ether linkage was not at C-4 (and therefore not at C-2 since both these carbon atoms are equidistant from the oxy radical) was obtained by hydrolysis of **5b** to the corresponding alcohol **5a** and subsequent oxidation to a compound identified as 11β,19-oxidocholest-4-ene-3,6-dione (**6**). The empirical formula, $C_{27}H_{40}O_3$, for this substance was confirmed by elemental and mass spectral analyses and the uv spectrum showed the characteristic absorption[13] for an enedione. As expected, the nmr spectrum exhibited a singlet at δ 6.48 (olefinic proton at C-4) as well as the appropriate signals for the five-membered oxide ring indicating that the latter was intact.

Experimental Section[14]

3β,6β-Dihydroxy-19-norcholest-5(10)-ene (2a). A. From 3β-Acetoxy-5,6β-oxido-5β-cholestan-19-ol (4).—The preparation of **4** by treatment of 3β-acetoxycholest-5-en-19-ol (**1**) with perphthalic acid has been described[10] elsewhere. It was subsequently found, however, that, when an ethereal solution of the crude product was eluted on a column of neutral alumina instead of Florisil to remove excess phthalic acid and the products were separated by chromatography over silica gel (600 g), a third product (in addition to the isomeric 5,6-oxides) could be isolated in 23% yield. It was also observed that the yield of the 5β,6β-oxide **4** decreased significantly from that previously obtained. The substance isolated was purified by crystallization from petroleum ether (bp 30–60°) and was identified as 3β-acetoxy-19-norcholest-5(10)-en-6β-ol (**2c**): mp 108–109°; ir

(10) R. R. Fraser, M. Kaufman, P. Morand, and G. Govil, *Can. J. Chem.*, **47**, 403 (1969).

(11) Treatment of 5,6β-oxido-19-oxo-5β-cholestan-3β-ol with KOH in CH_3OH has been reported [M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964)] to give the diol **2a**, which was characterized by its elemental analysis, optical rotation, and melting point.

(12) For example the 11β-oxy radical leads to formation of the 11β,19-oxide whereas the 11α-oxy radical leads to formation of the 1β,11α-oxide [K. Heusler, *Tetrahedron Lett.*, 3975 (1964)].

(13) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 44.

(14) Melting points were determined on a Hoover Uni-Melt apparatus and are uncorrected. Ir, nmr, uv, and mass spectra were recorded on a Beckman IR-8 infrared spectrophotometer, a Varian V-4302 60-Mc spectrometer, a Perkin-Elmer 202 recording spectrophotometer, and a Hitachi Perkin-Elmer R. M. U. 6D spectrometer. Microanalyses were determined in the laboratory of Dr. A. Bernhardt, Elbach uber Engelskirchen, West Germany. SilicaR (200–300 mesh) and neutral alumina (Woelm, activity I) were used as adsorbants in column chromatography. In working up the products of reactions, the organic extracts were washed with dilute HCl solution and/or $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure.

($CHCl_3$) 1670 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.1 (m, 1, $W_{1/2}$ = 15 Hz, CHOAc), 3.84 (m, 1, $W_{1/2}$ = 8 Hz, CHOH), 2.06 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* 412, 370, 352.

Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 77.63; H, 10.61.

Hydrolysis of **2c** (51 mg) with a 10% solution (10 ml) of KOH in methanol-water (9:1) at room temperature for 12 hr gave, after working up in the usual way and crystallizing the product from CH_3OH, an analytical sample of 3β,6β-dihydroxy-19-norcholest-5(10)-ene (**2a**): mp 164-166° (lit.[8,11] mp 174-175°, 165-168°); mass spectrum (70 eV) *m/e* 388 (M^+), 370, 352.

B. From 3β-Acetoxycholest-5-en-19-ol (1).—The product obtained by treatment of **1** with lead tetraacetate in the manner reported by Moriarty and Kapadia[8] was hydrolyzed as described above. Isolation of the product and crystallization from CH_3OH gave a substance identical in all respects with the 3β,6β-dihydroxy-19-norcholest-5(10)-ene (**2a**) obtained from **4**.

Lead Tetraacetate Oxidation of 3β-Acetoxy-5,6β-oxido-5β-cholestan-19-ol (4).—Lead tetraacetate (6.5 g, 14.6 mmol, previously dried over P_2O_5) and dry calcium carbonate (7.0 g) were added to cyclohexane (200 ml) and the solution was refluxed for 40 min by means of a 500-W lamp. Iodine and 3β-acetoxy-5,6β-oxido-5β-cholestan-19-ol (**4**) (0.53 g, 1.15 mmol) were then added and the mixture was refluxed for 5 hr. The insoluble white residue was removed by filtration and the filtrate was washed with a 30% aqueous solution of $Na_2S_2O_3$ (200 ml) and water. Removal of the solvent gave an oil (0.50 g) which was chromatographed over silica gel. Elution with benzene afforded a solid (216 mg) which, upon crystallization from aqueous CH_3OH, gave an analytical sample of a substance identified as **3β-acetoxy-5,6β:11β,19-dioxido-5-cholestane (5b)**: mp 109-111°; nmr ($CDCl_3$) δ 4.85 (m, 1, $W_{1/2}$ = 25 Hz, CHOAc), 4.02 (m, 2, CH_2OC), 3.75, 3.65, (m, 1, CHOC), 3.2 (m, 1, CHOC), 2.05 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* 458 (M^+), 440, 398, 382, 380, 351.

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 75.73; H, 9.74.

Hydrolysis and Oxidation of 3β-Acetoxy-5,6β:11,19-dioxido-5β-cholestane (5b).—Treatment of **5b** (70 mg) with a solution of $NaHCO_3$ (10 mg) in methanol-water (9:1, 5.0 ml) at 60° for 4 hr gave, after working up in the usual way, the crude alcohol **5a** (65 mg) which was subsequently oxidized with Sarett reagent[15] without further purification. Isolation of the product (52 mg) in the usual way gave, after crystallization from ether, a substance identified as **11β,19-oxidocholest-4-ene-3,6-dione (6)**: mp 156-158°; uv max ($CHCl_3$) 260 mμ (ε 11,600); ir ($CHCl_3$) ($CHCl_3$) 1690 cm^{-1} (C=C—C=O); nmr ($CDCl_3$) δ 6.49 (s, 1, CH=C), 4.29 (m, 1, CHOC), 4.20, 4.01, 3.85, 3.65 (m, 2, *J* = 10 Hz, CH_2OC); mass spectrum (70 eV) *m/e* 382, 370 (the mass spectrum of cholest-4-ene-3,6-dione prepared in our laboratory also exhibits a peak at $M^+ - 42$).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.69; H, 9.73.

Registry No.—**2c**, 33487-93-3; **5b**, 33537-29-0; **6**, 33487-94-4; lead tetraacetate, 546-67-8.

Acknowledgments.—The financial support of the National Research Council of Canada is gratefully acknowledged.

(15) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

Esters and Flavenes from 2-Hydroxychalcones and Flavylium Salts

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Esters prepared from hydroxychalcones are well known except for those of the 2-hydroxychalcones. 2-Acetoxy-2′,3,4′-trimethoxy- and 2-acetoxy-2′,4′,6-trimethoxychalcones[1] in addition to the tetra-*p*-chlorobenzoate of 2,5,2′,5′-tetrahydroxychalcone[2] are reported. Such references are few in number probably because acetylation of 2-hydroxychalcone could yield either the ester of the chalcone itself or the esters of the 2-phenylbenzopyranols, **2** and **3**. The latter flavene esters would be 2-acetoxy-2-phenyl-2*H*-1-benzopyran or 4-acetoxy-2-phenyl-4*H*-1-benzopyran. In addition these esters have not been readily distinguishable and, therefore, the structure of 2-hydroxychalcone esters and a flavene are determined here.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Clark Microanalytical Laboratory, Urbana, Ill., performed the C,H analyses and the University of Illinois provided the nmr spectra with a Varian HA 100 spectrometer using TMS internal standard. Ir spectra were obtained with a Beckman IR-8 spectrometer utilizing KBr pellets or neat liquid.

2-Hydroxychalcone, mp 154-155° dec (lit.[3] mp 154-156° dec), and 4-hydroxychalcone, mp 183-184° (lit.[4] mp 182.5°), were synthesized by condensation of acetophenone and salicylaldehyde or 4-hydroxybenzaldehyde. Flavylium perchlorate, mp 190-191° (lit.[5] mp 190-191°), and flavylium tetrachloroferrate(III), mp 137-138° (lit.[6] mp 137-138°), were prepared from 2-hydroxychalcone. Acetylation of 4-hydroxychalcone yielded 4-acetoxychalcone, mp 128-129° (lit.[4] mp 129°).

2-Acetoxychalcone.—Acetylation of 2-hydroxychalcone with acetic anhydride and acid,[7] or sodium acetate[8] catalysts, at 50-60° for 15 min, and recrystallization of the crude product with hexane yielded 2-acetoxychalcone, 60%, mp 65-66°.

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.29. Found: C, 76.90; H, 5.28.

Flavylium Tetrachloroferrate(III) from 2-Acetoxychalcone.—A stream of dry hydrogen chloride was bubbled into 13 g of 2-acetoxychalcone stirred in 200 ml of glacial acetic acid for 2 hr. Addition of 10g of anhydrous ferric chloride to the solution produced a precipitate which was recrystallized with glacial acetic acid. The yield of flavylium tetrachloroferrate(III) was 17 g (72%), mp and mmp 137-138°.

Hydrolysis of 2-Acetoxychalcone.—2-Acetoxychalcone, 8.0 g, in 250 ml of water containing 4.3 g of dissolved sodium hydroxide was refluxed for 3 hr. The reaction mixture was extracted with ether which was washed, dried with Drierite, and allowed to evaporate. An oil remained, 3 g (48.5%), ir 2.95 (OH) and 6.08 μ (C=C), which was converted to flavylium tetrachloroferrate(III) (52%) as for 2-acetoxychalcone. Acidification of the basic hydrolysis solution, filtration, and recrystallization with ethanol yielded 2-hydroxychalcone, 2.8 g (45%).

2-Benzoyloxychalcone.—To 25 g of 2-hydroxychalcone in 200 ml of 1 *M* aqueous sodium hydroxide was added 20 g of benzoyl chloride in 200 ml of chloroform dropwise with cooling and stirring for 3 hr. The chloroform layer was separated, washed, dried, and allowed to evaporate. The solid residue was recrystallized from cyclohexane, yielding 24 g (63%) of yellow crystals, mp 101-102°.

Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.78; H, 4.68.

Piperidinoflavene.[9]—To a suspension of 15.3 g (0.05 mol) of

(1) D. N. Dhar, *J. Indian. Chem. Soc.*, **38**, No. 10 (1961).
(2) V. G. Manecke and D. Zerpner, *Makromol. Chem.*, **108**, 198 (1967).
(3) R. C. Elderfield and T. P. King, *J. Amer. Chem. Soc.*, **76**, 5439 (1954).
(4) P. Klinke and H. Gilian, *Chem. Ber.*, **94**, 26 (1961).
(5) R. L. Shriner and R. Sutton, *J. Amer. Chem. Soc.*, **85**, 3989 (1963).
(6) A. N. Nesmeyanov, N. K. Kochetkov, and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **93**, 71 (1953); *Chem. Abstr.*, **49**, 3953d (1955).
(7) A. J. Vogel, "Elementary Practical Organic Chemistry, Small Scale Preparations, Part I," Longmans, Green and Co., New York, N. Y., 1957, p 324.
(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 247.
(9) Procedure after R. E. Schaeffer, "Studies of the Structure of Compounds Resulting from Reactions of Flavylium Salts and *sec*-Amines," M.S. Thesis, University of Iowa, Iowa City, Iowa, 1953.

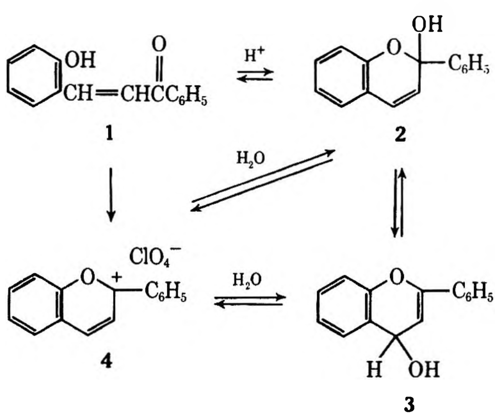
flavylium perchlorate stirred in 600 ml of petroleum ether (bp 60–70°) cooled to 0–5° was added 9 g (0.105 mol) of piperidine dissolved in 150 ml of petroleum ether. The addition required 1.25 hr and the mixture was stirred for an additional 3.5 hr. White piperidinium hydroperchlorate, 9.2 g (0.05 mol), was filtered from the yellow petroleum ether solution which then deposited 13 g of yellow, oily crystals upon evaporation. The product was recrystallized with petroleum ether, yielding 9.1 g (62%) of product, mp 83–85°.

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.62; N, 4.81. Found: C, 82.43; H, 7.42; N, 5.00.

A stream of dry hydrogen chloride was directed into 5 g of piperidinoflavene in 200 ml of glacial acetic acid for 2 hr followed by addition of 5 ml of 70% perchloric acid. The precipitate was collected and recrystallized from glacial acetic acid. The yield of flavylium perchlorate was 3.5 g (67%), mp and mmp 190–191°.

Discussion

The reactions of 2-hydroxychalcone (**1**) and flavylium salts are complicated by the ease of their interconversion through the probable 2-phenyl-2*H*-1-benzopyran-2-ol intermediate (**2**).



The cyclization occurs in syntheses of flavylium salts from 2-hydroxychalcones. Hydrolysis of flavylium perchlorate (**4**) yields an oil which is a mixture[5] because the intermediate **2** isomerizes to **1** and 2-phenyl-4*H*-1-benzopyran-4-ol (**3**). Thus Hill and Melhuish[10] isolated the unstable 4-*O*-ethyl derivative of **3** and other products characteristic of this mixture, while Jurd[11] has identified chalcones in the hydrolysis products of flavylium salts.

Hydrolysis of the acetate of 2-hydroxychalcone, prepared with sodium acetate or acid catalysts, yielded 2-hydroxychalcone and an oil which was converted to flavylium tetrachloroferrate(III). In addition, the chalcone acetate formed flavylium tetrachloroferrate(III) when allowed to react directly with hydrogen chloride and ferric chloride. These reactions are characteristic of either 2-acetoxychalcone or esters of the benzopyranols, **2** and **3**. Similarly, it was not possible for Freudenberg, *et al.*,[12] to give the structure of the ester from acetylation of 7-hydroxy-4-methoxyflavylium chloride. Some chalcone or flavene esters from flavylium salts have been characterized by hydrogenation but others gave indistinguishable amorphous polymers.[13]

For comparison, a flavene was synthesized by treating piperidine with flavylium perchlorate. Flavylium perchlorate is reactive in the 2 and 4 positions[5,10] while the 2° melting point range and nmr spectrum prove that the product is a mixture of flavenes **5** and **6**.

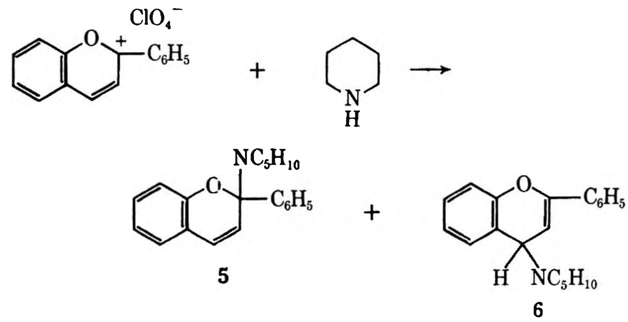


Table I lists the positions, splitting, and assignments of the two typically distorted AB quartets in the nmr spectrum of the flavene mixture. The splitting (J = 10 Hz) and chemical shift of the A′B′ quartet are typical of cis olefinic hydrogens, as in 2-piperidino-2-phenyl-2*H*-1-benzopyran (**5**). The hydrogens in 4-piperidino-2-phenyl-4*H*-1-benzopyran (**6**) are responsible for the AB quartet being at the lower chemical shift.

Table I

100-MHz Nmr Spectrum of Piperidinoflavene ($CDCl_3$)

	A′ B′ quartet	AB quartet	$C_5H_{10}N$– multiplets	C_6H_4, C_6H_5 multiplet
J, Hz	10, 10	4, 4		
δ, ppm	6.44, 5.68	5.80, 4.59	2.42, 1.42	7.8–6.8
Area	8	12	100	87

Flavylium perchlorate was regenerated from the piperidino flavene mixture as additional evidence for the structure assignment. The double bond, 6.00 μ, in the ir spectrum of the piperidinoflavene is found where the carbonyl group of 2-hydroxychalcone absorbs, 6.03–6.09 μ. This is in agreement with the observation of Freudenberg and Weingas[13] that flavene and chalcone double bond absorptions are not distinctive in ir spectra.

The AB or A′B′ quartets of the flavenes are absent from the nmr spectra of 2-acetoxychalcone and 2-benzoyloxychalcone. The nmr peaks from the olefinic hydrogens in these two esters, and for 4-acetoxychalcone, are buried in the aromatic multiplets. Therefore, esterification of 2-hydroxychalcone yielded chalcone esters.

Registry No.—**5**, 33777-35-4; **6**, 33777-36-5; 2-acetoxychalcone, 33777-37-6; flavylium tetrachloroferrate(III), 33775-42-7; 2-benzoyloxychaleone, 33777-38-7.

Acknowledgment.—Students who participated in this work are David Noves, Robert Rothstein, Kaye Pinkerton, and Gretchen Schulp.

(10) D. W. Hill and R. R. Melhuish, *J. Chem. Soc.*, 1161 (1935).

(11) L. Jurd, *Tetrahedron*, **25**, 2367 (1969).

(12) K. Freudenberg, J. H. Stocker, and J. Porter, *Chem. Ber.*, **90**, 960 (1957).

(13) K. Freudenberg and K. Weingas, *Justus Liebigs Ann. Chem.*, **613**, 61 (1958).

Further Examination of the Actions of Bases and of Zinc and Acids on *trans*-2,3-Dibenzoylspiro-(cyclopropane-1,9′-fluorene)

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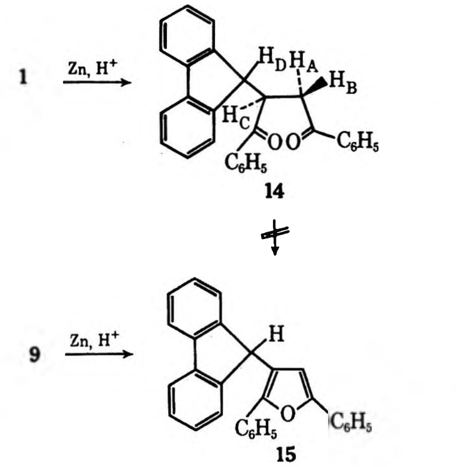
9-Diazofluorene reacts with *trans*-dibenzoylethylene to give *trans*-2,3-dibenzoylspiro(cyclopropane-1,9′-fluorene) (1)[2] in quantitative yield. Cyclopropane 1 was reported to undergo various transformations which were not understood and which led to crystalline products of unknown structures.[2] Of special interest is the reaction of 1 with hot excess methanolic potassium hydroxide (Scheme I) to form a red potassium salt, tentatively designated as the dipotassium derivative of dienolate 3, which upon treatment with methanolic hydrogen chloride gave a yellow compound melting at 195°.[2] This product, unlike 1, was oxidized by potassium permanganate in acetone and yielded an inner azine readily on treatment with hydrazine hydrate.[2] Finally reduction of 1, as well as the at 195° melting material, with zinc and acetic acid gave a derivative melting at 209°.[2]

Although the initial workers[2] did not designate a specific structure for the product melting at 195°, *Chemical Abstracts* has assigned it as *cis*-1,2-dibenzoylspiro-(cyclopropane-1,9′-fluorene) (4).[3] Mechanistically such an isomerization could be rationalized on the basis of kinetic control in which 2, the monoenolate base of 1, accepts a proton from the least hindered side. The properties of the isomeride as a *cis*-spirocyclopropane of structure 4 are inconsistent, however, with its color and its rapid oxidation by neutral permanganate.[2] Since in the present authors' opinion, conversions of 1 to 3 and to 4 were probably unlikely because of the expected susceptibility of 2 to ring opening,[4] the actions of base on 1 were investigated further in some detail. A study has also been made of the reduction of 1 and its related derivatives with zinc and acetic acid.

Reaction of 1 with methanolic potassium hydroxide as previously described yields a pink potassium salt from the blood-red alkaline solution. The dry salt was unstable and could not be adequately characterized directly. When 1 was reacted with hot methanolic potassium hydroxide followed by treatment with hydrogen chloride, as far as possible according to the conditions reported previously,[2,5] a pale yellow product, $C_{30}H_{22}O_2$[6] (44% yield), mp 112–123°, was found. Although the reaction sequence has been repeated many times under these conditions, thus far we have not encountered any compound melting at 195°. Surprisingly the compound obtained contained a methoxy group,[7a] it did not show carbonyl absorption, it did not react with hydrazine, and its ultraviolet absorption was quite different from that of 1.[7b] The product has been identified as 2,5-diphenyl-3-(9′-fluorenyl)-furan (9) upon oxidation and by synthesis. In accordance with the properties of furans,[8] 9 was readily converted by nitric acid–acetic acid to 1,2-dibenzoyl-1-(9′-methoxy-9′-fluorenyl)ethylene (10) in 85% yield.[9] Diketone 10 was also obtained from 9 by ozonolysis and also by oxidation with potassium permanganate in acetone.

Formation of 9 from 1 can be rationalized on the basis of opening of the conjugate base 2 to delocalized ion 5 which on treatment with methanolic hydrogen chloride could undergo protonation to 6 and subsequently give 9 by a sequence of steps involving highly stabilized cation 8. Synthesis and proof of structure of 9 were indeed achieved on the basis of the rationalization involving 8 as an intermediate. Reaction of fluorenone (11) with the Grignard reagent 12 from 3-bromo-2,5-diphenylfuran[10] resulted in 2,5-diphenyl-3-(9′-hydroxy-9′-fluorenyl)furan[11] (13, 17% yield) upon hydrolysis; solution of 13 in methanolic hydrogen chloride gave 9 (88% yield) identical with that derived from 1.

A study was then made of reduction of spirocyclopropane 1 and of methoxyfuran 9 with zinc and acetic acid. In principle, 1 (eq 1) and 9 (eq 2) could yield the same product, 2,5-diphenyl-3-(9′-fluorenyl)furan (15). Such a result would be in accordance with the



(1)

(2)

previous report[2] that 1 and the unidentified product derived therefrom, mp 195°, yield a derivative, mp 209°, upon reduction. Upon reaction of 1 with zinc–acetic acid–hydrochloric acid, a product, mp 212°, was

(1) Author to whom corerspondence should be directed, The Ohio State University.

(2) L. Horner and E. Lingnau, *Justus Liebigs Ann. Chem.*, **591**, 21 (1955).

(3) *Chem. Abstr.*, **50**, 1695*g* (1956).

(4) R. Breslow, J. Brown, and J. J. Gajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967), however, have reported base-catalyzed methyne hydrogen exchange in *cis*-2,3-diphenyl-*trans*-1-benzoylcyclopropane without ring opening.

(5) *"Die blut rote losung wird filtriert, und es wird solange ein trockner HCl-Gas Strom hindurchgeleitet, bis die Farbe in Gelb umgeschlagen ist. Die heisse losung wird from Kalium Chlorid abfiltriert."*[2]

(6) The molecular formulas of 1, 4, 6, and 13 are $C_{29}H_{20}O_2$, respectively.

(7) (a) The methoxy group was indicated by nuclear magnetic resonance ($CDCl_3$) at δ 2.84 (s, $-OCH_3$); (b) the ultraviolet properties of 9 (λ_{max} EtOH) are 224 mμ (ϵ 34,150), 229 (33,490), 286 (25,360), 301 (25,250), and 310 (shoulder, 24,160).

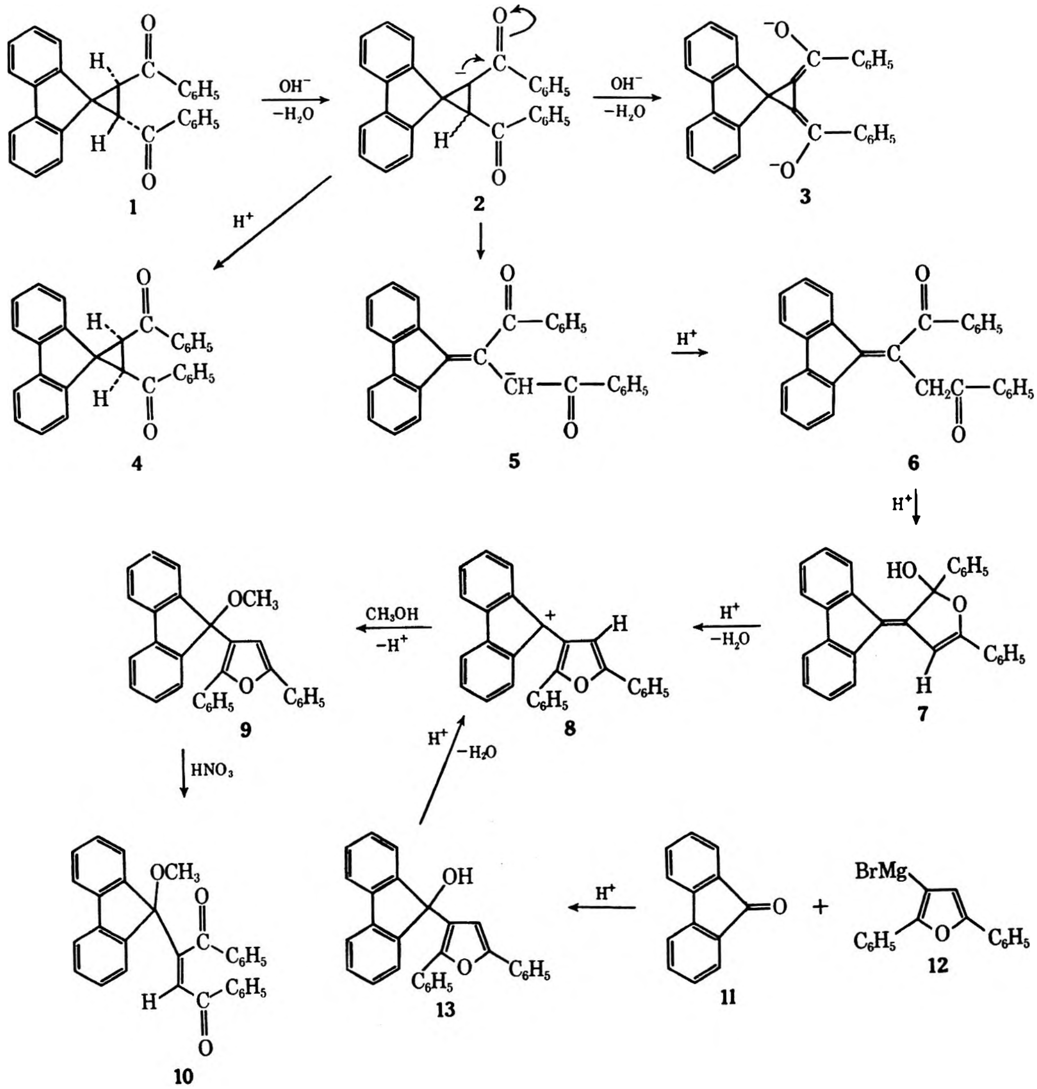
(8) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold, New York, N. Y., 1953, p 47.

(9) Infrared absorption by 10 (λ_{max}, KBr) occurs at 5.85 (>C=O) and 6.12 μ (>C=O); nuclear magnetic resonance for the methoxy group ($CDCl_3$) is exhibited at δ 2.9 (s, $-OCH_3$).

(10) R. F. Lutz and J. M. Smith, Jr., *J. Amer. Chem. Soc.*, **63**, 1148 (1941).

(11) Alcohol 13 exhibited infrared absorption (λ_{max}, KBr) at 2.87 (OH) and 8.9 μ (CO) and nuclear magnetic resonance ($CDCl_3$) at δ 7.0 (s, furan H).

SCHEME I



obtained in 39% yield whose properties are in close agreement with that previously reported.[2] The reduction product, $C_{29}H_{22}O_2$, was assigned the structure 1,2-dibenzoyl-1-(9′-fluorenyl)ethane (**14**) on the basis of its mass spectrum (*m/e* 402), its carbonyl absorption (6.01 μ), and its distinctive ABCD nmr spectrum.[12] In contrast, reduction of **9** gave 2,5-diphenyl-3-(9′-fluorenyl)furan (**15**, $C_{29}H_{20}O$), mp 158–159°, in 20% yield. The structure of **15** was confirmed by its nmr ($CDCl_3$): δ 5.5 (s, 1, 9′-fluorenyl H) and 6.33 (s, 1, furan H). All attempts to effect cyclization of **14** to **15** under vigorous acidic conditions were not fruitful.

Combination of the present and previous observations rules out the possibility that the isomer of **1** found to melt at 195° [2] is **4**. Further, the characterization of **14**, the compound melting at 212° reported in the initial work[1] from reduction of **1**, made **6** an attractive possibility for the 195° melting compound, since this would readily explain the reported zinc–acetic acid transformation to **14**. To our great surprise this belated reasoning led to isolation of the 195° melting substance by minor alteration of the reaction conditions! The blood-red filtrate resulting from **1** and methanolic potassium hydroxide, on saturation with dry hydrogen chloride *in the cold*, precipitated the yellow isomer melting at 195° and characterized as **6**[13] (Scheme I).

The involvement of **6** in the change of **1** to **9** was quickly demonstrated by isolation of **9** on saturation of a hot methanolic solution of **6** with dry hydrogen chloride. Interestingly examination of this reaction mixture by thin layer chromatography showed no unchanged **6**. Finally, as reported earlier, **6** was transformed to **14** by zinc–acetic acid (20% yield).

The study initiated to understand the reported transformations of **1** is now complete.

Experimental Section

General Procedure.—All melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord spectrometer. Ultraviolet spectra were obtained with a Cary 14 spectrophotometer. A Varian A-60 spectrometer was used for determining the nmr spectra (in $CDCl_3$ solution unless otherwise specified) and the results are expressed in parts per million downfield from internal tetramethylsilane.

Reaction of *trans*-2,3-Dibenzoylspiro(cyclopropane-1,9′-fluorene) (1) with Methanolic Potassium Hydroxide. Isolation of

(12) The nmr properties of **14** ($CDCl_3$) are δ 2.1 (d of d, J_{AB} = 18, J_{AC} = 3 Hz, A), 3.38 (d of d, J_{AB} = 18, J_{BC} = 10 Hz, B), 4.45 (d, J_{CD} = 3 Hz, D), and 5.1 (d of t, J_{BC} = 10, J_{AC} = 3, J_{DC} = 3 Hz, C).

(13) The ir absorption of **6** (λ_{max} KBr) occurs at 5.91 and 6.02 μ (>C=O); nmr for the $-CH_2C_6H_5$ protons is exhibited at δ_{CDCl_4} 4.81 (s). The data clearly rule out any isomer of **6** in which the double bond is conjugated with both benzoyl groups.

2,5-Diphenyl-3-(9'-methoxy-9'-fluorenyl)furan (9).—To a suspension of 1 (5.0 g, 0.0125 mol) in methanol (125 ml) was added 30% methanolic potassium hydroxide (25 ml), and the red mixture was refluxed for 0.5 hr. The hot solution was filtered and the filtrate was treated with dry hydrogen chloride until it became yellow. The mixture was filtered and the filtrate was cooled. The yellow precipitate was collected, washed free of acid, and dried to give crude 9 (2.754 g), mp 113–120°. Crystallization from methanol gave pure 9 (2.283 g, 44.3% yield), mp 122–123°.

Anal. Calcd for $C_{30}H_{22}O_2$: C, 86.95; H, 5.31; OCH_3, 7.49. Found: C, 86.88; H, 5.19; OCH_3, 7.80.

Oxidation of 2,5-Diphenyl-3-(9'-methoxy-9'-fluorenyl)furan (9) with Nitric Acid.—To a stirred suspension of 9 (0.09 g, 0.00022 mol) in glacial acetic acid (0.5 ml) was added a mixture of nitric acid (concentrated, *d* ~1.42, 0.1 ml) in glacial acetic acid (0.3 ml). The mixture became clear in 0.25 hr. After 0.5 hr a white solid precipitated from solution. Stirring was continued for another 0.5 hr. After excess ice–water had been added, the precipitate was collected, washed free of acid, dried, and crystallized from ethanol to give 1,2-dibenzoyl-1-(9'-methoxy-9'-fluorenyl)ethylene (10, 0.079 g, 85%), yellow crystals, mp 159–160°.

Anal. Calcd for $C_{30}H_{22}O_3$: C, 83.72; H, 5.11. Found: C, 83.71; H, 4.97.

Oxidation of 2,5-Diphenyl-3-(9'-methoxy-9'-fluorenyl)furan (9) with Potassium Permanganate.—A solution of 9 (0.2 g, ~0.0005 mol) and potassium permanganate (0.40 g, ~0.0025 mol) in acetone–water–acetic acid (26–3–0.5 ml) was stirred at room temperature for 2 hr. Sodium bisulfite was added and the mixture was made strongly acidic with dilute hydrochloric acid. After most of the acetone had been removed under reduced pressure, the residue was extracted with excess ether, washed with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. The residual oil (~0.2 g) on trituration with ether gave 10 (0.1 g, 48% yield), mp 160–161°.

Ozonolysis of 2,5-Diphenyl-3-(9'-methoxy-9'-fluorenyl)furan (9).—A solution of 9 (0.40 g, ~0.001 mol) in methylene chloride was ozonized at 40° for 20 min. The ozonide was reduced with zinc dust and a trace of hydroquinone. The crude product on trituration with ether gave 10 (0.064 g, 15.2% yield), mp 159–161°.

2,5-Diphenyl-3-(9'-hydroxy-9'-fluorenyl)furan (13).—To stirred magnesium turnings (0.15 g, ~0.006 g-atom) and dry ether (20 ml) was added dropwise a solution of 3-bromo-2,5-diphenylfuran (1.5 g, ~0.005 mol) in dry ether (20 ml). A crystal of iodine was added and the stirred suspension was held at 38° for 22 hr. A solution of fluorenone (11, 0.9 g, 0.005 mol) in dry ether (20 ml) was then added dropwise and the mixture was heated for another hour. The reaction solution was poured onto crushed ice–dilute sulfuric acid and then extracted with ether. The ethereal extract was washed with water and with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel. Elution with benzene–hexane gave nearly pure 13 (0.34 g, 17% yield) as a pale yellow solid which was crystallized from hot benzene, mp 163–164°.

Anal. Calcd for $C_{29}H_{20}O_2$: C, 86.97; H, 5.0. Found: C, 87.06; H, 5.1.

Synthesis of 2,5-Diphenyl-3-(9'-methoxy-9'-fluorenyl)furan (9).—A solution of 2,5-diphenyl-3-(9'-hydroxy-9'-fluorenyl)furan (13, 0.075 g, ~0.0002 mol) in methanolic hydrochloric acid (7–8 ml) was stored overnight. The filtrate was poured into cold water (100 ml) and the yellow solid was filtered to yield additional 9, mp 116–117°. The crude products were combined and crystallized from methanol to give pure 9 (0.068 g, 88%), mp 122–123°. This material was identical (analysis, tlc, mixture melting point, ir, and nmr) with 9 as obtained from 1 and methanolic potassium hydroxide.

Reduction of *trans*-2,3-Dibenzoylspiro(cyclopropane-1,9'-fluorene) (1) with Zinc–Acetic Acid–Hydrochloric Acid.—A stirred suspension of 1 (0.25 g, 0.0006 mol) and zinc dust (0.25 g, ~0.0035 g-atom) in acetic acid (3 ml) was kept at 75–80° for 0.5 hr. Concentrated hydrochloric acid (3 ml) was added in one lot and heating was continued for an additional hour. The yellow mixture was decanted and diluted with saturated sodium chloride solution (15 ml). The resulting mixture and the zinc residue were extracted with ether. The ether extracts were washed with aqueous sodium carbonate and with saturated sodium chloride, dried ($MgSO_4$), and evaporated. The crude product on crystallization from benzene gave 1,2-dibenzoyl-1-(9'-fluorenyl)ethane (14, 0.99 g, 39.4% yield), mp 212–213°.

Anal. Calcd for $C_{29}H_{22}O_2$: C, 86.56; H, 5.47. Found: C, 86.64; H, 5.50.

Reduction of 2,5-Diphenyl-3-(9'-methoxy-9'-fluorenyl)furan (9) with Zinc–Acetic Acid–Hydrochloric Acid.—Under conditions described for 1, 9 (0.26 g, ~0.0006 mol) was reduced to give 2,5-diphenyl-3-(9'-fluorenyl)furan (15, 0.048 g, 20% yield), white crystals, mp 158–159°.

Anal. Calcd for $C_{29}H_{20}O$: C, 90.62; H, 5.21. Found: C, 90.82; H, 5.55.

Reaction of *trans*-2,3-Dibenzoylspiro(cyclopropane-1,9'-fluorene) (1) with Methanolic Potassium Hydroxide Followed by Hydrogen Chloride at 0°. Isolation of 1,2-Dibenzoyl(1-fluorenylidene)ethane (6).—To a suspension of 1 (1.0 g, 0.0025 mol) in absolute methanol (25 ml) was added 30% methanolic potassium hydroxide (5 ml) and the mixture was refluxed for 0.5 hr. The blood-red solution was filtered, cooled in ice, and treated with dry hydrogen chloride until precipitation of yellow 6 was complete. The reaction mixture was filtered, washed free of acid and salt, and dried, and the resulting crude product (0.4 g, mp 195–196°) was crystallized from benzene to give pure 6, mp 198° (0.382 g, 38.2% yield).

Anal. Calcd for $C_{29}H_{20}O_2$: C, 86.97; H, 5.04. Found: C, 86.84; H, 5.29.

Reduction of 1,2-Dibenzoyl(1-fluorenylidene)ethane (6) with Zinc–Acetic Acid. Isolation of 1,2-Dibenzoyl-1-(9'-fluorenyl)-ethane (14).—Under conditions described for 1, 6 (0.125 g, 0.0003 mol) was reduced to 14 (0.025 g, 20% yield), mp 213–214°. This product was identical (mixture melting points, tlc, ir) with that obtained from 1.

Transformation of 1,2-Dibenzoyl(1-fluorenylidene)ethane (6) to 2,5-Diphenyl-3-(9'-methoxy-9'-fluorenyl)furan (9).—A suspension of 6 (0.075 g, 0.00018 mol) in absolute methanol (8 ml) was refluxed for 0.25 hr. The hot suspension was saturated with dry hydrogen chloride. The mixture became clear in 2 min. After 0.1 hr excess methanol was removed under reduced pressure and the residue was cooled. The yellow crystals were collected and crystallized from hot methanol to give pure 9, mp 122–123° (0.030 g, 30.8% yield).

The compound was identical (tlc, mixture melting point, ir) with that prepared from 1.

Registry No.—1, 31684-96-5; 6, 31684-97-6; 9, 31684-98-7; 10, 31684-99-8; 13, 31685-00-4; 14, 31685-01-5; 15, 31685-02-6; zinc, 7440-66-6; nitric acid, 7697-37-2; acetic acid, 64-19-7; hydrochloric acid, 7647-01-0; potassium permanganate, 7722-64-7.

Acknowledgment.—We acknowledge support of this research by the Kettering Foundation and the National Science Foundation.

Solvent Steric Effects. V. Azobis-2-methyl-3-phenyl-2-butane. The Absolute Configuration of Some Derivatives of 2-Methyl-3-phenylbutane[1]

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A stereoselective memory effect has been reported for the coupling of 3-methyl-2-phenyl-2-butyl radical

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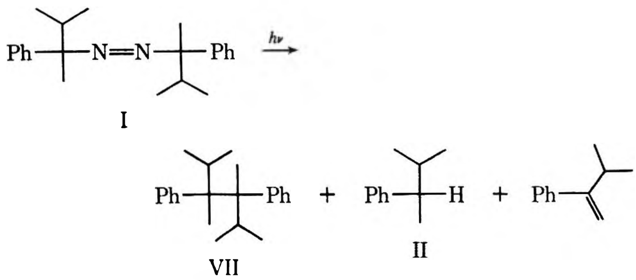
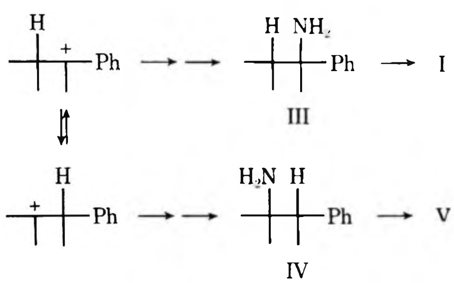
(3) Alfred P. Sloan Foundation Fellow.

pairs generated by photolysis of meso and chiral azobis-3-methyl-2-phenyl-2-butane (I) in rigid media.[4,5] We have observed substantial optical activity in 2-methyl-3-phenylbutane (II) from disproportionation of such a radical pair from partially resolved I.[6] The optical



rotation of enantiomerically pure II is needed to use this result for elucidating details of the behavior of radical pairs within a rigid solvent cage. The *S* absolute configuration has previously been assigned to (−)-II on the basis of synthesis from (*R*)-hydratropic acid.[7]

The optical purity of this sample was, however, questionable because of the intermediacy of the 2-methyl-3-phenyl-2-butyl cation in the synthesis and the possibility of its racemization through equilibration with the 3-methyl-2-phenyl-2-butyl cation.[8] Our original synthesis of I involved preparation of 3-methyl-2-phenyl-2-butylamine (III) by a Ritter reaction, and this same equilibration plagued the synthetic reaction resulting in amine mixtures containing as much as 40% of 2-methyl-3-phenyl-2-butylamine (IV).[4,9]



Results and Discussion

In part because of the availability of substantial amounts of IV as a by-product from synthesis of III, we have used it as a source of optically pure II by way of resolution with tartaric acid, oxidative coupling to azobis-2-methyl-3-phenyl-2-butane (V), and homolysis of this azoalkane with disproportionation of the radicals to II and 2-methyl-3-phenyl-1-butene (VI).

(4) P. D. Bartlett and J. M. McBride, *Pure Appl. Chem.*, **15**, 89 (1967).

(5) In the polyazane nomenclature system [see P. C. Huang and E. M. Kosower, *J. Amer. Chem. Soc.*, **90**, 2362 (1968)] I and V would be named 1,2-bis(3-methyl-2-phenyl-2-butyl)diazene and 1,2-bis(2-methyl-3-phenyl)-diazene, respectively.

(6) M. J. Tremelling, unpublished work.

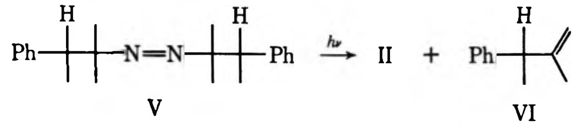
(7) O. Červinka and L. Hub, *Collect. Czech. Chem. Commun.*, **33**, 1911 (1968).

(8) The assignment of ref 7 was based on work with partially resolved materials. Comparison of this data with ours suggests that about 22% racemization occurred at the cation stage of this preparation.

(9) It has been reported that 3-methyl-2-phenyl-2-butanol, 2-methyl-3-phenyl-2-butanol, and 2-methyl-3-phenyl-2-butene all give III from Ritter reaction in *n*-butyl ether,[10] but in our hands the amine mixture was about 90% IV under these conditions.

(10) H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 2319 (1961).

This scheme has several advantages for preparing optically pure II. (1) The oxidative coupling provides a



check on the resolution of IV. (2) Resolved chiral V is crystalline allowing reinforcement of partial resolution by recrystallization. (3) Racemization should not occur in the intermediate radicals[11] as it may well do for the corresponding cation.[8]

The diastereomers of V may be readily distinguished by pmr spectroscopy. Oxidation of racemic IV with iodine pentafluoride[12] resulted in negligible asymmetric induction in coupling to V, since equal peak heights were found for the corresponding methyl signals of the diastereomers of V both in the crude product and in that purified by preparative tlc. Coupling of resolved (−)-IV gave (+)-V with no detectable *meso*-V (<5%). Amine IV must thus have been >95% optically pure. Three recrystallizations from ether at Dry Ice temperature gave (+)-V which was presumably optically pure. An ORD curve for this azo compound showed a Cotton effect at slightly longer wavelength than the absorption maximum as was reported by Kosower and Severn for other azoalkanes.[13]

Differential scanning calorimetry confirmed the expectation of a high (~200°) thermolysis temperature for V. Photolysis in benzene at room temperature gave rapid decomposition to equal parts of the disproportionation products II and VI, which were stable to the reaction conditions. An identical photolysis with thiophenol scavenger gave II and VI in the ratio 3.5:1 indicating a 45% cage effect.

For preparation of optically pure II recrystallized (+)-V was photolyzed at room temperature without scavenger to avoid the possibilities of high temperature racemization of the radicals during thermolysis and of racemization through reversible atom abstraction from II by scavenger radical. The resulting products purified by gas chromatography were (−)-II and (+)-VI.

The absolute stereochemistries and rotations of II, IV, V, and VI are presented in Table I. We include comparable data for I, III, and 2,3,4,5-tetramethyl-3,4-diphenylhexane (VII) with absolute configurations based on the assumption that retention predominates in both coupling and disproportionation within the solvent cage.[4,14,15]

Experimental Section

Rotations at 589 nm were obtained using an O. C. Rudolph & Sons Model 80 polarimeter[16] and those at 546 nm using a Bendix Ericsson automatic polarimeter. The ORD curve was obtained using a Cary 60 ORD-CD instrument.[16] Pmr spectra were measured with Varian A-60 A and HA-100 and Jeolco Minimar 100 instruments.

(11) C. Walling in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Wiley, New York, N. Y., 1963, Chapter 7.

(12) T. E. Stevens, *J. Org. Chem.*, **26**, 2531 (1961); *cf.* S. F. Nelsen and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966).

(13) E. M. Kosower and D. J. Severn, *ibid.*, **91**, 1710 (1969).

(14) F. D. Greene, M. A. Berwick, and J. C. Stowell, *ibid.*, **92**, 867 (1970), and references cited therein.

(15) Details of this work will be published separately.

(16) We are grateful to Professors J. A. Berson and J. M. Sturtevant, respectively, for use of the Rudolph and Cary instruments.

TABLE I
ABSOLUTE CONFIGURATIONS AND ROTATIONS

Compd	Configuration	Rotation[a] [α]	λ, nm	c, g/100 ml	Solvent
$PhCH(CH_3)CH(CH_3)_2$ (II)	S	−36.2	546	1.6	CCl_4
		−30.0	589	1.6	CCl_4
		−24.5	589	0.7	CH_3OH
$PhCH(CH_3)C(CH_3)=CH_2$ (VI)	S	94 ± 2	546	1.9	CCl_4
		79 ± 2	589	1.9	CCl_4
$(PhCH(CH_3)C(CH_3)_2N=)_2$ (V)	R,R	60.2	546	0.86	CH_3OH
$PhCH(CH_3)C(CH_3)_2NH_2$ (IV)	R	−30.4[b]	546	3.95	CH_3OH
$PhC(CH_3)(i\text{-}Pr)NH_2$ (III)	R	−22.1[c]	546	1.8	CH_2Cl_2
$(PhC(CH_3)(i\text{-}Pr)N=)_2$ (I)	R,R	10.5[d]	546	1.6	CCl_4
$(PhC(CH_3)(i\text{-}Pr))_2$ (VII)	R,R	4[e]	546	0.59	CCl_4

[a] Samples greater than 98% optically pure except as noted. [b] Greater than 95% optically pure, see text. [c] Judged to contain 8.5% (S)-III from meso/nonmeso ratio of oxidation product I. [d] Sample from oxidative coupling of III. 84.4% nonmeso of which 83.7% is R,R and 0.7% is S,S, since statistical coupling is observed for *rac*-III. [e] Optical purity unknown.

2-Methyl-3-phenyl-2-butylamine (IV) was collected as a forerun during a spinning band distillation used to remove this byproduct from amine III after alkaline hydrolysis of the product from a Ritter reaction of 2-methyl-3-phenyl-2-butanol.[17] Combined foreruns from several distillations (115 g) were dissolved in 100 ml of ethanol and added to a hot solution of 160 g of *d*-tartaric acid in 600 ml of ethanol with cooling and stirring. The resulting salt was recrystallized five times from methanol to give 8.3 g of salt which was converted to 4.1 g of amine and distilled [bp 93° (8 mm)]. The resulting (*R*)-(−)-IV had $[\alpha]_{546}$ −31.1° (*c* 3.25, methanol); pmr (20% in CCl_4, 60 MHz) δ 7.30 (5 H, s, Ar H), 2.65 (1 H, q, *J* = 7.3 Hz, $CHCH_3$), 1.28 (3 H, d, *J* = 7.3 Hz, $CHCH_3$), 1.03 (2 H, s, NH_2), 1.00 (3 H, s, $C(CH_3)CH_3$), 0.86 (3 H, s, $C(CH_3)CH_3$).

Azobis-2-methyl-3-phenyl-2-butane (V) was prepared as a mixture of diastereoisomers by oxidative coupling of 11 g of amine mixture containing 85% IV and 15% III with 5 ml of IF_5 in 150 ml of CH_2Cl_2–18 ml of pyridine at −20 to −30°. Washing through Florisil with pentane gave 3.6 g of a yellow oil shown by pmr to contain the diastereomers of V (in equal amounts by peak heights) and a small amount of what are presumably the cross coupling products between III and IV. Preparative tlc (Merck F-254 developed five times with pentane) gave a mixture of the diastereomers of V as a yellow oil free of impurities and showed negligible fractionation of the diastereomers between early and late fractions confirming the absence of asymmetric induction in the coupling reaction. Pmr (CCl_4, 100 MHz): *meso*-V, δ 7.20 (5 H, s, Ar H), 3.19 (1 H, q, *J* = 7.5 Hz, $CHCH_3$), 1.22 (3 H, d, *J* = 7.5 Hz, $CHCH_3$), 1.02 (3 H, s, $C(CH_3)CH_3$), 0.98 (3 H, s, $C(CH_3)CH_3$); *rac*-V, 7.20 (5 H, s, Ar H), 3.17 (1 H, q, *J* = 7.5 Hz, $CHCH_3$), 1.22 (3 H, d, *J* = 7.5 Hz, $CHCH_3$), 1.05 (3 H, s, $CH(CH_3)CH_3$), 0.96 (3 H, s, $C(CH_3)CH_3$). The racemate peaks were identified by comparison with the spectrum of (*R,R*)-V.

(*R,R*)-(+)-V was prepared by a similar oxidation of 2.74 g of the resolved (−)-amine. Crude chromatography on Florisil gave 1.07 g of a yellow-brown liquid shown by pmr to be IV with less than 5% *meso*-IV. This material was recrystallized three times from ether in a Dry-Ice–acetone bath to give yellow crystals: mp 61.2–61.8°; $[\alpha]_{546}$ 60.2° (*c* 0.86, CH_3OH); λ_{max}^{MeOH} 373 nm (ϵ_{max} 30); pmr as above. ORD showed a Cotton effect at 393 nm.

Anal. Calcd for $C_{22}H_{30}N_2$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.62; H, 9.18; N, 8.46.

Thermolysis of V was investigated using a Perkin-Elmer DSC-1b calorimeter with a 2.9-mg sample of mixed diastereomers of V sealed in an aluminum volatile sample capsule. A scan from 107 to 257° at 10°/min showed an exotherm beginning near 185° and peaking at 217°.

Photolysis of mixed diastereomers of V was investigated with 30-mg samples degassed by freezing and thawing in benzene solution under vacuum and sealed in nmr tubes. One tube contained 2.8 mol of practical thiophenol per mol of V. The tubes were photolyzed in a 30–40° water bath by light from a 450-W Hanovia L lamp with Pyrex filter. After 80 min pmr showed complete disappearance of starting material in both samples. The pmr spectra were unchanged after another 75 min of photolysis. Both samples showed signals for II and VI, and there were no other appreciable peaks except for solvent and scavenger. In the unscavenged run the II/VI ratio was estimated at 1.1–1.2 on the basis of integration. For the scavenged run this ratio was 3.5–4 implying that 2.5/3.5–3/4 of II was the product of scavenging and that the cage effect was 40–45%.

(*S*)-**2-Methyl-3-phenylbutane (II) and** (*S*)-**2-methyl-3-phenyl-1-butene (VI)** were prepared from 400 mg of pure (*R,R*)-V in 4 ml of benzene, degassed, sealed, and irradiated for 3.5 hr at room temperature. The sample was opened and solvent was removed, and II and VI were bulb-to-bulb distilled under high vacuum. II and VI were separated by preparative vpc using $^3/_8$ in. × 8 ft 20% DEGS on Chromosorb P at 105°. Pmr (100 MHz, CCl_4): II, δ 7.25 (5 H, m, Ar H), 2.38 (1 H, p, *J* = 7.0 Hz, ArCH), 1.76 (1 H, octet, *J* = 7 Hz, $CH(CH_3)_2$), 1.27 (3 H, d, *J* = 7 Hz, Ar $CHCH_3$), 0.98 (3 H, d, *J* = 7 Hz, $CH(CH_3)CH_3$), 0.78 (3 H, d, *J* = 7 Hz, $CH(CH_3)CH_3$); VI, 7.20 (5 H, s, Ar H), 4.89 and 4.85 (2 H, d, $=CH_2$), 3.34 (1 H, q, *J* = 7 Hz, Ar CH), 1.56 (3 H, s, $CH_3C=$), 1.36 (3 H, d, *J* = 7 Hz, $ArCHCH_3$). See Table I for rotations.

Registry No.—(*S*)-(−)-II, 19643-73-3; (*R*)-(−)-IV, 33686-47-4; *meso*-V, 33686-48-5; *rac*-V, 33686-49-6; (*R,R*)-(+)-V, 33686-50-9; (*S*)-(+)-VI, 25145-46-4.

(17) For details of this preparation see J. M. McBride, Thesis, Harvard University, 1967. Subsequent preparations by this method have given higher yields of IV as a by-product as did preparation by another method.[10]

The α-Methyl/Hydrogen Reactivity Ratio for the *anti*-7-Norbornenyl and 7-Norbornadienyl Systems

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The very large α-Me/H solvolytic rate ratio for the 7-norbornyl system (4/1) has been attributed to the "enormous demand on substituents for further stabilization" of the unusually strained 7-norbornyl cation.[2,3]

(1) (a) NIH Postdoctoral Fellow, 1966–1968; address inquiries to Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pa. 15213. (b) Fellow of the French Centre National de la Recherche Scientifique, on leave from the University of Strasbourg, 1967–1968. (c) Deceased, Nov 23, 1969.

(2) (a) H. Tanida, Y. Hata, S. Ikegami, and H. Ishitobi, *J. Amer. Chem. Soc.*, **89**, 2928 (1967); (b) H. Tanida, *Accounts Chem. Res.*, **1**, 239 (1968).

(3) It has been noted[4] that "steric ground state strain . . . in tertiary tosylates would enhance α-Me/H rate ratios" with the implication that the **4/1** tosylate rate ratio may be an inflated value. Comparison of the **4**-Cl/**2**-Cl ratio with the corresponding tosylate ratio (Table II of this paper) would indicate the inflation to be worth *ca.* $10^{1.9}$. On the other hand, the tosylate ratio will be deflated to the extent that solvent nucleophilicity (k_s)

Table I

Solvolytic Rate Constants for Systems 1–6[a]

Compd	Temp, °C	k, sec^{-1}
1-OTs	25.0	2.1×10^{-14} [b]
2-OTs	25.0	$(3.70 \pm 0.08) \times 10^{-4}$ [c]
2-Cl	25.0	$(8.1 \pm 0.2) \times 10^{-7}$ [d]
2-OPNB	125.0	$(2.84 \pm 0.16) \times 10^{-6}$
	100.0	$(2.05 \pm 0.10) \times 10^{-7}$
	25.0	(5.67×10^{-12})[e]
3-Cl	25.0	$(1.45 \pm 0.10) \times 10^{-3}$ [f]
3-OPNB	100.0	$(3.93 \pm 0.13) \times 10^{-5}$
	75.0	$(3.26 \pm 0.05) \times 10^{-6}$
	25.0	(6.53×10^{-9})[g]
4-OTs	25.0	3.36×10^{-6} [h]
4-Cl	125.0	$(7.02 \pm 0.10) \times 10^{-6}$
	100.0	$(7.36 \pm 0.20) \times 10^{-7}$
	25.0	(9.09×10^{-11}) [i]
5-Cl	50.0	$(2.37 \pm 0.04) \times 10^{-3}$
	25.0	$(1.93 \pm 0.03) \times 10^{-4}$ [j]
5-OPNB	100.0	$(2.68 \pm 0.08) \times 10^{-5}$
	75.0	$(1.86 \pm 0.02) \times 10^{-6}$
	25.0	(2.38×10^{-9}) [k]
6-OPNB	75.0	$(3.05 \pm 0.07) \times 10^{-4}$
	50.0	$(2.29 \pm 0.07) \times 10^{-5}$
	25.0	(1.12×10^{-6}) [l]

[a] Tosylates were solvolyzed in acetic acid. Chlorides were solvolyzed in 80% aqueous acetone. *p*-Nitrobenzoates were solvolyzed in 70% aqueous acetone. [b] Computed by extrapolating data of ref 2a for the corresponding brosylate and assuming a brosylate:tosylate ratio of 2.90. An earlier value of 6.36×10^{-15} [S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, **77**, 4183 (1955)] had been obtained from a longer temperature extrapolation than that of ref 2a. [c] S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956). [d] S. Winstein and C. Ordronneau, *ibid.*, **82**, 328 (1960). [e] Extrapolated. $\Delta H^{\ddagger} = 30.3 \pm 0.9$ kcal/mol; $\Delta S^{\ddagger} = -8.5 \pm 2.3$ eu. (In 50% acetone, $\Delta H^{\ddagger} = 28.2 \pm 0.8$ kcal/mol; $\Delta S^{\ddagger} = -10.2 \pm 2.2$ eu.) [f] This chloride exhibits common ion rate depression (see Experimental Section) and the (undepressed) value reported here is slightly higher than that previously reported in *d*. D. F. Hunt, C. P. Lillya, and M. D. Rausch, *J. Amer. Chem. Soc.*, **90**, 2561 (1968), report a value of $(1.33 \pm 0.1) \times 10^{-3}$, with $\Delta H^{\ddagger} = 15 \pm 1.5$ kcal/mol; $\Delta S^{\ddagger} = -22 \pm 4$ eu. A. F. Breaziale, Ph.D. Thesis, University of Washington, 1965, reports a value of 1.47×10^{-3}. [g] Extrapolated. $\Delta H^{\ddagger} = 25.0 \pm 0.4$ kcal/mol; $\Delta S^{\ddagger} = -12.2 \pm 1.1$ eu. [h] Extrapolated from data of ref 2a. [i] Extrapolated. $\Delta H^{\ddagger} = 25.9 \pm 0.4$ kcal/mol; $\Delta S^{\ddagger} = -17.7 \pm 1.0$ eu. [j] $\Delta H^{\ddagger} = 18.6 \pm 0.2$ kcal/mol; $\Delta S^{\ddagger} = -13.2 \pm 0.6$ eu. [k] Extrapolated. $\Delta H^{\ddagger} = 26.8 \pm 0.3$ kcal/mol; $\Delta S^{\ddagger} = -8.0 \pm 0.9$ eu. [l] Extrapolated. $\Delta H^{\ddagger} = 22.5 \pm 0.3$ kcal/mol; $\Delta S^{\ddagger} = -10.3 \pm 1.0$ eu.

We report here that similar comparisons for the corresponding *anti*-7-norbornenyl (**5**/**2**) and 7-norbornadienyl (**6**/**3**) systems show a marked attenuation in the demand for stabilization placed by the 7-methyl group.

Except for **6**, the derivatives studied in the present work were prepared from previously described alcohols. Ester **6**-OPNB was prepared from the corresponding quadricyclyl isomer, **7**-OPNB (not shown),[6] which was prepared, in turn, from the corresponding alcohol.[7]

and σ participation[5] contribute selectively to the observed rate for **1**-OTs. We do not expect a quantitative clarification of these effects to significantly alter the present argument.

(4) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2540 (1970).

(5) (a) F. B. Miles, *ibid.*, **90**, 1265 (1968); (b) P. G. Gassman, J. M. Hornback, and J. L. Marshall, *ibid.*, **90**, 6238 (1968).

(6) Rate data for this compound in 70% acetone are $k_{100°} = (1.30 \pm 0.02) \times 10^{-4}$ sec^{-1}; $k_{75°} = (1.00 \pm 0.03) \times 10^{-5}$ sec^{-1}; $\Delta H^{\ddagger} = 25.8 \pm 0.4$ kcal/mol; $\Delta S^{\ddagger} = -7.7 \pm 1.0$ eu.

(7) R. K. Lustgarten, M. Brookhart, and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2347 (1972).

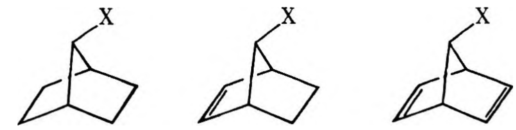
Table II

Relative Solvolytic Rate Constants for 1–6 at 25°[a]

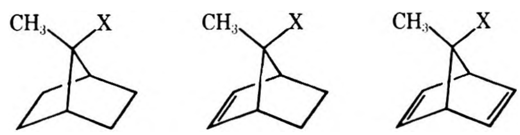
System	OTs	Cl	OPNB
1-X	10^{0}		
2-X	$10^{10.3}$	$10^{4.0}$	10^{0}
3-X		$10^{7.2}$	$10^{3.1}$
4-X	$10^{8.2}$	10^{0}	
5-X		$10^{6.3}$	$10^{2.6}$
6-X			$10^{5.3}$

[a] See Table I, footnote *a*.

Kinetic measurements were made using standard titrimetric procedures, and the collected first-order solvolytic rate constants for **1**–**6** are given in Table I. Table II contains the relative rate comparisons which may be drawn from the data in Table I, tabulated according to leaving group.



1 **2** **3**



4 **5** **6**

It would be desirable to keep leaving group and solvent invariant through the entire series **1**–**6**, but the very wide range of reactivity involved presents serious experimental difficulties in that regard. For the particular purpose of comparing α-Me/H ratios from the data in Table II, the uncertainty incurred by variation of leaving group and solvent is not likely to be nearly as large as the gap between the **4**/**1** ratio and the other two α-Me/H ratios.[3] On this basis, it is concluded that there is a real and substantial attenuation of the α-Me/H ratio for the unsaturated systems relative to the saturated model, *i.e.*, from $10^{8.2}$ for 7-norbornyl to $10^{2.6}$ and $10^{2.2}$ for the monoenyl and dienyl OPNB's, respectively. This striking compression is a measure[4] of the diminished extent to which the methyl probe experiences charge in the solvolytic transition states for **2** and **3**, and it represents yet another manifestation of the delocalized nature of these transition states. Indeed, it is now well established that the high reactivities of **2** and **3** are due to π-electron participation which leads to quite stable, bridged carbonium ions.[8] The greater reactivity of **3** (and **6**) relative to **2** (and **5**) may be attributed to the "bicycloaromaticity"[9,10] of the 7-norbornadienyl cation, though strain effects may also play a contributing role.

It is of interest that the α-Me/H ratio diminished only slightly in going from the monoenyl to dienyl systems. The similar responses of **2** and **3** to α-methyl substitution may represent the onset of a "leveling"

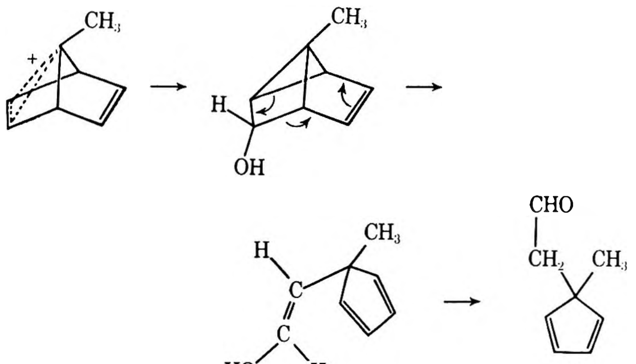
(8) S. Winstein, *Quart. Rev., Chem. Soc.*, **23**, 141 (1969).

(9) (a) M. J. Goldstein, *J. Amer. Chem. Soc.*, **89**, 6357 (1967); (b) H. E. Zimmerman, *Accounts Chem. Res.*, **4**, 272 (1971).[10]

(10) Using the Mobius description for the 7-norbornadienyl cation, one notes that the unsymmetrically bridged ground state,[7,8] with attendant "tetrahedral" hybridization at C_7, serves to minimize the localized antibonding overlap between the rear of the vacant ("sp^3") lobe at C_7 and the unbridged vinyl function.

phenomenon[11] wherein the stabilization afforded the solvolytic transition states by bridging is sufficiently large that the additional stabilization afforded by methyl has become a minor and diminishing factor.

The only detectable products from buffered hydrolysis of **4**-Cl, **5**-Cl, and **5**-OPNB were the corresponding (unrearranged) alcohols. Ester **6**-OPNB gave a more interesting result. Three products were detected by glpc in a 1:1:6.3 ratio. One of the minor components was **6**-OH and the other was not identified. The major component proved to be an aldehyde which was isomeric with **6**-OH. Consideration of the spectral data (see Experimental Section) led to the assignment of structure **8** to this compound. The mechanism for conversion of the 7-methyl-7-norbornadienyl cation to **8** is formulated, as shown below, in terms of an endo-directed attack by water at C_2 followed by a retrograde Diels–Alder-like ring opening to give **8** or its enolate.



8

This mechanism bears strict analogy to those postulated to explain the formation of tricyclic and cyclopentadienyl derivatives from the reaction of the 7-norbornenyl and 7-norbornadienyl cations with strong nucleophiles.[12] Rearrangement has not been observed, however, for the parent system (**3**-X) under neutral hydrolytic conditions. It may be that tertiary 7-norbornadienyl cations are less susceptible to capture of nucleophile at C_7 than is the secondary system. This circumstance could be a consequence of the bridged nature of these ions which results in the presentation of a nonplanar, relatively crowded face at C_7.[8]

Experimental Section

Melting points are uncorrected. Analyses were performed by Miss H. King. Nmr spectra were recorded on a Varian A-60 instrument for CCl_4 solutions unless noted otherwise. Shifts are referred to internal TMS at τ 10.00. Infrared spectra were recorded for CCl_4 solutions on a Perkin-Elmer Model 421 grating spectrometer.

anti-**7-Norbornenyl** ***p*****-Nitrobenzoate** (**2-OPNB**).[13]—This ester was prepared routinely using *p*-nitrobenzoyl chloride in pyridine: mp 121.5–122.0°; nmr τ 1.84 (4, arom), 3.94 (2 H, vinyl), 5.45 (1 H, bridge), 7.09 (2 H, bridgehead), 8.14 (2 H, *exo*-ethano), 8.86 (2 H, *endo*-ethano).

Anal. Calcd for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05. Found: C, 65.00; H, 5.16.

7-Norbornadienyl ***p*****-Nitrobenzoate** (**3-OPNB**).—This compound was described previously.[14]

7-Methyl-7-norbornyl Chloride (**4-Cl**).—7-Methyl-7-norbornanol (0.450 g, 3.5 mmol) was stirred vigorously with 120 ml of concentrated HCl solution for 35 hr at ambient temperature. The resulting mixture was extracted well with petroleum ether (bp 30–60°), and the combined organic extracts were washed with saturated $NaHCO_3$ solution, with water, and with a saturated NaCl solution and dried over anhydrous K_2CO_3. The solvent was removed by distillation through a Vigreux column leaving a semicrystalline residue which was purified by sublimation (25° at 2 Torr): yield 0.305 g (2.1 mmol, 60%); mp 96.0–97.5°; nmr τ 8.38 (s, methyl), 7.7–8.2 (m, *ca.* 5 H), 8.5–8.8 (m. *ca.* 5 H).

Anal. Calcd fcr $C_8H_{13}Cl$: C, 66.42; H, 9.06; Cl, 24.52. Found: C, 66.45; H, 9.13; Cl, 24.81.

Attempted preparation of 4-Cl with $SOCl_2$ in ether gave the corresponding dialkyl sulfite: mp 80.0–81.5°; nmr τ 8.46 (s, methyl), 7.92, 8.65, 8.80 (10 H, broad absorptions).

Anal. Calcd for $C_{16}H_{26}SO_3$: C, 64.38; H, 8.78; S, 10.74. Found: C, 64.91; H, 8.69; S, 10.54.

7-Methyl-*anti*-7-norbornenyl ***p*****-Nitrobenzoate** (**5-OPNB**).—This was prepared as described above for 2-OPNB: mp 126.5–127.0°; nmr τ 1.87 (4 H, arom), 3.96 (2 H, vinyl), 6.92 (2 H, bridgehead), 8.44 (3 H, methyl), 8.25 (2 H, *exo*-ethano), 8.97 (2 H, *endo*-ethano).

Anal. Calcd for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53. Found: C, 66.08; H, 5.67.

7-Methyl-*anti*-7-norbornenyl Chloride (**5-Cl**).—Alcohol 5-OH (0.485 g, 3.9 mmol) in 20 ml of anhydrous ether was treated with 0.6 ml of redistilled $SOCl_2$ at 0°. The solution was allowed to stand overnight at 5°, and the solvent was removed at reduced pressure without warming. The residue was taken up in 20 ml of petroleum ether and passed through a column of 5 g of $CaCO_3$. The solvent was removed at reduced pressure leaving 0.395 g (2.3 mmol, 72%) of transparent oil. Purification by sublimation (25° at 2 Torr) or preparative glpc on Carbowax 4000 yielded highly volatile material, mp 40–44°, which failed to give a correct analysis but which was adequate for rate measurements: nmr τ 4.00 (2 H, vinyl), 7.37 (2 H, bridgehead), 7.79 (2 H, *exo*-ethano), 8.41 (3 H, Me), 9.00 (2 H, *endo*-ethano); mass spectrum (70 eV) calcd for parent peak, 142; found, 142.

7-Methyl-7-quadricyclyl ***p*****-Nitrobenzoate** (**7**).[6]—This was prepared routinely from the corresponding alcohol:[7] mp 147–148°; nmr ($CDCl_3$) τ 1.70 (4 H, arom), 8.05 (3 H, methyl), 8.18 (6 H, mult, cyclopropyl).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; 4.83; N, 5.16. Found: C, 66.31; H, 4.75; N, 5.00.

7-Methyl-7-norbornadienyl ***p*****-Nitrobenzoate** (**6-OPNB**).—To a mixture of 0.901 g of **7** in 0.4 ml of CH_2Cl_2 was added 5 mg of μ-dichlorotetraethylenedirhodium(I).[15] The mixture was agitated and monitored by nmr, using the methyl singlets. After 10 hr, conversion to 6-OPNB was *ca.* 95% complete. A bit more catalyst was added, and the reaction mixture was agitated for 2 days whence none of **7** could be detected. The mixture was diluted with CH_2Cl_2 and filtered, and the product was precipitated by addition of petroleum ether. Crystallization from ether at −20° gave an analytical sample: mp 130.5–132.0°; nmr ($CDCl_3$) τ 1.88 (4 H, arom), 3.31 (2 H, vinyl), 3.40 (2 H, vinyl), 6.12 (2 H, bridgehead), 8.37 (3 H, methyl).

Anal. Calcd: same as **7**. Found: C, 66.32; H, 4.88; N, 4.81.

Kinetics.—All measurements were titrimetric and were done on *ca.* 0.01 *M* solutions. The standard sealed ampoule technique was used for the *p*-nitrobenzoates and for **5**-Cl. Liberated acid was titrated with NaOMe in MeOH using the *p*-bromothymol blue end point. This technique gave unsatisfactory results for **4**-Cl, and so each aliquot was treated using a standard Volhard chloride analysis (back titration of added $AgNO_3$ with KSCN standard solution to the $FeNH_4(SO_4)_2$ end point in the presence of nitrobenzene). The rate for dienyl chloride **3**-Cl was obtained by removing aliquots directly from the master solution which was submerged in the rate bath. In this case, the integrated rate constant was found to decrease with time. A measurement in the presence of added tetrabutylammonium chloride (0.035 *M*) confirmed that common ion rate depression(mass law effect) was being exhibited at the concentration used (0.01 *M*). The data were therefore treated according to the appropriate kinetic ex-

(11) P. G. Gassman and A. F. Fentiman, Jr., *J. Amer. Chem. Soc.*, **92**, 2549, 2551 (1970).

(12) (a) P. R. Story, *ibid.*, **83**, 3347 (1961); (b) H. C. Brown and H. M. Bell, *ibid.*, **85**, 2324 (1963); (c) H. Tanida and Y. Hata, *J. Org. Chem.*, **30**, 977 (1965); (d) H. Tanida, T. Tsuji, and T. Irie, *J. Amer. Chem. Soc.*, **88**, 864 (1966); (e) A. Diaz, M. Brookhart, and S. Winstein, *ibid.*, **88**, 3133 (1966).

(13) This compound was first prepared at UCLA by C. Ordronneau in 1959.

(14) Table I, footnote *d*.

(15) R. Cramer, *Inorg. Chem.*, **1**, 722 (1962).

pression,[16] and the true solvolytic rate constant was obtained by graphical analysis. This measurement represents a mild adjustment of a previously determined value which was not corrected for common ion rate depression.[17]

Product Studies. **5-OPNB.**—A solution of 10 ml of 70% acetone, 0.5 mmol of **5**-OPNB, and 0.75 mmol of sodium acetate was placed in a sealed ampoule and maintained at 100° for 72 hr (*ca.* 10 half-lives). After cooling, the solution was diluted with petroleum ether and the resulting aqueous phase was saturated with NaCl and extracted with six 5-ml portions of petroleum ether. The combined petroleum ether layers were washed three times with saturated $NaHCO_3$ solution and twice with NaCl solution and dried over anhydrous K_2CO_3. The solution was concentrated to less than 10 ml by careful distillation through a Vigreux column and then brought to value in a 10-ml volumetric flask. An aliquot of this solution was combined with a known quantity of tridecane and analyzed by glpc (5% XF-1150 on Chromsorb W, 75°). A single peak with the same retention time as **5**-OH was detected. After correction for the relative detector response of the standard, the yield of **5**-OH was determined as 89%. The remainder of the solution in the volumetric flask was stripped of solvent leaving a residue whose nmr spectrum was identical with that of **5**-OH.

5-Cl.—An 80% acetone solution (10 ml) that was 0.03 *M* in **5**-Cl and 0.06 *M* in NaOAc was maintained at 25° for 5 hr (*ca.* 5 half-lives) and treated as described above for the PNB. Glpc and nmr analysis revealed only **5**-OH as the product.

4-Cl.—A solution was prepared as described above for **5**-Cl and was maintained at 125° for 90 hr (*ca.* 3.5 half-lives). After work-up as described above, glpc analysis on XF-1150 and Carbowax 4000 columns revealed the presence of **4**-OH, **4**-Cl, mesityl oxide and diacetone alcohol, identified by comparison with authentic materials.

6-OPNB.—A 70% acetone solution (10 ml), which was *ca.* 0.15 *M* in ester and 0.35 *M* in NaOAc, was maintained at 75° for 8.25 hr (*ca.* 12 half-lives). It was worked up as described above. Glpc analysis on 5% Carbowax 4000 operated at 80° indicated the presence of three products in the ratio 6.3:1.0:1.0, with relative retention times of 1.0:2.0:6.0, respectively. In a separate experiment, the absolute yield of the major product was shown to be *ca.* 59%. The peaks were isolated by preparative glpc and the final one proved to be **6**-OH by spectral comparison with authentic material. The other minor product showed *m/e* 122 for the parent ion in a low-resolution mass spectrum but was not further investigated. The major component was a liquid: ir (CCl_4) 1723 (aldehydic carbonyl), 2720 cm^{-1} (aldehydic CH); nmr τ 0.76 (1 H, J = 2.5 Hz, aldehydic H), 3.68 (4 H, broad s, olefinic H's), 7.56 (2 H, d, J = 2.5 Hz, CH_2), 8.79 (3 H, s, CH_3); high-resolution mass spectrum, calcd for $C_8H_{10}O$, 122.073-161; found 122.07316. From these data, structure **8** was assigned to this material.

Registry No.—**1**-OTs, 16265-27-7; **2**-OTs, 13111-74-5; **2**-Cl, 1121-10-4; **2**-OPNB, 16558-31-9; **3**-Cl, 1609-39-8; **3**-OPNB, 33686-56-5; **4**-OTs, 33686-57-6; **4**-Cl, 33686-58-7; **4** disulfite, 33686-59-8; **5**-Cl, 33686-60-1; **5**-OPNB, 33686-61-2; **6**-OPNB, 33686-62-3; **7**, 33686-63-4; **8**, 33686-64-5.

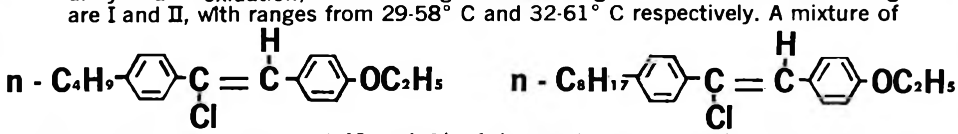
Acknowledgment.—The authors gratefully acknowledge gifts of **3**-OH and **3**-Cl from Dr. M. Brookhart. Computer time was donated by the NMR Facility for Biomedical Research, NIH Grant No. RR00292.

(16) S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc., Spec. Publ.*, No. 19, 109 (1965); *cf.* eq 1 of this paper.

(17) Table I, footnote *f*.

Stable, Colorless Liquid Crystals
With Very Large Enantiotropic Nematic Ranges

W. R. Young et al[1] have shown recently that a series of trans-stilbenes are unique among such nematogenic compounds in being colorless, stable to hydrolysis and oxidation, and have large nematic ranges. The two most interesting are I and II, with ranges from 29-58° C and 32-61° C respectively. A mixture of

I  II

60 mole% of the butyl and 40 mole% of the octyl has a nematic range of 8-59° C.

1. W. R. Young, A. Aviram and R. J. Cox, Angew. Chem. Internat, Ed., 10, 410 (1971).

16,408-9 trans-4-Butyl-alpha-chloro-4'-ethoxystilbene I $35./1 gram
16,407-0 trans-4-Octyl-alpha-chloro-4'-ethoxystilbene II $35./1 gram

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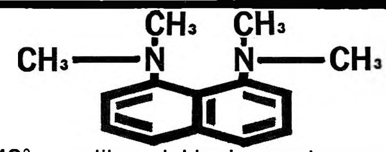
PROTON SPONGE*



Proton Sponge* is a stable crystalline compound, m.p. 47-48°, readily soluble in most organic solvents, which possesses an unusual combination of properties: —

1. It is one of the most powerful uncharged bases known, pKa 12.34.[1]
2. Its nitrogens are quite unreactive towards other electrophiles besides H^+. Thus it does not coordinate Lewis acids or metal ions and cannot[1,2] be N-alkylated (under extreme conditions ring attack might occur).
3. Proton-transfer reactions with Proton Sponge* are unusually slow, despite its strong basicity.[2] Thus while attempted E2 eliminations with this compound in N-methylpyrrolidone give good yields of olefins, it is the solvent which removes the proton in the first place. Proton Sponge* fails to react with CH_3COCl (no ketene formed).

Proton Sponge* should be useful wherever a soluble and powerful but non-nucleophilic and non-coordinating base is needed.

1. R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, Chem. Comm., 1968, 723.
2. R. W. Alder, D. T. Edley, and D. R. Winterman, unpublished results.

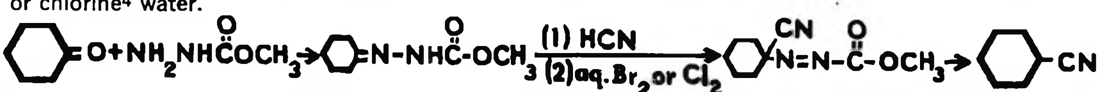
*Trademark of the Aldrich Chemical Co.

15,849-6 Protón Sponge*(1,8-Bis-(dimethylamino)-naphthalene) 10g — $7.50; 50g — $25.50

From KETONES to NITRILES via METHYL CARBAZATE

$$NH_2\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3$$

Ziegler and Wender[1] have developed a new synthesis of nitriles from ketones through the intermediacy of carbomethoxyhydrazones.[2] Addition of HCN to these hydrazones readily gives methyl dialkylcyanodiazanecarboxylates, which can also be prepared[3,4] from ketone cyanohydrins and methyl carbazate. The corresponding **diazenes** are then obtained by oxidation of the diazanes with bromine[3] or chlorine[4] water.



Treatment of these diazenes with a base, such as sodium methoxide, results in decomposition to nitrogen and the anion of the newly generated nitrile which is then protonated to give the nitrile in high yield. Such anions can be trapped with dimethyl carbonate to yield cyano esters or with methyl iodide to give α-methylnitriles.

Carbomethoxyhydrazones of aldehydes are hydrogenated[2,5] to methyl alkyldiazanecarboxylates which are oxidized[6] with peracetic acid to the diazene esters. Decarboxylation[5] with acid gives monosubstituted diazenes (the postulated intermediate in the Wolff-Kishner reduction of ketones) which undergo further decomposition to hydrocarbons and symmetrical hydrazines.

1. F. E. Ziegler and P. A. Wender, J. Am. Chem. Soc., 93, 4318 (1971).
2. M. C. Chaco and N. Rabjohn, J. Org. Chem., 27, 2765 (1962).
3. M. C. Ford and R. A. Rust, J. Chem. Soc., 1297 (1958).
4. E. Mueller, H. Eck and H. Scheurlein, Fr. 1,433,719; C. A., 65, 16879b.
5. T. Tsuji and E. M. Kosower, J. Am. Chem. Soc., 93, 1992 (1971).
6. L. Horder and H. Ferenkess, Ber., 94, 712 (1961).

15,165-3 Methyl carbazate 100g — $9.80; 500g — $38.