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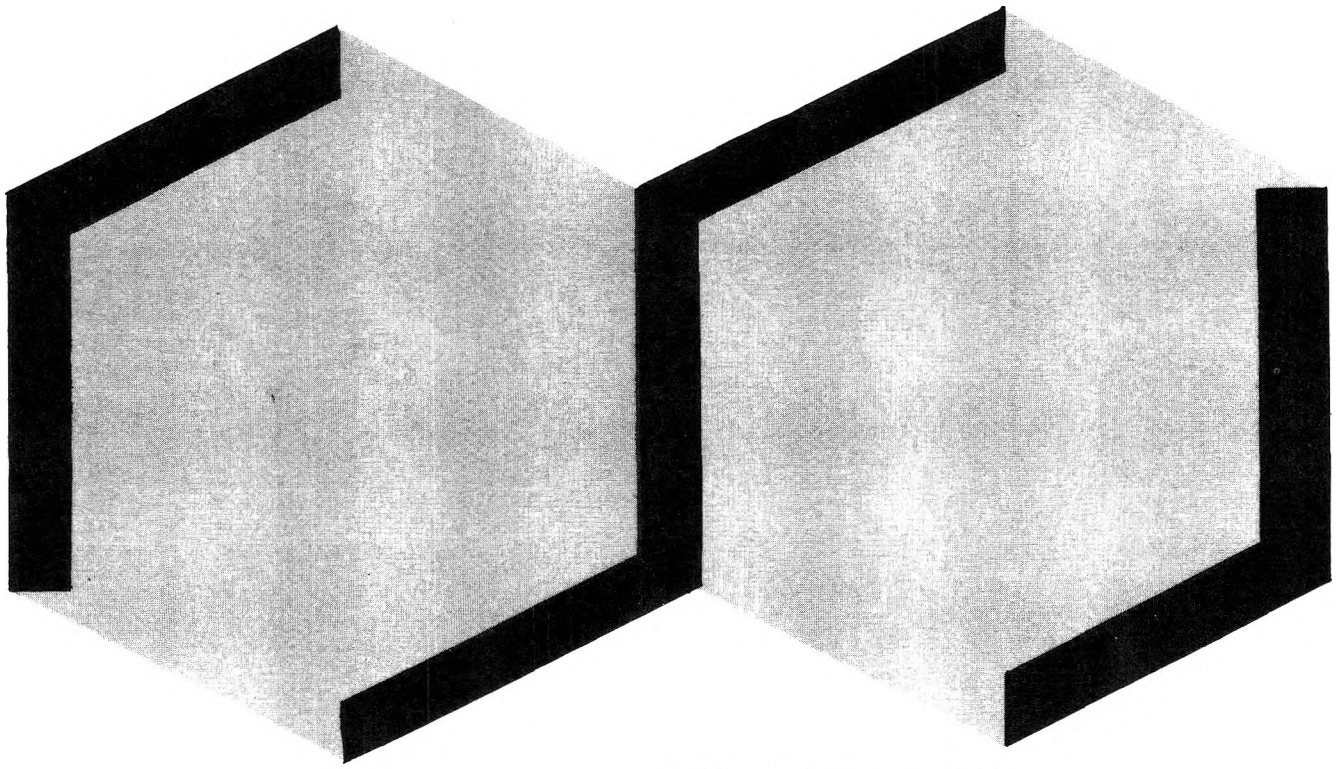

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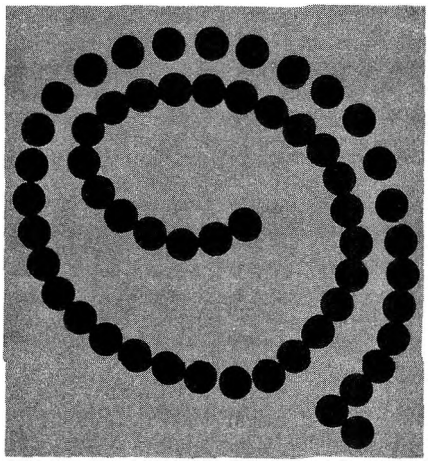

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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 16

AUGUST 9, 1974

Alkylation of Hagemann's Ester. Preparation of an Intermediate for Trisporic Acid Synthesis

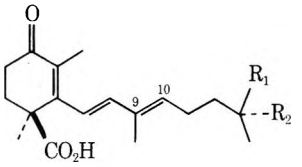
James D. White* and Wing Lam Sung

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

Received February 28, 1974

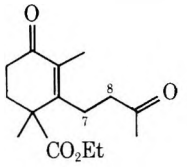
Alkylation of Hagemann's ester (3) with methyl and methallyl halides gave predominantly C-3 substitution. Further alkylation afforded a mixture of 1,3- and 3,3-disubstituted products. A method for the separation of these isomers based upon selective ketalization is described. Methylation at C-1 of a 3,3-dialkylated derivative of 3 was found to proceed well when lithium diethylamide was used as the base. By a sequence in which first a methyl and then a methallyl group were introduced into Hagemann's ester, 18 was prepared and separated from 19 by formation of a ketal (23). Methylation of the latter gave 26, which upon hydrolysis furnished ketodiene 27. This substance underwent Cope rearrangement with transposition of the methallyl group from C-3 to C-7. Selective, oxidative cleavage of the terminal olefin led to 2, a key intermediate for synthetic entry to the trisporic acid system.

The family of naturally occurring, fungal hormones known as trisporic acids (**1a–c**)[1] possesses a structure based upon an alkylated cyclohexenone carboxylic acid.[2] Two previous syntheses of this system have each relied upon a relatively inefficient, intramolecular aldol condensation of an acyclic precursor for construction of the cyclohexenone moiety.[3,4]



1a, $R_1 = R_2 = H$
b, $R_1 = R_2 = O$ (and cis-9,10)
c, $R_1 = H$, $R_2 = OH$ (and cis-9,10)

The diketo ester **2** potentially represents a highly versatile intermediate for elaboration of the trisporic skeleton and its analogs. In fact, Isoe, *et al.*,[4] have shown that the 7,8-dehydro version of **2** can be converted into cis and trans isomers of methyl trisporates B and C by a straightforward Wittig reaction. A particularly attractive means of access to **2** appeared to lie through sequential alkylation of Hagemann's ester (**3**), and we describe herein the outcome of alkylation studies on **3** with methyl and methallyl halides which has led to a convenient synthesis of the key trisporic acid intermediate **2**.



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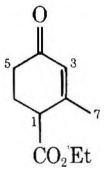


3

Since Hagemann's ester has four possible sites (C-1, -3, -5, and -7) at which alkylation could, in principle, occur, and since the synthesis of **2** depends upon selective introduction of substituents at three of these, it became of primary importance to determine the relative site preference for alkylation in this ambident system. Aside from the generally accepted dictum that alkylation of Hagemann's ester occurs at C-3,[5] little is known of the behavior of **3** in multiple alkylation, and such scanty information as exists is largely contradictory.[6-8]

Results

Hagemann's ester (**3**) was allowed to react with methyl iodide in the presence of sodium ethoxide to give monomethylated product in 83% yield. Nmr evidence revealed that **4** (C-3 CH_3, δ 1.81) and **5** (C-1 CH_3, δ 1.42) were formed in an approximate ratio of 4:1, a result in general agreement with the findings of Nasipuri, *et al.*[9] Alkylation of **3** under similar conditions with methallyl chloride gave **6** in 82% yield. No C-1 methallyl derivative could be found in this case, although possibly as much as 5% could have escaped detection.

The mixture of **4** and **5** was treated with methyl iodide and potassium *tert*-butoxide as base to give a mixture of **7** and **8** accompanied by unreacted **5** (Scheme I). The three keto esters were easily distinguished by means of their characteristic methyl group shifts, which indicated the ratio of **7** (C-2 CH_3, δ 2.00):**8** (C-3 CH_3, δ 1.82):**5** (C-2 CH_3, δ 1.96) as 2:2:1. By monitoring this reaction using gas chromatography, it was ascertained that both **7** and **8** arose from **4** and that **5** was methylated only very slowly if at all. This accords with the anticipated ease of formation of the endocyclic and more extensively conjugated enolate from **4**, as contrasted with the exocyclic enolate from **5**. The formation of both **7** and **8** from **4** is at variance with the results of Nazarov and Zavyalov,[7] who reported exclusive formation of **7**, but it does support the earlier work of Mukharji.[6] The mixture of **7** and **8** could not be cleanly separated by distillation, and hence a method based upon their differing reactivity toward ketalization was employed.[10] Upon treatment of the mixture with ethylene

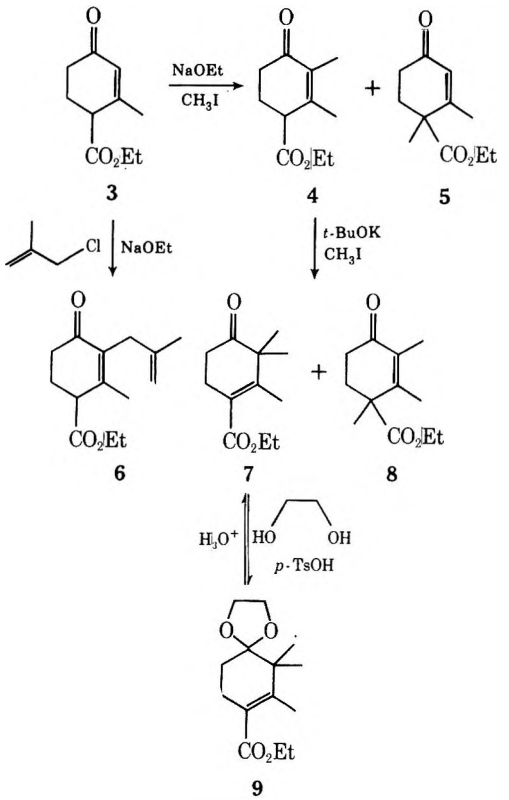
Table I
Methallylation of Keto Ester 4

Base	Temps °C	Methallyl halide	Ratio[a] of 18:19
NaOEt–EtOH	−25	Chloride	2:1
LICA[b]	−5	Chloride	1:1
LDA[c]	−70	Chloride	3:5
NaH–dioxane	101	Chloride	**19** only
t-BuOK–*t*-BuOH	83	Chloride	**19** only
t-BuOK–*t*-BuOH	83	Bromide	**19** only

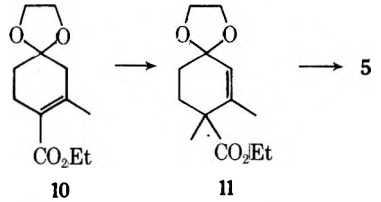
[a] Ratio calculated from area comparison on gas chromatogram. [b] Lithium *N*-isopropylcyclohexylamide. [c] Lithium diethylamide.

glycol in benzene containing *p*-toluenesulfonic acid, only 7 formed a ketal (**9**). This was readily separated from 8 by distillation, and 7 was recovered in high yield by hydrolysis. The overall yield of the desired isomer 8 from Hagemann's ester was *ca.* 20%.

Scheme I

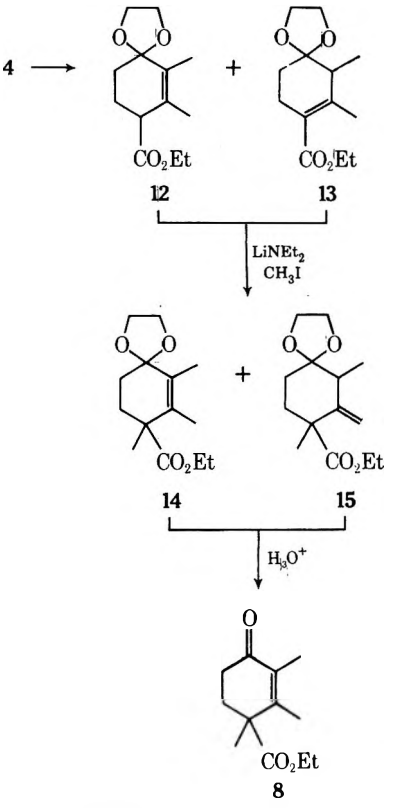


An alternate route to 8 which avoids formation of the unwanted 2,3,3-trisubstituted isomer 7 is shown in Scheme II. As a model for this approach, the ethylene ketal (**10**),[11] derived from Hagemann's ester, was treated with methyl iodide in the presence of lithium diethylamide to give **11** in 71% yield. The latter, upon hydrolysis of

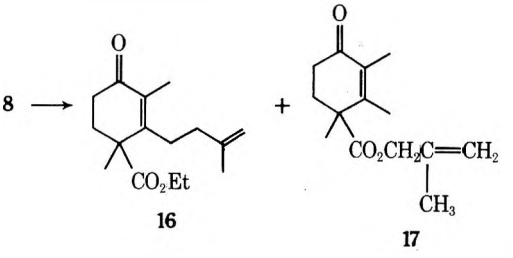


the ketal function, afforded **5**. The strong preference by **10** for α- rather than γ-alkylation of the unsaturated ester function has ample precedent,[12] and methylation at C-1 of this enolate is probably further enhanced by hindrance from the spiro center adjacent to the γ site. An analogous alkylation of the mixture of isomeric ketals **12** and **13** (1:1) derived from **4** (86%)[13] gave endocyclic (**14**) and exocyclic (**15**), C-1 methylated, β,γ-unsaturated esters (*ca.* 1:1) in 75% yield (Scheme II). Acidic hydrolysis of this mixture gave keto ester **8** in 56% overall yield from **4**.

Scheme II



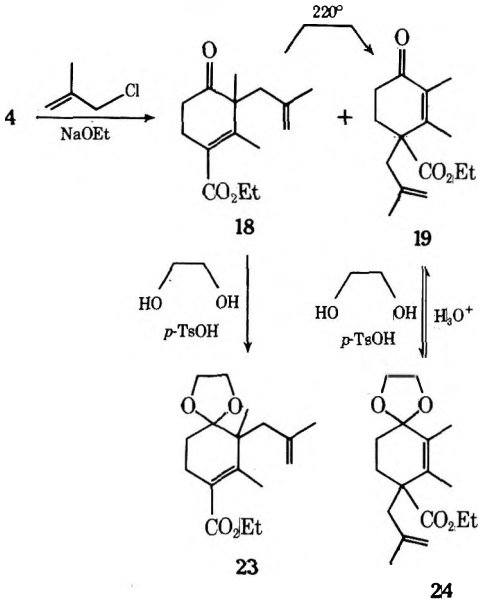
Unfortunately, attempts to alkylate **8** were less successful. For example, treatment of **8** with methallyl bromide and potassium *tert*-butoxide gave only 5% of **16**; vigorous conditions gave up to 35% of transesterification product **17**. The use of other bases such as lithium diethylamide,



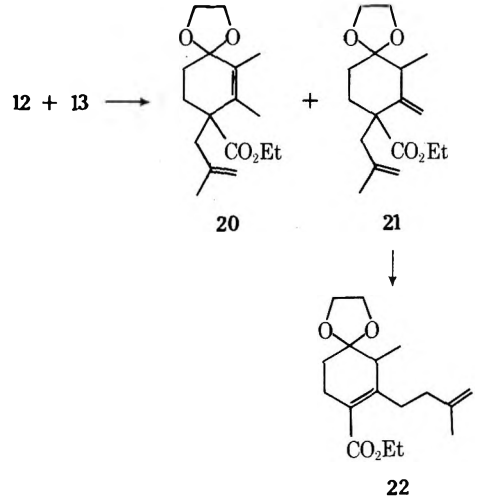
lithium hexamethyldisilylamide, and sodium hydride in benzene were equally unrewarding. It became apparent from these studies that the conjugated enolate from α,β-unsaturated ketone **8** is formed with considerable difficulty and only under conditions where side reactions, particularly decarboxylation, become competitive.

The introduction of alkyl substituents into the nucleus of Hagemann's ester clearly makes succeeding alkylations more difficult, with the effect most pronounced when the alkyl group is first incorporated at C-1 (for example, **5** is resistant to further alkylation). On the other hand, the introduction of the initial alkyl substituent at C-3 does not interfere with a subsequent C-1 alkylation, since **12** and **13** undergo smooth methylation to **14** and **15**, respectively. Consequently, **4** was subjected to methallyl chloride and sodium ethoxide (Scheme III), leading to a mixture of **18** (1715 cm^{-1}; C-3 CH_3, δ 1.22) and **19** (1738, 1675 cm^{-1}; C-3 CH_3, δ 1.81). As can be seen from the results in Table I, the proportion of methallylated products is markedly

Scheme III



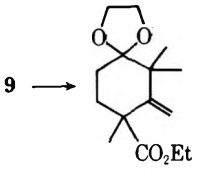
dependent upon temperature and the base employed. That 19 is the thermodynamically favored isomer of this pair is apparent from the Cope rearrangement of 18 to 19 in >90% yield at 220°. Presumably, a similar driving force is operative in the alkylation reaction, since more vigorous conditions generally led to a higher proportion of 19. In contrast to the methallylation of 4, the analogous alkylation of the mixture of ketals 12 and 13 gave exclusively C-1 methallyl derivatives as a mixture of endocyclic (20) and exocyclic (21) olefins. The latter underwent a Cope



rearrangement to 22 upon pyrolysis, the migration of the exo double bond to an endo position in concert with its conjugation to the ester providing obvious thermodynamic advantage. No Cope rearrangement of 20 is observed under these conditions. Attempts to complete the alkylation sequence by methylation of 22 at C-1 in analogy with the methylation of 13 gave extensive polymerization, with little prospect of a viable synthesis of 2 by this route.

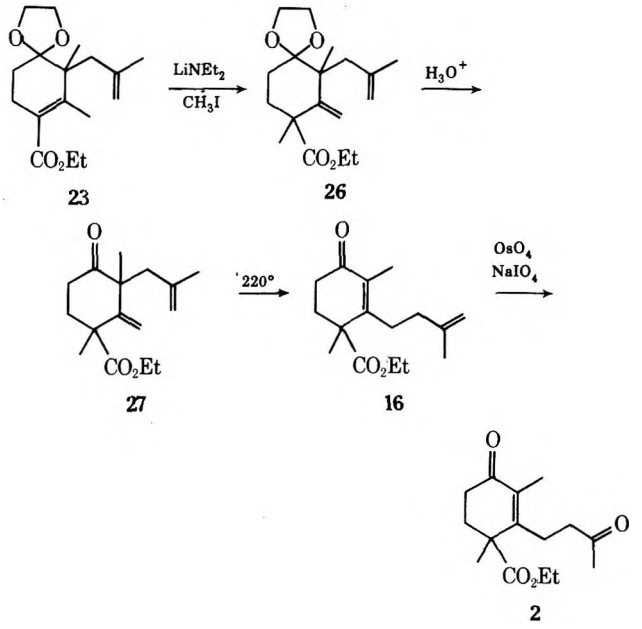
The remaining avenue to a derivative of Hagemann's ester having appropriate substitution for conversion to 2 lay through keto ester 18. In order to separate 18 from its isomer 19 produced in the methallylation of 4, the mixture was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid to effect a selective ketalization of 18. In contrast to the situation with 7 and 8, where only the β,γ-unsaturated ketone formed an ethylene ketal, both ketals 23 and 24 were isolable. However, 24 was hydrolyzed very rapidly in water, thus permitting a facile removal of 23 by distillation.

As a model for the projected C-1 methylation of 23, ketal 9 was treated with methyl iodide and lithium diethylamide to give 25 in 83% yield. The presence of a new

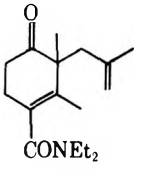


methyl group and an exocyclic methylene function was confirmed by both ir (906 cm^{-1}) and nmr data [δ 5.21 (2 H), 1.35 (3 H, s)]. The analogous methylation of 23 gave 26 [δ 5.30 (2 H), 4.77 (2 H), 1.37 (3 H, s)], which upon hydrolysis with ethanolic hydrochloric acid for 20 hr produced keto ester 27 in 72% overall yield based upon 23 (Scheme IV). Direct methylation of 18 was less satisfacto-

Scheme IV



ry and led to 27 in only 46% yield, accompanied by a substance having the properties of amide 28.



Transposition of the methallyl group from C-3 to C-7 in 27 was effected by pyrolysis at 220° for 13 min, resulting in a 97% yield of 16 (1728, 1668, 1620 cm^{-1}). As in the conversion 21 → 22, the genesis of a conjugated carbonyl as well as an endocyclic, tetrasubstituted olefin makes this reorganization highly favorable. The terminal C=C of 16 underwent rapid, oxidative cleavage with a catalytic quantity of osmium tetroxide, followed by 1 equiv of sodium periodate in aqueous dioxane, to give a 78% yield of diketo ester 2. The synthesis of 2 from Hagemann's ester *via* 4, 18, 23, 26, 27, and 16 allows its preparation in an overall yield of *ca.* 15%, and requires only one distillative separation (of 23) en route. This approach therefore offers a convenient pathway from a readily available starting

material to a system having appropriate substitution for elaboration of the trisporic acids.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 137 infrared spectrophotometer as liquid films. Nmr spectra were obtained with a Varian HA-100 spectrometer in $CDCl_3$ solution, with TMS as internal reference. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., or by Dr. Susan Rottschaefer at the Department of Chemistry, University of Oregon, Eugene, Oreg. Low- and high-resolution mass spectra were measured by Dr. Rottschaefer. Analytical and preparative gas chromatography was carried out on a Varian Aerograph Model 700 gas chromatograph, using a 5 ft × 0.25 in. SE-30 (20% on Chromosorb G) column.

Methylation of Hagemann's Ester (3). Hagemann's ester (27.0 g, 0.148 mol) was added to a solution of sodium ethoxide, prepared from 3.85 g (0.167 mol) of sodium in 250 ml of absolute ethanol. After stirring at 65° for 2.5 hr, 25 ml of methyl iodide was added. The solution was stirred at room temperature for 20 min, and then at 65° for 1 hr. Ethanol was removed under reduced pressure and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo* and the residue was distilled at 95–105° (0.2 mm), affording 24.3 g (83%) of **4** (C-3 CH_3, δ 1.81) and **5** (C-1 CH_3, δ 1.42) in a ratio of 4:1.

Methylation of Ethyl 2,3-Dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (4). The mixture of keto esters **4** and **5** (2.01 g, 10.2 mmol) was added to a solution prepared from 1.60 g (14.5 mmol) of potassium *tert*-butoxide in 30 ml of dry *tert*-butyl alcohol. The solution was stirred at 50° under nitrogen for 30 min. The solution was then cooled to room temperature, and 2 ml of methyl iodide was added. The resulting mixture was stirred for 10 min at 26° and then at 45° for another 20 min. The solvent was removed under reduced pressure, ether was added to dissolve the residue, and the solution was filtered. The filtrate was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 96–110° (0.2 mm) afforded 1.51 g (66%) of a mixture of keto esters **7** (C-2 CH_3, δ 2.00), **8** (C-3 CH_3, δ 1.82), and **5** (C-2 CH_3, δ 1.96) in a ratio of 2:2:1. Preparative gas chromatography afforded a sample of **8**: ir (film) 1725, 1667, 1620, 1242, 1180, 1095, 1020 cm^{-1}; nmr ($CDCl_3$) δ 4.18 (2 H, q, J = 7.2 Hz), 2.60–1.80 (4 H, m), 1.90 (3 H, s), 1.82 (3 H, s), 1.44 (3 H, s), 1.26 (3 H, t, J = 7.2 Hz); mass spectrum m/e 210 (M^+).

Anal. Calcd for **8** $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.36; H, 8.73.

Ethyl 4,4-Ethylenedioxy-2,3,3-trimethylcyclohex-1-enyl-1-carboxylate (9). A 20.0-g sample of keto esters **7**, **8**, and **5** was heated under reflux in 150 ml of benzene with a catalytic amount of *p*-toluenesulfonic acid and 6 ml of ethylene glycol for 12 hr, with provision for water removal *via* a Dean-Stark trap. Benzene was removed from the mixture under reduced pressure, and the solution was extracted with ether. The ethereal extract was washed with aqueous potassium carbonate solution and brine, and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. The crude product weighed 20.5 g. Distillation of the product through a 36-in. spinning-band column afforded 5.9 g (25% overall yield from **4**) of keto ester **8**, 90% pure, bp 63° (0.15 mm). Evaporative distillation of the high-boiling, residual oil at 110° (0.3 mm) yielded 6.4 g (*ca.* 22% overall yield from **4**) of **9**: ir (film) 1715, 1630, 1235, 1205, 1086, 1056 cm^{-1}; nmr ($CDCl_3$) 4.19 (2 H, q, J = 7.0 Hz), 3.99 (4 H, s), 2.45 (2 H, t, J = 6.6 Hz), 1.93 (3 H, s), 1.77 (2 H, t, J = 6.6 Hz), 1.27 (3 H, t, J = 7.0 Hz), 1.11 (6 H, s); mass spectrum m/e 254 (M^+).

Anal. Calcd for $C_{14}H_{22}O_4$(**9**): C, 66.12; H, 8.72. Found: C, 66.66; H, 8.79.

Ethyl 2,3,3-Trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (7). Ketal ester **9** (140 mg, 0.55 mmol) was added to a solution of 10 ml of 6 *N* hydrochloric acid in 30 ml of ethanol, and the mixture was stirred at room temperature for 15 hr. Brine (100 ml) was added and the solution was extracted twice with dichloromethane. The dichloromethane extract was washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*. Evaporative distillation of the residue at 90° (0.2 mm) afforded 105 mg (91%) of **7**: ir (film) 1725, 1630, 1222, 1048 cm^{-1}; nmr ($CDCl_3$) δ 4.25 (2 H, q, J = 7.0 Hz), 2.80–2.40 (4 H, m), 2.00 (3 H, s), 1.30 (3 H, t, J = 7.0 Hz), 1.22 (6 H, s); mass spectrum m/e 210 (M^+).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.20; H, 8.54.

Ketalization of Keto Ester 4. Keto ester **4** (8.50 g, 0.43 mol) was added to a solution containing 1.5 g of *p*-toluenesulfonic acid and 20 ml of ethylene glycol in 200 ml of benzene, and the mixture was heated under reflux for 20 hr, with provision for water removal *via* a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*, and evaporative distillation of the residue at 111° (1.5 mm) gave 8.9 g (86%) of **12** (2 CH_3, s, δ 1.68 and 2.03) and **13** (CH_3, s, δ 2.03).

Methylation of Ketal Esters 12 and 13. A mixture of ketal esters **12** and **13** (120 mg, 0.50 mmol) was added to a solution of lithium diethylamide, prepared from 2.8 mmol (1.5 ml of a 1.9 *M* hexane solution) of *n*-butyllithium and 300 mg (4.1 mmol) of diethylamine in 10 ml of tetrahydrofuran, precooled in an ice–water bath. A red solution was formed after stirring for 30 min. Methyl iodide (1 ml) was added and the mixture was stirred for a further 2 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*, leaving 95 mg (75%) of ketal esters **14** and **15**. The nmr spectrum of this mixture showed the following: a doublet (equivalent to 1 H) at δ 4.97, two singlets at δ 4.02 and 3.95, a singlet at δ 1.62, and two singlets at δ 1.35 and 1.28.

Ethyl 1,2,3-Trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (8). A 70-mg (0.27 mmol) sample of the mixture of methylated ketal esters **14** and **15** was stirred with 20 ml of 6 *N* hydrochloric acid in 60 ml of ethanol for 7 hr. Brine (100 ml) was added and the solution was extracted twice with dichloromethane. The dichloromethane extract was washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*, leaving 50 mg (86%) of **8** identical with the material prepared by methylation of **4**.

Ethyl 4,4-Ethylenedioxy-2-methylcyclohex-1-enyl-1-carboxylate (10). A 2.0-g (0.011 mol) sample of Hagemann's ester (**3**) was heated under reflux in 50 ml of benzene with a catalytic amount of *p*-toluenesulfonic acid and 3 ml of ethylene glycol for 21 hr, with provision for water removal *via* a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*. Evaporative distillation of the residual oil at 105° (0.25 mm) gave 1.9 g (78%) of **10**: ir (film) 1720, 1650, 1238, 1088, 1066 cm^{-1}; nmr ($CDCl_3$) δ 4.21 (2 H, q, J = 7.0 Hz), 3.99 (4 H, s), 2.55 (2 H, t, J = 6.5 Hz), 2.39 (2 H, s), 2.03 (3 H, s), 1.75 (2 H, t, J = 6.5 Hz), 1.28 (3 H, t, J = 7.0 Hz).

Ethyl 4,4-Ethylenedioxy-1,2-dimethylcyclohex-2-enyl-1-carboxylate (11). Ketal ester **10** (0.10 g, 0.44 mmol) was added to a solution of lithium diethylamide, prepared from 1.9 mmol (1.0 ml of a 1.9 *M* hexane solution) of *n*-butyllithium and 0.20 g (2.7 mmol) of diethylamine in 10 ml of tetrahydrofuran, precooled in an ice–water bath. A dark solution was obtained after stirring for 30 min. Methyl iodide (0.5 ml) was added and the mixture was stirred for a further 1 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 115° (0.2 mm) afforded 75 mg (71%) of **11**: ir (film) 1738, 1648, 1250, 1106, 1080, 1022 cm^{-1}; nmr ($CDCl_3$) δ 5.47 (1 H, s), 4.18 (2 H, q, J = 7.0 Hz), 3.98 (4 H, s), 2.50–1.70 (4 H, m), 1.73 (3 H, s), 1.30 (3 H, s), 1.23 (3 H, t, J = 7.0 Hz); mass spectrum m/e 240 (M^+).

Ethyl 1,2-Dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (5). Ketal ester **11** (250 mg, 1.04 mmol) was shaken with 50 ml of 3 *N* hydrochloric acid in 50 ml of ether for 3 min. The aqueous layer was extracted with ether once. The combined, ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 95° (0.2 mm) afforded 140 mg (65%) of **5**: ir (film) 1738, 1685, 1635, 1245, 1175, 1090, 1020 cm^{-1}; nmr ($CDCl_3$) δ 5.94 (1 H, s), 4.21 (2 H, q, J = 6.4 Hz), 2.70–1.60 (4 H, m), 1.96 (3 H, s), 1.42 (3 H, s), 1.26 (3 H, t, J = 6.4 Hz); mass spectrum m/e 196 (M^+).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.60; H, 8.27.

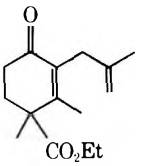
Methallylation of Keto Ester 8. Keto ester 8 (0.50 g, 2.4 mmol) was added to a solution prepared from 98 mg (2.5 mmol) of potassium in 0.5 ml of *tert*-butyl alcohol and 6 ml of tetrahydrofuran. The mixture was stirred at room temperature for 1 hr, during which a deep red color was formed. Methallyl bromide (0.34 g, 2.5 mmol) in 2.5 ml of tetrahydrofuran was added, and the mixture was stirred for 15 min and then at 73° for 14 hr. Solvent was removed under reduced pressure. The residue was taken up into water and ether. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*, leaving 0.40 g of crude product. Gas chromatographic analysis of the product showed that 60% was the unreacted keto ester 8, 35% was the transesterified compound **17**, and 5% was the methallylated product **16**. The latter two compounds were obtained in pure form by preparative gas chromatography. Methallyl 1,2,3-trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (**17**) had ir (film) 1735, 1671, 1624, 1230, 1170, 1085, 895 cm^{-1}; nmr ($CDCl_3$) δ 4.92 (2 H, s), 4.52 (2 H, s), 2.70–1.50 (4 H, s), 1.89 (3 H, s), 1.79 (3 H, s), 1.72 (3 H, s), 1.44 (3 H, s).

Ethyl 2-(3-methylbut-3-enyl)-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (**16**) had ir (film) 1728, 1668, 1620, 1240, 1180, 1092, 1022, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.76 (2 H, s), 4.17 (2 H, q, J = 7.0 Hz), 2.70–1.55 (8 H, m), 1.82 (3 H, s), 1.75 (3 H, s), 1.45 (3 H, s), 1.24 (3 H, t, J = 7.0 Hz); mass spectrum m/e 264 (M^+).

Anal. Calcd for $C_{16}H_{24}O_3$ (**16**): C, 72.69; H, 9.15. Found: C, 72.37; H, 9.35.

Ethyl 3-Methallyl-2-methyl-4-oxocyclohex-2-enyl-1-carboxylate (6). Hagemann's ester (**3**, 10.0 g, 0.055 mol) was added to a solution of sodium ethoxide, prepared from 1.5 g (0.065 of sodium in 40 ml of absolute ethanol, and the mixture was stirred at 80° for 5 hr. Methallyl chloride (8.0 g, 0.087 mol) was added, and the mixture was stirred for 13 hr. Ethanol was removed under reduced pressure, and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 106–130° (0.7 mm) afforded 10.5 g (82%) of **6**: ir (film) 1730, 1672, 1635, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.65 (2 H, d, J = 14 Hz), 4.22 (2 H, q, J = 7.0 Hz), 3.34 (1 H, t, J = 4.2 Hz), 3.06 (2 H, d, J = 5.0 Hz), 2.80–1.80 (4 H, m), 1.94 (3 H, s), 1.72 (3 H, s), 1.26 (3 H, t, J = 7.0 Hz).

Methylation of Keto Ester 6. Keto ester 6 (2.0 g, 8.5 mmol) was stirred with 1.05 g (9.4 mmol) of potassium *tert*-butoxide in 60 ml of glyme at room temperature for 10 hr. A dark solution was obtained. Methyl iodide (2.0 g, 14 mmol) was added, and the mixture was stirred for 2 hr at 26° and for a further 0.5 hr at 55°. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 110° (0.05 mm) afforded 1.2 g (56%) of ethyl 3-methallyl-1,2-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (**29**) (3 CH_3 singlets at δ 1.85, 1.73, and 1.44) and 18 (3 CH_3 singlets at δ 2.04, 1.63, and 1.22) in a ratio of 1:1.



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Ethyl 3-Methallyl-2,3-dimethyl-4-oxocyclohex-1-enyl-1-carboxylate (18). Keto ester 4 (34.0 g, 0.173 mol) in a solution of sodium ethoxide, prepared from 4.9 g (0.21 mol) of sodium in 250 ml of absolute ethanol, was stirred at room temperature for 33 hr. Methallyl chloride (40 ml) was added, and the mixture was stirred for 40 min. and then for a further 4 hr at 60°. Ethanol was removed under reduced pressure and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residual oil at 105–130° (0.7 mm) afforded 35.1 g of a mixture of **4**, **18** and **19**, which gas chromatographic analysis (column temperature 170°) showed to be in the ratio 50:33:17. Nmr analysis confirmed the ratio of **18** to **19** as 2:1. Distillation of the product through a 36-in. spinning-band column afforded **18**: bp 88° (0.15 mm); *ca.* 85% pure; ir (film) 1715, 1645, 1242, 1203, 1044, 898 cm^{-1}; nmr ($CDCl_3$) δ 4.70 (2 H, d, J = 16 Hz), 4.25 (2 H, q, J = 7.0 Hz), 2.80–2.10 (6 H, m), 2.04 (3 H, s), 1.63 (3 H, s), 1.35 (3 H, t, J = 7.0 Hz), 1.22 (3 H, s); mass spectrum m/e 250.157 (parent, calcd for $C_{15}H_{22}O_3$, 250.157).

Pyrolysis of Keto Ester 18. Keto ester **18** (0.10 g, 0.40 mmol) was heated in an air bath at 220° for 25 min. Evaporative distillation at 110–120° (0.2 mm) gave 0.09 g (90%) of **19**: ir (film) 1738, 1675, 1623, 1204, 1168, 1072, 1018, 895 cm^{-1}; nmr ($CDCl_3$) δ 4.86 (2 H, d, J = 11 Hz), 4.20 (2 H, q, J = 7.0 Hz), 3.00–2.00 (6 H, m), 1.97 (3 H, s), 1.81 (3 H, s), 1.69 (3 H, s), 1.25 (3 H, t, J = 7.0 Hz); mass spectrum m/e 250.156 (M^+, calcd for $C_{15}H_{22}O_3$, 250.157).

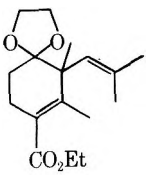
Methallylation of the Mixture of 12 and 13. A mixture of ketal esters **12** and **13** (8.65 g, 0.036 mol) was added to a solution of lithium diethylamide, prepared from 0.112 mol (48 ml of a 2.34 *M* hexane solution) of *n*-butyllithium and 8.6 g (0.18 mol) of diethylamine in 180 ml of tetrahydrofuran, precooled in an ice–water bath. The solution was stirred for 25 min, methallyl chloride (20 g, 0.215 mol) was added, and the mixture was stirred for a further 40 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 120–160° (0.4 mm) afforded 8.1 g (76%) of a mixture of **20** and **21** (vinyl H at δ 5.36, exocyclic methylene).

Ethyl 4,4-Ethylenedioxy-2-(3-methylbut-3-enyl)-3-methylcyclohex-1-enyl-1-carboxylate (22). A mixture of **20** and **21** (0.50 g) was heated in an air bath at 220° for 15 min. Evaporative distillation afforded 0.43 g of a mixture of **20** and **22**. Preparative gas chromatography afforded a sample of **20**: ir (film) 1728, 1655, 1064, 892 cm^{-1}; nmr ($CDCl_3$) δ 4.80 (2 H, d, J = 5.8 Hz), 4.14 (2 H, q, J = 7.0 Hz), 4.00 (4 H, s), 3.00–1.50 (6 H, m), 1.72 (3 H, s), 1.65 (3 H, s), 1.61 (3 H, s), 1.23 (3 H, t, J = 7.0 Hz).

The mixture of **20** and **22** (0.35 g) was shaken with a solution containing 50 ml of ether and 50 ml of 6 *N* hydrochloric acid for 2 min. The ether layer was separated and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*, leaving 0.25 g of residual oil which by chromatographic analysis was found to be a mixture of **19** and **22** (1:1). Preparative gas chromatography afforded a sample of **22**: ir (film) 1719, 1652, 1635, 1240, 1138, 1083, 886 cm^{-1}; nmr ($CDCl_3$) δ 4.74 (2 H, s), 4.19 (2 H, q, J = 7.0 Hz), 3.97 (4 H, s), 3.00–1.50 (9 H, m), 1.74 (3 H, s), 1.27 (3 H, t, J = 7.0 Hz), 1.16 (3 H, d, J = 7.4 Hz); mass spectrum m/e 294 (M^+).

Ethyl 4,4-Ethylenedioxy-3-methallyl-2,3-dimethylcyclohex-1-enyl-1-carboxylate (23). A mixture of keto esters **18** and **19** (18.0 g, 0.072 mol) was added to a solution containing 200 mg of *p*-toluenesulfonic acid and 20 ml of ethylene glycol in 150 ml of benzene. The solution was heated under reflux for 12 hr, with provision for water removal *via* a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*, leaving 16.5 g of a mixture of ketals **20**, **23**, and **30** in the ratio of 2:3:1.

The mixture of ketals (6.6 g, 0.024 mol) was shaken with a mixture of 0.20 g of *p*-toluenesulfonic acid, 20 ml of water, and 20 ml of benzene for 5 min. The benzene layer was washed with brine and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*. The crude product was distilled with a 12-in. spinning-band column at 83° (0.06 mm), affording 3.0 g of a mixture of keto esters **18** and **19** and ketal ester **30**. Preparative gas chromatography gave **30**: nmr ($CDCl_3$) δ 5.01 (1 H, s), 4.18 (2 H, q, J = 7.0 Hz), 3.51 (2 H, t, J = 6.4 Hz), 2.0–1.5 (2 H, m), 1.91 (3 H, s), 1.71 (3 H, s), 1.61 (3 H, s), 1.27 (3 H, t, J = 7.0 Hz), 1.22 (3 H, s); mass spectrum m/e 294 (M^+).



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Further distillation of the residue at 130–145° (0.6 mm) gave 2.5 g (*ca.* 48% from **18**) of **23**: ir (film) 1740, 1678, 1240, 1078, 1054, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.82 (2 H, d, J = 6.0 Hz), 4.20 (2 H, q, J = 7.0 Hz), 4.00 (4 H, s), 2.60–1.50 (6 H, m), 1.94 (3 H, s), 1.74 (3 H, s), 1.28 (3 H, t, J = 7.0 Hz), 1.09 (3 H, s); mass spectrum m/e 294.181 (M^+, calcd for $C_{17}H_{26}O_4$, 294.183).

Ethyl 4,4-Ethylenedioxy-1,3,3-trimethyl-2-methylenecyclohexyl-1-carboxylate (25). Ketal ester **9** (0.30 g, 1.18 mmol) was added to a solution of lithium diethylamide, prepared from 5.7 mmol (3.0 ml of 1.9 *M* hexane solution) of *n*-butyllithium and 0.43 g (5.7 mmol) of diethylamine in 40 ml of tetrahydrofuran, precooled in an ice-water bath. The mixture was stirred for 5 min. Methyl iodide (2 ml) was added, and the mixture was stirred for a further 5 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 112° (0.1 mm) afforded 0.26 g (83%) of **25**: ir (film) 1730, 1635, 1254, 1090, 906, 806 cm^{-1}; nmr ($CDCl_3$) δ 5.21 (2 H, d, J = 4.8 Hz), 4.12 (2 H, q, J = 7.2 Hz), 3.95 (4 H, s), 2.40–1.30 (4 H, m), 1.35 (3 H, s), 1.22 (3 H, s, J = 7.2 Hz), 1.11 (3 H, s), 1.03 (3 H, s); mass spectrum m/e 268.169 (M^+, calcd for $C_{15}H_{24}O_4$, 268.167).

Ethyl 4,4-Ethylenedioxy-3-methallyl-1,3-dimethyl-2-methylenecyclohexyl-1-carboxylate (26). Ketal ester **23** (1.9 g, 6.5 mmol) was added to a solution of lithium diethylamide, prepared from 28.1 mmol (12 ml of 2.34 *M* hexane solution) of *n*-butyllithium and 2.2 g (30.1 mmol) of diethylamine in 50 ml of tetrahydrofuran, precooled to −78°. The mixture was stirred for 1 hr. Methyl iodide (5 g, 35.1 mmol) was added, and the mixture was stirred for a further 0.5 hr. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 140° (0.4 mm) afforded 1.6 g (81%) of **26**: ir (film) 1730, 1630, 1250, 1080, 895 cm^{-1}; nmr ($CDCl_3$) δ 5.30 (2 H, d, J = 7.2 Hz), 4.77 (2 H, s), 4.21 (2 H, q, J = 7.2 Hz), 3.93 (4 H, s), 2.50–1.50 (6 H, m), 1.67 (3 H, s), 1.37 (3 H, s), 1.22 (3 H, t, J = 7.2 Hz), 1.05 (3 H, s); mass spectrum m/e 308.199 (M^+, calcd for $C_{18}H_{28}O_4$, 308.199).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.19.

Ethyl 3-Methallyl-1,3-dimethyl-2-methylene-4-oxocyclohexyl-1-carboxylate (27). A. From 26. Ketal ester **26** (0.25 g, 0.81 mmol) was stirred with 10 ml of 5 *N* hydrochloric acid and 30 ml of ethanol for 20 hr. Brine (100 ml) was added and the solution was extracted twice with dichloromethane. The dichloromethane extract was washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*. Evaporative distillation of the crude product at 99–105° (0.4 mm) afforded 0.19 g (89%) of keto ester **27**: ir (film) 1730, 1675, 1633, 1242, 1168, 1020, 898 cm^{-1}; nmr ($CDCl_3$) δ 5.22 (2 H, d, J = 3.0 Hz), 4.73 (2 H, d, J = 17 Hz), 4.19 (2 H, q, J = 7.0 Hz), 2.80–1.40 (6 H, m), 1.63 (3 H, s), 1.40 (3 H, s), 1.25 (3 H, t, J = 7.0 Hz), 1.25 (3 H, s).

B. From Keto Ester 18. Keto ester **18** (0.90 g, 3.6 mmol) was added to a solution of lithium diethylamide, prepared from 18.0 mmol (7.7 ml of 2.34 *M* hexane solution) of *n*-butyllithium in 40 ml of tetrahydrofuran, precooled in an ice-water bath. The mixture was stirred for 25 min. Methyl iodide (3.0 g, 21 mmol) was added, and the mixture was stirred for a further 5 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 117° (0.15 mm) afforded 0.44 g (46% yield) of **27** and 0.13 g of a high-boiling residue which was identified as amide **28**: ir (film) 1712, 1625 (strong), 895 cm^{-1}; nmr ($CDCl_3$) δ 4.73 (2 H, d, J = 16 Hz), 3.00–3.80 (4 H, broad), 1.73 (3 H, s), 1.70 (3 H, s), 1.21 (3 H, s).

Pyrolysis of Keto Ester 27. Keto ester **27** (0.44 g) was heated at 220° for 13 min in an air bath. Evaporative distillation afforded 0.43 g (97%) of keto ester **16**, identified by comparison with the methallylation product from **8**.

Ethyl 2-(3-Oxobutyl)-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (2). Keto ester **16** (0.50 g, 1.9 mol) was added to a solution containing *ca.* 10 mg of osmium tetroxide in 100 ml of water–dioxane (1:3) and the mixture was stirred for 0.5 hr. Sodium periodate (0.45 g, 2.1 mmol) in 3 ml of water was added dropwise during 2 hr, and the mixture was stirred for a further 4 hr. Saturated brine (100 ml) was added, and the solution was extracted with ether twice. The ethereal extract was washed with brine and dried over anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 132° (0.6 mm) afforded 0.39 g (78%) of **2**: ir (film) 1725, 1670, 1620, 1244, 1184, 1164, 1095, 1022 cm^{-1}; nmr ($CDCl_3$) δ 4.20 (2 H, q, J = 7.2 Hz), 2.70–1.75 (8 H, m), 2.15 (3 H, s), 1.80 (3 H, s), 1.44 (3 H, s), 1.26 (3 H, t, J = 7.2 Hz); mass spectrum m/e 266 (M^+).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.47; H, 8.26.

Registry No.—**2**, 51716-30-4; **3**, 487-51-4; **4**, 39880-26-7; **5**, 28790-87-6; **6**, 25533-27-1; **7**, 51716-31-5; **8**, 51716-32-6; **9**, 51716-33-7; **10**, 32917-26-3; **11**, 51716-34-8; **12**, 51716-35-9; **13**, 51716-36-0; **14**, 51716-37-1; **15**, 51716-38-2; **16**, 51716-39-3; **17**, 51716-40-6; **18**, 51716-41-7; **19**, 51752-02-4; **20**, 51716-42-8; **21**, 51716-43-9; **22**, 51716-44-0; **23**, 51716-45-1; **25**, 51716-46-2; **26**, 51716-47-3; **27**, 51716-48-4; **29**, 51716-49-5; **30**, 51716-50-8; methallyl bromide, 1458-98-6; methallyl chloride, 563-47-3.

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Reaction of Phenyl(trihalomethyl)mercury Compounds with Azodicarboxylate Esters. A New Route to Hydrazonodihalomethanes of Type $(RO_2C)_2NN{=}CX_2$[1,2]

Dietmar Seyferth* and Houng-min Shih

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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The reaction of phenyl(trihalomethyl)mercury compounds with azodicarboxylate esters in benzene at 80° gives hydrazonodihalomethanes of type $(RO_2C)_2NN{=}CX_2$ (X = Cl and/or Br). Sodium trichloroacetate reacts similarly, giving the same type of product (X = Cl). A study of this reaction (R = Me) as carried out at room temperature provided evidence for an intermediate in these reactions to which structure **10** was tentatively assigned on the basis of spectroscopic (^1H, ^{13}C, ir) evidence. In the case of the $PhHgCBr_3$-$MeO_2CN{=}NCO_2Me$ reaction the intermediate was isolated as a pure substance and a kinetic study of its thermal decomposition showed a first-order process to be operative with the following activation parameters: $\Delta H^* = -19.75$ kcal/mol; $\Delta S^* = -17.16$ eu.

In previous papers of this series we have reported concerning reactions of phenyl(trihalomethyl)mercury compounds in which CX_2 was added to C=N,[3] C=S,[4] and C=O[5] bonds. However, attempted addition of $PhHgCCl_2Br$-derived CCl_2 to the N=N bond of azoarenes was not successful, the only reaction observed being a fragmentation process (eq 1).[3] In spite of this observation

$$ArN{=}NAr + PhHgCCl_2Br \longrightarrow ArN{=}CCl_2 + [ArN] + PhHgBr \quad (1)$$

we extended our studies to include azodicarboxylate esters. In this work we have found the course of the $PhHgCX_3$-$RO_2CN{=}NCO_2R$ reactions to be completely different from that of the $PhHgCX_3$-$ArN{=}NAr$ reactions, and the chemistry which was uncovered has potential for synthetic applications.

Results and Discussion

The $RO_2CN{=}NCO_2R$-$PhHgCX_3$ Reaction. The Final Product. The reaction of phenyl(bromodichloromethyl)-mercury with diethyl azodicarboxylate proceeded as shown in eq 2. Analysis of the product, a distillable liquid, indicated the composition shown in eq 2. In its mass spectrum (70 eV) $[M - Cl]^+$ was the largest fragment observed. The ir spectrum showed, in addition to the ester carbonyl bands at 1805 (sh) and 1770 cm^{-1} (s), a medium band at 1590 cm^{-1}. The product absorbed in the uv region: λ_{max} (cyclohexane) 248 nm (ϵ 1655). A single ethoxy group resonance was observed in its proton nmr spectrum and its ^{13}C nmr spectrum confirmed the presence of apparently equivalent OEt groups. In addition, signals due to carbon atoms assignable to a C=O and a C=N moiety were observed.

$$EtO_2C{-}N{=}N{-}CO_2Et + PhHgCCl_2Br \xrightarrow[\text{reflux 3 hr}]{\text{benzene}} PhHgBr + C_7H_{10}Cl_2N_2O_4 \quad (2)$$
(98%) (87%)

Five structures (**1-5**) were given further consideration. Since the product obtained is very soluble in nonpolar solvents and is quite volatile at moderate temperature, the ionic structure **2** is excluded. If **1** and **2** were in equilibrium and the 1590-cm^{-1} band were due to the C=N vibration of **2**, then the solvent polarity should have a marked effect on the equilibrium and a solvent-dependent ir spectrum in the C=N region would be expected. In actual fact, there was no significant change in intensity of the ir band at 1590 cm^{-1} (C=N vibration) even when the spectrum was taken in a very polar medium such as acetonitrile. Further evidence against a mixture of **1** and **2** is that both the ^1H and ^{13}C nmr spectra showed only resonances which account for one structure rather than a mixture. The ir and uv spectral features of the product are not compatible with the diazirine structure of **1**.[6]

1 **2**

3 **4**

5

Structures **3** and **4** could be ruled out on the basis of the proton nmr spectrum of the product, which showed only a single resonance due to equivalent CO_2Et groups. In order to establish that it was a matter of equivalent CO_2Et groups, not of accidentally coincidental chemical shifts of nonequivalent ethoxy groups, two model compounds, **6** and **7**, were synthesized by the procedures of Fahr, *et al.*[7] Compound **6** displayed *three* different sets of OEt resonances in its nmr spectrum, while compound **7** showed only *two*, and thus it is likely we are dealing with equivalent CO_2Et groups in our product.[8]

6 **7**

Table I
Reactions of $PhHgCX_3$ with $RO_2CN{=}NCO_2R$ in Benzene at Reflux

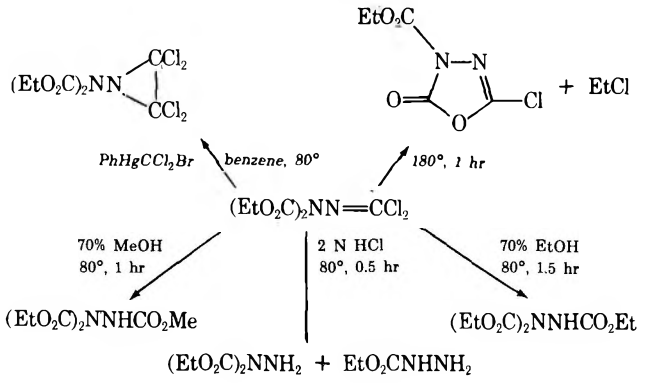
$RO_2CN{=}NCO_2R$ (registry no.)	Product (yield, %)[a] (registry no.)	Mp or bp, °C (mm)
	$PhHgCCl_2Br$ (3294-58-4)	
$MeO_2CN{=}NCO_2Me$ (2446-84-6)	$(MeO_2C)_2NN{=}CCl_2$ (61) (51381-23-8)	57–58
$EtO_2CN{=}NCO_2Et$ (1972-28-7)	$(EtO_2C)_2NN{=}CCl_2$ (87) (36133-63-8)	88 (0.24)
$Me_3CO_2CN{=}NCO_2CMe_3$ (870-50-8)	$(Me_3CO_2C)_2NN{=}CCl_2$ (38) (51381-24-9)	42–45
$PhCH_2O_2CN{=}NCO_2CH_2Ph$ (2449-05-0)	$(PhCH_2O_2C)_2NN{=}CCl_2$ (53) (51381-25-0)	*c*
$PhO_2CN{=}NCO_2Ph$ (2449-14-1)	$(PhO_2C)_2NN{=}CCl_3$ (34) (51381-26-1)	100–103[b]
	$PhHgCBr_3$ (3294-60-8)	
$MeO_2CN{=}NCO_2Me$	$(MeO_2C)_2NN{=}CBr_2$ (47) (51381-27-2)	82–84
$EtO_2CN{=}NCO_2Et$	$(EtO_2C)_2NN{=}CBr_2$ (59) (51381-28-3)	85–90 (0.02)[b]
$Me_3CO_2CN{=}NCO_2CMe_3$	$(Me_3CO_2C)_2NN{=}CBr_2$ (30) (51381-29-4)	108–109
$PhCH_2O_2CN{=}NCO_2CH_2Ph$	$(PhCH_2O_2C)_2NN{=}CBr_2$ (65) (51381-30-7)	*c*
$PhO_2CN{=}NCO_2Ph$	$(PhO_2C)_2NN{=}CBr_2$ (41) (51381-31-8)	138–140
	$PhHgCBr_2Cl$ (3294-59-5)	
$EtO_2CN{=}NCO_2Et$	$(EtO_2C)_2NN{=}CBrCl$ (55) (51381-32-9)	78–83 (0.02)[b]
$Me_3CO_2CN{=}NCO_2CMe_3$	$(Me_3CO_2C)_2NN{=}CBrCl$ (15) (51381-33-0)	77–79

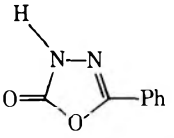
[a] Isolated yield. [b] Analytically pure sample was not obtained. [c] Vacuum distillation failed; crude oil product failed to crystallize.

Further evidence supports a phosgene hydrazone structure **5** as the structure of the isolated product of the $PhHgCCl_2Br$–$EtO_2CN{=}NCO_2Et$ reaction. The ir absorption of the C=N vibration for compounds of the type $RN{=}CCl_2$ normally appears at 1645–1660 cm^{-1} when R is an alkyl or aryl group,[9] but is seen at 1560–1610 cm^{-1} when R is a rather electronegative group, such as Cl, CH_3SO_2, $Cl_2C{=}N$, $N(CF_3)_2$, and $N(SiMe_3)_2$.[10] Our observation of $\nu_{C=N}$ at 1590 cm^{-1} falls within this latter range. The uv absorption of the product is also comparable to that of a carbonimidoyl dichloride. For instance, $Me_2CHN{=}CCl_2$[3] shows an uv absorption at λ_{max} (cyclohexane) 253 nm (ϵ 1040).

A brief chemical study of the product of the $PhHgCCl_2Br$–$EtO_2CN{=}NCO_2Et$ reaction summarized in Scheme I also supports structure **5** for the reaction product. Addition of CCl_2 to a C=N bond of $RN{=}CCl_2$ to give a tetrachloroaziridine is a known reaction.[3] The pyrolysis of **5** to give a 5-halo-1,3,4-oxadiazolin-2-one can be rationalized in terms of the known chemistry of the hydrazonoyl halides.[11] For instance, the thermolytic conversion of $EtO_2CNHN{=}C(Cl)Ph$ to **8** has been described.[12]

Scheme I





8

The solvolysis reaction of a carbonimidoyl dichloride ($PhN{=}CCl_2$) with ethanol to give a N-substituted urethane ($PhNHCO_2Et$) was reported by Sell and Zierold.[13] In our case, the N substituent was a $N(CO_2Et)_2$ group, therefore a hydrazine derivative was obtained. Methanolysis and acid hydrolysis support that the CO_2Et groups in the compound in question are geminal rather than vicinal.

This study was extended to reactions of other phenyl(trihalomethyl)mercurials and other azodicarboxylate esters as well. The results are summarized in Table I. While the syntheses of a number of carbonyl halide hydrazones have been described,[10c,d,14-16] no carbonyl halide dicarboalkoxy or dicarbophenoxy hydrazones have been reported prior to our description of these phosgene dicarboalkoxy hydrazones prepared *via* the reactions of $PhHgCX_3$ compounds with azodicarboxylate esters.

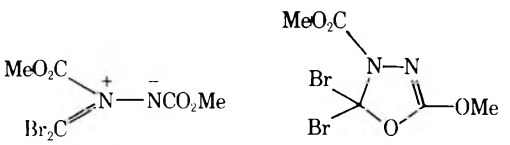
The carbonyl halide dicarboalkoxy and dicarbophenoxy hydrazones are either colorless oils or solids. The compounds are characterized by their infrared absorption bands at 1770–1780 (very strong) and 1800–1825 cm^{-1} (shoulder) due to the $N(CO_2R)_2$ groups, 1570–1590 cm^{-1} (medium band) due to the C=N stretching vibration, and 960 ($=CCl_2$), 878–890 ($=CBr_2$), and 924–925 cm^{-1} ($=CBrCl$) (strong bands). Their ^1H and ^{13}C nmr spectra

showed only one CO_2R signal. The ^{13}C nmr chemical shifts of the $=CCl_2$ carbon were observed at −17.5 (R = Me) and −18.6 ppm (R = Et) (*vs.* benzene).

The carbonyl halide hydrazones appeared to be rather stable to air, but the thermal stability of these hydrazones varied widely. For instance, $(MeO_2C)_2NN{=}CBr_2$, $(EtO_2C)_2NN{=}CBr_2$, and $(EtO_2C)_2NN{=}CBrCl$ have only marginal stability at room temperature, but $(PhO_2C)_2NN{=}CCl_2$ and $(PhO_2C)_2NN{=}CBr_2$ are stable at 160° for several hours. Generally speaking, phosgene hydrazones are more stable than either the carbonyl bromide or chloroformyl bromide hydrazones.

The Reaction Course. Detection and Isolation of an Intermediate. The carbonyl halide hydrazones isolated from reactions of $PhHgCX_3$ and azodicarboxylate esters cannot be the products formed initially, and to obtain further information concerning the reaction course, we followed the progress of the slow reaction at room temperature[17] of $PhHgCCl_2Br$ with dimethyl azodicarboxylate by means of ^1H and ir spectroscopy in carbon tetrachloride solution. Initially, a single methyl resonance at 4.0 ppm due to the starting ester was observed. After 1 day, two new singlets at 3.95 and 3.83 ppm were seen as well. These continued to increase in area, but another singlet at 3.80 ppm, which was due to the presence of $(MeO_2C)_2NN{=}CCl_2$, appeared and grew at the expense of the 3.95 and 3.83 ppm singlets.[18] Clearly, an intermediate with nonequivalent OCH_3 groups was formed initially and rearranged at room temperature to the final product. In an experiment where ir spectroscopy was applied, it was seen that the formation of the intermediate in the $MeO_2CN{=}NCO_2Me$–$PhHgCCl_2Br$ reaction correlated with the growth of a band at 1640 cm^{-1}.

Successful isolation of one such intermediate was realized in the reaction of $PhHgCBr_3$ and dimethyl azodicarboxylate at room temperature. After 6 days, about 50% of the starting azo compound had been consumed and the products formed contained the intermediate and the final product, $(MeO_2C)_2NN{=}CBr_2$, in about 2:1 ratio (by the nmr). The starting azo compound and the final product, as well as unreacted mercurial compound, could be removed from the reaction mixture by washing with 5% aqueous sodium sulfide solution, a treatment which the reaction intermediate survived. The crude intermediate was recrystallized from pentane, giving large crystals, mp 55–56.5°, which appeared to be air stable and could be stored in the refrigerator for weeks. Analysis indicated the composition $C_5H_6N_2Br_2O_4$. The product showed absorption in the ultraviolet region, λ_{max} (pentane) 224 nm (ϵ 1390). Its ^1H nmr spectrum indicated the presence of two nonequivalent OMe groups separated by 6.8 Hz. Both structure **9** and **10** are compatible with these spectral



9

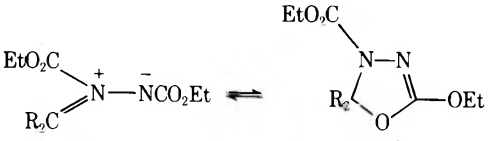
10

$(MeO_2C)_2NN{=}CBr_2$

11

data. However, the CBr_2 of **9** (sp^2 carbon) and **10** (sp^3 carbon) might be expected to show very different chemical shifts in their ^{13}C nmr spectra, so distinction between the two structures might be possible if a model compound were available for comparison. Compound **11**, the final reaction product, having a CBr_2 group very similar to that of **9**, would be a reasonable model for this purpose. Both CBr_2 groups of **9** and **11** have sp^2-hybridized carbons, but an additional deshielding effect on the carbon nucleus due to the adjacent positive charge in **9** is expected. Thus the ^{13}C chemical shift of the CBr_2 group of **9** would be expected to appear further downfield than that of **11**. On the other hand, the CBr_2 carbon of **10** which is sp^3 hybridized, is expected to show a resonance at substantially higher field than an sp^2 carbon CBr_2, as in **11**. In actual fact, compound **11** showed its CBr_2 resonance at 9.15 ppm, while the CBr_2 resonance of the intermediate occurred at 31.93 ppm (*vs.* benzene), 22.78 ppm upfield from that of **11**. Therefore, on the basis of the ^{13}C nmr results, the reaction intermediate would appear to have the 1,3,4-oxadiazoline structure **10**. This structural question, however, cannot be considered as definitely settled at this time.

Related ring–chain isomerization in solution, azomethinimine (**12a**) ⇌ oxadiazoline (**12b**), has been described,[19]



12a **12b**

but no decisive infrared assignments were reported. Nevertheless, it seems that the azomethinimine structure of **12a** showed two distinguishable C=O stretching vibrations at 1783 and 1745 cm^{-1} and a C=N vibration at 1645 cm^{-1}. On the other hand, the same compound in the solid state, where **12b** is believed to be the sole consituent, showed one C=O vibration at 1715, cm^{-1} and a C=N vibration at 1672 cm^{-1} in its ir spectrum (KBr pellet). A similar system was studied by Bettinetti and Capretti[20] with comparable results.

The infrared spectrum of our reaction intermediate, either in solution or as a Nujol mull, showed only one C=O band at 1790 cm^{-1} and a C=N vibration at 1640 cm^{-1}, in agreement with the proposed oxadiazoline structure **10**. Although the intermediates in reactions of other azodicarboxylates with the various $PhHgCX_3$ were not isolated, spectroscopic studies of these reactions at room temperature indicated that similar 1,3,4-oxidiazoline intermediates were formed in all these reactions.

Kinetic Study of Thermal Rearrangement of the Intermediate. Thermal rearrangement of the 1,3,4-oxidiazoline intermediate to the final carbonyl halide hydrazone proceeded quantitatively on moderate heating in CCl_4 solution. In the case of the assumed 2-methoxy-4-carbomethoxy-5,5-dibromo-Δ^2-1,3,4-oxadiazoline **(10)**, kinetic measurements of the reaction rate by means of ^1H nmr spectroscopy at various temperatures (73–99°) showed that the rearrangement was a first-order reaction. Plots of log (area)/(area)$_0$ *vs.* time allowed first-order rate constants (k) to be calculated from the slopes of the straight lines and the results are summarized in Table II. The following activation parameters were determined: $\Delta H^* = 19.75$ kcal/mol; $\Delta S^* = -17.16$ eu.

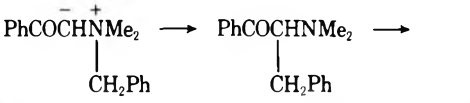
The rearrangement of **10** to **11** involves the migration of a carbomethoxy group from one nitrogen atom to another, and several mechanisms are possible for this kind of migration.[21]

The relatively large negative entropy of activation found in this reaction is of interest. The Stevens-type 1,2 shift involving cleavage–recombination *via* ionic or radical pair mechanisms does not seem likely to be involved in this rearrangement, since the activation parameters observed in a typical Stevens rearrangement (eq 3) ($\Delta H^* = 31.4$ kcal/mol and $\Delta S^* = -2.5$ eu) are quite different from those of our reaction.[22] However, our activation parame-

Table II
First-Order Reaction Rates of Thermal Rearrangement of 10 to 11 and Correlation of Log (Area) with t

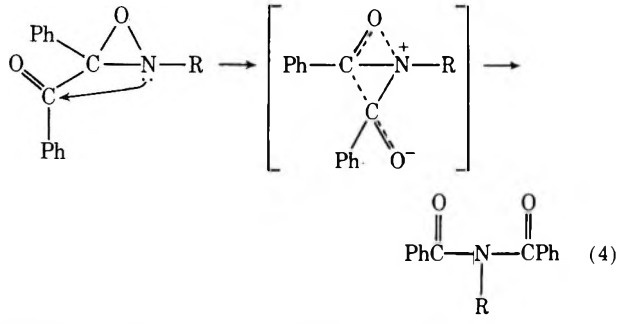
Temp, °C	k, sec^{-1}	S_E[a]
73.0	3.60×10^{-4}	0.0016
79.5	5.34×10^{-4}	0.0060
87.0	1.13×10^{-3}	0.0021
91.5	1.71×10^{-3}	0.0049
99.0	2.85×10^{-3}	0.0011

[a] Standard error of estimation, $S_E = [\Sigma d^2/(n-1)]^{1/2}$ (where d = standard deviation). For details see C. L. Perrin, "Mathematics for Chemists," Wiley-Interscience, New York, N. Y., 1970, p 161, and E. L. Bauer, "A Statistical Manual for Chemists," 2nd ed, Academic Press, New York, N. Y., 1971.



(3)

ters can be compared with those of the intramolecular rearrangement of an oxaziridine to a dibenzoylamine (eq

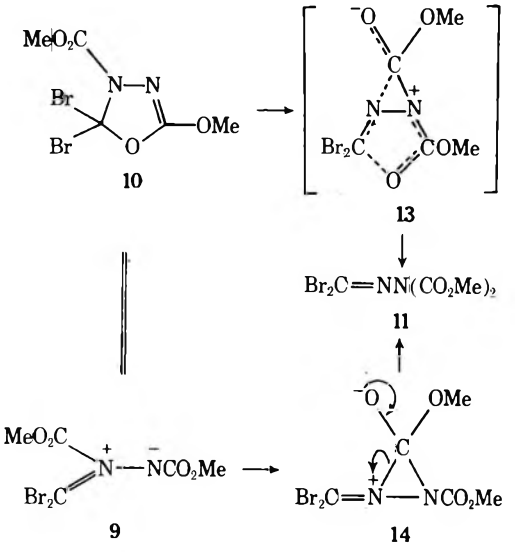


(4)

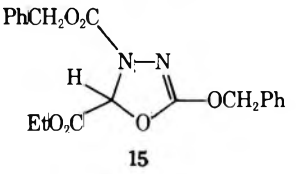
4) involving migration of a benzoyl group *via* a transition state as shown, where ΔH^* and ΔS^* were found to be 21.7 kcal/mol and −22.0 eu, respectively.[23]

Although the exact mechanism of this rearrangement (10 to 11) cannot be assessed at this time, the observed large negative entropy of activation can be reasonably accommodated by a cyclic transition state such as 13 or 14 in an intramolecular reaction as shown in Scheme II. At-

Scheme II



tempts to trap the possible azomethinimine 9 with 1,3-dipolarophiles such as dimethyl acetylenedicarboxylate or phenyl isocyanate failed, but on the basis of these two experiments alone, 9 still cannot be excluded. The facile rearrangement of 10 to 11 finds precedent in the thermal isomerization of 15 to $(PhCH_2O_2C)_2NN{=}CHCO_2Et$.[7]



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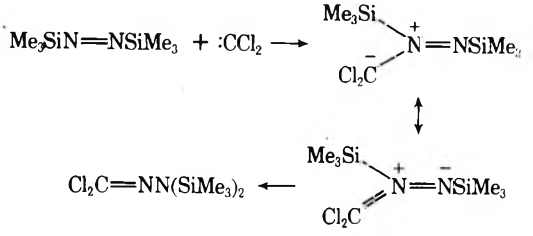
Reaction Mechanism. The reactive species which interacts with the azodicarboxylate esters in the case of $PhHgCCl_2Br$ could be either the mercurial itself or CCl_2 formed by decomposition of this mercurial. That it is the latter seems likely, since decarboxylation of CCl_3CO_2Na in the presence of $EtO_2CN{=}NCO_2Et$ in refluxing 1,2-dimethoxyethane also gives $(EtO_2C)_2NN{=}CCl_2$ in 69% yield. In terms of the final products obtained, there is a striking similarity between the reactions of azodicarboxylate esters with dihalocarbenes and with diazoalkanes.[19,24,25] However, very different reaction pathways are involved. In the case of the latter reagents, direct attack of the diazoalkanes as *carbon nucleophiles* at an azo ester nitrogen atom (rather than a carbene mechanism) was established by Fahr, *et al.*[7,26] A kinetic study showed that in the presence of azodicarboxylate esters, the diazoalkanes decomposed readily with evolution of nitrogen at 80°, but in the absence of the azodicarboxylate esters, no apparent decomposition of diazoalkanes occurred under the same reaction conditions.[26] Similar rate enhancement of the decomposition of dicyanodiazomethane in the presence of azodicarboxylate esters was noted by Ciganek.[25]

In the case of dihalocarbene reactions, we presumably are dealing with an initial *electrophilic* attack of the carbene at nitrogen to form a highly reactive nitrogen ylide intermediate which then undergoes further reaction. Formation of the 1,3,4-oxadiazoline intermediate in these reactions most likely involves the cyclization shown in Scheme III.

(Although none of our evidence speaks in favor of the formation of a diaziridine as a stable intermediate, it cannot be excluded as a transitory intermediate.)

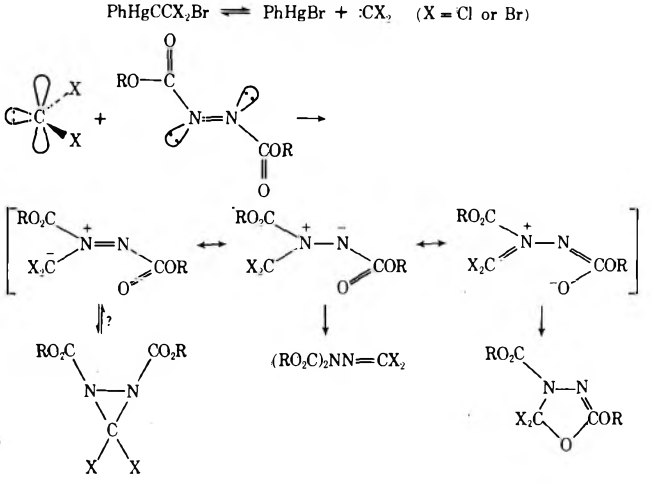
The mechanism shown in Scheme III finds support in the reaction of CCl_2 with $Me_3SiN{=}NSiMe_3$,[10d] where a phosgene hydrazone product was obtained. The product apparently is derived from the rearrangement of an ylide intermediate, as in the scheme shown below.



Experimental Section

General Comments. All reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen. Solvents were carefully dried. Infrared spectra were recorded using a Perkin-Elmer Model 457A, 257, or 337B grating infrared spectrophotometer, ultraviolet spectra using a Cary-14 spectrophotometer, and proton nuclear magnetic resonance spectra using a Varian Associates T-60 or a Hitachi Perkin-Elmer R-20B high-resolution nmr spectrometer. Chemical shifts are expressed in δ units, in parts per million downfield from tetramethylsilane. Carbon-13 nuclear magnetic resonance spectra were recorded using a Bruker HFX-90 nmr spectrometer interfaced with Digilab NMR/FTS-3 Fourier transform data system. The carbon-13 chemical shifts are expressed in parts per million with respect to internal benzene.

Scheme III



Mass spectra were recorded using a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Gas-liquid partition chromatographs (glc) used were F & M Model 5750, 700, or 720 and MIT isothermal units. Thin layer chromatography (tlc) was used to examine high-boiling reaction mixtures; Eastman silica gel tlc sheets, type 6061, were used. The pretreated neutral alumina (activity III) (a product of M. Woelm, Germany) and Nylon tubing for dry-column chromatography[27] were obtained from Waters Associates Inc.

Phenyl(trihalomethyl)mercury compounds were prepared by our THF method.[28] Dimethyl azodicarboxylate was prepared by the oxidation of dimethyl *sym*-hydrazinedicarboxylate (Aldrich) with concentrated nitric acid.[29] Dibenzoyl azodicarboxylate was obtained from Lucidol Division, Pennwalt Corp., as a gift. Other azodicarboxylate esters were purchased from Aldrich Chemical Co.

Reaction of Diethyl Azodicarboxylate with Phenyl(bromodichloromethyl)mercury. A 50-ml three-necked flask equipped with a reflux condenser topped with a nitrogen inlet tube, a thermometer, and a magnetic stirbar (the "standard apparatus") was charged with diethyl azodicarboxylate (5.00 g, 26.0 mmol, obtained from Aldrich), $PhHgCCl_2Br$ (8.80 g, 20.0 mmol), and 30 ml of dry benzene. The reaction mixture was stirred and heated at reflux under nitrogen for 3 hr. The orange color of the solution gradually was discharged and PhHgBr precipitated. The reaction mixture was cooled to room temperature and filtered from 6.90 g (98%) of PhHgBr, mp 270–273° (lit.[30] mp 276°). Glc (4 ft × 0.25 in., 10% UC W-98, 110°) showed that a single product was present in 87% yield. The product, bp 88° (0.24 mm), $n^{25}D$ 1.4730, was isolated by vacuum distillation in 70% (3.60 g) yield: ir (neat) 2990 m, 2960 w, 2930 w, 1805 m, 1770 s, 1590 m, 1489 w, 1475 w, 1402 w, 1400 w, 1378 m, 1250 s, 1180 w, 1100 s, 1002 w, 970 m, 865 w, 760 cm^{-1} m; ^1H nmr (CCl_4) δ 1.38 (t, 6, J = 7.0 Hz, OCH_2CH_3) and 4.40 ppm (q, 4, J = 7.0 Hz, OCH_2CH_3); ^{13}C nmr ($CHCl_3$) δ −22.2 (C=O), −18.6 (C=N), 63.1 (OCH_2CH_3), and 113.0 ppm (OCH_2CH_3) *vs.* benzene; mass spectrum (70 eV) *m/e* (rel intensity) 221 (6), 184 (4), 148 (40), 138(19), 121 (77), 112 (35), 82 (27), 45 (38), and 29 (100). The molecular ion was not detected.

Anal. Calcd for $C_7H_{10}Cl_2N_2O_4$: C, 32.70; H, 3.90; N, 27.58; Cl, 10.90. Found: C, 32.47; H, 3.98; N, 27.48; Cl, 10.99.

A. Ethanolysis of the Product. A 0.50-g sample (1.95 mmol) was treated with 3.0 ml of 70% aqueous ethanol at 80° for 1.5 hr. The resulting reaction mixture was concentrated to *ca.* 1.0 ml and then was extracted with ether. The organic layer was separated, dried, and distilled. The colorless oil isolated by distillation (0.39 g, 80% yield) was identified as the 1,1,2-tricarboethoxyhydrazine $(EtO_2C)_2NNHCO_2Et$: bp 113° (0.10 mm); $n^{25}D$ 1.4490; ir (neat) 3340 m, 3000 m, 2960 w, 2930 w, 1800 m, 1750 s, 1520 w, 1480 w, 1378 m, 1270 s, 1181 w, 1110 s, 1070 m, 1020 w, 880 w, 785 cm^{-1} m; nmr ($CDCl_3$) δ 1.28 (t, 3, J = 7.0 Hz, $NHCO_2CH_2CH_3$), 1.32 [t, 6, J = 7.0 Hz, $N(CO_2CH_2CH_3)_2$], 4.42 (m, 6, CH_2), and 7.58 ppm (s, 1, NH).

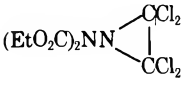
Anal. Calcd for $C_9H_{16}N_2O_6$: C, 43.54; H, 6.50; N, 11.29. Found: C, 43.46; H, 6.50; N, 11.66.

B. Methanolysis of the Product. To a 0.50-g sample (1.95 mmol) was added 3.0 ml of 70% aqueous methanol and the mixture was heated at 80° for 1 hr. The reaction mixture was worked up as described above. The product, a colorless oil, isolated by distillation and further purified by glc (6 ft × 0.25 in., 20% DC-200, 150°), was identified as 1-carbomethoxy-2,2-dicarboethoxyhydrazine, $MeO_2CNHN(CO_2Et)_2$: bp 89° (0.07 mm); $n^{25}D$ 1.4518; ir (neat) 3330 m, 3000 m, 1810 m, 1760 s, 1520 m, 1460 w, 1375 w, 1270 s, 1180 w, 1110 m, 1070 w, 1020 w, 920 w, 870 w, 775 cm^{-1} m; nmr (CCl_4) δ 1.30 (t, 6, J = 7.2 Hz, OCH_2CH_3), 3.75 (s, 3, OCH_3), 4.28 (q, 4, J = 7.2 Hz, OCH_2CH_3) and 7.81 ppm (broad, 1, NH).

Anal. Calcd for $C_8H_{14}N_2O_6$: C, 41.02; H, 6.02; N, 11.96. Found: C, 41.05; H, 6.16; N, 12.29.

C. Acid Hydrolysis of the Product. The sample (0.50 g, 1.95 mmol) was treated with 3.0 ml of 2 *N* HCl at 80° for 30 min. The solution was neutralized with aqueous sodium hydroxide and then was extracted with ether. The organic layer was separated, dried over sodium sulfate, and concentrated to *ca.* 1.0 ml. The products isolated by glc (4 ft × 0.25 in., 10% UC W-98, 130°) were ethyl hydrazinecarboxylate, EtO_2CNHNH_2, mp 46–47° (lit.[31] mp 45°), ir (CCl_4) 3460 and 1630 (NH_2), 3360 cm^{-1} (NH), nmr (CCl_4) δ 1.20 (t, 3, J = 7.0 Hz, OCH_2CH_3), 4.02 (q, 2, J = 7.0 Hz, OCH_2CH_3), 4.10 (broad, 2, NH_2), and 6.80 ppm (broad, 1, NH); diethyl 1,1-hydrazinedicarboxylate, $(EtO_2C)_2NNH_2$, mp 27–29° (lit.[31] mp 29°), ir (CCl_4) 3360 and 1630 cm^{-1} (NH_2), nmr (CCl_4) δ 1.22 (t, 6, J = 7.1 Hz, OCH_2CH_3), 4.11 (q, 4, J = 7.1 Hz, OCH_2CH_3), and 4.45 ppm (s, 2, NH_2); and a small amount of diethyl 1,2-hydrazinedicarboxylate, $EtO_2NHNHCO_2Et$, mp 135° (lit.[31] mp 135°), ir ($CHCl_3$) 3300 cm^{-1} (broad, NH), nmr ($CDCl_3$) δ 6.88 ppm (broad, 2, NH). The last compound was found to be a secondary product derived from the rearrangement of diethyl 1,1-hydrazinedicarboxylate on the glc column during the isolation of the products.

D. Reaction of the Product with $PhHgCCl_2Br$. The product (2.57 g, 10.0 mmol) and $PhHgCCl_2Br$ (4.40 g, 10.0 mmol) in 10.0 ml of benzene were stirred and heated at reflux under nitrogen for 3 hr. The reaction mixture was filtered from 3.50 g of PhHgBr (98%, mp 257–277°). After removal of the solvent using a rotary evaporator, the residue, which contained both an oil and a solid product, was filtered to collect the latter. The crude solid was purified by pentane extraction using a Soxhlet extractor. The colorless crystals were obtained in 25% yield (0.26 g) when the pentane extracts were cooled to room temperature. The product, mp 119–120°, was identified as a tetrachloroaziridine (i): ir ($CHCl_3$) 2980



i

w, 1800 m, 1765 s, 1460 w, 1395 w, 1370 m, 1245 s, 1100 s, 1002 w, 950 m, 880 s, and 660 cm^{-1} w; nmr ($CDCl_3$) δ 1.45 (t, 6, J = 7.2 Hz, OCH_2CH_3) and 4.39 ppm (q, 4, J = 7.2 Hz, OCH_2CH_3).

Anal. Calcd for $C_8H_{10}Cl_4N_2O_4$: C, 28.26; H, 2.97; N, 8.24; Cl, 41.71. Found: C, 28.14; H, 2.93; N, 8.09; Cl, 41.33.

The oily product from the reaction was found to be thermally unstable. Attempted vacuum distillation at 0.02 mm (80°) gave impure products.

Reactions of Phenyl(bromodichloromethyl)mercury with Other Azodicarboxylate Esters. All these reactions were carried out as described for the $PhHgCCl_2Br$ + $EtO_2CN{=}NCO_2Et$ reaction. Approximately equimolar quantities of the reactants in benzene solution (*ca.* 20 ml for 10 mmol of mercury reagent) were stirred and heated at reflux, under nitrogen, for 3 hr. After filtration of the phenylmercuric bromide formed (usually 95–98% yield), the filtrate was concentrated at reduced pressure to remove solvent. Further work-up is described for each individual case. In most cases, the reactions were carried out on a 10-mmol scale.

A. Dimethyl Azodicarboxylate. The residue was fractionally distilled to give 6.28 g (61%) of $(MeO_2C)_2NN{=}CCl_2$. The sample for analysis was further purified by glc (4 ft × 0.25 in., 10% UC W-98, 130°): bp 69–70° (0.04 mm); mp 57–58°; ir (CCl_4) 3000 w, 2950 m, 2890 w, 1802 m, 1760 s, 1579 m, 1432 s, 1340 w, 1260 s, 1190 w, 1115 s, 970 s, 940 w, 650 w, 630 cm^{-1} w; ^1H nmr (CCl_4) δ 3.81 ppm (s); ^{13}C nmr ($CHCl_3$) δ −21.0 (C=O), −17.5 (N=CCl_2) and 74.1 (OCH_3) *vs.* benzene.

Anal. Calcd for $C_5H_6Cl_2N_2O_4$: C, 26.22; H, 2.64; N, 12.23; Cl, 30.96. Found: C, 26.40; H, 2.76; N, 12.28; Cl, 30.88.

B. Di-*tert*-butyl Azodicarboxylate. The oily residue was crystallized from ether at −78° (0.85 g, 38% yield, mp 42–45°). Attempted recrystallization from acetone or ether at −78° failed to

Table III
Nmr and Ir Spectra of the Initial Product from the Reaction of $PhHgCCl_2Br$ with $RO_2CN{=}NCO_2R$ at Room Temperature

R	Me	Et	*t*-Bu	CH_2Ph	Ph
$\nu_{C=N}$, cm^{-1}	1640	1640	1624	1638	1655
Nmr, ppm	3.82 (s)	1.22 (t)	1.42 (s)	5.19 (s)	
	3.93 (s)	1.28 (t)	1.51 (s)	5.31 (s)	7.32 (m)
		4.36 (q)[a]		7.36 (m)	

[a] Two resonances coincide.

give an analytically pure sample. However, the compound showed nmr and ir spectra consistent with the structure $(t\text{-}BuO_2C)_2NN{=}CCl_2$: nmr ($CCl_4$) δ 1.52 ppm (s); ir (CCl_4) 1800 w, 1760 s (CO_2CMe_3), 1570 m (C=N), and 960 cm^{-1} (CCl_2).

C. Diphenyl Azodicarboxylate. The crude product remaining after removal of solvent was twice recrystallized from methylene chloride at −78° to give white, solid product (1.20 g, 34% yield, mp 100–103°), $(PhO_2C)_2NN{=}CCl_2$: nmr (CCl_4) δ 7.20 ppm (m); ir (CCl_4) 1820 m, 1780 s (CO_2Ph), 1580 m (C=N), and 970 cm^{-1} m (CCl_2). An analytically pure sample was not obtained. The best analysis found follows.

Anal. Calcd for $C_{15}H_{10}N_2Cl_2O_4$: C, 51.01; H, 2.85; N, 7.93; Cl, 20.08. Found: C, 50.04; H, 3.03; N, 7.76; Cl, 19.25.

D. Dibenzyl Azodicarboxylate. The oily residue failed to crystallize from acetone or ether at −78°. However, the crude oil product (1.69 g, 53% yield) showed characteristic ir and nmr spectra indicative of the structure $(PhCH_2O_2C)_2NN{=}CCl_2$: nmr (CCl_4) δ 5.20 (s, 4, CH_2) and 7.20 ppm (m, 10, Ph); ir (CCl_4) 1800 w and 1760 s (CO_2CH_2Ph), 1580 m (C=N), and 960 cm^{-1} s (CCl_2).

Reactions of Phenyl(tribromomethyl)mercury with Azodicarboxylate Esters. Essentially the same procedure was used as is described in the $PhHgCCl_2Br$ experiments.

A. Dimethyl Azodicarboxylate (50-mmol scale). The oily residue was redissolved in CCl_4 and the solution then was washed quickly with 10 ml of cool, 5% aqueous sodium sulfide solution to remove most of the unconverted starting azo compound and the mercurial residue. The yellow precipitate formed during the washing was separated by centrifugation. The organic layer was dried and evaporated to dryness. The residue (8.30 g, mp 70–75°) was crystallized from acetone at −78° to give 7.40 g (47%) of white solid product, $(MeO_2C)_2NN{=}CBr_2$, mp 82–84°, which was found to be of only marginal stability at room temperature over prolonged times. A satisfactory combustion analysis could not be obtained: ir (CCl_4) 3000 w, 2985 w, 2840 w, 1805 m, 1770 s, 1565 m, 1432 s, 1330 w, 1260 s, 1190 w, 1105 s, 878 cm^{-1} s; ^1H nmr ($CDCl_3$) δ 3.82 ppm (s); ^{13}C nmr (CCl_4) δ −20.9 (C=O), 9.15 (CBr_2), and 77.8 ppm (CH_3) *vs.* benzene.

B. Diethyl Azodicarboxylate. Attempted isolation of the product by vacuum distillation at 0.02 mm (85–90°) or its glc isolation at 160° (4 ft × 0.25 in., 10% UC W-98) failed. The crude product also failed to crystallize from acetone or ether at −78°. However, the oily crude product (2.04 g, 59%) showed spectroscopic properties of the expected $(EtO_2C)_2NN{=}CBr_2$: nmr (CCl_4) δ 1.37 (t, 6, J = 7.0 Hz, CH_3) and 4.26 ppm (q, 4, J = 7.0 Hz, CH_2); ir (CCl_4) 1818 m, 1775 s (CO_2Et), 1582 m (C=N), and 885 cm^{-1} (CBr_2).

C. Di-*tert*-butyl Azodicarboxylate. The oily residue was redissolved in ether and the solution was filtered. Crystallization at −78° gave white solid product (2.20 g, 37% yield, mp 100–104°) which was further recrystallized from ether at room temperature to give 1.80 g (30%) of colorless crystals of $(t\text{-}BuO_2C)_2NN{=}CBr_2$: mp 108–109°; ir ($CCl_4$) 2982 m, 2940 w, 1801 m, 1760 s, 1573 m, 1476 w, 1453 w, 1392 w, 1371 m, 1298 w, 1240 s, 1160 s, 1115 w, 890 m, 872 m, 851 cm^{-1} m; nmr (CCl_4) δ 1.57 ppm (s, *t*-BuO).

Anal. Calcd for $C_{11}H_{18}Br_2N_2O_4$: C, 32.85; H, 4.51; N, 6.97; Br, 39.75. Found: C, 32.83; H, 4.61; N, 7.00 Br, 39.44.

D. Diphenyl Azodicarboxylate. The yellow solid (2.40 g, mp 115–120°) obtained after the filtrate had been evaporated to dryness was recrystallized from ether and then acetone at −78° to give colorless, solid product in 41% yield (1.80 g): mp 138–140°; ir ($CHCl_3$) 3060 w, 1825 m, 1780 s, 1570 m, 1492 m, 1265 s, 1180 s, 1162 s, 1070 w, 1045 w, 1002 w, 890 m, 690 cm^{-1} m; nmr ($CDCl_3$) δ 7.32 ppm (m, Ph).

Anal. Calcd for $C_{15}H_{10}Br_2N_2O_4$: C, 40.75; H, 2.28; N, 6.34. Found: C, 40.75; H, 2.31; N, 6.18.

E. Dibenzyl Azodicarboxylate. The oily residue was dissolved in CCl_4 and washed with 10 ml of 5% sodium sulfide solution. The organic layer was separated, dried, and evaporated to dryness. Attempted purification of the oily product (5.00 g, 65%) by crystallization from acetone or ether at −78° failed. However, the product was the expected $(PhCH_2O_2C)_2NN{=}CBr_2$, according to its spectra: nmr (CCl_4) δ 5.21 (s, 4, OCH_2Ph) and 7.33 (s, 10, Ph); ir (neat) 1805 w, 1760 s (CO_2CH_2Ph), 1570 m (C=N), and 880 cm^{-1} m (CBr_2).

Reactions of Phenyl(dibromochloromethyl)mercury with Azodicarboxylate Esters (Same Procedure). A. Diethyl Azodicarboxylate. Attempted purification of the product oil by vacuum distillation at 0.02 mm (100°) or by low-temperature crystallization failed. However, the product appeared to be $(Et\text{-}O_2C)_2NN{=}CClBr$: bp 78–83° (0.02 mm); 1.67 g (55% yield) nmr (CCl_4) δ 1.32 (t, 6, J = 7.0 Hz) and 4.13 ppm (q, 4, J = 7.0 Hz); ir (neat) 1802 m, 1770 s (CO_2Et), 1572 m (C=N), and 925 cm^{-1} s (CBrCl).

B. Di-*tert*-butyl Azodicarboxylate. The ir spectrum of the yellow, oily residue indicated the presence of the expected $(t\text{-}BuO_2C)_2NN{=}CClBr$ [absorptions at 1580 (C=N) and 875 (CClBr) cm^{-1}], but the residue contained large portions of the unconverted starting azo compound, which made the product isolation by low-temperature fractional crystallization difficult. However, when the residue was subjected to dry-column chromatography (1.0 ft × 1.5 in., Nylon tubing packed with activity III neutral alumina, Woelm, Germany) developed with benzene, the starting azo compound decomposed (exothermally) and was absorbed on the column. Extraction of the alumina with ether was followed by chilling the extracts at −78° to give colorless, solid product in 23% yield (0.71 g), mp 55–60°. The crude product was further recrystallized from ether at 5° by slow evaporation of the solvent in the refrigerator. The crystals were collected by filtration and washed quickly with cold ether to give colorless needles in 15% yield (0.46 g): mp 77–79°; ir (CCl_4) 2980 m, 2930 w, 1996 w, 1752 s, 1580 m, 1470 w, 1450 w, 1390 w, 1367 s, 1295 w, 1265 s, 1240 s, 924 s, 850 cm^{-1} m; nmr (CCl_4) δ 1.55 ppm (s).

Anal. Calcd for $C_{11}H_{18}ClBrN_2O_4$: C, 36.94; H, 5.07; N, 7.83. Found: C, 36.72; H, 5.12; N, 7.68.

Detection of the Initially Formed Products of $PhHgCCl_2Br$-$RO_2CN{=}NCO_2R$ and $PhHgCBr_3$-$RO_2CN{=}NCO_2R$ Reactions by Proton Nmr. The organomercury reagent and the azodicarboxylate ester (1:1 molar ratio) were dissolved in carbon tetrachloride and the reaction was allowed to proceed at room temperature. After about 3 days the nmr spectral parameters given in Tables III and IV for the (assumed) cyclic intermediates were determined. Other samples were used to record the ir spectrum in each case.

Reaction of Diethyl Azodicarboxylate with Sodium Trichloroacetate. A 50-ml, three-necked flask equipped with a thermometer, a magnetic stirbar, and a condenser topped with a nitrogen inlet tube was charged with the azo compound (1.75 g, 10.0 mmol), sodium trichloroacetate (1.00 g, 5.40 mmol), and 15 ml of dry 1,2-dimethoxyethane (DME). The reaction mixture was stirred and heated at reflux under nitrogen for 8 hr. The resulting light brown solution was filtered from sodium chloride and the filtrate then was trap-to-trap distilled at 0.02 mm (pot temperature to 80°). Glc analysis of the distillate showed the major product (formed in 69% yield, 3.72 mmol) to be the phosgene hydrazone. The product isolated by glc (4 ft × 0.25 in., 10% UC W-98, 120°) has nmr and ir spectra as well as glc retention time identical with those of the authentic sample of $(EtO_2C)_2NN{=}CCl_2$ prepared *via* the mercurial route.

Isolation of the Initial Product of the Reaction of Dimethyl Azodicarboxylate with Phenyl(tribromomethyl)mercury. A 50-ml flask was charged with the azo compound (1.46 g, 10.0 mmol), $PhHgCBr_3$ (10.0 g, 19.0 mmol), and 30 ml of carbon tetrachloride. The reaction mixture was stirred at room temperature for 6 days. At this time, about 50% of the starting azo compound had been consumed and the products contained 65% of the initial

Table IV
Nmr and Ir Spectra of the Initial Product from the Reaction of $PhHgCBr_3$ with $RO_2CN{=}NCO_2R$ at Room Temperature

R	Me	Et	*t*-Bu	CH_2Ph	Ph
$\nu_{C=N}$, cm^{-1}	1640	1639	1624	1635	1650
Nmr, ppm	3.88 (s)	1.38 (t)	1.50 (s)	5.20 (s)	
	4.02 (s)	1.44 (t)	1.61 (s)	5.32 (s)	7.33 (m)
		4.40 (q)[a]		7.41 (m)	

[a] Two resonances coincide.

product and 35% of the rearranged final product, as indicated by the nmr spectrum of the mixture. After the reaction mixture was filtered from phenylmercuric bromide and the unconverted starting mercurial, the filtrate was washed thoroughly with 5% aqueous sodium sulfide solution until both the organic and aqueous layers no longer were colored. The organic layer was separated, dried over magnesium sulfate, and then distilled to remove the solvent (the pot temperature was kept below 15° to prevent thermal rearrangement of the initial product). The white solid residue from the distillation was extracted with pentane. The product crystallized from the pentane extracts at 0–5° as nice, colorless crystals which were collected by filtration in 30% (0.99 g) yield: mp 55–56.5°; uv λ_{max} (pentane) 224 nm (ϵ 1390); ir (CCl_4) 3002 w, 2960 w, 1811 w, 1790 s, 1643 s, 1450 w, 1440 m, 1335 m, 1222 s, 1190 s, 1112 w, 1005 w, 940 m, 845 w, 750 cm^{-1} m; ^1H nmr (CCl_4) δ 3.88 (s, OMe) and 4.02 ppm (s, OMe); ^{13}C nmr (CCl_4) −25.76 (C=O), −20.87 (C=N), 31.93 (CBr_2), 70.95 (OCH_3), and 71.99 ppm (OCH_3) *vs.* benzene.

Anal. Calcd for $C_5H_6Br_2N_2O_4$: C, 18.89; H, 1.90; N, 8.81; Br, 50.27. Found: C, 19.02; H, 1.99; N, 8.88; Br, 50.19.

Kinetic Study of the Rearrangement of the Initial Product of the Reaction of Dimethyl Azodicarboxylate with Phenyl(tribromomethyl)mercury. A sample of a 0.18 *M* carbon tetrachloride solution of the initial product obtained above was prepared and stored in the refrigerator. The reactions at various temperatures were carried out directly in a sealed nmr tube in the nmr probe of a Hitachi Perkin-Elmer R20 spectrometer with a R-202VT variable temperature accessory. The temperatures inside the probe were determined by measuring the differences of the chemical shifts ($\Delta\delta$) between the methylene and hydroxyl protons of ethylene glycol. A calibration chart of $\Delta\delta$ *vs.* temperature (°C) provided by the manufacturer of the spectrometer was used. The accuracy of the temperature control system was within ±0.1°.

The progress of the reaction was monitored by the integrated intensity of the less shielded OMe group of the initial product, **10**, at δ 4.02 ppm, using a 120-Hz sweep width and 100-sec sweep time.

Attempts to Trap an Azomethinimine Intermediate (9) in the Rearrangement of 10 to 11. The 1,3,4-oxadiazoline **10** (0.50 g, 1.58 mmol), dimethyl acetylenedicarboxylate (0.23 g, 1.60 mmol), and 0.5 ml of $CDCl_3$ were placed in an nmr tube. The reaction mixture was heated at 50° and the progress of the reaction was monitored by nmr. During the entire course of the rearrangement, no additional nmr resonances other than those of **10**, **11**, and dimethyl acetylenedicarboxylate were observed. No 1,3-dipolar adduct was detected by tlc. Even in reactions that were carried out using the dipolarophile (either dimethyl acetylenedicarboxylate or phenyl isocyanate) as a solvent at room temperature, no 1,3-dipolar adduct was detected.

Acknowledgment. The authors are grateful to the U. S. Air Force Office of Scientific Research (NC)-AFSC (Grant AF-AFOSR-72-2204) for generous support of this work.

Registry No.—**10**, 51464-57-4; 1,1,2-tricarboethoxyhydrazine, 18283-23-3; 1-carbomethoxy-2,2-dicarboethoxyhydrazine, 36133-65-0; ethyl hydrazinecarboxylate, 4114-31-2; tetrachloroaziridine, 36271-58-6.

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Application of Phenyl(trihalomethyl)mercurials in the Preparation of Heterocyclic Compounds[1,2]

Dietmar Seyferth* and Houng-min Shih

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Pyrolysis of hydrazonodihalomethanes of type $(RO_2C)_2NN{=}CX_2$ (R = Me, Et; X = Cl, Br) resulted in formation, in high yield, of alkyl 5-halo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylates. A different mode of decomposition was observed when R = Ph. The reaction of $PhHgCX_2Br$ (X = Cl and Br) with azodibenzoyl gave the respective benzoyl halide and 2-halo-5-phenyl-1,3,4-oxadiazole in a reaction that may have involved initial 1,4-addition of CX_2 to the N=NC=O system. Reaction of $PhHgCCl_2Br$ with $RO_2CN{=}C(CO_2Et)_2$ (R = Me or Et) resulted in formation of $ClCO_2R$ and the 2-chloro-4-carboethoxy-5-ethoxy-1,3-oxazole **16**. The possible mechanisms of these reactions are discussed.

In the previous paper of this series,[1] we reported concerning the reaction of phenyl(trihalomethyl)mercurials with azodicarboxylate esters (eq 1). We now report extensions of this research which have led to new preparative routes to heterocyclic compounds.

$$PhHgCX_3 + RO_2CN{=}NCO_2R \xrightarrow{80^\circ} PhHgX + \underset{\mathbf{1}}{(RO_2C)_2NN{=}CX_2} \quad (1)$$

X = Cl, Br; R = Me, Et, Me_3C, $PhCH_2$, Ph

Results and Discussion

A. Preparation of Alkyl 5-Halo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylates. Among the chemical conversions of the hydrazonodihalomethanes of type **1** which were examined at the time we were gathering chemical information relevant to the elucidation of their structure was their pyrolysis.

When the product of the reaction of $PhHgCCl_2Br$ and diethyl azodicarboxylate, $(EtO_2C)_2NN{=}CCl_2$, was heated at 200° for 1–2 hr, ethyl chloride was evolved and a high-boiling, colorless solid, mp 46–48°, was formed in high yield (80%). This product was very stable, surviving several hours of heating at 200–250°, and it could be purified by vacuum distillation and gas chromatography (glc). Its analysis indicated the composition $C_5H_5O_4N_2Cl$. Structure **2a** was compatible with most of the spectral features of this product (ir and ^{13}C nmr) except for the unusually high carbonyl frequency (1880 cm^{-1} in CCl_4) in its ir spectrum.[3]

Pyrolysis of those compounds of type **1** where R = CH_3 and C_2H_5 proceeded in similar fashion to give products believed to have structure **2** on the basis of their spectroscopic properties (eq 2). The mixed halide $(EtO_2C)_2$-

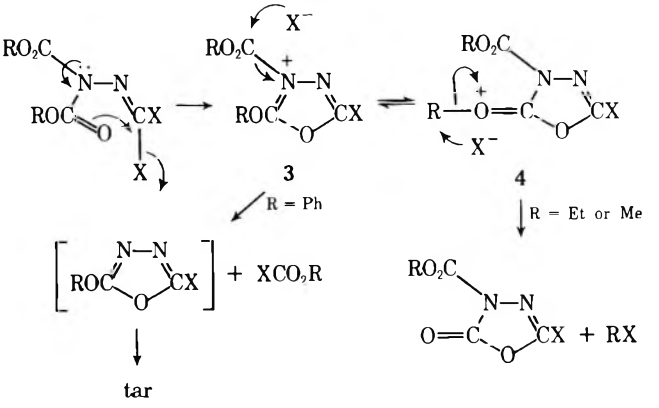
$$(RO_2C)_2NN{=}CX_2 \xrightarrow{\Delta} \underset{\mathbf{2}}{\text{5-halo-2-oxo-}\Delta^4\text{-1,3,4-oxadiazoline-3-carboxylate}} + RX \quad (2)$$

R = Et; X = Cl	**2a**, 80% yield
R = Et; X = Br	**2b**, 75% yield
R = Me; X = Cl	**2c**, 90% yield
R = Me; X = Br	**2d**, 94% yield

NN=CClBr gave a 10:1 mixture of **2a** and **2b** on pyrolysis.

In contrast, the only volatile compound obtained from the thermolysis of $(PhO_2C)_2NN{=}CX_2$ was the phenyl haloformate (XCO_2Ph, X = Cl or Br), and a tarry residue remained. This may be understood in terms of an equilibrium established between immonium ion **3** and oxonium ion **4** intermediates (Scheme I). Alkyl-group stabilization of the oxonium ion would shift the equilibrium in favor of **4**.

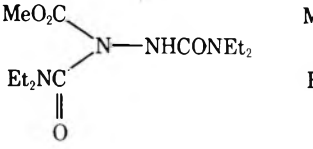
Scheme I



Elimination of RX (X = Cl or Br) from **4** would give a 1,3,4-oxadiazolinone. On the other hand, when R is phenyl, the stabilization of **4** is very much diminished, decomposition of immonium ion **3** becomes the main reaction course, and the phenyl haloformate is formed. The presumed 1,3,4-oxadiazoles formed in the latter reaction may not be stable under the reaction conditions and may undergo further reaction. In the thermolysis of $(PhCH_2O_2C)NN{=}CX_2$ (X = Cl or Br), a tarry residue and low yields of benzyl halides were obtained. It was not clear whether the benzyl halides were derived from the decomposition of **4** or from decarboxylation of benzyl haloformate initially formed in the decomposition of **3**. In the case of $(t\text{-}BuO_2C)_2NN{=}CX_2$, evolution of gas was observed, leaving an ill-defined solid residue which showed no apparent solubility in organic solvents or in water.

In order to confirm the proposed cyclic structure of **2a–d** and to obtain structural information which might serve to explain the spectroscopic properties, an X-ray crystal structure analysis of **2d** was undertaken. The results showed that the structure is indeed that assigned on the basis of spectroscopic evidence.[4]

By this new route, new alkyl 5-halo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylates are readily accessible. Their reactive carbon–halogen linkage may provide entry to other derivatives. For instance, as we have found, the C–Br bond of **2d** may be reduced to C–H by tri-*n*-butyltin hydride. Reaction of **2d** with diethylamine or ethanol gave ring-opened products, namely, the hydrazine derivatives **5** and **6**, re-



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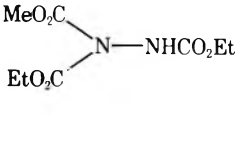

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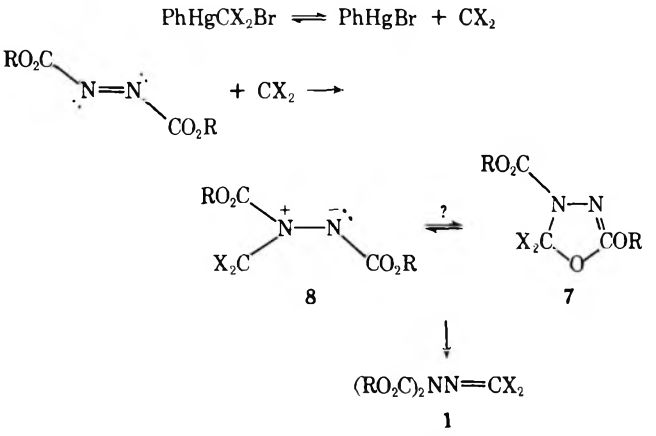
spectively. Acid hydrolysis of **2d** gave ethyl hydrazinecarboxylate, EtO_2CNHNH_2.

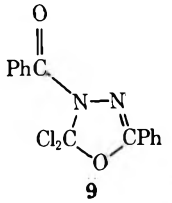
B. Preparation of Oxadiazoles and Oxazoles. The formation of compounds of type **1** in $PhHgCX_3$–$RO_2CN{=}NCO_2R$ reactions is believed to occur as shown in Scheme II.[1] An intermediate was isolated as a crystalline solid in the room-temperature reaction of $PhHgCBr_3$ with $MeO_2C{-}N{=}NCO_2Me$. The spectral properties (ir and nmr) of this intermediate were interpreted as favoring the cyclic structure **7**, but did not exclude the open dipolar form **8**. If **7** is the correct structure of the intermediate, then its formation would involve a formal 1,4-addition of CX_2 to the $-N{=}NC{=}O$ system of the azodicarboxylate.

Scheme II



In general, carbenes add in a 1,2 fashion to C=C bonds of conjugated polyunsaturated systems of type >C=C–C=C< and >C=C–C=O,[5] rather than by 1,4-addition;[6] so possible 1,4-addition to $-N{=}N{-}C{=}O$ compounds merited further study. During the course of this investigation we found two types of compounds which reacted with $PhHgCX_3$ reagents to give stable heterocyclic products *via* apparent 1,4-addition reactions.

Azodibenzoyl might be expected to react with $PhHgCCl_2Br$ to give $(PhCO)_2NN{=}CCl_2$ as final product *via* intermediate **9** if the reaction course were the same



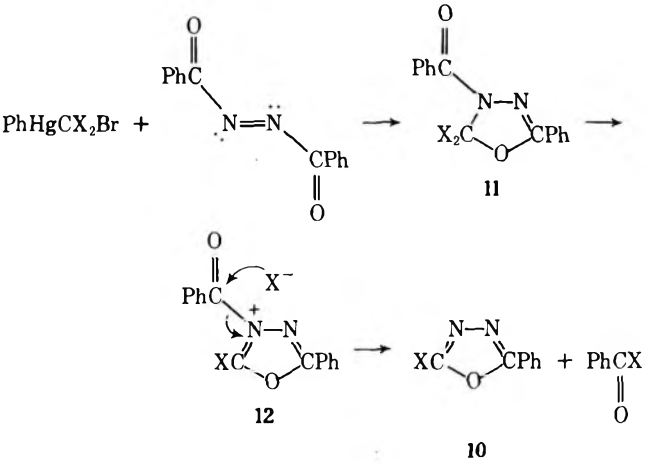
9

as that encountered in the $PhHgCCl_2Br$–$RO_2CN{=}NCO_2R$ reaction. Such, however, was not the case.

Reaction of $PhHgCCl_2Br$ with azodibenzoyl in benzene at 80° gave a complicated product mixture, presumably owing to the decomposition of azodibenzoyl; so the reaction was studied at room temperature. The mercurial and azodibenzoyl in CCl_4 were stirred at room temperature for 8 days and this was followed by a heating period of 1 hr at 80°. Two products, identified as benzoyl chloride and 2-chloro-5-phenyl-1,3,4-oxadiazole (**10**, X = Cl),[7] were obtained.

A spectroscopic study of the reaction by ir revealed that an intermediate with an ir band at 1610 cm^{-1} (probably a C=N vibration) had been formed and that this intermediate readily underwent further reaction at 80° to give the two observed products. Although the intermediate failed to crystallize, it very likely is a 1,3,4-oxadiazoline (**11**, X = Cl) as well, resulting from the 1,4(N,O)-addition of dichlorocarbene to azodibenzoyl *via* a mechanism similar to that postulated for azodicarboxylates. When $PhHgCBr_3$ was used instead of $PhHgCCl_2Br$, benzoyl bromide and bromo-1,3,4-oxadiazole (**10**, X = Br) were obtained. The products from these reactions possibly are derived from the dissociation of carbon–halogen bonds of the intermediate **11** to form an immonium salt **12** which then decomposes *via* nucleophilic attack of halide ion at the benzoyl carbonyl to give the benzoyl halide and **10**. Scheme III illustrates this possible mechanism.

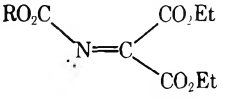
Scheme III



The quite different observed courses of the thermal reactions of **11** and **7** may be attributed to the presence of a better electrophilic carbonyl center (the benzoyl group) in **11**, which undergoes halide ion attack, resulting in elimination of benzoyl halide to give **10**.

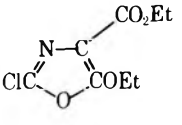
The yields of these novel oxadiazoles with a reactive halogen function, in these reactions were high enough (**10**, X = Cl, 54%; X = Br, 80%) to make these reactions preparatively useful. However, it was beyond the scope of this study to develop the potentially interesting C–X bond chemistry of **10**.

In view of these results with $-N{=}N{-}C{=}O$ compounds, it was of interest to extend this investigation to a compound containing an $-N{=}C{-}C{=}O$ system. Compounds of type **13** were chosen for further study.



13a, R = Et
b, R = Me

Reaction of $PhHgCCl_2Br$ with either the *N*-carboethoxyketimine **13a** or the *N*-carbomethoxyketimine **13b** at 80° in benzene solution gave one identical product in addition to ethyl chloroformate (R = Et) or methyl chloroformate (R = Me), depending on whether **13a** or **13b** was used. Apparently, the *N*-alkoxycarbonyl group was the one which was eliminated from the reaction intermediate to form the observed alkyl chloroformate. The analysis of the common product indicated the composition $C_8H_{10}ClNO_4$. The ^1H nmr spectrum of this product showed two nonequivalent OEt groups and its ir spectrum indicated the presence of C=O, C=C, and C=N functions by bands at 1720 s, 1620 s, and 1535 m cm^{-1}, respectively. The structure most compatible with these data is the 1,3-oxazole **14**.



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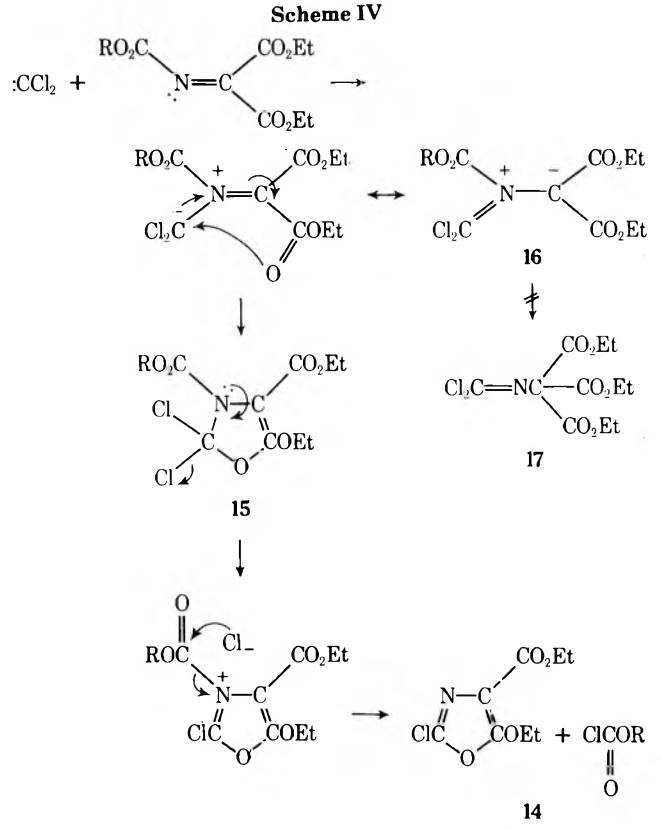
A spectroscopic study of a $PhHgCCl_2Br$–**13b** reaction mixture after it had been stirred at room temperature for 4 days clearly indicated the formation of an intermediate by the ir absorption at 1630 cm^{-1} assignable to a C=C stretching vibration and its nmr signal for a OMe group at δ 3.86 ppm (this signal is differentiable from that of the $ClCO_2Me$ at δ 3.98 ppm). The same ir band at 1630 cm^{-1} was also observed when **13a** was used instead of **13b**, but in this case, the nmr spectrum of the OEt groups was too complex to analyze.

Although the intermediate was not isolated, in view of the final products obtained, **14** and $ClCO_2R$, as well as the spectral features, it is reasonable to believe that the 1,4(N,O)-addition of the dichlorocarbene to these ketimines to form **15** has also been achieved (Scheme IV). In Scheme IV, an azomethinimine intermediate **16** may or may not be involved. However, even if it had been formed, the bulky substituents on the carbanion center could prevent it from approaching the *N*-alkoxycarbonyl to realize the possible alkoxycarbonyl migration to give **17** *via* a mechanism similar to that proposed for the rearrangement of **8** to **7**.

Scheme IV



In these reactions also a novel heterocyclic product with a potentially reactive C–Cl bond has been formed. The yields of **14** were not high (20–35%), and the reaction study was not extended to include $PhHgCBr_3$, although one might expect better yields of product with this mercurial owing to the higher lability of a C–Br bond (*vs.* C–Cl) in an intermediate of type **15**.

Another reaction of $PhHgCCl_2Br$ was tried with >C=C–C=O type substrates, this time at room temperature rather than at 80°.[8] However, the reaction mixtures obtained after 6-day reactions with mesityl oxide and diethyl fumarate contained only the expected dichlorocyclopropanes, as seen by the nmr spectra of the reaction mixtures and by the subsequent isolation of the products.

Since the presence of a terminal nitrogen atom seems to facilitate 1,4-addition of CX_2 to α,β-unsaturated systems, we propose that the initial interaction between the substrate and CX_2 (or possibly with $PhHgCX_2Br$ rather than with free CX_2) occurs at the nitrogen atom and that this is followed by ring closure, as we have indicated. This 1,4-addition of CX_2 to –N=N–C=O and –N=C–C=O systems should be capable of further generalization and of application in the synthesis of heterocyclic systems containing halogen which are difficult to prepare by other routes.

Experimental Section

General Comments. All reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen. Solvents were carefully dried. Infrared spectra were recorded using a Perkin-Elmer Model 457A, 257, or 337B grating infrared spectrophotometer, ultraviolet spectra using a Cary-14 spectrophotometer, and proton nuclear magnetic resonance spectra using a Varian Associates T-60 or a Hitachi Perkin-Elmer R-20B high-resolution nmr spectrometer. Chemical shifts are expressed in δ units, parts per million downfield from tetramethylsilane. Carbon-13 nuclear magnetic resonance spectra were recorded using a Bruker HFX-90 nmr spectrometer interfaced with a Digilab NMR/FTS-3 Fourier transform data system. The carbon-13 chemical shifts are expressed in parts per million with respect to internal benzene. Mass spectra were recorded using a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Gas–liquid partition chromatographs (glc) used were F & M Model 5754, 700, or 720 and M.I.T. isothermal units. Thin layer chromatography (tlc) was used to examine high-boiling reaction mixtures; Eastman silica gel tlc sheets, type 6061, were used.

Preparation of Starting Materials. Phenyl(bromodichloromethyl)mercury and phenyl(tribromomethyl)mercury were prepared by our THF method.[9] Azodibenzoyl, mp 118–119°, was prepared[10] by *N*-bromosuccinimide oxidation of *sym*-dibenzoylhydrazine (Aldrich). The reaction of diethyl ketomalonate with the respective *N*-carboalkoxy triphenylphosphinimine in THF at reflux[11] provided *N*-carboalkoxy diethyl ketomalonate ketimines. The *N*-carbomethoxy compound, $CH_3O_2CN{=}C(CO_2C_2H_5)_2$, is a new compound: bp 98–99° (0.08 mm); $n^{25}D$ 1.4391; ir (CCl_4) 2900 m, 1740 s, 1680 m, 1480 m, 1430 w, 1370 w, 1300 s, 1230 s, 1072 s, 1030 w, 910 w, 860 cm^{-1} w; nmr (CCl_4) δ 1.40 (t, 6, J = 7.0 Hz, OEt), 3.85 (s, 3, OMe), and 4.37 ppm (q, 4, J = 7.0 Hz, OEt).

Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.45; H, 5.82; N, 6.14.

The preparation of the $(RO_2C)_2NN{=}CX_2$ compounds whose thermolysis is reported was described in our previous paper in this series.[1]

Thermolysis of $(RO_2C)_2NN{=}CX_2$ Compounds. A. $(EtO_2C)_2NN{=}CCl_2$. The hydrazone (1.00 g, 3.80 mmol) was sealed in a Pyrex glass tube and heated at 180° for 1 hr. The resulting reaction mixture was a light yellow oil. After the tube was chilled in liquid nitrogen, it was opened and warmed up *slowly* to room temperature. The low-boiling material distilled and collected in a receiver at −78° at 1 atm (pot temperature to 30°) was a clear liquid which had an infrared spectrum identical with that of an authentic sample of ethyl chloride. The high-boiling product was isolated in 80% yield (0.60 g) by distillation at 0.02 mm (100°) as a colorless solid, mp 46–48°. An analytical sample was further purified by glc (6 ft × 0.25 in., 20% DC-200, 160°). The structure of the product was assigned as ethyl 5-chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 2990 m, 1880 s, 1830 m, 1790 s, 1600 m, 1460 m, 1400 w, 1375 m, 1321 s, 1310 s, 1260 m, 1211 m, 1152 w, 1100 w, 1020 m, 925 m, 845 cm^{-1} w; ^1H nmr ($CDCl_3$) δ 1.42 (t, 3, J = 7.2 Hz, CH_3) and 4.40 ppm (q, 2, J = 7.2 Hz, CH_2); ^{13}C nmr ($CHCl_3$) −20.3 (C=O in CO_2Et), −19.9 (C=O in ring), −17.9 (C=N), 61.6 (CH_2), and 112.5 (CH_3) *vs.* benzene; mass spectrum (70 eV) *m/e* (rel intensity) 192 (1, M^+), 149 (3), 120 (25), 103 (13), 44 (17), 29 (100).

Anal. Calcd for $C_5H_5ClN_2O_4$: C, 31.18; H, 2.62; N, 14.55; Cl, 18.42. Found: C, 31.10; H, 2.87; N, 14.35; Cl, 18.20.

B. $(EtO_2C)_2NN{=}CBr_2$. Thermolysis of the hydrazone (1.00 g, 2.9 mmol) in a sealed tube at 180° for 30 min gave a brown reaction mixture. The tube was opened as described above. Distillation of the crude products gave one low-boiling compound which showed an infrared spectrum identical with that of an authentic sample of ethyl bromide and one high-boiling product (0.75 g, 75%). Further purification of the latter by glc (4 ft × 0.25 in., 10% UC-W98, 150°) yielded a white, crystalline substance, mp 52–53°, which was identified as ethyl 5-bromo-2-oxo-Δ^4-1,3,4-oxadiazo-

line-3-carboxylate: ir (CCl_4) 2980 w, 1870 s, 1816 m, 1781 s, 1580 m, 1560 w, 1390 w, 1370 m, 1316 s, 1300 s, 1240 m, 1200 s, 1140 m, 1090 w, 1015 m, 980 w, 915 m, 840 cm^{-1} w; nmr ($CDCl_3$) δ 1.44 (t, 3, J = 7.2 Hz, CH_3) and 4.52 ppm (q, 2, J = 7.2 Hz, CH_2).

Anal. Calcd for $C_5H_5BrN_2O_4$: C, 25.34; H, 2.20; N, 11.82; Br, 33.71. Found: C, 24.70; H, 2.13; N, 11.77; Br, 34.01.

C. $(EtO_2C)_2NN{=}CClBr$. Thermolysis of the hydrazone (0.5 g, 1.65 mmol) as described above gave a brown reaction mixture. Glc (4 ft × 0.25 in., 10% UC W98, 140°) analysis of the products showed that ethyl 5-chloro- and 5-bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate had been formed in a 10:1 ratio.

D. $(MeO_2C)_2NN{=}CCl_2$. The hydrazone (0.50 g, 2.20 mmol) was placed in a 5-ml, pear-shaped flask and heated at 180° for 30 min under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, a solid product formed. The crude product was purified twice by sublimation at 180° (100 mm) to give 3.50 g (90%) of colorless crystals, mp 107–109°, of methyl 5-chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 3000 w, 2950 w, 1870 s, 1815 m, 1785 s, 1760 s, 1592 m, 1438 m, 1320 s, 1252 m, 1220 m, 1150 w, 1002 m, 915 cm^{-1} w; nmr ($CDCl_3$) δ 4.06 ppm (s).

Anal. Calcd for $C_4H_3ClN_2O_4$: C, 26.91; H, 1.69; N, 15.69; Cl, 19.86. Found: C, 26.77; H, 1.96; N, 15.11; Cl, 20.13.

E. $(MeO_2C)_2NN{=}CBr_2$. Thermolysis of the hydrazone (0.73 g, 2.30 mmol) in a flask at 160° for 20 min gave a light yellow liquid which solidified after cooling to room temperature. Purification of the product by sublimation at 90–100° (0.15 mm) gave 0.48 g (94%) of colorless crystals. Further recrystallization from chloroform gave nice hexagonal crystals, mp 119–120°. An X-ray crystal structure determination[4] confirmed the proposed structure of methyl 5-bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 2980 w, 1910 w, 1870 s, 1790 s, 1580 m, 1437 m, 1330 w, 1310 s, 1240 m, 1210 m, 1142 m, 1000 w, 910 cm^{-1} w; nmr (CCl_4) δ 4.30 ppm (s).

Anal. Calcd for $C_4H_3BrN_2O_4$: C, 21.54; H, 1.35; N, 12.57; Br, 35.84. Found: C, 21.47; H, 1.61; N, 12.38; Br, 36.01.

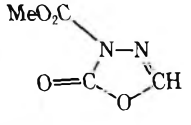
F. $(PhO_2C)_2NN{=}CCl_2$. Thermolysis of the hydrazone (0.70 g, 2.0 mmol) at 200° for 30 min gave a black reaction mixture. Distillation of the mixture at 60–70° (0.30 mm) gave a colorless distillate (0.20 g, 67%) and a tar residue. The volatile compound was identified as phenyl chloroformate, ir (neat) 3060 w, 1780 s, 1590 m, 1490 s, 1461 m, 1172 s, 1160 s, 1120 s, 1070 w, 1020 w, 1012 m, 856 s, 745 s, 680 s, 580 s, 500 cm^{-1} m, which is identical with the Sadtler Standard Spectrum No. 13473 of authentic phenyl chloroformate.

G. $(PhO_2C)_2NN{=}CBr_2$. When this hydrazone (0.50 g, 1.14 mmol) was thermolyzed at 190° for 30 min, a similar black reaction mixture was obtained. The only volatile compound (0.14 g, 50%) isolated by distillation at 80–90° (0.30 mm) was identified by ir spectrum (neat, 3060 w, 1780 s, 1588 s, 1460 w, 1282 w, 1170 s, 1150 s, 1120 s, 1025 w, 1000 m, 912 m, 840 s, 740 s, 685 s, 640 m, 562 m, 498 cm^{-1} m) as phenyl bromoformate.

H. $(PhCH_2O_2C)_2NN{=}CCl_2$. This hydrazone (0.50 g, 1.32 mmol) was heated at 200° for 30 min to give a black reaction mixture. The only volatile compound found by distillation (80–90°, 0.01 mm) was benzyl chloride (0.06 g, 33%). The product was identified by the comparison of its ir spectrum with that of an authentic sample from Aldrich.

Benzyl bromide was the only volatile product of the pyrolysis of $(PhCH_2O_2C)_2NN{=}CBr_2$.

Reduction of Methyl 5-Bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate. The oxadiazolinone (0.35 g, 1.56 mmol) and tri-*n*-butyltin hydride (0.47 g, 1.60 mmol) were heated at 80° for 4 hr. The starting compound completely dissolved on heating while the reduced product precipitated when it was formed. The reaction mixture was cooled in an ice bath and then filtered from the solid product. The product, after recrystallization from acetone at −78°, was a colorless solid, mp 85–87°, 0.17 g (75% yield). The compound was identified as methyl 2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 3125 w, 3002 w, 2950 w, 1910 w, 1840 s, 1780 s, 1595



m, 1435 m, 1340 s, 1320 s, 1285 w, 1220 m, 1160 w, 1105 m, 1000 m, 905 cm^{-1} w; nmr ($CDCl_3$) δ 4.10 (s, 3, CH_3) and 7.68 ppm (s, 1, N=CH).

Anal. Calcd for $C_4H_4N_2O_4$: C, 33.34; H, 2.80; N, 19.45. Found: C, 33.27; H, 3.02; N, 19.56.

Reaction of Methyl 5-Bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate with Diethylamine. The oxadiazolinone (0.50 g, 2.0 mmol) in 2 ml of tetrahydrofuran was treated dropwise with 0.15 g (2.0 mmol) of diethylamine at 0–5°. Immediate formation of a white precipitate was observed. Glc analysis (M.I.T. isothermal unit, 4 ft × 0.25 in., 10% SE-30, at 150°) of the solution showed that one high-boiling product had formed and that most of the starting material remained intact. An additional 0.45 g (6.00 mmol) of diethylamine was added to complete the reaction. The reaction mixture was filtered from the precipitate of $Et_2NH{\cdot}HBr$, and the filtrate was examined by glc. The same high-boiling product found above was the sole reaction product. The product, **5**, was isolated by glc: ir (CCl_4) 3290 m, 2970 m, 1730 s, 1660 s, 1430 m, 1330 m, 1310 w, 1260 s, 1220 w, 1160 w, 1100 m, 850 cm^{-1} w; nmr (CCl_4) δ 1.18 (t, 3, J = 7.1 Hz, CH_2CH_3), 1.20 (t, 3, J = 7.1 Hz, CH_2CH_3), 3.27 (q, 2, J = 7.1 Hz, CH_2CH_3), 3.36 (q, 2, J = 7.1 Hz, CH_2CH_3), 3.50 (s, 3, OCH_3), and 8.39 (s, 1, NH).

Anal. Calcd for $C_{12}H_{24}N_4O_4$: C, 49.98; H, 8.39; N, 19.43. Found: C, 50.18; H, 8.25; N, 19.93.

Ethanolysis of Ethyl 5-Chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate. The 1,3,4-oxadiazolinone (0.10 g) was treated with 3 ml of 95% ethanol at room temperature for 20 hr. The resulting reaction mixture was examined by glc (4 ft × 0.25 in., 10% UC W98, 160°) which showed that all the starting material had been converted to 1,1,2-tricarboethoxyhydrazine. The product was identified by comparison of its glc retention time and ir spectrum to those of the authentic compound obtained in a previous reaction.[1]

Acid Hydrolysis of Ethyl 5-Chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate. The oxadiazolinone was treated with 2 *N* hydrochloric acid at 80° for 1 hr. The reaction mixture was neutralized with 2 *N* sodium hydroxide solution and then extracted with ether. The product, isolated from the dried organic layer by glc (4 ft × 0.25 in., 10% UC W98, 130°), showed an identical glc retention time and ir spectrum with those of authentic carboethoxyhydrazine, EtO_2CNHNH_2 (obtained from Aldrich).

Reaction of Phenyl(bromodichloromethyl)mercury with Azodibenzoyl. The azo compound (1.30 g, 5.00 mmol), the mercurial (2.20 g, 5.00 mmol), and 10 ml of carbon tetrachloride were placed in a 25-ml flask and stirred at room temperature under a nitrogen atmosphere. The progress of the reaction was monitored by ir spectroscopy. After a 3-day reaction period, an initial reaction product formed as indicated by new ir bands at 1775 s, 1610 s, 1580 w, 1060 s, and 960 cm^{-1} m. The reaction was discontinued at the end of 8 days. At this time, the reaction mixture showed additional new ir bands at 1780 sh, 1500 w, 1488 w, 1195 w, and 870 cm^{-1} m. The mixture was filtered from phenylmercuric bromide and unconverted starting mercurial and the filtrate was evaporated to dryness, leaving an oily residue and some solid. The oil contained mainly the initial reaction product as indicated by its ir spectrum. Attempted isolation of the initial product by recrystallization from acetone or ether at −78° failed. However, heating this oil at 80° for 1 hr gave two products, one a solid, the other a liquid. The latter was separated by filtration, and its further purification by glc showed an identical glc retention time and ir spectrum with those of an authentic sample of benzoyl chloride. The crude solid was recrystallized from carbon tetrachloride to give colorless crystals of 2-chloro-5-phenyl-1,3,4-oxadiazole, mp 76–78° (lit.[7] mp 75°). The spectral properties which were not reported are shown below: ir (CCl_4) 3060 w, 1970 w, 1955 w, 1910 w, 1890 w, 1810 w, 1760 w, 1740 m, 1607 w, 1590 w, 1550 m, 1498 s, 1450 m, 1370 w, 1330 w, 1285 w, 1196 s, 1178 w, 1075 w, 1064 s, 1028 m, 1008 m, 960 m, 950 m, 922 w, 708 s, 690 cm^{-1} s; nmr (CCl_4) δ 7.50 (m, 3) and 8.00 ppm (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 182 (12), 180 (36), 145 (33), 126 (9), 124 (27), 105 (73), 103 (37), 96 (20), 95 (5), 93 (4), 89 (21), 86 (13), 84 (24), 78 (7), and 77 (100).

Reaction of Phenyl(tribromomethyl)mercury with Azodibenzoyl. A 50-ml flask was charged with the azo compound (2.30 g, 9.80 mmol), the mercurial (10.0 g, 19.0 mmol), and 30 ml of carbon tetrachloride. The reaction mixture was stirred at room temperature for 5 days. The resulting mixture was a light yellow solution whose ir spectrum showed the formation of the initial reaction product as indicated by bands at 1775, 1755, 1610, 1576, 1485, 1170, 1060, and 952 cm^{-1}. The reaction mixture was filtered from phenylmercuric bromide and unconverted mercurial. The filtrate was then washed with 5% aqueous sodium sulfide solution and water. The dried organic layer was evaporated to dryness to give 1.20 g (30%) of oily products. Attempted crystallization of the oil at low temperature (−78°) failed. The oil was redissolved in carbon tetrachloride and refluxed for 1.5 hr. When the reaction was followed by ir spectroscopy, an increase in the intensities of ir bands at 1775, 1485, 1170, and 825 cm^{-1} at the expense of the

bands due to the initial product at 1755, 1610, 1575, and 1060 cm^{-1} was observed. Glc (4 ft × 0.25 in., UC W98, 160°) analysis of the resulting solution showed that two products had been formed in 1:1 ratio. The low-boiling product, isolated by glc, was found to be benzoyl bromide, identified by the comparison of its glc retention time and ir spectrum to those of the authentic compound (Aldrich). Colorless crystals of the second product (0.23 g, 80% based upon the initial reaction product) were obtained from carbon tetrachloride solution at 0°. Further recrystallization from carbon tetrachloride at 0° gave colorless needles, mp 107–109°. The compound was identified as 2-bromo-5-phenyl-1,3,4-oxadiazole: ir (CCl_4) 3060 w, 1975 w, 1955 w, 1910 w, 1890 w, 1770 m, 1610 w, 1550 m, 1485 s, 1450 m, 1340 w, 1320 w, 1170 s, 1075 sh, 1060 m, 1025 w, 995 w, 958 w, 950 w, 925 w, 850 w, 710 m, 690 cm^{-1} m; nmr (CCl_4) δ 7.52 (m, 3) and 8.00 ppm (m, 2).

Anal. Calcd for $C_8H_5BrN_2O$: C, 42.69; H, 2.24; N, 12.45; Br, 35.31. Found: C, 42.62; H, 2.32; N, 12.29; Br, 35.20.

Reaction of *N*-Carboethoxy Diethyl Ketomalonate Ketimine with Phenyl(bromodichloromethyl)mercury. The imine (2.45 g, 10.0 mmol), phenyl(bromodichloromethyl)mercury (4.40 g, 10.0 mmol), and 10 ml of benzene were stirred and heated at reflux under a nitrogen atmosphere for 2 hr. The resulting reaction mixture was filtered from 2.80 g (80%) of white, crystalline phenylmercuric bromide, mp 270–272°. Glc analysis of the filtrate (M.I.T. isothermal unit, 10% SE-30, 4 ft × 0.25 in., 145°) showed the presence of a large quantity of the unconverted starting imine and one product having a shorter glc retention time than that of the imine. Because of the presence of the big portion of the imine, isolation of the product from the reaction mixture by glc was not feasible. Therefore, the crude product obtained after evaporation of the solvent was column chromatographed (neutral alumina column). The product was easily eluted while the imine remained on the column. The analytical sample was further purified by glc (4 ft × 0.25 in., UC W98, 140°), $n^{25}D$ 1.4833. The structure was assigned as 2-chloro-4-carboethoxy-5-ethoxy-1,3-oxazole (**14**): ir (neat) 2900 m, 1720 s, 1620 s, 1535 m, 1380 w, 1350 w, 1250 m, 1170 s, 1060 s, 1000 w, 890 w, 860 w, 840 w,780 m, 650 cm^{-1} w; nmr (neat) δ 1.16 (t, 3, J = 7.1 Hz), 1.29 (t, 3, J = 7.1 Hz), 4.05 (q, 2, J = 7.1 Hz), and 4.38 ppm (q, 2, J = 7.1 Hz) due to OEt groups.

Anal. Calcd for $C_8H_{10}ClNO_4$: C, 43.75; H, 4.59; N, 6.38; Cl, 16.15. Found: C, 43.54; H, 4.60; N, 6.09; Cl, 16.21.

The imine (1.30 g, 5.00 mmol), the mercurial (2.20 g, 5.00 mmol), and 8 ml of benzene were stirred and heated at reflux for 3 hr. Glc (M.I.T. isothermal unit, 4 ft × 0.25 in., 20% SE-30, 155°, *n*-tridecane internal standard) analysis of the resulting reaction mixture showed that **14** was present in 28% yield (1.40 mmol). When additional 2.20 g of the mercurial was added and the mixture was refluxed for another 3 hr, the yield of **14** was found to be 15%. In another run using a threefold excess of the mercurial, the yield of **14** was found to be 14%. When equimolar amounts of the mercurial and the imine (5.00 mmol each) in 5 ml of benzene were stirred at room temperature for 12 days, the yield of **14** was 18%.

Attempted detection of ethyl chloroformate formed in the above reactions in benzene solution failed because the compound has a very close glc retention time to that of the solvent. Therefore, the reaction was run without solvent. The imine (2.54 g, 10.0 mmol) and the mercurial (2.20 g, 5.0 mmol) were placed in an 25-ml, pear-shaped flask equipped with a reflux condenser topped with a vacuum distillation head with a receiver chilled in a Dry Ice–acetone bath. The reaction mixture was stirred and heated at 85° (100 mm) for 3 hr. The low-boiling (0.10 g, 20%) product which collected in the receiver was a colorless liquid and was identified as ethyl chloroformate by comparison of its ir spectrum with that of an authentic sample (Aldrich). The reaction product **14** was formed in 35% yield in this reaction, and 7.0 mmol of the starting imine was recovered.

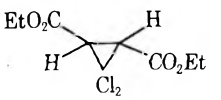
Reaction of *N*-Carbomethoxy Diethyl Ketomalonate Ketimine with Phenyl(bromodichloromethyl)mercury. The imine (2.30 g, 10.0 mmol), the mercurial (4.40 g, 10.0 mmol), and 10 ml of benzene were stirred and heated at reflux for 3 hr. The reaction mixture was filtered from 3.0 g (85%) of white phenylmercuric bromide, mp 263–265°. Glc (M.I.T. isothermal unit, same column and conditions used above) analysis of the filtrate showed one product peak which overlapped with the starting imine peak. The product showed an identical glc retention time with that of the product obtained from the *N*-carboethoxy imine reaction and was purified by column chromatography (neutral alumina). Its glc retention time and spectra (ir and nmr) were identical with those of **14**. The yield determined by glc (M.I.T. isothermal unit, 4 ft × 0.25 in., 10% SE-30, 155°) was found to be 15% (0.15 mmol).

Spectroscopic Study of the Reaction of *N*-Carbomethoxy Diethyl Ketomalonate Ketimine with $PhHgCCl_2Br$ at Room Temperature. When the imine (1.0 g, 5.0 mmol) and the mercurial (2.00 g, 5.0 mmol) in 5 ml of CCl_4 were stirred at room temperature for 4 days, the ir spectrum of the reaction mixture showed a new band at 1630 cm^{-1} assignable to a C=C stretching vibration. Its nmr spectrum showed new resonances (singlets) at δ 3.86 and 3.98 ppm. The latter was most likely due to the OMe signal of the methyl chloroformate, since this signal was enhanced when $ClCO_2Me$ was added to the reaction mixture. After 12 days, the nmr signal of the reaction mixture at 3.86 ppm disappeared. The ir band at 1630 cm^{-1} and nmr resonance at 3.86 ppm were most likely due to the reaction intermediate **15** (R = Me), which can rearrange to the observed final products, **14** and $ClCO_2Me$, at room temperature. The nmr signals of OEt groups were too complex to analyze.

The reaction mixture of $PhHgCCl_2Br$ (4.40 g, 10.0 mmol) and $(EtO_2C)N{=}C(CO_2Et)_2$ (2.45 g, 10.0 mmol) in 10 ml of CCl_4 at room temperature for 2 days also showed the new ir band at 1630 cm^{-1}. However, its nmr spectrum was too complex to analyze.

Reaction of Diethyl Fumarate with $PhHgCCl_2Br$. Diethyl fumarate (1.74 g, 10.0 mmol) and the mercurial (4.00 g, 9.8 mmol) in 10 ml of CCl_4 were stirred at room temperature for 6 days. The nmr spectrum of the reaction mixture showed one new resonance at δ 2.96 ppm (singlet) which is most likely due to the cyclopropyl CH protons. The OEt signal of the product was hardly distinguishable from that of the starting olefin. Its ir spectrum showed no band other than the C=C vibration of the starting olefin. Therefore, the 1,4-addition of the CCl_2 to a C=C–C=O conjugated system of diethyl fumarate was not realized.

The reaction mixture was heated at 80° for 2 hr, and then was filtered from 3.00 g (85%) of PhHgBr, mp 265–269°. The filtrate was trap-to-trap distilled (100°, 0.02 mm) and the product was isolated by glc (4 ft × 0.25 in., 10% UC-W98, 145°) in 31% yield (3.04



mmol): $n^{25}D$ 1.4611; ir (neat) 3022 w, 2980 m, 2940 w, 2900 w, 1740 s, 1460 w, 1440 w, 1372 w, 1366 m, 1310 s, 1260 m, 1180 s, 1090 w, 1060 m, 1030 m, 980 m, 970 w, 940 m, 930 m; nmr (neat) δ 1.25 (t, 6, J = 7.5 Hz, CH_3), 4.20 (q, 4, J = 7.5 Hz, CH_2), and 2.96 ppm (s, 2, cyclopropyl CH).

Anal. Calcd for $C_9H_{12}Cl_2O_4$: C, 42.37; H, 4.74; Cl, 27.80. Found: C, 42.83; H, 4.92; Cl, 27.46.

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Registry No.—**1** (R = Et; X = Cl), 36133-63-8; **1** (R = Et; X = Br), 51381-28-3; **1** (R = Et; X = Br + Cl), 51381-32-9; **1** (R = Me; X = Cl), 51381-23-8; **1** (R = Me; X = Br), 51381-27-2; **1** (R = Ph; X = Cl), 51381-26-1; **1** (R = Ph; X = Br), 51381-31-8; **1** (R = Ph; X = Cl), 51381-25-0; **2a**, 36133-66-1; **2b**, 51806-26-9; **2c**, 51806-27-0; **2d**, 38658-91-2; **2** (r , me; X = H), 51806-28-1; **5**, 51806-29-2; **10** (X = Cl), 1483-31-4; **10** (X = Br), 51039-53-3; **13a**, 36106-23-7; **13b**, 51039-55-5; **14**, 51039-54-4; diethyl ketomalonate, 609-09-6; *N*-carbomethoxytriphenylphosphinimine, 40438-23-1; phenyl bromoformate, 51806-30-5; phenyl (bromodichloromethyl)mercury, 3294-58-4; azodibenzoyl, 959-31-9; phenyl(tribromomethyl)mercury, 3294-60-8; diethyl fumarate, 623-91-6; diethyl *trans*-3,3-dichlorocyclopropane-1,2-dicarboxylate, 51806-31-6.

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Hydrogen Cyanide Chemistry. VIII. New Chemistry of Diaminomaleonitrile. Heterocyclic Synthesis[1]

R. W. Begland, D. R. Hartter, F. N. Jones, D. J. Sam, W. A. Sheppard,*
O. W. Webster, and F. J. Weigert

Contribution No. 2112 from the Central Research Department, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware 19898.

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Alkyl derivatives of diaminomaleonitrile (DAMN), are prepared by direct methylation and by reduction of Schiff bases. Cyclic anhydrides and DAMN produce amide acids. 2,3-Dicyanodiazepines and 2,3-dicyanodihydrodiazepines are prepared by condensation of DAMN with 1,3-diketones or other carbonyl derivatives. 2-Substituted 4,5-dicyanoimidazoles are prepared by improved cyclization procedures of Schiff bases and amides of DAMN. Tetrasubstituted pyrazines are prepared by condensation of DAMN with diimines prepared from alcohols and cyanogen.

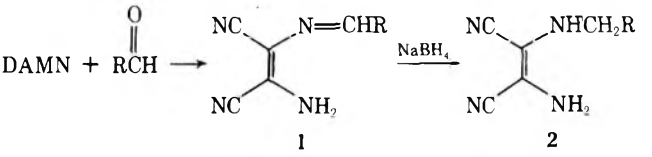
Diaminomaleonitrile (DAMN), a weakly basic diamine resembling *o*-phenylenediamine in reactivity, can be prepared directly from hydrogen cyanide by oligomerization[2] and indirectly by hydrogenation of diiminosuccinonitrile.[3] DAMN has been proposed to be an essential intermediate to purines in prebiotic origin of life[4] and has been used to prepare a variety of heterocyclic compounds, including 4,5-dicyanoimidazoles,[5,6] 5,6-dicyanopyrazines,[1,7] and purines[8] (including caffeine[5]), as well as amides[5,7a,9] and Schiff bases.[7a,9] We now report synthesis of new alkyldiaminomaleonitriles and seven-membered diazaheterocycles from DAMN; also we have extended the synthesis of five- and six-membered heterocycles and Schiff bases from DAMN.

Results and Discussion

Schiff Bases of Diaminomaleonitrile. DAMN condenses rapidly with aliphatic and simple aromatic aldehydes in methanol without a catalyst.[7a,9] However, if the aldehyde is substituted by a strong electron-withdrawing group, acid catalysis (sulfuric acid) is required to make the condensation proceed at a reasonable rate. For amides, phosphorus oxychloride promotes condensation and the product may be isolated as a hydrochloride.

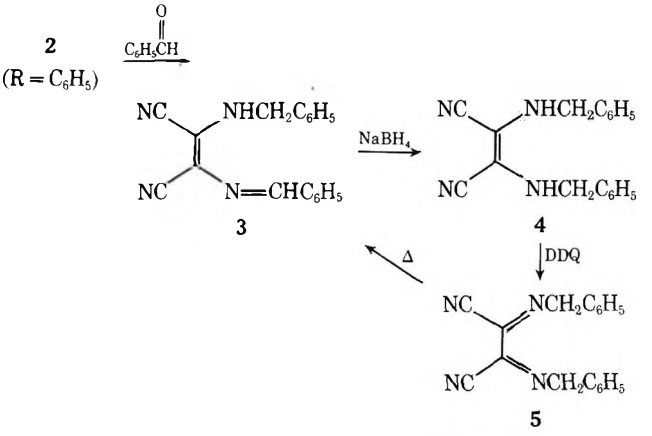
***N*-Alkyldiaminomaleonitriles.** Di-(*tert*-octylamino)-maleonitrile has been prepared indirectly from reaction of diisobutene, hydrogen cyanide, and hydrogen fluoride.[10] *N*-Alkyldiaminomaleonitriles (alkyl group is ethyl, isopropyl, *tert*-butyl, and cyclohexyl) and *N,N'*-dialkyldiaminomaleonitriles (alkyl group is isopropyl and cyclohexyl) have been prepared in low yield from *N*-alkyliminoacetonitriles.[11] Di-(*tert*-butylamino)maleonitrile was obtained in low yield by oligomerization of *tert*-butyl isocyanide with hydrogen chloride followed by hydrolysis.[12]

DAMN can be converted indirectly to an *N*-alkyl derivative **2** by conversion to Schiff base **1** followed by reduction. *N*-Benzyldiaminomaleonitrile results from a benzaldehyde anil (**1**, R = C_6H_5) and *N*-alkyldiaminomaleonitriles are prepared from aliphatic aldehydes (R = cyclohexyl and *tert*-butyl). Schiff base **1** does not react with a second mole of aldehyde but *N*-benzyldiaminomaleonitrile (**2**, R = C_6H_5) forms Schiff base **3**, which can be reduced



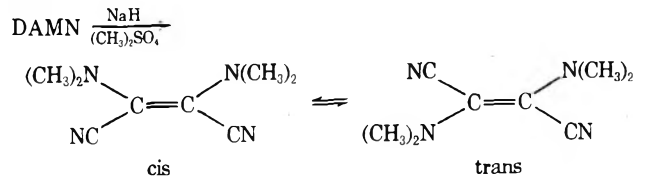
1 2

to *N,N'*-dibenzyldiaminomaleonitrile (**4**). This new DAMN derivative was oxidized to dibenzyldiiminosuccinonitrile (**5**), which on standing isomerizes to **3** and an



isomer that also is reduced to **4**. Schiff base **3** has four possible isomeric forms about the imine and the carbon–carbon double bond. The structure of the intermediate **1** was established as the Schiff base rather than the isomeric dihydroimidazole by the presence of a low-field =CH proton in the nmr.

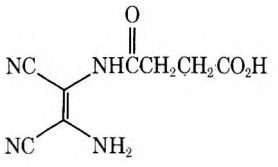
Direct tetramethylation of DAMN was accomplished by reaction of DAMN with excess sodium hydride at −30 to −20° to form the colorless monoanion followed by treatment with dimethyl sulfate at −10°. Nmr showed the



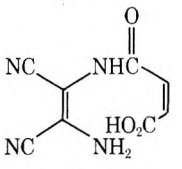
product to contain about 15% bis(dimethylamino)fumaronitrile (trans), and pure bis(dimethylamino)maleonitrile (cis) was isolated by low-temperature crystallization. On slow distillation of the crude reaction product, the cis isomer isomerizes to the lower boiling trans isomer.[13] Both cis and trans forms *isomerize* to the equilibrium mixture, 43% trans. The isomerization in DMSO at 105° is slow unless iodine is added as a catalyst. This is in marked contrast to DAMN, in which the cis configuration is much more stable than the trans[14] and is similar to bis(methylmercapto)maleonitrile and bis(methylmercapto)fumaronitrile, where the cis and trans forms equilibrate at 191° in 9 hr (melt, iodine catalysis) to 32% trans.[15] The cis and trans assignments of the tetramethylated products are based on their dipole moments in dioxane (Table I) and are similar to the bis(methylmercapto)dicyanoethylenes.[15] The C=C stretch absorption for the methylated cis isomer is as expected (see Table I). The strong absorption for the trans isomer is not normal (note trans methylmercapto derivatives) and could result if the double bond is slightly twisted or if one of the dimethylamino groups is held out of plane of the molecule by steric interaction. The dipole moment of 2.78 D for the trans isomer is higher than expected (calculated value employing group moments for the aromatic series is 1.50). The calculated value for the cis isomer (9.78 D) is also higher than the measured value (calculated value for DAMN is 9.62 D; these high values could result from use of group moments that are determined from aromatic systems). The steric interaction of dimethylamino groups is expected to be much more significant than for the methylmercapto group. The marked stability of cis over trans isomers in diaminodicyanoethylenes is not understood but may be analogous to the 1,2-dithiodicyanoethylenes.[15]

Amides and Ureas from Diaminomaleonitriles. Amides of DAMN have been reported from reaction of acyl halides and anhydrides with DAMN.[5,6,7a,9,16]

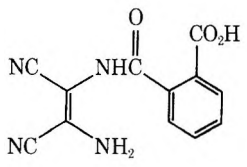
Some new amides with free acid groups (**6**, **7**, and **8**) are readily prepared by reaction of succinic, maleic, and phthalic anhydride with DAMN. With phthalic anhydride the imide **9** was also isolated in 21% yield.



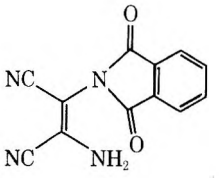
6



7



8



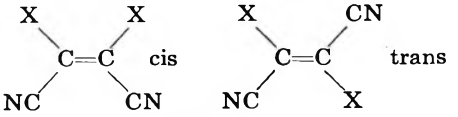
9

The acrylamide of DAMN was formed from acryloyl chloride and DAMN. Low molecular weight polyamides can be prepared from reaction of DAMN with diacid chlorides and will be described in other publications.

DAMN with phenyl isocyanate gives a monourea **10** at room temperature in CH_3CN and a diurea **11** in DMF at 80°.

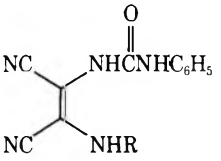
Synthesis of Heterocycles. Five-Membered Rings. The synthesis of 4,5-dicyanoimidazoles[5,6] has been extended to preparation of a series of 2-alkyl and 2-aryl derivatives. The Schiff bases **1** from condensation of DAMN with aldehydes can be oxidized to imidazoles **12** by reagents such as diiminosuccinonitrile (DISN) or dichlorodicyanoquinone (DDQ). A series of 2-aryl-4,5-dicyanoimidazoles was prepared to determine the structure of products from reaction of diazodicyanoimidazole with halobenzenes.[17]

Table I
Dipole Moments and Infrared Absorption of 1,2-Dicyanoethylene Derivatives

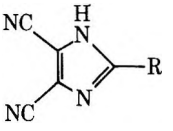


X	Isomer	Dipole moment, D	C=C stretch, cm^{-1}	Registry no.
NH_2	Cis	7.9[a]	1626 (s)	1187-42-4
$N(CH_3)_2$	Cis	6.98	1605 (s)	51801-84-4
	Trans	2.78	1600 (s)	51801-85-5
SCH_3	Cis	5.08	1493 (s)	7373-02-6
	Trans	1.57	None	7373-03-7

[a] R. L. Webb, S. Frank, and W. C. Schneider, *J. Amer. Chem. Soc.*, **77**, 3491 (1955).

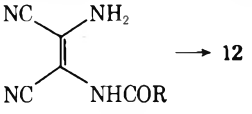


10, R = H
11, R = $CONHC_6H_5$



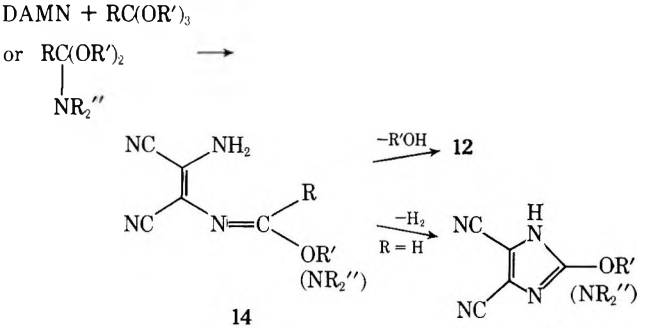
12

Condensation of DAMN with acid chlorides or anhydrides gives 1:1 products **13** which for R = CH_3 can be dehydrated to the imidazole **12** (R = CH_3). Imidazoles can



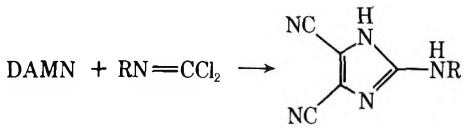
13

be produced from DAMN in one step from ortho esters[5] or imino ether hydrochlorides.[6] If the initial condensation of DAMN and ortho esters or ortho amides is run under mild conditions, the intermediate alkoxy imine or amidine **14** can be isolated. Amidines, **14**, can also be made by treatment of DAMN with *N,N*-dialkylamides and $POCl_3$. Oxidation of **14** leads to a new family of 2-heterosubstituted imidazoles **15**.[18] Other N-substituted aminoimidazoles **16**



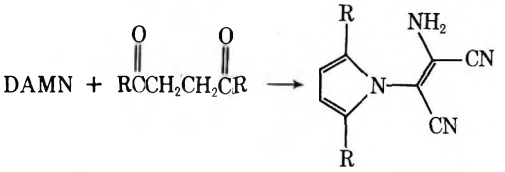
14 **15**

can be prepared from DAMN and isocyanide dichlorides. The parent 2-amino-4,5-dicyanoimidazole (**16**, R = H) is prepared from DAMN and cyanogen chloride and is used to prepare the reactive diazodicyanoimidazole.[17]



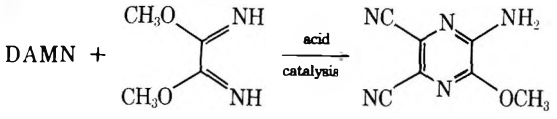
16

DAMN reacts with 1,4-diketones to give substituted pyrroles **17**.



17, R = CH_3, C_6H_5

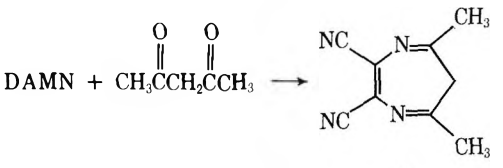
Six-Membered Rings. The synthesis of aminocyanopyrazines by condensation of DAMN with DISN is a major synthetic development.[1] The condensation of DAMN with 1,2-dimethoxy-1,2-diiminoethane (methanol–cyanogen adduct) leads to tetrasubstituted pyrazine **18**. As in



18

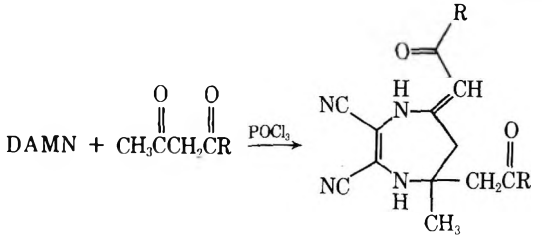
DISN–DAMN condensation, the amount of acid is critical to control the condensation to give a single major product. The synthesis of 5,6-dicyano-2-arylpyrazines[19] has been extended to preparation of 2-methyl-5,6-dicyanopyrazine by condensation of α-chloroacetone or pyruvaldehyde with DAMN.

Seven-Membered Rings. DAMN condenses with acetylacetone to give the 6*H*-1,4-diazepine **19**. Benzoylaceto-



19

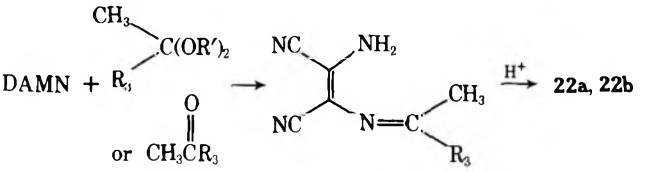
phenone and β-keto esters give uncyclized products under mild conditions, but methyl acetoacetate and *N,N*-dimethylacetoacetamide gave the tetrahydro-6*H*-1,4-diazepine **20** when phosphorus oxychloride was used as catalyst.



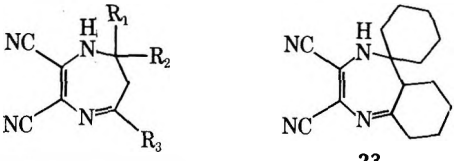
20

R = OCH_3 or $N(CH_3)_2$

Under very mild conditions the Schiff base from DAMN and acetophenone ketal **21** (R_3 = C_6H_5) can be isolated, but it readily hydrolyzes in moist air. However, with an acid catalyst DAMN condenses with 2 mol of ketones or their ketals to give a variety of 1,7-dihydro-6*H*-1,4-diazepines (**22a, 22b**), including the unusual spiro dihydrodiazepine **23** from cyclohexanone. Dihydrodiazepines (**22a, 22c, 22d, 22f**) can also be produced from DAMN and α,β-unsaturated ketones. However, cinnamaldehyde gives only the Schiff base.[9] The diazepine **24b** was produced from

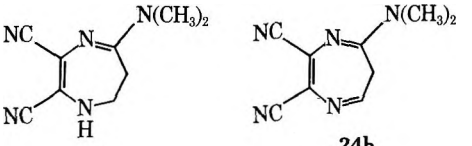


21



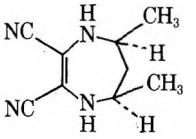
22a, $R_1 = R_2 = R_3 = CH_3$
b, $R_1 = CH_3$; $R_2 = R_3 = C_6H_5$
c, $R_1 = R_2 = H$; $R_3 = CH_3$
d, $R_1 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$
e, $R_1 = H$; $R_2 = R_3 = CH_3$
f, $R_1 = H$; $R_2 = R_3 = C_6H_5$

condensation of DAMN with *N,N*-dimethylacrylamide to give **24a** followed by oxidation with DDQ.



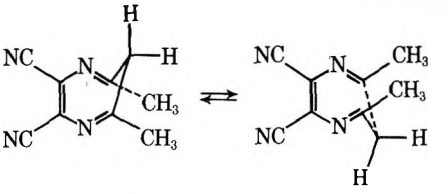
24a 24b

Diazepine **19** was reduced to the 1,4,5,7-tetrahydro-6*H*-1,4-diazepine **25**, which is a cyclic dialkyl DAMN derivative. Only the cis product was formed, since the proton nmr showed multiplets of equal intensity for the two C-6 protons. Compound **25** oxidized readily to the dihydrodiazepine **22e**.

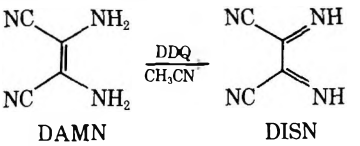


25

The room-temperature pmr spectrum of diazepine **19** showed only a single line which resolved at low temperature (−30° in acetonitrile solution) to the expected singlet for the two methyl groups and an AB δ 1.94 and 4.41 (J_{AB} = 10 Hz) for the methylene. The low-temperature chemical shift and the coalescence temperature (about room temperature) indicate a moderately low free energy of activation for the ring-inversion process. A similar nmr spectrum was observed for a benzodiazepine derivative.[20]

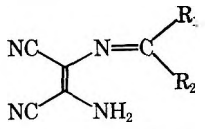


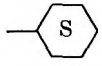
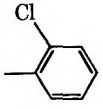
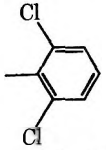
Oxidation and Hydrolysis of Diaminomaleonitrile. The chlorination of DAMN led to dichlorodiiminosuccinonitrile, presumably by initial oxidation of DAMN to DISN.[3] Direct oxidation of DAMN to DISN has been accomplished in essentially quantitative yield by treatment of DAMN with DDQ in acetonitrile.



DAMN DISN

Table II
Diaminomaleonitrile Schiff Bases and Amidines[a]



R_1	R_2	Registry no.	Method[b]	Yield, %	Crystn soln	Mp, °C	Ir, cm^{-1}	Nmr, δ
CH_2CH_3	H	51801-86-6	A	68	Ether–hexane	71–72	3425, 3300, 2250, 2210, 1630, 1610, 1470, 1380, 1100, 893	
$CH(CH_3)_2$	H	51801-87-7	A	87	Ether–hexane	82–83	3425, 3320, 2250, 2210, 1610, 1460, 1385, 1315, 975	($CDCl_3$) 1.10 (6 H, d, CH_3), 2.50 (1 H, m, CH), 5.37 (2 H, br s, NH_2), 7.85 (1, H, d, CH)
$C(CH_3)_3$	H	51801-88-8	A	85	Hexane	86–88	3425, 3300, 2250, 2210, 1620, 1465, 1385, 1360, 943, 916	($CDCl_3$) 1.10 (s, 3 CH_3), 5.40 (2 H, br s, NH_2), 7.78 (s, CH)
$CH(CH_2)_3CH_3$ CH_2CH_3	H	51801-89-9	A	81	Hexane	51–52	3425, 3330, 3175, 2210, 1610, 1000–900 (br)	
	H	51801-90-2	A	60	Ether–hexane	89–90	3425, 3300, 2250, 2210, 1610, 1590, 1460, 1380, 1360	
	H	51801-91-3	B	89	THF–anisole	222–223	3464, 3426, 3334, 2240, 2204, 1608, 1604, 1590, 1570, 1563	
	H	51801-92-4	B	88	Ethyl acetate	199–200	3455, 3320, 2240, 2200, 1610, 1578, 1548	
CH_2CHCH_3 OH	H	51801-93-5	A	79	THF–hexane	133–135	3225, 3125, 2200, 1640, 1600, 1460, 1380, 1140, 1110, 1075, 955, 930	1.00 (3 H, d, CH_3), 2.35 (2 H, t, CH_2), 3.88 (1 H, m, (CHO), 4.60 (1 H, d, OH), 7.35 (2 H, br s, NH_2), 7.68 (1 H, t, CH)
C_6H_5	CH_3	51802-34-7	B	65	Petroleum ether	123–123.5		
CF_3	H	51801-94-6	B	28	Benzene	154–155	3375, 3270, 3150, 2195, 1640, 1620, 1580	7.7 (1 H, m)
$N(CH_3)_2$	H	51801-95-7	C	60	Benzene	152–154	3570, 3450, 2270, 2250, 1610, 1430, 1350, 1270, 1240, 1120, 890	2.95, 3.08 (ss, 2 CH_3), 5.83 (NH_2), 7.59 (s, =CH)
$N(CH_3)_2$	CH_3	51801-96-8	C	54	Benzene	110–112	3400, 3300, 2205, 2195, 1565	2.15 (s, 3 H), 3.05 (s, 6 H), 4.4 (m, 2 H)
$N(CH_2CH_3)_2$	CH_3	51801-97-9	D	57	Methanol–ether	185–186	3600, 3360, 2240, 1640, 1600	1.1 (t, J = 6 Hz, 6 H), 2.2 (s, 3 H), 3.6 (m, 4 H), 8.4 (m, 2 H)
$N(CH_2CH_3)_2$	$CH_2CH_2CH_3$	51801-98-0	D	27	Methanol–ether	188–189	3300–3000, 2185, 1640, 1585	0.9–1.7 (m, 11 H), 2.3–2.6 (m, 2 H), 3.4–3.7 (m, 4 H), 8.5 (br, 2 NH)

$N(CH_3)_2$	CH_2CH_3	51801-99-1	D	35	Methanol–ether	185–186	3300, 3150, 2230, 1650, 1600	1.35 (t, J = 7.5 Hz, CH_3), 2.80 (q J = 7.5 Hz, CH_2), 3.45 (br, NCH_3)
	H	51802-00-7	B	100	None	>280	3425, 3300, 3195, 2240, 2210, 1605, 1570, 1510	Insoluble
		51802-01-8	C	55	Benzene	159–160	3450, 3360, 2225, 2210, 1620, 1590, 1575	2.1 (m, 2 H), 2.8 (m, 2 H) 2.91 (s, 3 H), 3.49 (t, 2 H), 5.2 (m, 2 H)
		51802-02-9	C	67	Benzene	132–135	2980, 2210, 1640, 1605, 1565	3.10 (s, 12 H), 7.98 (s, 2 H)

[a] Satisfactory analytical data for C, H, and N were reported for all new compounds listed in the table. [b] See Experimental Section for general procedure. [c] From terephthalaldehyde.

Hydrolysis of DAMN in alkali solution leads to glycine, ammonia, and carbon dioxide or with barium hydroxide to oxalic acid, ammonia, and carbon dioxide.[21a] With alkaline peroxide, DAMN is quantitatively converted to oxamide.[21b]

Experimental Section

The ir spectra were obtained on a Perkin-Elmer Model 21 spectrometer; the uv spectra on a Cary Model 14; the nmr spectra on a Varian A-60; and the mass spectra on a Du Pont CEC 21-110B high-resolution double-focusing instrument. Where a number of compounds were made by a more or less standard procedure a typical method is given and the compounds are listed in tables. The petroleum ether used boiled at 37–50°.

Diaminomaleonitrile Schiff Bases and Amidines (Table II). Method A. Aldehyde plus DAMN in Methanol, No Catalyst. See ref 7a and 9.

Method B. Acid Catalysis. 2-Amino-3-(2,2,2-trifluoroethylideneamino)maleonitrile (1, R = CF_3). To a solution of 5.4 g (0.05 mol) of DAMN in 100 ml of THF was added 5 drops of H_2SO_4. Fluoral gas (9.8 g, 0.10 mol) was passed over the solution and maintained in the flask with a Dry Ice condenser. After a mild exotherm, the resulting solution was stirred for 4 hr and stripped and the resulting solid–oil was dried on a porous plate to give a white solid. Recrystallization from benzene gave 2.64 g (28%) of white needles: mp 154–155° dec; ir (Nujol) 3375, 3270, 3150, 2195, 1640, 1620, and 1580 cm^{-1}; nmr (acetone-d_6) δ 7.7 (multiplet).

Method C. Amide Condensation, Phosphorus Oxychloride Catalysis. 2-Amino-3-(*N,N*-dimethylaminoethylideneamino)-maleonitrile (14). To a solution of 4.0 g (0.037 mol) of DAMN in 30 ml of dimethylacetamide at 10° was added dropwise over 10 min 4.8 g (0.031 mol) of $POCl_3$. The temperature rose to 30° and a precipitate formed. After 1.5 hr 400 ml of cold water was added and the resulting solution was neutralized with concentrated ammonium hydroxide. The precipitate was collected, dissolved in 150 ml of chloroform, and dried over anhydrous $MgSO_4$ and the solvent was removed to give 3.5 g (54%) of 2-amino-3-(*N,N*-dimethylaminoethylideneamino)maleonitrile.

Method D. Amide Condensation, Phosphorus Oxychloride Catalysis, Hydrochloride Isolation. 2-Amino-3-(*N,N*-diethylaminobutylideneamino)maleonitrile Hydrochloride (14). To a solution of 10.8 g (0.10 mol) of DAMN and 20 g of *N,N*-diethylbutyramide in 100 ml of THF was added 10 ml of $POCl_3$ over 10 min. After stirring for 1.5 hr the resulting tan solid was collected and recrystallized from methanol–ether.

These and other Schiff bases and amidines prepared by these methods are listed in Table II.

Alkyl Derivatives of Diaminomaleonitrile (Table III). Method A. Reduction of Diaminomaleonitrile Schiff Bases. *N*-Benzyldiaminomaleonitrile (2, R = C_6H_5). To a solution of 3.92 g (0.02 mol) of Schiff base (1, R = C_6H_5) in 50 ml of methanol and 75 ml of THF was added 0.76 g (0.02 mol) of sodium borohydride in portions. This solution was stirred for 15 min and poured into 500 ml of ice water. The resulting precipitate was collected and dried to give 3.63 g (90%) of 2 (R = C_6H_5) as a light tan powder. Recrystallization from ether–petroleum ether gave light yellow needles: mp 114–116°; ir (Nujol) 3450, 3355, and 3250 ($-NH_2$, NH), 2220 and 2210 (-CN), 1640, 1620, and 1590 cm^{-1} (C=C, C=N, $-NH_2$); uv (CH_3CN) 311 mμ (ϵ 15,800); nmr (acetone-d_6) δ 4.32 (s, 2), 4.9 (br, 3), 7.35 (s, 5). See Table III for analysis.

***N*-Benzyl-*N'*-benzylidinediaminomaleonitrile (3).** To a solution of 6.0 g (0.03 mol) of 2 in 100 ml of ether was added 3.7 g (0.035 mol) of benzaldehyde and 5 drops of concentrated H_2SO_4. A mild exotherm occurred and a yellow precipitate slowly formed. After 1 hr the solid was collected and rinsed with ether to give 8.2 g (95%) of 3. Recrystallization from ethyl acetate gave bright yellow crystals: mp 182.5–184.0°; ir (KBr) 3345 (NH), 3060 (=CH-), 2240 and 2200 (-C≡N), 1610, 1585, and 1500 cm^{-1} (C=C and C=N); uv (CH_3CN) 263 mμ (ϵ 15,600), 379 (28,600), 397 (22,500); nmr (DMSO-d_6) δ 4.64 (s, 2), 7.40 (m, 8), 8.10 (m, 2), 8.35 (s, 1), 8.75 (br, 1). For reduction of this compound see Table III.

Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.5; H, 4.9; N, 19.6. Found: C, 75.6; H, 4.9; N, 19.7.

***N,N*-Dibenzyldiiminosuccinonitrile (5). Synthesis and Rearrangement to *N*-Benzyl-*N'*-benzylidinediaminomaleonitrile (3).** A solution of 2.88 g (0.01 mol) of 4 in 75 ml of benzene was cooled to 7° and added to a cold solution of 2.27 g (0.01 mol) of DDQ in 75 ml of benzene. Dihydrodichlorodicyanoquinone imme-

diately precipitated. The resulting mixture was stirred for 15 min and filtered cold and the benzene was removed under reduced pressure to give 2.60 g (91%) of **5** as a yellow powder: ir (Nujol) no -NH, 2240 and 2210 (weak, -CN), 1620, 1600, and 1580 cm^{-1} (-C=N and C_6H_5); nmr ($CDCl_3$) δ 5.21 (s, 4), 7.38 (s, 10).

Recrystallization of **5** from benzene gave complete conversion to **3**. Upon standing at room temperature for several days or upon recrystallization from ether, **5** is converted into an unknown isomer of **3** and upon heating is converted to **3**. The unknown isomer shows ir (KBr) 3310 (-NH), 3030 (=CH), 2240 and 2200 (-CN), 1620, 1590, and 1500 cm^{-1} (-C=N and C_6H_5); uv λ_{max} (CH_3CN) 265 mμ (ϵ 11,100), 367 (30,000).

Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.5; H, 4.9; N, 19.6. Found: C, 75.3; H, 4.7; N, 19.7.

Method B. Alkylation of Diaminomaleonitrile. Bis(dimethylamino)maleonitrile and Bis(dimethylamino)fumaronitrile. A solution of 54.0 g (0.50 mol) of DAMN in 300 ml of glyme was added dropwise to a suspension of 2.5 mol of sodium hydride in 1 l. of glyme at −30 to −20°. Hydrogen (13.3 l.) was evolved. The reaction mixture was warmed to −10° and 237 ml (2.5 mol) of dimethyl sulfate was added over 3.0 hr. During the addition 38.2 l. of hydrogen was produced. The reaction mixture was stirred for 1 hr at −10° and filtered. The precipitate of unreacted sodium hydride and sodium methyl sulfate was washed with 500 ml of glyme and the combined filtrate and wash was concentrated at room temperature to about 250 ml of solution containing dimethyl sulfate, bis(dimethylamino)maleonitrile, and bis(dimethylamino)fumaronitrile (nmr). The ratio of maleo- to fumaronitrile product was 85:15. On cooling the mixture to −80° bis(dimethylamino)maleonitrile crystallized (44.3 g, 54%). An analytical sample was recrystallized at −80° from glyme: mp 35–36°; ir (KBr) 2985, 2200, 1605, 1480, 1460, 1380, 1175, 1135, 1105, 1060, 1030, 870 cm^{-1}; uv λ_{max} (CH_2Cl_2) 328 nm (ϵ 8540); dipole moment 6.98 D (dioxane); nmr ($CDCl_3$) δ 2.75 (s).

The mother liquor from the crystallization of the cis-methylated product was slowly distilled through a spinning band column (5 hr). Bis(dimethylamino)fumaronitrile (33.0 g, 40%), bp 89° (0.25 mm), was obtained. An analytical sample was obtained by recrystallization from glyme at −80°: mp 46–47.5°; ir (KBr) 2940, 2875, 2840, 2790, 2230, 2175, 1600, 1450, 1400, 1290, 1105 cm^{-1}; uv λ_{max} (CH_2Cl_2) 318 nm (ϵ 9360); dipole moment 2.78 D (dioxane); nmr ($CDCl_3$) δ 2.82 (s). See Table III for analysis.

Isomerization of Bis(dimethylamino)maleonitrile and -fumaronitrile. A solution of 0.10 g of bis(dimethylamino)maleonitrile and 1 ml of deuterated DMSO was heated at 105–110° for 3 days. Nmr showed the sample to be 38% isomerized to the fumaronitrile. A crystal of iodine was added and heating continued at 105–110° for 4.5 hr. Nmr showed the sample to be 44% trans.

The above experiment was repeated with bis(dimethylamino)-fumaronitrile. After 3 days 30.6% of the cis isomer was present. After an additional 4.5 hr with iodine present, the equilibrium point with 42% trans and 58% cis isomer was reached.

***Diaminomaleonitrile Succinamide* (6).** A solution of 5.4 g (50 mmol) of DAMN and 5.0 g (50 mmol) of succinic anhydride in 150 ml of THF was refluxed for 20 hr. The solvent was removed at reduced pressure, leaving 10.3 g of crude **6** which was recrystallized from THF, 9.1 g (87%) of white powdery crystals: mp 183–186°; uv (CH_3CN) 288 mμ (ϵ 13,300); ir (KBr) 3400–2500 (NH_2, NH, OH, CH), 2248, 2210 (C≡N), 1690 (acid C=O), 1671, 1522 (RNCO-), 1636 (NH_2), 1608 cm^{-1} (C=C); nmr (DMSO-d_6) δ 2.54 (s, 4), 6.97 (s, 2), 9.15 (s, 1), 11.78 (broad s, 1).

Anal. Calcd for $C_8H_8O_3N_4$: C, 46.2; H, 3.9; N, 26.9. Found: C, 46.2; H, 4.0; N, 27.1.

Diaminomaleonitrile Maleamide (7). Under similar conditions maleic anhydride gave a monoamide: mp 185–198° from anisole; 70% yield; uv (CH_3CN) 393 mμ (ϵ 19,700), 295 (4930), 256 (4960); ir (KBr) 3400–3100 (OH, NH_2, NH), 2240, 2200 (C≡N), 1786, 1751, 1690 (C=O), 1635, 1594, 1560, 1528 cm^{-1} (NH, C=C, N=C and/or $RCOO^-$); nmr (DMSO-d_6) δ 6.31 (d, 1, J = 6 Hz), 7.10 (d, 1, J = 6 Hz), 7.53 (s, broad, 4).

Anal. Calcd for $C_8H_6O_3N_4$: C, 46.6; H, 2.9; N, 27.2. Found: C, 46.7; H, 2.9; N, 27.2.

Diaminomaleonitrile Phthalamide (8). Refluxing phthalic anhydride and DAMN in THF for 20 hr gave a 24% yield of the phthalamide **8**: mp 181°; uv (CH_3CN) 382 mμ (ϵ 14,500), 285 (6900), 265 (8820); ir (KBr) 3400, 3295, 3195 (NH_2, NH, OH), 2200 (C≡N), 1760, 1675, 1625 (C=O, NH_2), 1545 cm^{-1} (C=N); nmr (DMSO-d_6) δ 7.7 (m, 6), 8.0 (m, 2).

Anal. Calcd for $C_{12}H_8O_3N_4$: C, 56.3; H, 3.2; N, 21.9. Found: C, 56.4; H, 3.1; N, 21.9.

Diaminomaleonitrile Phthalimide (9). From the mother liquor of **8** was isolated 21% **9** by dissolving in DMF, precipitating with H_2O, and recrystallizing from CH_3OH: mp 275° dec; uv (CH_3CN) 287 mμ (ϵ 14,900), 217 (38,600); ir (KBr) 3350, 3295, 3240, 3176 (NH_2), 2242, 2216 (C≡N), 1787, 1720 (C=O), 1647 (NH_2), 1598 cm^{-1} (C=C); nmr (DMSO-d_6) δ 8.02 (s, 4), 8.33 (s, 2).

Anal. Calcd for $C_{12}H_6O_2N_4$: C, 60.5; H, 2.5; N, 23.5. Found: C, 59.9; H, 2.6; N, 23.1.

Diaminomaleonitrile Acrylamide. This amide was made from DAMN and acryloyl chloride in THF at 0–10° and was isolated as the hydrochloride salt. The monohydrate, mp 151.5–152°, crystallized from water in 52% yield: ir 3545, 3345, 3185, 2250, 2200, 1685, 1660, 1625, 1610, 1530 cm^{-1}; nmr (DMSO-d_6) δ 3.35 (s, NH), 5.63 (d, d, J = 7, 9 Hz, 1 H), 6.1 (m, 2 H), 7.05 (s, NH + OH).

Anal. Calcd for $C_7H_6N_4O \cdot H_2O$: C, 47.3; H, 4.5; N, 31.5. Found: C, 47.3; H, 4.1; N, 31.3.

The water was removed from the monohydrate by heating under reduced pressure.

Anal. Calcd for $C_7H_6N_4O$: C, 51.9; H, 3.7. Found: C, 51.8; H, 3.7.

Phenylurea Derivative of Diaminomaleonitrile (10). A solution of 1.08 g (10 mmol) of DAMN and 2.38 g (20 mmol) of phenyl isocyanate was kept for 20 hr at 25° as crystals slowly separated. The mixture was warmed on steam bath for 1.5 hr. The solid monoadduct, mp 180–210° dec, was collected and dried, yield 2.1 g (93%).

Anal. Calcd for $C_{11}H_9N_5O$: C, 58.2; H, 4.0; N, 30.8. Found: C, 58.3; H, 4.0; N, 31.1.

Bis(phenylurea) Derivative of Diaminomaleonitrile (11). A mixture of 3.36 g of DAMN, 12 g of phenyl isocyanate, and 40 ml of DMF was stirred at 80° for 4 hr. The dark red solid was collected and digested with warm acetonitrile. Filtration and drying gave 8.7 g of pale yellow crystals, ir (KBr) CN very weak, 1685, 1670, 1610, 970, 750, 695 cm^{-1}.

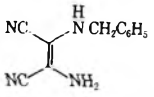
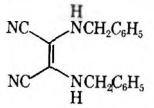
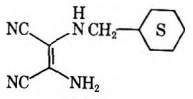
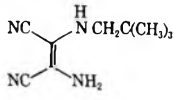
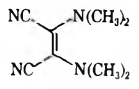
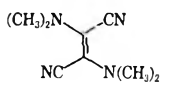
Imidazoles (12) from Diaminomaleonitrile (Table IV). Method A. Oxidation of Diaminomaleonitrile Schiff Base with Dichlorodicyanoquinone. 2-(2-Chlorophenyl)-4,5-dicyanoimidazole (12, R = 2-ClC_6H_4). A solution of 38 g (0.16 mol) of Schiff base from DAMN and 2-chlorobenzaldehyde and 38 g (0.16 mol) of 2,3-dichloro-5,6-dicyanoquinone (DDQ) in 1200 ml of CH_3CN was refluxed for 4 days. The solution was evaporated to dryness and the residual solid was slurried at reflux with 3 l. of benzene and filtered to remove the insoluble hydroquinone. The benzene filtrate was concentrated at reduced pressure, affording about 30 g of 2-(2-chlorophenyl)-4,5-dicyanoimidazole. Recrystallization from CH_2Cl_2–ether gave 24.8 g (66%) of **12** (R = 2-ClC_6H_4) as white needles: mp 205–208° dec; uv λ_{max} (CH_3CN) 264 mμ (ϵ 17,050); ir (KBr) 3290 (NH), 3080 (CH), 2240 (C≡N), 1590, 1568, 1543, 1508 cm^{-1} (C=C and/or C=N). See Table III for analysis.

Method B. *In Situ* Formation of Diaminomaleonitrile Schiff Base and Oxidation with Diiminosuccinonitrile. 2-*tert*-Butyl-4,5-dicyanoimidazole [12, R = $C(CH_3)_3$]. A solution of 25.9 g of pivaldehyde, 32.4 g of DAMN, 31.8 g of diiminosuccinonitrile (DISN), and 5.0 g of oxalic acid in 1 l. of anhydrous acetonitrile was refluxed under N_2 for 17 hr. The dark solution was preadsorbed on 140 g of Silicar CC-7 and chromatographed. Elution with chloroform gave a viscous, oily solid which was recrystallized from ether–hexane to give 30.0 g (57%) of colorless 2-*tert*-butyl-4,5-dicyanoimidazole, mp 150–151°. See Table III for analysis.

Method C. Reaction of *N,N*-Dialkylamides with Diaminomaleonitrile. 4,5-Dicyanoimidazole (12, R = H). A solution of 10.8 g (0.10 mol) of DAMN in 75 ml of dimethylformamide was cooled in an ice bath and 10.0 g (0.065 mol) of $POCl_3$ was added dropwise below 10°. The solution was heated to 160° over 1 hr and cooled to approximately 100° and most of the solvent was removed under vacuum. Water (100 ml) was added; the solution was warmed to 70° and filtered and the aqueous filtrate was extracted nine times with 200-ml portions of ether. The combined ether extracts were dried over $MgSO_4$ and the ether was removed to give 10.7 g (90%) of 4,5-dicyanoimidazole.[7a]

2-Aminoimidazoles. 2-*tert*-Butylamino-4,5-dicyanoimidazole [16, R = $C(CH_3)_3$]. To a solution of 8 g of *tert*-butyl isocyanide dichloride in 100 ml of THF was added 5.0 g of DAMN. The temperature rose to 43° and a precipitate formed. Upon stirring for 18 hr the precipitate redissolved and the resulting dark solution was preadsorbed and chromatographed on Silicar. Chloroform elution gave 0.94 g (11%) of **16**, R = $C(CH_3)_3$, as white crystals from ether–petroleum ether: mp 171.0–172.5°; ir (Nujol) 3311 (-NH), 2250 (-CN), 1645 cm^{-1} (C=C or C=N); nmr (acetone-d_6) δ 1.41 (s, 9), 6.10 (br, 1).

Table III
Alkyl Derivatives[a] of Diaminomaleonitrile

Compd	Registry no.	Method[b]	Yield, %	Crystn soln.	Mp, °C	Formula	Anal, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Nitrogen Calcd	Nitrogen Found
	51802-03-0	A	91	Ether–petroleum ether	114–116	$C_{11}H_{10}N_4$	66.7	66.6	5.1	5.1		
	51802-04-1	A	75	Ether–petroleum ether	76–79	$C_{18}H_{16}N_4$	75.0	74.6	5.6	5.5	19.4	19.6
	51802-05-2	A	67	CH_2Cl_2–hexane	133–134	$C_{11}H_{16}N_4$	64.7	64.5	7.9	7.8	27.4	27.5
	51802-06-3	A	87	CH_2Cl_2–hexane	165–166	$C_9H_{14}N_4$	60.7	60.4	7.9	7.8	31.4	31.3
		B	94	Glyme	35–36	$C_8H_{12}N_4$	58.5	58.1	7.4	7.4	34.1	34.6
		B	94	Glyme	46–47.5	$C_8H_{12}N_4$	58.5	58.5	7.4	7.2	34.1	34.0

[a] Structures were confirmed by nmr and ir. [b] See Experimental Section for general procedure.

Anal. Calcd for $C_9H_{11}N_5$: C, 57.1; H, 5.9; N, 37.0. Found: C, 56.6; H, 6.3; N, 37.7.

2-Anilino-4,5-dicyanoimidazole (16, R = C_6H_5). A solution of 4.3 g (0.04 mol) of DAMN and 6.2 g (0.035 mol) of phenyl isocyanide dichloride in 100 ml of THF was refluxed for 1 hr, stirred at room temperature for 18 hr, and chromatographed on Silicar. Chloroform–ether elution gave 2.82 g (39%) of **16** as white crystals from chloroform: mp 210–213° dec; ir (KBr) δ 3225 and 3115 (-NH), 2240 and 2230 (-CN), 1635, 1610, 1590, 1550, 1520, and 1500 cm^{-1} (C=C and C=N); uv (CH_3CN) 256 mμ (ϵ 21,700), 309 (9200); nmr (DMSO-d_6) δ 7.0–7.6 (m, 6), 9.6 (br, 1).

Anal. Calcd for $C_{11}H_7N_5$: C, 63.2; H, 3.4; N, 33.5. Found: C, 62.9; H, 3.6; N, 33.1.

2-Amino-4,5-dicyanoimidazole (16, R = H). To a solution of 89.8 g (1.46 mol) of cyanogen chloride in 2.0 l. of THF at 3° was added 157.7 g (1.46 mol) of DAMN. The solution was slowly (1 hr) warmed to reflux temperature (about 50°), and at this point occasional cooling was necessary to control the reflux rate. After an additional 1 hr the mixture was cooled to 0° and 1500 ml of ether was added. The hydrochloride of the imidazole was collected on a filter and was added to 3250 ml of water containing 120 g of sodium acetate. 2-Amino-4,5-dicyanoimidazole (142.6 g, 75% yield) precipitated. This product was purified by dissolving it in a solution of 1099 g of sodium bicarbonate in 2150 ml of water and treating with carbon black. White 2-amino-4,5-dicyanoimidazole (106 g) was reprecipitated by adding 250 ml of 6 *N* HCl. An analytical sample was recrystallized from CH_3CN: mp 270° dec; ir (KBr) 3487, 3380, 3280, 3225, 3030, 2860, 2740, 2650, 2230, 1660, 1600, 1560, 1460, 1410, 1370, 1316, 1280, 1090, 1050, 910, 790, 735 cm^{-1}.

Anal. Calcd for $C_5H_3N_5$: C, 45.1; H, 2.3; N, 52.6. Found: C, 45.3; H, 2.4; N, 52.6.

α-Amino-β-(*N*-2,5-dimethylpyrryl)maleonitrile (17, R = CH_3). A solution of 16.2 g (0.15 mol) of DAMN, 17.1 g (0.15 mol) of hexane-2,5-dione, and 1.0 g of *p*-toluenesulfonic acid in 600 ml of benzene was refluxed for 24 hr under a Dean-Stark trap. The reaction mixture was concentrated *in vacuo* to give 30 g of yellow solid. This material was dissolved in 200 ml of ether, treated with Darco, and recrystallized from ether–hexane. The yield of pale yellow product was 24.6 g (88%): mp 166.0–166.5°; ir (Nujol) 3450, 3330, 3225, 2220, 1640, 1600, 1410, 1380, 1315, 1220 cm^{-1}; nmr (DMSO-d_6) δ 2.08 (s, CH_3), 5.88 (s, CH), 7.73 (s, NH_2).

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.4; H, 5.3; N, 30.1.

α-Amino-β-(*N*-2,5-diphenylpyrryl)maleonitrile (17, R = C_6H_5). A solution of 10.8 g (0.10 mol) of DAMN, 23.8 g (0.10 mol) of 1,4-diphenylbutane-1,4-dione, and 1.0 g of *p*-toluenesulfonic acid in 400 ml of acetonitrile was refluxed for 17 hr. The reaction mixture was concentrated *in vacuo* to give 32 g of yellow solid: This material was dissolved in 200 ml of THF, treated with Darco, and recrystallized from THF–hexane. The yield of pale yellow product was 27.0 g (87%): mp 198–199°; ir (Nujol) 3450, 3330, 2220, 1610, 1590, 1370, 1315, 1075 cm^{-1}; nmr (DMSO-d_6) δ 6.55 (s, CH), 7.45 (s, aromatic), 8.08 (s, NH_2).

Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.4; H, 4.6; N, 18.1. Found: C, 77.7; H, 4.6; N, 18.3.

Pyrazines from Diaminomaleonitrile. 2-Amino-3-methoxy-5,6-dicyanopyrazine (18). A mixture of 55.5 g (0.20 mol) of diaminomaleonitrile tosylate and 23.2 g (0.20 mol) of 1,2-dimethoxy-1,2-diiminoethane[22] in 800 ml of THF was stirred for 3 days, filtered, and stripped. The resulting solid was slurried with water, collected, and recrystallized from ethyl acetate to give 24.5 g (70%) of light tan crystals of **18**: mp 211.5–213.0°; ir (KBr) 3413, 3345,, and 3185 (-NH_2), 2240 (-CN), 1650, 1570, 1550, and 1520 cm^{-1} (C=C, C=N, -NH_2); uv (CH_3CN) 215 mμ (ϵ 20,900), 296 (19,600); nmr (DMSO-d_6) δ 4.06 (s, 3), 8.1 (br, 2).

Anal. Calcd for $C_7H_5ON_5$: C, 48.0; H, 2.9; N, 40.0. Found: C, 48.2; H, 2.9; N, 40.1.

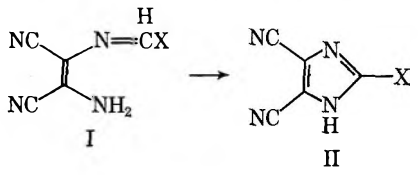
2-Methyl-5,6-dicyanopyrazine. A. From Chloroacetone. A suspension of 10.8 g (0.1 mol) of DAMN, 20 g of chloroacetone, and 100 ml of ethanol was stirred overnight at room temperature. Silicar was added to the dark solution and the solution was stripped to dryness and chromatographed. Eluting with benzene gave the product, which was recrystallized from carbon tetrachloride to give 2.2 g of pale yellow solid: mp 97°; ir (KBr) 3058, 2922, 2242, 1552, 1518, 1438 cm^{-1}; nmr ($CDCl_3$, TMS) δ 2.79 (s, CH_3), 8.82 (s, =CH); uv λ_{max} (CH_3CN) 280 mμ (ϵ 6320), 237 (11,000).

Anal. Calcd for $C_7H_4N_4$: C, 58.4; H, 2.8; N, 39.0. Found: C, 57.8; H, 2.6; N, 39.2.

B. From Pyruvaldehyde. A solution of 54 g of DAMN, 100 g of 40% aqueous pyruvic aldehyde, and 750 ml of ethanol was refluxed for 3 hr, treated with 25 g of Darco, and filtered. On cooling the product crystallized and was recrystallized from CCl_4, giving 59.5 g (80%) of light tan solid.

Diazepine Derivatives from Diaminomaleonitrile. 2,3-Dicyano-5,7-dimethyl-6*H*-1,4-diazepine (19). A mixture of 21.6 g (0.2 mol) of DAMN, 20.0 g (0.2 mol) of acetylacetone, 0.5 g of oxalic acid, and 200 ml of benzene was refluxed in a 1-l. flask with a Dean-Stark trap. In a few minutes, half the expected 7.2 ml of water was collected. After 3 hr, the mixture was cooled and filtered. The solid was rinsed with hexane and dried to give 32.9 g (96%) of product which was purified by dissolving in hot acetonitrile, decolorizing with Darco, and cooling to give colorless crystals, mp 199–200° dec, ir 2250, 1600, 1375, 1260 cm^{-1}.

Table IV
2-Substituted 4,5-Dicyanoimidazoles[a]



X	Registry no. I	Registry no. II	Prepn method[b]	Yield, %	Crystn soln	Mp, °C	Ir, cm^{-1}	Nmr, δ
o-C_6H_4F	51802-07-4	40953-38-6	A[c]	25	Acetone–benzene	246–247	3150, 2220, 1610, 1300, 1230, 1210, 1090, 965, 825, 770, 740	fmr 115.6
m-C_6H_4F	51802-08-5	40953-39-7	A[c]	29	Benzene	198–200	3150, 2220, 1580, 1310, 1263, 1200, 970, 890, 875, 800, 730	fmr 112.9
p-C_6H_4F	51802-09-6	40953-40-0	A[c]	24	Acetone–benzene	220–221	3150, 2220, 1600, 1285, 1235, 1160, 1110, 960, 845, 735	fmr 109.2
o-C_6H_4Cl		41021-16-3	A	66	CH_2Cl_2–ether	211–212	3270, 2220, 1310, 1225, 1115, 1050, 960, 780, 755, 735, 695, 685	
m-C_6H_4Cl	51802-10-9	40953-41-1	A	40	Acetone–benzene	227–228.5	3200, 2220, 1300, 1125, 1095, 1085, 975, 805, 795, 725, 690, 680	
p-C_6H_4Cl	51802-11-0	40953-42-2	A	33	CH_3CN	300–301	3200, 3100, 2260 2240, 1600, 1310, 1280, 1120, 1110, 1095, 1015, 965, 845, 832, 760, 735	
2,6-$C_6H_3Cl_2$		51802-37-0	A	65	Benzene	143–144.5	3210, 2255, 2240, 1590, 1560, 1550, 1510, 962, 795, 783, 720	
o-C_6H_4Br	51802-12-1	40953-43-3	A	34	$CHCl_3$–petroleum ether	182–183	3300, 2240, 1300, 1220, 1100, 1035, 1025, 960, 778, 745, 732	
m-C_6H_4Br	51802-13-2	51802-38-1	A	50	$CHCl_3$–petroleum ether	212–213	3150, 2260, 2230, 1570, 1300, 1120, 1080, 1000, 975, 800, 773, 727	
p-C_6H_4Br	51802-14-3	40953-44-4	A	50	CH_3CN	226 dec	3150, 3050, 2280, 2210, 1600, 1300, 1270, 1115, 1100, 1070, 1010, 990, 840, 830, 815, 730	
o-$C_6H_4CF_3$	51802-15-4	51802-39-2	A	51	$CHCl_3$–petroleum ether	92–93.5	3600, 2270, 1310, 1280, 1240, 1230, 1210, 1060, 1040, 970, 780, 770, 760, 740, 735, 730	fmr 57.80
m-$C_6H_4CF_3$	51802-16-5	40953-37-5	A	64	$CHCl_3$–hexane	205–206	3300, 3200, 2240, 1550, 1330, 1180, 1160, 1125, 1115, 1085, 1075, 970, 900, 820, 760, 725	fmr 62.41
p-$C_6H_4CF_3$	51802-17-6	51802-40-5	A	55	$CHCl_3$	251–252	3200, 2250, 1570, 1320, 1180, 1140, 1120, 1065, 1010, 960, 858, 843, 750, 728, 710, 695	fmr 62.45
CF_3		51802-41-6	A	50	Sublimed	86–88	3200–2300, 2250, 1570, 1515	
$CH_2CH_2CH_3$	51802-18-7	51802-42-7	B	37	Ether–hexane	142–143	3225–2270 (br), 2250, 1565, 1530, 1300, 1265, 1090	($CDCl_3$) 1.07 (3 H, t, CH_3), 1.90 (2 H, sextet, CH_2), 2.91 (2 H, t, CH_2), 11.67 (s, NH)
$C(CH_3)_3$		51802-43-8	B	57	Ether–hexane	150–151	3225, 3225–2500 (br), 2220, 1490, 1350, 1280, 1260, 1210, 1005	1.43 (9 H, s, CH_3), 11.67 (s, NH)
$CHCH_2CH_2CH_3$ | CH_3	51802-19-8	51802-44-9	B	37	Ether–hexane	75–76	3225, 3225–2325 (br), 2220, 1560, 1515, 1280, 1090, 1010	0.8–2.0 (10, H, m), 3.10 (1 H, q, CH), 11.43 (s, NH)

Cyclohexyl	40953-36-4	B	41	Ether–hexane	150–152	3030–2325 (br), 2220, 1575, 1530, 1460, 1380, 1300, 1250, 1060, 1040, 995, 900	1.0–2.5 (10 H, m, CH_2), 2.90 (1H, broad, CH)
$CH_3CH(OH)CH_3$	51802-45-0	B	44	Ether–hexane	125–126	3330–2500 (br), 2220, 1515, 1460, 1380, 1310, 1290, 1120, 1100, 1030, 940, 850	1.08 (3 H, d, CH_3), 2.72 (2 H, d, CH_2), 3.92 (1 H, CH), OH and NH broad
Cyclopropyl	51802-20-1	51802-46-1	B	96		169–172	2800–2500, 2210, 1570, 1525	0.7–0.9 (m, 4 H), 1.7–2.1 (m, 1 H,
$OCH_2CH{=}CH_2$	51802-21-2	51802-47-2	A	27	Water	95–97	3225, 3125, 2260, 1590, 1540, 1315, 1280, 1265, 1135, 1090, 1060, 1010, 965, 935, 925, 825	7.25 (NH + OH), 6.13 (m, =CH), 5.48 (d, J = 18 Hz, m, J = 1 Hz, =CH), 5.57 (d, J = 7 Hz, m, J = 1 Hz, =CH), 5.02 (d, J = 7 Hz, CH_2)
OCH_2CH_3	51802-22-3	51802-48-3	A	54	Water	98–99	3330, 2700, 2250, 1640, 1610, 1470 1450, 1390, 1360, 1315, 1080, 1060, 1015, 1010, 1000, 760, 735	1.45 (t, J = 7 Hz, CH_3), 3.88 (q, J = 7 Hz, CH_2), 10.3 (s, NH)
$N(CH_3)_2$		51802-49-4	A	34	Water	164–166 dec	3225, 2270, 2250, 1650, 1330, 1030, 925	2.98 (s, 6 H), 11.7 (br, NH)
$(CH_2)_4CN(CH_3)_2$ (=O)	51802-23-4	51802-50-7	C	27	CH_2Cl_2–benzene	153.5–155.0	2900–2500, 2265, 1610, 1510	1.4–1.7 (m, 4 H), 2.1–2.7 (m, 4 H), 2.78 (s, 3 H), 2.93 (s, 3 H), 12.5 (br, NH)

[a] Satisfactory analytical data for C, H, and N were reported for all new compounds listed in the table. [b] See Experimental Section for general procedure. [c] Base extraction procedure in separation of product resulted in considerable loss of product.

Anal. Calcd for $C_9H_8N_4$: C, 62.7; H, 4.7; N, 32.6. Found: C, 62.5; H, 4.7; N, 32.3.

2,3-Dicyano-4,5,6,7-tetrahydro-5,7-dimethyl-1*H*-1,4-diazepine (25). To a slurry of 5.00 g (0.029 mol) of **19** in 200 ml of methanol was added 1.14 g (0.03 mol) of $NaBH_4$ in three portions. The temperature rose from 25° to 40° and the solid dissolved. Most of the solvent was removed, 300 ml of water was added, and the resulting solution was extracted with two 400-ml portions of ethyl acetate. Removing the solvent gave nearly colorless product which was recrystallized from ether to give 4.39 g (85%) of **26** as colorless needles: mp 158–160°; ir (KBr) 3370 (–NH), 2985, 2950, and 2890 (CH), 2210 (–CN), 1630 cm^{-1} (–C=C–); uv (CH_3CN) 208 mμ (ε 10,500), 314 (13,300); nmr (CD_3CN) δ 1.15 (m, 1) 1.17 (d, J = 6.2 Hz, 6), 1.5 (m, 1), 2.5–3.0 (m, 2), 4.45 (br, 2).

Anal. Calcd for $C_9H_{12}N_4$: C, 61.3; H, 6.9; N, 31.8. Found: C, 61.1; H, 6.9; N, 32.0.

2,3-Dicyano-5,7-dimethyl-6,7-dihydro-1*H*-1,4-diazepine (22e). To a slurry of 1.76 g (0.01 mol) of **25** in 50 ml of benzene at 10° was added 2.27 g (0.01 mol) of DDQ in 100 ml of benzene. The resulting mixture was stirred for 15 min, filtered to remove dihydrodichlorodicyanoquinone and stripped to dryness without warming. The infrared spectrum of the crude product showed no diimine. Recrystallization from benzene gave 1.46 g (84%) of tan crystals: mp 143–145°; ir (KBr) 3205 (–NH), 2240 and 2210 (–CN), 1620, 1560, and 1530 cm^{-1} (C=C and –C=N); uv (CH_3CN) 255 mμ (ε 3060), 337 (9700); nmr (acetone-d_6) δ 1.28 (d, J = 6.5 Hz, 3), 2.17 (s, 3), 2.78 (m, 2), 3.9 (br, 1), 7.2 (br, 1).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.1; H, 5.8; N, 32.2. Found: C, 62.3; H, 5.9; N, 32.1.

2,3-Dicyano-5,7,7-trimethyl-6,7-dihydro-1*H*-1,4-diazepine (22a). To a solution of 2.50 g (0.023 mol) of DAMN and 10 ml of acetone in 50 ml of THF was added 5 drops of concentrated sulfuric acid. The resulting solution was stirred for 3 days and filtered to remove 0.71 g (0.003 mol) of diaminomaleonitrile sulfate. Removal of the solvent and recrystallization from methylene chloride gave 3.35 g (89.5%) of **22a** as light yellow needles: mp 181–182° from CH_2Cl_2; ir 3305, 3205 (NH), 2990, 2875 (CH); 2240, 2200 (C≡N); 1630, 1555 (C=C, C=N); 1395, 1375 cm^{-1} (H_3CCCH_3); uv λ_{max} (CH_3CN) 225 mμ (ε 2680), 335 (9400); nmr (DMSO-d_6) δ 1.18 (s, 6 H), 2.16 (s, 3 H), 2.63 (s, 2 H), 8.35 (s, 1 H, NH); high-resolution mass spectrum molecular ion m/e 188.1058 (calcd for $C_{10}H_{12}N_4$, 188.1062).

Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.8; H, 6.4; N, 29.8. Found: C, 63.8; H, 6.6; N, 30.1.

Dicyanodihydrodiazepine (23) from Cyclohexanone. The reaction of DAMN with cyclohexanone under similar conditions gave dicyanodihydrodiazepine (**23**), 89% yield, mp 193–194°, from chloroform–ether as yellow needles: ir (KBr) 3285 (NH), 2960, 2930, and 2855 (NH), 2960, 2930, and 2855 (CH), 3065 and 3015, 2210 (–CN), 1610, 1557, and 1518 cm^{-1} (C=N, C=C); uv (CH_3CN) 222 mμ (ε 11,600), 343 (9000); nmr (DMSO-d_6) δ 1.0–2.1 (broad peak centered at δ 1.40, m, 17), 2.1–2.3 (br, 2), 7.88 (s, 1).

Anal. Calcd for $C_{16}H_{20}N_4$: C, 71.6; H, 7.5; N, 20.9. Found: C, 71.6; H, 7.7; N, 21.0.

2,3-Dicyano-6,7-dihydro-7-methyl-5,7-diphenyl-1*H*-1,4-diazepine (22b). The reaction of DAMN with acetophenone ethylene ketal gave **22b** in 72% yield: mp 158–159.5° from ether; ir (KBr) 3325 (NH), 3040 (aromatic =CH), 2930 (–CH), 2230 and 2210 (–CN), 1592, 1582, 1530, 1492 cm^{-1} (C=C, C=N); uv (CH_3CN) 254 mμ (ε 11,900), 375 (13,900); nmr (CD_3CN) δ 1.69 (s, 3), 2.87 (d, J = 14 Hz, 1), 3.90 (d, J = 14 Hz, 1), 7.0–7.5 (m, 10).

Anal. Calcd for $C_{20}H_{16}N_4$: C, 76.9; H, 5.2; N, 17.9. Found: C, 77.3; H, 5.4; N, 18.1.

2,3-Dicyano-4,5,6,7-tetrahydro-5,*N*,*N*-trimethyl-7-dimethylcarbamoyl-1-1*H*-1,4-diazepin-5-acetamide [20, R = $N(CH_3)_2$]. To a solution of 5.4 g (0.05 mol) of DAMN in 30 ml of *N*,*N*-dimethylacetoacetamide was added 2 g of $POCl_3$ over 30 sec. The temperature rose to 97°; the reaction mixture was stirred until cool and the resulting solid was collected. Recrystallization from ethyl acetate gave 9.1 g (55%) of **20** as a yellow powder: mp 178–179°; ir (Nujol) 3200, 2200, 2190, 1630, 1575, 1520 cm^{-1}; nmr ($CDCl_3$) δ 1.40 (s, 3), 2.5–2.8 (m, 4), 2.95–3.05 (m, 12), 5.0 (s, 1), NH's not seen.

Anal. Calcd for $C_{16}H_{22}O_2N_6$: C, 58.2; H, 6.7; N, 25.4. Found: C, 58.1; H, 6.7; N, 25.1.

2,3-Dicyano-4,5,6,7-tetrahydro-5-methyl-7-methoxycarbonylmethylene-1*H*-1,4-diazepin-5-acetic acid (20, R = OCH_3). To a solution of 5.4 g (0.05 mol) of DAMN in 40 ml of methyl acetoacetate was added dropwise over 5 min 3.0 g of $POCl_3$. The temperature reached 45° during the addition. After stirring for 1 hr the solution was poured into 200 ml of ice water. The resulting

precipitate was collected and recrystallized from benzene to give 3.9 g (25%) of **20** (R = OCH_3) as yellow crystals: mp 150–152°; ir (Nujol) 3250, 2205 (w), 2195, 1715, 1650, 1600, 1530 cm^{-1}; nmr (DMSO-d_6) δ 1.19 (s, 3), 2.52 (s, 2), 2.78 (s, 2), 3.53 (broad peak, 6), 4.75 (s, 1), 7.55 (br, 1, exchanges with D_2O), 8.72 (br, 1, exchanges with D_2O).

Anal. Calcd for $C_{14}H_{16}O_4N_4$: C, 55.3; H, 5.3; N, 18.4. Found: C, 55.4; H, 5.3; N, 18.7.

Diaminomaleonitrile Acetophenone Schiff Base 21. A solution of 10.8 g (0.10 mol) of DAMN, 26.4 g (0.22 mol) of acetophenone, and 5 drops of sulfuric acid in 300 ml of THF was stirred at room temperature for 20 hr, filtered, and stripped to dryness, giving a yellow oil. The oil was dissolved in petroleum ether and upon standing 1.6 g of yellow needles grew from solution. Recrystallization from ether gave light yellow needles: mp 123.0–123.5°; ir (Nujol) 3445 and 3280 (-NH_2), 2230 and 2190 (-CN), 1591, 1567, and 1548 cm^{-1} (NH_2, C=C and/or C=N); uv (CH_3CN) 258 mμ (ϵ 13,450), 283 (10,400), 360 (12,300); nmr (CD_3CN) δ 2.47 (s, 3), 5.61 (br, 2), 7.45 (m, 3), 7.94 (m, 2).

Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.53; H, 4.80; N, 27.03.

2,3-Dicyano-5-dimethylamino-1.7-dihydro-6*H*-1,4-diazepine (24a). To a solution of 10.0 g of DAMN and 12.0 g of *N,N*-dimethylacrylamide in 100 ml of THF was added 10 ml of $POCl_3$ over 15 min. The resulting solution was stirred for 4 hr as a tan precipitate formed. This solid was collected (6.5 g) and recrystallized from methanol–ether to give 3.5 g of the hydrochloride as colorless crystals, mp 234–236° dec. The hydrochloride was dissolved in water and neutralized with NH_4OH to give an immediate yellow precipitate. Recrystallization from chloroform gave the diazepine **24a** as yellow needles: mp 190–192°; ir (Nujol) 3280, 2195, 1580, 1540, 1510 cm^{-1}; nmr (acetone-d_6) δ 2.9 (m, 2), 3.03 (s, 6), 3.55 (m, 2).

Anal. Calcd for $C_9H_{11}N_5$: C, 57.1; H, 5.9; N, 37.0. Found: C, 57.1; H, 5.6; N, 37.4.

2,3-Dicyano-5-dimethylamino-6*H*-1,4-diazepine (24b). A solution of 0.68 g (3.0 mmol) of DDQ in 25 ml of benzene was added to 0.59 g (3.0 mmol) of **24a** in 100 ml of benzene. The solution turned green and then to a yellow slurry over 1 hr. After stirring for 18 hr the solution was filtered to remove dihydrodichlorodicyanoquinone. Concentration and recrystallization from benzene gave 0.52 g (88%) of **24a** as colorless crystals: mp 130–132°; ir (KBr) 2220, 1595, 1570, 1480 cm^{-1}; nmr ($CDCl_3$) δ 3.17 (s, 3), 3.26 (s, 3), 3.2 (2 H under singlets), 6.96 (t, J = 5.5 Hz, 1).

Anal. Calcd for $C_9H_9N_5$: C, 57.8; H, 4.9; N, 37.4. Found: C, 57.6; H, 4.8; N, 37.5.

2,3-Dicyano-5-methyl-6,7-dihydro-1*H*-1,4-diazepine (22c). A solution of 10.8 g (0.100 mol) of DAMN and 7.00 g (0.100 mol) of methyl vinyl ketone in 200 ml of absolute ethanol was refluxed for 5 hr. Twenty grams of Silicar was added and the solution was stripped to dryness. Chromatography with ether and THF gave crude product, which was recrystallized from THF–petroleum ether, giving light yellow needles: mp >290°; 5.0 g (31%); ir (Nujol) 3220, 2270, 2220, 1640, 1590, 1560, 1370, 1330, 1320, 1220, 1010, 980 cm^{-1}; nmr (DMSO-d_6) δ 2.1 (s, CH_3), 2.65 (m, CH_2), 3.4 (m, CH_2), 8.3 (broad singlet, NH); uv (CH_3CN) 338 mμ (ϵ 9080), 258 (2720).

Anal. Calcd for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0. Found: C, 59.6; H, 5.0; N, 34.6.

2,3-Dicyano-5-methyl-7-phenyl-6,7-dihydro-1*H*-1,4-diazepine (22d). A solution of 5.4 g (0.050 mol) of DAMN, 7.3 g (0.050 mol) of benzalacetone, 1 g of oxalic acid, and 200 ml of absolute ethanol was refluxed for 4 hr. A yellow solid was deposited after 1 hr. The solution was cooled to 0° and the product was collected by filtration and washed with ether. The solid was recrystallized from acetone–petroleum ether, giving 7.0 g (60% yield) of pale yellow crystals: mp 200–202°; ir 3225, 2275, 2220, 1640, 1370, 1330, 1320, 1280, 850, 700 cm^{-1}; nmr (DMSO-d_6) δ 1.73 (s, CH_3), 3.0 (AB of ABX, 2 H), 5.07 (br, CH), 7.3 (m, 5 H), 8.65 (br, NH).

Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.2; H, 5.08; N, 23.7. Found: C, 71.1; H, 5.16; N, 23.8.

2,3-Dicyano-5,7-diphenyl-6,7-dihydro-1*H*-1,4-diazepine (22f). A solution of 5.4 g (0.050 mol) of DAMN, 10.4 g (0.050 mol) of chalcone, and 15 drops of cooncentrated sulfuric acid in 250 ml of THF was refluxed for 3 days. The products were preadsorbed on Silicar CC-7 and chromatographed. Methylene chloride eluted a sticky orange solid which crystallized when triturated with ether. Recrystallization from ether gave 5.0 (33% yield) of yellow solid: mp 156–161°; ir 3225, 3075, 2220, 1560, 1350, 1330, 1220, 925, 780, 765, 750, 705, 690 cm^{-1}; nmr (DMSO-d_6) δ 3.20 (d, J = 14 Hz, 1 H), 3.75 (d, d, J = 14, 5 Hz, 1 H), 5.17 (d, J = 5 Hz, 1 H), 7.2–7.7 (m, 10 H), 9.12 (s, NH); uv (CH_3CN) λ_{max} 378 nm (ϵ 13,100), 256 (12,600).

Anal. Calcd for $C_{19}H_{14}N_4$: C, 76.5; H, 4.7; N, 18.8. Found: C, 76.1; H, 4.8; N, 18.7.

Oxidation of Diaminomaleonitrile to Diiminosuccinonitrile with Dichlorodicyanobenzoquinone. A mixture of 3.24 g (30 mmol) of DAMN and 6.78 (30 mmol) of dichlorodicyanobenzoquinone in 75 ml of acetonitrile was stirred at room temperature for 30 min. Dichlorodicyanohydroquinone (6.53 g, 95%) was removed by filtration. The filtrate yielded 3.32 g of residue which was DISN containing a small amount of dichlorodicyanohydroquinone according to its infrared spectrum.

Registry No.—**3,** 51802-24-5; **5,** 51802-51-8; **6,** 51802-25-6; **7,** 51802-26-7; **8,** 51802-27-8; **9,** 51802-28-9; **10,** 51802-29-0; **11,** 51802-30-3; **12** (R = H), 1122-28-7; **14** (R = R″ = CH_3), 51801-96-8; **14** (R = Pr; R″ = Et)·HCl, 51802-31-4; **16** [R = $C(CH_3)_3$], 51802-52-9; **16** (R = C_6H_5), 51802-53-0; **16** (R = H), 40953-34-2; **17** (R = CH_3), 51802-32-5; **17** (R = C_6H_5), 51802-33-6; **18,** 51802-54-1; **19,** 51802-55-2; **20** [R = $N(CH_3)_2$], 51802-56-3; **20** (R = OCH_3), 51802-57-4; **21,** 51802-34-7; **22a,** 51802-58-5; **22b,** 51802-59-6; **22c,** 51802-60-9; **22d,** 51802-61-0; **22e,** 51802-62-1; **22f,** 51802-63-2; **23,** 51802-64-3; **24a,** 51802-65-4; **24b,** 51802-66-5; **25,** 51802-35-8; propionaldehyde, 123-38-6; isobutyraldehyde, 78-84-2; pivaldehyde, 630-19-3; 2-ethylhexanal, 123-05-7; cyclohexanecarboxaldehyde, 2043-61-0; 2-chlorobenzaldehyde, 89-98-5; 2,6-dichlorobenzaldehyde, 83-38-5; 3-hydroxybutyraldehyde, 107-89-1; acetophenone, 98-86-2; fluoral, 75-90-1; *N,N*-dimethylformamide, 68-12-2; *N,N*-dimethylacetamide, 127-19-5; *N,N*-diethylacetamide, 685-91-6; *N,N*-diethylbutyramide, 1114-76-7; *N,N*-dimethylpropionamide, 758-96-3; terephthalaldehyde, 623-27-8; *N*-methyl-2-pyrrolidinone, 872-50-4; benzaldehyde, 100-52-7; succinic anhydride, 108-30-5; maleic anhydride, 108-31-6; phthalic anhydride, 85-44-9; diaminomaleonitrile acrylamide, 51802-36-9; acryloyl chloride, 814-68-6; phenyl isocyanate, 103-71-9; *tert*-butyl isocyanide, 7188-38-7; phenyl isocyanide dichloride, 622-44-6; cyanogen chloride, 506-77-4; 2,5-hexanedione, 110-13-4; 1,4-diphenyl-1,4-butanedione, 495-71-6; 1,2-dimethoxy-1,2-diiminoethane, 30986-09-5; chloroacetone, 78-95-5; acetylacetone, 123-54-6; acetone, 67-64-1; cyclohexanone, 108-94-1; acetophenone, 98-86-2; *N,N*-dimethylacetoacetamide, 2044-64-6; methyl acetoacetate, 105-45-3; *N,N*-dimethylacrylamide, 2680-03-7; methyl vinyl ketone, 78-94-4; benzalacetone, 122-57-6; chalcone, 94-41-7; DISN, 28321-79-1.

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Macroheterocycles. The Oxetane Function Spiro to Macrocyclic Polyether Rings

Carl G. Krespan

Contribution No. 2122 from the Central Research Department, E. I. du Pont de Nemours and Company, Inc., Experimental Station, Wilmington, Delaware 19898

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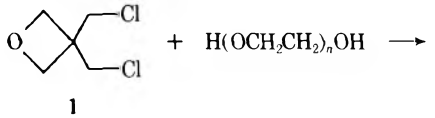
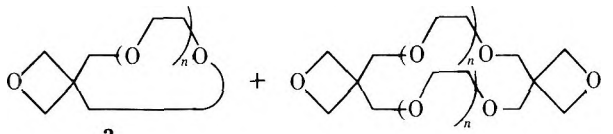
Macrocyclic polyethers bearing one and two spirooxetane rings are easily obtained in one step from polyethylene glycols and 3,3-bis(halomethyl)oxetanes. Crystalline complexes of these cyclic polyethers are readily obtained from alkali and alkaline earth metal thiocyanates or iodides. For complexes with KSCN, incorporation of the carbon bearing a spirooxetane ring is shown to cause a 10- to 100-fold decrease in stability constant. Some new macrocycles containing sulfide groups are also described.

The original work by Pedersen[1] and subsequent studies by Frensdorff[2] established that macrocylic polyethers of appropriate ring size complex strongly with cations of the alkali and alkaline earth metals. In only a few cases has later work on macrocyclic polyethers dealt with rings having additional functionality. In particular, the problem of incorporating a polymerizable function into such molecules has apparently been approached exclusively through substituted benzo derivatives. In one case,[3] a dibenzocrown polyether was converted to a mixture of isomeric diamines which was then incorporated into polyamides. In another case,[4] styrene analogs of monobenzocrowns were prepared and homopolymerized. Since these syntheses require several steps to produce the functionalized macrocyclic polyether, a more direct route seemed desirable. This paper describes the one-step synthesis of macrocyclic polyethers containing a spirooxetane unit starting from available materials.

Synthesis. 3,3-Bis(chloromethyl)oxetane (**1**), readily obtained from pentaerythritol[5] and itself polymerizable cationically,[6] is subject to anionic displacement of chlorine, leaving the oxetane ring intact.[5] Polyethylene glycols have now been found to react with **1** in the presence of strong base to yield macrocyclic polyethers of types **2** and **3** in up to 60% yield of isolated product. Dipolar aprotic



1



2 **3**

solvents such as dimethylformamide can be used, but *tert*-butyl alcohol has proved most convenient, since it can be used as purchased and is easily removed after reaction is complete. At reflux in *tert*-butyl alcohol, reaction of **1** with a polyethylene glycol salt is complete in 4–5 days. Under similar conditions, 3,3-bis(bromomethyl)oxetane reacts in less than 1 day to give similar products. Potassium *tert*-butoxide was used in most cases, but it has been demonstrated that sodium hydroxide or potassium hydroxide can be employed with only a slight yield loss. The yields cited were obtained at concentrations of *ca.* 10 wt % of each reactant, providing evidence that a template effect[7] is operating even in the protic solvent, *tert*-butyl alcohol. Except where excess *tert*-butoxide was included as a reactant, no trace of butoxy group was seen in the volatile products.

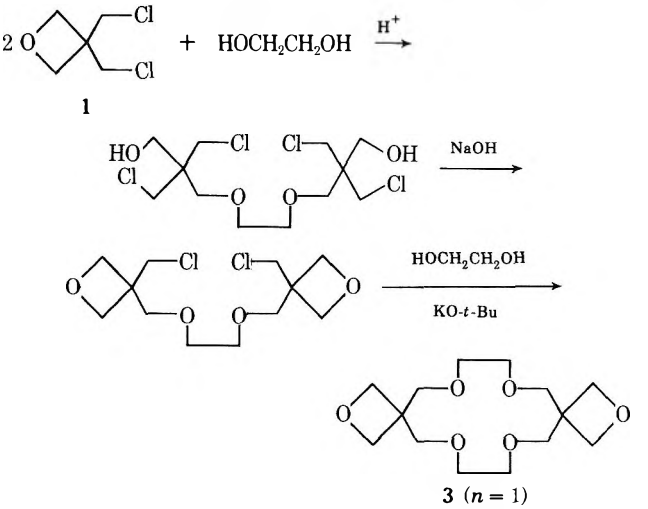
The product ratio **2**:**3** is governed by ring size. For cases in which **2** contains a macrocyclic polyether ring of 10 or 13 atoms, *i.e.*, products derived from diethylene glycol and triethylene glycol where $n = 2$ and 3, steric crowding results in a low ratio. For $n > 3$, formation of **2** is favored and the ratio is correspondingly high. The special case of glycol leads mainly to **2** ($n = 1$) with less than 1% of **3** ($n = 1$).

Table I
Spirooxetanes from the Glycols $HO(CH_2CH_2O)_nH$

n	Glycol registry no.	2, % yield	Registry no.	3, % yield	Registry no.
1	107-21-1	42	51652-65-4	0.7	51652-71-2
2	111-46-6	0.2	51652-66-5	47	51652-72-3
3	112-27-6	30–35	51065-93-1	20–25	51065-94-2
4	112-60-7	53	51652-67-6		
5	4792-15-8	60	51652-68-7		
7	5617-32-3	35	51652-69-8	3	51652-73-4
9	3386-18-3	11	51652-70-1		

Table I shows the isolated yields for each glycol studied. For most $n > 3$, the yield of **3** was not determined; crystallization of **3** ($n = 7$) led to the isolation of this 50-membered-ring product in low but significant yield.

Dispirooxetanes which are difficult to obtain in reasonable yield by the one-step procedure, as well as dispirooxetanes having two different polyether bridges, can be made by a three-step route in which the two glycol molecules are introduced separately. An example is the synthesis of **3** ($n = 1$) according to the following scheme.

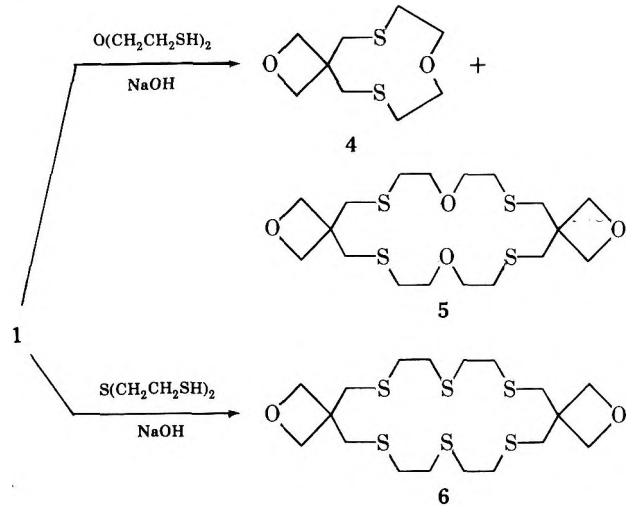


3 ($n = 1$)

Even at temperatures over 100°, sulfuric acid is an ineffective catalyst for the first step, presumably because intermediate sulfate ester derived from the oxetane does not solvolyze readily. Trifluoromethanesulfonic acid proved to be a useful catalyst.

Extension of the one-step synthesis to dimercaptans was feasible, although a pronounced tendency to form polymer necessitated the use of dilute solutions. A greatly reduced

template effect is not surprising, since sulfur coordinates poorly to alkali metal ions.[2] Bis(2-mercaptoethyl) ether gave both monooxetane **4** and dioxetane **5**, while bis(2-mercaptoethyl) sulfide gave only dioxetane **6**.



Determination of the mono- and dispirooxetane structures rested on their nmr spectra, as well as on elemental analyses, infrared spectra, and molecular weight measurements. For products containing only oxygen as heteroatom, the isolated methylene and ethylene units appear as singlets at positions progressively further upfield as the distance from the oxetane ring increases. All ethylene units beyond those nearest the oxetane ring appear together as a broadened singlet. Figure 1 schematically illustrates some observed spectra along with those of reference oxetanes. Infrared absorption(s) at 10–10.5 μ are characteristic of the oxetane ring.[5]

Complex Formation. Stuart–Briegleb models indicated a minimum amount of space available inside the four-oxygen macrocycle, **2** (n = 3). In accord with the model, lithium thiocyanate formed a stable, crystalline, 1:1 complex with **2** (n = 3), whereas sodium thiocyanate formed a weak complex easily distrupted by ether extraction of the macrocycle, and a solid complex with potassium thiocyanate could not be obtained. The polyethers **2** (n = 4) and **2** (n = 5) formed well-defined 1:1 complexes with sodium and potassium thiocyanate, but lithium thiocyanate gave glassy complexes which resisted attempts at crystallization. These 1:1 complexes are assumed to involve a near-planar structure in which the cation is centrally located inside the ring with oxygen atoms oriented toward the cation, similar to the structures determined for other 1:1 M^+–macrocyclic polyether complexes.[8a] Note that in the case of **2** (n = 4) and KSCN, the addition of one carbon atom to the ring allows K^+ to fit inside sufficiently well to favor a 1:1 complex, whereas crown polyethers containing five oxygen atoms form 2:1 sandwich structures with K^+.[8b]

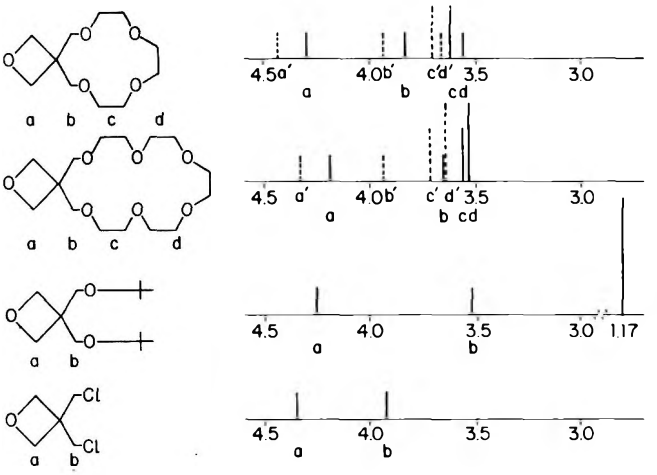
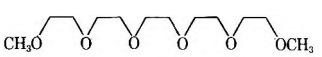
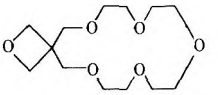
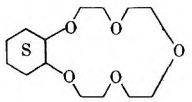
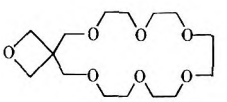
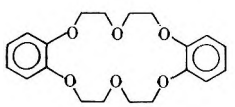
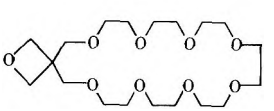
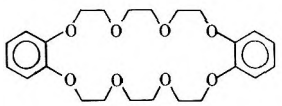
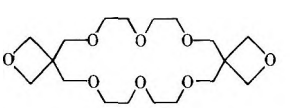
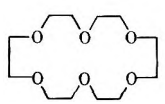
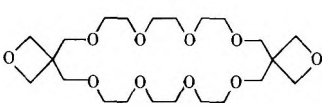


Figure 1. ^1H chemical shifts observed with and without K^+ present. Shifts are given in parts per million for 20% solutions in acetone-d_6. Dotted lines designated by primed letters are for chemical shifts with 1 equiv of KSCN present.

The dispirooxetane **3** (n = 3) preferentially forms 2:1 alkali metal thiocyanate–polyether complexes, a stoichiometry apparently not observed by Pedersen,[1] and reported by Truter, *et al.*, for similar 2:1 complexes involving K^+, but not Na^+. The smaller polyether ring in **3** (n = 2) accommodates fewer sodium ions and even fewer potassium ions.

Ability to complex alkaline earth metal ions was demonstrated in one case; calcium iodide formed a 1:1 complex with **2** (n = 5).

Table II
K_{stab} for K^+–CH_3OH Systems at 25°

Polyether	Log stability constant	Compd	Log stability constant
	2.20		2.08
	3.60		3.81
	5.00		2.43
	3.49		1.67
	6.10		<0.7

Complexation with alkali metal cations produced only small (*ca.* 0.1–0.3 ppm) downfield shifts in the large ring proton nmr positions.[9] Furthermore, the deshielding of protons on the oxetane ring was as great as or greater than that of the macrocyclic protons. In one case, that of **2** (n = 5)·KSCN, where a particularly stable complex with potassium ion was present (*vide infra*), splitting of the protons in one ethylene unit was induced by the fixed geometry. The effects of metal ions on the ^{1}H nmr spectra are exemplified in Figure 1.

Ability to form crystalline complexes with well-defined melting points and stoichiometry is, of course, not a reliable indicator of relative stability. Although the macrocyclic polyethers prepared in this work form such complexes, their stability in the presence of such strongly coordinating solvents as water and methanol can be expected to vary greatly. Stability constants of selected spirooxetane derivatives with potassium ion in methanol solution are presented in Table II.[10] For comparison, similar values for an acyclic polyether and several crown ethers are also included in Table II. Just as has been observed with the crown ethers, cyclic polyethers containing an additional carbon bearing a spirooxetane unit form the most stable complexes with K^+ when six ether oxygen atoms are present. Inspection of Table II reveals that a penalty of one to two powers of ten in stability constant results from each spirooxetane unit incorporated into the ring.

Rather surprisingly, polysulfide **5** forms a crystalline complex with sodium thiocyanate. The 2:1 ligand–NaSCN stoichiometry suggests that, unlike complexes of the related polyethers, this complex has a sandwich structure with Na^+ in the center coordinated to four ether oxygen atoms. Both **5** and **6** form complexes with mercuric chloride with well-defined 1:1 stoichiometry.[11]

Experimental Section[12]

2,6,9-Trioxaspiro[3.6]decane (2, n = 1) and 2,6,9,13,16,19-hexaoxadispiro[3.6.3.6]eicosane (3, n = 1). A solution of 12.4 g (0.20 mol) of glycol, 47.0 g (0.42 mol) of potassium *tert*-butoxide, and 31.1 g (0.20 mol) of 3,3-bis(chloromethyl)oxetane in 500 ml of *tert*-butyl alcohol was stirred and refluxed under nitrogen for 2 days. The mixture was cooled, addition of the three reactants repeated, and reaction continued for an additional 5 days. Evaporation of volatiles to 50° (0.5 mm) and continuous extraction of the residue with pentane gave 58.9 g of high-boiling oil along with 0.8 g of 2,6-dioxaspiro[3.3]heptane as a volatile solid. Sublimation of this solid gave 0.31 g (0.8%) of pure dioxaspiroheptane: mp 89–90° subl (lit.[5] mp 90°); mass spectrum m/e 100 (parent$^+$), 70 ($P^+ - CH_2O$); ir (Nujol) 10.31 and 10.92 μ (oxetane ring); ^{1}H nmr δ 4.70 ppm (s).

Distillation of the high-boiling oil gave 24.2 g (42%) of **2**, n = 1: bp 97–99° (10 mm); ir 3.41 and 3.48 (saturated CH), 8.8–9.1 (COC), 10.19 and 10.85 μ (oxetane ring); ^{1}H nmr δ 4.36 (s, 1, oxetane CH_2), 3.99 (s, 1, CCH_2), and 3.63 ppm (s, 1, OCH_2CH_2O).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.40; O, 33.29. Found C, 57.99; H, 8.23; O, 32.89.

Isolation of solid from the distillation residue gave, after recrystallization from ether, 0.42 g (0.7%) of 2,6,9,13,16,19-hexaoxadispiro[3.6.3.6]eicosane (**3**, n = 1), mp 163–165°, recrystallized from acetone for analysis: mass spectrum m/e 288 (weak parent$^+$), 289 (weak P + H$^+$), 258 (strong $P^+ - CH_2O$); ir (Nujol) 8.7–9.1 (COC), 10.29, 10.42, and 10.68 μ (oxetane); ^{1}H nmr δ 4.30 (s, 1, oxetane CH_2), 3.80 (s, 1, CCH_2), and 3.63 ppm (s, 1, OCH_2CH_2O).

Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.40. Found: C, 58.88, 58.92; H, 8.05, 8.47.

Stepwise Synthesis of 3, n = 1. As catalyzed by sulfuric acid, the reaction of polyethylene glycols with bis(chloromethyl)oxetane is unusually sluggish. However, trifluoromethanesulfonic acid at elevated temperatures does catalyze the addition of glycol to this oxetane to form 2,2,9,9-tetrakis(chloromethyl)-4,7-dioxadecane-1,10-diol as a major product. Reaction of the bulk mixture gave only 10% of crude 3-chloromethyl-3-[6-(3′-chloromethyl-3′-oxetanyl)-2,5-dioxahexyl]oxetane after treatment with base, a low yield owing to excessive polymerization in the first step. Use of a solvent (CH_2Cl_2 glyme, or $CHCl_2CHCl_2$) resulted in a yield of bisoxetane of 32–42%.

A mixture of 24.8 g (0.40 mol) of glycol, 128.0 g (0.80 mol) of 3,3-bis(chloromethyl)oxetane, 0.5 ml of trifluoromethanesulfonic acid, and 160 ml of *sym*-tetrachloroethane was heated at 110° for 5 days. Solvent was removed under vacuum, 50 ml of xylene was added, and volatiles were again removed under vacuum. The viscous residue was dissolved in 300 ml of *tert*-butyl alcohol, 32.0 g (0.80 mol) of sodium hydroxide was added, and the mixture was stirred and heated. After an initial exothermic reaction carried the temperature to 80°, the mixture was heated at 70° overnight. Neutralization with concentrated HCl showed that 84% of the base had reacted. The mixture was filtered and volatiles were removed from the filtrate to give 127 g of residual oil. Continuous extraction of this oil with pentane yielded 120 g of high boilers in the extract. Distillation of this oil gave 40.2 g (34%) of the bisoxetane: bp 110–115° (0.05 μ); ir 3.38 and 3.47 (saturated CH), 9.0 (broad COC), 10.19 (oxetane), and 13.78 μ (CCl); ^{1}H nmr δ 4.36 (s, 2, oxetane), 3.91 (s, 1, CH_2Cl), 3.77 (s, 1, CCH_2O), and 3.67 (s, 1, OCH_2CH_2O).

Anal. Calcd for $C_{12}H_{20}Cl_2O_4$: C, 48.17; H, 6.74; Cl, 23.70. Found: C, 48,31; H, 6.44; Cl, 23.97.

A solution of 29.9 g (0.10 mol) of the bisoxetane, 6.2 g (0.10 mol) of glycol, and 24.0 g (0.21 mol) of potassium *tert*-butoxide in 500 ml of *tert*-butyl alcohol was stirred and refluxed for 12 days. The reaction mixture was neutralized with concentrated HCl and filtered and the filter cake was extracted with 3 × 100 ml of CH_2Cl_2. Evaporation of the CH_2Cl_2 solution gave 2.8 g of **3**, n = 1. Evaporation of the mother liquor to 50° (0.5 mm), treatment of the residue with 20 ml of ether, and filtration gave 9.9 g of **3**, n = 1. The combined solids were recrystallized by continuous extraction with ether in a Soxhlet, yielding 9.1 g (32%) of **3**, n = 1, mp 163–165°, not depressed by admixture with an authentic sample.

2,6,9,12-Tetraoxaspiro[3.9]tridecane (2, n = 2) and 2,6,9,12,16,19,22,25-Octaoxadispiro[3.9.3.9]hexacosane (3, n = 2). Reaction of 228 g (2.04 mol) of potassium *tert*-butoxide, 106 g (1.00 mol) of distilled diethylene glycol, 155 g (1.00 mol) of 3,3-bis(chloromethyl)oxetane, and 3.0 l. of *tert*-butyl alcohol at reflux was continued for 2 days. Then the addition of *tert*-butoxide, glycol, and oxetane was repeated, and the reaction mixture was refluxed and stirred for 3 days. Another repeat addition was made and reaction was continued for 2 days. A last repeat addition was made, and the reaction mixture was refluxed for 6 days, filtered, and volatiles removed. The residual mixture of solid and oil, 770 g, was kept molten at 90° while being continuously extracted with heptane for 3 days. The cold heptane extract was filtered, and the solid thus isolated was extracted in a Soxhlet with ether. Filtration of the chilled ether extract gave 342 g of **3**, n = 2, mp 84.5–85.5°. Second and third crops raised the yield to 357 g (47%) of purified **3**, n = 2. An analytical sample was prepared by recrystallization from ether: mp 86–87°; ir (Nujol) 8.7–9.1 (COC), 10.05, 10.32, 10.55, and 10.76 μ (oxetane ring); ^{1}H nmr δ 4.36 (s, 1, oxetane CH_2), 3.73 (s, 1, CCH_2), and 3.63 ppm (s, 2, OCH_2CH_2O).

Anal. Calcd for $C_{18}H_{32}O_8$: C, 57.43; H, 8.57; O, 34.00; mol wt, 376.5. Found: C, 58.02; H, 8.79; O, 33.68; mol wt, 390 (ebullioscopic in benzene).

Distillation of the filtrate from a similar preparation of **3**, n = 2, on a 2-mol scale gave 1.44 g of impure **2**, n = 2, bp 100–120° (0.3 mm). The crude distillate was extracted with 20 ml of ligroin, the extracts were evaporated, the residue was dissolved in 20 ml of water and insolubles were removed by extraction with 2 × 2 ml of ligroin. The aqueous layer was evaporated to give 0.68 g (0.2%) of 2,6,9,12-tetraoxaspiro[3.9]tridecane: mass spectrum m/e 188 (weak parent$^+$), 189 (weak P + H$^+$), and 158 (strong $P^+ - CH_2O$); ir 3.45 and 3.52 (saturated CH), 8.7–9.2 (COC), 10.08, and 10.7 μ (oxetane ring); ^{1}H nmr δ 4.28 (s, 1, oxetane CH_2), 3.92 (s, 1, CCH_2) and 3.62 ppm (s, 2, OCH_2CH_2O) with weak impurity peaks also present.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.38; H, 8.48.

2,6,9,12,15-Pentaoxaspiro[3.12]hexadecane (2, n = 3) and 2,6,9,12,15,19,22,25,28,31-Decaoxadispiro[3.12.3.12]dotriacontane (3, n = 3). A mixture of 233.4 g (2.08 mol) of potassium *tert*-butoxide, 150.2 g (1.00 mol) of triethylene glycol, and 155.0 g (1.00 mol) of 3,3-bis(chloromethyl)oxetane was heated at reflux in 3 l. of *tert*-butyl alcohol. Two additions, each of 75.1 g (0.50 mol) of triethylene glycol, 77.5 g (0.50 mol) of 3,3-bis(chloromethyl)oxetane, and 114.4 g (1.02 mol) of potassium *tert*-butoxide, were made at 2–3-day intervals, and reaction finally continued for 5 days. Filtration and evaporation of volatiles gave residual oil which was extracted continuously with pentane for 3 days. Distil-

lation of the extract through a Vigreux column gave 150.3 g (32%) of 2,6,9,12,15-pentaoxaspiro[3.12]hexadecane and 119.9 g (26%) of crude 2,6,9,12,15,19,22,25,28,31-decaoxadispiro[3.12.3.12]dotriacontane as a distillation residue which largely crystallized.

Redistillation of **2**, n = 3, through a spinning band still gave pure product: bp 97–98° (6 μ); n^{26}D 1.4785; ir 3.40 (sh) and 3.47 (saturated CH), 9.0 (broad COC), 10.02, and 10.25 μ (oxetane ring); ^{1}H nmr δ 4.30 (s, 1, oxetane CH_2), 3.83 (s, 1, CCH_2), 3.62 (s, 2, OCH_2CH_2O), and 3.57 ppm (s, 1, OCH_2CH_2O).

Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68; O, 34.44; mol wt, 232. Found: C, 56.81; H, 8.73; O, 34.41; mol wt, 232 (field ionization mass spectrum).

A sample of **3**, n = 3, purified by recrystallization from acetone of the complex with KSCN and liberation from the complex by boiling xylene, crystallized, mp 52–53°.

Anal. Calcd for $C_{22}H_{40}O_{10}$: C, 56.88; H, 8.68; O, 34.44; mol wt, 464. Found: C, 56.91; H, 8.69; O, 34.27; mol wt, 498 (ebullioscopic in benzene).

3,3-Bis(*tert*-butoxymethyl)oxetane. Dimethylformamide is also a suitable solvent if all the reactants are added at once. An attempt to carry out the reaction by addition of triethylene glycol and 3,3-bis(chloromethyl)oxetane to a solution of potassium *tert*-butoxide in dimethylformamide resulted in considerable substitution of *tert*-butoxide groups for chlorine in the oxetane.

A solution of 49.2 g (0.44 mol) of potassium *tert*-butoxide in 400 ml of dry dimethylformamide was stirred and heated under a nitrogen atmosphere. At 80–90°, the mixture darkened considerably, so addition of 30.0 g (0.20 mol) of triethylene glycol and 31.0 g (0.20 mol) of 3,3-bis(chloroethyl)oxetane in 200 ml of dimethylformamide was started. The temperature of the reaction mixture rose rapidly to 115° and remained near there until the addition was complete (45 min). After an additional 3 hr at 110°, the solution was cooled and neutralized with 2 ml of acetic acid. After removal of the solvent under reduced pressure, the product was dissolved in chloroform and the solution was filtered. Distillation of the filtrate gave a two-phase mixture of product and triethylene glycol, bp 40–100° (0.1 μ). Redistillation of the upper layer gave 5.4 g (12%) of 3,3-bis(*tert*-butoxymethyl)oxetane: bp 44–46° (0.1 μ); ir 3.36 and 3.48 (saturated CH), 9.2 (broad COC), 10.20 μ (oxetane ring); ^{1}H nmr (CCl_4) δ 4.25 (s, 2, oxetane CH_2), 3.52 (s, 2, CCH_2), and 1.17 ppm [s, 9, $C(CH_3)_3$].

Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.78; H, 11.37. Found: C, 67.91; H, 11.56.

2,6,9,12,15,18-Hexaoxaspiro[3.15]nonadecane (2, n = 4). Reaction of 38.8 g (0.20 mol) of tetraethylene glycol, 47.0 g (0.42 mol) of potassium *tert*-butoxide, and 31.0 g (0.20 mol) of 3,3-bis(chloromethyl)oxetane was carried out at reflux in 500 ml of *tert*-butyl alcohol. A second, equivalent addition of the three reagents was made after 1 day. Distillation of the pentane-soluble product in a molecular still gave 58.2 g (53%) of 2,6,9,12,15,18-hexaoxaspiro[3.15]nonadecane as a colorless oil: bp 105–108° (0.2 μ); n^{24}D 1.4771; mp 28–30°; ir 3.40 (sh) and 3.47 (saturated CH), 8.7–9.1 (COC), 10.23, and 10.68 μ (oxetane ring); ^{1}H nmr δ 4.32 (s, 1, oxetane CH_2), 3.73 (s, 1, CCH_2), 3.59 (s, 2, OCH_2CH_2O), and 3.55 ppm (s, 2, OCH_2CH_2O).

Anal. Calcd for $C_{13}H_{24}O_6$: C, 56.50; H, 8.75; O, 34.74. Found: C, 56.49; H, 8.70; O, 34.78.

Equivalent or better yields were obtained with 3,3-bis(bromomethyl)oxetane. Yields were nearly as high when potassium *tert*-butoxide was replaced by NaOH (52% yield) or KOH (47% yield) in reactions involving 3,3-bis(bromomethyl)oxetane.

2,6,9,12,15,18,21-Heptaoxaspiro[3.18]docosane (2, n = 5). Pentaethylene glycol was prepared by dropwise addition of 468 g (2.5 mol) of 1,2-bis(2-chloroethoxy)ethane to a solution of 331 g (5.0 mol) of 85% KOH pellets in 930 g (15 mol) of glycol stirred and heated at 110° under nitrogen. The addition was carried out at a rate sufficient to maintain a reaction temperature of 120° with no external heating (2 hr). The mixture was stirred and heated at 120° for an additional 3 hr, cooled, acidified with concentrated HCl, and distilled. Pentaethylene glycol, 213.9 g (36%), n^{27}D 1.4582, was obtained as a fraction of bp 148–154° (20 μ).[13]

A mixture of 600 ml of *tert*-butyl alcohol, 47.0 g (0.42 mol) of potassium *tert*-butoxide, 47.6 g (0.20 mol) of pentaethylene glycol, and 31.0 g (0.20 mol) of 3,3-bis(chloromethyl)oxetane was stirred at reflux under nitrogen for 5 days. The mixture was cooled and filtered, and the filter cake was rinsed with *tert*-butyl alcohol and dried to give 30.1 g of KCl. Removal of volatiles from the filtrate to 50° (0.5 mm) afforded 67 g of viscous residue, which was extracted continuously with pentane for 3 days. The extracts yielded 49.3 g of high-boiling residue. Distillation gave 38.5 g (60%) of 2,6,9,12,15,18,21-heptaoxaspiro[3.18]docosane, mainly bp 136–137° (1 μ) in a molecular still: $n^{25.5}$D 1.4741; ir 3.40 (sh) and 3.47 (saturated CH), 9.0 (COC), and 10.21 μ (oxetane ring); ^{1}H nmr δ 4.29 (s, 1, oxetane CH_2), 3.65 (s, 1, CCH_2), 3.56 (s, 2, OCH_2CH_2O), and 3.52 ppm (s, 3, OCH_2CH_2O).

Anal. Calcd for $C_{15}H_{28}O_7$: C, 56.23; H, 8.81. Found: C, 56.51; H, 9.18.

An essentially equivalent result was obtained with 3,3-bis(bromomethyl)oxetane in place of 3,3-bis(chloromethyl)oxetane.

2,6,9,12,15,18,21,24,27-Nonaoxaspiro[3.24]octacosane (2, n = 7) and 2,6,9,12,15,18,21,24,27,31,34,37,40,43,46,49,52,55-octadecaoxadispiro[3.24.3.24]hexapentacontane (3, n = 7). To prepare heptaethylene glycol, a mixture of 1590 g (15 mol) of diethylene glycol and 200 g (5.0 mol) of NaOH pellets was stirred and heated to 110° under nitrogen. Dropwise addition of 468 g (2.5 mol) of 1,2-bis(2-chloroethoxy)ethane was carried out at a rate sufficient to keep the temperature near 120° without external heating; addition time was 1.5 hr. The mixture was heated and stirred at 120° for another 3 hr, cooled, filtered, and distilled through a Vigreux column. Heptaethylene glycol was obtained as 270.6 g (33%) of an oil, bp 207–213° (4.5 μ), n^{26}D 1.4627.[13]

Reaction was carried out in 700 ml of *tert*-butyl alcohol using two additions, each of 65.2 g (0.20 mol) of heptaethylene glycol, 47.0 g (0.42 mol) of potassium *tert*-butoxide, and 31.0 g (0.20 mol) of 3,3-bis(chloromethyl)oxetane. Distillation of the pentane-soluble products in a molecular still gave 58.0 g (35%) of **2**, n = 7: bp 182–183° (0.3 μ); ir 3.48 (saturated CH), 8.7–9.2 (COC), 10.23, and 10.65 μ (oxetane ring); ^{1}H nmr δ 4.37 (s, 1, oxetane CH_2), 3.72 (s, 1, CCH_2), 3.63 (s, 2, OCH_2CH_2O), and 3.60 ppm (s, 5, OCH_2CH_2O).

Anal. Calcd for $C_{19}H_{36}O_9$: C, 55.87; H, 8.88; O, 35.25. Found: C, 55.62; H, 8.66; O, 35.02.

The distillation residue slowly deposited crystals on standing. The mixture of solid and oil was crystallized from 1:1 ether–ligroin at −80°, from 1:1 ether–acetone at −80°, from 1:1 ether–acetone at 0°, and finally from ether at 0° to give 2.2 g of **3**, n = 7, mp 42–43°. A second crop, 2.1 g, mp 40–41°, was obtained by concentration of the filtrates and two recrystallizations from ether at 0°, bringing the yield to 4.3 g (2.6%): ir (Nujol) 8.7–9.2 (COC), 10.07, 10.29, and 10.37 μ (oxetane ring); ^{1}H nmr δ 4.36 (s, 1, oxetane CH_2), 3.67 (s, 1, CCH_2), 3.61 (s, 2, OCH_2CH_2O), 3.58 and 3.57 ppm (two singlets, combined area 5, OCH_2CH_2O).

Anal. Calcd for $C_{38}H_{72}O_{18}$: C, 55.87; H, 8.88; O, 35.25; mol wt, 817. Found: C, 56.39; H, 8.58; O, 34.82; mol wt, 798 (ebullioscopic in benzene).

2,6,9,12,15,18,21,24,27,30,33-Undecaoxaspiro[3.30]tetratriacontane (2, n = 9). A mixture of 2252 g (15 mol) of triethylene glycol and 200 g (5.0 mol) of NaOH pellets was treated with 468 g (2.5 mol) of 1,2-bis(2-chloroethoxy)ethane as described above. Distillation through a Vigreux gave 251.2 g (24%) of orange oil, bp 235–249°, n^{26}D 1.4644. As expected for nonaethylene glycol, the product solidified slowly at 0°.[14]

Two additions, each of 82.8 g (0.20 mol) of nonaethylene glycol, 47.0 g (0.42 mol) of potassium *tert*-butoxide, and 31.0 g (0.20 mol) of 3,3-bis(chloromethyl)oxetane, were made to a reaction carried out in 1 l. of *tert*-butyl alcohol as described above. From the pentane-soluble products there was isolated 22.0 g (11%) of **2**, n = 9: bp 250–260° (1 μ) in a molecular still; ir 3.45 (saturated CH), 8.7–9.1 (COC), 10.20, and 10.62 μ (oxetane ring); ^{1}H nmr δ 4.37 (s, 1, oxetane CH_2), 3.70 (s, 1, CCH_2), 3.63 (s, 2, OCH_2CH_2O), and 3.60 ppm (s, 7, OCH_2CH_2O).

Anal. Calcd for $C_{23}H_{44}O_{11}$: C, 55.63; H, 8.93; O, 35.44. Found: C, 55.88; H, 8.76; O, 35.76.

2,9-Dioxa-6,12-dithiaspiro[3.9]tridecane (4) and 2,9,16,22-Tetraoxa-6,12,19,25-tetrathiadispiro[3.9.3.9]hexacosane (5). A mixture of 31.0 g (0.20 mol) of 3,3-bis(chloromethyl)oxetane, 27.7 g (0.20 mol) of bis(2-mercaptoethyl) ether, 3.8 l. of absolute ethanol, and 16.0 g (0.40 mol) of sodium hydroxide pellets was stirred and refluxed under nitrogen for 1 day. Addition of the oxetane, mercaptoethyl ether, and sodium hydroxide was repeated and reaction was continued for another day. The addition was repeated once more and reaction was continued for an additional 3 days. The reaction mixture was filtered, the filtrate was evaporated to 500 ml, and supernatant was decanted. The viscous residue was extracted with 3 × 100 ml of hot ethanol; then the combined supernatant and extracts were evaporated to give high-boiling residue. Continuous ether extraction of this residue, removal of ether from the extracts, and sublimation of the extracted product at 100° (0.1 mm) gave 21.0 g (16%) of **4**, mp 102–105°. An analytical sample, mp 104–105°, was prepared by resublimation at 75° (0.025 mm), followed by trituration of the sublimate with ether and drying: ir (Nujol) 9.03 (COC), 10.21, and 10.70 μ

Table III
Complexes of Macrocyclic Polyethers

Complex[a]	Mp, °C	Yield, %	Registry no.
2 (n = 3)·LiSCN	138–139	57	51652-74-5
2 (n = 3)·NaSCN	164–165	*b*	51652-75-6
2 (n = 4)·NaSCN	135.5–137	25	51652-76-7
2 (n = 4)·KSCN	105–109	55	51652-77-8
2 (n = 5)·NaSCN	127–128	72	51652-78-9
2 (n = 5)·KSCN	124–126	73	51652-79-0
2 (n = 5)·CaI_2·H_2O	176–178	77	51731-29-4
2[**3** (n = 2)]·3NaSCN	70	91	51652-80-3
7[**3** (n = 2)]·8KSCN	103–105	96	51652-81-4
3 (n = 3)·2LiSCN	192–193	65	51652-83-6
3 (n = 3)·2NaSCN	165–166	82	51652-84-7
3 (n = 3)·2KSCN	140–141	55	51652-85-8
2(**5**)·NaSCN	167.5–169	87	51652-87-0

[a] Satisfactory analyses for C, H, N, and metal were recorded except for the complexes with **2** (n = 3). [b] Deliquescent complex which could not be recrystallized owing to a tendency to lose ligand.

(oxetane); ^{1}H nmr δ 4.22 (s, 1, oxetane CH_2), 3.52 (s, 1, CCH_2S) with rough triplets for AA'BB' at 230, 226, and 220 (1, CH_2CH_2O) and 172, 167, and 162 Hz (1, CH_2CH_2S).

Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.05; H, 7.32; S, 29.10; mol wt, 220. Found: C, 49.49; H, 7.31; S, 28.61; mol wt, 221 (ebullioscopic in benzene).

The involatile sublimation residue was kept molten at 90–95° and continuously extracted with heptane for 2 days. Evaporation of heptane from the extract and recrystallization from acetone gave 17.7 g of **5**, mp 100–101°. A second crop, 1.9 g, mp 98.5–100°, was also obtained, for a total of 19.6 g (15%) of **5**. An analytical sample, mp 100.5–101.5°, was prepared by recrystallization from acetone: ir (Nujol) 9.05 (COC), 10.15, and 10.53 μ (oxetane); ^{1}H nmr δ 4.35 (s, 1, oxetane CH_2) and 3.14 (s, 1, CCH_2S) with rough triplets for AA'BB' at 229, 223, and 217 (1, CH_2CH_2O) and 175.5, 169.5, and 163.5 Hz (1, CH_2CH_2S).

Anal. Calcd for $C_{18}H_{32}O_4S_4$: C, 49.06; H, 7.32; S, 29.10; mol wt, 440.7. Found: C, 49.41; H, 7.75; S, 29.32; mol wt, 438 (ebullioscopic in benzene).

Preparation of **4** and **5** in much more concentrated solution, 0.4 *vs.* 3.8 l. of absolute ethanol, resulted in only 2% of **4** and 4% of **5** along with considerable polymer.

2,16-Dioxa-6,9,12,19,22,25-hexathiadispiro[3.9.3.9]hexacosane (6). A mixture of 31.0 g (0.20 mol) of 3,3-bis(chloromethyl)oxetane, 30.8 g (0.20 mol) of bis(2-mercaptoethyl) sulfide, 16.0 g (0.40 mol) of sodium hydroxide, and 3.8 l. of absolute alcohol was stirred and refluxed under nitrogen for 1 day. Addition of the oxetane, sulfide, and sodium hydroxide was repeated and reaction was continued for another day. The addition was repeated once more and reaction was continued for an additional 3 days. Solvent was removed and the residue was heated at 70° during continuous extraction with benzene for 15 days. Solvent was removed from the extract and the residue was heated at 95° during continuous extraction with heptane for 12 days. Removal of solvent from the extract gave a viscous residue from which only a little oil was volatilized at 100° (0.4 mm). Crystallization of the residue from toluene gave 15.6 g (11%) of **6**, mp 129–131°. An analytical sample was prepared by recrystallization from acetone: mp 131–132°; ir (Nujol) 10.21 and 10.57 μ (oxetane); ^{1}H nmr (benzene-d_6) δ 4.23 (s, 1, oxetane CH_2), 2.73 (s, 1, CCH_2S) 2,54 (s, 2, SCH_2CH_2S).

Anal. Calcd for $C_{18}H_{32}O_2S_6$: C, 45.72; H, 6.82; S, 40.69; mol wt, 473. Found: C, 46.15; H, 6.84; S, 40.83; mol wt, 490 (ebullioscopic in benzene).

$HgCl_2$ Complexes of the Macrocyclic Polysulfides 5 and 6. Solutions of 0.44 g (0.001 mol) of **5** and of 0.54 g (0.002 mol) of mercuric chloride in glyme were mixed and concentrated to 8 ml total volume to give 0.66 g (93%) of the 1:1 complex, mp 174–175°. Recrystallization from glyme gave an analytical sample, mp 174–174.5°.

Anal. Calcd for $C_{18}H_{32}Cl_2HgO_4S_4$: C, 30.35; H, 4.53; Cl, 9.96; Hg, 28.17. Found: C, 30.36; H, 4.47; Cl, 9.89; Hg, 28.75.

A similar reaction of 0.47 g (0.001 mol) of **6** and 0.54 g (0.002 mol) of $HgCl_2$ gave 0.67 g (90%) of the 1:1 complex, mp ~205° dec.

Anal. Calcd for $C_{18}H_{32}Cl_2HgO_2S_6$: C, 29.94; H, 4.33; Cl, 9.53; Hg, 26.95. Found: C, 30.48; H, 4.51; Cl, 9.49; Hg, 27.59.

Preparation of Complexes. Derivatives of the macrocyclic polyethers were prepared from alkali metal thiocyanates and calcium iodide starting with homogeneous acetone solutions of the salts. These solutions (filtered in the case of LiSCN to remove insolubles) were added either to the liquid macrocycle or to a solution of macrocycle in acetone. Concentration to low volume under nitrogen and scratching were generally effective in causing crystallization. Recrystallizations were from acetone or acetone–ether. Complexes of the monospiro macrocycles were far more soluble in acetone than those of the dispiro compounds and tended to be hygroscopic. Melting points were characteristically sharp. Ir spectra of the thiocyanate complexes were similar to those of the parent macrocycles with a band for thiocyanate added at ~4.9 μ. Alkali metal analyses by atomic absorption are considered to be less accurate than the other analyses; stoichiometry of the complexes was determined primarily by C, H, and N values. Table III summarizes the results of these syntheses.

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Registry No.—**1**, 78-71-7; **4**, 51652-82-5; **5**, 51652-86-9; **5** $HgCl_2$ complex, 51652-88-1; **6**, 51652-89-2; **6** $HgCl_2$ complex, 51652-90-5; LiSCN, 556-65-0; NaSCN, 540-72-7; KSCN, 333-20-0; 2,2,9,9-tetrakis(chloromethyl)-4,7-dioxadecane-1,10-diol, 51652-91-6; 3-chloromethyl-3-[6-(3'-chloromethyl-3'-oxetanyl)-2,5-dioxahexyl]oxetane, 51652-92-7; 1,6-bis(3'-chloromethyl-3'-oxetanyl)-2,5-dioxahexane, 51652-93-8; 3,3-bis(*tert*-butoxymethyl)oxetane, 33867-48-0; 3,3-bis(bromomethyl)oxetane, 2402-83-7; 1,2-bis(2-chloroethoxy)ethane, 112-26-5; bis(2-mercaptoethyl) ether, 2150-02-9; bis(2-mercaptoethyl) sulfide, 3570-55-6; mercuric chloride, 7487-94-7; calcium iodide, 10102-68-8.

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(10) The author is grateful to Dr. H. K. Frensdorff for determination of these values by potentiometric titration as described in ref 2.
(11) As has been pointed out by a referee, there is no reason to assume other than the normal covalent structures for adducts of the cyclic polysulfides with mercuric chloride.
(12) Melting points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as internal reference. Chemical shifts are reported in parts per million (ppm), the downfield direction from tetramethylsilane being taken as positive. Solutions were approximately 20% in acetone-d_6 unless otherwise specified.
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Oxidation and Mass Spectra of 4,4-Dimethyloxazolidine-*N*-oxyl (Doxyl) Derivatives of Ketones

Sunwen Chou, J. A. Nelson, and T. A. Spencer*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

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4,4-Dimethyloxazolidine-*N*-oxyls (doxyls), the very useful nitroxide spin labels, can be reconverted rapidly and efficiently to their parent ketones with nitrogen dioxide (conveniently as contained in commercial nitric oxide) in ethanol at room temperature. This reaction is interpreted as involving initial oxidation to give an oxoammonium salt, *e.g.*, **5** from **1**, followed by fragmentation to an oxonium ion, *e.g.*, **6**, and cleavage to ketone. The mass spectra of several doxyls and their precursor oxazolidines have been studied. The latter show a fragmentation pattern like that of ethylene ketals. The more interesting mass spectra of the doxyls can be interpreted on the basis of formation of the same molecular ion, *e.g.*, **5**, which results from chemical oxidation. This leads in a major fragmentation mode to protonated parent ketone as the base peak. Deuterium-labeled substrates and high-resolution identification of ion formulas were used to gain evidence for this pathway as well as for several other modes of breakdown of the oxoammonium molecular ions.

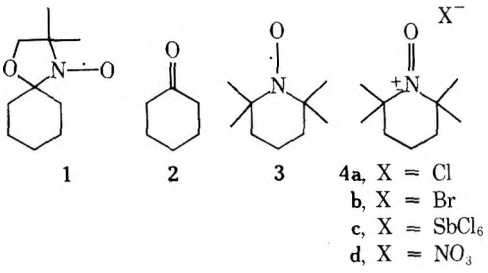
4,4-Dimethyloxazolidine-*N*-oxyl (doxyl) derivatives of ketones are among the more useful of the stable nitroxide free radicals which have recently gained prominence as spin labels. Since the first report[1] of their preparation in 1967, doxyls have been extensively used in the study of biological membranes and membrane models.[2-4] However, very little of the chemistry of these substances has been investigated.[5] In the course of another study[6] we discovered a rapid, efficient method for the reconversion of doxyl derivatives to the parent ketones.[7] This reaction and an analysis of the mass spectra of doxyls, which display a fragmentation pattern reminiscent of the doxyl → ketone conversion, are the subjects of this paper.

Reaction of Doxyls with Chemical Oxidizing Agents. If commercial nitric oxide is bubbled through an ethanol solution of doxyl **1** at room temperature for 5 min, cyclohexanone (**2**) is produced in 95% yield. The necessary reagent for this reaction is actually nitrogen dioxide, because no reaction occurs when the commercial NO is first bubbled through base to remove NO_2. Absolute ethanol is superior to the other solvents tried. The reaction, particularly in nonpolar solvents, is a visual delight: the initial orange-colored solution of nitroxide turns dark, then green or blue, and finally chartreuse.

Table I lists the doxyls and conditions which have been used in this reaction. The ketone is the only isolable product aside from an intractable, tarry residue. The fate of the heterocyclic portion of the nitroxides remains obscure. An extensive gc search for other products revealed only a few very weak, transient, unidentified peaks. Because isobutene is a possible product of this reaction, attempts were made, using gc, to determine whether it would have been detected if formed. Small added amounts (<1 equiv) of isobutene were not detectable, but larger amounts were, suggesting that isobutene, if formed, might itself have reacted further.[8]

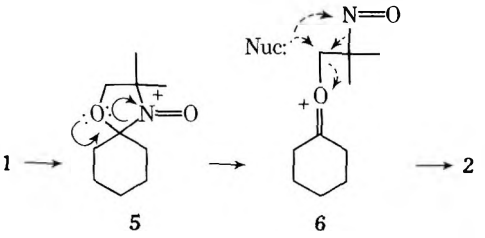
In the absence of any information regarding what happened to the heterocyclic moiety, assignment of a mechanism to the reaction of NO_2 with doxyls must remain incomplete in detail and tentative. However, a well-documented reaction[9-11] of other types of nitroxides with oxidizing agents to form oxoammonium salts suggested that analogous removal of an electron might be the first step in the conversion of doxyl to ketone. Typical examples of this type of oxidation are the conversions of nitroxide **3**[12] to **4a**, **4b**, or **4c** by chlorine,[9] bromine,[10] or $SbCl_5$,[11] respectively.

If such electron removal occurred with a doxyl, *e.g.*, **1**, to give **5**, fragmentation to oxonium ion **6** could ensue as a consequence of the unshared electrons of the ethereal oxygen, as shown in Scheme I. Elucidation of the details of the decomposition of **6** would depend on knowledge of the products from the doxyl moiety, but the fact that the reaction proceeds more cleanly in ethanol than in cyclohexane is consistent with the kind of nucleophilic attack suggested in **6** → **2** in Scheme I.



1 **2** **3** **4a**, X = Cl; **b**, X = Br; **c**, X = $SbCl_6$; **d**, X = NO_3

Scheme I



5 **6**

Evidence consistent with this hypothesis was obtained from treatment of nitroxide **3** with NO_2, which afforded 93% of oxoammonium nitrate **4d**. Treatment of doxyl **1** with chlorine led to formation of **2**,[13] plus 2-chlorocyclohexanone and a small amount of blue oil which eventually was assigned tentatively the intriguing structure **7**.

Blue oil **7** crystallized at low temperatures to a white solid which regenerated the blue oil upon melting. This behavior, plus its spectral properties (*e.g.*, ir 7.93 and 8.85 μ; uv max (EtOH) 295 nm) clearly suggested that it was a nitroso compound in equilibrium with its dimer. The substance was extremely difficult to characterize, however, owing to its instability even, for example, in solutions prepared for determination of its nmr spectrum.

Accordingly the nitroso compound was oxidized with *m*-chloroperbenzoic acid to the corresponding nitro compound **8**. This more tractable substance gave a clean nmr spectrum [δ 1.63 (s, 6), 1.6–2.3 (m, 6), 4.07 (s, 2), and 4.1–4.7 (m, 2)], and had a mass spectrum with an M^+ ion indicating that the compound contained three chlorine atoms. Structure **8** (stereochemistry uncertain) is the only one we have been able to formulate consistent with these data.[14]

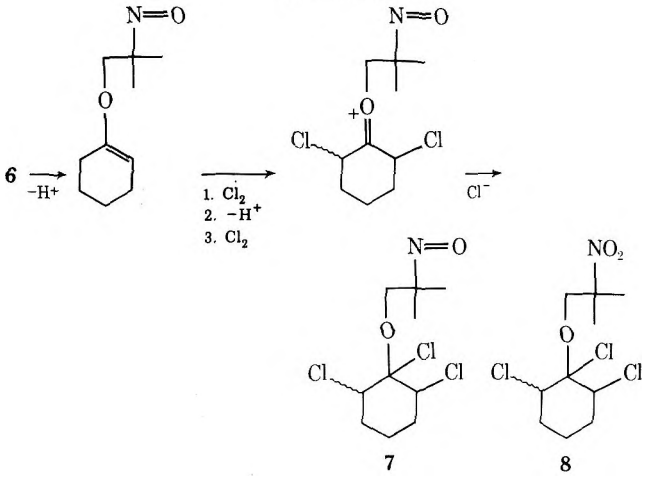
Table I
Reaction of Doxyls with Commercial Nitric Oxide[a]

Doxyl derivative of	Registry no.	Ketone: Yield,[b] %	Ketone: Solvent	Ketone: Registry no.	Gc reference compd
Cyclohexanone[c]	16302-61-7	48	Benzene	108-94-1	Dodecane
		62	CCl_4		Dodecane
		66	Cyclohexane		Dodecane
		95	Absolute ethanol		Dodecane
2-Methylcyclohexanone[d]	35328-05-3	81	Cyclohexane	583-60-8	2,4-Dichlorotoluene
		100	Absolute ethanol		2,4-Dichlorotoluene
Cycloheptanone[d]	35328-03-1	93	Absolute ethanol	502-42-1	Tetradecane
Heptan-2-one[c]	16263-51-7	74	Cyclohexane	110-43-0	Tetradecane
Cholestan-3-one[c]	18353-76-9	68[e]	Cyclohexane	566-88-1	
		85[e]	Absolute ethanol		

[a] Room temperature, 5 min. [b] Determined by gc as described in the Experimental Section, unless otherwise noted. [c] Reported in ref 1. [d] New compound; see Experimental Section. [e] Yield of isolated, recrystallized ketone with mp 127–130°.

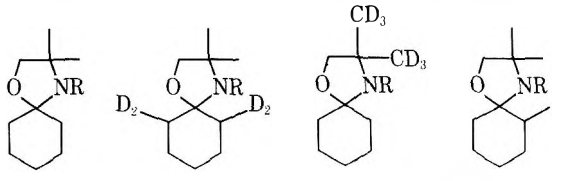
The precursor **7** could arise through the sequence shown in Scheme II, and its isolation is consistent with the proposed mechanism.

Scheme II

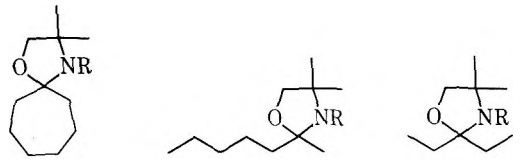


Mass Spectra of Doxyls. During attempts to gain information about possible intermediates in the conversion **1** → **2** by gc–mass spectral examination of reaction mixtures, the fragmentation patterns of the nitroxides themselves were determined, and these proved to be of sufficient interest to deserve careful analysis. Mass spectra of doxyls have not previously been investigated, although those of a few other nitroxides have been examined.[15-18]

In the present work, the mass spectra of doxyl derivatives **1** and **9–14** were studied. All of these substances were



1, R = O; **17**, R = H
9, R = O; **18**, R = H
10, R = O; **19**, R = H
11, R = O; **20**, R = H



12, R = O; **21**, R = H
13, R = O; **22**, R = H
14, R = O; **23**, R = H

prepared by the general method of Keana.[1] The deuterium-labeled compound **9** was prepared from cyclohexanone-2,2,6,6-d_4. The heterocyclically labeled **10** was made by the sequence shown in Scheme III, involving a Strecker synthesis[19] of amino acid **15** from acetone-d_6 and subsequent reduction of its trimethylsilyl derivative with lithium aluminum hydride[20] to produce aminopropanol **16**.

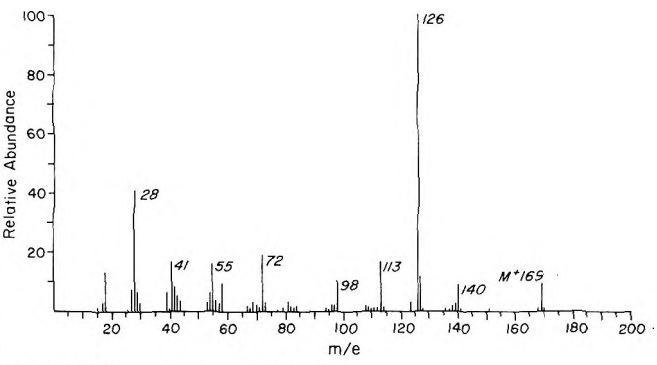
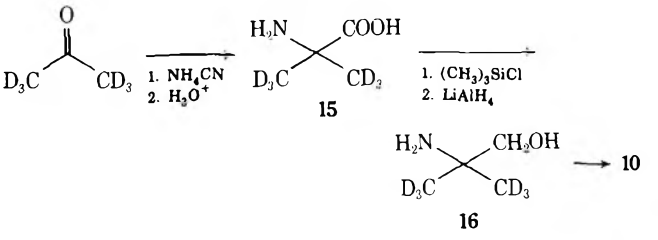


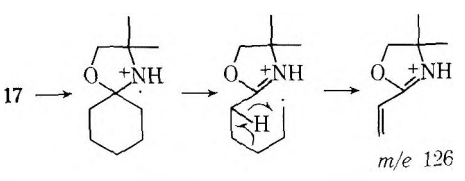
Figure 1. Mass spectrum of **17**.

Scheme III



For purposes of comparison the mass spectra of the precursor oxazolidines **17–23** were determined first. These spectra are characterized by the dominance of one or two peaks, suggesting formation of relatively stable ions, as with ethylene ketals.[21] Figure 1 shows the mass spectrum of **17**, with the typically dominant base peak at *m/e* 126 accounting for 25% of the total ion current. The mode of formation of this base peak is given in Scheme IV. Confirmation of this pathway was obtained from the mass spectra of the deuterated oxazolidines **18** and **19**, which displayed base peaks at *m/e* 127 and 132, respectively. Oxazolidine **20** showed a base peak at *m/e* 126 and one nearly as intense at *m/e* 140 corresponding to the two modes of cleavage of the

Scheme IV



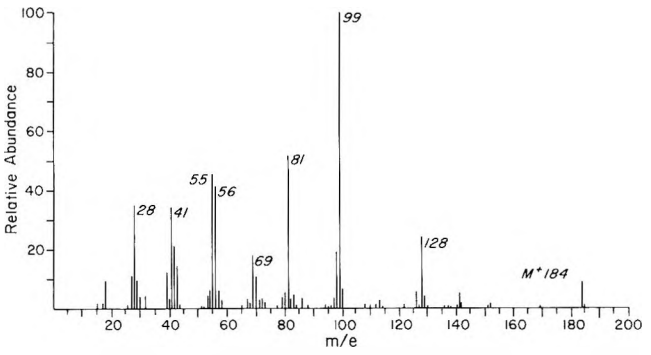


Figure 2. Mass spectrum of **1**. High-resolution data support the elemental compositions indicated, within an error of ±0.002 amu: C_3H_3O, C_4H_7, C_4H_8, C_5H_9, C_4H_7N, C_6H_9, C_5H_8NO, $C_6H_{10}O$, $C_6H_{12}N$, $C_6H_{11}O$, $C_6H_{11}NO$, $C_6H_{10}NO_2$, $C_7H_{11}NO_2$, $C_9H_{14}NO$.

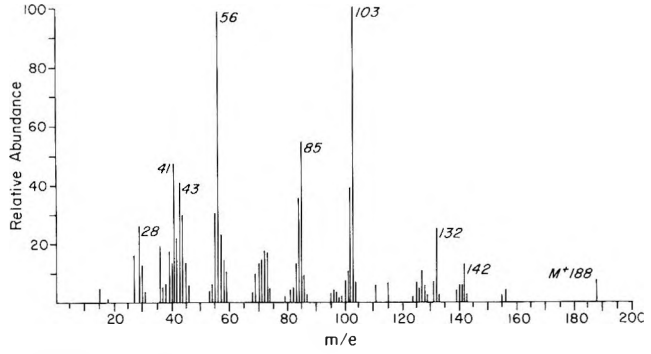


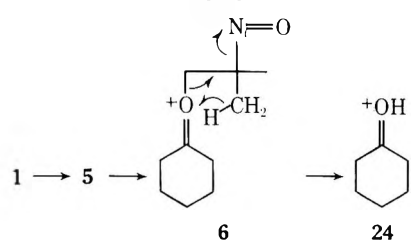
Figure 3. Mass spectrum of **9**.

cycloalkyl ring. **22** showed peaks at *m/e* 114 and 170 reflecting loss of one or the other of the alkyl groups.

The mass spectra of the doxyls (see Figures 2–5) are markedly different. The dominant peaks reflect ions which tend not to retain charge on nitrogen, a pattern also found with other nitroxides.[15-18] The ether oxygen does, however, retain its charge-stabilizing capability, and has a profound influence in the spectrum. As will be demonstrated in the following, the fragmentation patterns of doxyls, *e.g.*, **1**, can be best represented as proceeding *via* a molecular ion of the same type, *e.g.*, **5**, encountered above in the chemical oxidation of these nitroxides.

For all the doxyls the base peak occurs at M − 85, one mass unit higher than the molecular weight of the parent ketone. High-resolution data for **1** and **13** show that this peak corresponds in elemental formula to protonated ketone. The most plausible pathway for formation of protonated ketone is illustrated for doxyl **1** in Scheme V. The initially formed molecular ion **5** undergoes the familiar fragmentation to **6**, which forms protonated ketone **24** *via* intramolecular hydrogen atom abstraction as shown.[22] That the proton on oxygen in **24** originated in the heterocyclic *gem*-dimethyl group is proved by the shift of the base peak to one mass unit higher with **10** (Figure 4).

Scheme V



Peaks are present in the mass spectrum of **1** which indicate that oxonium ion intermediate **6** can also decompose

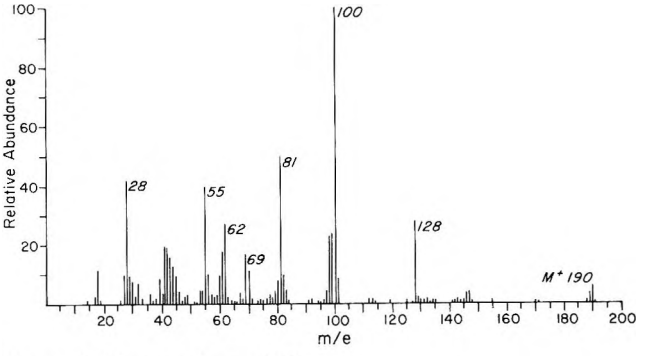


Figure 4. Mass spectrum of **10**.

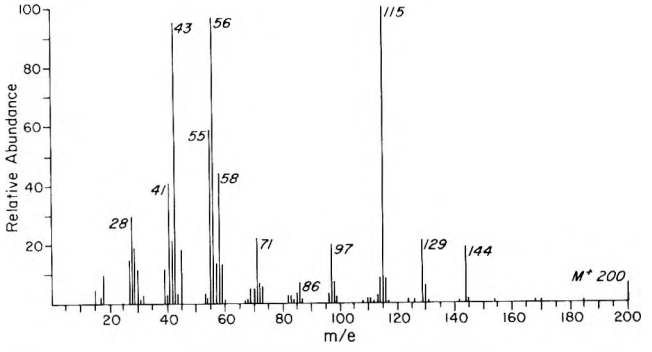
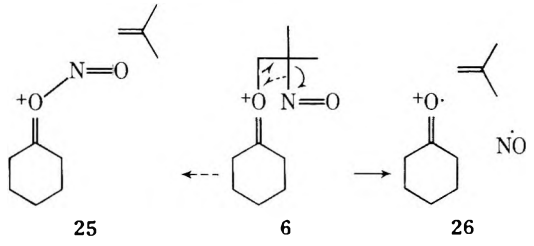


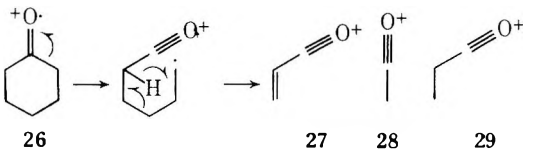
Figure 5. Mass spectrum of **13**. High-resolution data support the elemental compositions indicated, within an error of ±0.002 amu: C_4H_7, C_4H_8, C_3H_6N, C_2H_4NO, C_3H_6O, C_3H_8N, C_4H_9N, C_5H_{11}, C_4H_8NO, $C_5H_{12}N$, $C_6H_{11}N$, C_7H_{13}, $C_7H_{15}O$, $C_6H_{11}NO_2$, $C_7H_{14}NO_2$.

with elimination of isobutene to form **25** (*m/e* 128), *via* an unusual intramolecular transfer of NO, or of isobutene and nitric oxide to form **26** (*m/e* 98) as shown in Scheme VI. Structures **25** and **26** are in accord with high-resolution data, and all the other doxyls have peaks of analogous origin. In particular, the peak at *m/e* 128 is shifted to *m/e* 132 in **9** and remains unchanged in **10**.

Scheme VI

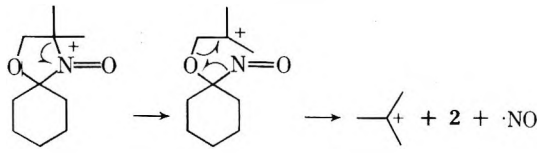


It should be noted that ion **26** is the molecular ion of cyclohexanone. Consequently, the more intense ions in the spectrum of the parent ketone **2** should also be significant in the spectrum of doxyl **1**. Such is the case. The base peak from cyclohexanone is due to **27** with *m/e* 55.[23] High-resolution measurements and shifts in the mass spectra of **9** and **10** (particularly the enhancement of the *m/e* 56 peak from **9**) allow at least a substantial portion of the *m/e* 55 ions to be assigned structure **27**. Similarly, the peaks at *m/e* 43 from **13** and *m/e* 57 from **14** can reasonably be assigned structures **28** and **29** as major contributors.



The mass spectral data suggest that some degree of fragmentation of molecular ion **5** occurs by the alternate path shown in Scheme VII, leading to tertiary carbonium ion **30** rather than oxonium ion **6**. This pathway is evidenced by the appearance in the spectra from all the nitroxides except **10** of a strong peak at *m/e* 56 arising from ion **31**. The appearance of a peak at *m/e* 62 with doxyl **10** (Figure 4) and high-resolution data for **1** and **13** support this interpretation.

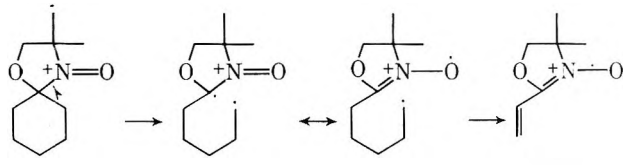
Scheme VII



5 30 31

A third pattern of fragmentation of molecular ion **5**, shown in Scheme VIII, is required to account for some relatively minor peaks which are especially noticeable in the mass spectra of the open-chain doxyls **13** (Figure 5) and **14**. The peaks at *m/e* 141 from **1** (**32**), *m/e* 129 from **13**, and *m/e* 143 from **14** have such an origin, as confirmed by high-resolution data for **1** and **13** and the shift to *m/e* 142 in the spectrum of **9**.

Scheme VIII



5 *m/e* 141 32

Finally, a number of lower mass ions can be readily explained as secondary fragmentation products. A prominent metastable at *m/e* 66.3 (calcd, 66.27) can be observed for the transition from **24** (*m/e* 99) to an ion with mass 81. High-resolution data confirm that this transition is a loss of H_2O leading to a $C_6H_9^+$ hydrocarbon fragment of uncertain structure.

The mass spectra of doxyl derivatives, although fairly complex, thus can be rationalized successfully on the basis of formation of an oxoammonium molecular ion like **5**. Although several fragmentation pathways are observed for the high-energy **5** produced upon electron impact, the principal pattern very reasonably is the same as that of **5** produced by chemical oxidizing agents.

Experimental Section

Low-resolution mass spectra were recorded with a Perkin-Elmer 270B double-focusing spectrometer using an ionizing voltage of 75 eV and a source temperature of 200°. Samples were introduced upon elution from a gas chromatograph equipped with a 20% SE-30 column operated with temperature programming at 20°/min from 70 to 200°, the eluted sample being passed through a Watson-Biemann molecular separator to remove most of the helium carrier gas. The spectrometer output was digitized by an auxiliary PDP-12 computer using a perfluorokerosene spectrum as reference. High-resolution mass spectra were recorded on an AEI MS-9 spectrometer using an ionizing voltage of 70 eV and a source temperature of 150°. Samples were introduced by direct insertion into the source; perfluorotributylamine was used as an internal standard. Nuclear magnetic resonance (nmr) spectra were recorded on a 60-MHz Perkin-Elmer R-24 spectrometer using CCl_4 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Shifts are reported in parts per million downfield from TMS. Infrared (ir) spectra were recorded on a Perkin-Elmer 137 spectrophotometer using potassium bromide pellets for solids (unless indicated otherwise) and thin films for liquids. Ultraviolet (uv) spectra were recorded on a Unicam SP800 spectrometer. Melting points were determined in open capillaries using Thomas-Hoover apparatus and are uncorrected. Elemental analyses are performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or by Meade Microanalytical Laboratory, Amherst, Mass.

Gas chromatography (gc) was carried out either on a Perkin-Elmer 154 gas chromatograph using a 10 ft × 0.25 in. glass column packed with 30–60 mesh acid-washed Chromosorb P coated with 20% didecyl phthalate and operating at about 140° with a helium flow rate of 60 ml/min or on a Varian 2100 chromatograph using a 2 m × 4 mm glass column packed with 100–120 mesh Gas-Chrom Q coated with 3% of the indicated stationary phase and operating at about 100° with a nitrogen flow rate of 30 ml/min. The instruments used thermal conductivity and flame ionization detectors, respectively. In both cases peak areas are determined by Disc chart integration. In all yield determinations an appropriate internal reference compound was used, with prior determination of the relative detector response to reference and to the analyzed compound. Thin layer chromatography (tlc) was carried out on 5 × 20 cm plates coated with 0.25 mm thick layers of Merck silica gel $PF_{254+366}$ using various mixtures of ether and hexane as solvents. Preparative layer chromatography (preparative tlc) was generally carried out on 20 × 20 cm plates coated with 1.5 mm thick layers of the same silica gel using the solvents indicated. About 200 mg of material could be chromatographed per plate.

Commercial ketones used as starting materials were redistilled before use. The 2-amino-2-methyl-1-propanol and 85% *m*-chloroperbenzoic acid (Aldrich Chemical Co., Milwaukee, Wis.) were used as received. Deuterium oxide (99%) and acetone-d_6 (99.5%) were supplied by Stohler Isotope Chemicals, Rutherford, N. J. Reagent gases were supplied by Matheson Gas Products, E. Rutherford, N. J.

Preparation of Oxazolidines. Generally according to the procedure of Hancock and Cope,[24] the ketone (0.5 mol), 2-amino-2-methyl-1-propanol (0.8 mol), and *p*-toluenesulfonic acid (3.0 g) were refluxed under nitrogen in 150 ml of benzene for 8 hr with azeotropic water removal by means of a Dean-Stark apparatus. The product was diluted with 50 ml of ether, washed with 3 × 200 ml of water and once with saturated aqueous sodium chloride, and dried over Na_2SO_4. Evaporation of the solvent gave the crude oxazolidine derivative, which was fractionally distilled at reduced pressure to give the product as reported below.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]decane (17) was formed in 74% yield: bp 99–100° (24 mm) [lit.[24] bp 95–97.5° (20 mm)]; ir 3.04 and 9.62 μ; nmr ($CDCl_3$) δ 1.18 (s, 6), 1.51 (m, 10), and 3.43 (s, 2).

2,4,4-Trimethyl-2-pentyloxazolidine (22) was formed in 67% yield: bp 95° (15 mm) [lit.[24] bp 102–103° (19 mm)]; ir 3.00 and 9.55 μ.

3,3-Dimethyl-1-oxa-4-azaspiro[4.6]undecane (21) was formed in 64% yield: bp 122–123° (23 mm); ir 2.97 and 9.58 μ; mass spectrum M^+ *m/e* 183; base *m/e* 126.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.11; H, 11.42; N, 7.63.

3,3,6-Trimethyl-1-oxa-4-azaspiro[4.5]decane (20) was formed in 80% yield: bp 108–109° (20 mm); ir 3.0 and 9.5 μ; mass spectrum M^+ *m/e* 183, base *m/e* 126.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.02; H, 11.54; N, 7.62.

2,2-Diethyl-4,4-dimethyloxazolidine (23) was formed in 22% yield (incomplete reaction): bp 89–91° (50 mm); ir 3.0 and 9.58 μ; nmr (CCl_4) δ 0.84 (t, 6), 1.17 (s, 6), 1.49 (q, 4), and 3.40 (s, 2); mass spectrum (high resolution) M^+ *m/e* 157.1460 (calcd for $C_9H_{19}NO$, 157.1466).

Preparation of Nitroxides. According to Keana's procedure,[1] a solution of 85% *m*-chloroperbenzoic acid (0.06 mol) in 80 ml of anhydrous ether was added dropwise over 15 min to an ice-cold, stirred solution of the appropriate oxazolidine derivative or secondary amine (0.05 mol) in 80 ml of anhydrous ether. The reaction mixture was allowed to warm to room temperature and stand for 12–24 hr. The product was washed with 4 × 75 ml of 5% aqueous sodium bicarbonate and once each with water and saturated aqueous sodium chloride and dried over $MgSO_4$, and the ether was evaporated to give the crude nitroxide.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy (1) was formed in 30% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane. A sample sublimed at 35° (0.1 mm) had mp 58–59° (lit.[1] mp 57–58°); ir 7.44 and 9.67 μ; uv max(Et_2O) 234 and 415 nm.

2,4,4-Trimethyl-2-pentyl-3-oxazolidinyloxy (13) was obtained as an orange oil which was not fully purified by distillation at 78–80° (0.3 mm) [lit.[1] 80° (0.08 mm)]. Chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane gave 11% yield of an orange liquid, ir 7.37 and 9.58 μ.

3,3-Dimethyl-1-oxa-4-azaspiro[4.6]undec-4-yloxy (12) was obtained in 14% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane. A sample sublimed at 40° (0.05 mm) had mp 59–60°, ir 9.59 μ.

Anal. Calcd for $C_{11}H_{20}NO_2$: C, 66.62; H, 10.17; N, 7.06. Found: C, 66.59; H, 10.05; N, 6.63.

3,3,6-Trimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy (11) was obtained in 23% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with 5% ether in hexane: bp 60° (0.1 mm); ir 7.32 and 9.67 μ.

Anal. Calcd for $C_{11}H_{20}NO_2$: C, 66.62; H, 10.17; N, 7.06. Found: C, 66.76; H, 10.10; N, 7.16.

2,2-Diethyl-4,4-dimethyl-3-oxazolidinyloxy (14) was prepared in 41% yield after chromatography on Florisil eluting with 5% ether in hexane: bp 60° (1.8 mm); ir 7.34 and 9.57 μ; mass spectrum (high resolution) M$^+$ *m/e* 172.1334 (calcd for $C_9H_{18}NO_2$, 172.1337).

2,2,6,6-Tetramethylpiperidinooxy (3) was obtained in 32% yield after chromatography on Woelm acid-washed alumina (activity I) eluting with hexane. The crude 3 thus obtained purified itself by spontaneous sublimation within its container at room temperature and atmospheric pressure: mp 38–39° [lit.[12] mp 38–39°]; ir 7.37 μ.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy-*6,6,10,10-d*$_4$ (9). Cyclohexanone-*2,2,6,6-d*$_4$ was prepared by treatment of cyclohexanone with D_2O containing potassium carbonate. This product was converted to oxazolidine **18** in the usual manner using 2-amino-2-methyl-1-propanol which had previously been treated with D_2O and had then been dried by azeotropic distillation with benzene. This labeled **18** (1.8 g) was treated with 85% *m*-chloroperbenzoic acid (2.0 g), as described earlier. Chromatography of the product on 40 g of Woelm acid-washed alumina (activity I) using 5% ether in hexane as eluent gave after sublimation at 38° (0.05 mm) 0.800 g of **9**: mp 58–59°;[25] ir 4.54 and 9.73 μ; mass spectrum M$^+$ *m/e* 188, 75% d_4 species as estimated by molecular ion intensities.

2-Amino-2-methylpropanoic Acid-*d*$_6$ (15). Exactly according to the procedure of Steiger,[19] a solution of 9.0 g of acetone-d_6 in 25 ml of methanol was treated with an aqueous solution of 6.9 g of NaCN, 8.3 g of NH_4Cl, and 9.6 ml of NH_4OH to afford, after crystallization from absolute ethanol, 9.7 g (55%) of **15**: mp >300°; no chloride ion by aqueous $AgNO_3$; ir 4.55, 6.15, and 8.76 μ.

2-Amino-2-methyl-1-propanol-*d*$_6$ (16). Following a published procedure,[20] 2.4 g of the oven-dried amino acid **15** prepared above was suspended in 100 ml of dry benzene which was then refluxed under nitrogen with 20 ml of freshly distilled triethylamine and 6 g of distilled chlorotrimethylsilane for 12 hr. The cooled mixture was filtered and dried (Na_2SO_4), and the benzene was evaporated. The residue containing the silyl derivative was dissolved in 200 ml of anhydrous ether and the resulting solution was added dropwise during 1 hr to a stirred, ice-cold solution of 0.95 g of lithium aluminum hydride in 150 ml of ether. After 1 hr at room temperature and 2 hr at reflux, the mixture was cooled in ice and 100 ml of water-saturated ether was added dropwise over 45 min with stirring. After filtration of the inorganic precipitate the solution was dried (K_2CO_3) and the ether was evaporated. The residue was heated with 1 ml of water on a steam bath for 1 hr; the mixture was saturated with potassium carbonate and extracted with ether. Evaporation of the extract gave 1.48 g of light yellow liquid containing **16** (ir 4.56 μ) which was used without purification in the next step.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]decane-*d*$_6$ (19). All of this product containing **16** was refluxed under nitrogen with cyclohexanone (1.8 g) and *p*-toluenesulfonic acid (1.0 g) in 150 ml of benzene for 10 hr with azeotropic water removal by means of a Dean-Stark apparatus. The work-up described earlier for oxazolidine preparation gave after distillation at 50° (1.5 mm) 0.58 g of **19**, slightly contaminated with cyclohexanone: ir 4.54 and 9.63 μ; nmr 1.47 (br s, 10) and 3.42 (s, 2); mass spectrum M$^+$ *m/e* 175, deuterium incorporation about 90% by nmr.

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]dec-4-yloxy-*d*$_6$ (10). A solution of 85% *m*-chloroperbenzoic acid (0.8 g) in 30 ml of anhydrous ether was added dropwise over 15 min to a stirred, ice-cold solution of oxazolidine derivative **19** (0.55 g) in 30 ml of anhydrous ether. After 4 hr at room temperature the mixture was worked up as described earlier. Chromatography on 10 g of Woelm acid-washed alumina (activity I) gave upon elution with hexane and 5% ether in hexane 0.081 g of orange solid **10**: mp 58–59°; ir 4.48 and 9.87 μ; mass spectrum M$^+$ *m/e* 190, 55% d_6 species and 35% d_5 species as estimated by molecular ion intensities.

Reactions of Nitroxides with Oxidizing Agents. All reactions were carried out at room temperature. Solutions were flushed with nitrogen for 30 min prior to introduction of the reactant gas. Only glass equipment was used in these reactions.

Reactions of Doxyls with Commercial Nitric Oxide. In a general procedure, 1 mmol of the appropriate nitroxide was dissolved in 10 ml of solvent together with a known, approximately equal weight of an unreactive internal reference compound whose gc retention time did not coincide with that of starting material or any of the products. Upon bubbling commercial nitric oxide (from a tank) through the solution for 5 min, the initially light orange color of the solution deepened and then turned green or blue, finally lightening to a yellowish, sometimes cloudy mixture. Samples of this mixture were analyzed by gc. The predominant product was shown to be the parent ketone by correspondence of gc retention times, and also in the case of **1** by a mass spectrum from the eluted gc peak. The yield of ketone was determined by the relative areas of the product and reference peaks; averages from two or more chromatograms are reported in Table I.

Reaction of 3 with Commercial Nitric Oxide. Treatment of 100 mg (0.642 mmol) of **3** in 5 ml of cyclohexane with commercial nitric oxide for 4 min gave a bright yellow precipitate which was filtered and washed with hexane to give 130 mg (93%) of **4d**: mp 110–120° dec; ir (Nujol mull) 6.2 μ; uv max (CH_3CN) 244 nm (ϵ 1680) and 450 (26); positive brown ring test with H_2SO_4–$FeSC_4$ for nitrate ion.

Anal. Calcd for $C_9H_{18}N_2O_4$: C, 49.53; H, 8.31; N, 12.84. Found: C, 49.75; H, 8.25; N, 12.97.

Reactions with Purified Nitric Oxide. Solutions of nitroxides **3** and **11** were treated in the same manner with nitric oxide which had been passed through 3 *N* aqueous sodium hydroxide and sodium hydroxide pellets to remove the nitrogen dioxide. No reaction occurred (as monitored by gc) even after 0.5–1 hr of treatment. Injection of air at this point rapidly initiated the reaction observed with unpurified commercial nitric oxide.

Reaction of 1 with Nitrogen Dioxide. Commercial nitrogen dioxide was bubbled through a solution of 187 mg (1.02 mmol) of **1** and 73.6 mg of dodecane in 5 ml of cyclohexane for 30 sec. Cyclohexanone was formed in 65% yield as determined by gc.

Reaction of 1 with Chlorine. Dry chlorine was bubbled through a solution of 300 mg (1.63 mmol) of **1** in 5 ml of ether until the initially orange solution was deep green (about 2 min). Cyclohexanone and 2-chlorocyclohexanone were identified as products by comparison of gc retention times with those of commercially available samples of the authentic ketones on two columns (SE-30 and QF-1). Evaporation of the solvent followed by preparative tlc (20% ether in hexane) gave 2-chlorocylohexanone (10 mg) and **7** as a blue oil (50 mg): ir 8.0 and 8.92 μ; nmr ($CDCl_3$) 1.19 (s), 1.6–2.5 (m), 3.8–4.9 ppm (m). The latter formed a white powder upon standing at −10°. Trituration with petroleum ether gave 9.5 mg: mp 101–103° (melt was a dark blue liquid); ir 7.93 and 8.85 μ; uv max (95% EtOH) 295 nm; nmr (CCl_4) δ 1.17 (s), 1.5–2.0 (m), 4.0–4.7 (m).

Oxidation of 7 with *m*-Chloroperbenzoic Acid. Crude blue oily **7** (120 mg) was dissolved in 20 ml of chloroform and added dropwise over 5 min to a refluxing solution of 85% *m*-chloroperbenzoic acid (2.0 g) in 20 ml of chloroform. Refluxing was continued for another 5 min, during which the reaction mixture became colorless. The cooled mixture was diluted to 60 ml with chloroform and washed twice with 50-ml portions of 10% aqueous sodium sulfite and twice with saturated aqueous sodium bicarbonate. The chloroform layer was separated, dried over $MgSO_4$, filtered, and evaporated. Chromatography of the residue on Woelm base-washed alumina (activity III) gave upon elution with hexane 26.4 mg of **8**. Preparative tlc of this material on Merck silica gel $PF_{254+366}$ impregnated with KOH with 40% ether in hexane as solvent gave in one band 20 mg of a clear liquid: ir 6.53 μ; nmr (CCl_4) 1.63 (s, 6), 1.6–2.3 (m, 6), 4.07 (s, 2), 4.1–4.7 (m, 2); mass spectrum weak M$^+$ *m/e* 303, 305, and 307.[26]

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Concentration Effects in the Photochemical Syn–Anti Isomerization of an Oxime Ether

Albert Padwa*[1] and Fred Albrecht[2]

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

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Upon irradiation with ultraviolet light, the *O*-methyl oxime ethers of 2-acetonaphthone undergo facile syn–anti photoisomerization. At low concentrations the syn isomer predominates in the photostationary state. High oxime ether concentrations, however, were found to enhance the fraction of the anti isomer in the photoequilibrium. Evidence supporting the involvement of the singlet state was obtained from fluorescence quenching studies and photosensitized isomerization experiments. Fluorescence quenching of both isomers by 1,3-cyclohexadiene was found to be more sensitive toward the quencher concentration than chemical quenching. The excited syn isomer was much less sensitive toward chemical quenching and showed a less intense emission than the corresponding anti form. The data obtained are consistent with the involvement of an excimer which is capable of inducing efficient syn–anti isomerization and whose decay ratio differs from that of excited monomer.

The thermal[3-9] and photo-[10-33] interconversions of the syn and anti isomers of imines are a subject of long-standing interest. The mechanism for the thermal interconversion of imine diastereomers is currently the subject of considerable debate,[34-45] and has been considered in terms of either a planar inversion mechanism or a rotation mechanism. The rotation or torsion mechanism involves a twisting about the C=N double bond. The inversion mechanism, on the other hand, is characterized by an increase in the angle of the C=N–C bond from approximately 120° in the ground state to 180° in the transition state. Evidence obtained from studies of substituent effects (steric and electronic) suggests that most simple imines interconvert by the inversion mechanism,[44] although some of the results obtained have been considered to be inconclusive.[34-36]

The mechanism by which the syn and anti isomers of imines are interconverted in the excited state is even more complicated. Whether isomerization about the C=N double bond proceeds by rotation or linear inversion remains to be clarified. A major complication with the photochemical studies is that the thermal barrier between the two diastereomers of most imines is sufficiently low that the photochemically induced shift in the configurational equilibrium is only temporary at ambient temperatures and is frequently followed by a rapid, thermal relaxation which reestablishes the initial configurational equilibrium between the syn and anti isomers.

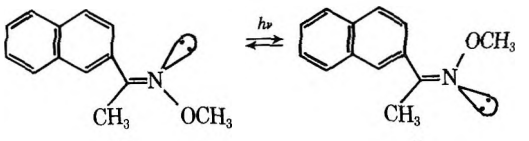
In previous work[31] we showed that irradiation of an oxime ether brings about a rapid syn–anti isomerization. The oxime ether molecule is an attractive system for mechanistic photostudies, since the presence of the methoxyl group drastically reduces the rate of thermal interconversion of the syn and anti forms (*i.e.*, $k < 10^{-13}$ at 60°)[3] and allows mechanistic studies to be carried out at ambient temperatures.

In order to secure additional information on the reactivity of the excited state(s) involved in the syn–anti photoisomerization reaction, we decided to study the photochemistry of a naphthyl-substituted oxime ether. It is reasonable to assume that in the naphthyl oxime ether system, the excitation energy will be heavily localized on the

naphthyl portion of the molecule. Concentration of the excitation at one end of the molecule seemed a possible way of modifying the photoisomerization reaction. In the present paper we report on some aspects of the direct and sensitized isomerization of the syn and anti isomers of 2-acetonaphthone oxime *O*-methyl ether, where we note that *marked discrepancies exist between predicted and measured photostationary states*. The results obtained are of fundamental interest by virtue of their superficial parallels to and mechanistic differences from the corresponding situation in olefin photochemistry.[46,47]

Results and Discussion

The anti *O*-methyl ether of 2-acetonaphthone oxime (**2**) was synthesized by treating 2-acetonaphthone with methoxylamine hydrochloride according to the procedure of Karabatsos and Hsi[48] [nmr ($CDCl_3$) δ 2.36 (s, 3 H), 4.12 (s, 3 H)]. The corresponding syn isomer **1** was prepared by



2 **1**

irradiation of **2** in pentane using 3130-Å light [nmr ($CDCl_3$) δ 2.28 (s, 3 H), 3.94 (s, 3 H)]. The two isomers could readily be separated by vapor phase chromatography and their thermal stability was established by heating each isomer separately at 140° and noting the absence of isomerization. Thermal equilibration of the two compounds could be achieved by iodine catalysis. In both cases, the equilibrium is, within experimental error, predominantly on the anti-isomer side (96% anti and 4% syn oxime ether). The ultraviolet absorption spectra of both the syn and anti forms resembled that of naphthalene.

Irradiation of degassed pentane (or benzene) solutions of syn (or anti) oxime ethers (**1** or **2**) at 3130 Å led to photostationary states whose composition varied, as shown in Table I, from 64% syn at [oxime ether] = 0.003 *M* to 42% syn at [oxime ether] = 1.35 *M*. The analyses by vpc were reproducible typically to better than ±0.3% in the comparison of the mean value of replicate samples and to ±0.5% for the average deviation from the mean of replicate injections of the same sample; the modest changes we observe are thus unquestionably real. The data obtained (Table I) indicate that the final photostationary state composition is dependent on both the temperature maintained and the concentration and solvent used during the course of the irradiation [*i.e.*, [syn]/[anti] at 0.1 *M* pentane = 0.92 ± 0.03 at 25° and 1.20 ± 0.05 at 80°; [syn]/[anti] = 1.80 ± 0.06 at 0.003 *M* (25°), 1.11 ± 0.05 at 0.05 *M* (25°), and 0.72 ± 0.04 at 1.35 *M* (benzene, 25°)]. These results show that high oxime ether concentrations enhance the fraction of the anti isomer in the photostationary state. High temperatures, however, tend to diminish the fraction of the thermodynamically more stable anti form. This type of behavior was not observed in the photoisomerization of the related acetophenone oxime ether system.[31]

The concentration dependence in the oxime ether system was also reflected in the quantum yields for photoisomerization. Quantum yields for the isomerization reaction were determined using benzophenone–benzhydrol actinometry.[49] The results obtained (Table I) indicate that as the total concentration of the oxime ether increased, the quantum efficiency of the anti → syn isomerization ($\Phi_{A\rightarrow S}$) decreased while the $\Phi_{S\rightarrow A}$ increased. The ratio of the quantum efficiencies ($\Phi_{A\rightarrow S}/\Phi_{S\rightarrow A}$) was found to vary in a manner analogous to the variation of the photostationary state ratio. The sum of the quantum yields, however, remained constant.

Table I
Quantum Yield and Photostationary State Dependence of Oxime Ethers 1 and 2 on Concentration, Solvent, and Temperature[a-c]

Total concn, *M*	Syn/Anti: Pentane	Syn/Anti: Benzene	$\Phi_{A\rightarrow S}$[d]	$\Phi_{S\rightarrow A}$[d]	Φ_A/Φ_S
0.003	1.80				
	1.86 (80°)				
0.008	1.67				
0.012	1.59	1.64			
0.023	1.34	1.57	0.56	0.35	1.60
0.042	1.18	1.45	0.48	0.36	1.41
0.05	1.11		0.53[e]	0.49[e]	1.08[e]
	1.32 (80°)				
0.08		1.31	0.46	0.39	1.18
0.10	0.92				
	1.20 (80)				
0.17		1.14	0.42	0.37	1.14
0.34		0.96	0.42	0.41	1.02
0.67		0.79	0.40	0.46	0.87
1.35		0.72	0.39	0.48	0.81

[a] 3130-Å light. [b] The analyses by vpc were reproducible typically to better than ±0.5% in the comparison of the mean value of replicate samples. [c] All values reported at 25° unless otherwise stated. [d] All quantum yields determined in benzene unless otherwise stated. [e] Determined in pentane solution.

Two possibilities come to mind in seeking an explanation for the cause of the syn/anti isomer variation. These are (1) association between ground-state molecules which give rise to dimers and higher aggregates, and (2) specific interactions between ground-state and excited oxime ether molecules. With respect to the first possibility, theoretical considerations indicate that association should lead to a new absorption at longer or shorter wavelengths than that due to monomer.[50,51] We have examined both the syn and anti isomers over a wide concentration range and have found no evidence of spectral change in the ultraviolet region; both the position of the absorption bands and the extinction coefficients are, within experimental error, independent of the concentration. Since no evidence for ground-state complexation could be found by uv as well as ir and nmr spectroscopy, it would seem as though the observed variation in the photostationary state is due to interactions between excited and ground-state molecules.[52]

The interaction between excited and ground-state molecules is a well-documented phenomenon.[53-56] These interactions will be expected to be somewhat dependent on the temperature and solvent system employed.[53] The data obtained above are consistent with the involvement of an excimer which is capable of inducing efficient syn–anti isomerization and whose "decay ratio" differs from that of the excited monomer. The variation of the photostationary state composition as a function of temperature can be attributed to the dissociation of the excimer with re-formation of the excited monomer at higher temperatures. The equilibrium associated with excimer formation and its corresponding "decay ratio" will also be exected to be influenced by the nature of the solvent system used. Excimers have been reported to play an important role in the photoisomerization of certain olefinic systems.[57-60] In these cases it was found that a high olefin concentration also enhances the fraction of the trans isomer in the photostationary state.

In this connection, it is worthy to note that the fluorescence emission spectrum of oxime ether **1** is subject to concentration quenching. The fluorescence emission curve for **1** at 0.03 *M* was essentially identical in shape and

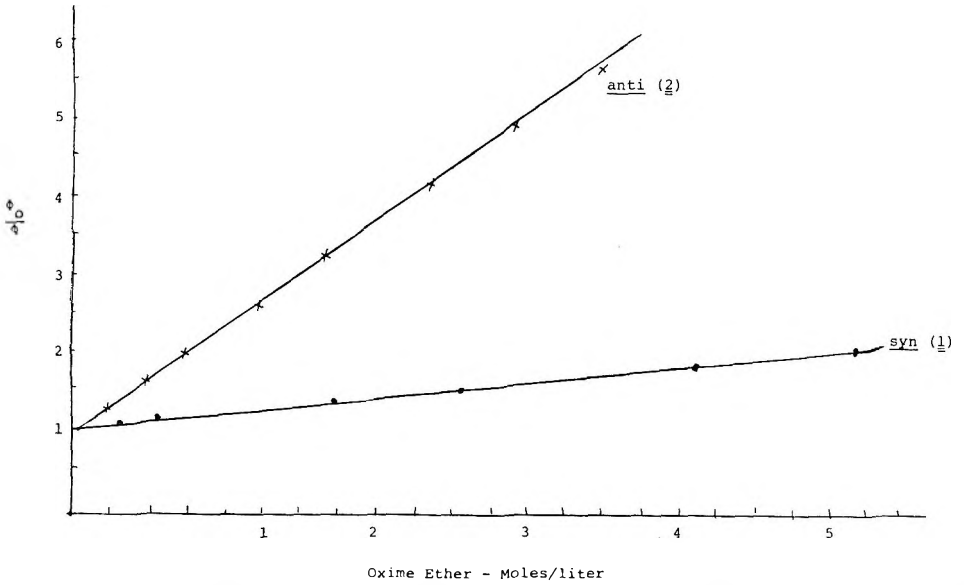


Figure 1. 1,3-Cyclohexadiene quenching of the fluorescence of the syn and anti isomers of the *O*-methyl ether of 2-acetonaphthone oxime in pentane (25°).

wavelength with that of naphthalene. Most importantly, a new component (*ca.* τ 500 nm) became evident in the fluorescene spectrum as the concentration of the syn isomer increased (0.1–1.2 *M*). This new fluorescence component is similar to that observed with other systems which involve associative interactions and most likely derives from excimer formation.[61]

In order to determine whether the phosphorescence emission spectrum of **1** (and/or **2**) showed a similar concentration dependence, we examined the emission spectra of the oxime ethers at 77°K in an EPA glass. Surprisingly, both isomers showed no phosphorescence. The lack of phosphorescence would imply that either the intersystem crossing efficiency of the oxime ethers is extremely low or else the triplet state of the oxime ethers undergoes nonradiative decay at a faster rate than radiative emission. To test these possibilities, an attempt was made to sensitize the phosphorescence emission of the oxime ethers. This was done by irradiating a 1:1 mixture of benzophenone and the oxime ether at 77°K in an EPA glass. The sample tube was irradiated under conditions where 100% of the light was absorbed by benzophenone (*i.e.*, 3660 Å). The results obtained showed that benzophenone's emission was completely quenched and no new emission from the oxime ethers appeared. This experiment indicates that nonradiative decay from the triplet state (*i.e.*, syn $\rightleftarrows$ anti photoisomerization) proceeds at a faster rate than radiative decay. Consequently, the lack of phosphorescence from the oxime ethers does not necessarily reject the involvement of a triplet state in the direct irradiation (*vide infra*).

A major point which needed to be established is whether the concentration effects noted in the photoisomerization and fluorescence experiments are derived from a common intermediate. In order to establish this point, quenching experiments using 1,3-cyclohexadiene as a singlet quencher[62] (1.0–3.0 *M*) were carried out. Addition of 1,3-cyclohexadiene to pentane solutions of the oxime ethers resulted in substantial quenching of the fluorescence emission of both **1** and **2**. The data are plotted in the usual Stern–Volmer fashion and are shown in Figure 1. 1,3-Cyclohexadiene was also found to quench the syn–anti photoisomerization. Figure 2 shows the Stern–Volmer plot for 1,3-cyclohexadiene quenching of the syn–anti isomerization. Slopes were calculated by least-squares analysis of the data. The quenching slopes obtained with 1,3-cyclohexadiene are $k_q\tau(1)_{isom}$ = 0.04, fluorescence quenching = 0.13 and $k_q\tau(2)_{isom}$ = 0.30, fluorescence quenching = 1.20 for the syn (**1**) and anti (**2**) oxime ethers, respectively. The results demonstrate that the anti isomer is more sensitive to fluorescence quenching (*i.e.*, factor of 9.2) than the corresponding syn form. The difference in quenching efficiency between the anti and syn forms was slightly smaller (*i.e.*, 7.5) when the photoisomerization reaction was monitored. It is interesting to note that chemical quenching is only one-quarter as efficient as fluorescence quenching. This phenomenon is not totally unprecedented, as variations in fluorescence *vs.* chemical quenching have been observed by others.[63]

One interpretation of the above observations is that the photoisomerization reaction does not proceed from a singlet state but rather involves a short-lived reactive triplet which is quenched at high quencher concentration. If this were true, then the lack of correspondence between the chemical and fluorescence quenching would be expected, since two different excited precursors would be involved. That this is not the case was shown by triplet sensitization

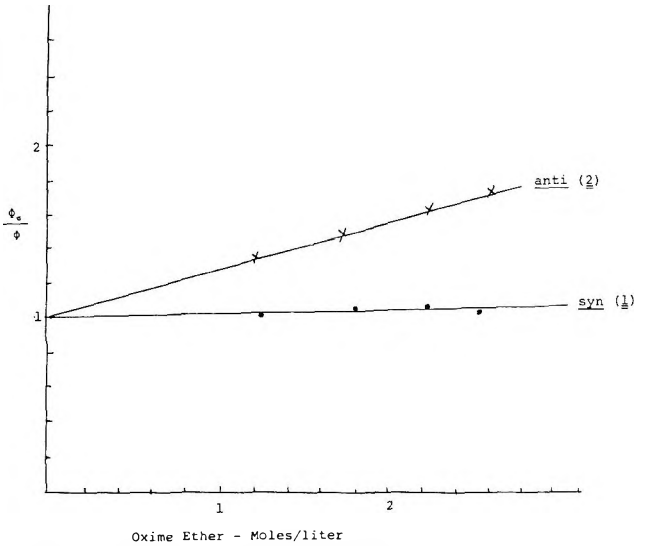


Figure 2. 1,3-Cyclohexadiene quenching of the syn (1)–anti (2) photoisomerization.

experiments in which benzophenone was used as the sensitizer (*i.e.*, 3660-Å source). The quantum yield for the benzophenone-sensitized anti → syn isomerization ($\Phi_{A\to S}$) at 0.05 *M* was 0.37 + 0.02 in the 4–5% reaction range, while that for syn → anti ($\Phi_{S\to A}$) was 0.51. The ratio of triplet quantum yields ($\Phi_{A\to S}/\Phi_{S\to A}$) is 0.73, in good agreement with the experimental value of the sensitized photostationary state (0.77). If decay from a common state is involved in both the sensitized and unsensitized experiments, the decay ratio should be the same for the two processes. It should be pointed out that the triplet-sensitized isomerization, in contrast to the unsensitized isomerization, was independent of the initial oxime ether concentration. The difference between the two numbers [*i.e.*, 0.73 (triplet) and 1.08 (singlet)] is an indication that crossing to triplets is not the sole fate of excited oxime ether singlets. The closeness of the above values could be construed to mean that the isomerization induced by direct irradiation is also passing in part through the triplet state. It should be emphasized, however, that the closeness of the values does not demand that the triplet state of the oxime ether be involved in the direct isomerization. As was pointed out by Saltiel,[64] the correlation of the natural decay ratios in sensitized and unsensitized photoisomerization processes may be fortuitous.

An alternate rationale to account for the variation in fluorescence *vs.* chemical quenching observed with 1 would involve the partial involvement of a short-lived unquenchable precursor to photoisomerization. This may possibly be an upper excited state or a nonquenchable upper vibrational level of the first excited state (singlet or triplet). The diminished 1,3-cyclohexadiene quenching of the isomerization reaction would then reflect a combination of partial quenching of isomerization from the vibrationally equilibrated S_1 state and zero quenching of reaction from the upper vibrational levels of S_1 or an upper excited state. In order to test for the possible involvement of upper excited states in the photoisomerization reaction, we examined the quantum efficiency of the oxime ether isomerization using 2537-Å light. Surprisingly, the quantum yields for isomerization at 2537 Å showed a substantial diminution in value (*i.e.*, $\Phi_{A\to S} = 0.28$, $\Phi_{S\to A} = 0.27$) when compared to the values obtained at 3130 Å (*i.e.*, $\Phi_{A\to S} = 0.53$, $\Phi_{S\to A} = 0.49$). This might at first glance seem to be inconsistent with the participation of upper vibrational or excited states. However, by using short-wavelength light the possibility exists that both the n–π^* (or π–π^*) state of the oxime ether and the π–π^* state of the naphthalene moiety are populated. The lower quantum efficiency may be attributed to either an incomplete internal energy transfer, a diminished intersystem crossing from the naphthyl π–π^* state(s) to the imine excited state(s), or a radiationless decay path of the excited naphthyl state(s) which maintains the geometric integrity of the oxime ether. Another possibility which can account for the difference between fluorescence and chemical quenching is to assume the involvement of an exciplex in the quenching reaction. All that would be necessary to explain the preferred fluorescence quenching is to assume that exciplex decay will result in the partial isomerization of the oxime ether. The overall effect would then be less efficient chemical quenching than fluorescence quenching.

Considerable information has now been accumulated for the photochemical syn–anti isomerization of the oxime ether of 2-acetonaphthone. The more readily derived facts about the photoisomerization reaction are the following. (a) At low concentration the syn isomer predominates in the photostationary state. (b) High oxime ether concentrations tend to enhance the fraction of the anti isomer in the photostationary state. (c) Evidence supporting the involvement of the singlet state was obtained from fluorescence quenching studies and photosensitized isomerization experiments. The data also indicate that the fluorescence quenching of both isomers by 1,3-cyclohexadiene is more sensitive than chemical quenching. (d) The fluorescence and photoisomerization quenching studies also show that the excited syn isomer is less sensitive to collisional interaction than the corresponding anti form. The intensity of emission from the syn isomer was found to be much less (*i.e.*, *ca.* factor of 10) than that from the anti isomer. These observations imply that the excited spectroscopic state of the syn isomer has a much shorter lifetime than the related anti form.

The mechanism we propose here to explain these observations (see below) involves excitation of the oxime ether (X_o = syn or anti oxime ether) to its spectroscopic singlet state followed by formation of a twisted excited state

$$X_o \xrightarrow{h\nu} X^{*1}$$

$$X^{*1} \xrightarrow{k_f} X_o + h\nu'$$

$$X^{*1} \xrightarrow{k_d} X_o$$

$$X^{*1} \xrightarrow{k_1} P^*$$

$$X^{*1} + X_o \xrightarrow{k_2} [X\text{–}X]^{*1}$$

$$[X\text{–}X]^{*1} \xrightarrow{k_3} \alpha S_o + \beta A_o$$

$$P^* \xrightarrow{k_4} S_o$$

$$P^* \xrightarrow{k_5} A_o$$

$$P^* + X_o \xrightarrow{k_6} \alpha' S_o + \beta' A_o$$

$$X^{*1} + C_o \xrightarrow{k_7} [X\text{–}C_o]^{*1}$$

$$[X\text{–}C_o]^{*1} \xrightarrow{k_8} C_o + \alpha'' S_o + \beta'' A_o$$

(P*). The spectroscopic singlet state can decay (k_d), fluoresce (k_f), or undergo collisional interaction with a ground-state molecule (k_2) to produce an excimer. The excimer's decay ratio differs from that of monomer (P* or possibly X*[1]) and leads to preferential formation of the thermodynamically more stable anti isomer (A_o). In this scheme α and β represent partitioning factors. This rationale is reinforced by quantum yield studies which show that the $\Phi_{A\to S}$ decreases while the $\Phi_{A\to S}$ increases with increasing substrate concentration. The formation of the syn isomer (S_o) would also be expected to result from collisional quenching; however, the partitioning coefficient seems to favor the anti form. Quenching of the spectroscopic singlet by 1,3-cyclohexadiene (C_o) may involve an exciplex. Other reactions involving collisional quenching of the twisted state (P*) by a ground-state molecule (*i.e.*, k_6) may well occur, but the experimental data are not accurate enough to determine this. It should be noted here that, while the mechanism outlined above adequately accounts for the observations, it may be incomplete. For example, the isomerization may also proceed by inversion from the spectroscopic singlet state or pass, in part, through a reactive triplet or an upper excited state.

Experimental Section

Syn and Anti *O*-Methyl Ethers of 2-Acetonaphthone Oxime. A mixture containing 40.5 g of 2-acetonaphthone and 22.1 g of

methoxylamine hydrochloride in 500 ml of 95% ethanol which contained 360 g of sodium acetate trihydrate was heated at reflux for 12 hr. Removal of the solvent under reduced pressure left 45 g (97%) of a solid which was recrystallized from ethanol to give the anti *O*-methyl ether of 2-acetonaphthone oxime (**2**) as a white, crystalline solid, mp 89.5–90°.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.71; H, 6.63; N, 7.00.

The infrared spectrum of this material (KBr) showed a series of strong bands at 3.40, 6.22, 8.84, 9.30, 9.55, 11.00, 11.18, 11.60, 12.00, and 13.45 μ. The nmr spectrum ($CDCl_3$) showed sharp singlets at δ 2.36 (3 H) and 4.12 (3 H), and contained a multiplet centered at δ 7.7 (7 H). The ultraviolet spectrum (pentane) exhibited maxima at 338, 295, 283, 274, 249, and 238 nm (ϵ 140, 15,100, 17,400, 14,000, 36,770, and 40,180). The mass spectrum showed the molecular ion at m/e 199 and contained major peaks at m/e 184, 169, 158, 128, 127 (base), and 77.

The corresponding syn oxime ether (**1**) was prepared by irradiating the anti isomer in pentane at 3100 Å. The mixture of isomers was separated by column chromatography. The syn isomer was further purified by distillation at 90–100° (0.01 mm). The syn isomer was a low-melting solid, mp 25–26°. Analysis of the low-melting solid by glpc using a 0.25 in. × 10 ft copper column packed ing solid by glpc using a 0.25 in. × 10 ft copper column packed with 10% FS-1265 on Diasaport S at 215° revealed that the solid was better than 99% isomerically pure. The infrared spectrum (neat) of **1** showed a series of strong bands at 3.30, 3.42, 3.60, 6.19, 6.25, 6.65, 6.81, 6.95, 7.29, 9.12, 9.50, 11.10, 12.20, and 13.40 μ. The nmr spectrum ($CDCl_3$) showed sharp singlets at δ 2.28 (3 H) and 3.94 (3 H) and also contained a multiplet centered at δ 7.70 (7 H). The ultraviolet spectrum (pentane) exhibited maxima at 224 (ϵ 36,000), 279 (ϵ 8400), and 337 nm (ϵ 110). The mass spectrum showed the molecular ion at m/e 199 and contained major peaks at m/e 184, 169, 158, 128, 127 (base), and 77.

Determination of Photostationary State. Solutions containing the substrate at a fixed concentration in a chosen solvent were irradiated through Pyrex culture tubes at 3130 Å. In these studies, a 1-cm path of 0.002 *M* potassium chromate in a 1% aqueous solution of potassium carbonate was used to isolate the 3130-Å region of the medium-pressure (450-W) Hanovia lamp.[65] All samples were degassed using a vacuum line which achieved a pressure of $<5 \times 10^{-4}$ mm. In every case the photostationary states were approached from both sides and duplicate samples were measured to ensure that the actual stationary composition had been reached.

Quantum Yield Determinations. Solutions were prepared in various solvents as described in the Results and Discussion, and 3.0 ml of each was placed in separate Pyrex culture tubes (13 × 100 mm). Each sample was degassed three times to 0.005 mm and sealed *in vacuo*. Similar results were obtained when samples were degassed by bubbling argon through the solution for 30 min. In a given run all tubes were irradiated in parallel for the same length of time in a "merry-go-round" apparatus which assured that each sample absorbed the same intensity of light. Benzophenone–benzhydrol[49] actinometry was used for the quantum yield determinations. Analyses were performed on a Hewlett-Packard Model 5750 gas chromatograph using a 10% FS-1265 Diasaport S column at 215°. The mole ratio:area ratio response of the instrument was calibrated for the oxime ethers and internal standard, so that yields of product could be measured accurately. The conversions in the oxime ether series were run to 5% or less. The mass balances in these runs were generally better than 98%.

Emission Studies. The emission spectra were made on an Aminco-Bowman spectrophotofluorometer equipped with a phosphoroscope and transmission attachments. The spectrophotofluorometer was equipped with a 1P21 photomultiplier and a high-pressure xenon lamp, as supplied by the manufacturer. All fluorescence emission spectra were recorded using pentane or cyclohexane as the solvent. The solvent was checked for emission each time a spectrum was recorded and no interference due to solvent was found at any time. Emission intensities were reproducible for different samples prepared from the same solution.

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Observations on Photochemically and Thermally Induced Rearrangements and Fragmentations in 2,5-Dihydrothiophene Derivatives

Richard M. Kellogg* and W. L. Prins

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

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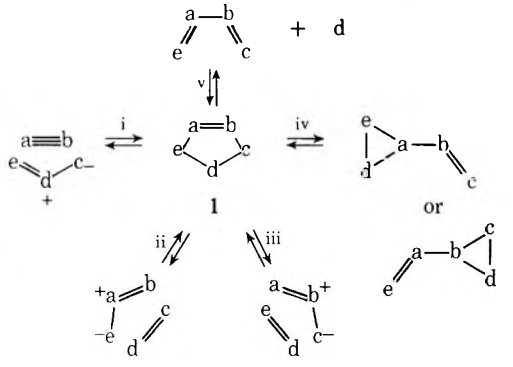
By means of the addition of thiocarbonyl ylides to dimethyl acetylenedicarboxylate, a series of 2,5-dialkyl-substituted 2,5-dihydrothiophenes (**4**) was prepared. These compounds were also oxidized to the respective sulfoxides (**20**) and sulfones (**19**). The compounds **4** undergo ring contraction on irradiation, producing vinyl episulfides. These on desulfurization afford dienes. The sulfoxides **20** provide the same dienes on either irradiation or thermolysis. The only exception is the 2,2,5,5-tetramethyl derivative (**20b**), which gives a complex mixture of products on thermolysis. The sulfones **19** also yield dienes on either irradiation or thermolysis. The stereochemistry of all these reactions has been determined. In complete accord with earlier work, the sulfone thermolyses are completely stereospecific and follow expectations from orbital symmetry considerations. All other reactions studied exhibit lessened stereoselectivity and this is construed as evidence for the intervention of biradical intermediates. In the photochemical reactions of **4** both cisoid and transoid forms of the allylic portion of the biradical formed on cleavage of a carbon–sulfur bond are involved. Related mechanisms are thought to be involved in the photochemical reactions of **19** and **20**. Arguments are advanced that the thermolysis of **19** and **20** involve different mechanisms because the reaction coordinate for the latter reaction cannot be symmetrical; this forces the reaction into a nonconcerted pathway.

Imagine a generalized five-membered heterocycle **1** derivable in principle through a 1,3-dipolar cycloaddition.[1] Routes i–iii (eq 1) all have adequate precedent. Nearly



(1)

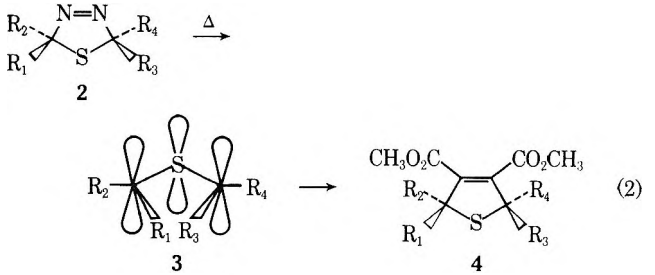
unanimously these reactions involve 1,3-dipole and dipolarophile in their *ground states*. *Excited states* of **1** could conceivably fragment through one of these pathways. This seems not to be common, however.[2] Although the detailed explanations differ widely from compound to compound, a rationale might be that excited states of **1** must attain a sterically unfavorable antarafacial–suprafacial geometry to fulfill orbital symmetry demands for fragmentations through paths i–iii.[3]

The number of examples is limited, but path iv, a vinyl cyclopropane-like rearrangement,[4] and path v appear to be possible for both ground and excited states. Photochemical examples are restricted chiefly to fragmentations of **1**.[5-7] In these cases orbital symmetry considerations place less stringent steric requirements on the required transition states.

More complete descriptions of the extent to which orbital symmetry factors control these types of reactions, especially those involving excited states, should be forthcoming from stereochemical studies. Such investigations require in practice systems in which carbon atoms with their unique stereochemical properties are present at points at which bonds are made or broken. The common philosophy is that if a given reaction leads to only one of several possible geometrical isomers, all of which are accessible through stereochemically acceptable transition states, and if the isomer formed is that predicted by orbital symmetry factors, this can be considered *ipso facto* as evidence for orbital symmetry control.[3] We offer here the descriptive aspects of the photo- and thermochemistry of 2,5-dihydrothiophenes **4** and their sulfoxide and sulfone derivatives.[8,9] This is a limited study of only one compound type. We hope nevertheless that the results obtained are not only interesting in their own right but lend also some insight into the broader problems hinted at in eq 1.

Results

A. Thermochemistry and Photochemistry of 4. The genesis of compounds **4** lies in the thermally induced ste-

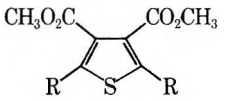


(2)

a, $R_1 = R_4 = t\text{-}C(CH_3)_3$; $R_2 = R_3 = H$
b, $R_1 = R_2 = R_3 = R_4 = CH_3$
c, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
e, $R_1 = R_4 = C_2H_5$; $R_2 = R_3 = H$
f, $R_1 = R_2 = C_2H_5$; $R_2 = R_4 = H$

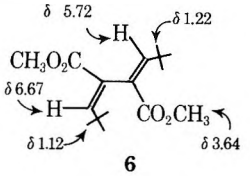
reospecific addition of thiocarbonyl ylides **3** to dimethyl acetylenedicarboxylate (eq 2).[9]

No significant thermochemistry of cycloadducts **4** is observed up to 500° save that **4d** and **4f** dehydrogenate, affording thiophenes **5a** and **5b**, respectively.



5a, R = CH_3
b, R = C_2H_5

In contrast, these compounds proved to be very photolabile. The reaction of **4a** serves as an example. On irradiation in degassed solution using a high-pressure mercury lamp, **4a** provided two products in a ratio of about 4:1 as determined by gas–liquid partition chromatography (glpc) using copper columns. A small amount of a third compound was also observed. These three products were isolated and were identified as dienes **6** (*Z,E*, major product), **7** (*E,E*, minor product), and **8** (*Z,Z*, trace product).



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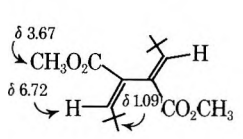

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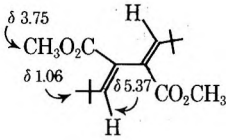
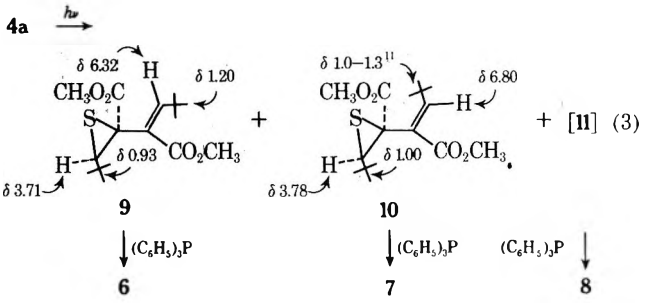


8

No ambiguity exists in stereochemical assignment of **6** owing to the nonequivalence of the vinyl and *tert*-butyl protons in the pmr spectrum (CCl_4). Assignment of the various protons can be made with confidence, for carboalkoxy groups exert a stronger deshielding effect than either vinyl or alkyl groups on cis-oriented vinylic protons.[10] These same shielding arguments allow assignment of *E,E* and *Z,Z* configurations to **7** and **8**, respectively.

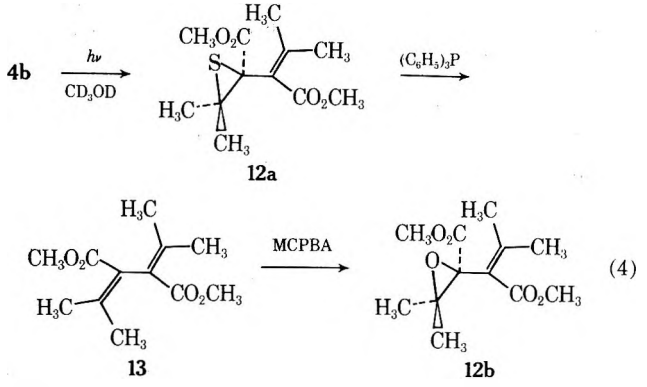
Monitoring of the reaction of **4a** using either pmr spectroscopy or glpc on glass columns showed that **6**–**8** *are not* primary photochemical products. Two unstable compounds, **9** and **10**, in the same ratio as **6** and **7** were seen in the glpc traces (a precursor to **8** was never detected, perhaps because of its low concentration). On glpc with copper columns, or on standing at room temperature, **6** and **7** were formed. By careful preparative glpc small samples of **9** and **10** (contaminated with about 20% of **6** and **7**, respectively) were isolated. Mass spectrometry (glpc coupled directly to mass spectrometer) established that **9** and **10** had the same molecular composition ($C_{16}H_{26}O_4S$) as starting material. Osmometric measurements demonstrated that the compounds were monomeric. The infrared spectra showed carbonyl absorptions at 1720 (sh) and 1739 cm^{-1} whereas **6** and **7** have a single carbonyl absorption at 1720 cm^{-1}. On treatment with triphenylphosphine **9** and **10** were converted quantitatively to **6** and **7**, respectively. On the basis of the above coupled with the pmr absorptions (eq 3) **9** and **10** must be assigned vinyl episulfide (thiirane) structures.

In **10** the episulfide linkage is perforce at a potentially *E* double bond. In **9**, however, the episulfide linkage could be at either potentially *E* or *Z* double bond positions. The former assignment is made since the vinylic proton is shifted upfield relative to **10**, indicating a change in configuration about the double bond; also, the chemical shifts of the methine protons in both **9** and **10** are similar, indicating the same configuration about the episulfide ring. A vinyl episulfide **11** is thought to be a precursor of trace



product **8**, but the amount was too small to allow detection. Conversions are quantitative providing that the solutions are well degassed; otherwise some oxidation to a thiophene occurs.

Evidence was also accumulated for the presence of vinyl episulfide intermediates in the photochemically induced reactions of **4b–f.** This is described in the Experimental Section. Compound **12a** was observed by nmr spectroscopy as the product of irradiation of **4b.** This was converted to diene **13.** Treatment of **13** with *m*-chloroperbenzoic acid (eq 4) led to vinyl epoxide **12b** with pmr spectral characteristics closely resembling those of **12a**, which was too unstable to be isolated.



Test reactions demonstrated that desulfurization of the intermediate vinyl episulfides with triphenylphosphine occurred with retention of configuration. The same was true if the vinyl episulfides were desulfurized by contact with a metal injector port in the glpc. For stereochemical investigations one or the other of these techniques was used and the resulting diene isomers were examined. To establish stereospecificities the diene ratios were determined at various levels of conversion and extrapolated back to zero time. Up to about 20% conversion there was no significant deviation in the ratios. For cis isomers **4d** and **4f** fewer checks were made owing to a shortage of material; these isomers could be purified only by tedious preparative glpc. Both compounds contained about 5% thiophene arising from frustratingly facile dehydrogenation during isolation.

The results of the stereochemical investigations are compiled in Table I. The stereochemistries of the dienes were assigned on the basis of the shielding arguments developed previously. Cis,trans pair **4c,d** proved most tractable to work with and data obtained for these two compounds are most accurate. Trans isomers **4c** and **4e** underwent during irradiation isomerization to cis isomers **4d** and **4f**, respectively. This is illustrated in eq 5 for **4c.** The amount of trans–cis isomerization was 25–35% that of ring contraction. Accurate determinations of the exact amount of isomerization were difficult because of the error in ex-

Table I
Stereochemistry of Dienes Obtained on Desulfurization of Primary Photoproducts from 2,5-Dihydrothiophenes 4

Compd	Diene[a] (yield, %)		
	Z,E	*E,E*	*Z,Z*
4a	**5** (65)	**6** (31)	**7** (4)
4c[b]	**14** (50)	**15** (50)	**16** (1)
4d	**14** (30)	**15** (60)	**16** (10)
4e[b]	**17** (96)	**18** (4)	*c*
4f	**17** (50)	**18** (50)	*c*

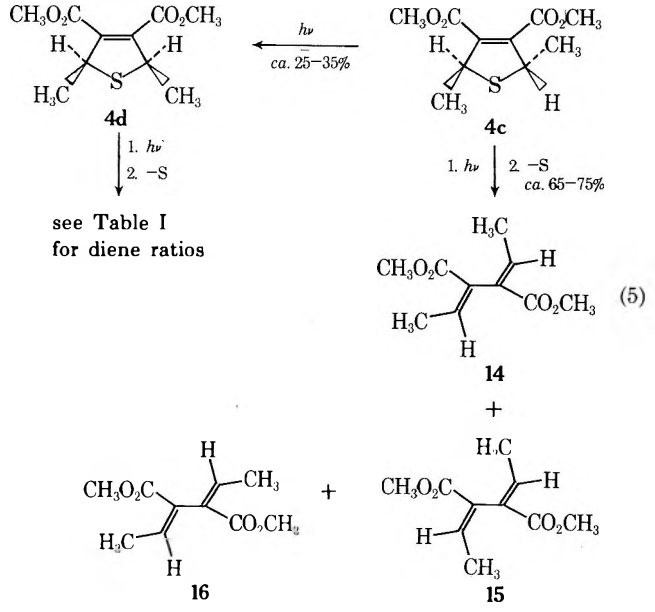
[a] Yields account quantitatively for consumed starting material. [b] Undergoes isomerization; see text. [c] Not detected.

Table II
Results of Photochemical Experiments[a] with 19

Compd	Diene[b] (yield, %)			
	Z,E	*E,E*	*Z,Z*	Other
19a	**5** (72)	**6** (10)	**7** (18)	
19b				**12** (100)
19c	**14** (58)	**15** (29)	**16** (13)	
19d	**14** (64)	**15** (36)	**16** (0)	

[a] Reactions run in CD_3OD at room temperature with analysis by nmr; essentially the same product distribution is obtained using diethyl ether. [b] All consumed material accounted for as diene.

trapolation back to zero time. This mechanistically significant process is within experimental error irreversible; no trace of cis to trans isomerization of the dihydrothiophenes was ever observed.



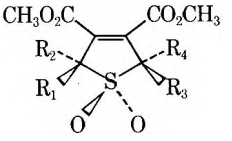
(5)

Some quenching and sensitization studies were carried out with **4b**. This isomer was most suitable for study because oxidation to a thiophene derivative is impossible. This problem complicated investigation of 2,5-dialkyl derivatives. Benzophenone (E_T 69.3 kcal/mol) and acetophenone (E_T 73.6 kcal/mol) both sensitized ring contraction; phenanthrene (E_T 64 kcal/mol) had no effect. This brackets the triplet level of **4b** between 64 and 68 kcal/mol, a conclusion that would agree also with a weak, structureless phosphorescence emission observed from **4b** with a maximum at 540 nm (66 kcal/mol).[12] Somewhat surprisingly, the ring contraction of **4b** brought about with 300-nm excitation was only weakly quenched by 1,3-pentadiene. A maximum of 20% retardation was observed with 2.5×10^{-2} *M* **4b** 0.1 *M* in diene (highest concentration used).

Table III
Results of the Thermolysis of 19a–d

Compd	Diene (yield, %)			
	Z,E	*E,E*	*Z,Z,*	Other
19a	**5** (100)	**6** (0)	**7** (0)	
19b				**12** (100)
19c	**14** (100)	**15** (0)	**16** (0)	
19d	**14** (0)	**15** (0)	**6** (100)	

B. Photochemistry and Thermochemistry of 2,5-Dihydrothiophene *S*-Dioxide Derivatives. The sulfones **19a–d** were prepared by oxidation of **4a–d** with 2 equiv of



19a, $R_1 = R_4 = t\text{-}C(CH_3)_3$; $R_2 = R_3 = H$
b, $R_1 = R_2 = R_3 = R_4 = CH_3$
c, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$

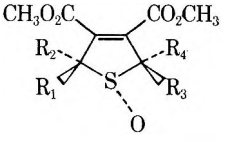
m-chloroperbenzoic acid. On irradiation they cleanly lost sulfur dioxide, yielding dienes. No other products were detectable. The relative thermal instability of the sulfones made glpc analysis impossible; reactions were monitored in a quartz nmr tube using a high-pressure mercury lamp as light source. The results of this investigation are assembled in Table II. About 20% conversions were necessary to obtain nmr spectra that could be integrated well. The dienes did not isomerize appreciably during the irradiation times used. No cis–trans or trans–cis isomerization was detected with **19c,d.**

Attempts to run reactions at lower temperatures in the hope of trapping ring contraction products failed; in all solvents used the starting material precipitated at nmr concentrations. A vinyl sulfone would be expected to be thermally unstable.[13]

Loss of sulfur dioxide from **19b** was sensitized by both acetophenone and benzophenone but not by phenanthrene. At 300 nm loss of sulfur dioxide was somewhat inhibited by 1,3-pentadiene. A concentration of 0.1 *M* halves the rate of sulfur dioxide loss (2.5×10^{-2} *M* in **19b**).

As expected, thermolysis of **19a–d** also led cleanly to dienes. In preparative runs yields were >80% and near quantitative in small-scale experiments. The reactions are at least 99.9% stereospecific when pyrolyses were carried out at 250° in a glass-lined injector port of a glpc apparatus. The results are assembled in Table III.

C. Photochemistry and Thermochemistry of 2,5-Dihydrothiophene *S*-Oxides. The sulfoxides **20a–d** were



20a, $R_1 = R_4 = t\text{-}C(CH_3)_3$; $R_2 = R_3 = H$
b, $R_1 = R_2 = R_3 = R_4 = CH_3$
c, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_2 = CH_3$; $R_2 = R_4 = H$

prepared by careful oxidation of **3a–d** with 1 equiv of *m*-chloroperbenzoic acid. The S–O linkage in **20d** (single diastereomer) is tentatively placed anti to the methyl groups on the basis of shielding data (Experimental Section).[14,15]

On irradiation clean conversion to dienes occurred with no detectable production of side products. Using the same

Table IV
Results of Photochemical Experiments with Sulfoxides 20

Compd	Diene (yield, %) Z,E	E,E	Z,Z	Other
20a	**5** (57)	**6** (25)	**7** (18)	
20b				**12** (100)
20c	**14** (79)	**15** (21)	**16** (0)	
20d	**14** (52)	**15** (37)	**16** (11)	

Table V
Results of Thermolyses of Sulfoxides 20

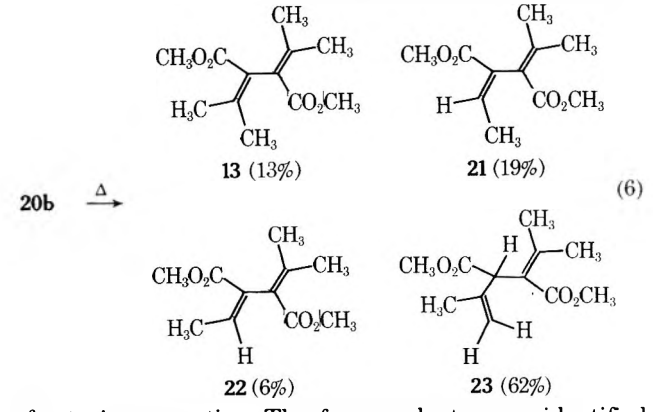
Compd	Diene (yield, %) Z,E	E,E	Z,Z
20a	**5** (75)	**6** (12)	**7** (13)
20c	**14** (95)	**15** (2.5)	**16** (25)
20d	**14** (6)	**15** (10)	**16** (84)

techniques employed for sulfones **19**, the stereospecificities of these reactions were determined; the results are compiled in Table IV. Irradiations were carried out in perdeuteriomethanol. Attempts to identify unstable intermediates, *i.e.*, vinyl episulfoxides, were again frustrated as with sulfones **19** by the insolubility of the compounds in acceptable solvents at low temperatures. At room temperature no indications of any intermediates were obtained. No isomerization of starting material was found.

Smooth conversion to dienes also occurred on thermolysis. Pyrolyses were carried out preparatively at 350–400° in a short pyrolysis tube leading to >80% overall yields of dienes. Experiments with **20a,c,d** wherein pyrolysis was carried out in a glass-lined injector port at *ca.* 250° led only to dienes and no detectable side products. The stereochemical results are compiled in Table V.

Attempts to trap sulfur monoxide, presumably produced in thermal reactions, were frustrated by the relatively high temperatures needed for pyrolysis of **20.** Some experiments with 3,4-diphenylbutadiene as trapping agent were carried out, but any addition product, if formed, would almost certainly be pyrolyzed again at the temperatures employed.[16] Appropriate conditions could not be devised for the trapping of sulfur monoxide that might have been produced in photochemical reactions.

The pyrolysis of **20b** led to a completely different product distribution than that observed in any other reactions. When pyrolyzed under the conditions used for the other isomers, **20b** gave in *ca.* 70% overall yield the products shown in eq 6, where the percentages (in parentheses)



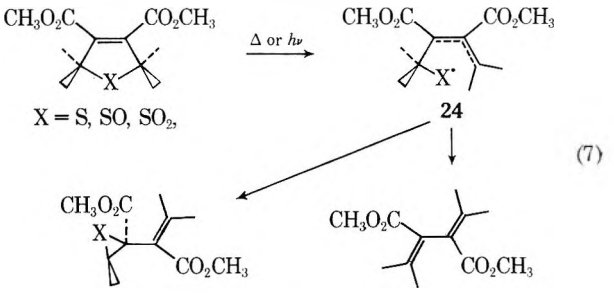
(6)

refer to isomer ratios. The four products were identified from analytical and spectroscopic data as described in the Experimental Section.

Discussion

A. General Points. All the reactions here described, be they thermally or photochemically induced, lead ultimately to loss of the sulfur unit with retention of the carbon skeleton. The pyrolytic results with **20b** provide the only (partial) exception. Of the possibilities with precedent outlined in eq 1 (and others are conceivable), paths iv and/or v are followed. No hint was ever obtained of the operation of paths i–iii to any detectable extent. In the case of **4**, path i would be a reversal of the route employed for synthesis (eq 2).

Only the thermolyses of the sulfones **19** are distinguished by complete stereospecificity. This agrees in all respects with earlier experiments on closely related systems.[6] We believe that the present results can be divided into two sharply different categories. The sulfone thermolyses stand apart, representing, as maintained by Lemal[6b] and Mock,[6a] concerted $[4_s + 2_s]$ reactions in which orbital symmetry considerations dictate a disrotatory motion of the alkyl groups at the 2,5 positions. Steric effects influence stereochemistry only in cis isomer **19d** by directing the reactions into the disrotatory mode that rotates the alkyl groups outward leading to *Z,Z* diene **16.** In our opinion all the other reactions reported here are best interpreted as involving initial fragmentation of a carbon–sulfur bond leading to biradicals **24** that may either undergo ring contraction or lose immediately the sulfur segment (eq 7).[17] Only one of several possible conformations of **24** is



(7)

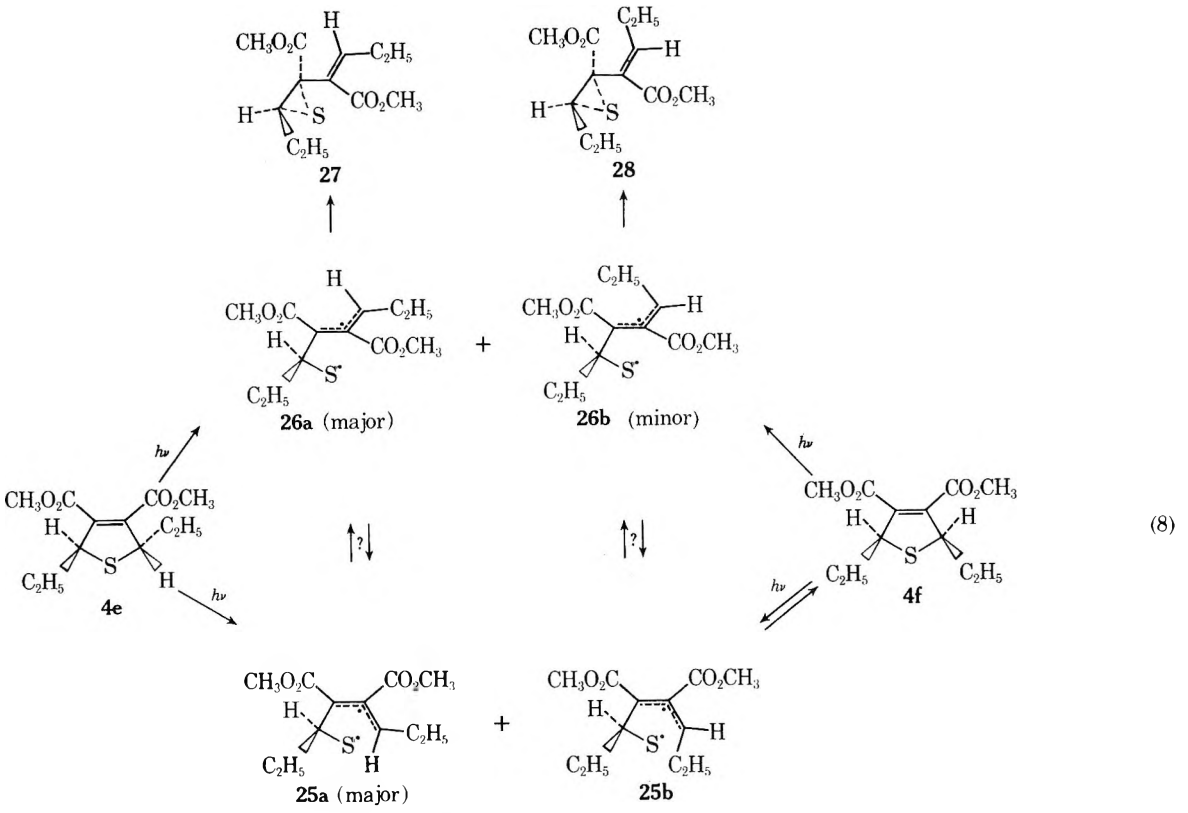
indicated. The stereochemistry of the products is determined by conformational factors in **24.** The pictorial representation **24** does not communicate differences in internal energy that likely exist between intermediates formed from thermal and photochemical pathways; we intend no more than to represent rupture of a σ bond induced by light or heat. Indeed, we make a sweeping generalization in lumping photochemical and thermal reactions together; this ignores myriad details of exactly how the biradicals **24** behave dependent on their mode of generation.

Evidence for biradical intermediates can be found as discussed in the following sections. Some guesses concerning their geometry can be made.

The stereochemical results could be explained in terms of pericyclic reactions invoking either combinations of $[{}_\sigma 2 + {}_\pi 2]$ reactions or nonlinear chelotropic eliminations.[3,17] We are less convinced by such an approach for reasons that will become clear in the subsequent discussion. However, although the point is well-nigh impossible to prove, orbital symmetry might well play a decisive role, particularly in the photochemical reactions, by imposing on fragmentation pathways i–iii (especially i) of eq 1 a sterically difficulty accessible antarafacial–suprafacial geometry in the transition state.

B. Photochemical Reactions. Some details of the photochemical reactions of **4, 19,** and **20** will now be considered.

The most complete information comes from the 2,5-dihydrothiophenes **4.** Here intermediates, vinyl episulfides, were intercepted. The available data indicate that some factor or factors control the stereochemistry of the episulfide linkage fairly rigorously. The alkyl groups and the carboalkoxy groups are oriented trans, *i.e.*, a poten-

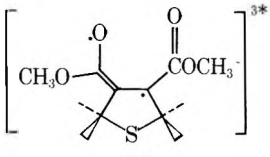


(8)

tially *E* double bond (on desulfurization) is generated. Stereochemical control is less at the vinylic carbon but from the trans isomers chiefly *Z* double bonds are formed. There is little tendency for either a cis or a trans isomer to yield a *Z,Z* diene on desulfurization (Table I).

The strongest evidence in favor of biradical intermediates is the observed trans to cis isomerization of **4c** to **4d** and **4e** to **4f**. This must involve cleavage and recombination of a carbon–sulfur bond. This process competes well with ring contraction. It is reasonable that isomerization and ring contraction are both manifestations of the behavior of a common precursor.

A rationalization of the photochemical results illustrated with **4e** and **4f** is given in eq 8. The most important aspect of this fairly complicated scheme is the postulation of the cisoid and transoid biradicals, **25a,b** and **26a,b**. In the formalism introduced by Zimmerman[18] one representation of an excited triplet state of **4** is **29**. The sulfur atom is positioned for β-elimination as a thiyl radical; this coupled with a turning of the methylene group produces cisoid **25a** and **25b**. This type of β-elimination process has much precedent in radical chemistry[19a] and also in some known photochemical reactions.[19b] However, the excited triplet states of dialkyl maleates, in common with other simpler olefins, should twist about the double bond.[20] This motion in excited **29** coupled with breaking of the

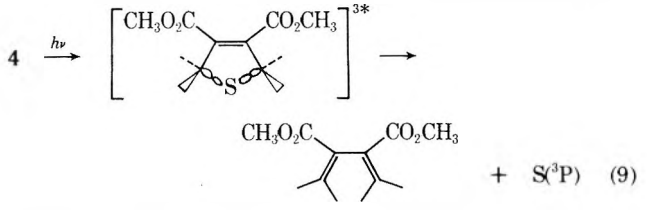


29

carbon–sulfur bond leads to transoid biradicals **26a,b**. Inspection of molecular models leads to the conclusion that this twisting motion occurs with the least steric interference by holding substituents on the carbon atom originally bonded to sulfur "outside," leading ultimately to **26a** in preference to **26b**. Ring closure arranging the alkyl and carbomethoxy groups trans on the episulfide ring produces the observed major products.[21,22]

The most reasonable fate of **25a,b** is recoupling to form **4**; this process seems to form exclusively cis isomer (with the exception of 2,5-di-*tert*-butyl-substituted **4a**, which shows no trace of isomerization). We do not have any reasonable explanation for this selectivity.

It is interesting that the dihydrothiophenes show no detectable tendency to make use of the route of eq 9. The



(9)

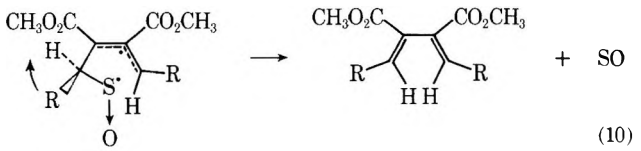
reactions originate from the triplet state, and reaction leading to diene and triplet sulfur, a species well characterized in the photolysis of carbonyl sulfide,[23] should be possible through an "allowed" $[4_s + 2_a]$ reaction.

The photolyses of sulfones **19** and sulfoxides **20** likely involve similar mechanisms. Ring-contracted intermediates analogous to those isolated in the photoreactions of **4** were not identified. Vinyl episulfoxide or episulfone intermediates should be very unstable, however.[13] A ring-contraction step is not mandatory; loss of the sulfur oxide from the biradical intermediates in the manner indicated in eq 7 (only one possible conformer shown) is a reasonable alternative.

C. Thermal Reactions. The sulfoxide pyrolyses, with the exception of **20b**, afford diene with a fairly high tendency toward disrotatory participation of this component. However, in no case do the stereospecificities match those observed with sulfones **19**. Lemal and Chao[16a,b] have demonstrated both 1,4-addition of sulfur monoxide to 2,4-hexadienes and thermal elimination from the respective 2,5-dihydrothiophene *S*-oxides. Reasonable stereospecificity was observed in the addition reaction but relatively little in the elimination reaction. A mechanism involving biradicals was suggested to account for the experimental results.

On a energetic basis one might anticipate a changeover

in mechanism from sulfones **19** to sulfoxides **20**. The dienes formed are identical but there is a drastic difference in the sulfur oxides being eliminated. Oxidation of sulfur monoxide to sulfur dioxide by molecular oxygen is 61 kcal/mol exothermic.[24] Sulfur monoxide is a ground-state triplet with a singlet state lying 18 kcal/mol higher.[25] If spin conservation holds the energetically even less favorable singlet would have to be formed. Avoidance of this difficulty by cleavage of the sulfoxide–carbon bond (bond dissociation energy *ca.* 50 kcal/mol)[26] with subsequent fragmentation of the biradical **30** is reasonable (eq 10). The predominance of diene product formed from a

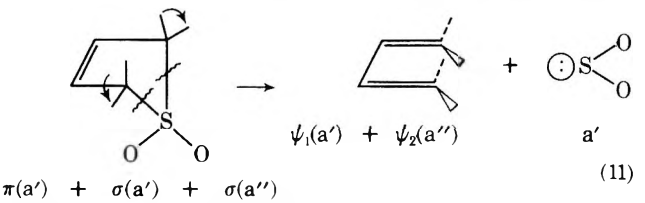


(10)

30

disrotatory motion of the 2,5-carbon atoms in **20** is readily understandable if rupture of the sulfur–carbon bond is accompanied by an outward rotation of the bulky alkyl substituent, placing it cis to the carboalkoxy group. Thereafter outward rotation of the sulfur unit in cisoid biradical **30** (a strong driving force for formation of a transoid biradical as in the photochemical experiments is lacking) concomitant with its departure would produce the observed major diene product.

Possible support for initial rupture of a sulfur–carbon bond in the thermal reactions of **20** is provided by Pearson's[27] approach to the analysis of orbital symmetry effects. For a concerted [4_s + 2_s] cycloelimination of sulfur monoxide to occur, a disrotatory motion of the 2,5 substituent is required. This means that a σ plane perpendicular to the five-membered ring is maintained. In the Pearson analysis a reaction can be concerted and subject to orbital symmetry requirements only if the total reaction coordinate is symmetrical. In 2,5-dihydrothiophene sulfones this condition is met in a thermal reaction (eq 11), since in the



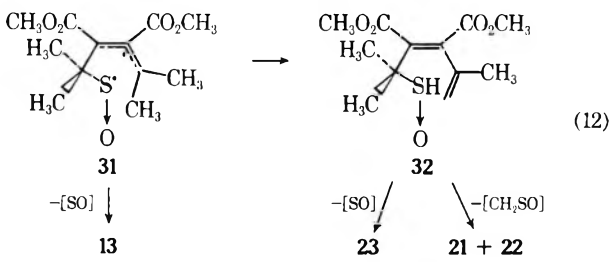
(11)

$\pi(a')$ + $\sigma(a')$ + $\sigma(a'')$

C_s point group applicable for a disrotatory movement of the carbon atoms the breaking σ bonds have a′ and a″ symmetry and the π orbital has a′ symmetry; in butadienes the filled MO's are a′ and a″ and the filled lone pair in sulfur dioxide is a′. The reaction coordinate can be totally symmetrical. This is, of course, exactly the conclusion reached by Woodward and Hoffmann,[3] who describe this as a linear chelotropic reaction.

This situation changes for the same type of concerted reaction involving loss of sulfur monoxide; the highest occupied MO in sulfur monoxide is antibonding and lies in the length of the molecule.[28] It has a″ symmetry, forcing the total reaction coordinate to be not symmetrical; the reaction would be forbidden. This analysis is exceedingly simple minded. Detailed examination of the electronic structure of sulfur monoxide coupled with an analysis of the reaction along the lines developed by Kearns[29] indicates that a concerted path is probably available.[30] The experimental evidence would suggest, however, that the molecules investigated here choose nevertheless to avoid concerted decomposition.

One interpretation of the complicated reaction seen



(12)

with **20b** is that an intermediate biradical **31** partitions itself between "normal" reaction leading to **13** and intramolecular hydrogen abstraction producing sulfenic acid **32**. The latter serves as precursor of the "anomalous" products **21–23** (eq 12). Although a cyclic pathway, well known in simpler sulfoxides,[31] provides access to **32**, the formation of **13** through this route is difficult to explain.

Experimental Section

Melting points and boiling points are not corrected. Gas chromatography was done on F & M Models 700 and 810 apparatus; for preparative work an F & M 775 was used. Nmr spectra were obtained on a Varian A-60 or XL-100 apparatus. Phosphorescence measurements were made using on Aminco-Bowman spectrofluorimeter. Most of the compounds used in this study have been described in ref 9. The properties of the dienes isolated from the various photochemical and thermal reactions are compiled in Table VI.

Preparation of *trans*- and *cis*-2,5-dimethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene (4c and 4d) was carried out by a modification of the procedure described in ref 9. A mixture of hydrogen sulfide (15 g, 0.44 mol) and freshly distilled acetaldehyde (39 g, 0.89 mol) was vigorously stirred at −90°. To this mixture was added over 30 min hydrazine hydrate (20 g, 0.40 mol). After 2 hr of stirring a white precipitate had formed. The solution was warmed to *ca.* 5°, 100 ml of water was added, and the reaction mixture was extracted three times with ether. The ether extracts were dried at −20° over $MgSO_4$. The ether was removed at −5°. A crude oil (33 g) remained that was dissolved in petroleum ether (bp 40–60°) and then immediately cooled to −50°. By this means there was obtained 5 g (9% yield) of an unstable white solid that was chiefly *trans*-2,5-dimethyl-1,3,4-thiadiazolidine; nmr (CCl_4) δ 1.47 (d, J = *ca.* 7 Hz, 6, CH_3) and 4.63 (m, 2, methine H) (the NH resonances were not observed); ir (Nujol) 3250 cm^{-1}.

The above solid (5 g, 42 mmol) and diethyl azodicarboxylate (10 g, 57 mmol) were dissolved in 200 ml of ether and stored overnight at 5°. Working at about 5°, the hydrazo ester was removed and the ether solution was washed with 100 ml of a cold aqueous solution of 10 g of sodium metabisulfite. The solution was dried over $MgSO_4$ and the ether was thereafter removed to leave 3.05 g of crude *trans*- (chief product) and *cis*-2,5-dimethyl-Δ^3-1,3,4-thiadiazoline, which was used immediately without characterization. The crude mixture was dissolved in 5 ml of ether and dimethyl acetylenedicarboxylate (15 ml, excess) was added. The temperature of the solution was gradually raised by distilling off the ether; vigorous gas evolution occurred. The temperature eventually reached 120°. Distillation afforded a mixture of **4c** and **4d** (6.5 mmol, 25%), bp 80–110° (1 mm).

The isomers were separated by preparative glpc using an SE-30 stainless steel column. Compound **4c** had ir (neat) 1050, 1215, 1375, 1435, 1645, 1720, and 2950 cm^{-1}; nmr (CCl_4) δ 1.43 (broad d, J = *ca.* 7 Hz, 6, CH_3), 3.75 (s, 6, OCH_3), and 4.52 (complex m, 2, 2,5-H).

Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13; S, 13.92. Found: C, 51.80; H, 6.13; S, 13.62.

Owing to a shortage of material no other analyses of any derivatives or of the cis isomer were carried out.

Compound **4d** had ir (neat) 1020, 1050, 1090, 1200, 1270, 1370, 1430, 1650, 1720, 2900–3000 cm^{-1}; nmr (CD_3OD) δ 1.52 (broad d, J = *ca.* 7 Hz, 6, CH_3), 3.78 (s, 6, OCH_3), and 4.41 (complex m, 2, 2,5-H).

***cis*-2,5-Dimethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene *S*-oxide (20d)** was prepared by allowing **4d** (50 mg, 0.218 mmol) dissolved in 1 ml of cold distilled methylene chloride to react with *m*-chloroperbenzoic acid (43.3 mg, 0.217 mmol) dissolved in 3 ml of methylene chloride. After stirring overnight the solution was washed with aqueous Na_2SO_3 solution and thereafter with water. After drying over $MgSO_4$ evaporation of the solvent yielded 53 mg

Table VI

Diene	Ir, cm^{-1}	Pmr, δ	Anal., %
6	2900–3000, 1740, 1455, 1380, 1260, 1220[a]	1.12 (s, 9, (*E*)-*t*-Bu), 1.22 (s, 9, (*Z*)-Bu), 3.64 (s, 6, 4,5-OCH_3) 5.72 (s, 1,3-H), 6.67 (s, 1, 6-H)[b]	Calcd: C, 68.15; H, 9.29[c] Found: C, 67.74; H, 9.07
7	*a*	1.09 (s, 18, (*E*)-*t*-Bu), 3.67 (s, 6,3,5-OCH_3), 6.72 (s, 2,3,6-H)[b]	*c*
8	*a*	1.06 (s, 18, (*Z*)-*t*-Bu), 3.75 (s, 6,3,5-OCH_3), 5.37 (s, 2,3,6-H)[b]	*c*
13	2900–3000, 1770, 1720, 1630, 1430, 1210, 1080[a]	1.68 (s, 6, (*E*)-CH_3), 2.13 (s, 6, (*Z*)-CH_3), 3.58 (s, 6,3,4-OCH_3)[b]	Calcd: C, 63.71; H, 8.03 Found: C, 63.38; H, 8.03
14	2900, 1700, 1620, 1420, 1240, 1200, 1010, 750[a]	1.81 (d, *J* = 7.5 Hz, (*E*)-CH_3), 2.18 (d, *J* = 7.5 Hz, 3 (*Z*)-CH_3), 3.72 (s, 6,3,4-OCH_3), 6.12 (q, *J* = 7.5 Hz, 1, (*E*)-vinyl *H*), 7.04 (q, *J* = 7.5 Hz, 1, (*Z*)-vinyl *H*)[d]	Calcd: C, 60.59; H, 7.12 Found: C, 60.53; H, 7.19
15	2900, 1700, 1620, 1420, 1230, 1030, 760[a]	1.69 (d, *J* = 7.5 Hz, 6, (*E*)-CH_3), 3.72 (s, 6, 3,4-OCH_3), 7.15 (q, *J* = 7.5 Hz, vinyl H)[d]	Calcd: C, 60.59; H, 7.12 Found: C, 60.21; H 7.22
16	2950, 1710, 1630, 1430, 1190, 1010[d]	2.04 (d, *J* = 7.0 Hz, 6, (*E*)-CH_3), 3.72 (s, 6, 3,4-OCH_3), 6.29 (q, *J* = 7.0 Hz, 2, vinyl H)[e]	*g*
17	1725, 1635, 1220, 1250[a]	1.04, 1.07 (overlapping t, 6, *J* = 7.0 Hz, 1,8-CH_3), 2.15 (m,[f] 2,7-CH_2), 2.62 (m,[f] 2,2-CH_2), 3.66, 3.67 (overlapping s, 6, OCH_3), 5.28 (t, 1, *J* = 7.5 Hz, (*E*)-H), 6.75 (t, 1, *J* = 7.5 Hz, (*E*)-H)[b]	Calcd: C, 63.69; H, 8.04 Found: C, 63.39; H, 8.06
18	*g*	0.94 (t, *J* = 7.0 Hz, 6,1,8-CH_3), 1.95 (m,[f] 4, 2,7-CH_2), 3.60 (s, 6, 4,5-OCH_3), 6.80 (t, *J* = 7.4 Hz, 2,3,6-H)	*g*

[a] Measured neat; **7** and **8** not determined separately. [b] In CCl_4. [c] Mixture of **6**, **7**, and **8**. [d] In $CDCl_3$. [e] In CD_3OD. [f] Confirmed by decoupling experiments. [g] Not measured separately.

(0.215 mmol, 99% yield) of **20d** as an oil: nmr (CD_3OD) δ 1.54 (broad d, *J* = 7.5 Hz, 6, CH_3), 3.85 (s, 6, OCH_3), and 4.01 (complex m, 2 H, 2,5-H). Only one isomer could be detected; the somewhat lower shifts of the methyl groups in **20d** compared to **20c** (below) as well as the selectivity of oxidation leads to the tentative conclusion that the sulfoxide bond is located anti to the methyl groups.

trans-**2,5-Dimethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene S-oxide (20c)** was prepared as described for **20d** using **4c** (791 mg, 3.44 mmol). There was obtained 710 mg (2.71 mmol, 79% yield) of **20c**: nmr ($CDCl_3$) δ 1.47 (broad d, *J* = 7.5 Hz, 6, CH_3), 3.80 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), and 4.14 (complex q, *J* = *ca.* 7 Hz, 2 H, 2,5-H); ir (neat) 1070 cm^{-1}.

cis-**2,5-Dimethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene S-dioxide (19d)** was prepared in the same manner as described for **20d** using **4d** (45 mg, 0.195 mmol) and *m*-chloroperbenzoic acid (76 mg, 0.390 mmol) in 1 ml of dry, cold methylene chloride. Work-up gave 43 mg (0.165 mmol, 85% yield) of **19d** as a white solid: nmr (CD_3OD) δ 1.43 (d, *J* = 7.0 Hz, 6, CH_3), 3.83 (s, 6, OCH_3), and 4.14 (q, *J* = 7.0 Hz, 2, 2,5-H).

trans-**2,5-Dimethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene S-dioxide (19c)** was prepared as described for **20d** using **4c** (1.38 g, 6 mmol) and *m*-chloroperbenzoic acid (2.39 g, 15 mmol). There was obtained 1.57 g (6 mmol, 100% yield) of **19c**: nmr ($CDCl_3$) δ 1.52 (d, *J* = 7.2 Hz, 6, CH_3), 3.85 (s, 6, OCH_3), and 4.10 (broad q, *J* = 7.2 Hz, 2, 2,5-H); ir (neat) 1320, 1135 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_6S$: C, 45.79; H, 5.38; S, 12.23. Found: C, 45.77; H, 5.35; S, 12.24.

Photochemical Experiments. Most of the photochemical reactions were carried out using a Rayonet R.P.R. 100 photochemical reactor equipped with 16 2537-, 3000- or 3500-Å lamps. The reaction vessels consisted of cylindrical quartz irradiation tubes with either 0.25 in. i.d. and 2 ml capacity, 2.05 in. i.d. and 0.5 l. capacity, or 3 mm i.d. and 0.5 ml capacity. The latter tube fit in a Varian A-60D spectrometer probe and was used for experiments in which the instability of starting material or products required immediate nmr analysis. Degassing was accomplished by at least five freeze–thaw cycles. The irradiated solutions were also monitored by glpc (6 ft × 0.125 in., 10% Carbowax 20M or 10% SE-30 on Chromosorb W AW 80–100 mesh at 200°). Some preparative-scale reactions were done using a Hanau TQ-81 lamp provided with Vycor glass filters. Low-temperature reactions were carried out in the quartz nmr tube mentioned above using an adapted temperature control unit from an esr apparatus to maintain the temperature; the light source was a Philips SP-500 superhigh-pressure lamp. Quantum yields were determined using ferrioxalate actinometry.

Remarks on Individual Irradiations. The spectra of the diene products are described in Table VI. In the case of dihydrothiophenes **4** considerable attention was paid to the isolation and identification of vinyl episulfide intermediates. (In the irradiations of compounds **19** and **20**, when followed by pmr, no trace of an intermediate could be detected. Unfortunately, temperatures in solution could rarely be brought lower than about −20° because of the tendency of the compounds to precipitate.) The vinyl episulfides (spectra given in text) were isolated by carefully concentrating a freshly irradiated solution of **4a** in ether and injecting the solution on a 4-ft glass Carbowax column held at 200°. The effluent was fed through a 10:1 stainless steel splitter connected to a heated outlet and a flame detector, respectively. The material was essentially blown through the column (retention time about 2 min). In this manner about 70–80% pure samples of **9** and **10** were obtained, the pmr spectra of which were obtained with aid of a CAT system. In independent experiments **9** and **10** were shown to be the only products detectable from **4a** directly after irradiation (nmr and glpc). On adding triphenylphosphine at room temperature desulfurization occurred before nmr spectra could be run; the products, **6** and **7**, were formed in the same ratio as **9** and **10**. To establish that **9** and **10** were monomeric, a 200-mg sample of **4c** was irradiated to 23% conversion. Determination of the molecular weight by osmometry in ethyl acetate gave a value of 311.1 ± 4.0 for four measurements. The molecular weight of **4a** (and **9** and **10**) is 314. If **9** and **10** were dimeric the observed molecular weight would have been 314 + (0.103 × 628) = 378. Both **9** and **10** exhibited in the mass spectrum parent peaks at *m/e* 314 with a cracking pattern completely different from that observed with **4a**.

The vinyl episulfides from **4e** were isolated in a manner similar to that described above. A reasonably pure (about 70%) sample of the precursor to **17** was isolated. Overlap with the absorptions for **17** prevents complete assignment. The following partial nmr spectrum was obtained: nmr (CCl_4) δ 2.57 (q, *J* = *ca.* 7 Hz, 2, allylic CH_2CH_3), 3.57–3.90 (complex m, 1, methine H on episulfide ring), and 6.42 (t, *J* = 7.2 Hz, vinyl H). From chemical shift considerations (text) the ethyl group and carboalkoxy group on the double bond are considered to be cis. Desulfurization with triphenylphosphine produced exclusively **17**. Although the precursor to diene **18** was clearly apparent in glpc traces, isolation in sufficient quantities to allow spectral identification was not possible. Because of the symmetry of diene **18**, there exists no ambiguity in the structure of its precursors; the carboalkoxy group and the ethyl group on the three-membered ring must be trans.

A vinyl episulfide (**12a**) was also detected as an intermediate in the photochemical reactions of **4b**. This succeeded only in CD_3OD and the intermediate seemed to be quite unstable. A sample of **4b** was irradiated to 32% conversion and a single new product was detected by nmr (94% yield). In CD_3OD this product had singlet absorptions for four different methyl groups at δ 1.71, 1.91, 1.99,

and 2.14. The methoxy peaks could not be located with certainty. Treatment with triphenylphosphine immediately gave **13**. A sample of **13** (0.5 g, 2.21 mmol) and *m*-chloroperbenzoic acid (1.0 g, 5 mmol) were dissolved in 90 ml of carbon tetrachloride and held at 80° for 20 hr. Work-up gave 0.69 g of crude material that was reasonably pure vinyl epoxide **12b**. Purification by thin layer chromatography gave a sample: ir (neat) 2950, 1710, 1620, 1430, 1370, 1280, 1210, 1060, 1000, 790, and 730 cm^{-1}; nmr (CCl_4) δ 1.23 (s, 3, CH_3), 1.34 (s, 3, CH_3), 1.93 (s, 3, CH_3), 2.12 (s, 3, CH_3), and 3.72 (s, 6, OCH_3). The close resemblance to the spectrum of the vinyl episulfide **12a** is to be noted.

Pyrolysis Reactions. Pyrolyses on a gram scale were carried out in a quartz apparatus of standard design consisting of a 30-cm long tube filled with glass shards and heated by electric ovens held at the desired temperature. The tube was connected on one side to a distillation flask (containing starting material, heated by an air bath) and on the other side to two cold traps hooked in series to cool the products. The system was evacuated to 0.05–0.1 mm pressure.

Pyrolyses on a milligram scale could most easily be carried out in tubes, heated in an air bath, or by pyrolysis in a glass injection port of a gas chromatograph.

All diene products were identified by comparison with authentic dienes obtained from photochemical experiments. In the case of **20b**, for which anomalous results were obtained, the pyrolysis was carried out with 429 mg (1.56 mmol) at 540° (0.1–0.4 Torr). An oil (322 mg) was collected in the cold trap. This was separated into **13** (13%), **21** (19%), **22** (6%), and **23** (62%). Compound **13** was identified by comparison with a known sample (Table VI). Product **21** had ir (CCl_4) 1720, 1650, 1630, 1075 and 1035 cm^{-1}; nmr (CCl_4) δ 1.67 (d, J = 7 Hz, 3, CH_3), 1.70 (s, 3, CH_3), 2.22 (s, 3, CH_3), 3.70 (s, 3, OCH_3), 3.77 (s, 3, OCH_3), and 6.86 (q, J = 7 Hz, 1, vinyl H). These nmr data can be reconciled only with **21**. The relatively low field absorption of the vinylic proton indicates it as being cis to the carbomethoxy group. Compound **21** has mass spectrum parent m/e 212 (calcd for $C_{11}H_{16}O_4$, 212).

Product **22** had ir (CCl_4) 1710 and 1430 cm^{-1}; nmr (CCl_4) δ 1.80 (s, 3, CH_3) 2.12 (d, J = 8 Hz, 3, CH_3), 2.15 (s, 3, CH_3), 3.16 (s, 3, OCH_3), 3.66 (s, 3, OCH_3), and 5.93 (q, J = 8 Hz, 1, vinyl H); mass spectrum parent m/e 212 (calcd for $C_{11}H_{16}O_4$, 212). This compound is clearly an isomer of **21**; the higher shift of the vinyl proton indicates that it is trans to the carboalkoxy group.

Compound **23** had ir (CCl_4) 1740, 1720, 1640, 1090, and 1040 cm^{-1}; nmr (CCl_4) δ 1.78 (s, 6, CH_3), 2.02 (s, 3, CH_3), 3.62 (s, 3, OCH_3), 3.65 (s, 3, OCH_3), 4.07 (broad s, 1, CH), 4.78 (broad s, 1, vinyl H), and 4.88 (broad s, 1, vinyl H); mass spectrum parent m/e 226 (calcd for $C_{12}H_{18}O_4$, 226). The fact that two apparently equivalent methyl groups are present was not readily rationalized. However, this was shown to be an accident of chemical shift by using $Eu(thd)_3$ as shift reagent. The δ 1.78 peak in CCl_4 in the presence of 0.3 equiv of $Eu(thd)_3$ separated into separate absorptions at δ 1.99 and 2.05; the methoxy absorptions were at δ 3.92 and 4.00. With 0.7 equiv of $Eu(Thd)_3$ the δ 1.78 peak had separated into a doublet at δ 2.45 and 2.55; the methoxy peaks were at δ 4.44 and 4.85; no other significant changes occurred in the spectrum. These data are all fully consistent with structure **23**.

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Registry No.—**4a**, 30465-51-1; **4b**, 36614-53-6; **4c**, 50443-46-4; **4d**, 50443-47-5; **4e**, 30465-50-0; **4f**, 30646-53-8; **6**, 32016-99-2; **7**, 32017-00-8; **8**, 3207-01-9; **12b**, 51667-98-2; **13**, 6117-26-6; **14**, 51667-95-9; **15**, 51667-96-0; **16**, 51667-97-1; **17**, 32016-97-0; **18**, 32016-98-1; **19a**, 36611-67-3; **19b**, 36614-55-8; **19c**, 50443-40-8; **19d**, 50443-42-0; **20a**, 36611-66-2; **20b**, 36614-54-7; **20c**, 50443-39-5; **20d**, 51744-50-4; **21**, 50443-49-7; **22**, 50443-50-0; **23**, 50443-51-1; *trans*-2,5-dimethyl-1,3,4-thiadiazolidine, 51667-99-3.

References and Notes

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(17) For recent critical discussions of orbital symmetry factors, see (a) J. A. Berson, *Accounts Chem. Res.*, **5**, 406 (1972); (b) J. E. Baldwin, A. H. Andrist, and R. K. Pinschmidt, *ibid.*, **5**, 402 (1972). (c) Professor N. D. Epiotis has indicated to us that he is engaged in calculations on "stretched" thiophenes, the geometry of which can correspond to **24** in the configuration drawn. Professor Epiotis has emphasized, and correctly to our minds, the crudeness of the generic term "biradical."

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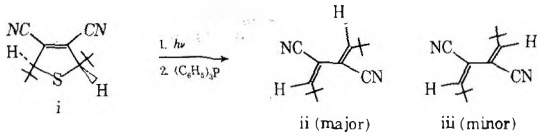
(19) (a) For a review of thiyl radicals, see R. M. Kellogg, "Methods in Free Radical Chemistry," Marcel Dekker, New York, N. Y., 1969, pp 1–120. (b) W. C. Lumma, Jr., and G. A. Berchtold, *J. Amer. Chem. Soc.*, **89**, 2761 (1967); *J. Org. Chem.*, **34**, 1566 (1969); P. Y. Johnson and G. A. Berchtold, *ibid.*, **35**, 584 (1970); K. K. Maheshwari and G. A. Berchtold, *Chem. Commun.*, 13 (1969); A. Padwa and A. Battisti, *J. Amer. Chem. Soc.*, **93**, 1304 (1971); P. Y. Johnson, *Tetrahedron Lett.*, 1991 (1972); J. Kooi, H. Wynberg, and R. M. Kellogg, *Tetrahedron*, **29**, 2135 (1973).

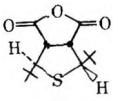
(20) See, for example, P. J. Kropp, E. J. Reardon, Jr., Z. L. F. Gaibel, K. F. Williard, and H. H. Hattaway, Jr., *J. Amer. Chem. Soc.*, **95**, 7058 (1973), and references cited therein. This applies to $\pi-\pi^*$ excited states of olefins; in **4** we do not know if the lowest excited state (presumably a triplet) is $n-\pi^*$ or $\pi-\pi^*$. The ready cis–trans isomerization of virtually all olefinic systems on excitation certainly suggests that twisting about the double bond is a very important process.

(21) An alternative is that the barriers to isomerization in the allylic portions of the biradical are low. The barrier in the allyl radical itself is calculated to be 12 kcal/mol: S. W. Benson, "Thermochemical Kinetics," Wiley, New York, N. Y., 1968. Whether this fairly high barrier is applicable here in unknown.

(22) (a) Carboalkoxy groups are not essential chromophores. Compound **i**, formed from addition of the appropriate thiocarbonyl ylide to dicyanoacetylene, is transformed rapidly on irradiation to unstable products that on treatment with triphenyl phosphine yield **ii** and **iii**. (b) After much effort compound **iv** was prepared in abominable yield by addition of the thiocarbonyl ylide to acetylenedicarboxylic acid followed by dehydration with dicyclohexylcarbodiimide. All other routes attempted failed utterly. It could not be obtained, however, in sufficient quantity or purity to allow investigation of the effect of geometrical constriction.



i ii (major) iii (minor)



iv

(23) For a review, see O. P. Strausz, *Organosulfur Chem.*, 11 (1967).
(24) Landolt-Börnstein, Vol. II, Part 4, Springer-Verlag, West Berlin, 1961, pp 180–184.
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(29) D. R. Kearns, *J. Amer. Chem. Soc.*, **91**, 6554 (1969).
(30) We are much indebted to Professor D. M. Lemal for an incisive discussion concerning the questions of "allowedness" in these compounds. Professor Lemal's analysis will be published by his group in due course.
(31) (a) C. A. Kingsburg and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960); (b) C. Walling and L. Bollyky, *J. Org. Chem.*, **29**, 2699 (1964); (c) I. D. Entwistle and R. A. W. Johnstone, *Chem. Commun.*, 29 (1965).
(32) A portion of this work has been abstracted from the Ph.D. Thesis of W. L. Prins, submitted Sept 1973.

Rearrangement of the Tricyclic Orthothio Esters Derived from Mercaptoacetic Acid and Alkanedithiols. Crystal Structure of a Rearrangement Product

John F. Blount, David L. Coffen,* and Frederick Wong

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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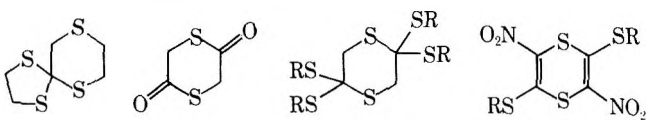
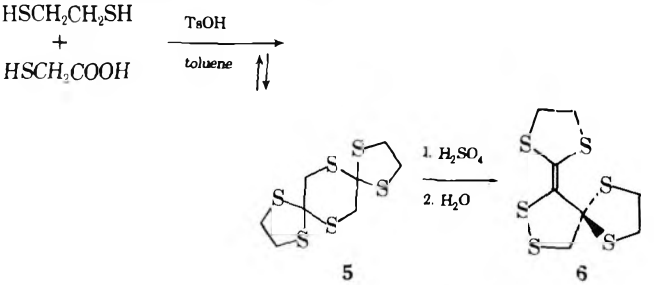
Equimolar amounts of mercaptoacetic acid and ethanedithiol undergo acid-catalyzed condensation to produce a tricyclic ortho ester, 1,4-dithiane-2,5-dione bis(ethylene thioketal). Dissolving this substance in concentrated sulfuric acid followed by quenching with water results in formation of a highly rearranged tricyclic disulfide. By X-ray crystallography the structure of this rearrangement-oxidation product was determined to be 1-[2-(1,3-dithiolanylidene)]-2,3,6,9-tetrathiaspiro[4.4]nonane. Similar condensation and rearrangement reactions were observed when 1,3-propanedithiol was used instead of ethanedithiol. A reaction mechanism involving acid-catalyzed dissociation and recombination is formulated to account for these rearrangements.

Orthothio esters of several simple carboxylic acids have been prepared,[1] generally by straightforward methods involving the direct condensation of the acid, an ester, or its chloride with 3 equiv of the RSH component. The ortho ester **1** of mercaptoacetic acid was described by Backer and Wiggerink[2] as the product resulting from the condensation of chloroacetyl chloride with ethanedithiol. Schöberl and Wiehler[3] prepared symmetrical ortho esters of type **3** by treating dithioglycolide (**2**) with various mercaptans. Boron trifluoride catalyzed self-condensation of mercaptoacetic acid produced the orthothio ester **3b**. Schöberl and Wiehler also described an unusual reaction of their compounds of type **3**, namely their nitration in nitric acid which produced the 1,4-dithiin derivatives **4**.



1 **2** **3a**, R = phenyl, benzyl; **b**, R = CH_2COOH **4**

The possibility of utilizing compounds of type **4** as progenitors of protected α-mercaptoamino acids evoked our interest in the orthothio esters of mercaptoacetic acid. During the course of our work with compounds of this type, we had occasion to prepare the tricyclic ortho ester **5**, which is easily done, albeit in modest yield, by the direct, acid-catalyzed condensation of equimolar quantities of ethanedithiol and mercaptoacetic acid. The structure of

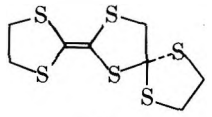


5 **6**

this high-melting, poorly soluble, colorless substance is evident from its nmr and mass spectra. The former consists of two signals, an AB quartet at 3.49 ppm (J = 6 Hz)

and a singlet at 3.61 ppm in 2:1 ratio; and the latter contains a weak M^+ peak at m/e 300 and an intense peak (100%) at m/e 150.

One of the few liquids in which compound **5** is appreciably soluble is concentrated sulfuric acid. When the resulting yellow solution of **5** is kept overnight at room temperature and then quenched by pouring over crushed ice, a bright yellow product is obtained in high yield. Following the acquisition of routine spectroscopic and analytical data, **7** and **8** appeared to be tenable structures for



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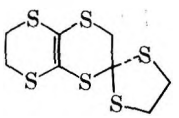
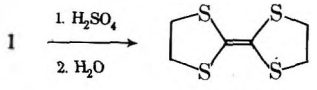


8

this rearrangement product. The nmr spectrum consists of a multiplet (>20 lines) and a singlet in a 4:1 ratio in which the former can easily be construed as two overlapping AA'BB' multiplets. A strong infrared band at 1540 cm^{-1} and a weak (ϵ 550) uv absorption at 370 mμ encouraged the contemplation of tetrathioethylene derivatives as candidate structures,[4] as did also the observation that compound **1** can be rearranged to the tetrathioethylene **9** under similar reaction conditions.

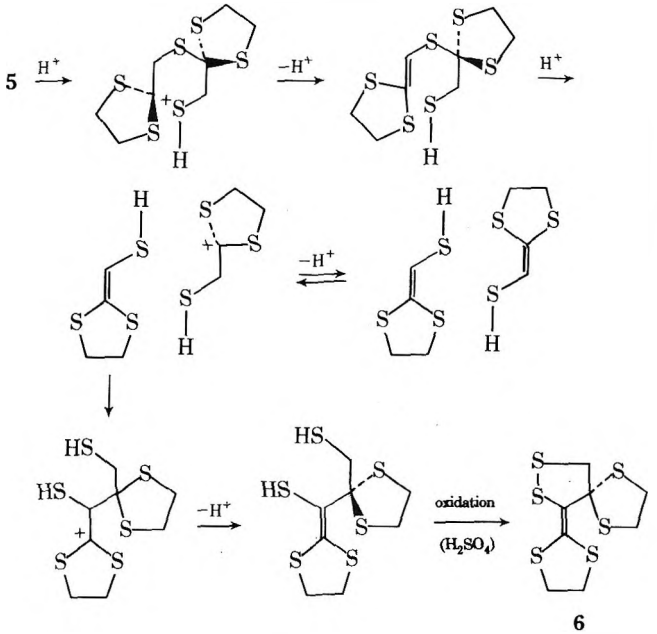


9

An X-ray crystallographic structure determination was undertaken to distinguish between structures **7** and **8**. In this way it evolved that neither structure is correct, as the rearrangement product actually has structure **6**.

The genesis of compound **6** posed an intriguing mechanism problem. While several pathways may perhaps be contrived, we find that shown in Scheme I, which entails

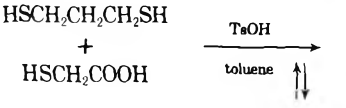
Scheme I

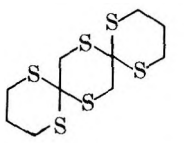


6

the symmetrical scission and unsymmetrical recombination of the starting orthothio ester, to be quite reasonable. The oxidation of a dimercaptan to a cyclic disulfide by sulfuric acid is not wholly without precedent,[5] although somewhat surprising in the case of a presumably strained 1,2-dithiolane.[6]

This rearrangement appeared to be sufficiently novel as to merit the existence of at least two examples. Accordingly 1,3-propanedithiol and mercaptoacetic acid were condensed to give the orthothio ester **10**. The rearrangement of this material proceeded more slowly but again cleanly to provide in good yield the product **11**. Structures **10** and **11** were assigned by analogy but nicely corroborated by their spectroscopic properties as iterated in the Experimental Section.





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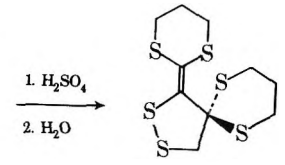

11

Table I
Crystal Data for Compound 6

Crystal system Space group	Monoclinic $P2_1$	Orthorhombic $Fdd2$
a, Å	9.035 (8)	16.197 (8)
b, Å	7.981 (6)	37.91 (2)
c, Å	8.988 (6)	8.037 (6)
β, deg	107.93 (4)	
Z	2	16
d_{calcd}, g cm^{-3}	1.607	1.607
μ (Mo Kα), cm^{-1}	10.2	10.2

Table II
"Distances" and "Angles" Involving the Half-Atoms of the Two Conformers

Bond	Distance, Å	Bond	Angle, deg
C7A–C7B	0.81	S5–C7A–C8B	116
C7A–C8B	1.16	S5–C7B–C8A	111
C7B–C8A	1.53	S6–C8A–C7B	115
C8A–C8B	0.71	S6–C8B–C7A	118
S4A–S4B	2.00		

Crystallography. Crystals of compound **6** were found to exist in both monoclinic and orthorhombic forms, but it was not established that both are obtained in a single crystal crop. Efforts to solve the structure by both direct methods and Patterson methods using an orthorhombic crystal were fruitless. However, a complete crystal structure analysis of the monoclinic form was successfully carried out using a multiple solution procedure.[7]

The intensity data were collected on a Hilger-Watts diffractometer using Zr filtered Mo Kα radiation and crystals of approximate size 0.1 × 0.2 × 0.4 mm (monoclinic) and 0.2 × 0.2 × 0.25 mm (orthorhombic). The crystal data are presented in Table I.

Early in the refinement of the structure it became apparent that the crystal contained at least two conformers. A disordered model involving two conformers was adopted in which it was possible to resolve S(4), C(7), and C(8) each into two half-atoms. All half-atoms were assigned occupancy factors of 0.5. Toward the conclusion of the refinement, hydrogen atoms were introduced at their calculated positions. Two pairs of protons (H5Aa, H5Ab and H5Ba, H5Bb) were introduced at C(5) to correspond to the two different conformations (A and B). The final refinement was carried out by full-matrix least squares. Anisotropic thermal parameters were used for all atoms except the hydrogen and the four half-carbons, C7A, C7B, C8A, and C8B, which had isotropic temperature factors. The hydrogen atom parameters were not refined. The

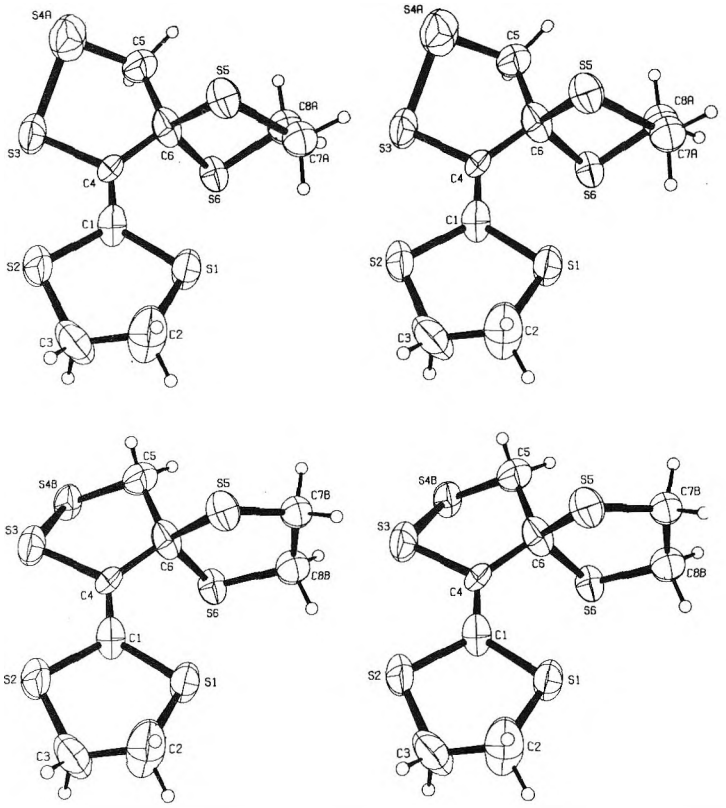

Figure 1. Stereodrawings of 6 showing the two most probable conformations.

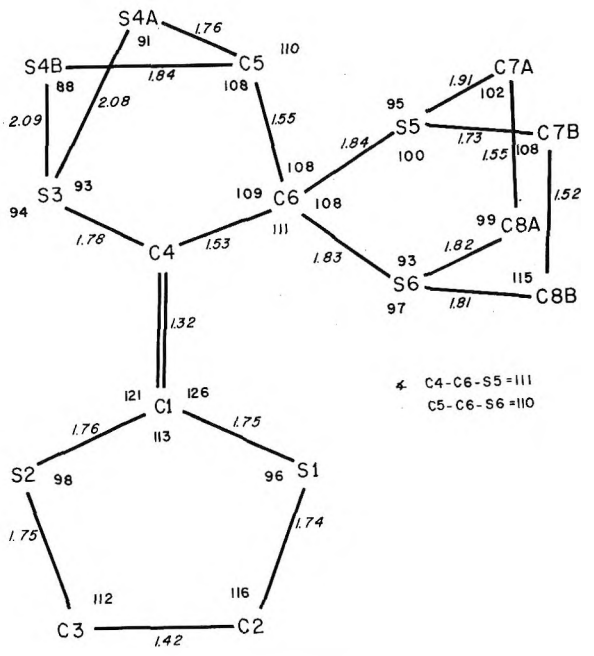

Figure 2.

final discrepancy index is $R = 5.2\%$ for 1251 observed data.[8]

The two most probable conformational arrangements involving the six half-atoms are shown in the stereodrawing in Figure 1. The bond distance and angles are given in Figure 2 and Table II. The conformer involving S4B, C7A, and C8A was ruled out because of the close intramolecular contact of 2.34 Å (H5Bb–H8Ab). Other atoms, particularly S(2), C(2), and C(3), probably occupy slightly different positions in the two conformers, but these differences were too small to resolve as separate half-atoms. The standard deviations of the bond distances and angles are larger than desired, owing in part to the disorder involving the different conformers. One of the more reliable distances is that of the ethylenic C(1)–C(4) bond, which is 1.32 (1) Å.

Experimental Section[9]

1,4-Dithiane-2,5-dione Bis(ethylene Thioketal) (5). A solution of mercaptoacetic acid (27.6 g, 0.3 mol), ethanedithiol (28.3 g, 0.3 mol), and *p*-toluenesulfonic acid (1.5 g) in toluene (500 ml) was heated under reflux for 2.5 days while collecting water in a Dean–Stark trap. The solution was cooled, diluted with ether (400 ml), and set aside while the product crystallized. The product was collected and washed with ether to give 9.45 g (21%) of colorless crystals, mp 268–270°. An analytical sample was prepared by high-vacuum sublimation. The infrared spectrum (Nujol) shows no bands above 1500 cm^{-1}. The nmr spectrum (recorded in DMSO-d_6) and mass spectrum are described in the text.

Anal. Calcd for $C_8H_{12}S_6$: C, 31.97; H, 4.02; S, 64.01. Found: C, 31.72; H, 4.08; S, 64.23.

1-[2-(1,3-Dithiolanylidene)]-2,3,6,9-tetrathiaspiro[4.4]nonane (6). Compound 5 (500 mg) was added gradually to concentrated sulfuric acid (5 ml) with swirling to give a clear solution. This was kept overnight and then poured over crushed ice. After the ice had melted, the product was collected, washed with water, and air dried to give 500 mg of a yellow solid showing a single, yellow spot on tlc. A recrystallization from benzene gave 410 mg (82%) of bright yellow crystals, mp 135–137°, in two crops. The product had an ir (Nujol) band at 1540 cm^{-1} and uv (CH_2Cl_2) bands at 232 mμ (ε 8090), 298 (7200), and 370 (550). The nmr spectrum ($CDCl_3$) consisted of a complex multiplet centered at 3.43 ppm (8 H) and a singlet at 3.71 ppm (2 H), mass spectrum *m/e* 298 (100%, M^+).

Anal. Calcd for $C_8H_{10}S_6$: C, 32.18; H, 3.38; S, 64.44. Found: C, 32.14; H, 3.25; S, 64.04.

Rearrangement of Compound 1 to Compound 9. A solution of compound 1[2] (500 mg) in concentrated sulfuric acid (10 ml) was kept for 5 min and then quenched by rapid dilution with water. The resulting mixture was extracted three times with methylene chloride. The extract was dried, treated with charcoal, and evaporated. The residue was vacuum sublimed and the solid sublimate was triturated with ether, collected, and washed with ether to give 180 mg (36%) of compound 9 as a light yellow solid, mp 196–197° (lit.[10] mp 202–204°). The compound was identified by comparison of its ir and nmr spectra and of its tlc behavior with those of an authentic sample.[10]

1,4-Dithiane-2,5-dione Bis(trimethylene Thioketal) (10). A solution of mercaptoacetic acid (27.6 g, 0.3 mol), 1,3-propanedithiol (32.5 g, 0.3 mol), and *p*-toluenesulfonic acid (1.0 g) in toluene (500 ml) was heated under reflux for 4 days while collecting water in a Dean-Stark trap. The resulting orange solution was cooled and diluted with ether (500 ml). The product was collected, washed with ether, and air dried to give 32.4 g (66%) of colorless crystals. A sample for analysis was recrystallized from chlorobenzene and had mp 253–258°. The ir (Nujol) spectrum shows no bands above 1500 cm^{-1}. An nmr spectrum was not recorded because of the poor solubility. The mass spectrum had peaks at *m/e* 132 (100%), 165, 196, and 328 (M^+).

Anal. Calcd for $C_{10}H_{16}S_6$: C, 36.55; H, 4.91; S, 58.54. Found: C, 36.70; H, 4.91; S, 58.47.

1-[2-(1,3-Dithianylidene)]-2,3,6,10-tetrathiaspiro[4.5]decane (11). Compound 10 (8 g) was added gradually to concentrated sulfuric acid and the resulting solution was stirred for 3 days at room temperature. The solution was poured over ice and the precipitate was extracted into methylene chloride. After drying with sodium sulfate, the solvent was boiled off with gradual addition of benzene. The product crystallized from the resulting benzene solution to give, in three crops, 6.4 g (80%) of compound 11 as yellow crystals: mp 202–205°; ir (Nujol) 1500 cm^{-1}; uv (CH_2Cl_2) 238 mμ (ε 8100), 300 (7300), and 355 (1300, shoulder); nmr ($CDCl_3$) 2.10 (m, 4 H), 3.00 (m, 8 H), and 4.06 ppm (s, 2 H); mass spectrum *m/e* 156 (100%), 220, and 326 (M^+).

Anal. Calcd for $C_{10}H_{14}S_6$: C, 36.78; H, 4.32; S, 58.91. Found: C, 36.88; H, 4.40; S, 57.97.

Registry No.—**1**, 177-29-7; **5**, 51795-67-6; **6**, 51795-68-7; **9**, 24719-68-4; **10**, 51795-69-8; **11**, 51795-70-1; mercaptoacetic acid, 68-11-1; ethanedithiol, 540-63-6; 1,3-propanedithiol, 109-80-8.

Supplementary Material Available. Listings of atomic coordinates and thermal parameters for **6** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2374.

References and Notes

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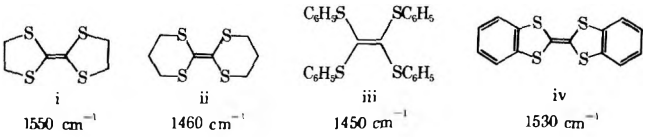
(4) Compound i exhibits uv absorption at 358 mμ (ε 470). Symmetrical tetrathioethylenes exhibit no infrared C=C bands, but we have examined the laser Raman spectra of several and find that these bands appear at exceptionally low frequencies as listed below (recorded with solid samples). We are greatly indebted to Mrs. Fie Chang for recording these data.



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(7) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
(8) See paragraph at end of paper regarding supplementary material.
(9) Melting points are uncorrected. Nmr spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.
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Stereospecific Synthesis of 3,7-Disubstituted Bicyclo[3.3.0]octanes[1]

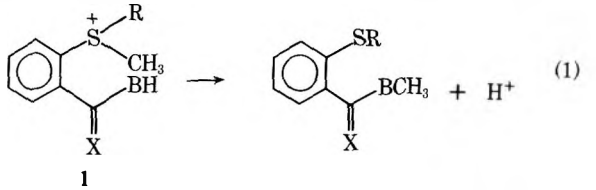
Roger Lok[2] and James K. Coward*

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510

Received March 18, 1974

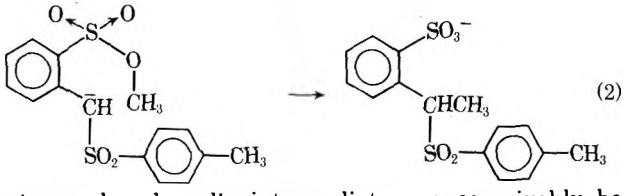
The synthesis of several 3,7-disubstituted bicyclo[3.3.0]octanes has been accomplished by a series of stereospecific reactions, starting with the monoethylene ketal of 3,7-bicyclo[3.3.0]octanedione. The configurations at carbons 3 and 7 were established by the use of pmr spectroscopy.

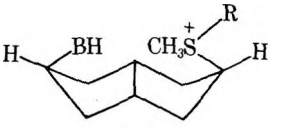
As part of a project aimed at understanding biochemical one-carbon transfer, we have been studying several types of molecules in order to elucidate the stereochemistry and the nature of catalysis involved in nonenzymic transalkylation reactions.[3] Specifically, we are interested in providing a chemical model for enzyme-catalyzed methylations involving *S*-adenosylmethionine (SAM).[4] In a previous paper[5] we noted the stability of **1** under conditions where one might observe intramolecular transmethylations (eq 1). Independently, Eschenmoser and his coworkers[6] were unable to observe any intramolecular transmethylation in the reaction shown in eq 2. In both reactions, a six-membered cyclic intermediate can conceivably be formed, but no product resulting from intramolecular nucleophilic attack at the sp^3 carbon was obtained. Failure of these reactions may be ascribed to the inability of the atoms involved to achieve the required linear geometry in the transition state. This is in marked contrast to the numerous intramolecular reactions involving six-membered cyclic intermediates occurring at sp^2 carbons.[7] We have continued to examine models[8] of compounds in which the nucleophile, the leaving group, and the electrophilic center can be aligned in the collinear array required for a nucleophilic displacement. A molecule which can achieve such a conformation is the methylsulfonium salt **2** of a 3,7-disubstituted bicyclo[3.3.0]octane.



1

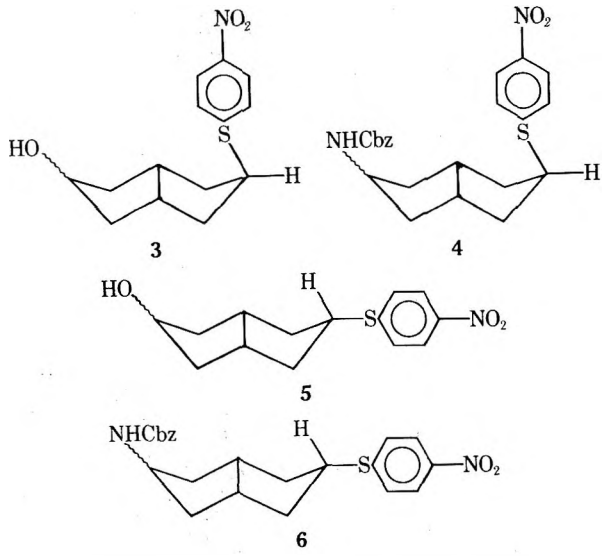
a, R = CH_3; X = H_2; BH = NH_2 → a, R = CH_3; X = H_2; B = NH
b, R = CH_3; X = O; BH = OH → b, R = CH_3; X = O; B = O
c, R = CN; X = O; BH = OH
d, R = CN; X = O; BH = NH_2
→ c,d, R = CN; X = O; B = O





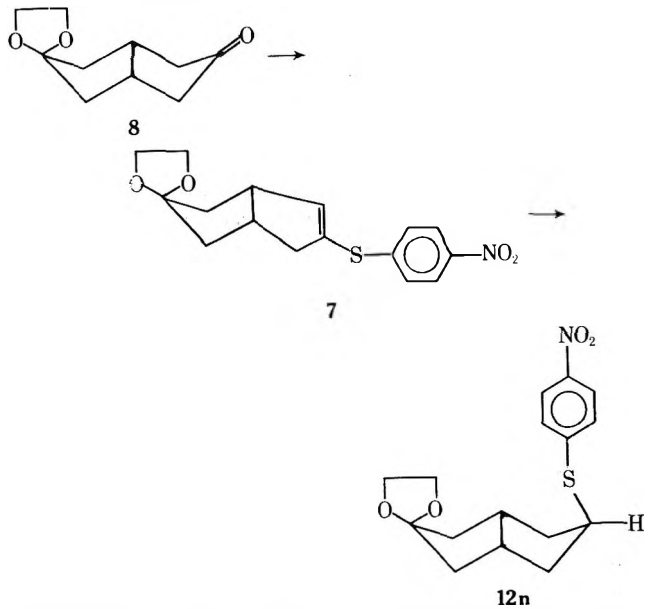
2

Tabushi and his coworkers[9] have shown that 3-substituted bicyclo[3.3.0]octanes prefer a "W" conformation. Models of **2** indicate that the rigid backbone of this bicyclic ring system allows an endo nucleophilic base (BH) at C-7 and the methyl of an endo sulfonium moiety at C-3 to come in close proximity to one another. Only a small deviation from the fully extended "W" conformation brings the nucleophilic and electrophilic centers within bond-making distance for a possible intramolecular transmethylation reaction. The compound in which RS of **2** is homocysteine appears to be a plausible model for enzymic methylations involving SAM. There are very little data on the 3,7-disubstituted bicyclooctanes in the literature.[10a] We have carried out the synthesis of some stereospecifically substituted bicyclooctane derivatives, **3**–**6**, and the results of these efforts are the subject of this paper.



3 4 5 6

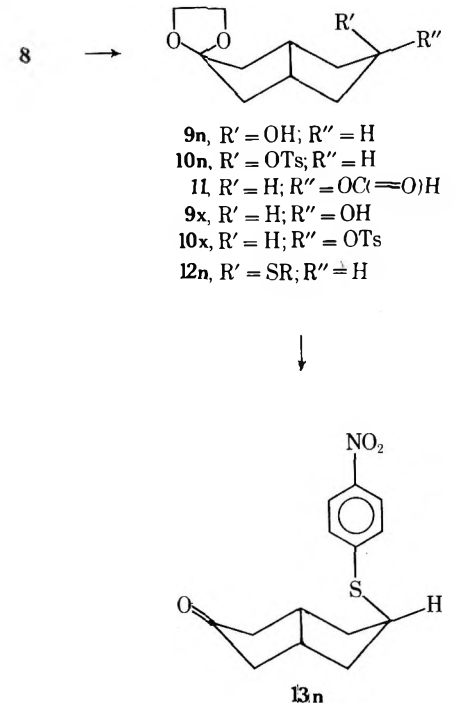
Our initial approach to **3** was to attempt the preparation of vinyl sulfide **7** from the known bicyclo[3.3.0]octane-3,7-dione monoethylene ketal (**8**).[10a] Sulfide **7** could then be stereospecifically reduced to the endo ketal sulfide **12n**. Cyclohexanone was reported[11] to condense with benzenethiol in the presence of *p*-toluenesulfonic acid to give phenyl cyclohexenyl sulfide in one step. Similarly, we were able to convert cyclopentanone to the corresponding *p*-nitrophenyl cyclopentenyl sulfide in good yield. However, the analogous reaction between **8** and benzenethiol gave a complex mixture with none of the desired product.



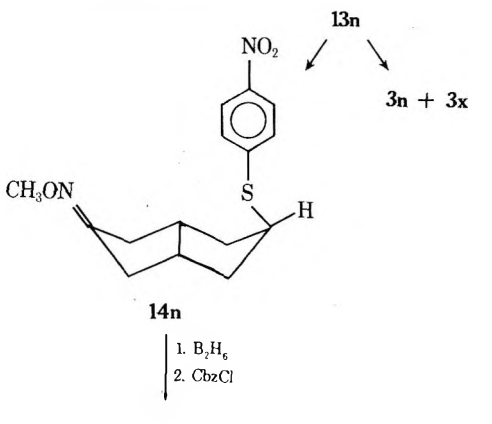
8 7 12n

We then turned our attention to the reaction sequence in Scheme I. Tabushi and his coworkers[9] reported the reduction of bicyclo[3.3.0]octan-3-one to the corresponding alcohol with a ratio of endo OH:exo OH of 4:1. In our hands, reduction of **8** by $LiAlH_4$ gave exclusively the endo product **9n**, which was readily converted to the tosylate **10n**. However, when treated with sodium acetate, the tosylate of *endo*-bicyclo[3.3.0]octan-3-ol was known to give extensive olefin formation.[12] Recently, Corey[13] and Weinshenker[14] described the use of tetraalkylammonium formates as mild reagents for effecting displacement reactions with only minor olefin formation. When **10n** was mixed with tetra-*n*-butylammonium formate in acetone at ambient temperature the product consisted of a mixture of exo formate **11** and an olefinic material in a ratio of *ca.* 5:1 estimated by nmr. This mixture was solvolyzed to the exo alcohol **9x**, which was then tosylated to give **10x**. To convert the exo tosylate **10x** to the endo sulfide **12n** we used the reagent tetra-*n*-butylammonium *p*-nitrobenzenethiolate. Although a recent paper described kinetic studies of displacement reactions with tetraalkylammonium thiophenolates,[15] we are not aware of the use of these reagents for the synthetic preparation of sulfides. Thus, formation of the endo sulfide **12n** was effected in good yield with no presence of isomeric exo sulfide **12x**. The ketal group was removed by acid-catalyzed ketal exchange with acetone. Reduction of the resulting ketone **13n** with $NaBH_4$ gave the desired endo hydroxy compound **3n** together with a small amount of the exo hydroxy isomer **3x** (endo:exo = 7:1). Treatment of **13n** with *O*-methyl oxime hydrochloride produced the oxime **14n** in good yield. Reduction of **14n** by diborane and derivatization of the resulting amine with carbobenzyloxy chloride (CbzCl) gave only the endo *N*-carbobenzyloxyamino sulfide **4n**.

Scheme I



8 → 9n, R′ = OH; R″ = H
10n, R′ = OTs; R″ = H
11, R′ = H; R″ = OC(=O)H
9x, R′ = H; R″ = OH
10x, R′ = H; R″ = OTs
12n, R′ = SR; R″ = H
→ 13n



13n → 3n + 3x
14n
1. B_2H_6
2. CbzCl
4n

Stereochemistry. Reduction of bicyclo[3.3.0]octan-3-one is known to give the endo alcohol **15n** as the major product, and results from attack of the carbonyl function from the least hindered exo side.[12] Tabushi and his coworkers[9] found that the α protons of the endo alcohol **15n** and its acetate **16n** are more shielded than the α protons of the isomeric exo alcohol **15x** and its acetate **16x**. For nmr

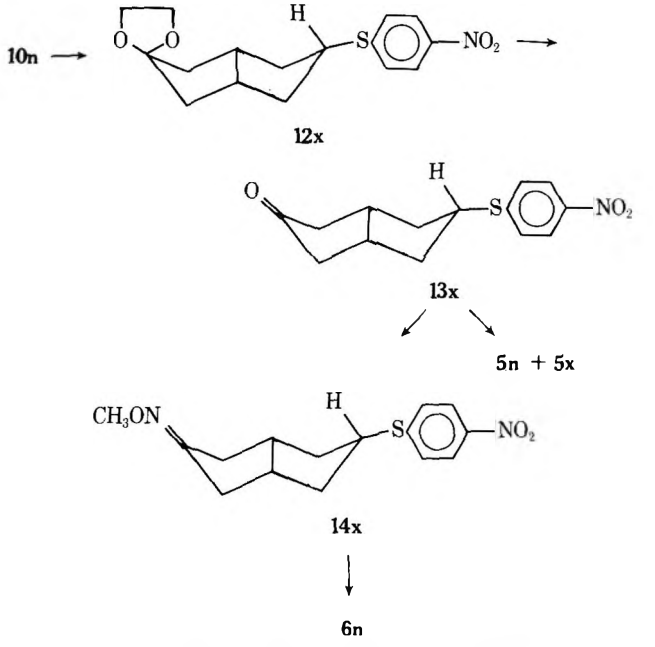
Table I[a]

Compd	H_3	H_7	Compd	H_3	H_7
15n	3.93[b]		**15x**	4.16[b]	
16n	4.92[b]		**16x**	5.18[b]	
9n	4.14		**9x**	4.37	
10n	4.83		**10x**	5.05	
12n	3.65		**12x**	3.96	
13n	3.83		**13x**	3.98	
14n	3.72		**14x**	3.83	
3n	3.57	4.35	**5n**	4.13	4.13
3x	3.58	4.47	**5x**	3.73	4.45

[a] Chemical shifts in δ units. [b] Data from Tabushi, *et al.*[9]

comparison, we prepared the series of exo sulfides **5** and **6**, using analogous reactions as in the endo series (Scheme II). The exo sulfide series also provide access to the corresponding methylsulfonium compounds, in which the nucleophile and methyl group are not correctly aligned for intramolecular methyl transfer. These sulfonium compounds, in contrast to **2**, should not undergo facile transmethylation, and therefore could be used in control experiments to probe the stereochemical requirements of the reaction.

Scheme II

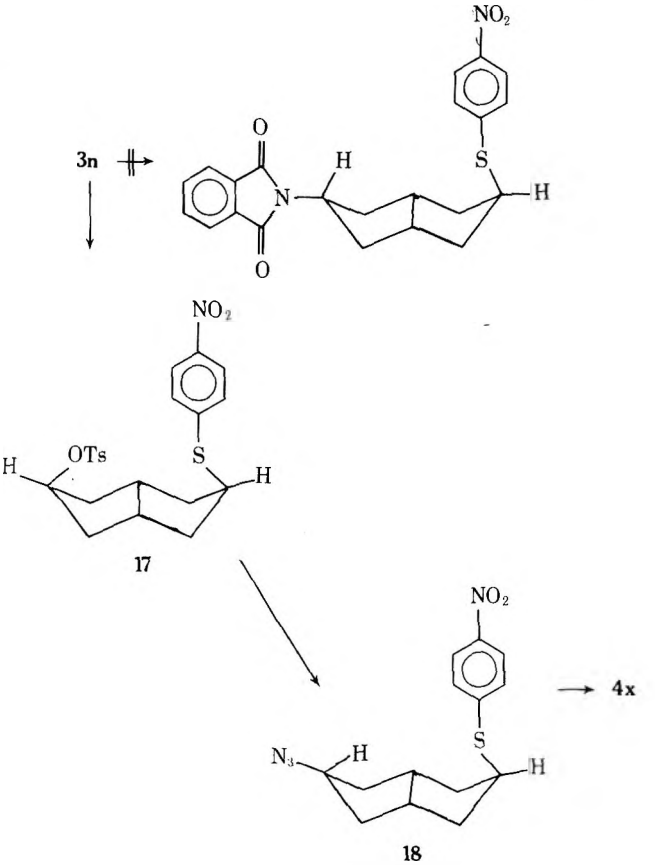


The chemical shifts of the α H's in the endo and exo series along with those obtained by Tabushi are listed in Table I. We observe a similar upfield shift of the α H's in the endo sulfides compared to the exo sulfides. The difference of 0.23 ppm between **15n** and **15x** is identical with the difference between **9n** and **9x**. The position of the H_7 proton of the hydroxy sulfide **3n** at δ 4.35 compared to δ 4.47 of **3x** confirms the endo configuration of the hydroxy moiety of **3n**. Similarly, the upfield shift of the H_7 proton of **5n** relative to that of **5x** indicates the endo geometry of the hydroxy group of **5n**. The chemical shift of the α H's of the sulfides also vary within each series. In particular, a difference of 0.4 ppm is observed between the H_3 protons of **5n** and **5x**. This difference may be an indication of the influence of the endo hydroxy at C-7 of **5n** on the endo proton at C-3. Such an influence demonstrates the close proximity of the two endo groups. This is encouraging in terms of bringing the nucleophile of **2** in close proximity to the sulfonium moiety.

Reduction of ketoxime acetates by diborane is known to occur stereospecifically from the less hindered side.[16] In support of this mode of attack, we obtained exclusively the endo alcohol **9n** when the ketone **8** was treated with diborane. However, since it is critical that the nucleophile at C-7 of **2** be in the endo configuration, we felt it important to establish beyond a doubt the geometry of the C-7 substituent. For this reason, we converted the endo hydroxy sulfide **3n** to the exo *N*-carbobenzyloxyamino sulfide **4x** for direct comparison with its endo isomer **4n**.

Mitsunobu and coworkers[17] reported that an optically active alcohol could be converted to an optically active amine by treatment with diethyl azodicarboxylate, triphenylphosphine, and phthalimide at room temperature. We carried out the analogous reaction with **3n**, but recovered only starting material (Scheme III). Therefore, we prepared the tosylate **17** and converted it to the exo azido sulfide **18**. Reduction of the azide **18** by diborane followed by CbzCl treatment gave the exo *N*-carbobenzyloxyamino sulfide **4x**. The isomers **4n** and **4x** have identical R_f values on tlc and identical elemental composition. Their ir spectra are identical except in the 1000–1300-cm^{-1} region. A broad multiplet at δ 3.3–4.4 is observed in the nmr spectrum of **4n**; this peak is assigned to the protons α to the sulfide and *N*-Cbz-amino groups. In the exo isomer **4x**, the multiplet at δ 4.13 is assigned to the proton α to the *N*-carbobenzyloxyamino group and, analogous to other sulfides, the higher field multiplet at δ 3.43 is attributed to the proton α to the sulfide moiety. Finally, the two isomers differ in melting point by 25°.

Scheme III



Experimental Section[18]

Cyclopentenyl *p*-Nitrophenyl Sulfide. A mixture of cyclopentanone (0.84 g, 10 mmol), 1.55 g (10 mmol) of *p*-nitrobenzenethiol, *ca.* 0.1 g of *p*-toleuenesulfonic acid, and 30 ml of toluene was refluxed for 22 hr with continuous water removal. The solution was then extracted several times with 6 *N* aqueous NaOH and the combined aqueous solution was backwashed with $CHCl_3$. The organic phases were combined and dried. The solvents were removed under vacuum and the residue was distilled. A yellow liquid weighing 1.15 g (52%) was obtained: bp 127° (0.07 mm); ir

1500, 1340 cm^{-1} (NO_2); nmr δ 8.05, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 6.15 (1 H, m, HC=C), 2.25 (6 H, m, ring protons).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.69; H, 5.01; N, 6.29. Found: C, 59.83; H, 4.95; N, 6.42.

Bicyclo[3.3.0]octane-3,7-dione Monoethylene Ketal (8). The dione[19] (17.0 g, 0.123 mol) was heated overnight with ethylene glycol (7.61 g, 0.123 mol) and a catalytic amount of *p*-toluenesulfonic acid in 200 ml of benzene while the water formed was continuously removed. The mixture was extracted with aqueous $NaHCO_3$ solution and dried. Benzene was removed and the residue was passed through a silica gel column with ether as the eluent. The first eluate consisted of 6.57 g of the diketal, nmr 3.78 (8 H, s, 2 OCH_2CH_2O), 1.35–2.80 (10 H, m, ring protons). The second eluate was a mixture primarily of the monoketone 8 with a trace of the diketal (8.67 g). A pure sample of 8 gave the following data: ir (neat) 1740 cm^{-1} (C=O); nmr δ 3.77 (4 H, s, OCH_2CH_2O), 1.3–3.0 (10 H, m, ring protons). The third fraction, weighing 2.15 g, was the unreacted dione plus a small trace of monoketone 8. These spectral data are in agreement with those previously obtained.[10b]

3-*endo*-Hydroxybicyclo[3.3.0]octan-7-one Ethylene Ketal (9n). A. By Reduction with $LiAlH_4$. The monoketone (5.15 g) prepared as described above was heated at reflux for 1 hr with 1.07 g of $LiAlH_4$ in 30 ml of ether. Excess $LiAlH_4$ was destroyed by addition of MeOH and H_2O. Insoluble solids were removed by filtration and the aqueous phase was extracted with $CHCl_3$. The organic phases were combined and concentrated. The residue was eluted on a silica gel column with ether. The first eluate contained unreacted diketal (0.76 g) and the second eluate was pure hydroxy ketal **9n** (3.07 g, 69%) obtained as a colorless oil: ir 3360 cm^{-1} (OH); nmr δ 4.14 (1 H, p, J = 6 Hz, HCO), 3.83 (s, 4 H, OCH_2CH_2O), 3.0 (1 H, s, OH), 2.5–1.2 (m, 10 H, ring protons).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.69. Found: C, 64.95; H, 8.77.

B. By Reduction with BH_3. The usual Brown procedure was employed.[20] The crude product from 182 mg of unpurified monoketone 8 weighed 143 mg. Its nmr, tlc, and ir indicated only the presence of the endo hydroxy ketal **9n** and a trace of diketal.

3-*endo*-*p*-Toluenesulfonatobicyclo[3.3.0]octan-7-one Ethylene Ketal (10n). *p*-Toluenesulfonyl chloride (6.1 g, 0.032 mol) was added slowly to a solution of 2.94 g (0.016 mol) of **9n** in 50 ml of dry pyridine with stirring and cooling. After stirring for another hour in the cold, it was left at room temperature overnight. The mixture was then poured into ice water, and the precipitate was collected and redissolved in ether. The ether solution was dried and concentrated, leaving a white solid. This material was recrystallized from ether–petroleum ether mixture, giving two crops of material (3.07 g, 57%): mp 85–86°; ir 1350, 1170 cm^{-1} (SO_2); nmr δ 7.77, 7.32 (4 H, two sets of d, J = 9 Hz, ArH), 4.83 (1 H, p, J = 6.5 Hz, CHOTs), 3.84 (4 H, s, OCH_2CH_2O), 2.8–1.4 (13 H, m, $ArCH_3$ and ring protons).

Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.34; H, 6.55. Found: C, 60.53; H, 6.53.

3-*exo*-Hydroxybicyclo[3.3.0]octan-7-one Ethylene Ketal (9x). Tetra-*n*-butylammonium formate[21] (62.5 mmol) and 4.2 g (12.5 mmol) of the endo tosylate **10n** were dissolved in 150 ml of dry acetone. The mixture was allowed to stand overnight at room temperature. Acetone was then evaporated and the residue was extracted several times with ether. The ethereal solution was concentrated to a small volume and then passed through a silica gel column using ether as the eluent. Evaporation of ether from the eluate gave 2.18 g of a colorless oil: nmr δ 7.96 [s, OC(=O)H], 5.58 (m, HC=CH), 5.35 (p, J = 3 Hz, CHO), 3.82 (s, OCH_2CH_2O), 3.0–1.2 (m, ring protons). The peak intensity of the formyl proton *vs.* the vinylic protons was 7:3, giving a ratio of 5:1 of the formate **11** to the olefinic by-product.

The formate mixture was stirred for 4.5 hr in a solution of 20 g of anhydrous K_2CO_3 and 250 ml of anhydrous MeOH. The solid was then filtered, and MeOH was removed from the filtrate. The residue was partitioned between ether and water, the ether phase was dried and concentrated, and the oily residue was purified on a silica gel column with ether as the eluent. The eluate consisted of two fractions. The first fraction (0.17 g), with nmr δ 5.6 (2 H, m, HC=CH), 3.83 (4 H, s, OCH_2CH_2O), 3.4–1.2 (m, 9.2 H, ring protons), is in accord with the olefin obtained in the previous step. The second fraction **9x** weighed 1.4 g (61% from the tosylate): ir (neat) 3400 cm^{-1} (OH); nmr δ 4.37 (1, H, p, J = 5 Hz, CHO), 3.83 (4 H, s, OCH_2CH_2O), 3.17 (1 H, s, OH), 3.0–1.3 (10 H, m, ring protons).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.69. Found: C, 64.94; H, 8.88.

3-*exo*-*p*-Toluenesulfonatobicyclo[3.3.0]octan-7-one Ethylene Ketal (10x). The exo alcohol **9x** (1.1 g, 6 mmol) was treated with *p*-toluenesulfonyl chloride (3.44 g, 18 mmol) as before except that the work-up was modified as follows. The reaction mixture was poured into ice–water. The resulting aqueous solution, in which no precipitate appeared, was extracted with $CHCl_3$ and the dried $CHCl_3$ extract was concentrated *in vacuo*. The remaining pyridine was evaporated by a mechanical pump and the final trace was removed by an aqueous cupric chloride wash. The product weighed 1.4 g (69%): mp 55–60° (recrystallized from petroleum ether); ir 3400 cm^{-1} (OH); nmr δ 7.77, 7.32 (4 H, two sets of d, J = 9 Hz, ArH), 5.05 (1 H, p, J = 4 Hz, HCOTs), 3.81 (4 H, s, OCH_2CH_2O), 3.0–1.2 (13 H, m, $ArCH_3$ and ring protons).

Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.34; H, 6.55. Found: C, 60.23; H, 6.43.

3-*endo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one Ethylene Ketal (12n). Tetra-*n*-butylammonium *p*-nitrobenzenethiolate was prepared by mixing a solution of 64.87 g (25 mmol) of 10% aqueous tetra-*n*-butylammonium hydroxide in 60 ml of MeOH with a solution of *p*- nitrothiophenol (4.267 g, 27.5 mmol) in 60 ml of MeOH. The mixture was concentrated *in vacuo* and then lyophilized overnight. The excess thiophenol was removed by washing the red crystals with ether several times.

To the red solid was added 1.69 (5 mmol) of the exo tosylate **10x** followed by 250 ml of freshly distilled CH_3CN. The solution was allowed to stand at room temperature for 48 hr. At this time, the solvent was removed and the solid was extracted in a Soxhlet extractor overnight with ether. The ethereal solution was concentrated, leaving a yellow solid (0.81 g). Additional product could be obtained from repeated extractions. A total of three extractions gave 1.66 g of crude **12n.** A small sample was purified by preparative tlc and recrystallized from 95% ethanol: mp 143–145°; ir 1470, 1320 cm^{-1} (NO_2); nmr δ 8.10, 7.34 (4 H, two sets of d, J = 9 Hz, ArH), 3.87 (4 H, s, OCH_2CH_2O), 3.65 (1 H, p, J = 6 Hz, CHSAr), 3.0–1.3 (10 H, m, ring protons).

Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.81; H, 5.95; N, 4.35. Found: C, 59.55; H, 5.92; N, 4.35.

3-*endo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one (13n). The crude ketal sulfide **12n** (1.61 g, 5 mmol) was refluxed in dry acetone (200 ml) with 30 mg of *p*-toluenesulfonic acid for 4 hr. Acetone was evaporated and the residue was extracted between $CHCl_3$ and saturated $NaHCO_3$. The $CHCl_3$ phase was dried and concentrated, leaving a (yellow solid) residue weighing 1.4 g. A small quantity of pure **13n** was obtained by preparative tlc: mp 95–96°; ir 1730 cm^{-1} (C=O); nmr δ 8.09, 7.33 (4 H, two sets of d, J = 9 Hz, ArH), 3.83 (1 H, p, J = 7 Hz, CHSAr), 3.2–1.2 (m, 10 H, ring protons).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.53; H, 5.39; N, 5.24.

Reduction of 3-*endo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one (13n). The crude keto sulfide **13n** (70 mg, 0.25 mmol) dissolved in 3 ml of dry THF was added to a mixture of $NaBH_4$ (37.8 mg, 1 mmol) in 0.2 ml of MeOH in the cold. Stirring was continued at room temperature for 2 hr. Solvent was then removed, the residue was covered with ether, and excess $NaBH_4$ was destroyed with 1 *N* aqueous HCl. The ether layer was separated, and the aqueous phase was extracted several more times with ether. The combined ether fractions were dried and concentrated. The residue was chromatographed on a preparative tlc plate. The major yellow band followed by a minor yellow band were extruded and washed with $CHCl_3$. Evaporation of the solvent gave 40 mg from the major band and 6 mg from the minor band. The yield from tosylate **10x** to the hydroxy sulfides was 66%. The major product **3n** had the following characteristics: mp 115–117°; ir 3200 cm^{-1} (OH); nmr δ 8.15, 7.36 (4 H, 2 sets of d, J = 9 Hz, ArH), 4.35 (1 H, m, HCO), 3.57 (1 H, m, CHSAr), 2.8–1.0 (11 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.07; H, 6.19; N, 4.75.

The minor product **3x** had the following characteristics: mp 132°; ir 3280 cm^{-1} (OH); nmr δ 8.17, 7.36 (4 H, two sets of d, J = 9 Hz, ArH), 4.47 (1 H, p, J = 5 Hz, CHO), 3.58 (1 H, m, HCSAr), 3.0–0.8 (11 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.01; H, 6.19; N, 5.02.

3-*endo*-*p*-Nitrophenylthio-7-(*O*-methyl)oximinobicyclo[3.3.0]octane (14n). A mixture of 753 mg (2.7 mmol) of crude

keto sulfide **13n** and 226 mg (2.7 mmol) of *O*-methyl oxime hydrochloride in 15 ml of absolute EtOH and 15 ml of dry pyridine was refluxed overnight. The solvents were evaporated and the residue was extracted between 1 *N* aqueous HCl and ether. The ether wash was dried and concentrated and a residue weighing 575 mg was obtained. Part of the product was purified by preparative tlc, and a pure sample had the following characteristics: mp 78°; ir 1640 cm^{-1} (C=N); nmr δ 8.08, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 3.8 (3 H, s, OCH_3), 3.72 (1 H, m, CHSAr), 2.5 (8 H, m, ring protons), 1.45 (2 H, m, ring protons).

Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.79; H, 5.92; N, 9.15. Found: C, 58.92; H, 5.92; N, 9.12.

3-*endo*-*p*-Nitrophenylthio-7-*endo*-*N*-carbobenzyloxyaminobicyclo[3.3.0]octane (4n). The crude oximino sulfide **14n** (546.3 mg, 1.8 mmol) dissolved in 18 ml of dry THF was treated with 7.2 ml of a 1 *M* BH_3 in THF solution (7.2 mmol of BH_3) in the cold over N_2. After addition, the solution was refluxed for 2 hr and cooled, and excess BH_3 was destroyed with 2 ml of H_2O followed by 5.4 ml of 5% aqueous HCl solution. The mixture was heated to reflux for another hour, and the THF was removed by evaporation. The yellow residue was extracted with 170 ml of water and ether. The aqueous phase was covered with 130 ml of ether and made basic with 10.8 ml of 5% aqueous NaOH solution, and carbobenzyloxy chloride (7.2 mmol, 1.08 ml) was then added slowly to the mixture. Stirring was continued for 3 hr, and the phases were separated. The aqueous phase was extracted several times with ether, and the ethereal solutions were combined and washed with 1 *N* aqueous HCl solution. Finally, the ether phase was dried and concentrated. The residue was purified by trituration with petroleum ether, recrystallization from ether–petroleum ether mixture, and final purification by preparative tlc. A total of 398 mg of pure **4n** was obtained: mp 91–93°; ir 3400 (NH), 1709 cm^{-1} (C=O); nmr δ 8.09, 7.31 (4 H, two sets of d, J = 9 Hz, ArH), 7.32 (5 H, s, PhH), 5.1 (2 H, s, CH_2Ph), 4.87 (1 H, d, J = 7 Hz, NH), 4.4–3.3 (2 H, br m, HCN, HCSAr), 2.4 (6 H, m, ring protons), 1.47 (4 H, m, ring protons).

Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.33; H, 6.00; N, 6.85.

3-*exo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one Ethylene Ketal (12x). The same procedure for the preparation of ketal sulfide **12n** was employed. From 676.4 mg (2 mmol) of the tosylate **10n**, 682 mg of crude sulfide **12x** was obtained. A small quantity of **12x** purified by preparative tlc and then recrystallized from 95% ethanol gave the following characteristics: mp 120–122°; ir 1500, 1335 cm^{-1} (NO_2); nmr δ 8.10, 7.33 (4 H, two sets of d, J = 9 Hz, ArH) 3.96 (1 H, m, CHSAr), 3.89 (4 H, s, OCH_2CH_2O), 2.8 (2 H, m, ring protons), 2.3–1.4 (8 H, m, ring protons).

Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.81; H, 5.95; N, 4.35. Found: C, 59.81; H, 5.78; N, 4.29.

3-*exo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one (13x). The same procedure for the preparation of keto sulfide **13n** was used. The crude ketal sulfide **12x** from above (682 mg) gave 583 mg of crude keto sulfide **13x**. A sample of **13x** was purified by preparative tlc and recrystallization from ethanol and water: mp 98–100°; ir 1730 cm^{-1}; nmr δ 8.11, 7.33 (4 H, two sets of d, J = 9 Hz, ArH), 3.98 (1 H, p, J = 7 Hz, CHSAr), 3.0–1.6 (10 H, m, ring protons).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.68; H, 5.42; N, 4.86.

Reduction of Keto Sulfide 13x by $NaBH_4$. The keto sulfide **13x** (70 mg, 0.25 mmol) was reduced as described for the reduction of **13n** to give two products which were separated by preparative tlc. The major, fast-running material **5n** weighed 57 mg: mp 86–88°; ir 3500 cm^{-1} (OH); nmr δ 8.12, 7.35 (4 H, two sets of d, J = 9 Hz, ArH), 4.13 (2 H, two sets of overlapping p, HCO, HCSAr), 3.0–1.0 (11 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.26; H, 5.92; N, 4.75.

The slower moving, minor product **5x** weighed 12 mg: mp 83–85°; ir 3200 cm^{-1} (OH); nmr δ 8.1, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 4.45 (1 H, m, HCO), 3.73 (1 H, p, J = 7 Hz, CHSAr), 2.9 (2 H, m, ring protons), 2.0–1.0 (9 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.41; H, 6.37; N, 5.03.

3-*exo*-*p*-Nitrophenylthio-7-(*O*-methyl)oximinobicyclo[3.3.0]octane (14x). The crude keto sulfide **13x** (277 mg, 1.0 mmol) was treated with *O*-methyl oxime hydrochloride (91.9 mg, 1.1 mmol) in 5 ml each of pyridine and absolute ethanol as described for the preparation of **14n**. The product after work-up gave 250 mg of yellow solid. A pure sample was obtained by preparative tlc: mp 71–72°; ir 1640 cm^{-1} (weak C=N); nmr δ 8.09, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 3.83 (1 H, m, HCSAr), 3.8 (3 H, s, OCH_3), 3.0–1.8 (10 H, m, ring protons).

Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.79; H, 5.92; N, 9.15. Found: C, 59.09; H, 6.15; N, 8.96.

3-*exo*-*p*-Nitrophenylthio-7-*endo*-*N*-carbobenzyloxyaminobicyclo[3.3.0]octane (6n). The reduction of the oximino sulfide **14x** and formation of the carbobenzyloxy derivative of the amino sulfide were carried out in a similar fashion as in the preparation of **4n**. The crude **14x** (190 mg, 0.62 mmol) in 6 ml of THF was reduced with 2.48 ml of a 1 *M* solution of BH_3 in THF, while 37.2 μl (2.48 mmol) of CbzCl was used for derivatizing the amine. The product (147 mg) melted at 67–93°. A sample purified by preparative tlc and recrystallized from a petroleum ether–ether mixture melted at 92–94°: ir 3380 (NH), 1710 cm^{-1} (C=O); nmr δ 8.06, 7.32 (4 H, two sets of d, J = 9 Hz, ArH), 7.3 (5 H, s, PhH), 5.09 (2 H, s, CH_2Ph), 4.93 (1 H, d, J = 6 Hz, NH), 3.8 (2 H, m, HCN, HCSAr), 3.0–0.8 (10 H, m, ring protons).

Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.09; H, 6.08; N, 6.78.

3-*endo*-*p*-Nitrophenylthio-7-*endo*-*p*-toluenesulfonatobicyclo[3.3.0]octane (17). The hydroxy sulfide **3n** (150 mg, 0.536 mmol) was tosylated in the usual manner with 286 mg (1.5 mmol) of tosyl chloride in pyridine. The product consisted of 24 mg of unreacted hydroxy sulfide and 117 mg (60%) of tosylate **17** which was purified by preparative tlc: mp 98–100°; ir 1340, 1175 cm^{-1} (SO_2); nmr δ 8.07 (2 H, d, J = 9 Hz, ArH), 7.77 (2 H, d, J = 9 Hz, Ar'H), 7.3 (4 H, d, J = 9 Hz, ArH, Ar'H), 4.97 (1 H, p, J = 5 Hz, CHOTs), 3.5 (1 H, m, CHSAr), 2.9–1.1 (13 H, m, ring protons, plus s, $ArCH_3$).

Anal. Calcd for $C_{21}H_{23}NO_5S_2$: C, 58.19; H, 5.34; N, 3.23. Found: C, 57.99; H, 5.29; N, 3.29.

3-*endo*-*p*-Nitrophenylthio-7-*exo*-azidobicyclo[3.3.0]octane (18). The tosylate **17** (86.6 mg, 0.2 mmol) in 1 ml of dry HMPT was added to 65 mg (1 mmol) of NaN_3. The solution was stirred at ambient temperature for 2 hr. The entire mixture was chromatographed on a preparative plate, and the major yellow band extruded. The yellow material thus isolated weighed 52 mg (85.5%): mp 51–52°; ir 2100 cm^{-1} (N_3); nmr δ 8.05, 7.28 (4 H, two sets of d, J = 9 Hz, ArH), 4.01 (1 H, p, J = 6 Hz, HCN_3), 3.57 (1 H, septet, J = 5 Hz, HCSAr), 3.0–0.8 (10 H, m, ring protons).

Anal. Calcd for $C_{14}H_{16}N_4O_2S$: C, 55.24; H, 5.30; N, 18.41. Found: C, 55.37; H, 5.50; N, 18.15.

3-*endo*-*p*-Nitrophenylthio-7-*exo*-*N*-carbobenzyloxyaminobicyclo[3.3.0]octane (4x). The azido sulfide **18** (30.4 mg, 0.1 mmol) in 1 ml of THF was mixed with 0.4 ml of a 1 *M* solution of BH_3 in THF (0.4 mmol) in the cold over N_2. The solution was refluxed for 2.5 hr and cooled, and excess BH_3 was destroyed with 1 ml of H_2O followed by 0.4 ml of a 1 *N* aqueous HCl solution. THF was removed *in vacuo*, and the residue was dissolved in *ca.* 20 ml of H_2O, extracted with ether, and filtered. The filtrate was covered with 20 ml of ether and made basic with 0.8 ml of 1 *N* aqueous NaOH solution, and 60 μl (0.4 mmol) of CbzCl was then added. The biphasic mixture was stirred for another 2 hr and the phases were separated. The aqueous phase was extracted several times with ether, and the ethereal solutions were combined, dried, and concentrated. The residue was purified by preparative tlc. The product (25 mg, 61%) had the following properties: mp 116–118°; ir 3400 (NH), 1710 cm^{-1} (C=O); nmr δ 8.10 (2 H, d, J = 9 Hz, ArH), 7.33 (7 H, s overlapping with d, PhH and ArH), 5.1 (2 H, s, $PhCH_2$), 4.8 (d, J = 8 Hz, NH), 4.13 (1 H, m, CHN), 3.43 (1 H, m, CHSAr), 3.0–1.0 (10 H, m, ring protons).

Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.05; H, 6.06; N, 6.95.

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Registry No.—**3n**, 51716-27-9; **3x**, 51773-30-9; **4n**, 51716-28-0; **4x**, 51773-33-2; **5n**, 51773-34-3; **5x**, 51773-35-4; **6n**, 51773-36-5; **8**, 51716-62-2; 8 dione derivative, 51716-63-3; **9n**, 51716-64-4; **9x**, 51773-37-6; **10n**, 51716-65-5; **10x**, 51773-38-7; **11**, 51716-66-6; **12n**, 51716-67-7; **12x**, 51773-39-8; **13n**, 51716-68-8; **13x**, 51716-69-9; **14n**, 51716-70-2; **14x**, 51716-71-3; **17**, 51716-72-4; **18**, 51716-73-5; cyclopentenyl *p*-nitrophenyl sulfide, 51716-74-6; cyclopentanone, 120-

92-3; *p*-nitrobenzenethiol, 1849-36-1; tetra-*n*-butylammonium formate, 35733-58-5; tetra-*n*-butylammonium *p*-nitrobenzenethiolate, 20627-93-4; *O*-methyl oxime hydrochloride, 4229-44-1; carbobenzyloxy chloride, 501-53-1; *p*-toluenesulfonyl chloride, 98-59-9.

References and Notes

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Stereoselective Synthesis of 3-Exo-Substituted 2-*endo*-Acyl-5-norbornene Derivatives[1]

S. W. Baldwin* and J. C. Tomesch

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

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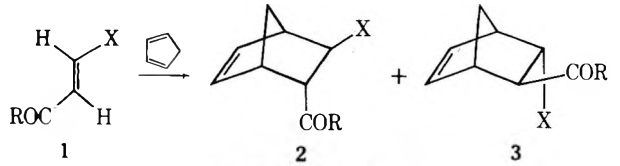
The stereoselective addition of a variety of nucleophiles (ROH, RSH) to several 2-acylnorbornadienes provides an efficient synthesis of the title compounds. The allyl ethers derived from the addition of allyl alcohol are stable to many synthetic transformations and readily liberate the 3-exo alcohol on reductive cleavage.

During the course of model studies for the synthesis of several tetracyclic sesquiterpenes,[2] we required an efficient preparation of various 3-exo-substituted 2-*endo*-acylnorbornenes (*e.g.*, **2**). In particular we had need of a substituent at C-3 which could be readily converted to an hydroxyl group but which would also survive further intended synthetic transformations. To this end we have investigated the reaction of cyclopentadiene with trans-β-substituted α,β-unsaturated carbonyl compounds and the addition of nucleophiles to 2-acylnorbornadienes. We have also determined that allyl ethers are effective as masked alcohols, thus satisfying our final criterion.

The results of the Diels–Alder reaction between trans-β-substituted α,β-unsaturated carbonyl compounds (**1**) and cyclopentadiene are summarized in Table I. As expected for an uncatalyzed reaction, the product with an endo acyl group was always predominant, the isomer ratios ranging from 2.6:1 to 5.6:1.[3-6] Predictably the addition of catalytic amounts of cupric[7] and stannic[8] salts led to significant increases in both the rate and stereoselectivity of the Diels–Alder reaction.[9] The rather low yields (not optimized) are apparently due to extensive polymerization of the diene and resultant difficulties in the isolation procedure. However, the high specificity of the reaction makes the catalyzed procedure preferable when isomerically pure adducts are desired.



1 2 3

a, R = H; X = $OCOCH_3$
b, R = H; X = $OCOC_6H_5$
c, R = CH_3; X = $OCOCH_3$
d, R = i-C_3H_7; X = $OCOCH_3$
e, R = OH; X = Cl
f, R = CH_3; X = OCH_3

Table I
Reaction of Cyclopentadiene with Several Acrylic Dienophiles (1)

Dienophile	Catalyst	Yield, %[a]	[2]:[3][b]
1a[c]		75	2.6:1
1b[c]		50	3:1
1c[d]		58	2.6:1
1d		67	3.5:1
1d	$SnCl_4$[e]	47	>15:1
1e[f]		87	5.6:1
1f		0	
1f	$Cu(BF_4)_2$[g]	11	>15:1
1f	$SnCl_4$	51	15:1

[a] Isolated yields, not optimized. [b] Reference 5. [c] Reference 20. [d] Reference 21. [e] Reference 9. [f] Reference 22. [g] Reference 8.

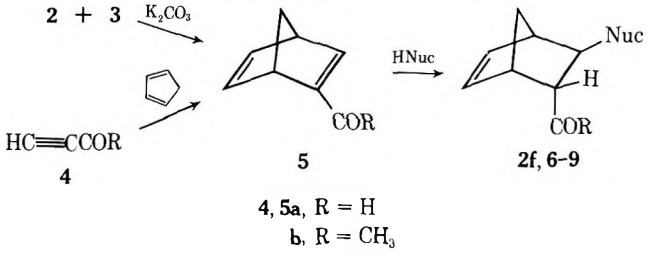
Although the acyl esters **2a–d** were thus available in quantity, they did not prove to be synthetically useful, since treatment with most basic reagents led to significant decomposition of starting material.[10] A more generally useful procedure was found to be the conjugate addition of nucleophiles to 2-acylnorbornadienes (**5**). For instance,

Table II
Reaction of Several 2-Acylnorbornadienes (5) with Nucleophiles

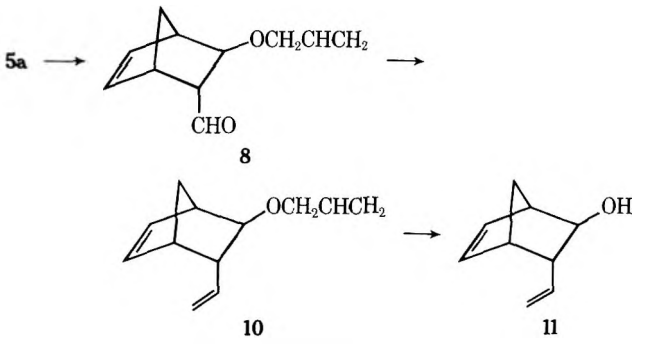
Electrophile	Source[a]	Nucleophile	Catalyst	Product	Yield,[b] %	Isomer[c] ratio
5a	A	CH_3OH[d]	K_2CO_3	**6**	35	8:1
5a	A	C_6H_5SH[e]	K_2CO_3	**7**	75	9:1
5a	B	$CH_2{=}CHCH_2OH$[f]	K_2CO_3	**8**	82	6:1
5b	A	CH_3OH	K_2CO_3	**2b**	77	10:1
5b	B	CH_3OH	p-TsOH	**2f**	65	11:1
5b	A	$CH_2{=}CHCH_2OH$	K_2CO_3	**9**	68	15:1

[a] Method A, treatment of a solution of **2** and **3** with K_2CO_3; method B, reaction of cyclopentadiene with alkynone **4**. [b] Isolated yields, not optimized. [c] The ratio of the major isomer to the sum of the minor isomers, determined by nmr spectroscopy as described in the text and ref 5. [d] Registry no., 67-56-1. [e] Registry no., 108-98-5. [f] Registry no., 107-18-6.

exposure of a mixture of acetates **2c** and **3c** to methanolic potassium carbonate afforded methyl ether **2f**, contaminated with only trace amounts of other isomers. That unsaturated ketone **5b** was intervening in an elimination–addition process was easily demonstrated by observing its build-up from the acetate mixture in a nonnucleophilic solvent (acetone) and then noting its behavior on treatment with methanol and a trace of potassium carbonate. In fact a variety of related dienones **5** could be either generated *in situ* by elimination of acetic acid from a mixture of the Diels–Alder adducts **2–3** (method A) or by cycloaddition of the appropriate alkynone with cyclopentadiene (method B).[11] In each case the product smoothly added a variety of nucleophiles as summarized in Table II. It is noteworthy that in the reported examples the isomer ratio was generally significantly greater than 6:1 in a process which resulted in the simultaneous generation of two asymmetric centers.[12] Although the synthetic logic of such an addition process to generate contiguous asymmetry has been previously demonstrated,[13] the consequences are of sufficient utility to be of interest. It is also worth noting that the related conjugate addition of diethyl malonate to 2-carbomethoxynorbornadiene has been reported to give analogous results[14] and that similar chemistry is observed in the bicyclo[2.2.2]octene series.[15] In each case the observed stereochemistry is presumably the consequence of initial attack of the nucleophile at the β carbon from the more accessible exo side of the norbornene ring followed by thermodynamic protonation of the resulting enolate.[16]



4, **5a**, R = H
b, R = CH_3



It was possible to apply this reaction to an efficient synthesis of the needed norbornene derivatives. Thus allyl alcohol added smoothly and stereoselectively to unsaturated aldehyde **5a**. Unlike the corresponding acetate (**2a**), the resulting allyl ether group of **8** was stable to basic reaction conditions typified by Wolff–Kishner reduction, Grignard addition, and Wittig reaction (**8** → **10**). Furthermore the free alcohol was readily liberated by the action of sodium in liquid ammonia,[17] effectively satisfying the remaining criterion established at the outset of the study. Allyl ethers have been used only sparingly as masked alcohols, although the analogy with the chemically similar benzyl group is clear.[18] The above reduction procedure for the removal of the allyl ether moiety is complementary to the recently reported hydrolytic cleavage of the same group employing rhodium(I)-catalyzed isomerization of the double bond and subsequent hydrolysis of the enol ether.[19] Taken together allyl ethers became both an effective hydroxyl masking group as well as a convenient means for effecting the addition of "protected" water to suitably activated olefins.

In conclusion we have determined that 3-exo-substituted 2-*endo*-acyl-5-norborenes can be conveniently and stereoselectively prepared by the addition of a variety of nucleophiles to 2-acylnorbornadienes and further that the allyl ether moiety is a versatile hydroxyl masking group.

Experimental Section

Ir spectra were recorded on Perkin-Elmer 137 and 237 spectrophotometers; nmr spectra were determined on either a Varian A-60 spectrometer or a Jeol MH-100 spectrometer with TMS as an internal standard, and are recorded in Table III. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., or M-H-W Laboratories, Garden City, Mich. Yields have not been optimized. The procedures detailed below are representative of the reaction in general and are not repeated for additional examples of a particular reaction type.[26]

Dienophiles 1 and 4. *trans*-3-Acetoxypropenal (**1a**),[20] *trans*-3-benzooxypropenal (**1b**),[20] and *trans*-4-acetoxy-3-buten-2-one (**1c**)[21] were prepared as described in the literature. *trans*-3-Chloroacrylic acid (**1e**) and *trans*-4-methoxy-3-buten-2-one (**1f**) were purchased from Aldrich Chemical Co. and used without further purification. The preparation of propynal[23] (**4a**) is described in the literature, while 1-butyn-3-one (**4b**) was purchased from Aldrich Chemical Co. and used as received.

***trans*-5-Acetoxy-2-methyl-4-penten-3-one (1d).** In a 2-l. flask equipped with an overhead stirrer and an N_2 inlet were placed 20.6 g (0.24 mol) of 3-methylbutanone, 5.7 g (0.25 mol) of sodium metal, 21.6 g (0.25 mol) of freshly distilled ethyl formate, 550 ml of dry ether, and 1.5 ml of ethyl alcohol and the resulting mixture was stirred at 0° under N_2 for 20 hr. The precipitated salt was collected by filtration, washed with 100 ml of dry ether, and dried *in vacuo* to afford 26 g (77%) of light yellow solid. After suspension of the above salt (26 g, 0.19 mol) in ether at 0°, 13.3 g (0.17 mol) of acetyl chloride was added dropwise and the reaction mixture was stirred at 0° under N_2 for 2 hr. Filtration and concentration of the filtrate afforded 25 g of mobile liquid which was distilled to afford 17.5 g (45% from ketone) of clear, colorless liquid, bp 53–55° (0.25 mm), that solidified on standing at −10°, ir (CCl_4) 1774 (acetate C=O), 1675 cm^{-1} (acetyl C=O).

In some preparations, when the crude product was a mixture of cis and trans isomer by nmr analysis, it was necessary to stir a benzene solution of the crude material with a trace of *p*-toluene-

Table III
Analytical Data for Selected New Compounds[a]

Compd	Bp, °C (mm)	Nmr,[b] δ
1d	53.5 (0.25)	1.08 [d, J = 7 Hz, 6 H, $-HC(CH_3)_2$], 2.18 (s, 3 H, $-COCH_3$), 2.72 [septet J = 7 Hz, 1 H $-CH(CH_3)_2$], 6.02 (d, J = 13 Hz 1 H, $-COCH=CH-$), 8.16 (d, J = 13 Hz, 1 H, $-COCH=CH-$)[c]
2a	64.5–65 (0.05)	1.48 and 1.74 (broad, 2 H, C-7 H), 2.02 (s, 3 H, $-COCH_3$), 2.70 (broad, 1 H, C-2 H), 2.98 and 3.13 (broad, 2 H, C-1 H and C-4 H), 4.73 (broad, 1 H, C-3 H), 6.19 (m, 2 H, vinyl H) 9.60 (d, J = 1.5 Hz, 1 H, $-CHO$)[c]
2c	89–91.5 (0.13)	1.70 (m, 2 H, C-7 H), 1.99 (s, 3 H, $-COCH_3$), 2.08 (s, 3 H, $-COCH_3$), 2.81 (t, J = 3 Hz, 1 H, C-2 H), 2.88 and 3.11 (broad, 2 H, C-1 H and C-4 H), 4.74 (broad, 1 H, C-3 H), 6.07 ($W_{1/2}$ = 4.5 Hz, 2 H, vinyl H)[c]
2d	95 (0.08)[d]	1.05 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.71 ($W_{1/2}$ = 7 Hz, 2 H, C-7 H), 1.99 (s, 3 H, $-COCH_3$), 2.66 [septet, J = 7 Hz, 1 H, $-CH(CH_3)_2$], 2.90 (m, 2 H, C-1 and C-4 H), 2.96 (t, J = 3 Hz, 1 H, C-2 H), 4.70 ($W_{1/2}$ = 5 Hz, 1 H, C-3 H), 6.06 ($W_{1/2}$ = 5 Hz, 2 H, C-5 and C-6 H)[c]
2f	70 (4)[d]	1.57 (m, 1 H, syn C-7 H), 1.76 (m, 1 H, anti C-7 H), 2.04 (s, 3 H, $-COCH_3$), 2.59 (t, J = 3 Hz, 1 H, C-2 H), 2.86 and 3.02 ($W_{1/2}$ = 8 Hz, 2 H, C-1 and C-4 H), 3.51 ($W_{1/2}$ = 6 Hz, 1 H, C-3 H), 3.26 (s, 3 H, $-OCH_3$), 5.99 ($W_{1/2}$ = 19 Hz, 2 H, vinyl H)[e]
6	90 (22)[d]	1.73 ($W_{1/2}$ = 10 Hz, 2 H, C-7 H), 2.58 ($W_{1/2}$ = 5 Hz, 1 H, C-2 H), 3.05 ($W_{1/2}$ = 18 Hz, 2 H, C-1 and C-4 H), 3.30 (s, 3 H, $-OCH_3$), 3.50 ($W_{1/2}$ = 5.5 Hz, 1 H, C-3 H), 6.15 (m, $W_{1/2}$ = 13 Hz, 2 H, vinyl H), 9.53 (d, J = 1.5 Hz, 1 H, $-CHO$)[c]
7	125–126.5 (0.06)	1.52 (m, 1 H, C-7 syn H), 1.86 (m, 1 H, C-7 anti H), 2.80 ($W_{1/2}$ = 12 Hz, 1 H, C-2 H), 3.12 ($W_{1/2}$ = 10 Hz, 2 H, C-1 and C-4 H), 3.38 (m, 1 H, C-3 H), 6.18 ($W_{1/2}$ = 20 Hz, 2 H, vinyl H), 7.25 (m, 5 H, aromatic H), 9.42 (d, J = 1.5 Hz, 1 H, $-CHO$)[c]
8	77–80 (0.05)	1.65 (m, 1 H, C-7 syn H), 1.90 (, 1 H, C-7 anti H), 2.65 (m, $W_{1/2}$ = 5.5 Hz, 1 H, C-2 H), 2.95 and 3.05 (broad, 2 H, C-1 and C-4 H), 3.65 ($W_{1/2}$ = 5 Hz, 1 H, C-3 H), 4.00 (m, 2 H, $-OCH_2CH=CH_2$), 5.21 (m, 2 H, $-CH=CH_2$), 5.93 (m, 1 H, $-CH=CH_2$), 6.14 (m, C-5 and C-6 H), 9.25 (d, J = 1.5 Hz, $-CHO$)[c]
9	90 (0.02)	1.70 (m, 2 H, C-7 H), 2.07 (s, 3 H, $-COCH_3$), 2.64 (t, 1 H, C-2 H), 2.88 and 3.05 (broad, 2 H, C-1 and C-4 H), 3.70 ($W_{1/2}$ = 5 Hz, 1 H, C-3 H), 3.99 (d, J = 5 Hz, 2 H, $-OCH_2CH=CH_2$), 5.17 (m, 2 H, $-CH=CH_2$), 5.71 (m, 1 H, $-CH=CH_2$), 6.04 ($W_{1/2}$ = 7 Hz, 2 H, C-5 and C-6 H)[c]
10	33 (0.06)	1.59 (m, 1 H, syn C-7 H), 1.84 (m, 1 H, anti C-7 H), 2.44 (m, 1 H, C-2 H), 2.85 ($W_{1/2}$ = 8 Hz, 2 H, C-1 and C-4 H), 3.18 ($W_{1/2}$ = 6 Hz, 1 H, C-3 H), 3.97 (m, 2 H, $-OCH_2CH=CH_2$), 5.00 (m, 4 H, $-CH=CH_2$), 5.45 (m, 1 H, $-CHCH=CH_2$), 5.71 (m, 1 H, $-OCH_2CH=CH_2$), 6.09 ($W_{1/2}$ = 18 Hz, 2 H, C-5 and C-6 H)[e]
11	55 (0.03)	1.58 (m, 1 H, syn C-7 H), 1.75 (m, 1 H, anti C-7 H), 2.31 ($W_{1/2}$ = 7 Hz, 1 H, C-2 H), 2.70 ($W_{1/2}$ = 7 Hz, 2 H, C-1 and C-4 H), 3.46 ($W_{1/2}$ = 5 Hz, 1 H, C-3 H), 4.11 (1 H, $-OH$), 5.02 (m, 2 H, $-CH=CH_2$), 5.54 (m, 1 H, $-CH=CH_2$), 6.11 ($W_{1/2}$ = 10 Hz, 2 H, C-5 and C-6 H)[e]

[a] Reference 26. [b] Reference 25. [c] 60 MHz. [d] Kugelrohr. [e] 100 MHz.

sulfonic acid for several hours prior to distillation to obtain the pure trans isomer.

Cycloadditions of Acrylic Dienophiles (1) with Cyclopentadiene. Uncatalyzed. The uncatalyzed reactions between cyclopentadiene and dienophiles 1 were performed using the diene as solvent at 35° for 10–50 hr. The disappearance of 1 could be conveniently monitored by glc, except for acid **1e**. When the reaction was judged to be complete, the volatile material was removed *in vacuo* and the ratio of products was determined by analysis of the nmr spectrum of the crude material (Table I). The product (2 and 3) was then separated from polymeric material by distillation. Isomer 2 could be separated from 3 by a combination of chromatographic techniques, although usually mixtures were employed in succeeding reactions. In general it was not possible to isolate the minor adduct (3) in a pure state.

2-*endo*-Acetyl-3-*exo*-acetoxybicyclo[2.2.1]hept-5-ene (2c). To a 500-ml round-bottom flask containing 113 g (0.89 mol) of dienophile **1c** was added 168 g (210 ml, 2.54 mol) of freshly cracked cyclopentadiene and the resulting solution was allowed to stir at room temperature under an N_2 atmosphere for 43 hr, at which time the reaction was shown to be nearly complete by gas chromatography. Removal of the volatile material (0.1 mm, bath 60°) resulted in 99.1 g of oily residue which was shown to be a mixture of the two trans cycloadducts **2c** and **3c** (ratio 2.6:1) and a small amount of unreacted dienophile by nmr.[5] Pure **2c** (27.3 g, 15.8%) was precipitated from a cold ether–petroleum ether solution of the residue, and then distilled to afford a colorless oil, bp 89–91.5° (0.13 mm). In general it was not feasible to separate large amounts of 2 and 3 by the usual techniques. Rather the distilled mixture of isomers was carried on through succeeding steps.

Catalyzed. 2-*endo*-Acetyl-3-*exo*-methoxybicyclo[2.2.1]hept-5-ene (2f). To a stirred solution of 0.71 g (0.003 mol) of cupric tetrafluoroborate[8] in 30 ml of acetonitrile in a 50-ml flask, cooled to 0° and under N_2 atmosphere, was added 1.00 g (0.01 mol) of dienophile **1f** in 10 ml of acetonitrile. After several minutes 6.61 g (0.10 mol, 8 ml) of cyclopentadiene was added and the gradual deposit of insoluble material was observed. Within 15 min the contents of the flask could no longer be stirred, and the flask was allowed to warm to room temperature, where it remained for 15 hr. The reaction mixture was then poured into a separatory funnel containing a solution of 0.03 mol of sodium tartrate and brine. Extraction of the aqueous layer with ether (3 × 50 ml) followed by drying of the combined organics ($MgSO_4$) and concentration afforded a brown oil which by nmr[5] contained the single isomer **2f** and some polymeric impurities. Distillation in the Kugelrohr fashion (70°, 4 mm) yielded 0.18 g (11% yield) of pure **2f**. The yields of other adducts by this procedure usually were higher (40%) but did not equal those of the uncatalyzed reactions. Other solvents tried included acetone and methanol, but in these solvents there was no apparent catalysis.

Cycloaddition of Alkynones (4) with Cyclopentadiene. 2-Formylbicyclo[2.2.1]hepta-2,5-diene (5a). In a 300-ml round-bottom flask was placed 43.3 g (54 ml, 0.66 mol) of freshly cracked cyclopentadiene and 150 ml of petroleum ether (bp 30–60°) and the resulting solution was cooled to 0° with stirring under an N_2 atmosphere. To the above was added over 30 min 32.1 g (0.60 mol) of propynal and the resulting solution was stirred at 0° for 3 hr and an additional 16 hr at room temperature. Removal of volatile material on a rotary evaporator and distillation of the residue (6-in. Vigreux column) afforded 39.5 g (55%) of pure adduct, bp 86–87.5° (27 mm) [lit.[11a] bp 80° (20 mm)]. In other runs the yields ranged from 40 to 67%.

Addition of Nucleophiles to 5. A. 2-*endo*-Acetyl-3-*exo*-methoxybicyclo[2.2.1]hept-5-ene (2f). A solution of 0.84 g (0.043 mol) of a mixture of acetates **2c** and **3c** (1.8:1), 1.38 g (10 mmol) of anhydrous K_2CO_3, and 20 ml of reagent grade methanol was stirred at room temperature under a nitrogen atmosphere for 30 min. The mixture was filtered and concentrated at reduced pressure, diluted with ether and filtered, and finally concentrated to give 0.58 g of crude product composed of essentially the single iso-

mer **2f** by nmr.[5] Distillation in the Kugelrohr fashion (70°, 4 mm) afforded 0.55 g (77%) of a clear, mobile liquid identical spectroscopically with that prepared by the cycloaddition.

B. 2-*endo*-Formyl-3-*exo*-allyloxybicyclo[2.2.1]hept-5-ene (8). In a flask containing 56.9 g (0.47 mol) of diene **5a** and cooled in an ice bath was added 200 ml of allyl alcohol and 2.3 g (0.017 mol) of anhydrous K_2CO_3. After stirring for 30 min under an N_2 atmosphere, the mixture was filtered, concentrated at reduced pressure, diluted with ether, refiltered, and concentrated to give crude allyl ether 8. Analysis by nmr[5] indicated the presence of three isomers (one major). Distillation of the crude product (6-in. Vigreux column) afforded 69.3 g (82%) of colorless product, bp 80–85° (0.05 mm).

2-*endo*-Vinyl-3-*exo*-allyloxybicyclo[2.2.1]hept-5-ene (10). According to the procedure of Hauser,[24] 16.35 g (0.05 mol) of methyltriphenylphosphonium bromide was placed in a 250-ml, three-neck flask equipped with a nitrogen inlet, addition funnel, and magnetic stirrer. The flask was alternately evacuated and filled with nitrogen (three times) and then 120 ml of dry THF was added and the resulting solution was stirred while 20.4 ml (0.045 mol) of 2.2 *M* butyllithium was added over 20 min. After the bright yellow slurry was stirred at room temperature for 20 min followed by cooling to −20°, 4.45 g (0.025 mol) of aldehyde 8 in 20 ml of dry THF was added over 10 min. The temperature was maintained at −20° for another 20 min and then allowed to warm to 5°, at which point 50 ml of water was added. The aqueous layer was extracted with hexane (2 × 100 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated to give an orange oil which was distilled (short path) to afford 2.0 g (45.5%, not optimized) of clear oil, bp 33–34.5° (0.06 mm).

2-*endo*-Vinyl-3-*exo*-hydroxybicyclo[2.2.2]hept-5-ene (11). In a 100-ml, three-neck, round-bottom flask equipped with a magnetic stirrer and a Dry Ice condenser and protected from atmospheric moisture by a drying tube was placed 1.61 g (0.092 mol) of allyl ether **10** and 60 ml of NH_3. Sodium (0.425 g, 0.018 mol) was added in small pieces over 20 min, plus a small additional amount until the blue color persisted. After stirring for an additional 15 min solid NH_4Cl was added to discharge the blue color and the NH_3 was allowed to evaporate. Water (20 ml) was added and the reaction mixture was extracted with ether (3 × 75 ml), dried ($MgSO_4$), and concentrated to give a residual oil which was distilled in the Kugelrohr manner (55°, 0.03 mm) to give 0.92 g (73.5%) of homogeneous alcohol **11**.

Registry No.—**1a**, 51731-22-7; **1c**, 51731-15-8; **1d**, 51731-16-9; **1f**, 51731-17-0; **2a**, 51731-18-1; **2c**, 51731-19-2; **2d**, 51731-20-5; **2f**, 51731-21-6; **3c**, 51773-70-7; **4a**, 624-67-9; **4b**, 1423-60-5; **5a**, 5212-50-0; **5b**, 38739-91-2; **6**, 51731-23-8; **7**, 51731-24-9; **8**, 51731-25-0; **9**, 51731-26-1; **10**, 51731-27-2; **11**, 51731-28-3; cyclopentadiene, 542-92-7; 3-methylbutanone, 563-80-4; acetyl chloride, 75-36-5.

References and Notes

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work. (b) Portions of this work were reported at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1–5, 1974.

(2) The sesquiterpenes of particular interest are (a) cyclosativene, L. Smedman and E. Zavarin, *Tetrahedron Lett.*, 3833 (1968); (b) longicyclene, U. R. Nayak and S. Dev., *ibid.*, 243 (1963); and (c) cyclocopacamphene, F. Kido, R. Sakuma, H. Uda, and A. Yoshikoshi, *ibid.*, 3169 (1969) (each of these compounds has been previously synthesized); (d) cyclosativene, J. E. McMurry, *ibid.*, 55 (1969); (e) longicyclene, S. C. Welch and R. L. Walters, *Syn. Commun.*, **3**, 15 (1973); and (f) cyclocopacamphene, E. Piers, R. W. Britton, R. J. Keziere, and R. D. Smillie, *Can. J. Chem.*, **49**, 2623 (1971). A fourth tetracyclic sequiterpene, cycloseychellene, has recently appeared: S. J. Turhune, J. W. Hogg, and B. M. Lawrence, *Tetrahedron Lett.*, 4705 (1973).

(3) We have found that the ratio of the two products was only modestly affected by changes in solvent. Thus the ratio of **2c**:**3c** changed from 2.6:1 to 3.5:1 in going from neat cyclopentadiene to acetonitrile. The ratio in methanol was 6:1; but in general the dienophiles (*e.g.*, **1**) reacted with hydroxylic solvents at a rate faster than they underwent cycloaddition.

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(5) The relative amounts of the two isomers were determined by integration of the nmr absorptions for the proton at C-3 in the crude reaction mixture while the structural assignments were made by considering the chemical shift and peak shape of the C-2 and C-3 proton absorptions. In general the signal for the endo C-3 proton of isomer **2** occurs at higher field than that for the exo C-3 proton of isomer **3** (δ 5.08 for **2b**, 5.62 for **3b**) and is less well resolved. The exo C-2 proton signal for isomer **2** occurs at lower field than that for the endo C-2 proton of **3** (δ 2.90 for **2b**, 2.32 for **3b**).

(6) Further confirmation of the assigned structures was gained by catalytic hydrogenation of the pure isomers. In compound **2d** the absorption for the C-3 proton moved from δ 4.67 to 4.70 ($\Delta\delta$ +0.03), while the same absorption for isomer **3d** changed from δ 5.15 to 4.91 ($\Delta\delta$ −0.24). The directions and magnitudes of these shifts are in accord with published values: W. C. Wong and C. C. Lee, *Can. J. Chem.*, **42**, 1245 (1964).

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(26) All new compounds gave satisfactory (±0.25%) combustion analyses.

Homolytic Aromatic Cyclohexylation. II. The Role of π-Complex Formation[1] and Competitions for Cyclohexyl Radical

J. Reid Shelton* and Arthur L. Lipman, Jr.

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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A study of the products resulting from the reactions of cyclohexyl radicals with halogenated aromatics has been conducted, and partial rate factors and relative reactivities determined. Thermolysis at 90° of di-*tert*-butyl peroxide in excess cyclohexane and mixtures of the dihaloaromatic and benzene resulted in these values: o-$C_6H_4Br_2$ f_x = 68, f_o = 31, f_m = 6.8, k_{rel} = 35; *o*-$C_6H_4Cl_2$ f_x = 15, f_o = 16, f_m = 5.2, k_{rel} = 12; *p*-$C_6H_4Br_2$ f_x = 13, f_o = 31, k_{rel} = 25; *p*-$C_6H_4Cl_2$ f_x = 7.5, f_o = 21, k_{rel} = 17. Thermolysis in excess aromatic gave the following ones: *o*-$C_6H_4Br_2$ f_x = 33, f_o = 18, f_m = 5.0, k_{rel} = 19; o-$C_6H_4Cl_2$ f_x = 6.7, f_o = 8.4, f_m = 3.4, k_{rel} = 6.1; *p*-$C_6H_4Br_2$ f_x = 6.8, f_o = 18, k_{rel} = 14; *p*-$C_6H_4Cl_2$ f_x = 3.5, f_o = 11, k_{rel} = 8.7. The marked solvent effect observed in the more polar aromatic media suggested reversible formation of a π complex between cyclohexyl radical and the aromatic. Rearrangement of the π complex to a σ complex would then be the rate- and product-determining step in the homolytic cyclohexylation of aromatics. Three trends revealed by the partial rate factors and relative rates are the activation of halogen ortho to another halogen toward displacement, the enhanced reactivity of the dihaloaromatic relative to that of benzene, and the activation of hydrogen ortho to a halogen toward displacement by cyclohexyl radical. The formation of bicyclohexyl, cyclohexanol, cyclohexanone, and *tert*-butyl cyclohexyl ethers in the reaction mixture demonstrate the important competing reactions for cyclohexyl radical of combination, interaction with oxygen, and the cross combination with *tert*-butoxy radicals.

Previous studies in our laboratories[2-4] have shown that cyclohexyl radicals, generated by either photolysis or thermolysis at 105° of di-*tert*-butyl peroxide (DTBP) in cyclohexane and an aromatic, can effect aromatic substitution. The cyclohexyl radical was found to be more selective than phenyl radical in reactions with aromatic compounds, as evidenced by Hammett ρ values of +1.1 for cyclohexylation[2] as compared to +0.05 for phenylation.[5] The observation that the amount of homolytic aromatic cyclohexylation was increased by the presence of electron-withdrawing substituents on the ring and decreased by electron-donating substituents suggested that cyclohexyl radical is "nucleophilic" in its reaction with aromatics.

Appreciable displacement of halogen from mixed dihalobenzenes occurred, with halogen ortho to another halogen being especially reactive toward displacement by cyclohexyl radicals. The order of halogen reactivity observed in homolytic cyclohexylation of selected mixed dihalobenzenes was F > I > Br > Cl[3] as compared to F > Cl ~ Br ~ I found for nucleophilic aromatic substitution.[6]

The initial study of the cyclohexylation of mixed dihalobenzenes concentrated on the products from halogen displacement. It was felt that a more detailed study of the reaction system was needed to determine the fate of the displaced halogen, to evaluate both intermolecular and intramolecular competition for cyclohexyl radicals in aromatic substitution, and to determine the nature and extent of other reactions which might compete for cyclohexyl radical to form additional products.

Homolytic cyclohexylation of o- and *p*-dichlorobenzene and *o*- and *p*-dibromobenzene in competition with benzene was chosen for this study, since the simple dihalobenzenes give fewer hydrogen displacement products than the corresponding mixed dihalobenzenes. Thermolysis of DTBP at 90° in cyclohexane and a mixture of the dihaloaromatic and benzene served to elucidate both intermolecular and intramolecular competition data.

Although much of the previous work[2,3] was done using excess aromatic in the reaction mixture, it was felt that excess cyclohexane should be used in the competition studies to minimize perturbation of the reaction medium as the aromatic species was varied. However, for comparison with previous results the reactions were also run in excess aromatic. The reaction products were analyzed directly by glpc.

Table I
Partial Rate Factors for Homolytic Cyclohexylation of Some Dihaloaromatics

Aromatic	Initial C_6H_{12}/aromatic	k_{rel}	f_x	f_o	f_m
o-$C_6H_4Cl_2$	5.0[a]	12	15	16	5.2
	0.5[b]	6.1	6.7	8.4	3.4
o-$C_6H_4Br_2$	5.0[c]	35	68	31	6.8
	0.5	19	33	18	5.0
p-$C_6H_4Cl_2$	5.0	17	7.5	21	
	0.5	8.7	3.5	11	
p-$C_6H_4Br_2$	5.0	25	13	31	
	0.5	14	6.8	18	

[a] Average of five separate reactions with varying amounts of benzene and *o*-dichlorobenzene. [b] Average of three reactions with varying amounts of benzene and o-dichlorobenzene. [c] Average of two chromatograph runs under different temperature conditions.

Results and Discussion

Part I. Solvent Effect. Partial rate factors calculated for the homolytic cyclohexylation of *o*- and *p*-dichlorobenzene and *o*- and *p*-dibromobenzene in excess cyclohexane, and in excess total aromatic, are presented in Table I. The accuracy of these data is limited by the chromatographic integration techniques used. Agreement between the two methods of manual integration employed was well within 5% of the peak area.

The most dramatic trend observed in Table I is the decrease in both intramolecular and intermolecular selectivity of the reaction when the nature of the medium is changed from excess cyclohexane to an excess of aromatics. The excess-aromatic medium has more dipolar character than the excess-aliphatic system, so that the selectivity of aromatic substitution is decreasing with an increase in the dipolar nature of the reaction system. This observation is consistent with some recent work by Davis and Ahmed in which they found a decrease in the 1-/2-selectivity of homolytic methylation of naphthalene as the solvent dielectric constant increased.[7] They argue that this implies some contribution of a charge-transfer inter-

Table II
Effect of Changing the Aromatic on the Selectivity of Homolytic Cyclohexylation

Initial C_6H_6/ o-$C_6H_4Cl_2$	k_{rel}	f_{Cl}	$f_{H\text{-}o}$	$f_{H\text{-}m}$
9.0	10	10	16	5
2.3	8	9	11	4
1.0	5	5	6	3
0.4	6	6	8	3

Table III
Competition for Cyclohexyl Radicals in Homolytic Cyclohexylation of Dihaloaromatics at 90°

Dihalobenzene	Initial C_6H_{12}/ aromatic	Aromatic substitution %	Aromatic substitution Mol × 10^{-4}	Combination %	Combination Mol × 10^{-4}
o-$C_6H_4Cl_2$	5.0	25	5.5	14	3.0
	0.5	46	10	1.9	0.14
p-$C_6H_4Cl_2$	5.0	44	6.0		
	0.5	45	10		
o-$C_6H_4Br_2$	5.0	20	3.3	26	4.2
	0.5	38	3.1	1.4	0.11
p-$C_6H_4Br_2$	5.0	43	11	0.9	0.23
	0.5	46	15	0.5	0.15

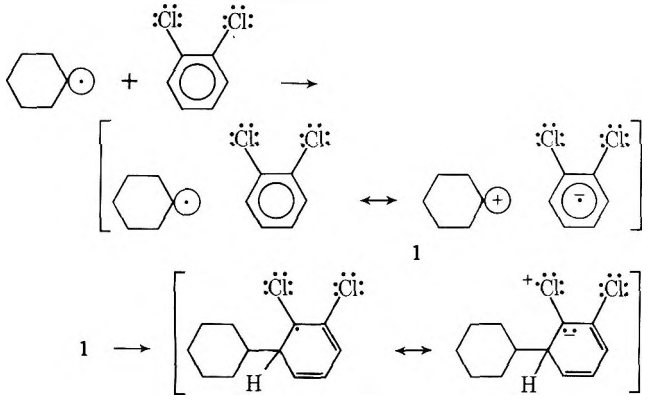
[a] Based on the total cyclohexyl reaction products found assuming that two cyclohexyl radicals are necessary to produce an aromatic substitution product and two cyclohexyl radicals are necessary for combination.

action in the transition state leading to formation of the σ complex, and stabilization of this transition state by more polar solvent would lower the activation energy for the process and cause the transition state to occur earlier along the reaction path, resulting in a decrease in selectivity.

Table II shows the results of varying the ratio of benzene to o-dichlorobenzene in a homolytic cyclohexylation in which the aromatics are in excess. The decrease in selectivity of the reaction as the amount of o-dichlorobenzene is increased is consistent with the results of Davis and Ahmed, since the dielectric constant of o-dichlorobenzene is 9.9 at 25° as compared to 2.3 for benzene.[8]

The nature of this charge transfer interaction may be the reversible formation of a π complex by donation of the odd electron of the cyclohexyl radical to the lowest antibonding π orbital of the aromatic as shown in Chart I. Such a donation would be a "nucleophilic" interaction by the cyclohexyl radical and would be aided by the presence of electron-withdrawing substituents on the ring. The rearrangement of this π complex to a σ complex would be the rate-determining and product-determining step in the aromatic substitution process.

Chart I
Formation of the π and σ Complexes for Homolytic Aromatic Cycloexylation

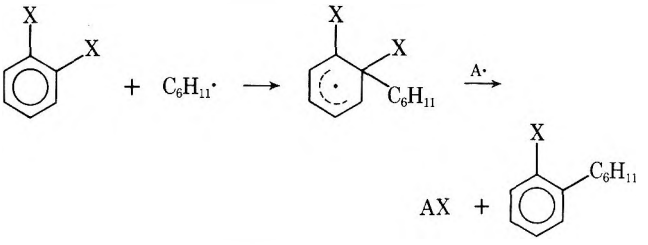


Additional evidence for π-complex formation can be found from the data in Table III. On the basis of relative rate data and partial rate factors (Table I), o-dibromobenzene is the most reactive of the aromatics toward homolytic cyclohexylation. However, the percentage of aromatic substitution for o-dibromobenzene in excess cyclohexane is much lower than the percentage for p-dibromobenzene, and for p-dichlorobenzene in the same system, as well as being much lower than for o-dibromobenzene in the excess aromatic system. Concurrently, there is a tremendous increase in the amount of bicyclohexyl formation from combination of two cyclohexyl radicals.

Suppression of the rates of combination of cyclohexyl radicals and isopropyl radicals in benzene as compared to the rates in cyclohexane has been used as evidence by Burkhart for the formation of a π complex between alkyl radical and benzene.[9] Rand and Strong uncovered direct, spectral evidence for the existence of a π complex between iodine atoms and benzene.[10] There is also a great deal of evidence available from the efforts of several groups for the effects of aromatic solvents on radical reactions which implicates the existence of π-complexed radicals.[11]

Our previous study of halogen displacement revealed that fluorine was the most readily displaced of the halogens and this evidence has been used in support of an addition-elimination mechanism shown in Chart II for the

Chart II
Addition-Elimination Mechanism for Halogen Displacement by Cyclohexyl Radical



free-radical cyclohexylation of the dihaloaromatics, in which the slow step is formation of the intermediate cyclohexadienyl radical. The evidence presented above suggests that σ-complex formation is preceded by reversible π-complex formation, and that the slow step of the reaction is rearrangement of the π complex to a σ complex. The position of the transition state for this rearrangement is determined by the dipolar nature of the medium. According to the Hammond postulate,[12] in a more polar reaction system the transition state resembles the π complex more than the σ complex and bond making has not occurred to an appreciable extent, resulting in a loss in selectivity, but a greater amount of aromatic substitution. In the less polar reaction medium the transition state resembles the σ complex and bond making is more advanced, resulting in a higher energy of activation and a greater selectivity of the reaction as illustrated in Figure 1.

Part II. Competitions for Cyclohexyl Radical. The data in Table I also reveal three interesting characteristics of the homolytic cyclohexylation of the simple dihalobenzenes. First, in agreement with the preliminary study,[3] halogen ortho to another halogen is activated toward displacement by cyclohexyl radical. Second, the dihaloaromatics are much more reactive than benzene, with all positions being activated to varying degrees toward displacement by cyclohexyl radicals. Third, in the o-dihalobenzenes, the hydrogen which is ortho to a halogen is much more reactive toward displacement than hydrogen which is meta to the nearest halogen.

Table IV
Competition for Cyclohexyl Radicals

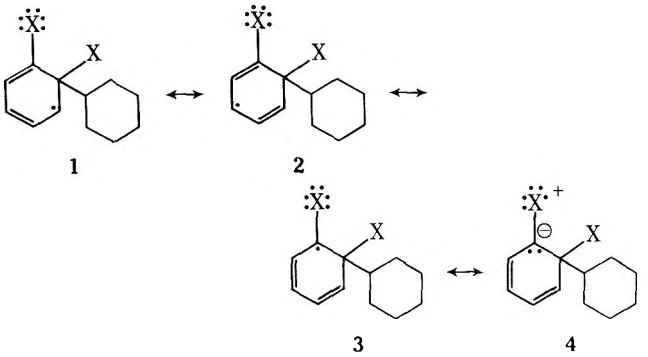
Aromatic substrate	Aromatic substitution %	Aromatic substitution Mol × 10^{-4}	Combination %	Combination Mol × 10^{-4}	Oxygenated products %	Oxygenated products Mol × 10^{-4}
o-$Cl_2C_6H_4$	24	5.5	16	3.8	15	3.6
o-$Br_2C_6H_4$	20	3.0	26	4.2	7	1.0
p-$Cl_2C_6H_4$	44	6.0			10	1.4
p-$Br_2C_6H_4$	43	11.0	0.9	0.2	3.5	0.9

Table V
Distribution of Oxygenated Products

Aromatic substrate	$C_6H_{10}O$-*t*-Bu %	$C_6H_{10}O$-*t*-Bu Mol × 10^{-4}	$C_6H_{10}O$ %	$C_6H_{10}O$ Mol × 10^{-4}	$C_6H_{11}OH$ %	$C_6H_{11}OH$ Mol × 10^{-4}
o-$Cl_2C_6H_4$	3	0.1	42	1.5	55	2.0
o-$Br_2C_6H_4$	1	0.01	50	0.5	50	0.5
p-$Cl_2C_6H_4$	14	0.2	50	0.7	36	0.5
p-$Br_2C_6H_4$	22	0.2	56	0.5	22	0.2

The activation of halogen toward displacement and the enhanced reactivity of the dihaloaromatics relative to that of benzene can be explained for the most part on the basis of stabilization of the various cyclohexyl-cyclohexadienyl radical intermediates which would be formed in the addition-elimination mechanism proposed for homolytic aromatic cyclohexylation (Chart II). As shown in Chart III an additional resonance structure can be drawn involving the halogen atom, for attack either ortho or para to the halogen. This could account for the enhanced reactivity of *o*- and *p*-dihalobenzenes since all positions in these molecules are either ortho or para to a halogen.

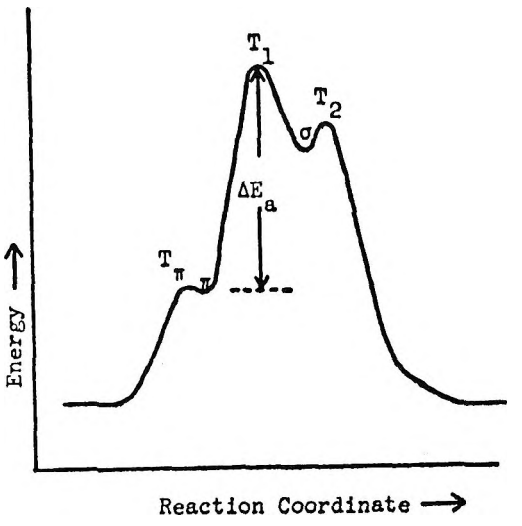
Chart III
Resonance Structures for the Intermediate Cyclohexadienyl Radical



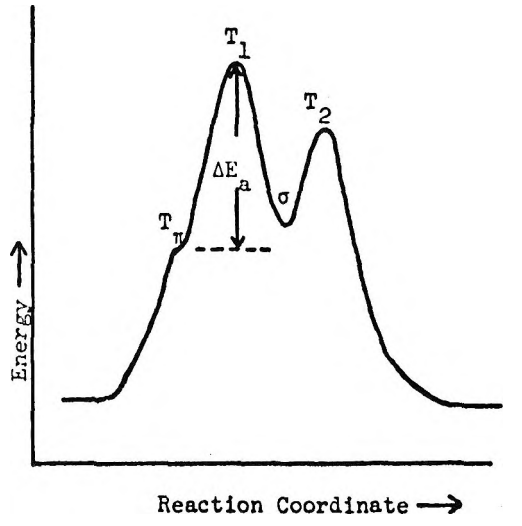
1 2 3 4

A likely driving force which supplements the resonance contribution is the relief of steric strain between two halogens in going to the intermediate σ complex for the *o*-dihalobenzenes. Bastiansen and Hassel[13] have provided evidence for the existence of this steric strain. Their calculations of the bond distances for o-dichloro- and *o*-dibromobenzene fit best with experimental values when they assumed that the carbon–halogen bonds were twisted 18° out of the plane of the benzene ring. The contribution of this relief of steric strain is illustrated in comparing the partial rate factors for the halogen displacement for *o*-dibromobenzene with those for o-dichlorobenzene and *p*-dibromobenzene. Bromine ortho to bromine is 5 times as readily displaced as bromine para to bromine, and about 4.5 times as readily displaced as chlorine ortho to chlorine.

The presence of a halogen atom on a carbon would also promote the attack of a "nucleophilic radical" at that carbon owing to its inductive electron-withdrawing effect. However, this effect would be minimized by the formation



a) Later transition state



b) Earlier transition state

Figure 1. Energy profile diagrams including π-complex formation for homolytic aromatic cyclohexylation: T_π represents the transition state for π-complex formation; T_1 represents the transition state for rearrangement of the π complex to the σ complex; T_2 represents the transition state for formation of products from the σ complex; π represents the π complex; σ represents the σ complex.

of a π complex as the initial interaction between the aromatic and the radical.

Although the contribution of resonance stabilization of the intermediate σ complex is an important factor in the enhanced reactivity of the dihaloaromatics relative to that of benzene, the activation of the two different types of hydrogen in the *o*-dihalobenzenes is not equivalent. This third trend revealed in Table I indicates that hydrogen ortho to a halogen is much more reactive than hydrogen which is para to a halogen. Preference for displacement of hydrogen which is ortho to the substituent is not uncommon in homolytic aromatic substitution, as has been shown for homolytic methylation by Cowley, Norman, and Walters[14] and Corbett and Williams.[15] Hey and Williams[16] also found an ortho directing effect in their studies of homolytic arylation of substituted aromatics.

Simamura and coworkers[5] observed that phenylation of aromatics using *N*-nitrosoacetanilides as sources of para-substituted phenyl radicals could be fit to a modified Hammett relationship. The conjugative contribution for

Table VI
Competition for Cyclohexyl Radicals in Monohalobenzenes as a Function of Temperature and Amount of O_2 Present

Monohalobenzene	Reaction temp, °C	Mol O_2 present, $\times 10^{-5}$	Aromatic substitution: % [a]	Aromatic substitution: Mol $\times 10^{-4}$	Combination: % [a]	Combination: Mol $\times 10^{-4}$	Oxygenated products: % [a]	Oxygenated products: Mol $\times 10^{-4}$	% total cyclohexylated product accounted for
C_6H_5Cl	90	230	7.8	1.1	2.3	0.33	79	12	99
	90	0.11	28	3.5	19	2.4	6.0	0.75	
	105	4.6	34	6.6	3.6	0.64	8.7	1.0	84
	117	4.6	35	18	5.2	3.5	6.0	2.6	86
C_6H_5Br	90	230	13	1.9	1.1	0.16	65	9.8	93
	90	4.6	17	1.3	27	2.1	11	0.85	
	105	4.6	39	7.6	3.8	0.80	6.0	2.0	92
	115	4.6	36	15	7.2	2.2	5.4	2.5	92

[a] Percentages are based on the total cyclohexyl reaction products observed assuming that it takes two cyclohexyl radicals to form an aromatic substitution product and two to form a combination product.

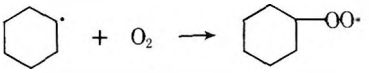
the ortho position in chlorobenzene was shown to be three times as large as that for the para position, indicating a greater resonance contribution for attack at the ortho position.

All of the factors discussed above require that the homolytic cyclohexylation of the aromatics proceeds *via* an addition–elimination mechanism as shown in Chart II. Such a mechanism is well documented for all modes of aromatic substitution, and is especially germane for homolytic aromatic substitution based on the recent demonstration by Fahrenholtz and Trozzolo through the use of CIDNP of the arylcyclohexadienyl radical intermediate for arylation.[17]

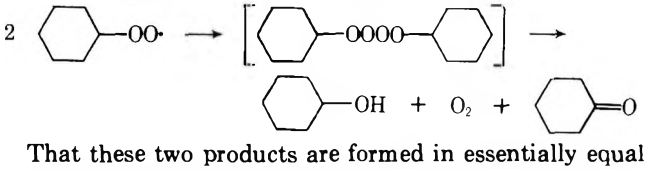
The identity of the acceptor radical, A· in Chart II, has now been established for the displacement of halogen from the dibromo- and dichlorobenzenes studied. Cyclohexyl halide completely accounts for the displaced halogen, so cyclohexyl radical is the acceptor, A·, for the halogen displaced. Direct loss of halogen atom from the σ complex would most likely lead to the production of hydrogen halide. No evidence for the presence of hydrogen halide was found in the reaction mixture.

Other reactions besides aromatic substitution occur for cyclohexyl radical in the reaction system used. Table IV lists the amounts of the other products formed. Unfortunately, the amount of combination in the cyclohexylation of *p*-dichlorobenzene could not be evaluated owing to the lack of resolution between bicyclohexyl and *p*-dichlorobenzene in the glpc for the reaction mixture.

The oxygenated products, which include cyclohexyl *tert*-butyl ether, cyclohexanone, and cyclohexanol, are particularly interesting. The amounts of these products formed are listed in Table V. Cyclohexanone and cyclohexanol most likely form as the result of the interaction of cyclohexyl radicals with molecular oxygen to give cyclohexylperoxy radicals.



The normal termination reaction for this process is the combination of two peroxy radicals with the splitting out of oxygen to give cyclohexanol and cyclohexanone.



That these two products are formed in essentially equal amounts in the o-dihalobenzene systems is consistent with this type of termination. However, in the *p*-dihalobenzene systems cyclohexanone forms to an appreciably greater extent than cyclohexanol. This probably results from increased formation of cyclohexyl hydroperoxide by abstraction of hydrogen by $RO_2\cdot$ from cyclohexadienyl radicals formed by addition of cyclohexyl radical at the positions ortho to the halogens. Dehydration of the hydroperoxide would produce ketone without an equivalent amount of alcohol.

Cyclohexyl *tert*-butyl ether can be formed by the cross combination of a cyclohexyl radical with a *tert*-butoxy radical. Why appreciably more of this process occurs in the *p*-dihalobenzene system than in the o-dihalobenzene reaction is not clear at this time.

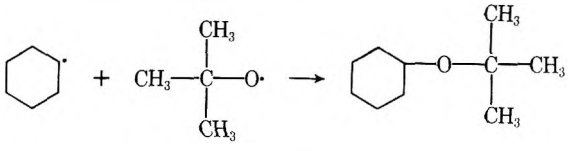


Table VI reveals information about the competition reactions for cyclohexyl radicals in reactions with monohalobenzenes, both as a function of temperature and as a function of the amount of oxygen present. Combination of two cyclohexyl radicals to form bicyclohexyl competes more favorably with aromatic cyclohexylation at 90° than at higher temperatures.

The large decrease in the amount of oxygenated products formed as the amount of oxygen present is decreased indicates that most of the oxygenated products are formed from the interaction of cyclohexyl radical and oxygen.

Thus, cyclohexyl radicals generated by decomposition of di-*tert*-butyl peroxide at 90° in cyclohexane and aromatics can effect aromatic substitution, combine with another cyclohexyl radical or a *tert*-butoxy radical to give bicyclohexyl or *tert*-butyl cyclohexyl ether, or interact with oxygen to ultimately yield cyclohexanol and cyclohexanone. Aromatic substitution is favored by electron-withdrawing groups which can stabilize an odd electron on the adjacent carbon, while the amount of cyclohexanol and cyclohexanone formed is dependent upon the oxygen concentration.

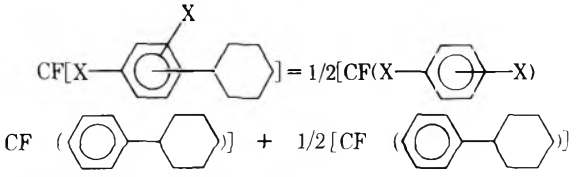
A marked solvent effect was observed consistent with the reversible formation of a π complex between cyclohexyl radical and the aromatic. Partial rate factors and relative rates demonstrated (1) the role of steric interaction in the displacement of halogen ortho to another halogen, (2) that the dihaloaromatics were activated toward homolytic cyclohexylation, and (3) that hydrogen ortho to a halogen is more reactive than hydrogen para to the halogen.

Experimental Section

Materials. Commercially available dihalobenzenes were used. o-Dibromobenzene was distilled at aspirator pressure (bp 103–109°) prior to use. Spectrophotometric grade benzene and cyclo-

hexane were used and DTBP was obtained from Columbia Organics and used without further purification.

Cyclohexylation of Dihalobenzenes in Competition with Benzene in Excess Cyclohexane. A mixture of 0.032 mol of the dihalobenzene, 0.032 mol of benzene, 0.320 mol of cyclohexane, and 0.0064 mol of DTBP was weighed into a Fischer-Porter aerosol compatibility vessel. The valve was closed and the vessel was frozen in a Dry Ice–isopropyl alcohol bath. The valve was then opened to an aspirator and the vessel was pumped for 15 min, resealed, and warmed under the hot water tap until thawed. The freeze–evacuation–thaw cycle was repeated twice more and the reaction vessel was immersed in an oil bath in the dark at 90° for 8 days. The reaction vessel was then removed from the bath, cooled, opened under nitrogen, and stored in a brown bottle until analyzed by glpc. Product mixtures were analyzed on a Varian Aerograph HiFi 600D, equipped with a linear column temperature programmer and a 10.5 ft × 0.125 in. 15% Carbowax 6000–Chromosorb W column at a temperature program of 60–190° at 2°/min. (A program of 4°/min was used for the o-dibromobenzene reaction products.) Retention times were measured relative to the leading edge of cyclohexane, and individual peaks were identified by comparison with authentic samples. Quantization was accomplished by averaging triangulation and peak height times width at half height integrations. The areas were normalized to the total area of the on-scale peaks (all but cyclohexane). The normalized areas were then divided by molar correction factors, which were determined from known solution with benzene = 1.00, and the resulting areas were then used to determine the competitive data. Molar corrections factors (CF) for the cyclohexylated aromatics were estimated on the basis of the response of cyclohexylbenzene and the appropriate halobenzene or dihalobenzene from the following relation.



Cyclohexylation of Dihalobenzene in Competition with Benzene with Aromatic in Excess. The same procedure was used as in excess cyclohexane, but with the following amounts of reagents: 0.064 mol of dihalobenzene, 0.064 mol of benzene, 0.064 mol of cyclohexane, and 0.0064 mol of DTBP, as compared to 0.032 mol of the dihalobenzene, 0.032 mol of benzene, 0.320 mol of cyclohexane, and 0.0064 mol of DTBP, in excess cyclohexane.

The production of hydrogen halide was tested by opening the sealed tubes into a silver nitrate trap with an aspirator pulling on the other side of the trap. No precipitate formed in the silver nitrate solution, indicating that no hydrogen halide was produced in the reaction.

Synthesis of Authentic Cyclohexylated Aromatics. Both monohalo- and dihalocyclohexylbenzenes were synthesized by Friedel-Crafts cyclohexylation of the appropriate aromatic using cyclohexylchloride and aluminum chloride according to the method of Mayes and Turner.[18] The isomeric products were separated by preparative glpc on a Matronic 500 dual column instrument equipped with a 15 ft × 0.25 in. Carbowax 6000–Chromosorb W column. Sufficient quantities of each isomer could be isolated by this method for ir and retention time analysis. Infrared analysis was performed on a Beckman IR-8 spectrometer.

Synthesis of *tert*-Butyl Cyclohexyl Ether. The method of Lawesson and Yang was used.[19] Crude product was isolated by vacuum distillation (62–67°, aspirator pressure) and purified by preparative glpc on a 15 ft × 0.25 in. 15% Carbowax W column with column temperature 86°, injection point temperature 152°, detector temperature 140°, and carrier gas pressure 30 psi.

Other Authentics. Cyclohexanone and cyclohexanol were purchased from Matheson Coleman and Bell. Bicyclohexyl was obtained from Eastman Organics. All were used without purification.

Acknowledgment. We are grateful to the Goodyear Tire and Rubber Co. for partial support of this investigation.

Registry No.—*o*-$C_6H_4Cl_2$, 95-50-1; *o*-$C_6H_4Br_2$, 583-53-9; *p*-$C_6H_4Cl_2$, 106-46-7; *p*-$C_6H_4Br_2$, 106-37-6; C_6H_{12}, 110-82-7; C_6H_5Cl, 108-90-7; C_6H_5Br, 108-86-1.

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Stable Carbocations. CLXVIII.[1] Protonation and Cleavage of Dialkyl Pyrocarbonates in FSO_3H–SbF_5 (Magic Acid)–SO_2 Solution

George A. Olah,* Yuval Halpern,[2] Philip W. Westerman,[3] and James L. Grant

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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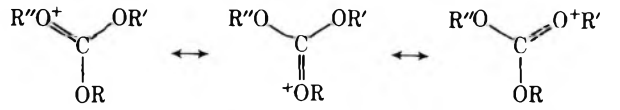
The protonation and cleavage reactions of dimethyl, diethyl, di-*n*-propyl, and diisopropyl pyrocarbonate in FSO_3H–SbF_5 (magic acid) solution have been studied by pmr and cmr spectroscopy. Cleveage products formed are protonated alkyl hydrogen carbonates, alkyl fluorosulfonates, and carbon dioxide. Di-*n*-propyl and diisopropyl pyrocarbonate give, in addition, a mixture of hexyl cations. In all cases small amounts of protonated carbonic acid and protonated alcohol were also formed. The mechanism of the cleavage reactions is discussed based on experimental data. Cmr parameters of dialkyl pyrocarbonates are also reported.

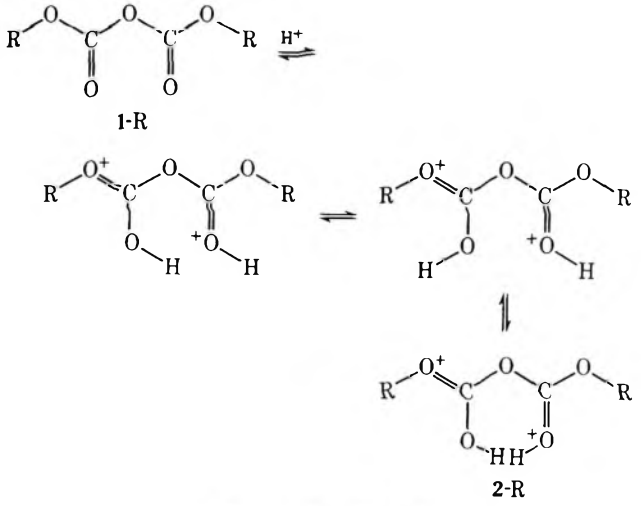
In the course of our investigation of heteroatom-substituted carbenium ions,[4] we have observed in FSO_3H–SbF_5 (magic acid) solution, by nmr spectroscopy, mono- (R = R′ = H), di- (R = H), and trialkoxycarbenium ions, including the parent ion (R = R′ = R″ = H).

Mono- and dialkoxycarbenium ions are formed by the



protonation of alkyl hydrogen carbonates and dialkyl hydrogen carbonates, respectively. Trialkoxycarbenium ions were first prepared by Meerwein by the alkylation of dialkyl carbonates and the acid cleavage of tetraalkyl orthocarbonates.[5]

We wish to report now the results of an attempt to prepare the related dications **2** by the protonation of dialkyl pyrocarbonates **1** in FSO_3H-SbF_5 (magic acid) solution under stable ion conditions.



1-R

2-R

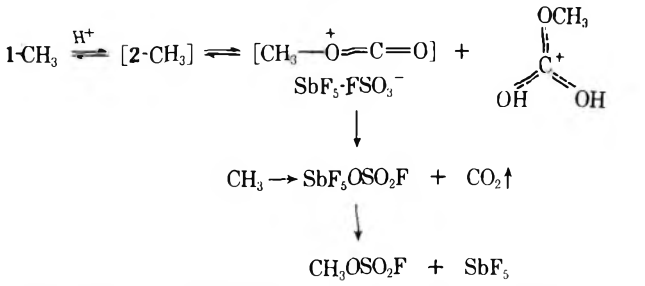
R = CH_3, C_2H_5, C_3H_7, i-C_3H_7

In addition, we wish to report the cmr spectra of the dialkyl pyrocarbonates studied. The structure of these compounds is of particular interest owing to recent reports concerning the biological consequences of the use of the enzyme inhibitor and bactericidal agent, diethyl pyrocarbonate, as a nuclease inhibitor.[6] Moreover, diethyl pyrocarbonate, a preservative in wines and beverages, has been found to react with ammonia to form carcinogenic urethan.[7-9]

Results and Discussion

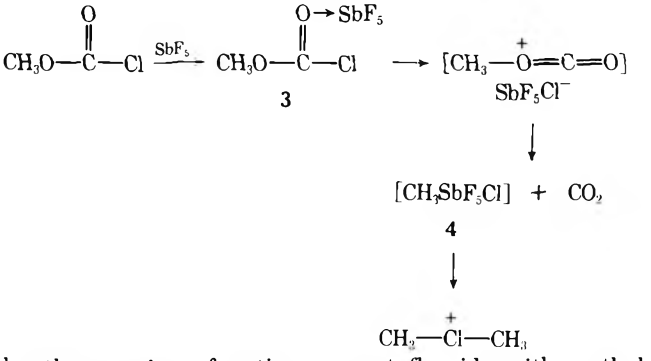
Dimethyl, diethyl, di-*n*-propyl, and diisopropyl pyrocarbonate were studied in FSO_3H-SbF_5-SO_2 at −78°. **Dimethyl pyrocarbonate** (**1**-CH_3) in 1:1 FSO_3H-SbF_5-SO_2 solution at −70° gave a pmr spectrum consisting of singlets at δ 12.9, 11.8, 11.4, 4.5, and 5.4. On standing at this temperature, the most deshielded signal moved upfield to approximately δ 10.5, while the signal at δ 5.4 increased in intensity until it almost reached that of the signal at δ 4.5 (3 H compared with each of the signals at δ 11.8 and 11.4). At −50°, an observed decrease in the signal at δ 5.4 was concurrent with the appearance and gradual increase of another signal at δ 4.3. Peak area integration indicated that the combined intensity of these two signals was equal to that of the singlet at δ 4.5. Ultimately the peak at δ 5.4 disappeared, so that the nmr spectrum of the final product consisted of peaks at δ 11.8 (1 H), 11.4 (1 H), 4.5 (3 H), and 4.3 (3 H) (excluding solvent acid peaks). The products were identified by the addition of authentic samples of assumed product ions to the reaction mixture: protonated methyl hydrogen carbonate (δ 4.5, 11.4, and 11.8) and methyl fluorosulfate (δ 4.3.). Also, a singlet at −31.0 ppm in the ^{19}F nmr spectrum of the sample confirmed the assignment of the latter signal (δ 4.3) to methyl fluorosulfonate.[10]

It is envisaged that the cleavage of dimethyl pyrocarbonate by FSO_3H-SbF_5 proceeds in the following way.

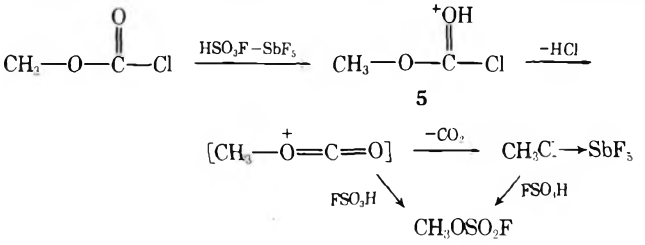


The structure of protonated dimethyl pyrocarbonate (2-CH_3) cannot be determined from the pmr data. Protonation most likely occurs on the carbonyl oxygen atoms, as in the case of protonated esters.[7,11] The data, however, show a rapid exchange process with the superacid system. Most likely it is the carbonyl diprotonated species which cleaves to give protonated methyl hydrogen carbonate. As in the case of cleavage of esters of primary alcohols by superacid, this cleavage is also probably of $A_{Ac}l$ type. The signal at δ 5.4 does not arise from protonated methyl hydrogen carbonate, since its reported spectrum[12] shows a singlet for the methyl protons at δ 4.47. The reason that only one signal is observed in this region of the spectrum must be due to the methyl proton signal of the rapidly exchanging protonated dimethyl pyrocarbonate being coincident with the methyl proton reasonance of protonated methyl hydrogen carbonate in the early stages of the cleavage reaction. The above reaction was carried out below −50°, in order to avoid the decomposition of protonated methyl hydrogen carbonate to protonated methanol and carbon dioxide, a process which occurs above this temperature in FSO_3H-SbF_5-SO_2.

We propose that the singlet at δ 5.4 arises from methyl fluoroantimonate. This is suggested from results of our recent studies[13] carried out on the fragmentation reaction of methyl chloroformate with antimony pentafluoride. Initially two methyl proton signals at δ 5.10 and 5.28 are observed in the pmr spectrum of complex **3**, which is formed



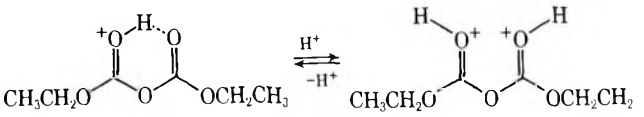
by the reaction of antimony pentafluoride with methyl chloroformate in SO_2ClF at −70°. These peaks were assigned to the cis and trans isomers. On warming to 10°, a peak at δ 5.7 appeared, which was assigned to methyl chlorofluoroantimonate (**4**). This compound reacts further according to the above scheme to give the dimethylchloronium ion. Methyl chloroformate also reacts with excess FSO_3H-SbF_5 in SO_2ClF at −70° to give a solution whose pmr spectrum consisted of singlets at δ 14.2 (1 H, C=OH^+, **5**) and 5.0 (3 H, CH_3, **5**). Warming to 10° again



results in the appearance of a transient signal at δ 5.7, followed by the appearance of a singlet at δ 4.4, which was shown to be due to methyl fluorosulfate. This behavior is analogous to that observed in the cleavage with FSO_3H-SbF_5 of dimethyl pyrocarbonate and confirms the proposed mechanism.

The pmr spectrum of a solution of **diethyl pyrocarbonate** in 1:1 *M* FSO_3H-SbF_5-SO_2 at −70° consisted of two quartets at δ 5.0 (2 H) and 4.9 (2 H), two triplets at δ 1.60 (3 H) and 1.52 (3 H), and two singlets at δ 11.28 (1 H) and 11.67 (1 H). Cleavage products were identified (by the addition of authentic products to the sample) as ethyl fluorosulfate and protonated ethyl hydrogen carbonate. In addition a triplet at δ 9.45 in the spectrum was attributed to the presence of protonated ethanol[14] (arising from acyl-oxygen cleavage of ethyl hydrogen carbonate), although the corresponding methyl and methylene proton signals were obscured by signals from the major products. This result contrasts with those from the cleavage of ethyl hydrogen *carbonate with* FSO_3H-SbF_5,[5] *where alkyl-oxygen* cleavage occurred and the *tert*-butyl cation and protonated carbonic acid were the observed products.

In FSO_3H-SO_2 protonated diethyl pyrocarbonate could be observed at −80°, before cleavage had occurred. The quartet at δ 4.05 (4 H) and the triplet at δ 1.00 (6 H) move downfield on protonation to δ 4.75 and 1.35, respectively. The species is undergoing rapid proton exchange with the acid medium because there is only one other signal in the spectrum at δ 11.2. The appearance of a single $=OH^+$ absorption could indicate either an intermolecularly rapidly exchanging monoprotonated species **6a**, a diprotonated species **6b**, or an equilibrium of the two. Both

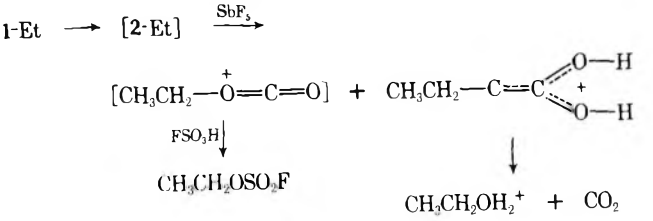


6a **6b**

would show equivalence of the two carbonyl groups. The smaller than expected deshielding of the $=OH^+$ absorptions compared with structurally related protonated carbonyl compounds would seem to indicate an equilibrating system. Pmr data, however, do not allow a clear differentiation (see, however, indication of subsequently discussed cmr studies). On the addition of SbF_5-SO_2ClF at −80°, cleavage of diethyl pyrocarbonate occurs immediately, as is evident from the appearance of peaks due to the two major products. Furthermore a quartet and triplet (decoupling experiments confirmed that they were part of the same molecule) were observed at δ 6.05 (2 H) and 1.8 (3 H). The combined intensity of these signals, together with *those of ethyl fluorosulfate*, was equal *to that of the* signals arising from protonated ethyl hydrogen carbonate. In analogy with the acid cleavage of dimethyl pyrocarbonate, these two deshielded signals were assigned to ethyl fluoroantimonate. The cleavage reaction of diethyl pyrocarbonate is thus (apart from alkyl-oxygen cleavage of the alkyl hydrogen carbonate) identical with that of dimethyl pyrocarbonate.

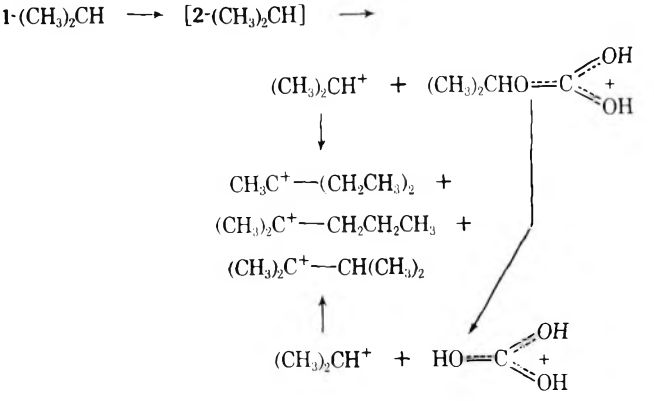
The proton-decoupled cmr spectrum of protonated diethyl pyrocarbonate in FSO_3H-SO_2 at −80°, recorded by the pulsed Fourier transform method, showed absorptions at $\delta(^{13}C)$ 12.8, 76.6, and 162.9. The latter signal was assigned to the carbonyl carbons, and indicated a downfield *shift from the corresponding resonances in the precursor* of 14.7 ppm. Slightly larger shifts in the carbonyl resonances of esters are observed upon their protonation (~20 ppm),[15] so that the above smaller value could possibly indicate that diethyl pyrocarbonate in FSO_3H-SO_2 is not completely protonated, but exists as a rapidly equilibrating mixture of monoprotonated and diprotonated species.

We also recorded the cmr spectrum of 1-CH_2CH_3 in FSO_3H-SbF_5-SO_2 at −80°, where peak area integration of the pmr spectrum indicated approximately 50% cleavage of the protonated diethyl pyrocarbonate. The major peaks in the cmr spectrum are at $\delta(^{13}C)$ *11.2, 12.8, 13.6, 14.2,* 75.5, 77.3, 78.4, 89.5, 94.6, 124.8, 161.8, and 162.9. The products, identified by comparison with the cmr spectra of authentic samples of assumed product ions, were protonated diethyl pyrocarbonate [$\delta(^{13}C)$ 162.9, 77.3, 12.8], protonated ethyl hydrogen carbonate [$\delta(^{13}C)$ 161.8, 78.4, 12.8], ethyl fluorosulfonate [$\delta(^{13}C)$ 75.5, 13.6], and ethyl fluoroantimonate [$\delta(^{13}C)$ 94.6, 14.2]. The set of peaks at $\delta(^{13}C)$ 124.8, 89.5, and 11.2 may arise from the ethyl carboxonium ion, initially formed in the decomposition of protonated diethyl pyrocarbonate.



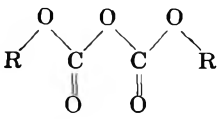
Protonated diisopropyl pyrocarbonate cleaves rapidly at −70° with the formation of a mixture of hexyl cations. (The formation of hexyl ions was established by ^1H nmr, based on comparison with the nmr assignments of these ions.)[16]

Also observed were two new peaks of equal area at δ 10.88 and 11.33 as well as the peak due to protonated carbonic acid. In addition, the methyl and methine regions became more complex, although it was impossible to resolve separate resonances. On allowing the reaction to proceed at −70° for an extended period of time, the δ 10.88 and 11.33 peaks in the -OH region disappeared and the resulting spectrum contained only absorptions corresponding to protonated carbonic acid and a mixture of tertiary hexyl cations. The new species appearing in the early stages of cleavage is assigned as protonated isopropyl hydrogen carbonate, which, like methyl hydrogen carbonate, would be expected to show two separate -OH resonances. The proposed mechanism for the cleavage is as follows.



If a solution of **di-*n*-propyl pyrocarbonate** in FSO_3H-SbF_5-SO_2 was allowed to stand for 24 hr at −80°, the final products, identified as above, were *n*-propyl hydrogen carbonate, dimethylisopropylcarbenium ion, and small amounts of protonated carbonic acid and 1-propanol. The nmr spectrum of the first species consisted of singlets at δ 11.17 (1 H) and 11.53 (1 H) due to the two nonequivalent -OH protons, a triplet at δ 4.83 (2 H) due

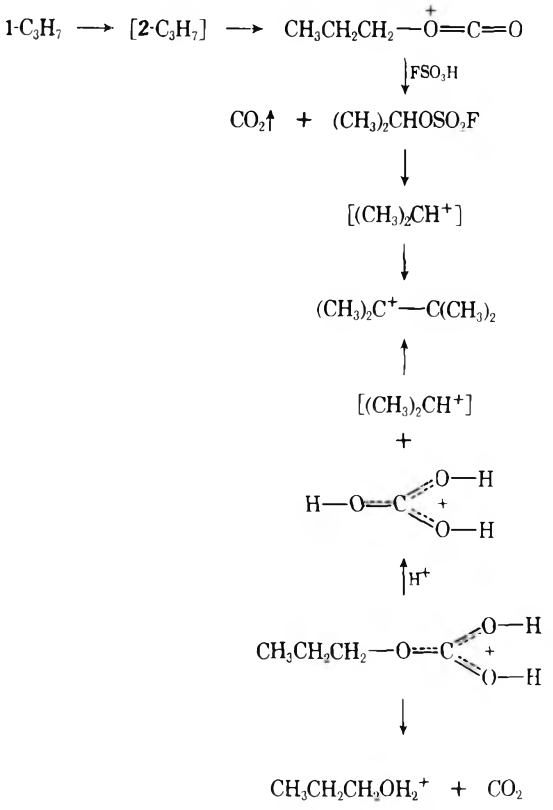
Table I
Carbon-13 Chemical Shifts in Dialkyl Pyrocarbonates[a]



R	C=O	C_α	C_β	C_γ
CH_3	147.9	58.3		
C_2H_5	148.2	66.3	14.1	
C_3H_7	148.0	71.4	21.6	10.4
i-C_3H_7	148.6	74.5	21.7	

[a] Parts per million from tetramethylsilane. Measured as neat liquid at ambient probe temperature (37°) from capillary of 60% ^{13}C-enriched methyl iodide (lock signal) and converted using $\delta(CH_3I) -18.5$.

to the α-methylene protons, a multiplet centered at δ 1.92 (2 H) due to the β-methylene protons, and a triplet at δ 0.97 (3 H) arising from the methyl protons. Examination of the nmr spectrum during the course of the above cleavage showed that isopropyl fluorosulfate was an intermediate. This may result directly from alkylation of fluorosulfonic acid by protonated di-*n*-propyl pyrocarbonate, or it may involve the intermediacy of *n*-propyl carboxonium ion, although its presence was not detected during the course of the reaction. The cleavage reaction may be summarized as follows.



Carbon-13 Nmr Spectra of Dialkyl Pyrocarbonates. The proton-decoupled carbon-13 nmr spectra of dialkyl pyrocarbonates were obtained by the Fourier transform method on a Varian HA-100 nmr spectrometer, and the results are summarized in Table I. Assignments were made by the usual methods, which included "off-resonance" proton decoupling, the application of previously observed substituent effects, as well as symmetry and relative intensity considerations. The C_β and C_γ shieldings in Table I are similar to the *O*-alkyl β- and γ-carbon shieldings in aliphatic esters.[17] C_α shieldings, however, are deshielded 5.9–8.9 ppm from the corresponding absorptions in aliphatic esters.

The most notable feature of the data in Table I is the highly shielded carbonyl absorptions in dialkyl pyrocarbonates (approximately 25 ppm shielded from the ester carbonyl shifts). The carbonyl shieldings are very similar to those in the closely related carbonates.[13,18]

Experimental Section

Materials. All compounds used to generate the ions studied were either commercially available or were prepared by a standard literature method. Dialkyl pyrocarbonates were prepared by the reaction of Na_2CO_3 with alkyl chloroformates[19,20] or by treating *p*-toluenesulfonyl chloride with sodium methyl carbonate.[21] Alkyl hydrogen carbonates (as the sodium salts) were prepared from the reaction of carbon dioxide with the appropriate sodium alkoxide. The method used for the generation of the ions in HSO_3F–SbF_5–SO_2 has been described in detail in a previous paper.[22]

Proton Nmr Spectra. Pmr spectra were obtained using a Varian Associates Model A56/60A equipped with a variable-temperature probe. External tetramethylsilane (capillary) was used as reference.

Carbon-13 Nmr Spectra. Proton decoupled carbon-13 nmr spectra were obtained using a Varian Associates Model HA-100 nmr spectrometer equipped with a Fourier transform accessory (V-4357 Pulsing and Control Unit), broad-band proton decoupler, and variable temperature probe. The instrument, lock, and referencing systems have been described in more detail elsewhere.[23] The cmr spectra of protonated diethyl pyrocarbonate was obtained by the pulsed Fourier transform method, using a Varian Associates Model XL-100 nmr spectrometer.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No.—1-CH_3, 4525-33-1; 1-C_2H_5, 1609-47-8; 1-C_3H_7, 43086-15-3; 1-i-C_3H_7, 24425-00-1; magic acid, 23854-38-8.

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Stable Carbocations. CLXXI.[1,2] 1-Fluoro(Chloro)-1-cycloalkyl Cations. Further Data on the Effect of Halogen Back-Donation and the Stability of Halocarbenium Ions

George A. Olah,* Gao Liang, and Yoke K. Mo

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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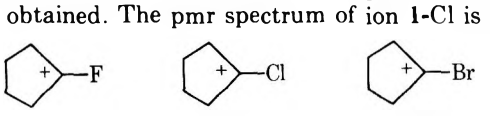
A series of 1-fluoro(chloro)-1-cycloalkyl cations have been prepared and investigated under stable ion conditions. The structure of the ions was studied by proton, carbon-13, and fluorine-19 nmr spectroscopy. Chlorocarbenium ions were found to be less stable than their corresponding fluorocarbenium ions, wherein strong fluorine "back-donation" is the dominant factor to stabilize these ions.

Extensive work has been carried out on the study of stable carbocations in this laboratory.[3] The influence of substitution by heteroatoms, especially halogen atoms, on the stability of carbenium ions has been noticed.[4] We have studied the carbon-13 nmr of dimethylhalocarbenium ions and found that the degree of halogen "back-donation" in these ions is dependent on the electronegativity of the halogen atoms.[4d]

Among the reported various types of halogen-substituted *carbenium ions*,[4,5] *cyclic halocarbenium ions* are of particular interest. Recently we have reported the preparation of 2-halonorbornyl cations and found that only the 2-fluoronorbornyl cation was stable under low-nucleophilicity superacid media.[4e] The 2-chloro- and 2-bromonorbornyl cations were rearranged to the corresponding protonated 4-halonortricyclenes under similar conditions. We how have undertaken a detailed study of monocyclic chloro- and fluorocarbenium ions by ^1H, ^{13}C, and ^{19}F nmr spectroscopy. The degree of halogen "back-donation" in halocarbenium ions is discussed based on the observed nmr data and the relative stabilities of these ions.

Results and Discussion[6]

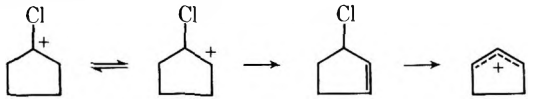
1-Halo-1-cyclopentyl Cations. When 1,1- or *trans*-1,2-dichlorocyclopentane was treated with SbF_5–SO_2ClF (SO_2) solution at −78°, 1-chloro-1-cyclopentyl cation (1-Cl) was obtained. The pmr spectrum of ion **1**-Cl is shown



1-F 1-Cl 1-Br

in Figure 1. As expected, it displays a AA′BB′ type coupling, somewhat similar to that of tetramethylenehalonium ions,[7a] but with substantial deshielding, particularly of the α-methylene protons, a good indication for ion **1**-Cl. The proton chemical shifts of ion *1-Cl* are solvent dependent (Table I). In the less nucleophilic SO_2ClF medium, more deshielded absorptions are observed. Similar observation was found in many other carbocations.[7b]

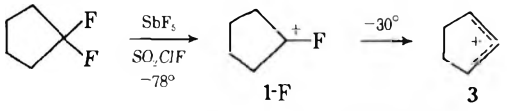
The formation of ion **1**-Cl from *trans*-1,2-dichlorocyclopentane is interesting and may involve the initial formation of the 2-chloro-1-cyclopentyl cation **2**, which then undergoes rapid 1,2-hydrogen shift. The mechanism has been previously discussed.[8]



1-Cl 2 3

In contrast, when 1,1-dibromocyclopentane was treated with SbF_5–SO_2ClF solution at −120°, the corresponding 1-bromo-1-cyclopentyl cation **1**-Br was not observed,[8] only formation of the cyclopentenyl cation **3**. The pmr spectrum of ion **3** has been reported previously.[8] The 1-chloro-1-cyclopentyl cation **1**-Cl is also not stable above −60° and slowly transforms into ion **3**. The mechanism for such transformation may involve a reversible 1,2-hydrogen shift between **1** and **2** with subsequent deprotonation and ionization leading to the formation of ion **3**.[8] It is thus suggested that this process may be extremely rapid (even at −120°) in the case of transformation of 1-bromo-1-cyclopentyl cation **1**-Br (not observable) to ion **3**.

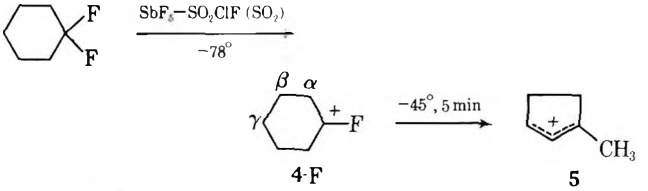
The 1-fluoro-1-cyclopentyl cation **1**-F could be prepared at −78° when 1,1-difluorocyclopentane was treated with a SbF_5–SO_2ClF solution. It was stable at temperatures below −30°, but formed **3** at higher temperature. The fluorine-substituted cyclopentyl cation is thus more stable



1-F 3

than its chlorine-substituted analog, which in turn is more stable than the bromine analog. In SbF_5–SO_2 solution, ion **1**-F was unstable even at −60° and quickly gave ion **3** upon short standing. The pmr spectrum of **1**-F (Figure 1) consists of a set of doublet multiplets centered at δ 4.25 (J_{HF} = 12 Hz) and a pentet at δ 3.04, in a ratio of 1:1. The ^{19}F nmr spectrum of **1**-F displays a deshielded quintet at ϕ −149.4 from external CCl_3F.

1-Halo-1-cyclohexyl Cations. When 1,1-difluorocyclohexane was treated with SbF_5–SO_2ClF (SO_2) solution at −78°, the corresponding 1-fluoro-1-cyclohexyl cation **4**-F was obtained. The pmr spectrum of ion **4**-F (in SO_2) shows a substantially deshielded doublet of multiplets at δ



4-F 5

3.95 (J_{HF} = 20 Hz) for the α-methylene protons (Figure 1). The β- and γ-methylene proton absorptions are two multiplets at δ 2.38 and 2.10 (in a ratio of 2:1). The ^{19}F nmr spectrum of ion **4**-F displays a highly deshielded quintet at ϕ −166.5 (from $CFCl_3$). All these data clearly suggest the formation of ion **4**-F. The proton chemical shifts of ion **4**-F are more deshielded in less nucleophilic SO_2ClF than in SO_2 (Table I). Ion **4**-F is slowly transformed to the methylcyclopentenyl cation **5** at higher temperature (*e.g.*, 5 min at −45°). Ion **5** could be readily identified by comparing the pmr spectrum with that of the ion reported previously.[8]

The 1-chloro-1-cyclohexyl cation **4**-Cl could only be formed from 1,1-dichlorocyclohexane in SbF_5–SO_2ClF solution at −120°. (When the dichloride was ionized at

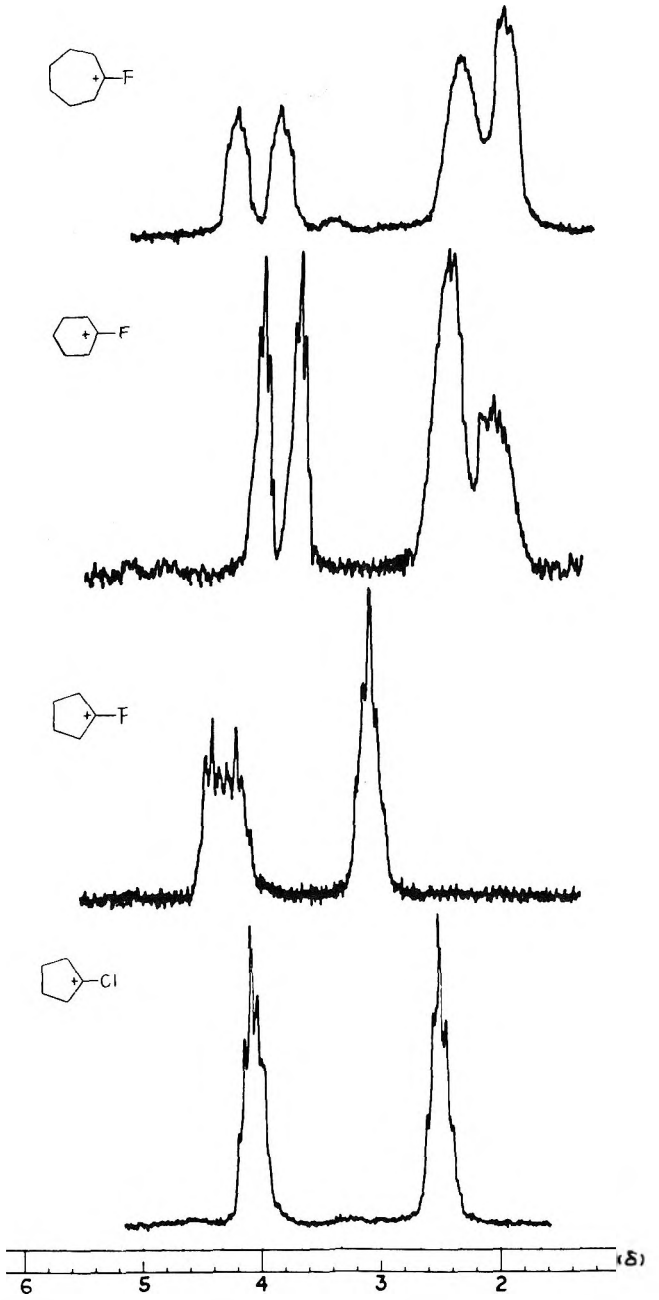
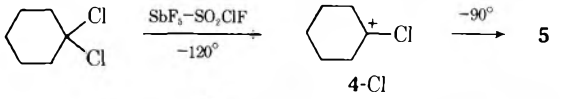


Figure 1. Pmr spectra of 1-fluoro(chloro)-1-cycloalkyl cations (60 MHz).

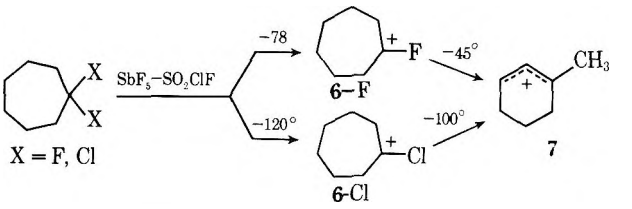
−78°, only the methylcyclopentenyl cation **5** was observed.) Ion **4-Cl** was not stable and was slowly transformed to **5** at −90°. The pmr spectrum of ion **4-Cl** shows



proton absorption at δ 4.25, 3.00, and 2.21 for α-CH_3 (4 protons), β-CH_2 (4 protons), and γ-CH_2 (2 protons), respectively (Table I).

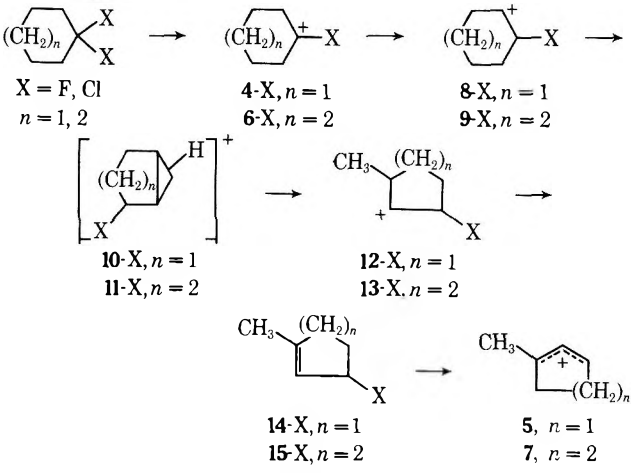
The great differences in stability between ions **4-Cl** and **4-F** as well as between **1-Cl** and **1-F** are interesting and will be discussed subsequently.

1-Halo-1-cycloheptyl Cations. The 1-halo-1-cycloheptyl cations **6-F** and **6-Cl** were prepared from 1,1-difluoro- and 1,1-dichlorocycloheptane, respectively, in SbF_5–SO_2ClF solution. Ion **6-Cl** can only be prepared at −120°. It is extremely unstable and rapidly transforms to the methylcyclohexenyl cation **7** at −100°. The 1-fluoro-1-cycloheptyl cation **6-F**, however, could be prepared at −78° without rearrangement. Ion **6-F** also slowly trans-



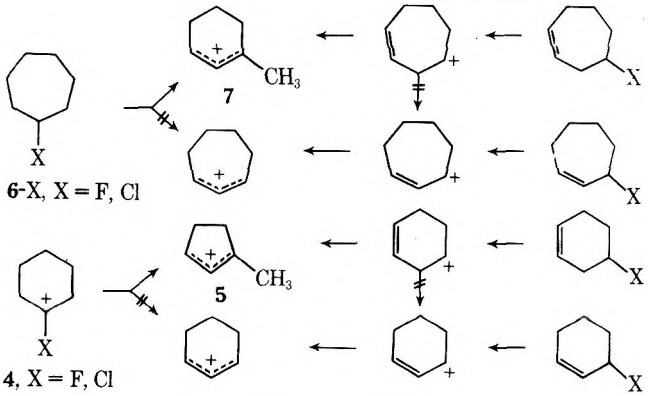
forms to **7** at −45° (5 min). The pmr spectrum of **7** is shown in Figure 1.

The transformation of both **4-F** and **4-Cl** to the methylcyclopentenyl cation **5** as well as ions **6-F** and **6-Cl** to the methylcyclohexenyl cation **7** is of mechanistic interest.[9]



1,2-Hydrogen shifts in cations **4-F** and **4-Cl** to **8-Cl** are likely to occur, since *trans*-1,2-dihalocyclohexanes also give the 1-methylcyclopentenyl cation **5** when treated with SbF_5–SO_2ClF solution under similar conditions.[8] Ring contraction may involve protonated cyclopropane intermediates (**10-X**) which subsequently will lead to ions **12-X**. Proton elimination of **12-X** to **14-X** is considered to be favorable. Ionization of **14-X** with SbF_5–SO_2ClF (SO_2) solution is a known process.[8]

Cyclohexenyl and cycloheptenyl cations have been shown to be stable under these reaction conditions studied.[8,9] It is surprising that the ring contraction reaction is faster than the formation of allylic cations. Cyclohexenyl and cycloheptenyl cations have been shown to be directly formed only from the allylic precursors and not from



homoallylic precursors.[1b,9] Ring contraction (path b) of **16** and **17** to **5** and **7**, respectively, must take place prior to intramolecular hydrogen shift (path a).[9]

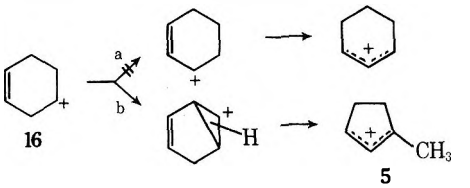


Table I
^{1}H and ^{19}F Nmr Parameters of Halocarbenium Ions

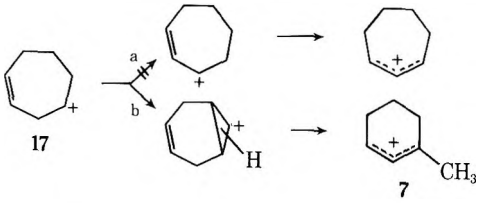
Cation	Solvent[a]	Hα[b]	Hβ[b]	Hγ[b]	φ[c]	J_{HF}[d]
1-Cl	A	4.40	2.98			
	B	4.05	2.50			
1-F[e]	A	4.25	3.04		−149.4, q	12
	B	3.92	2.54			
4-Cl	A, −105°	4.25	3.00	2.20		
4-F[e]	A	4.10	2.82	2.50	−166.5, q	20
	B	3.95	2.38	2.10		
6-Cl	A, −105°	4.30	3.15	2.35		
6-F[e]	A	4.34	2.65	2.38	−160.6, q	22
	B	4.07	2.30	1.85		
18-Cl	A	4.38				
18-F[e]	A	4.63			−185, h	26
19-F[e]	A	4.65 (CH_2)	1.98 (CH_3)		−183.5, m	24
		4.10 (CH_3)				26
20-F[e]	A	4.45	1.90		−173.7, q	24
21-F[e]	A	4.20	3.45	2.70	−126.4, t	17

[a] A, SbF_5–SO_2ClF; B, SbF_5–SO_2. Ions were measured at −80° unless otherwise indicated. [b] Pmr chemical shifts (δ) are given in parts per million from capillary tetramethylsilane. [c] ^{19}F chemical shifts are given in parts per million from capillary CCl_3F: q, quentet; h, heptet; m, multiplet; and t, triplet. [d] In hertz. [e] ^{1}H chemical shifts of α-H in fluorocarbenium ions are usually observed as doublet multiplets. Only averaged chemical shifts are given. Coupling constants [$(J(H_\alpha F)$] are shown in the last column.

Table II
Carbon-13 Nmr Parameters of Halocarbenium Ions[a]

Cation	C^+	C_α	$\Delta\delta_1$[c]	C_β	$\Delta\delta_2$[c]	C_γ	C_δ	J_{CF}[d]
1-Cl	316.3	65.9	15.9	27.9	38			
1-F	294.0[b]	50.0		27.4	25.6			439.2
4-Cl	318.6	68.7	20.6	29.4	39.3	22.3		
4-F	285.3[b]	48.1		29.4	28.7	23.4		424.8
6-Cl	319.3	70.3	19.5	28.5	41.8	23.9		
6-F	287.2[b]	50.8		28.8	22.0	25.6		427.7
18-Cl	313.7	50.5	13.3					
18-F	282.8[b]	37.2						420.0
19-F	283.6[b]	47.5 (CH_2)		5.8				421.0
		34.5 (CH_3)						
20-F	285.0[b]	46.5		6.1				429.1
21-F	301.6[b]	56.1		53.9	2.2	29.3	36.4	422.6

[a] ^{13}C chemical shifts [$\delta(^{13}C)$] are given in parts per million from capillary TMS. Ions were measured according to the conditions given in Table I. [b] Carbenium carbon shifts in fluorocarbenium ions are usually observed as doublets with coupling constants (J_{CF}) shown in the last column. Averaged ^{13}C chemical shifts are therefore given. [c] $\Delta\delta_1 = \delta(^{13}C_\alpha)$ (in chlorocarbenium ions $- \delta(^{13}C_\alpha)$ (in fluorocarbenium, ions). $\Delta\delta_2 = \delta(^{13}C_\alpha) - \delta(^{13}C_\beta)$. [d] In hertz.



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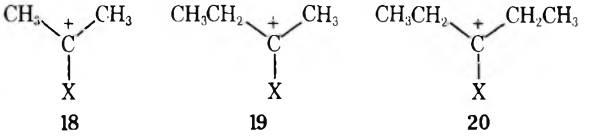

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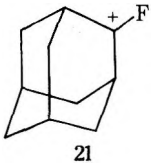
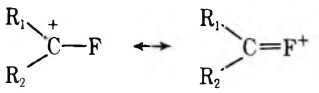


21

Nuclear Magnetic Resonance Spectroscopic Studies. Table I summarizes the proton nmr parameters of the studied 1-halo-1-cycloalkyl cations. We also have obtained ^{19}F nmr parameters of the ions, as shown in Table I, along with those of the model ions (18–21). Solvent dependency of the chemical shifts was noticed when ions were prepared in different acid systems. Protons α to the carbenium ion center in chlorocarbenium ions are generally more deshielded than those in fluorocarbenium ions, indicating that more positive charge is shared by the fluorine atom than by the chlorine atom. Fluorine shifts in cyclic fluorocarbenium ions are generally less deshielded than those in acyclic fluorocarbenium ions. This indicates that fluorine back-donation is less substantial in cyclic than in acyclic fluorocarbenium ions. Large deshielding of ^{19}F shifts observed in fluorocarbenium ions indeed strongly implies that significant charge delocalization unto fluorine occurred. It is generally believed to be due to π-donation by the fluorine lone pairs of electrons into the cationic center. We have also prepared the geometrically rigid 2-fluoro-2-adamantyl cation 21, which gives a less deshielded fluorine nmr shift (φ −126.4), indicating that fluorine back-donation is more feasible in conformationality mobile systems than in conformationally rigid systems. The extent of fluorine back-donation is therefore dependent on the molecular conformation.

An even better indication of the differing degree of back-donation in halocarbenium ions is revealed by the ^{13}C chemical shifts of the ions. Table II summarizes cmr parameters of the studied cyclic halocarbenium ions and several model ions. Carbenium carbon shifts in fluorocarbenium ions are found to be about 20 ppm deshielded from those corresponding chloro analogs. Owing to the substantial contribution of the resonance forms involving stronger fluorine back-donation, carbons α to the carben-



ium ion center in fluorocarbenium ions should experience less inductive deshielding effect than those in chlorocarbenium ions. This indeed is found to be the case as α carbon shifts in chlorocarbenium ions are about 13–20 ppm more deshielded than those in fluorocarbenium ions ($\Delta\delta_1$ in Table II). It is also found that carbon shift differences ($\Delta\delta_2$) between α and β carbons in chlorocarbenium ions are about 10–20 ppm larger than those in fluorocarbenium ions.

The conformational dependency of fluorine back-donation is also revealed from ^{13}C chemical shifts of carbenium ion centers, which in acyclic fluorocarbenium ions are less deshielded than those in the cyclic analogs. A lesser degree of fluorine back-donation should correspond to more deshielded carbenium carbon shifts, since in this case less positive charge should be shared by the fluorine atoms.

Halogen "back-donation" has been demonstrated previously by comparing the carbon-13 shifts of dimethylhalocarbenium ions and a series of haloolefins.[4d] For comparison we have now also reinvestigated the carbon-13 shifts of dimethylhalocarbenium ions by the Fourier transform method and data are included in Table II. The carbenium carbon shift of dimethylfluorocarbenium ion is found to be $\delta(^{13}C)$ 282.8 (In our quoted paper, owing to a computation error, a value of 345 was reported by the INDOR method. The recalculated value is in good agreement with the Fourier transform result.)[4e] The data for $(CH_3)_2C^+F$ and $(CH_3)_2{}^+CCl$ further substantiate the importance of fluorine "back-donation." Thus, without comparing the differences in carbon-13 shifts [$\Delta\delta(^{13}C)$] between halocarbenium ions and their corresponding olefins, the shielding of the carbenium carbon shift of $(CH_3)_2C^+F$ is a good indication of substantial charge being delocalized unto the fluorine through 2p–2p interaction. This is also in good agreement with the observed deshielded fluorine shift at ϕ −181.91 for $(CH_3)_2C^+F$.[4d]

Although steric and inductive effects may affect the ^{19}F chemical shifts, they cannot be the dominating factors which result in the observed variation for cyclic, acyclic, and polycyclic fluorocarbenium ions. ^{19}F nmr chemical shifts for the conformationally most rigid fluorocarbenium ions appear the least deshielded and those of the less rigid systems appear the most deshielded. Fluorine shifts of conformationally labile systems appear inbetween. These observations are in accord with the recent experimental results reported by Farnum and Patton[10] of the ^{19}F nmr parameters of a series of tertiary *p*-fluorophenylcarbenium ions in terms of steric restriction of rotation by solvation. They also have found that the ^{19}F chemical shifts fall into three main groups: acyclic fluorinated carbenium ions at lowest field, monocyclic at intermediate field, and bicyclic at highest field. The total range of 8 ppm represents about 6 kcal energy difference in stability. For the presently studied fluorocarbenium ions, a range of 57 ppm is observed.

From Table II it also can be seen that J_{CF} values of fluorocarbenium ions are unusually large (>400 Hz). The large J_{CF} values also correspond to the deshielded ^{19}F chemical shifts.[11] Although J_{CF} values generally vary widely depending on their environment, there are three major factors contributing to J_{CF}, *i.e.*, the extent of π-bond formation and the ionic character of the C–F bond, as well as the s character of the carbon orbital in the C–F bond. J_{CF} usually increases in magnitude with decreasing ionic character, decreasing s character, and increasing π-bond formation. J_{CF} values given in Table II for cyclic, acyclic, and polycyclic fluorocarbenium ions do not show substantial variation with the exception of the 1-fluorocyclopentyl cation, which also shows a more deshielded carbenium ^{13}C chemical shift. A consistent explanation of the fluorine back-donation unto the large J_{CF} values cannot be given at the present time. The greater extent of π-bond formation and the decrease of ionic character might be the major factors for larger J_{CF} values observed in fluorocarbenium ions.

Conclusions

The study of 1-halo-1-cycloalkylcarbenium ions shows that halogen "back-donation" as well as configuration (ring size) are the two most important factors affecting their stability. Owing to the better 2p–2p interaction in fluorocarbenium ions, we have previously shown that the degree of halogen "back-donation" is in the order F > Cl > Br. Our present data show good agreement with this order. 1-Bromo-1-cycloalkylcarbenium ions could even not be directly observed. For example, the 1-bromo-1-cyclopentyl cation was not stable even at −120° and immediately was transformed to the cyclopentenyl cation. This result enhances our previous conclusion that bromine "back-donation" is not significant in bromocarbenium ions. Indeed, bromine destabilizes carbenium ion through its obvious inductive effect. The different rate of transformation of 1-halo-1-cyclohexyl cations (**4**-F and **4**-Cl) into the 1-methyl-1-cyclopentenyl cation (**5**), on the other hand, clearly suggests that fluorine "back-donation" is more significant than that of chlorine.

Experimental Section

Materials. 1,1-Dichlorocyclopropane, -butane, and -pentane, 1,2-dichlorocyclopentane, and 1,1-difluorocyclohexane were obtained from either K & K Laboratories or Aldrich Chemical Co. 1,1-Difluorocyclopentane[12a] and -cycloheptane[12b] and 2,2-difluoroadamantane[12b] were prepared from the corresponding ketones with SF_4 according to literature procedures. 1,1-Dichlorocyclohexane and -heptane were prepared by reaction of the corresponding ketones with PCl_3–PCl_5.

Antimony pentafluoride and fluorosulfuric acid were purified as previously described.[13] The purified reagents were stored in Teflon bottles.

Nuclear Magnetic Resonance Spectra. Proton and fluorine nmr spectra were obtained on a Varian Model A56/60A nmr spectrometer equipped with a variable-temperature probe. External (capillary) TMS and $CFCl_3$ were used as references for ^1H and ^{19}F spectra, respectively. Carbon-13 nuclear magnetic resonance spectra were obtained by the Fourier transform method using a Varian XL-100 nmr spectrometer equipped with a variable-temperature probe. Carbon shifts are referred to capillary TMS.

Preparation of Ions. The procedure for the preparation of cyclic halocarbenium ion is essentially the same as that previously reported.[8,9]

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—1-Cl, 51608-49-2; **1**-F, 51608-50-5; 4-Cl, 51608-51-6; **4**-F, 51608-52-7; 6-Cl, 51608-53-8; 6-F, 51608-54-9; 18-Cl, 24154-14-1; 18-F, 14665-81-7; 19-F, 51608-55-0; **20**-F, 51608-56-1; 21-F, 51608-57-2.

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Positional Reactivities and Mechanisms of Deuteration of 1-Methylimidazole in pD and $-D_0$ Regions. Reinvestigation of the Kinetics of 2-Hydrogen Exchange in Imidazole

John L. Wong* and John H. Keck, Jr.

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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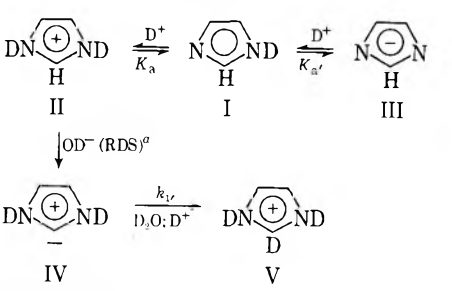
Of the rate equations 1–4 for 2-deuteration of imidazole *via* the ylide mechanism involving the OD^-, the imidazole free base, its conjugate anion, and D_2O, respectively, the experimental pD–rate profile conforms uniquely to eq 1. Rate expressions for the deuteration of the three ring sites in 1-methylimidazole by way of four independent routes are also presented (eq IIa–d). Successive exchanges of the three ring hydrogens were studied in D_2O as a function of the medium acidity. In the region of pD 0–13, the profiles for the 2-, 4-, and 5-hydrogen exchange are similar and as predicted by eq IIb. At pD > 13, eq IIa contributes significantly to the reaction at the 2 and 4 position. In strong acids, the rate of deuteration of all the ring positions increased fairly linearly with acidity as required by eq IId. Similar deuteration of 1,3-dimethylimidazolium iodide substantiates the above. These findings also allow the determination of the theoretical second-order rate constants which provide a quantitative account of the intrinsic reactivity of the 2, 4, and 5 position of 1-methylimidazole in undergoing deuteration. The relative rates are 54,500:1.6:1, respectively, *via* the ylide mechanism and 1:73:120, respectively, *via* the SEAr pathway involving the conjugate acid species.

The imidazole ring system has achieved textbook status because many substances of biological and chemical interest, both natural and synthetic, are imidazoles. Although there are many electrophilic substitution reactions of imidazoles known in the literature,[1] including, in some instances, kinetic analysis of a particular product, no quantitative data are as yet available for comparing the positional reactivities of the three potentially different carbon positions of the imidazole ring in any particular reaction. To this end 1-methylimidazole, the simplest model which possesses three unique ring positions, *viz.*, the C-5 position adjacent to a pyrrole nitrogen atom, C-4 to a pyridine nitrogen, and C-2 to both, was chosen for the present study of the reactive character of these three sites. Since typical aromatic substitutions,[1] *e.g.*, nitration, sulfonation, and halogenation, have invariably yielded a single product, they are unsuitable for a comparative study of positional reactivity. We, therefore, decided on the deuteration reaction for a comprehensive kinetic investigation. On account of what is known about the two general mechanisms of deuteration of heterocycles, *viz.*, one that proceeds *via* electrophilic aromatic substitution[2] and another *via* ionization of the carbon–hydrogen bond,[3] it is predictable that both of these pathways may be operative in the deuteration of 1-methylimidazole depending on medium acidity. This article details the kinetics and mechanisms of successive isotopic exchanges of the three ring hydrogens, and the derivation of the theoretical constants for the rate-determining steps which involve either a Wheland or an ylide intermediate. These rate constants allow the first quantitative comparison of the positional reactivities of this ring system, and may well be applicable to predicting or interpreting the orientation of other substitution reactions involving similar intermediates.

Results and Discussion

2-Deuteration of Imidazole. Consideration of General Acid and General Base Catalysis. The most general mechanism[3] of hydrogen–deuterium exchange in azoles and azolium systems involving an ylide intermediate is shown in Scheme I for the deuteration of imidazole at the

Scheme I



[a] Rate-determining step.

2 position. By analogy to the rate expression derived for thiazole exchange,[3a] the observed pseudo-first-order rate constant for imidazole 2-deuteration is given by eq 1,

$$k_{ob} = \frac{k_1 K_w'[D^+]}{K_a K_a' + K_a[D^+] + [D^+]^2} \quad (1)$$

where $K_w' = [D^+][OD^-] \approx$ the ion product constant for deuterium oxide, $K_a = [I][D^+]/[II]$, and $K_a' = [III][D^+]/[I]$. In the rate-determining hydrogen-abstraction step (II → IV), three general bases may participate: the imidazole free base (I), the imidazole anion (III), and deuterium oxide. By substituting the respective terms of I and III, which are both expressed as a function of the total imidazole concentration $[S]_t$, and $[D_2O]$ in place of $[OD^-]$ in the rate expression $d[V]/dt = k_1[OD^-][II]$, the following three equations for general base catalysis are obtained.

Imidazole [I] as the base

$$k_{ob} = \frac{k_2 K_a[D^+]^3[S]_t}{(K_a K_a' + K_a[D^+] + [D^+]^2)^2} \quad (2)$$

Imidazole anion [III] as the base

$$k_{ob} = \frac{k_3 K_a K_a'[D^+]^2[S]_t}{(K_a K_a' + K_a[D^+] + [D^+]^2)^2} \quad (3)$$

Deuterium oxide as the base

$$k_{ob} = \frac{k_4[D_2O][D^+]^2}{K_a K_a' + K_a[D^+] + [D^+]^2} \quad (4)$$

When general base catalysis does operate, k_{ob} may be given by any one or combination of these expressions.

The rate of deuteration at the 2 position was studied in the region of pD 0–16 at a constant concentration of 0.2 *M* of imidazole in deuterium oxide at unit ionic strength and 65°. The experimental rate profile shown in Figure 1A was obtained by plotting log k_{ob} *vs.* pD. This study was repeated at higher concentrations of imidazole, *viz.*, 0.5, 1.0, and 2.0 *M*, which yielded the same profile. For the sake of comparison, the sigmoid form rate profile reported by Vaughan, *et al.*,[4] for the same deuteration reaction is plotted in Figure 1B. On account of the shape of the profile in Figure 1A and its independence of substrate concentration, deuteration at the 2 position of imidazole must have followed the carbanion mechanism as shown in Scheme I and predicted by eq 1. The disparity between our rate plot and Vaughan's as shown in Figure 1 is most prominent in the regions of pD < 6 and pD > 14. Since their deuterium exchange of the 2 hydrogen of imidazole did not go beyond pD 13.65, the omission of the negative slope portion of the rate profile at pD > 14 is not unexpected. On the acidic side, however, the source of the discrepancy is less fathomable. The curve in their report levels off in the low pD region but ours decreases linearly with decreasing pD. The magnitude of k_{ob} differs considerably also, *viz.*, a $t_{1/2}$ (pD 2.88) of 11 hr is their result and 84 days being our observation. The abstraction of the 2 hydrogen by D_2O in the rate-determining step was proposed by them to account for the flattened profile in the acidic region. This proposal has prompted us to consider the operation of a certain general acid or general base catalysis. A general acid catalyzed mechanism can be readily dismissed, however, since the rate of the recombination step (k_1' of Scheme I) is not involved in the final rate expression. Whichever species furnishes the deuterium ion should be immaterial to the kinetic equation (1). General base catalysis by way of the imidazole free base I, the conjugate anion III, and D_2O may compete with the deuterioxide anion in the rate-determining step as expressed in terms of eq 2–4. In actuality, the inactive role of the imidazoles I and III is ascertained by the invariance of the observed pseudo-first-order rate constants in the range of

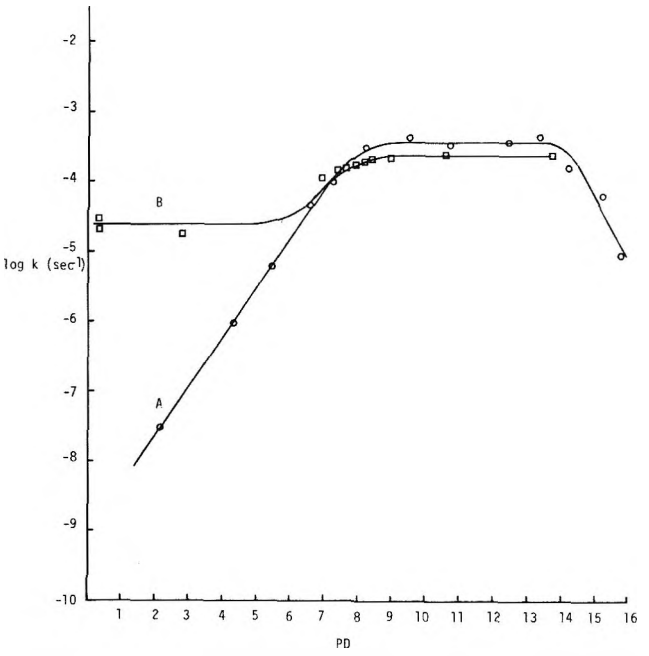
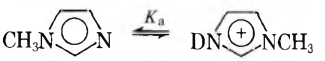


Figure 1. Experimental rate profile for 2-deuteration of imidazole at 65° and unit ionic strength: (A) this laboratory; (B) Vaughan, *et al.*, ref 6.

0.2–2 *M* of imidazole. Both eq 2 and 3 require k_{ob} to vary with $[S]_t$. In our following studies of the exchange of the three ring hydrogens of 1-methylimidazole and its methiodide salt, we have observed the same trend of declining rate in the low pD region as that shown in Figure 1A. It is pertinent to note that such decreasing rate with lower pD was also reported for the deuteration of thiazole by Olofson, *et al.*,[3a] and the deprotonation of the pyridinium ion by Zoltewicz, *et al.*[3b]

Successive Deuteration of 1-Methylimidazole and Its Methiodide Salt. Deuteration of any carbon position in a heteroaromatic system in aqueous medium may be envisaged either as an electrophilic aromatic substitution (SE) or ionization of the carbon–hydrogen bond giving rise to a carbanion intermediate (C^-). 1-Methylimidazole exists in the neutral form VI and the conjugate acid VII. Thus,



VI VII

there are four independent routes of deuteration of the three ring sites in 1-methylimidazole. In Scheme II are

Scheme II

Mechanism	Kinetic expression	Eq
(a) C^- (VI)	$k_{ob} = \frac{k_a K_a[OD^-]}{K_a + [D^+]}$	(IIa)
(b) C^- (VII)	$k_{ob} = \frac{k_b K_w'}{K_a + [D^+]}$	(IIb)
(c) SE(VI)	$k_{ob} = \frac{k_c K_a[D^+]}{K_a + [D^+]}$	(IIc)
(d) SE(VII)	$k_{ob} = \frac{k_d[D^+]^2}{K_a + [D^+]}$	(IId)

shown these four exchange mechanisms and their corresponding kinetic expressions. Equation IIa was derived in the same manner as eq 1 for imidazole, except $[S]_t$ = VI

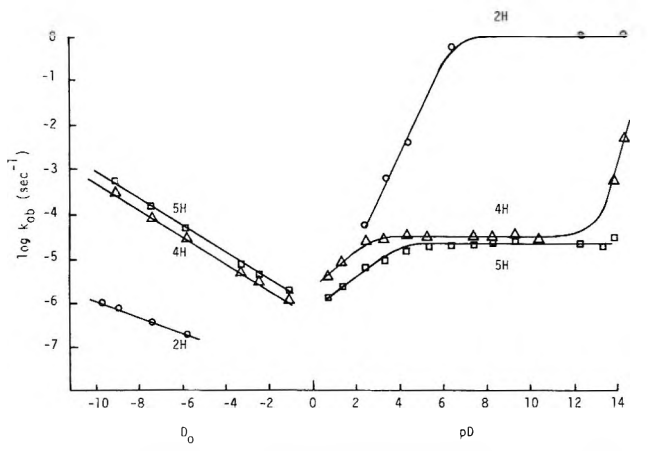


Figure 2. Experimental rate profiles for deuteration of 1-methylimidazole at 163°. Profile for the 2 position is projected from experimental values obtained at 81°.

+ VII; eq IIb from eq 1 by setting $[D^+] \gg K_a'$ and eq IIc and IId are those derived by Katritzky, *et al.*,[2] for the deuteration of heteroaromatic compounds *via* the S$_E$ route.

Deuterations at the 2, 4, and 5 position of 1-methylimidazole in a 0.2 *M* aqueous solution were studied as a function of the medium acidity. Their rate profiles are plotted in Figure 2. at the uniform temperature of 163°. All except the 2-hydrogen exchange in the pD region were conducted at this temperature. The rate constants for the latter depicted in Figure 2 were projected from the experimental values obtained at 81° using the Arrhenius equation and E_a = 20.2 kcal mol^{-1}. As a model for the deuteration of the conjugate acid species VII, 1,3-dimethylimidazolium iodide was used. The rate profiles for the deuteration at the 2 and 4(5) positions are drawn in Figure 3. The two rate equations which govern the two routes of exchange are eq 5 and 6. These equations are derivable from eq IIb and IId, respectively, by setting $[D^+] \gg K_a$.

$$k_{ob} = k_5[OD^-] \quad (5)$$

$$k_{ob} = k_6[D^+] \quad (6)$$

The rate profile for the 2-hydrogen exchange of 1-methylimidazole shown in Figure 2 is uniquely compatible with eq IIb. Thus, deuteration in this case also occurs *via* the ylide mechanism, the same as that shown for imidazole in Scheme I. The only difference in these two experimental rate profiles (*cf.* Figures 1A and 2) exists, predictably, in the high pD region where the imidazole plot becomes base dependent. The 1-methylimidazole profile continues to be level at high pD owing to the absence of the conjugate base form. The inflection point of the latter rate profile obtained at 81° at pD *ca.* 7.6 corresponds quite well to the room temperature pK_a^D of 1-methylimidazole of 7.89.[5] At 26°, the same hydrogen exchange studied by Harris, *et al.*,[6] in the acidic region is understandably sluggish. Their flattened curve of zero rate from pD 0 to 4.5 can be considered a fair representation in a preparative sense. However, it should be noted that the resulting sigmoid form of the rate plot is incompatible with eq IIb for the ylide mechanism. The profiles for the deuteration at the 4 and 5 position of 1-methylimidazole at 163° have the same general shape as that of 2-deuteration at 81° in the region of pD 0–13 (*cf.* Figure 2). This argues strongly that the same mechanism of exchange prevails in all of these cases.

At pD 13 and above the rate of 4-deuteration shows direct dependence on base concentration. This fits the equation $k_{ob} = k_a[OD^-]$ which can be derived from eq IIa

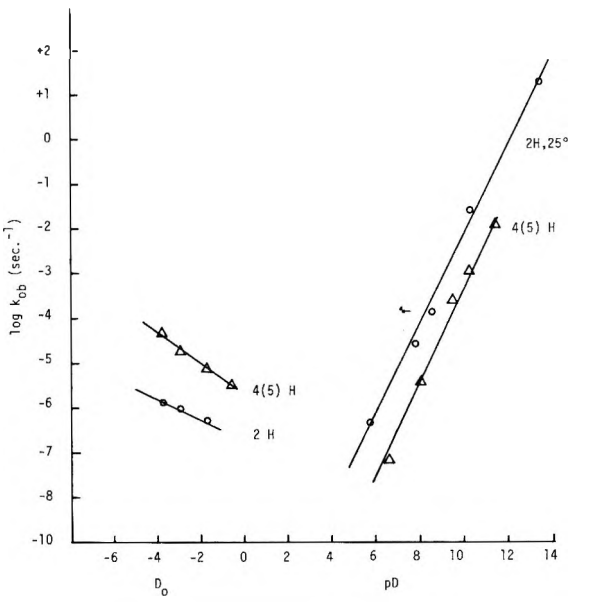


Figure 3. Experimental rate profiles for deuteration of 1,3-dimethylimidazolium iodide at 163°, except for 2 hydrogen at 25° in pD region.

when $K_a \gg [D^+]$. It appears that in this alkaline region a base-catalyzed reaction also occurred on the free base form VI, in the same way as the deuterium exchange of pyridine in NaOD-D_2O mixtures at 198° reported by Zoltewicz, *et al.*[3b] Although the rate enhancement in the high pD region was not found for 2-deuteration at 81°, a strong case of such involvement can be projected for this exchange at 163°, at which point the rate of 2-deuteration was too rapid to measure by the pmr technique. It is known that metalation of 1-methylimidazole with *n*-butyllithium occurs solely at the 2 position.[7] Thiazole 2-H exchange was shown[3a] to exhibit this rapid rate increase at higher base concentration, denoting ionization of the free base form. Since inductive stabilization of the carbanion intermediate is expected to be greatest at the 2 position of VI which is adjacent to both heteroatoms, the dual mechanism represented by eq IIa and IIb that was operative in 4-deuteration must also have prevailed in the 2-hydrogen exchange under the same conditions. The 5 position of the free base form VI, being next to a pyrrole nitrogen, showed much less tendency to follow eq IIa, and the entire profile for 5-deuteration is consistent with the ylide mechanism defined by eq IIb.

In strong acids in the $-D_0$ region and at 163°, the rate of exchange of all the ring hydrogens increased fairly linearly with acidity as depicted in Figure 2. This behavior is compatible with eq IId for an electrophilic substitution occurring on the conjugate acid VII. At $[D^+] \gg K_a$, eq IId becomes $k_{ob} = k_d[D^+]$. The strongly acidic conditions used necessitate the use of the acidity function D_x^+, and $D_x^+ = -\log [d_x^+]$. Thus, eq IId′ predicts that a plot of log

$$k_{ob} = k_d[d_x^+]$$

$$\log k_{ob} = \log k_d - D_x^+ \quad (IId')$$

k_{ob} *vs.* D_x^+ should increase with acidity and have a slope of −1. Since D_x^+ values are undetermined for the acidic conditions used, log k_{ob} is plotted as a function of D_0. D_0 is assumed[8] to be equal to H_0.[9] As the acids used deviate from ideal behavior, the slope of −1 no longer holds. The slope of the 4- and 2-hydrogen curves in Figure 2 are −0.50 and −0.25, respectively. A slope of −0.45 was observed by Katritzky, *et al.*,[2c] in the deuteration of 2,4,6-trimethylpyridine at 219° under these strong acid conditions.

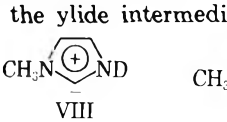
Table I
Calculated Second-Order Rate Constants of Deuteration at 163° for All Ring Sites[a]

Ring position	1-Methylimidazole k, M^{-1} sec^{-1}	1-Methylimidazole Rel rate	1,3-Dimethylimidazolium iodide k, M^{-1} sec^{-1}	1,3-Dimethylimidazolium iodide Rel rate
	A. pD 0–13			
2	1.11×10^{2} (25°)[b]		2.70×10^{2} (25°)[c]	
	9.00×10^{6} [b]	54,500		
4	2.60×10^{2}	1.56	3.42×10^{2}	
5	1.65×10^{2}	1.00	3.42×10^{2}	
	B. D_0 – 10–0			
2	8.32×10^{-7}	1.00	1.62×10^{-5}	1.0
4	6.03×10^{-5}	73	6.39×10^{-4}	39
5	9.78×10^{-5}	120	6.39×10^{-4}	

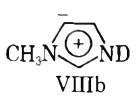
[a] Calculations are based on k_{ob} (163°) at pD 7.4 and D_0 – 2.84 for 1-methylimidazole and k_{ob} (163°) at pD 11.4 and D_0 – 2.84 for the imidazolium salt. [b] Calculated from k_{ob} (25°) and k_{ob} (163°) which are extrapolated from the experimental value of k_{ob} (81°) by the use of the Arrhenius equation and E_a = 20.2 kcal mol^{-1}, the latter being determined in the temperature range of 30–81°. [c] Calculated from the experimental value of k_{ob} (25°).

These mechanistic postulates for the deuterations of 1-methylimidazole in the pD and $-D_0$ regions are further reinforced by the kinetic behavior of the deuteration of 1,3-dimethylimidazolium iodide under similar conditions. With reference to Figure 3, the profiles observed in the pD region for deuteration at the 2 position at 25° and the 4(5) position at 163° increase linearly with basicity and have slopes of 1.0 and 1.2, respectively. This is ideally suited to eq 5 denoting the carbanion mechanism. In strong acids, the rates of 2- and 4(5)-hydrogen exchanges increase linearly with acidity as predicted by eq 6, and in the same manner as shown by the exchanges of the 1-methylimidazole hydrogens. This again corroborates the electrophilic substitution mechanism proposed for the latter heterocycle. Further revelation of the consistency of these deuteration mechanisms for the two compounds can be seen in the quantitative comparison of the calculated second-order rate constants shown in Table I and the discussion which follows.

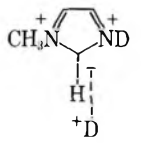
Positional Reactivities of 1-Methylimidazole. The kinetics of deuteration of the three ring positions of 1-methylimidazole are defined by eq IIb in the region of pD 0–13 and by eq IId in the $-D_0$ region. Given the observed pseudo-first-order rate constants at 163°, the second-order rate constants k_b and k_d can be obtained from the above equations for each ring position. These constants k_b and k_d, uncluttered by parameters such as the substrate concentration, solution pD, as well as pK_a^D and pK_w', have provided a quantitative account of the intrinsic reactivity of the 2, 4, and 5 positions in undergoing deuteration. In Table I are shown the theoretical constants for a specific deuteration site in 1-methylimidazole and its methiodide salt. These values are approximate solutions of eq IIb and IId, since pK_a^D,[5] pK_w',[10] and [D$^+$], which were measured at room temperature, are used in conjunction with k_{ob} at 163° uncorrected for the temperature difference. However, the accuracy of rate comparison is not compromised. The relative rates of deuteration at the 2, 4, and 5 positions at pD 0.13 are 54,500:1.6:1. These reflect the inherent stability of the ylide intermediates VIII, VIIIa, and VIIIb, respectively. The 2 hydrogen is expected to exchange fastest, since the carbanion is uniquely flanked by two nitrogens. The large inductive effect of nuclear nitrogen atoms in promoting deprotonation of some azoles was shown by Olofson, *et al.*[11] Similar inductive reasoning allows that the reaction at the 5 position should be depressed relative to that at the 4 position because of the proximity of the N_1-methyl group. By the same token the relationship of $k_2 > k_4 > k_5$ should also hold at pD > 13, although no meaningful numerical data are available to make the comparison.

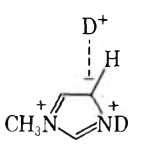

VIII

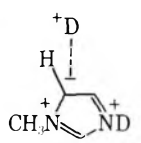

VIIIa


VIIIb

The relative rates of deuteration in strong acids in the 2, 4, and 5 position of 1-methylimidazole are 1:73:120, respectively. In comparing the transition states, the electrophile D$^+$ would encounter less charge repulsion in transition states VIIb and VIIc than in VIIa. The two positive


VIIa


VIIb


VIIc

nitrogens are cross conjugated in VIIb and VIIc but fully conjugated in VIIa; the latter, therefore, is destabilized more. Thus, the greater reactivity of the 4 and 5 position can be rationalized on the basis of the proposed SEAr mechanism involving the conjugate acid VII. The faster rate of 5- over 4-deuteration is attributable to the electron-donating effect of the N_1-methyl group.

The second-order rate constants for 1,3-dimethylimidazolium iodide undergoing the ylide deuteration route are very comparable to those for 1-methylimidazole. In strong acids where an electrophilic substitution mechanism prevails, the additional methyl group in the methiodide salt exerts further stabilization of the transition state. This results in higher rate constants than their counterparts in the deuteration of 1-methylimidazole.

Experimental Section

Materials. Imidazole and 1-methylimidazole were purchased from Aldrich Chemical Co.; the former was sublimed at 50° (2 mm) and recrystallized from benzene, mp 90°, and the latter was redistilled before use. 1,3-Dimethylimidazolium iodide was prepared according to Overberger.[12]

Sample Preparations. In the pD region, 1 ml of a 0.2 *M* solution of the imidazole in D_2O was prepared. To it was added 0.05 ml of a 0.2 *M* solution of 3-(trimethylsilyl)propanesulfonic acid sodium salt in D_2O as the internal pmr standard. Desirable acidities of pD 0–13 were obtained by adding micro amounts of 6 *N* NaOD or 38% DCl, and the pD values were calculated by adding 0.4 to the observed pH-meter values.[13] Strongly alkaline solutions with pD > 13 were prepared from concentrated NaOD solutions which were standardized by titration with standard 0.1 *N* acid, and the pD values were calculated from the equation pD + pOD = 14.86.[10] Generally, the initial and the final pD values measured at the end of the deuteration experiments agreed to within 0.1 pD unit. In a few instances additional runs were made using phosphate buffers. We found no real difference in rate when they were

Table II
Rate of Exchange of Imidazole at 65°

pD	k_{ob}, sec^{-1}
15.7	8.70×10^{-6}
15.3	6.55×10^{-5}
14.2	1.56×10^{-4}
13.3	4.22×10^{-4}
12.4	3.84×10^{-4}
10.7	3.24×10^{-4}
9.5	4.03×10^{-4}
8.2	3.06×10^{-4}
7.2	9.16×10^{-6}
6.5	4.34×10^{-5}
5.4	6.06×10^{-6}
4.3	8.83×10^{-7}
2.1	2.89×10^{-8}

compared to the unbuffered ones. For the exchange of the 2 hydrogen in imidazole, the ionic strength of the imidazole solutions was adjusted to 1.0 *M* with sodium chloride solution. This was done to reproduce precisely the reaction conditions described by Vaughan, *et al.*[4] This adjustment was not made in other exchange experiments, since 2-deuteration of 1-methylimidazole at pD 10.9 and 81° and ionic strength varying between 0.02 and 1.1 showed that the rate dependence on ionic strength is negligible and within experimental error. For experiments to be carried out at less than 100°, the sample was heated in the nmr tube. At >100°, samples were heated in a sealed glass ampoule or in a stainless steel bomb for strongly alkaline solutions (pD > 13). In the concentrated acid region, the deuteration of 1-methylimidazole was done in D_2SO_4–D_2O mixtures. Commerical 98% D_2SO_4 was standardized against sodium hydroxide solution of known molarity. Solutions of specific D_0 values were prepared by dilution with D_2O and it was assumed[8] that D_0 was numerically equal to the reported[9] values of H_0. Mixtures of DCl-D_2O of varying D_0 values[9] were used as media for the deuteration of 1,3-dimethylimidazolium iodide, since this salt was found to react with sulfuric acid at raised temperatures.

Kinetic Measurements. The kinetics of deuteration were followed by pmr technique using a Varian A-60A spectrometer. At various intervals until 1 half-life had elapsed, the pmr spectra of the sample were recorded and integrated at two or more spectrum amplitudes for four times each. The fraction of hydrogen left at a given time for an exchanging proton was calculated by reference to a nonexchanging proton or group. The *N*-methyl group was used as reference peak for 1-methylimidazole and the dimethyl salt. For imidazole, the trimethylsilyl peak of the internal standard 3-(trimethylsilyl)propanesulfonic acid sodium salt was integrated and used as reference. A plot of the natural logarithm of the fraction of hydrogen left *vs.* time gave a linear plot. This indicates a first-order or a pseudo-first-order reaction. The slope of the plot is the negative of the observed rate constant. The pseudo-first-order rate constants were calculated using a standard linear least-squares routine.[14] These were run on the IBM 360-40 computer. Statistical analysis produced correlation coefficients of greater than 98%. Specific conditions for the exchange study of the three different imidazoles are described below.

Imidazole. δ (D_2O, pD 12.4) H-2 7.80, H-4(5) 7.17. Exchange of the 2 hydrogen was done in a nmr sample tube at 65 ± 0.1° in a thermostatically controlled constant-temperature bath. The sample was quenched by cooling before pmr analysis. Rate data are summarized in Table II.

1-Methylimidazole. δ (D_2O, pD 12.4) H-2 7.63, H-4 7.13, H-5 7.03, NCH_3 3.27. Deuteration at the 2 position in the pD region at 81° was carried out as above. Other exchanges in the pD and $-D_0$ regions were done in a sealed tube at 163 ± 2.0° using refluxing bis(2-methoxyethyl) ether as the constant-temperature heating medium. The 2 hydrogen was measured directly by pmr technique. In acidic solutions of pD < pK_a, the 4 and 5 protons of 1-methylimidazole merge into a single peak. Therefore, a slightly different procedure was necessary in order to observe the exchange of these protons individually. In the region of pD 0–6, 3-ml samples were used in the exchange experiments. Aliquots of 0.5 ml were withdrawn at invervals of heating and cooled, and concentrated NaOD was added to bring the pD of the solution to *ca.* 8 so that the 4 and 5 protons were distinct. For the exchange studies in the $-D_0$ region, this treatment led to a large amount of sodium salt in the sample, which lowered the quality of the spectrum. Hence the 1-methylimidazole was extracted into carbon tetrachloride for spectral measurements. No decomposition was observed in any of these samples studied. The rate data are shown in Table III.

Table III
Rate of Exchange of 1-Methylimidazole

	k_{ob}, sec^{-1}		
pD (D_0)	2-H (81°) (163°)*	4-H (163°)	5-H (163°)
14.2	3.00×10^{-3}	3.64×10^{-3}	
13.9		4.86×10^{-4}	2.42×10^{-5}
13.4		1.07×10^{-4}	1.85×10^{-5}
12.4	2.94×10^{-3}	3.08×10^{-5}	1.72×10^{-5}
10.4		2.20×10^{-5}	
9.4		3.48×10^{-5}	2.66×10^{-5}
8.4		2.86×10^{-5}	2.25×10^{-5}
7.4		2.78×10^{-5}	1.84×10^{-5}
6.4	2.06×10^{-3}	3.50×10^{-5}	1.75×10^{-5}
5.4		2.78×10^{-5}	1.63×10^{-5}
4.4	1.49×10^{-5}	3.25×10^{-5}	1.23×10^{-5}
3.4	2.29×10^{-6}	2.92×10^{-5}	8.91×10^{-6}
2.4	2.20×10^{-7}	2.62×10^{-5}	6.22×10^{-6}
1.4		9.20×10^{-6}	1.97×10^{-6}
0.8		4.06×10^{-6}	1.37×10^{-6}
−1.06		1.37×10^{-6}	2.18×10^{-6}
−2.42		3.25×10^{-6}	4.50×10^{-6}
−3.30		5.67×10^{-6}	1.01×10^{-5}
−5.82	2.35×10^{-7} *	3.00×10^{-5}	4.08×10^{-5}
−7.46	3.92×10^{-7} *	9.66×10^{-5}	1.37×10^{-4}
−9.01	8.22×10^{-7} *	3.89×10^{-5}	5.28×10^{-4}
−9.98	1.03×10^{-6} *		

Table IV
Rate of Exchange of 1,3-Dimethylimidazolium Iodide

	k_{ob}, sec^{-1}	
pD (D_0)	2-H (25°) (163°)*	4(5)-H (163°)
13.4	1.81×10^{1}	
11.4		1.24×10^{-2}
10.3	2.52×10^{-2}	1.04×10^{-3}
9.5		2.44×10^{-4}
8.5	1.22×10^{-4}	
8.0		3.20×10^{-6}
7.8	2.35×10^{-5}	
6.6		5.95×10^{-8}
5.7	4.17×10^{-7}	
−0.615		3.17×10^{-6}
−1.73	4.72×10^{-7} *	6.65×10^{-6}
−2.84	8.56×10^{-7} *	1.84×10^{-5}
−3.80	1.12×10^{-6} *	4.42×10^{-5}

1,3-Dimethylimidazolium Iodide. δ (D_2O, pD 12.4) H-2 8.65, H-4(5) 7.43, NCH_3 3.98. The 2-hydrogen exchange was studied at 25° in the pD region and all other deuterations at 163° by methods as shown above. The pmr measurements of the 4(5) hydrogens, however, require a comment. Since the 4 and 5 protons of this salt are indistinguishable, initial exchange may occur at either position. This represents an example of two consecutive first-order reactions

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

where A = undeuterated salt, B = monodeuterated salt, and C = dideuterated salt, and $k_2 = k_1/2$ since the 4 and 5 protons are indistinguishable. During an exchange reaction the area of the pmr signal of the 4(5) protons is proportional to the concentration of A plus half the concentration of B at the given time. It follows directly from the usual kinetic treatment of consecutive first order reactions that when $k_2 = k_1/2$

$$A + B/2 = A_0 e^{-k_1 t/2}$$

so that

$$\ln \frac{A + B/2}{A_0} = -k_1 t/2$$

Since $(A + B/2)/A_0$ is measured directly by pmr, a plot of these ln values *vs.* time gives a straight line which has a slope of $-k_1/2$. Since $k_2 = k_1/2$, a pmr experiment gives k_2 directly. Therefore, the rate constant directly measured by nmr represents the rate of exchange of only one of the indistinguishable protons.

This quantity is comparable to the data for one-proton exchange determined for other imidazoles. The rate data are summarized in Table IV.

Registry No.—1-Methylimidazole, 616-47-7; 1,3-dimethylimidazolium iodide, 4333-62-4.

References and Notes

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Transfer-Hydrogenation and Transfer-Hydrogenolysis. IV. Catalytic Dehydrogenation by a Quinone

Takeshi Nishiguchi,* Akira Kurooka, and Kazuo Fukuzumi

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

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The dehydrogenation of 2-propanol by chloranil was found to occur in the presence of several transition metal complexes to give acetone and tetrachlorohydroquinone. Some of these reactions seem to be explained by a mechanism that requires both the donor and the acceptor to coordinate simultaneously on the central metal of the catalyst, and hydrogen atoms to be transferred directly from the former to the latter without forming hydride complexes. The dehydrogenation of tetralin and 2,5-dihydrofuran, which are unsaturated compounds, was not influenced by the addition of the metal complexes.

The dehydrogenation of unsaturated compounds by quinones is well known and has been considered to proceed *via* a two-stage ionic process involving a charge transfer complex.[1] The reaction usually requires double bonds or aromatic rings in the hydrogen donors, so that dehydrogenation of saturated heterocompounds by quinones is unusual.[1]

We have found that catalytic hydrogen transfer from 2-propanol[2] or dioxane[3] to olefins proceeds *via* hydride complexes. Moreover, direct hydrogen transfer involving no hydride complex seems not to have been reported in the hydrogenation of olefins[4] or quinones[1,4] catalyzed by transition metal complexes. This study was undertaken to examine the possibility that direct hydrogen transfer can take place from a hydrogen donor to a quinone, without involving a hydride complex, when the reactants do not form a charge transfer complex but are simultaneously coordinated to a transition metal complex.

Results

Hydrogen Donors. As hydrogen acceptor, chloranil was mainly used because of its relatively high thermal stability and hydrogen accepting power. Duroquinone also was used in some cases.

The desirable hydrogen donors for the purpose of this study are those which do not form charge transfer complexes with quinones but do coordinate to transition metals. From this viewpoint, various saturated heteroatom compounds were examined as hydrogen donors.

A hydrogen donor and chloranil (0.25 mol each) and 0.025 mol of $NiBr_2(PBu^n_3)_2$ were heated in o-dichlorobenzene at 170° for 2 hr. 2-Propanol gave a considerable amount of acetone along with 2-chloropropane. Cyclohexanol and cyclohexyl chloride gave phenol and chlorobenzene, respectively, but the yields were less than 5%. In the reaction of *N*-methylpyrrolidine as a hydrogen donor, neither the expected product, *N*-methylpyrrole, nor unreacted *N*-methylpyrrolidine was detected after the reaction. The same result was obtained in the reaction of the amine at 140°. This observation may be explained by the assumption that the tertiary amine reacted with chloranil.[5] In the reaction of the amine with duroquinone in the presence of $NiBr_2(PBu^n_3)_2$, *N*-methylpyrrolidine survived, but *N*-methylpyrrole was not detected.

The reaction in which 2-propanol was used as a hydrogen donor was examined in detail, because the alcohol donated hydrogen catalytically in spite of the formation of 2-chloropropane in a side reaction. For comparison, the reactions of tetralin and 2,5-dihydrofuran, which are unsaturated compounds, were also investigated.

Solvents. To find a suitable solvent, equimolar amounts of 2-propanol and chloranil were heated in several solvents in the presence of $NiBr_2(PBu^n_3)_2$ and the reaction mixtures were submitted to gas–liquid chromatographic analysis. The results are summarized in Table I. The solvents of moderate coordinating ability were found to be suitable. Because of the convenience of the analysis, the experiments hereafter were carried out in chlorobenzene.

Dehydrogenation of 2-Propanol. 2-Propanol and chloranil gave acetone, tetrachlorohydroquinone, and 2-chloropropane in the presence of catalysts. The formation of tetrachlorohydroquinone was confirmed by isolation of it as crystals from the reaction mixture and by comparison with an authentic sample. Though the yield of acetone based on the amount of charged chloranil was much higher when 2-propanol was used as hydrogen donor and solvent, the solubility of catalysts in the alcohol was small. The reactions were therefore carried out in chlorobenzene at 170° for 2 hr. The results are summarized in Table II.

Table I
Solvents in the Hydrogen Transfer from 2-Propanal to Chloranil[a]

Solvent	Yield, % Acetone	2-Chloropropane	Recovered 2-propanol, %
n-Butyl propionate	31	4	29
Bromobenzene	30	7	53
Anisole	26	12	59
Chlorobenzene	25	6	66
p-Chlorotoluene	18	19	53
o-Dichlorobenzene	13	6	57
o-Tolunitrile	12	24	40
Diethylbenzene	8	10	63
Pyridine	1	1	72

[a] 2-Propanol (0.25 mol), chloranil (0.25 mol), and $NiBr_2(PBu^n_3)_2$ (0.025 mol) were heated in the designated solvent at 170° for 2 hr.

The existence of side reactions was shown by the fact that 2-chloropropane was formed and the total amount of acetone, 2-chloropropane, and recovered 2-propanol was less than the amount of charged 2-propanol. When duroquinone was used instead of chloranil under the same reaction conditions in the presence of $NiBr_2(PBu^n_3)_2$, $PdCl_2(PPh_3)_2$, $Pt(PPh_3)_4$, or $RhCl\cdot 2H_2O$, neither acetone nor 2-chloropropane was formed, but 2-propanol was recovered quantitatively.

Dehydrogenation of Tetralin. The reactions in which 0.25 mol of tetralin, 0.25 mol of chloranil, and 0.025 mol of a metal complex were heated in chlorobenzene for 2 hr at 160 or 180° were carried out for comparison with the reaction of 2-propanol. In the reaction at 160°, about 0.01 mol of 1,2-dihydronaphthalene and 0.01–0.02 mol of naphthalene were formed; in the one at 180°, 0.01–0.02 mol of 1,2-dihydronaphthalene and 0.05–0.06 mol of naphthalene were detected. No significant effect of the addition of metal complexes was observed in any case, though all of the complexes used in the reaction of 2-propanol were examined. The total amount of 1,2-dihydronaphthalene, naphthalene, and recovered tetralin in the reaction mixtures was almost equal to the amount of charged tetralin in every case. This fact suggests that no side reaction took place in the reaction of tetralin and chloranil. In the reactions in which duroquinone was used instead of chloranil at 180° in the presence of $NiBr_2(PBu^n_3)_2$, $Pt(PPh_3)_4$, or $PtCl_2(PPh_3)_2$, 1,2-dihydronaphthalene and naphthalene were not detected and tetralin was recovered quantitatively.

The noncatalytic dehydrogenation of tetralins to naphthalenes by quinones has already been reported.[1]

Dehydrogenation of 2,5-Dihydrofuran. When 2,5-dihydrofuran and chloranil were heated in chlorobenzene at 140° for 2 hr, furan was obtained in 35% yield and the yield was not significantly influenced by the addition of $NiBr_2(PBu^n_3)_2$, $NiBr_2(PPh_3)_2$, or $CoBr_2(PPh_3)_2$. It has been reported that 3-phenylfuran was obtained in 10% yield by refluxing 3-phenyl-2,5-dihydrofuran and chloranil in ethylene glycol.[6]

Discussion

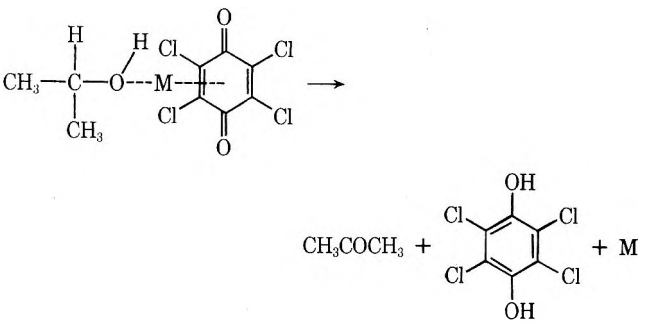
The reaction in which 2-propanol was used as a hydrogen donor is obviously catalytic, since the hydrogen transfer reaction did not occur at all in the absence of the metal complexes, and the amount of acetone formed varied greatly for different complexes, as seen in Table II. Two reaction pathways may be considered: (a) hydrogen atoms are transferred in the process of oxidative addition and reductive elimination which involves hydride complexes as is usual for hydrogenation,[4] and (b) the donor and the acceptor are brought together by simultaneous coordination to the central metal of the catalyst, and hydrogen atoms are transferred directly from the donor to the acceptor without involving hydride complexes and without changing the oxidation state of the metal.

Table II
Dehydrogenation of 2-Propanol by Chloranil[a]

Catalyst	Registry no.	Yield, % Acetone	2-Chloropropane	Recovered 2-propanol, %
None		0	0	98
$RhCl(PPh_3)_3$	14694-95-2	76	5	0
$RuCl_2(PPh_3)_3$	15592-49-4	73	5	12
$PdCl_2$	7647-10-1	38	5	56
$PdCl_2(PPh_3)_2$	13965-03-2	31	3	58
$MoCl_5$	10241-05-1	28	27	0
$RuCl_3\cdot H_2O$	10049-08-8	26	6	8
$NiBr_2(PBu^n_3)_2$	15242-92-9	21	6	76
$NiBr_2(PBu^n_3)_2$[b]		82	c	c
$Pt[P(p\text{-tolyl})_3]_4$	34053-78-6	21	4	72
$Al(OPr^i)_3$	51796-09-9	19	4	71
$Pt(PPh_3)_4$	14221-02-4	13	5	72
$PtCl_2(PPh_3)_2$	10199-34-5	12	7	69
$Pt[P(p\text{-ClPh})_3]_4$	51795-66-5	12	1	88
$NiCl_2(PPh_3)_2$		6	9	80
$FeCl_2(Bipy)$		5	1	85
$NiCl_2(PBu^n_3)_2$		4	15	71
$PdCl_2(PBu^n_3)_2$		4	7	72
$RhCl_3\cdot 2H_2O$		3	0	96
$CoCl_2(PPh_3)_2$		2	7	77
$RuCl_2(PPh_3)_3 + PPh_3$[d]		0	49	0
$FeCl_2(o\text{-Phen})$		0	0	96
$Ni(Acac)_2$		0	0	85

[a] 2-Propanol (0.25 mol), chloranil (0.25 mol), and a catalyst (0.025 mol) were heated at 170° for 2 hr in chlorobenzene. [b] 2-Propanol was used as a donor and solvent. [c] The yield could not measured. [d] Triphenylphosphine (0.25 mol) was added.

In catalytic hydrogen transfer from 2-propanol or dioxane to olefins, the formation of metal–hydride complexes occurs and is the rate-determining step.[2,3] In the transfer-hydrogenation of cyclopentane using 2-propanol as a donor, $RhCl(PPh_3)_3$, $RuCl_2(PPh_3)_3$, and $PtCl_2(PPh_3)_2$ showed catalytic activity under mild conditions, but $PdCl_2(PPh_3)_2$, $NiBr_2(PBu^n_3)_2$, $NiCl_2(PPh_3)_2$, and $CoCl_2(PPh_3)_2$ did not catalyze the reaction even after heating in 200° for 4 hr.[2] In the cases of those transition metal complexes that did not catalyze the transfer-hydrogenation of olefins, but did catalyze that of chloroanil, the assumption that hydrogen atoms are transferred directly *via* pathway b seems to be reasonable. Moreover, the assumption may be supported by the fact that the catalytic activity of $Al(OPr^i)_3$ in the reduction of chloranil was comparable to that of some transition metal complexes (Table II), and that Meerwein–Ponndorf–Verley reduction[7] and Oppenauer oxidation,[8] which are catalyzed by the aluminum complex, involve direct hydride transfer from alkoxide ions to coordinated carbonyl compounds.



It is presumed that vacant coordination sites on the metal are needed in this transfer-hydrogenation, since $RuCl_2(PPh_3)_3$ lost its high catalytic activity in the presence of excess triphenylphosphine; the complexes which had bidentate ligands also showed little activity.

When tetralin was used as a donor, the hydrogen transfer reaction was not influenced at all by the addition of metal complexes, suggesting that the reaction proceeds instead *via* change transfer complexes. That 1,2-dihydronaphthalene was always detected in the reaction of tetralin shows that this reaction is stepwise and that the driving force for the dehydrogenation of tetralin is not aromatization.

The dehydrogenation of 2,5-dihydrofuran, which has a heteroatom and a double bond, also was not influenced by the addition of metal complexes, and is again presumed to be a noncatalytic reaction.

Experimental Section

Materials. 2-Propanol, tetralin, 2,5-dihydrofuran, and all solvents were purified by distillation. Chloranil was recrystallized from toluene. Duroquinone, chlorotris(triphenylphosphine)rhodium(I),[10] dichlorotris(triphenylphosphine)ruthenium(II),[11] dichlorobis(triphenylphosphine)palladium(II),[12] dichlorobis(tri-*n*-butylphosphine)palladium(II),[13] tetrakis(triphenylphosphine)platinum(0),[14] tetrakis(tri-*p*-tolylphosphine)platinum(0),[14] tetrakis(tri-*p*-chlorophenylphosphine) platium(0),[14] dichlorobis(triphenylphosphine)platinum (II),[15] dichlorobis(tri-*n*-butylphosphine)nickel(II),[16] dibromobis(tri-*n*-butylphosphine)nickel(II),[16] dichlorobis(triphenylphosphine)nickel(II),[17] dibromobis(triphenylphosphine)nickel(II),[17] dichlorobis(triphenylphosphine)cobalt(II),[18] 2,2′-bipyridinedichloroiron(II),[19] o-phenanthrolinedichloroiron(II),[19] and dibromobis(triphenylphosphine)cobalt(II)[18] were prepared by the methods reported in the literature. $PdCl_2$, $MoCl_5$, $RuCl_3 \cdot H_2O$, $RhCl_3 \cdot 2H_2O$, $Al(OPr^i)_3$, $Ni(acac)_2$, 1,2-dihydronaphthalene, 2-chloropropane and tetrachlorohydroquinone were purchased and used without purification.

An Example of Dehydrogenation of 2-Propanol. Chloranil (61.5 mg, 0.25 mmol), 2-propanol (19.1 μl at 25°, 0.25 mmol), and $NiBr_2(PBu^n_3)_2$ (15.6 mg, 0.025 mmol) were put into a Pyrex glass tube which had been sealed at one side. Chlorobenzene was added to make the total volume of the solution 1.0 ml. The tube was sealed under vacuum after two freeze–pump–thaw cycles at 10^{-3} Torr on a vacuum line, using liquid nitrogen. The sealed tube was heated for 2 hr in a silicone oil bath kept at 170 ± 1°. Chloranil and the catalyst dissolved slowly at room temperature but quickly at the elevated temperature. Gc analysis was performed at 100° with a Hitachi Perkin-Elmer instrument equipped with a flame ionization detector, using a 2 m × 6 mm stainless column packed with 20% Carbowax on Celite 545. As an internal standard 15 μl of *n*-decane was used. By recrystallization of the resulting precipitate from acetone, pure tetrachlorohydroquinone was obtained, ν_{OH} 3350 cm^{-1} (sharp).

The other dehydrogenation reactions of 2-propanol were carried out in a similar way.

An Example of Dehydrogenation of Tetralin. Tetralin (34.1 μl at 25°, 0.25 mmol), chloranil, and $NiBr_2(PBu^n_3)_2$ were treated as in the reaction of 2-propanol described above, except that the reaction temperature was either 160 or 180°. Gc analysis was carried out at 170° using phenylcyclohexane as an internal standard.

An Example of Dehydrogenation of 2,5-Dihydrofuran. Chloranil, 2,5-dihydrofuran (18.4 μl at 25°, 0.25 mmol), and $NiBr_2(PBu^n_3)_2$ were treated as in the reaction of 2-propanol, except that the reaction temperature was 140°. Gc analysis was carried out at 100°, using a 2 m × 6 mm stainless steel column packed with 10% silicon DC 11 on Diasolid L. As an internal standard 15 μl of *n*-heptane was used.

Registry No.—2-Propanol, 67-63-0; chloranil, 118-75-2; tetralin, 119-64-2; 2,5-dihydrofuran, 1708-29-8.

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$HCo(CO)_4$ and the Hydroformylation Reaction

Alan C. Clark, John F. Terapane, Jr., and Milton Orchin*

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

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The rate of the stoichiometric hydroformylation reaction and the rate of the decomposition of $HCo(CO)_4$ are affected in a strikingly similar manner by the presence of *p*-methoxybenzonitrile. Apparently this results from a common dependence on the concentration of $HCo(CO)_3$, the key intermediate in both reactions.

The stability and reactivity of $HCo(CO)_4$ are key considerations in both the catalytic and the stoichiometric hydroformylation of olefins. The presence of nucleophiles such as tri-*n*-butylphosphine has a substantial effect on the catalytic process,[1] and in a recent paper[2] we have shown that the presence of *p*-methoxybenzonitrile has a profound effect on the course of the stoichiometric reaction. In the present paper, we show that the presence of *p*-methoxybenzonitrile affects the rate of $HCo(CO)_4$ decomposition in a manner virtually parallel to its effect on the hydroformylation reaction. This parallelism apparently resides in the effect that the nitrile has on the concentration of the key, coordinately unsaturated intermediate, $HCo(CO)_3$, which is in equilibrium with $HCo(CO)_4$.

Experimental Section

A typical reaction was conducted as follows. A toluene solution of $HCo(CO)_4$, prepared and analyzed according to established

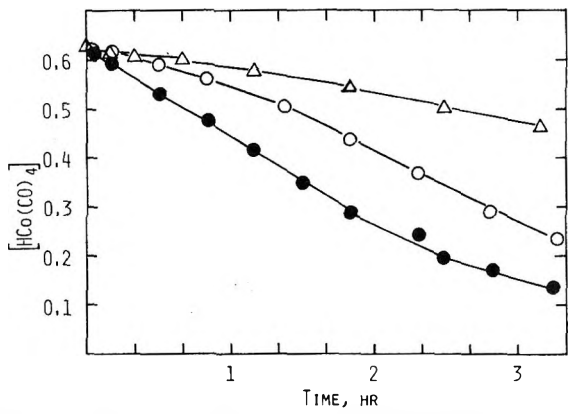


Figure 1. The decomposition of $HCo(CO)_4$ under CO at 25°: △, $DCo(CO)_4$; ○, $HCo(CO)_4$; ●, $HCo(CO)_4$, 0.059 *M* $Co_2(CO)_8$ ($k_H/k_0 = 1.7$).

procedures,[3] was equilibrated for 10 min at the desired reaction temperature under 1 atm of CO and syringed into a stirred toluene solution of *p*-methoxybenzonitrile, which had been equilibrated for 10 min under the desired reaction conditions. In each experiment, the quantity of toluene was adjusted to maintain the same initial reaction mixture volume in the presence of various amounts of nitrile. The concentration of remaining $HCo(CO)_4$ was determined at appropriate intervals: 1-ml aliquots were withdrawn, quenched by addition to excess 0.1 *N* NaOH under nitrogen, and back-titrated with 0.02 *N* HCl to the phenolphthalein end point.

Results

Our previous, unpublished observations[4] that the second-order decomposition of $HCo(CO)_4$ in solution was strongly inhibited by carbon monoxide and exhibited only a small kinetic deuterium isotope effect, as depicted in Figure 1, were essentially corroborated in the publication of Ungvary and Marko.[5] In addition, we found that the presence of as little as 0.1 equiv of $Co_2(CO)_8$ per $HCo(CO)_4$ substantially reduced the commonly observed induction period, apparent in Figure 1, and caused a slight rate increase.

During our study of the effect of *p*-methoxybenzonitrile on the hydroformylation of cyclopentene, we reexamined separately the decomposition of $HCo(CO)_4$ under similar conditions. We found a striking parallelism between the sensitivities of these seemingly dissimilar reactions to the presence of nitrile, as Figure 2 shows. In both instances, the presence of nitrile caused a severe rate reduction under N_2 and a significant rate enhancement under CO.

In order to clarify these findings, we examined the dependence of the rate of $HCo(CO)_4$ decomposition on the quantity of *p*-methoxybenzonitrile under both N_2 and CO atmospheres. The results of this study are depicted in Figure 3. Under N_2 the presence of as little as 0.1 equiv of nitrile causes a dramatic rate reduction but the effect rapidly diminishes with increasing amounts of nitrile and is even reversed when more than 1 equiv of nitrile is present. Under CO, the presence of small amounts of nitrile causes only a small but reproducible rate decrease; amounts greater than 1 equiv reverse the trend to such an extent that the decomposition becomes faster than in the absence of nitrile.

Discussion

The kinetics of the decomposition of $HCo(CO)_4$ in solution have been shown to be similar to, but more reproducible than, those obtained in the gas phase.[5] The derived rate expression exhibits a second-order dependence on $HCo(CO)_4$ and an inverse dependence on the partial pressure of CO; it is consistent with the mechanism depicted in the left half of Figure 4. The rate-retarding effect of CO

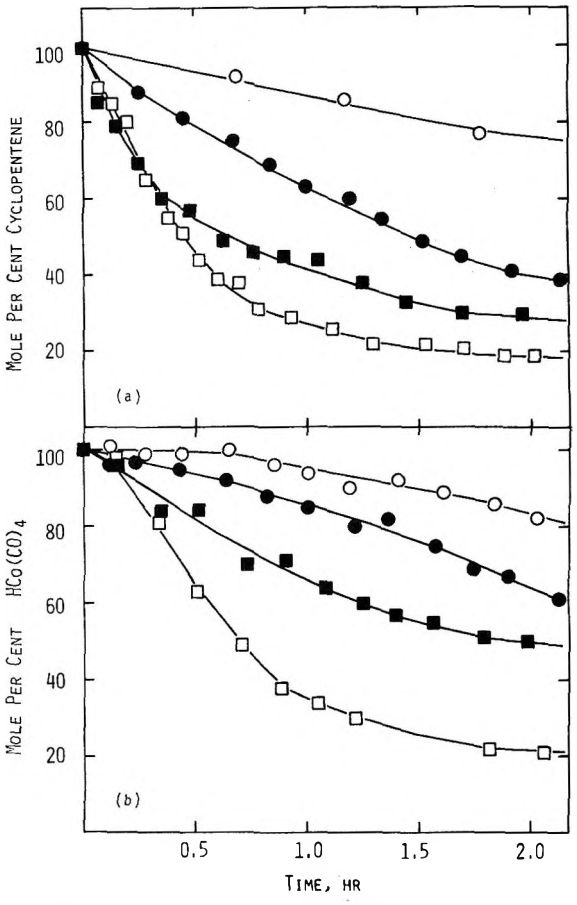


Figure 2. (a) The stoichiometric hydroformylation of cyclopentene ($[M]_0 = 0.02$) with excess $HCo(CO)_4$ ($[M]_0 = 0.32$), ArCN/Co = 1.0, at 30° and (b) the decomposition of $HCo(CO)_4$ ($[M]_0 = 0.27$), ArCN/Co = 1.8, at 30°: ●,○, under CO; ■,□, under N_2. Solid and open symbols represent data with and without *p*-methoxybenzonitrile, respectively.

is attributed to a reduction in the equilibrium concentration of $HCo(CO)_3$. In addition, the decompositions under CO characteristically exhibit substantial induction peri-

$$-\frac{d[HCo(CO)_4]}{dt} = \frac{k_2K}{p_{CO}}[HCo(CO)_4]^2$$

ods; and we suggest that during this initial phase of the decomposition, a reaction occurs, which increases the concentration of $HCo(CO)_3$. The apparent ability of added $Co_2(CO)_8$ to reduce these induction periods and the known lability of CO in this complex[6] suggest that $HCo(CO)_4$ may react with $Co_2(CO)_7$ to give a trinuclear complex which subsequently dissociates to give $Co_2(CO)_8$

$$HCo(CO)_4 + Co_2(CO)_7 \longrightarrow [HCo_3(CO)_{11}] \longrightarrow Co_2(CO)_8 + HCo(CO)_3$$

and $HCo(CO)_3$. Solvent cage effects such as those discussed previously[2] are consistent with such an irreversible bimolecular reaction giving rise to a higher equilibrium concentration of $HCo(CO)_3$ than the simple reversible dissociation of $HCo(CO)_4$. The possibility that $Co_2(CO)_8$ simply absorbs dissolved CO and hence increases the concentration of $HCo(CO)_3$ does not appear likely at atmospheric pressure.[7]

When an additional nucleophile, such as *p*-methoxybenzonitrile, is introduced into the reaction mixture, the mechanistic scheme is significantly complicated by the possible formation of several nitrile complexes. However, if we assume, as a first approximation, that the reactivity of each nitrile complex is similar to that of its corresponding carbonyl complex, the kinetic consequences are mini-

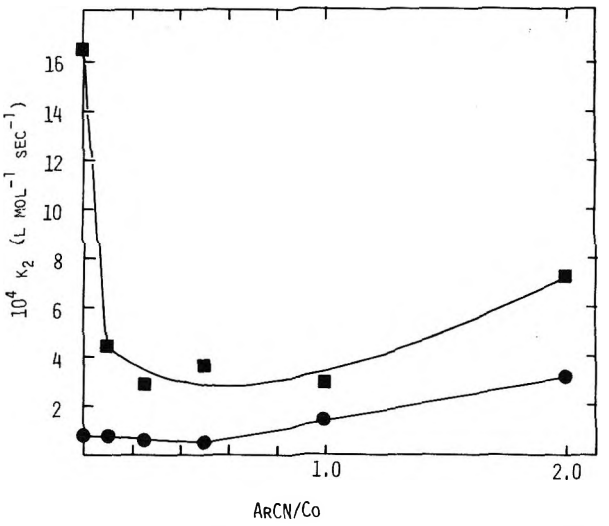


Figure 3. The effect of *p*-methoxybenzonitrile concentration on the decomposition of $HCo(CO)_4$ ($[M]_0$ = 0.29) at 25° under N_2 (■) and under CO (●).

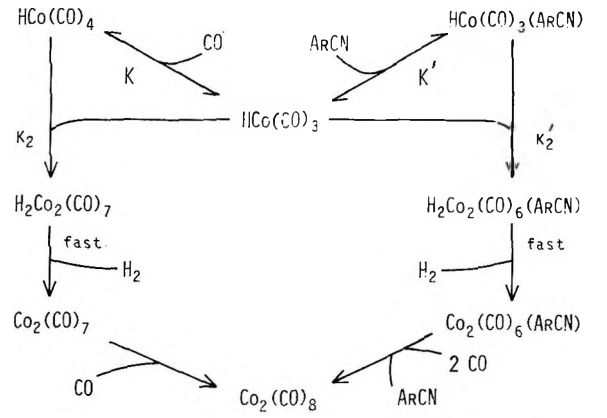


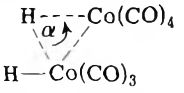
Figure 4. Scheme for the decomposition of $HCo(CO)_4$ with and without *p*-methoxybenzonitrile, (ArCN).

mal except for the expectation that the formation of $HCo(CO)_3(ArCN)$ would reduce the equilibrium concentration of $HCo(CO)_3$ as the scheme on the right of Figure 4 suggests. This expectation is apparently fulfilled, since small amounts of nitrile inhibit the decomposition of $HCo(CO)_4$ under both N_2 and CO. However, attempts to confirm the existence of $HCo(CO)_3(ArCN)$ by ir and nmr spectroscopy or to trap it with $Ni(o\text{-phen})_3Cl_2$[8] failed.

The much larger rate decrease observed under nitrogen can be attributed to the much greater amount of $HCo(CO)_3$ available for complexation of nitrile under N_2 as opposed to the few tenths of one per cent[5] available under CO. The fact that the minimum rate of decomposition achieved in the presence of nitrile (1 equiv, 0.288 *M*) under N_2 is much faster than the rate of decomposition in the absence of nitrile under CO (solubility, 7×10^{-3} *M* in toluene at 1 atm[6]) suggests that, as shown in Figure 4, $K' > K$. This conclusion is consistent with the suggestion that nitriles are more weakly bound than CO by virtue of their poorer σ-donating and π-accepting properties.[9]

The observation that the rate of decomposition increases with increasing amounts of nitrile after reaching a broad minimum under both N_2 and CO remains difficult to explain. At relatively high nitrile concentrations, the proportion of cobalt hydride present as $HCo(CO)_3(ArCN)$ may be large and this complex could be somewhat more reactive toward $HCo(CO)_3$ than $HCo(CO)_4$ is, *i.e.*, $k_2' > k_2$, Figure 4. However, before such a comparison can be made, it would be necessary to know more about the detailed mechanism by which the postulated, but as yet undetected, intermediate $H_2Co_2(CO)_7$ is formed.

Increasing amounts of nitrile undoubtedly increase the dielectric constant of the reaction medium. However, the dielectric increase can increase the rate of $HCo(CO)_4$ decomposition only if the rate-determining step involves the formation of charged species or a polar transition state. Similar solvent effects have been observed for the conversion of $CH_3Mn(CO)_5$ to $CH_3COMn(CO)_5$[10] and a variety of oxidative additions to $IrCl(CO)(PPh_3)_2$.[11] The small deuterium kinetic isotope effect which we and others have observed is not necessarily inconsistent with the concerted oxidative addition of $HCo(CO)_4$ to $HCo(CO)_3$ which we



propose as a reasonable rate-determining step. Hydrogen transfers which involve nonlinear ($\alpha < 180°$) transition states characteristically exhibit small isotope effects,[12] and indeed the oxidative addition of molecular hydrogen to $IrCl(CO)(PPh_3)_2$ to give $H_2IrCl(CO)(PPh_3)_2$ exhibits a $k(H_2/D_2)$ of only 1.22.[11]

Registry No.—$HCo(CO)_4$, 16842-03-8; *p*-methoxybenzonitrile, 874-90-8.

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Electroorganic Chemistry. II.[1] Electroreduction of Vicinal Dibromides

Joseph Casanova* and Harold R. Rogers

Department of Chemistry, California State University, Los Angeles, Los Angeles, California 90032

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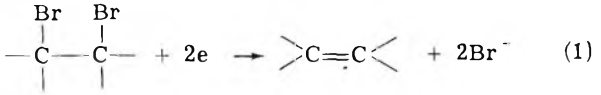
Electroreduction of vicinal dibromides at a stirred mercury cathode produces quantitative yields of olefins under very mild conditions. The resulting stereochemistry suggests that elimination from the trans-periplanar conformation is strongly preferred, if such conformation is accessible. Attempts to intercept a carbanionic intermediate were unsuccessful, indicating that the reductive elimination is either synchronous at both reacting centers or nearly so.

The reductive elimination of vicinal dibromides to produce olefins is a venerable reaction which has received limited attention,[2] inasmuch as the product olefin is usually also the starting point for the preparation of the dibromide. Reductive elimination involving zinc[3] has been exploited in steroid chemistry,[4] and more recently in the preparation of cyclobutadiene dimers.[5] Polarographic studies have shown a marked dependence of half-wave potential for the reduction of vicinal dibromides on the dihedral angle between the C–Br bonds,[6] and the product studies of this reaction[7] have shown that the overall process may be represented as follows.



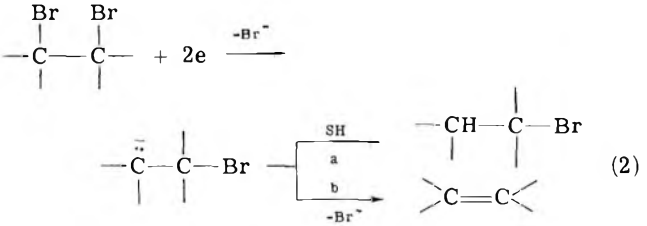
(1)

However, the details of the electrochemical process illustrated in eq 1 were ambiguous. Elving and coworkers[8] reported that both *meso*- and *dl*-2,3-dibromosuccinate ethyl esters gave diethyl fumarate at all values of pH, whereas *meso*-2,3-dibromosuccinic acid gave fumaric acid, but *dl*-2,3-dibromosuccinic acid gave maleic or fumaric acid, depending upon pH. The lack of stereospecificity suggests the intervention of an intermediate carbanion or, alternatively,[9a] steric requirements which preclude the trans-periplanar conformation. Fry[9b] proposed that the reduction is concerted in cases for which the dihedral angle is favorable for p overlap in the transition state, but stepwise carbanionic in cases for which overlap of developing p orbitals is unfavorable. Free-radical intermediates have also been proposed to account for the products.[10] In one system studied which was particularly susceptible to carbanion formation (1,2-dibromo-1-chloro-1,2,2-trifluoroethene), Feoktestov[11] has reported two polarographic waves, the height of which depended upon the acid concentration, and which were interpreted as due to carbanion formation from the two stable conformers.

Electroreduction of 1,2-dibromides as a preparative method offered at attractive alternative to existing procedures, owing to the potential mildness of the reaction conditions and to the unique feature of electrochemistry, which places more reaction variable control in the hands of the experimenter.[12] It was the purpose of this investigation to establish the stereochemistry of this elimination process, to search for the intervention of possible carbanionic intermediates, and to assess the synthetic utility of this method.

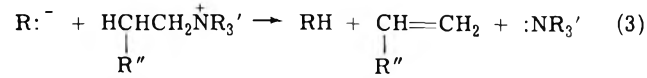
Results and Discussion

Electroreduction of seven representative 1,2-dibromides was carried out in a compartmented cell of the design shown in Figure 1. The reductions were conducted at a stirred mercury cathode, using controlled potential electrolysis (cpe). For those reactions in which a gaseous product would be expected, the effluent gas stream was collected at −190°, fractionated using standard vacuum line techniques, and analyzed by gas–liquid phase chromatography. In all reductions the olefinic products formed in quantitative or nearly quantitative yields. The reactions were conducted at potentials which were normally 0.2 V or more negative than the half-wave potentials for the particular dibromide. Table I shows the results of these experiments. Most striking is the observation that excellent yields of olefins form at low negative potentials in all cases studied. The complete stereospecificity observed requires that elimination take place from the trans-periplanar conformation, when such a conformation is possible. This result suggests that the elimination may be concerted (entries 1–4, Table I). In order to test this possibility and to examine the possibility of a discrete anion intermediate (eq 2), a number of reductions were



(2)

carried out in the presence of protonic substances known to be effective for anion capture during electroreduction of carbon–halogen bonds[10-14] (entries 5–9, 11, and 14, Table I). In no case was any product of proton capture obtained. This clearly implies the absence of a carbanion. Even those cases which should be most favorable to carbanion formation, 1,2-dibromo-2-phenylpropane (entry 9, Table I) and 1-bromo-*trans*-2-bromo-*trans*-4-*tert*-butylcyclohexane (entries 13 and 14, Table I), failed to yield any monobromide or saturated hydrocarbon. In the latter case, the Br–C–C–Br dihedral angle is approximately 65°, and should be unfavorable for concerted elimination. The present result with 1-bromo-*trans*-2-bromo-*cis*-4-*tert*-butylcyclohexane (entry 12, Table I) confirms a previously published account of the electroreduction of this compound,[15] in which reduction in dimethylformamide–5% water was found to yield no alkane. Olefins have been reported frequently as minor products from the Hofmann elimination reactions of tetraalkylammonium salts and presumed carbanions in electroreduction[11,16] (eq 3). The



(3)

complete absence of Hofmann products in the present study is further evidence against a discrete carbanionic intermediate, and is consistent with current views of the process.[17] Moreover, reduction of 1,2-dibromoethane, which had been previously reported to give ethane,[7] in our hands (entry 8, Table I) failed to produce any trace of

Table I
Electroreduction of Vicinal Dibromides

Registry no.	Entry	Compd, solvent	Potential −V, V[a]	Initial current, mA	Added proton source	Current[b] efficiency	Product(s) (yield, %)
5780-13-2	1	*meso*-2,3-Dibromobutane[c,d]	1.10	75	None	95	*trans*-2-Butene (quant)
	2	*meso*-2,3-Dibromobutane[d]	2.00	1000	None	95	*trans*-2-Butene (quant)
598-71-0	3	*dl*-2,3-Dibromobutane[d]	1.10	65	None	90	*cis*-2-Butene (quant)
	4	*dl*-2,3-Dibromobutane[d]	1.77	1000	None	95	*cis*-2-Butene (87)
	5	*dl*-2,3-Dibromobutane[d]	1.86	690	MeOH (10)[e]	79	*cis*-2-Butene (quant)
78-75-1	6	1,2-Dibromopropane[d]	1.50	375	MeOH (10)[e]	77	Propene:cyclopropane, 99.5:0.5[f] (95)
	7	1,2-Dibromopropane[g,h]	2.20	200[i]	H_2O[j]		Propene:cyclopropane, 99.6:0.4[f] (85)
106-93-4	8	1,2-Dibromoethane[g,h]	2.60	130[k]	H_2O[j]		Ethene (*ca.* 90)
36043-44-4	9	1,2-Dibromo-2-phenylpropane[d]	2.40[l]	450	AcOH (5)[m]		2-Phenylpropene (66)[n]
31734-61-9	10	1,2-Dibromo-4-*tert*-butylcyclohexane[d,o]	0.86	150	None	100	4-*tert*-Butylcyclohexene (quant)[p]
	11	1,2-Dibromo-4-*tert*-butylcyclohexane[d,q]	1.30	275	MeOH (10)[e]	87	4-*tert*-Butylcyclohexene quant)[r]
	12	1,2-Dibromo-4-*tert*-butylcyclohexane[d,s]	1.43	450	None	95	4-*tert*-Butylcyclohexene (94)
	13	1,2-Dibromo-4-*tert*-butylcyclohexane[d,t,u]	1.99	500	None	~75	4-*tert*-Butylcyclohexene (96)
	14	1,2-Dibromo-4-*tert*-butylcyclohexane[d,t,u]	1.90	375	MeOH (10)[e]	89	4-*tert*-Butylcyclohexene hexene (97)

[a] Potentials were measured *vs.* saturated calomel electrode. [b] Per cent calculated as $10^2 \times$ millifaradays required for a two-electron process/millifaradays passed. [c] Usually 5 mmol. [d] Dimethylformamide, with 0.2 *M* tetra-*n*-butylammonium fluoroborate. [e] 10 *M* methanol added to solvent. [f] Starting dibromide contained traces of 1,3-dibromopropane, and this product may be an artifact. [g] Dioxane–water (3:1 v/v). [h] Supporting electrolyte 0.05 *M* tetraethylammonium bromide. [i] Potential increased after 45 min to produce 450 mA. [j] See footnote *g*. [k] Potential increased after 45 min to produce 300 mA. [l] Vitreous carbon cathode. [m] 5 *M* acetic acid added to solvent. [n] Substantial amount of unidentified white solid in catholyte. [o] 75:25 mixture of diaxial:diequatorial dibromide, respectively. [p] 25% of pure diequatorial dibromide was recovered unreacted. [q] 60:40 mixture of diaxial:diequatorial dibromide, respectively. [r] 40% of pure diequatorial dibromide was recovered unreacted. [s] Pure diaxial isomer. [t] Pure diequatorial isomer. [u] Supporting electrolyte 0.2 *M* tetraethylammonium fluoroborate.

ethane using a dioxane–water solvent. Our conditions would have permitted the detection of as little as 0.3% of the saturated hydrocarbon. This previous report has given rise to speculation about a carbanion intermediate[18] which is no longer tenable.

Hence, the technique of electroreduction affords a superior method for the reductive elimination of vicinal dibromides, leading to the product of exclusively trans elimination, if the appropriate conformation is possible. The product appears to be formed in a synchronous two-electron transfer from the shape of the chronoamperometric (potentiostatic) curve,[19] and the process can be conducted in a highly protonic medium without deleterious results. It is noteworthy that, owing to the sensitivity of the reduction potential to the dihedral angle between vicinal C–Br bonds in rigid 1,2-dibromides, it is possible now to synthesize otherwise inaccessible isomers by selective destruction of the more easily reduced partner in a mixture. One example of this is seen in Table I (entries 10 and 11), in which the diequatorial dibromide could be recovered cleanly from the cpe of a mixture of the diaxial and diequatorial isomers. To our knowledge, the present procedure represents the only reduction procedure suitable for such a selective reduction. In addition, the mildness and variety of reduction conditions suggest this to be the method of choice for the synthesis of sensitive olefins from the dibromide. A recent example of this was reported recently in the preparation of benzocyclobutadiene dimer in 90% yield from 1,2-dibromobenzocyclobutene.[20]

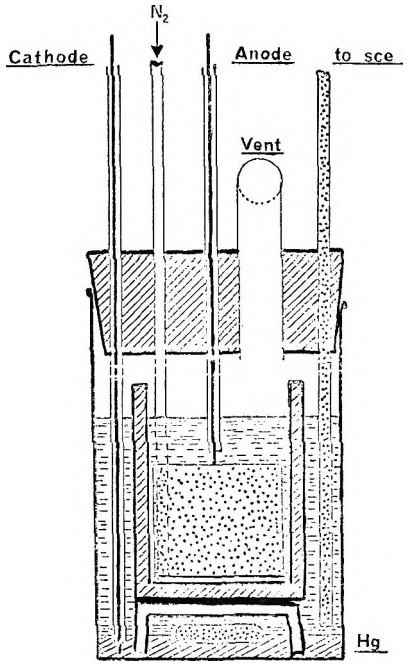


Figure 1.

Experimental Section

General. Boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer using carbon tetrachloride solutions with internal tetramethylsilane. Analytical glpc was performed using a Porapak Q, 80–100 mesh, 3 m × 0.125 in. column at 80° for gases. Liquids were analyzed on a Carbowax 20M column, 15%, 10 ft × 0.25 in., using a Varian Model 90P chromatograph.

Chemicals. Mercury was Bethleham instrument grade. It was recycled by washing three times with 50% nitric acid, flooding with water, washing three times with 95% ethanol, and finally washing three times with ether. It was dried and degassed at room temperature under vacuum (*ca.* 0.1 mm) for more than 24 hr. Dimethylformamide was purified by stirring for at least 48 hr over calcium hydride and distilling under vacuum, and the fraction boiling at 64° (30 mm) was collected, stirred with phthalic anhydride, and redistilled under the same conditions. Tetra-*n*-butylammonium fluoroborate was prepared[21] from tetra-*n*-buty-

lammonium hydrogen sulfate (Aldrich Chemical Co.) and sodium tetrafluoroborate (Alfa Chemical Co.). Tetraethylammonium fluoroborate (Southwest Analytical Chemicals) and tetraethylammonium bromide (Eastman Chemical Co.) were commercial and were used without further purification. 1,2-Dibromopropane was commercial and was distilled, the fraction of bp 32° (0.1 mm) being collected. *meso*- and *dl*-2,3-dibromobutane were prepared from *trans*- and *cis*-2-butene, respectively, by the method of Young,[22] and the fractions boiling at 28.5° (0.1 mm) and 27° (0.15 mm) were collected. 4-*tert*-Butylcyclohexene was prepared according to Sicher and coworkers,[23] bp 34° (2 mm), and converted to 1-bromo-*trans*-2-bromo-*cis*-4-*tert*-butylcyclohexane in 98% isomeric purity using pyridinium hydrobromide perbromide,[24,25] bp 105° (1.5 mm) [lit.[15] bp 78–80° (1 mm) and lit.[26] bp 68° (0.3 mm)]. 1-Bromo-*trans*-2-bromo-*cis*-4-*tert*-butylcyclohexane was converted to a mixture of geometric isomers (ratio diaxial:diequatorial normally *ca.* 3:2) by heating the neat liquid in the dark under nitrogen for 48 hr.[26]

1,2-Dibromo-2-phenylpropane.[27] α-Methylstyrene (2.84 g, 24 mmol) in 15 ml of chloroform was treated with a solution of 4.5 g (28 mmol) of bromine in 20 ml of chloroform at 0°. When the addition was complete, the mixture was washed with cold aqueous sodium sulfite, cold aqueous sodium bicarbonate, and finally water. It was dried over anhydrous calcium chloride, filtered, and concentrated. The residual oil was distilled to give a pale yellow liquid, bp 95–97° (0.07 mm), nmr 2.28 (3, s, $-CH_3$), 4.20 (2, q, $-CH_2Br$), 7.2–7.6 ppm (5, m, $-C_6H_5$).

Electrolysis Experiments. The electrolysis cell used in this work is shown schematically in Figure 1. It consisted of an unjacketed 150-ml cylinder (54 mm i.d. × 90 mm height) equipped with a magnetic stirring bar. The cathode was a *ca.* 5-mm depth pool of mercury placed in the bottom of the cell. Electrical connection was made by a small piece of platinum, sealed in glass and immersed in the mercury. A platinum anode (44 × 24 mm foil) was placed in a clean,[28] porous ceramic bucket (45 mm o.d.) that was supported in the cell by a glass tripod. The apparatus was fitted with a five-hole rubber stopper. Two holes were used for the cathode and anode connections, one for an agar bridge which was in contact with an external saturated calomel electrode (sce), one for the nitrogen inlet, and one for the outlet. The outlet hole was fitted with a ball joint that could be connected directly to a cold trap. During controlled potential electroreduction, achieved by means of a potentiostat,[29] a constant stream of nitrogen was passed through the cell, and the volatile products were collected in a cold trap at liquid nitrogen temperature. The trap was so designed that the contents could be pumped directly into a high-vacuum line after electrolysis was completed. For reactions in which no volatile products were expected the cold trap was replaced by a drying tube. All components of the cell were dried in an oven overnight at 110° prior to use. The ceramic bucket was dried at least three days after extraction.[28]

In a typical run, the substrate (1–5 mmol) was added to the catholyte and the system was purged with dry nitrogen. Typical catholyte and anolyte charges were 75 and 25 ml, respectively. Current yields were calculated by cut and weigh methods, using the data from an amperometric strip chart recorder connected as a coulometer.[30] Gaseous products, after transfer to a high-vacuum line, were fractionated at the appropriate temperatures to remove solvent, and the amount of gas was measured volumetrically. Yields were calculated from low-pressure samples using the gas law. A homogeneous gas sample was removed and analyzed by glpc, and the identity of various peaks was established by comparison to authentic samples of candidate compounds. Nmr and ir identification confirmed the structural assignment of all compounds. Nongaseous products were purified by extraction of the catholyte. Typically, the catholyte was diluted with 100 ml of water and extracted with 3 × 50 ml of ether. The combined organic extracts were washed with saturated salt solution (3 × 25 ml) and water (3 × 25 ml), then dried over anhydrous sodium sulfate. The extract was examined directly by glpc, then concentrated under vacuum (if appropriate) and analyzed by nmr and glpc. All runs were repeated several times to ensure reproducibility.

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(30) Simpson Multicorder 605, Simpson Electric Co., Chicago, Ill.

Correlation of Configuration of Chiral Secondary Carbinols by Use of a Chiral Lanthanide Nuclear Magnetic Resonance Shift Reagent[1]

Glenn R. Sullivan, David Ciavarella, and Harry S. Mosher*

Department of Chemistry, Stanford University, Stanford, California 94305

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The nmr chemical shifts induced in a series of 12 pairs of enantiomers of secondary carbinols of known configuration by the chiral shift reagent tris[(3-heptafluorobutyryl)-*d*-camphorato]europium(III), *d*-Eu(HFC)$_3$, have been measured and correlated. In the presence of this chiral shift reagent at least one signal from each carbinol serves to distinguish one enantiomer from the other. Thus this reagent can be used for the determination of enantiomeric purity of these secondary carbinols. The signal from the carbinyl proton uniformly has the largest europium-induced chemical shift ($\Delta\delta$) and generally but not always is the signal for which the largest chemical shift difference between enantiomers ($\Delta\Delta\delta_{R\text{-}S}$) is observed. A direct correlation between configuration and chemical shift differences, $\Delta\Delta\delta_{R\text{-}S}$, for the proton attached to the carbinyl carbon in the secondary carbinols RCHOHR' was not observed. However, there was a consistent pattern to the chemical shift differences for the protons in either R or R'. This study reveals that great care will be required in the application of chiral shift reagents for the establishment of configurations based on empirical correlations.

Since the first report of a chiral lanthanide shift reagent[2] (LSR), a wide variety of such chiral reagents have been synthesized and used with many compounds. It has been shown that in the presence of these reagents the nmr signals of enantiotopic groups on virtually all chiral molecules containing the necessary functionalities can be distinguished under the appropriate conditions.[3-15] This technique has been generally accepted for the direct determination of enantiomeric purity. Recently, the use of these reagents for the correlation of configuration in closely related compounds has been demonstrated for a series of α-amino esters,[3] a series of 1-deuterio primary alcohols,[4] and a series of alkyl aryl carbinols.[15] Whitesides[5] and Goering[6] have also considered the possible use of chiral shift reagents for configuration correlation but have not explored it further.

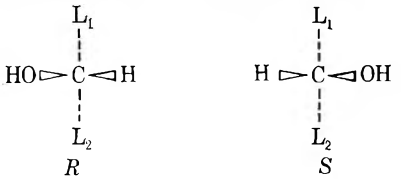
The use of the chiral europium shift reagent tris[(3-heptafluorobutyryl)-*d*-camphorato]europium(III), *d*-Eu(HFC)$_3$, for this purpose has now been extended to the 12 chiral secondary alcohols shown in Table I. The groups L_1 and L_2 in this table are specified such that L_1 has the lower priority in the Cahn, Ingold, and Prelog nomenclature scheme.[16] This is an arbitrary assignment which in the absence of heteroatoms in either R group generally designates the less bulky group as L_1. In Table I are listed the lanthanide-induced shifts (LIS or $\Delta\delta$) of the signals for the enantiomers, the differences in the lanthanide-induced shifts (ΔLIS or $\Delta\Delta\delta$) for the *R* and *S* enantiomers, and the molar ratios (LSR/substrate) at which the spectra were recorded.

There are basically three series represented by the compounds in Table I. In the first series L_1 is equal to methyl, while L_2, the larger group, is varied; in the second series L_2 is equal to phenyl (generally the more bulky group), while L_1 is varied. The third series comprises the four examples containing a *tert*-butyl group, namely, the last two entries and the member of each of the other series which contains a *tert*-butyl group. There is a definite correlation in the configuration of the carbinol and the sense of nonequivalence in the europium-induced shift difference ($\Delta\Delta\delta_{R\text{-}S}$) for the L_1 and L_2 proton resonances. Without exception the $\Delta\Delta\delta_{R\text{-}S}$ values for the protons on the L_1 substituents were negative. The corresponding values for the L_2 substituents were also negative where a difference was observed, but in the latter case four examples failed to show any difference. However, the $\Delta\Delta\delta_{R\text{-}S}$ values for the signals from the protons on the carbinyl carbon did not show this uniformity; four were zero, five were positive, and three were negative. It may be significant that the three examples with negative $\Delta\Delta\delta_{R\text{-}S}$ values for the carbinyl proton signals were substituted *tert*-butylcarbinols (methyl, *n*-butyl, and phenyl).

These limited results indicate that a reliable configurational correlation for secondary carbinols, L_1CHOHL_2, in general cannot be based on the $\Delta\Delta\delta_{R\text{-}S}$ value for the proton on the carbinyl carbon, contrary to the suggestion of Červinka, *et al.*[15] However, the uniformly negative $\Delta\Delta\delta_{R\text{-}S}$ values for the proton signals on the L_1 and L_2 substituents, when observable, indicate that the correlation of these signals with configuration may be general. Such a correlation should prove reliable and valuable when applied within a closely related series and with due consideration for the nature of the substituent groups. Secondary carbinols which have L_1 and L_2 substituents which are unsaturated or contain heteroatoms very likely will constitute special cases. By studying several members of a coherent series of such compounds, however, a suitably specialized correlation might emerge.

There seems to be no readily apparent direct relationship between the difference in steric requirements of L_1 and L_2 and the *magnitude* of the $\Delta\Delta\delta_{R\text{-}S}$ values, as one might have anticipated. There is a hint that as the substrate becomes more sterically hindered around the carbinol carbon by virtue of increasing size of both L_1 and L_2 the $\Delta\Delta\delta_{R\text{-}S}$ values increase. This is seen in progressing from methylethylcarbinol to methyl-*tert*-butylcarbinol and finally to *n*-butyl-*tert*-butylcarbinol. However, a similar progression is not followed in the alkylphenylcarbinol series. Under comparable conditions the largest induced shift difference, $\Delta\Delta\delta_{R\text{-}S}$, reported in Table I is -0.65 ppm for the carbinyl proton signal of (*R*)- and (*S*)-*n*-butyl-*tert*-butylcarbinol. This might be rationalized by postulating that the steric hindrance of the *n*-butyl group some distance from the site of the complexation of the europium to the oxygen was more important in determining the magnitude of enantiomer chemical shift differences than steric requirements closer to the carbinyl carbon. However, this is not borne out by the negligible $\Delta\Delta\delta$ value for the corresponding signal in methyl-*n*-hexylcarbinol. It is possible that the effect may be present in the methylene signals of the *n*-hexyl group (L_2), but the complex nature of the signals in this region renders such an analysis of the 100-MHz spectrum impractical. We conclude that the overall conformational fit of the chiral shift reagent with the *R* *vs.* *S* enantiomers is very specific and so sensitive to small steric and electronic differences in the substrate ligands that any *simple quantitative* correlation of magnitudes of $\Delta\Delta\delta_{R\text{-}S}$ values is not possible.

Table I
Chemical Shift Differences Induced by the Chiral Shift Reagent *d*-Eu(HFC)$_3$ in Enantiomeric Secondary Carbinols



Registry no. R	Registry no. S	L_1CHOHL_2 L_1	L_2	Carbinyl proton $\Delta\delta_R$[a]	$\Delta\delta_S$	$\Delta\Delta\delta_{R-S}$[b]	L_1 $\Delta\delta_R$	$\Delta\delta_S$	$\Delta\Delta\delta_{R-S}$	L_2 $\Delta\delta_R$	$\Delta\delta_S$	$\Delta\Delta\delta_{R-S}$	LSR/RCHOHR′ molar ratio[c]
14898-79-4	4221-99-2	CH_3	C_2H_5	9.55	9.55	0.0	5.09	5.15	−0.06	3.14[d]	3.14[d]	0.0	0.53
1572-93-6	1517-66-4	CH_3	*i*-Pr	12.29	12.29	0.0	6.51	6.58	−0.07	4.31[d]	4.32[d]	−0.01	0.56
1572-96-9	1517-67-5	CH_3	*t*-Bu	12.49	12.90	−0.41	6.61	6.65	−0.04[e]	4.53	4.66	−0.13	0.56[e]
5978-70-1	6169-06-8	CH_3	*n*-Hex	11.37	11.37	0.0	6.10	6.14	−0.04				0.62
3539-97-7	17628-73-8	CH_3	CF_3	6.17	5.91	0.26	3.14	3.20	−0.06				0.58
1517-69-7	1445-91-6	CH_3	C_6H_5	10.17	9.83	0.34	5.43	5.49	−0.06	4.44[f]	4.44[f]	0.0	0.52[g]
1565-74-8	613-87-6	C_2H_5	C_6H_5	10.81	10.54	0.27				4.66[f]	4.66[f]	0.0	0.57
22144-60-1	22135-49-5	*n*-Pr	C_6H_5	9.59	9.15	0.44	1.29[d]	1.32	−0.03	4.00[f]	4.00[f]	0.0	0.50
14898-86-3	34857-28-8	*i*-Pr	C_6H_5	9.73	9.44	0.29	3.51[h]	3.54	−0.03	3.98[f]	4.06[f]	−0.08	0.57[g]
23439-91-0	15914-85-9	*t*-Bu	C_6H_5	7.83	7.92	−0.09	2.57	2.71	−0.14	3.20[f]	3.44[f]	−0.22	0.52[g]
51716-29-1	35147-17-2	*n*-Bu	*t*-Bu	9.98	10.63	−0.65				3.30	3.56	−0.26	0.55
51773-31-0	51773-32-1	*t*-Bu	CF_3	4.24	4.24	0.0	1.40	1.49	−0.09				0.59

[a] $\Delta\delta$ is the amount of shift induced by addition of the designated molar ratio of *d*-Eu(HFC)$_3$ in parts per million downfield from TMS (not the chemical shift). [b] $\Delta\Delta\delta_{R-S}$ is the difference between the signals of the enantiomers ($\Delta\delta_R - \Delta\delta_S$) induced by the addition of the designated molar ratio of *d*-Eu(HFC)$_3$. [c] Refers to the ratio of the lanthanide shift reagent Eu(HFC)$_3$ to substrate. It should be noted that these ratios were only convenient values and were not chosen for maximum or optimum $\Delta\Delta\delta$. [d] This value refers to the CH_3 signal of the ethyl, *n*-propyl, or isopropyl groups. [e] At LSR/substrate molar ratios of 0.3 or less the $\Delta\delta_R - \Delta\delta_S$ values for the CH_3 group (L_1) were positive instead of negative. [f] This value refers to the ortho protons on the phenyl ring. [g] These examples have been reported previously with another chiral shift reagent in a different solvent and at lower LIS/substrate ratios by Červinka, *et al.*[15] [h] This value refers to the methyl signals of the isopropyl group. The internally diastereotopic methyl signals were also separated, thus giving four signals; for both sets of enantiomeric methyl signals $\Delta\delta_R - \Delta\delta_S$ was −0.03.

Others have reported that, as increasing amounts of chiral lanthanide shift reagents are added to some chiral substrates, the sense of nonequivalence (sign of $\Delta\Delta\delta$) for some signals is reversed.[5-7] This phenomenon was observed only for the methyl signal of methyl-*tert*-butylcarbinol among the compounds reported in Table I. At molar ratios of Eu(HFC)$_3$ to methyl-*tert*-butylcarbinol of 0.3 or below, $\Delta\Delta\delta_{R-S}$ was positive; in higher molar ratios the signals cross, leading to the negative value as reported in Table I at the 0.56 ratio. It is obviously crucial for correlation purposes to make such comparisons in any series of compounds at closely comparable LIS/substrate ratios. It should also be emphasized that the sign of $\Delta\Delta\delta_{R-S}$ is frequently not the same for signals from the various ligands of a given substrate. This substantiates the conclusion made by others[5,6] that a difference in the equilibrium constants for diasteriomeric forms of the complex is not necessarily the primary cause of the nonequivalence in the lanthanide-induced shift differences for enantiomeric substrates.

A problem in the study of the correlation of chemical shift differences of natural products by this method is that both enantiomers of the substrate are usually not available. In such cases a study of correlation of configuration with $\Delta\Delta\delta$ can be accommodated by the use of both enantiomeric forms of the chiral shift reagent rather than the substrate. Several enantiomeric shift reagents have been described by Whitesides and coworkers.[5] Since *l*- as well as *d*-camphor is available, the others bearing the *l*-camphorato group are potentially available. A study of this type should prove valuable.

Experimental Section

All nmr spectra were obtained with a Varian HA-100 nmr spectrometer. The *d*-Eu(HFC)$_3$ was purchased from Willow Brook Labs, Inc., and was stored *in vacuo* over P_4O_{10}. The substrate concentrations were 0.19–0.25 *M* in $CDCl_3$. Spectra were obtained by preparing a substrate solution from partially active material of known configuration[17,18] and enantiomeric composition. The nmr chemical shift differences were followed by incremental addition of *d*-Eu(HFC)$_3$, thereby shifting the signals progressively downfield from TMS. As observed by Whitesides and coworkers[5] at molar ratios of *ca.* 1.0, some broadening often occurred owing to a fine white precipitate which could be removed *via* filtration through a plug of glass wool, thereby restoring the resolution of the signals.

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Carbon-13 Nuclear Magnetic Resonance Spectra of Cinchona Alkaloids[1]

Charles G. Moreland,[2a] A. Philip,[2b] and F. I. Carroll* [2b]

Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709, and the Department of Chemistry, North Carolina State University at Raleigh, Raleigh, North Carolina 27607

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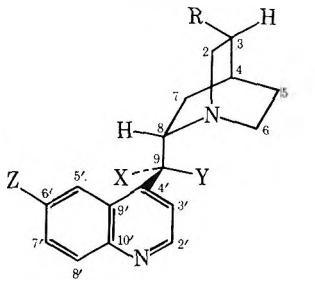
A comparison of the ^{13}C nmr spectra of eight cinchona alkaloids in $CDCl_3$ and in DMSO-d_6 has pointed out some important chemical shift differences which should be useful in the identification of similar compounds. The ^{13}C chemical shifts of carbons 2 and 6 of the quinuclidine ring can be used to distinguish between quinine and quinidine derivatives. Similarly, ^{13}C chemical shifts of C-4′ should provide a means of distinguishing between threo and erythro compounds (quinine and 9-epiquinine derivatives). Solvent studies on these compounds show that intramolecular hydrogen bonding has a large effect on the ^{13}C chemical shifts of the carbons 6, 7, and 4′, indicating that ^{13}C nmr will be a useful tool to study important conformational problems of these and related compounds.

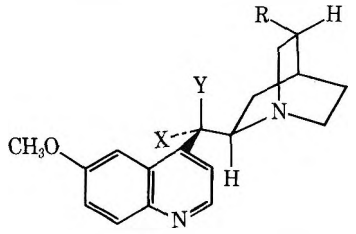
The cinchona alkaloids have been well characterized by structural and stereochemical investigations.[3] In 1971 Roberts and coworkers reported the first ^{13}C nmr chemical shift data on the nonaromatic portion of quinine.[4] More recently Wenkert and coworkers have reported on the ^{13}C nmr chemical shifts for all carbon resonances in quinine, quinidine, and the dihydro derivatives of these two naturally occurring cinchona alkaloids.[5]

In this report we present a study of the ^{13}C nmr spectra of eight cinchona alkaloids, including cinchonidine (I), quinine (II), 9-epiquinine (III), quinidine (IV), 9-epiquinidine (V), dihydroquinine (VI), dihydroquinidine (VII), and dihydro-9-epiquinidine (VIII) (see Chart I). A comparison is made between the ^{13}C nmr chemical shifts of the cinchona alkaloids which have the erythro configuration at the 8,9 positions (I, II, IV, VI, and VII) and the C-9 epimers (III, V, and VIII) which have the threo arrangement. Each of the eight alkaloids were run in $CDCl_3$ and in DMSO-d_6. Solvents effects on the ^{13}C nmr chemical shifts were observed and possible explanations are presented.

Chart I



I, R = $^{10}CH{=}^{11}CH_2$; X = OH; Y = Z = H
II, R = CH=CH_2; X = OH; Y = H; Z = CH_3O
III, R = CH=CH_2; X = H; Y = OH; Z = CH_3O
VI, R = CH_2CH_3; X = OH; Y = H; Z = CH_3O



IV, R = CH=CH_2; X = OH; Y = H
V, R = CH=CH_2; X = H; Y = OH
VII, R = CH_2CH_3; X = OH; Y = H
XIII, R = CH_2CH_3; X = H; Y = OH

Results and Discussion

Most of the ^{13}C nmr chemical shift assignments for the cinchona alkaloids in Tables I and II were based on empirical correlations which have been summarized in the equations of Lindemann and Adams[6] and of Grant and Paul.[7] Although these equations are for simple paraffins, the qualitative trends found for the ^{13}C shifts in paraffins have been extended to predict the relative order of ^{13}C chemical shifts in other compounds.[8] The most important of these trends are (1) that substitution of a carbon (or a more electronegative atom or group) for a directly attached hydrogen produces a *downfield* shift [*i.e.*, the more carbons which are α to the carbon in question, the more *downfield* the ^{13}C shift (α effect)], (2) that substitution of a carbon or other atom for a hydrogen attached to a carbon α to the carbon in question also produces a *downfield* shift [*i.e.*, the more substitution at the carbon α to the carbon in question, the more *downfield* the ^{13}C shift (β effect)], (3) that hydrogens or other groups that are attached to carbons which are γ to the carbon in question produce an *upfield* shift (γ effect). The α and β effects are presumably through-bond effects while the γ effect is a steric compression effect.[9,10]

The structures and the numbering system for the cinchona alkaloids are shown in Chart I. The ^{13}C chemical shifts for the alkaloids are given in Tables I and II. In each case a noise-decoupled and single-frequency off-resonance decoupled (SFORD) spectrum were obtained. The multiplicities generated in the SFORD spectra enabled distinction between methyl, methylene, methine, and quaternary carbon resonances. As is apparent from Tables I and II, the ^{13}C resonances of the cinchona alkaloids can be grouped into two main regions which correspond to the quinuclidine ring and the quinoline ring of the molecule. The assignments of these two heterocyclic rings will be considered in turn.

Quinuclidine Ring. There are seven separate signals in the 20–60 ppm ^{13}C chemical shift region relative to internal TMS. These have been assigned to the seven carbons in the quinuclidine ring for each of the eight cinchona alkaloids listed in Tables I and II. Off-resonance experiments performed on each of these compounds in $CDCl_3$ and in DMSO-d_6 gave a ^{13}C nmr spectrum with three doublets and four triplets for the seven signals. The doublet resonances are for carbons 3, 4, and 8 and can be readily assigned, since they have markedly different ^{13}C chemical shifts which are in the same order (*i.e.*, $\delta_{C\text{-}4} < \delta_{C\text{-}3} < \delta_{C\text{-}8}$), but at lower fields than the corresponding ^{13}C shifts in unsubstituted quinuclidine.[11] The chemical shifts for carbons 3, 4, and 8 are about the same for the

Table I
Carbon-13 Chemical Shifts for Some Cinchona Alkaloids in $CDCl_3$[a,b]

Identification and multiplicity of carbon[c,d]		Cinchonidine (I)	Quinine (II)	Epiquinine (III)	Quinidine (IV)	Epiquinidine (V)	Dihydroquinine (VI)	Dihydroquinidine (VII)	Dihydroepiquinine (VIII)
2	t	56.81	56.86	55.25	(49.85)	49.07	58.38	(50.88)	(49.07)
3	d	39.77	39.76	39.62	39.96	38.83	37.36	37.22	37.07
4	d	27.76	27.71	27.76	28.11	27.23	28.11	26.97	27.22
5	t	27.46	27.46	27.08	26.24	26.54	27.42	26.14	25.56
6	t	43.04	43.00	40.55	(49.42)	46.72	43.15	(49.95)	(48.87)
7	t	21.19	21.44	24.92	20.76	23.84	21.05	20.37	23.70
8	d	60.24	59.85	61.32	59.55	62.11	59.66	59.60	61.91
9	d	71.46	71.51	71.17	71.51	69.94	71.56	71.46	70.24
10	d	141.61	141.66	141.18	140.54	140.05	25.31 (t)	24.92 (t)	25.56 (t)
11	t	114.13	114.08	114.33	114.23	114.48	11.84 (q)	11.79 (q)	11.74 (q)
CH_3O	q		55.44	55.74	55.34	55.20	55.49	55.30	55.15
2′	d	149.75	147.01	147.30	147.06	147.35	147.06	147.06	147.35
3′	d	122.85	121.09	121.04	121.09	121.43	121.04	121.09	121.33
4′	s	149.75	148.33	(144.26)	148.18	(144.56)	148.43	148.73	(144.75)
5′	d	118.10	101.40	102.47	101.25	101.89	101.49	101.15	102.08
6′	s	126.38 (d)	157.44	157.25	157.34	157.25	157.44	157.34	157.25
7′	d	128.78	118.30	119.87	118.25	118.34	118.55	118.25	119.82
8′	d	129.46	130.89	131.33	130.94	131.43	130.93	130.89	131.42
9′	s	125.49	126.43	127.95	126.33	127.85	126.43	126.43	127.90
10′	s	147.84	143.67	(144.61)	143.63	(144.85)	143.72	143.63	(144.61)

[a] Chemical shifts are in parts per million relative to tetramethylsilane. [b] Uncertain assignments are shown along with the next nearest uncertain chemical shift in parentheses. [c] Numbering of carbon is shown in Chart I. [d] Signal multiplicity obtained from single frequency off-resonance experiments; s = singlet, d = doublet, t = triplet, q = quartet.

eight cinchona alkaloids listed in Tables I and II and are in close agreement with those reported for quinine in $CDCl_3$ by Roberts and coworkers[4] and with the chemical shifts for the same carbon resonances of quinine, dihydroquinine, quinidine, and dihydroquinidine in chloroform reported by Wenkert and coworkers.[5]

The four triplet resonances observed in the off-resonance spectrum are for carbons 2, 5, 6, and 7 and have been assigned by comparing the ^{13}C chemical shifts for the eight cinchona alkaloids and quinuclidine in $CDCl_3$ and in DMSO-d_6. Since carbons 2 and 6 are α to the quinuclidine nitrogen, they will be shifted downfield relative to carbons 5 and 7, and thus the problem is to assign C-2 in comparison to C-6 and C-5 in comparison to C-7. Any difference in chemical shifts for carbons 2 and 6 should depend on the following: (a) C-2 is α to the quinuclidine nitrogen and to the tertiary C-3 while C-6 is α to the nitrogen and to the secondary C-5 and thus C-2 should be more downfield, and (b) depending on the configuration at C-8, C-2 or C-6 will experience an upfield shift (γ effect) from substituents on C-9 which relies on the proximity of these centers (see Chart I). In cinchonidine (I), quinine (II), 9-epiquinine (III), and dihydroquinine (VI) models show that C-2 does not interact sterically with substituents on C-9 and thus by (a) would be shifted downfield relative to C-2 in unsubstituted quinuclidine[11] ($\delta_{C\text{-}2}$ 48.7 ppm). On the other hand, C-6 can interact sterically with the C-9 substituents and should be shifted upfield (γ effect). Thus, the triplet signals in the 55–58-ppm region have been assigned to C-2 and the triplet signals in the 40–43-ppm region to C-6 for compounds I, II, III, and VI.

In quinidine (IV), 9-epiquinidine (V), dihydroquinidine (VII), and dihydro-9-epiquinidine (VIII) the shifts for C-2 relative to the shift for C-2 in unsubstituted quinuclidine should be downfield by (a) and upfield by (b). Models show that C-6 should not experience a γ effect and thus should have a chemical shift approximately the same as that of C-2 in unsubstituted quinuclidine. The ^{13}C nmr spectrum of each of these compounds shows two triplet resonances in the 46–49-ppm region which have been assigned to carbons 2 and 6. It is not possible to specifically assign these two signals for compounds IV, VII, and VIII.

Similar reasoning can be used to assign carbons 5 and 7. Carbon 5, which is α to one tertiary carbon, should experience no γ effect from either the olefinic group or from substituent groups at C-9, whereas C-7, which is α to two tertiary carbons, should experience a γ effect from both groups. For each of the cinchona alkaloids listed in Tables I and II there is a triplet signal in the 26–28-ppm region of the ^{13}C nmr spectrum. This value is approximately the same as that of C-2 in unsubstituted quinuclidine (δ 27.7 ppm)[11] and has been assigned to C-5 which, for reasons cited above, should be very similar to C-2 of quinuclidine. The triplet signal in the 21–24-ppm region of the ^{13}C nmr spectrum of each compound has, therefore, been assigned to C-7. This is consistent with the reasons cited, since one would expect a net upfield shift of the C-7 resonance if the γ effect from either or both groups is greater than the influence of an additional α tertiary carbon. It should be noted that our assignments for C-5 and C-7 are reversed from those reported by Roberts and coworkers[4] for quinine but are in agreement with those reported by Wenkert and coworkers.[5]

A comparison of the ^{13}C chemical shifts assigned for the quinuclidine rings in cinchonidine (I), quinine (II), and 9-epiquinine (III) in $CDCl_3$ shows that the shifts for I and II are almost identical, but that they differ from those of III for the 2, 6, 7, and 8 carbons. Since compounds I and II differ from III in the configuration at C-9, the chemical shift differences seem likely due to intramolecular hydrogen bonding of the hydroxyl group at C-9 with the nitrogen in the quinuclidine ring. In order to test this hypothesis the spectra of the compounds were obtained in DMSO-d_6 *(Table II)*. A comparison of the shifts in Table I with those in Table II shows that there is a substantial change with solvent in the ^{13}C shift for carbons 6 and 7 in cinchonidine and quinine (erythro isomers) and that these values approach those for carbons 6 and 7 in 9-epiquinine (threo isomer) which does *not* show any solvent effects. There is also a smaller change in the ^{13}C chemical shifts with solvent for carbons 2 and 8 of cinchonidine and quinine as compared to the same carbons of 9-epiquinine. Chemical shifts in Tables I and II show a similar difference between quinidine and 9-epiquinidine as well as be-

Table II
Carbon-13 Chemical Shifts for Some Cinchona Alkaloids in DMSO-d_6[a]

Identification and multiplicity of carbon[a]		Cinchonidine (I)	Quinine (II)	Epiquinine (III)	Quinidine (IV)	Epiquinidine (V)	Dihydroquinine (VI)	Dihydroquinidine (VII)	Dihydroepiquinidine (VIII)
2	t	56.11	55.96	55.47	(49.20)	49.34	57.73	50.23	48.71
3	d	39.60	39.60	39.31	39.89	39.30	37.24	37.20	36.90
4	d	27.55	27.86	27.40	27.94	28.03	28.23	27.25	26.96
5	t	27.55	27.50	27.16	26.37	26.76	27.25	26.13	(25.69)
6	t	41.76	41.85	40.67	(48.56)	47.24	42.05	49.35	48.71
7	t	24.46	23.92	24.61	23.28	24.22	23.48	23.09	23.48
8	d	60.96	60.62	60.91	60.61	62.19	60.47	60.76	61.60
9	d	71.25	70.95	70.02	70.91	69.39	71.00	70.76	69.04
10	d	142.58	142.53	142.04	141.37	141.35	25.31 (t)	25.05 (t)	(25.10) (t)
11	t	114.11	114.02	114.07	114.41	115.04	12.01 (q)	11.97 (q)	11.87 (q)
CH_3O	q		55.47	55.47	55.47	56.01	55.47	55.38	55.37
2′	d	150.07	147.48	147.43	147.52	148.02	147.43	147.43	147.48
3′	d	(124.16)	120.93	121.07	120.97	121.86	120.87	120.93	121.27
4′	s	150.61	149.24	145.56	149.46	146.79	149.33	149.58	146.15
5′	d	119.16	102.50	102.95	102.50	103.04	102.50	102.46	102.70
6′	s	126.12 (d)	156.84	156.88	156.83	157.47	156.83	156.79	156.58
7′	d	128.76	119.11	120.24	119.01	120.68	119.01	118.92	120.14
8′	d	129.74	131.16	131.16	131.16	131.75	131.16	131.11	131.21
9′	s	(126.12)	127.05	127.67	127.10	128.22	127.05	127.10	127.69
10′	s	147.92	143.95	144.15	143.95	144.69	143.99	143.90	144.15

[a] See footnotes to Table I.

tween dihydroquinidine and dihydro-9-epiquinidine. The larger solvent effect on the chemical shifts of the erythro isomers when compared to the corresponding threo isomer is attributed to differences in intramolecular hydrogen bonding between the 9-hydroxyl group and the quinuclidine nitrogen. In the case of the erythro isomers, DMSO-d_6, a solvent known to be a good hydrogen-bond acceptor, can hydrogen bond to conformers not involved in intramolecular hydrogen bonding and might successfully compete for protons in conformers that are involved in weak intramolecular hydrogen bonding. Conversely, the strength of the intramolecular hydrogen bond in the case of threo isomers must be great enough to prevent disruption by the DMSO-d_6.

An alternate explanation for the solvent effect is that the erythro isomers have conformers which participate in intramolecular hydrogen bonding, while intramolecular hydrogen bonding does not occur in the case of the threo isomers. This explanation does not appear to us to be as likely as the first, since molecular models[12] reveal that intramolecular hydrogen bonding should be strongly opposed in the case of the erythro isomers by interference between the bulky quinoline and quinuclidine systems, and thus the conformer population is dominated by nonhydrogen-bonded species. However, in the threo isomers the same steric factors favor conformers which place the hydroxyl group and nitrogen proximate in space. In addition, the larger basicity of the 9-epi compounds compared to the natural alkaloids has been attributed to the more favorable intramolecular hydrogen bonding, possibly with participation of solvent, in the case of the epi isomers.[3]

Quinoline Ring. There are nine separate ^{13}C resonances for the quinoline ring for each of the cinchona alkaloids in Tables I and II. Relative to internal TMS these signals are in the 100–160-ppm region. Off-resonance experiments on each of these compounds in $CDCl_3$ and in DMSO-d_6 resulted in a ^{13}C spectrum having four singlets and five doublets.[13] The singlet resonances are for carbons 4′, 6′, 9′, and 10′. For each of the compounds II–VIII in $CDCl_3$ and in DMSO-d_6 the signal at ~157 ppm has been assigned to C-6′, since a directly bonded OCH_3 group produces a large downfield shift[14] and since this signal is absent in the ^{13}C nmr spectrum of cinchonidine (I), where there is no OCH_3 group at C-6′. For each of the compounds II–VIII the singlet resonance in the 126–127-ppm region has been assigned to C-9′ because the ^{13}C resonances for carbons 4′ and 10′ should be at much lower fields.[15]

The task then becomes one of assigning C-4′ as compared to C-10′. This was accomplished by comparing the ^{13}C shifts for quinine (II) with 9-epiquinine (III), quinidine (IV) with 9-epiquinidine (V), and dihydroquinidine (VII) with dihydro-9-epiquinidine (VIII). In the ^{13}C nmr spectrum of each of the erythro compounds (II, IV, VI, VII) there are singlets at ~148 and at ~144 ppm while for the threo compounds (III, V, VIII) there are two singlets at ~143–144 ppm. Since, as previously discussed, differences in intramolecular hydrogen bonding result in a difference in the ^{13}C chemical shifts for carbons 2, 6, 7, and 8 for the erythro compounds as compared to the threo compounds, it is very probable that intramolecular hydrogen bonding would also effect the chemical shift of the C-4′. It is also unlikely that this effect would show up at C-10′, and therefore the ^{13}C chemical shift for C-10′ should have approximately the same value in all the compounds. The singlet at ~148 ppm has been assigned to C-4′ and the singlet at ~144 ppm to C-10′ for each of the erythro compounds. It is not possible from these data to specifically assign C-4′ and C-10′ in the threo compounds.

The five doublet signals for carbons 2′, 3′, 5′, 7′, and 8′ in each of the cinchona alkaloids in $CDCl_3$ and in DMSO-d_6 have been assigned on the basis of the following arguments. (a) C-2′ which is α to the quinoline nitrogen is at low field and has approximately the same chemical shift as C-2′ in quinoline (~150 ppm).[16] (b) C-3′ should have about the same chemical shift in cinchonidine and the other cinchonia alkaloids. (c) C-5′ and C-7′ are ortho to the OCH_3 group and, therefore, should be substantially *upfield*[14] from their positions in cinchonidine (with no OCH_3 at C-6′). Carbon 5′ should be at a higher field than C-7′ since it can interact sterically with substituents on C-9′. (d) C-8′ (and C-9′) should be only slightly *downfield*[14] from their positions in cinchonidine since they are meta to the OCH_3 group. There is very close agreement between the ^{13}C chemical shifts reported in Table I for the quinoline ring carbons with those reported by Wenkert for compounds II, IV, VI, and VII.[5]

Other Assignments. With signal multiplicity data obtained from off-renance experiments, the assignments for carbons 9, 10, 11, and OCH_3 were straightforward and consistent with ^{13}C chemical shifts reported for similar carbon groups.

Experimental Section

Nmr Spectra. ^{13}C nmr spectra were determined at 24.92 MHz on a modified JEOL JNM-PS-100 Fourier-transform spectrometer interfaced with a Nicolet 1085 Fourier-transform computer system. Spectra were obtained in either chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) in 10-mm tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of $CDCl_3$ or DMSO-d_6 as the internal lock signal. All proton lines were decoupled by a broad-band (~2500 Hz) irradiation from an incoherent 99.075-MHz source. Interferograms were stored in 8*K* of computer memory (4*K* output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000-Hz sweep width spectra. Typical pulse widths were 12 μsec, and the delay time between pulses was fixed at 1.0 sec. Normally 512 (twice as many for single frequency off-resonance experiments) data accumulations were obtained on a 200 mg/2 ml of solvent sample. The chemical shifts reported are believed accurate to within ±0.05 ppm.

Chemicals. Cinchonidine and quinine were obtained from Sigma Chemical Co. Quinidine was purchased from Aldrich Chemical Co. 9-Epiquinine and 9-epiquininidine were prepared by conversion of the natural alkaloid tosylate.[17] The dihydro alkaloids were prepared by reduction of the corresponding unsaturated alkaloid in ethanol using 10% palladium on carbon catalyst. The melting points and $[\alpha]D$ values of all the compounds synthesized were in agreement with literature values.

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Registry No.—I, 485-71-2; II, 130-95-0; III, 572-60-1; IV, 56-54-2; V, 572-59-8; VI, 522-66-7; VII, 1435-55-8; VIII, 51743-68-1.

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(13) The ^{13}C nmr spectra of cinchonidine in $CDCl_3$ and in DMSO-d_6 contain three singlets and six doublets for the nine carbons of the quinoline ring.
(14) Reference 8, p 81.
(15) For quinoline in $CDCl_3$ the ^{13}C chemical shifts of C-9′ and C-10′ are at 128.0 and 148.0 ppm, respectively, and for 4-methylquinoline in $CDCl_3$ C-9′, C-4′, and C-10′ are at 127.9, 143.9, and 147.7 ppm, respectively.
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Reductive Defunctionalization of 1-Substituted Adamantanes in Molten Sodium Tetrachloroaluminate

V. R. Koch, L. L. Miller,*[1] and R. A. Osteryoung

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

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The reactivity of a number of substituted adamantanes in molten $NaAlCl_4$ at 175° was assessed. Those substituents with Lewis base character reacted with the melt to give adamantane and chloroadamantane. Neutral and Lewis acid substituents were recovered unchanged. Cyclic voltammetry revealed adamantane and 1-methyladamantane to be electroactive at a tungsten electrode well within the background limits of molten $NaAlCl_4$.

The use of molten salt media to effect a variety of organic transformations both homogeneously and at an electrode has recently been reviewed.[2] No reference was made, however, to the kinds of reactions undergone by aliphatic compounds in these ionic, aprotic solvents. Accordingly, we set out to survey the chemical stability of 1-substituted adamantanes (1-Ad-X) in a nominally 50:50 mol % $AlCl_3$–NaCl melt at 175°. By examining the behavior of a representative number of functionalities in this medium an appreciation of their reactivity or inertness can be achieved.

The availability of monofunctionalized bridgehead adamantanes and their resistance to skeletal rearrangement make them an ideal model system with which to probe the reactivity of different substituents. Indeed, the anodic behavior of a series of 1-Ad-X in acetonitrile has been reported.[3] Of particular interest to us is the feasibility of doing organic electrosythesis in molten salts. Cyclic voltammetry indicates that electrochemically generated oxidation intermediates of aromatic amines,[4] sulfur heterocycles,[5] and polycyclic aromatic hydrocarbons[6] are stabilized by the melt.

While the exact nature of this phenomenon is unknown, it appears that the absence of a nucleophilic organic solvent and the associated trace amounts of water accounts for the greatly extended lifetime of these reactive intermediates. If simple aliphatic cation radicals or cations are similarly stabilized it should be possible to do preparative electrochemistry without the chemical follow-up reactions common to organic solvent–electrolyte media.

Results and Discussion

The results of adding 1-Ad-X to approximately 5 ml of melt are summarized in Tables I–III. Substituents with Lewis base character reacted with the melt to give mixtures of adamantane, chloroadamantanes, hydrogen chloride, and, in two instances, carbon monoxide. Neutral and electrophilic substituents either complexed with the

Table I
Adamantyl Compounds Defunctionalized by 50:50 Mol % $AlCl_3$–NaCl Melt

Registry no.	X	1-Ad-X, mmol	% conversion Ad-H	% conversion 1-Ad-Cl[a]
768-92-3	F	0.36	25	0.2
935-56-8	Cl	0.80	28	0.2
768-90-1	Br	1.23	28	0.2
6221-74-5	OMe	0.63	38	9.5
768-95-6	OH	0.84	41	8.0
768-94-5	NH_2[b]	1.12	16	1.3
	NH_2[c]	1.18	13	1.7
828-51-3	CO_2H[d]	0.57	23	0.4
711-01-3	CO_2Me[d]	0.97	21	0.4

[a] Trace amounts of 2-Ad-Cl detected. [b] 0.30 mmol of 1-Ad-NH_2 recovered. [c] Reaction time doubled; 0.29 mmol of 1-Ad-NH_2 recovered. [d] Carbon monoxide evolved.

was recovered unchanged. Thus, there is no reason to suspect that the other substituents were cleaved by thermal decomposition.

An important feature of sodium tetrachloroaluminate melts is the ability to precisely vary the Lewis acidity over nine orders of magnitude. Boxall and coworkers[8] have completely described the equilibria of the various species comprising a melt over a range of 50–70 mol % aluminum chloride. In the region immediately about 50 mol % aluminum chloride, the predominant species are given by the equilibrium

$$2AlCl_4^- \overset{K_m}{\rightleftharpoons} Al_2Cl_7^- + Cl^-$$

where $Al_2Cl_7^-$ is considered to be a Lewis acid, and Cl^-, a Lewis base; $K_m = 1.06 \times 10^{-7}$ at 175°. The addition of small amounts of either aluminum chloride or sodium chloride to the melt dramatically shifts the above equilibrium as per Figure 1.

Table II
Effect of Melt Composition on Product Distribution

Melt composition, mol % $AlCl_3$	X	1-Ad-X Mmol	1-Ad-X Mg	% conversion Ad-H	% conversion 1-Ad-Cl	Isolated residue, mg
49.75	Br	1.89	403	30	0.7	90
	CO_2H	0.91	164	18	0.5	60
50.00	Br	1.23	264	28	0.2	50
	CO_2H	0.57	103	23	0.4	25
64.00	Br	1.47	316	Trace		132
	CO_2H	1.13	203	Trace		102

melt or sublimed out of solution. In these cases, 1-Ad-X was recovered unchanged.

1-Haloadamantanes. When added to the clear, colorless sodium tetrachloroaluminate at 175°, 1-fluoro-, 1-chloro-, and 1-bromoadamantane formed an immediate deep red solution with concomitant evolution of a white sublimate. This material was quantitatively collected and weighed. Though the reaction was over in 3–5 min the solution was maintained at 175° for 15 min prior to cooling and work-up of the solidified melt.

Infrared spectra of each of the gas mixtures sampled from above the melts showed the rotational fine structure and ν_0 characteristic of hydrogen chloride. Neither HBr nor HF were detected. Nmr spectra of the three sublimates revealed the presence of adamantane and 1-chloroadamantane. Further analysis of the sublimate disclosed a third product in trace amounts which had the same retention time as authentic 2-chloroadamantane. No starting material was found in the 1-bromo- and 1-fluoroadamantane sublimates.

The melt was pulverized and continuously extracted with ether. This led to the isolation of a gold, resinous material which could not be fully characterized. This substance was recovered from the solidified melt whenever 1-Ad-X reacted with sodium tetrachloroaluminate.

It is instructive to compare the products from the reaction of 1-chloroadamantane and aluminum chloride in carbon tetrachloride at room temperature to the products from the reaction of 1-chloroadamantane and melt reported in Table I. Kovacic and Chang[7] found that after 1 hr 10% adamantane, 75% 1-chloroadamantane, 2% 2-chloroadamantane, and 13% dichloroadamantane were obtained in contrast to the 30% yield of adamantane formed in the melt. Conceivably, the high temperature of the molten salt in conjunction with its Lewis acid properties effect a more rapid and complete dehalogenation.

To guarantee that loss of substituent was in fact due to the melt and not temperature alone, 1-bromoadamantane, which possesses the weakest 1-adamantyl carbon–substituent bond, was heated to 190° and maintained at that temperature for 5 min. After cooling, 1-bromoadamantane

Table III
Adamantyl Compounds Stable to 50:50 Mol % $AlCl_3$–NaCl Melt

Registry no.	X	1-Ad-X, mol	% recovery
281-23-2	H	0.77	98[a]
768-91-2	Me	0.57	88[a]
23074-42-2	CN	0.72	88
1660-04-4	COMe	0.72	89
700-58-3	2 =O	0.82	90

[a] Sublimed out of melt; others recovered by continuous extraction of pulverized melt with ether.

To determine the effect of melt composition and thereby the Lewis acidity on product distribution, 1-bromoadamantane was added to melts with aluminum chloride adjusted to 49.75 (Cl^- saturated) and 64.00 mol %. These

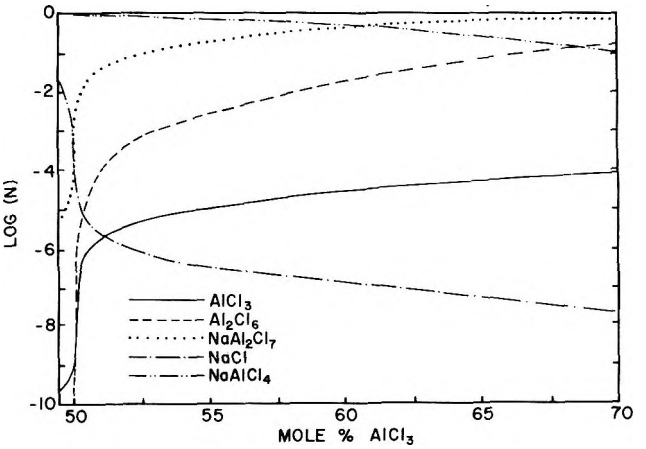

Figure 1. Mole fraction of the species in the chloroaluminate melt at 175° as a function of the net $AlCl_3$–NaCl ratio (49.75 ≤ mol % $AlCl_3$ ≤ 70).

values correspond to chloride ion (Lewis base) concentrations of 8.85×10^{-2} and 4.13×10^{-7} M, respectively. For comparison, the chloride ion concentration in 50 mol % aluminum chloride is 2.87×10^{-2} M.

As seen in Table II, very little change in either overall yield or product distribution occurs in going from 49.75 to 50.00 mol % aluminum chloride. At 64.00 mol % aluminum chloride, however, only trace amounts of adamantane were recovered while the quantity of organic residue extracted from the melt increased. Clearly, abrupt changes in the Lewis acidity are reflected in the product distribution.

The nature of the nonsublimable product is of interest not only because it is the major product of the reaction, but also because the amount formed is dependent upon melt composition. Accordingly, an attempt was made to delimit at least the gross structural features of this material.

The nmr spectra and glc traces of all isolated resins were virtually identical regardless of adamantyl functionality or melt composition. The complexity of this material is exemplified by glc analysis, which revealed five major and 15 minor components eluting closely together. When chromatographed on a silica gel column two distinct fractions were obtained, the first eluting with Skellysolve and the second with chloroform.

Fraction 1, a yellow oil comprising 59% of the resin by weight, included five major and ten minor closely eluting components by glc. The nmr spectrum of this fraction was virtually identical with that of the resin itself and exhibited a broad downfield absorption at δ 5.4 and absorptions from δ 3 to 0.8 characteristic of aliphatic protons. Infrared analysis disclosed a broad carbonyl band at 1705 cm^{-1}. An average molecular weight of 427 amu was calculated from vapor pressure osmometry measurements. This value agrees with mass spectrometric data in that the "parent" ion cluster was observed to occur between m/e 425 and 430. The base peak was m/e 135, indicative of the adamantyl cation.

Fraction 2 eluted as a dark red oil and accounted for the remainder of the resin. One major and six minor closely eluting components were indicated by glc. The nmr spectrum contained a distinct though broad doublet at δ 4. Aliphatic absorptions between δ 3 and 0.6 made up the rest of the spectrum. The infrared spectrum revealed a broad band from 3600 to 3200 cm^{-1} due to O–H stretch. A carbonyl band similar in shape to that in fraction 1 at 1720 cm^{-1} was also evident. Vapor pressure osmometry measurements gave an average molecular weight of 752 amu.

From the spectroscopic data it appears that fraction 1 contains ketone and the adamantyl moieties. In addition, fraction 2 includes hydroxyl functionalities. It is noteworthy that the proton geminal to the hydroxy group in 2-adamantanol absorbs at δ 3.8 in the nmr spectrum.[9] This value is close to the δ 4.0 resonance observed in the spectrum of fraction 2. Neither 1- nor 2- adamantanol was found in fraction 2.

Since all reductive defunctionalizations were conducted in a scrupulously dry nitrogen atmosphere, oxygen incorporation can only ensue during the work-up of the organics extracted from the melt and most probably from water, not oxygen. This was supported by infrared analysis of a chloroform extract prior to work-up. Neither hydroxy nor carbonyl bands were observed in the spectrum. In an attempt to scavenge nascent cations a chloroform extract was treated with anhydrous methanol, distilled to dryness, and the nmr spectrum taken. With the exception of a singlet at δ 3.5 indicative of a methyl ether functionality the spectrum was identical with that of the usual resin.

Oxygen-Substituted Adamantanes. Like the haloadamantanes, 1-adamantanol and 1-methoxyadamantane formed instantaneous dark red solutions when added to the melt with hydrogen chloride evolution. The sublimates of these compounds contained the best overall conversion to adamantane and chloroadamantane.

A similar reductive defunctionalization of 1-adamantanol with other Lewis acids has recently been reported. In either *n*-hexane or carbon disulfide 1-adamantanol reacted with aluminum bromide to give adamantane and 1-bromoadamantane; with tin tetrachloride 1-chloroadamantane was obtained.[10]

1-Aminoadamantane. This compound was partially stable in the melt as evidenced by the recovery of some unreacted amine *via* continuous extraction. Relatively small amounts of adamantane and 1-chloroadamantane were found. To ascertain if the amine was reacting slowly in comparison to the other substituents, this experiment was repeated, the reaction time being doubled. As seen in Table I there was no increase in sublimate yield and the amount of recovered amine remained constant.

1-Adamantyl Carboxylate Derivatives. When either 1-adamantanecarboxylic acid or 1-carbomethoxyadamantane was added to the melt a dark red solution was formed with copious gas evolution. Infrared spectra of the reaction gases confirmed the presence of carbon monoxide as well as hydrogen chloride.

The formation of carbon monoxide and *tert*-butyl cation from pivalyl chloride under Friedel–Crafts conditions is well documented.[11-13] Olah and coworkers[14] have found that pivalyl fluoride and antimony pentafluoride react to give carbon monoxide and *tert*-butyl cation. This facile decarbonylation was ascribed to the Lewis acid character of the antimony pentafluoride.

Mechanistic Aspects of Reductive Defunctionalization. By analogy with earlier work under Friedel–Crafts conditions[15] it is clear that C–X cleavage begins with the coordination of nonbonding substituent electrons with an electron-deficient species in the melt. The heptachlorodialuminate ion, $Al_2Cl_7^-$, free aluminum chloride, and its dimer, Al_2Cl_6, have all been shown to exist simultaneously in the melt[8] and are likely candidates. From the melt composition diagram (Figure 1) it is evident that above 55 mol % aluminum chloride concentrations of the more acidic $AlCl_3$ and Al_2Cl_6 species increase relative to the concentration of the $Al_2Cl_7^-$ ion. This is reflected in the sensitivity of 1-bromoadamantane and 1-adamantanecarboxylic acid reactions to precipitous changes in melt composition.

In any case, generation of 1-adamantyl cations leads directly to the volatile products: adamantane by hydride abstraction, and 1-chloroadamantane by reaction with a chloride-containing species in the melt.

This rationale is consistent with work done on 1-haloadamantanes in other Lewis acid systems. Schleyer and coworkers[16] identified 1-adamantyl cations as products of the reaction of 1-fluoro- or 1-chloroadamantane with antimony pentafluoride. When generated in the presence of pentane, 1-adamantyl cations were found to abstract hydride ion to give adamantane.[17] On the other hand, adamantane itself was found to be inert to strong Lewis acids. In molten aluminum bromide, for example, this hydrocarbon was recovered unchanged.[18] Since the sodium tetrachloroaluminate melt is free of organic material, the source of hydride ion must be substrate itself. This most certainly accounts for the partitioning of products between the sublimables (adamantane and monochloroada-

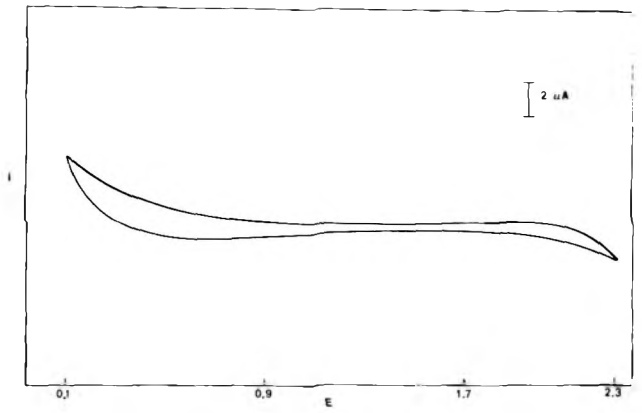

Figure 2. Cyclic voltammogram of melt background; sweep rate 200 mV/sec.

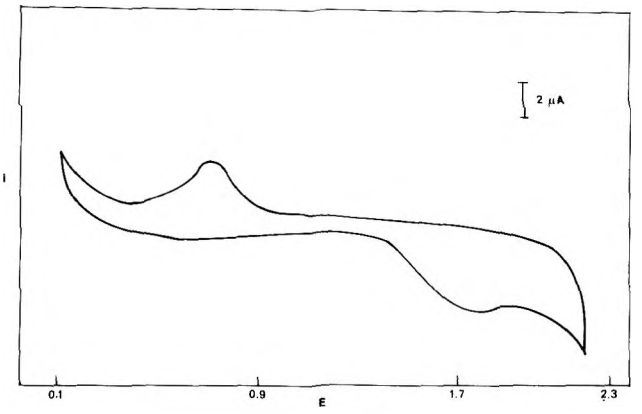

Figure 3. Cyclic voltammogram of adamantane or 1-methyladamantane at 200 mV/sec.

mantane) and the nonvolatile resinous material recovered from the melt.

The source of proton for hydrogen chloride is unclear. That proton does not exist in the melt prior to addition of substrate has been demonstrated by cyclic voltammetry, to be discussed later. Hydrogen chloride was identified as a reaction product in the chlorination of adamantane by ferric chloride and antimony pentachloride.[7] However, a free-radical mechanism was invoked to account for its formation. The chlorination of alcohols and acylation of carboxylic acids by aluminum chloride provides hydrogen chloride as a by-product.[19] However, in the absence of acidic substrate protons no hydrogen chloride is produced.

Adamantane and 1-Methyladamantane. These aliphatic hydrocarbons were stable to as well as soluble in the melt, though at 175° sublimation was rapid (Table III).

Cyclic voltammograms (Figures 2–4) were performed at a tungsten electrode at various sweep rates. At 200 mV/sec both compounds manifested an anodic wave, E_p = 1.80 V *vs.* an aluminum wire reference. The peak potential was sweep rate dependent and no reversible cathodic waves were observed at scans up to 100 V/sec. A cathodic wave, E_p = 0.70, absent in the voltammogram of background, was evident whenever the first and subsequent sweeps passed through the anodic wave. This process was determined to be the reduction of proton to hydrogen.

Cyclic voltammograms of melts through which hydrogen chloride had been bubbled show an identical cathodic wave, E_p = 0.70.

Adamantyl Ketones and Cyanide. All three of these compounds (Table III) formed stable complexes with the medium. When 1-acetyladamantane or 2-adamantone was added to the melt a light tan solution ensued. No sublimation was noted. Cyclic voltammograms of these solutions were identical with the voltammogram of background. Upon cooling and continuous extraction with ether good yields of starting material were recovered. When 1-cyanoadamantane was added to the melt a bright yellow solution resulted. Again, no sublimate was collected and a good yield of starting material was obtained.

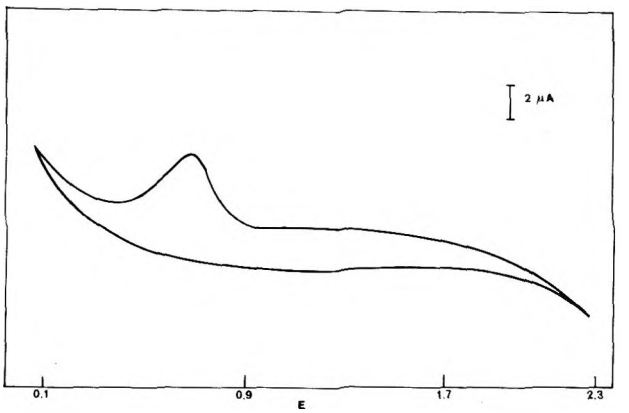

Figure 4. Cyclic voltammogram of melt through which anhydrous HCl has been bubbled; sweep rate 200 mV/sec.

It has been reported that aromatic nitriles and ketones are stable in an aluminum chloride melt, the latter forming a 1:1 complex with $AlCl_3$.[2] Olah and Calin[20] working in SbF_5–FSO_3H–SO_2 at −60° find that a variety of alicyclic ketones, including 2-adamantone, are stable albeit protonated in this Lewis acid medium.

Experimental Section

General. Starting materials and products were analyzed by ir on a Perkin-Elmer 457 grating spectrometer. Nmr spectra were taken on a Varian T-60 instrument. Glc analyses were performed on a Hewlett-Packard Model 5700 gas chromatograph equipped with thermal conductivity detectors. A 10 ft × 0.25 in., 8% SE-30 on Chromosorb W column was used for all determinations of product distribution. Average molecular weights were determined in chloroform at 30° with a Hewlett-Packard 302B vapor pressure osmometer. Mass spectra were recorded with an A.E.I. Model MS-12 spectrometer.

Dried Fluka A.G. (anhydrous, iron free) aluminum chloride and Fisher reagent-grade sodium chloride were quantitatively weight out into a Pyrex cell under a purified nitrogen atomosphere (Vacuum/Atmospheres Corp. drybox equipped with a HE-493 Dri-Train). The details of the cell and the electrolysis purification procedure are described elsewhere.[21] The purified melt (*ca.* 50:50 mol %) was completely clear and colorless. A Thermo Electric Model 400 thermoelectric controller was used to maintain the temperature of the melt at 175 ± 0.5°. The temperature was measured using a Chromel-Alumel Pyrex-sheathed thermocouple and a Fluke 8000A digital multimeter.

Materials. Adamantane, 2-adamantone, 1-bromoadamantane, 1-adamantanol, 1-aminoadamantane, 1-acetyladamantane, and 1-adamantanecarboxylic acid were commercial samples (Aldrich) and were used without further purification. 1-Carbomethoxyadamantane was supplied by Professor G. J. Gleicher. The other 1-substituted adamantanes were prepared as described previously.[3] 2-Chloroadamantane was obtained by the reduction of 2-adamantone to 2-adamantanol with lithium aluminum hydride followed by chlorination with phosphorus pentachloride.[7]

Reactions of 1-Ad-X with the Melt. All reactions were carried out in the drybox. In a typical run, 5 ml of molten salt was pipetted from the cell into a 30 × 80 mm Pyrex test tube preheated to and maintained at 175° via an aluminum block furnace. The test tube was fitted with a 29/26 female joint. A preweighed amount of 1-Ad-X was added to the melt and the test tube was immediately mated with a sublimation tower vented at the top. The sublimation tower was made by first sealing the end of a 30 × 150 mm Pyrex tube fitted with a 29/26 male joint and then opening up a small hole in the seal to which a short piece of 8-mm Pyrex tubing was attached. The length of the tower was heated and a number of Vigreux-type indentations were made. This simple device afforded a convenient and efficient method of quantitatively collecting material which sublimed out of the melt.

After 15 min at 175° with occasional swirling the sublimation tower was separated from the test tube, brought out of the dry-box, allowed to cool, and weighed. The contents were rinsed off the indentations with chloroform and subjected to glc as well as spectral analysis. The melt was allowed to cool, then pulverized and continuously extracted for 24 hr with ether. After 3 × 100 ml water washes the organic layer was dried over magnesium sulfate and concentrated on a Roto-Vap. Whenever 1-Ad-X reacted with the melt a tarry gold substance resulted which proved to be a complex mixture of substituted aliphatic hydrocarbons.

Gaseous products were detected by attaching an evacuated 10-cm Perkin-Elmer demountable gas cell to the sublimation tower *via* a short length of Tygon tubing. The observed ν_0 values for hydrogen chloride and carbon monoxide agreed with published data.[22]

Cyclic Voltammetry. Cyclic voltammograms were recorded with a PAR Model 170 electrochemistry system. The reference electrode was an aluminum wire (Alfa, m5N) separated from the working and counter electrodes by a fine glass frit. The melt in the reference compartment was saturated with sodium chloride. The working electrode, isolated in its own fritted compartment, was a 30-mil tungsten wire (Alfa, m3N8) sealed into a Pyrex tube with a bead of uranium glass, ground flat on an emery wheel and polished with 600 grit silicon carbide powder. The counter electrode was an aluminum wire.

Cyclic voltammograms were run at approximately 10^{-3} *M* substrate concentrations at 50, 100, 200, and 500 mV/sec. E_p values are quoted for rates of 200 mV/sec.

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Silalactones from Hydrosilyl Derivatives of Toluic Acids

Joanne M. Wolcott and Frank K. Cartledge*

Louisiana State University at Baton Rouge, Baton Rouge, Louisiana 70803

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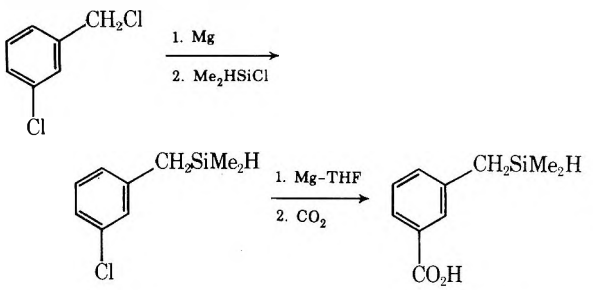
The preparation of 3- and 4-carboxybenzyldimethylsilane is reported, along with conversion of the acids under pyrolytic and hydrolytic conditions to dimeric or polymeric silalactones and to silanols and disiloxanes. In some cases, rather complex equilibria involving the various products can be displaced to result in virtually exclusive formation of one product. Of particular interest is a novel macrocyclic lactone dimer in the meta series which can be obtained in good yield. A general method for the preparation of silalactones is proposed, and the monomeric lactone from 2-carboxybenzyldimethylsilane is reported. Spectral properties of the products are reported and discussed.

The possible interactions between an aromatic ring and a Si atom β to the ring have been the subject of intense investigation in recent years. Two types of interactions have been proposed, first, a 1,3 p–d bonding in which electron density is donated from the phenyl ring to an empty d orbital on Si,[1] and second, a hyperconjugative interaction involving a C–Si σ bond.[2] Either type of interaction could give rise to hindered rotation about the ring to benzyl carbon bond. This restriction to rotation of the side chain could in principle be observed by variable-temperature nmr, since the methylene protons or the methyl groups on silicon would become diastereotopic and potentially distinguishable when an ortho or meta substituent is present. To investigate this possibility, 3-carboxybenzyldimethylsilane (1) was prepared. The carboxy group was chosen because of its anticipated ease of synthesis and because of the relatively large effects of carbonyl groups on chemical shifts of nearby protons. We chose to study the meta derivative first so that we could be sure that we would not be observing a steric interaction between the carboxyl and silylmethyl groups.

Results and Discussion

All attempts to prepare 1 by using standard Grignard preparations (eq 1) were unsuccessful. Although there is



(1)

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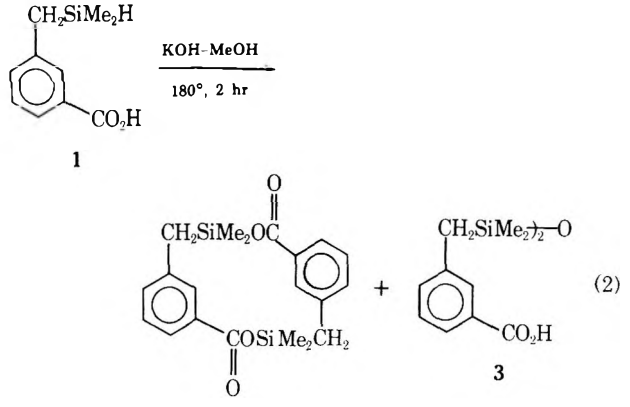
ample precedent for the generation of a C–Mg bond in the presence of a Si–H bond,[3] it is usually necessary to use forcing conditions to generate Grignards from aryl chlorides. Indeed, the only method that resulted in the formation of the Grignard reagent from *m*-chlorobenzyldimethylsilane involved the use of powdered Mg,[4] prior activation

of the Mg with dibromoethane, high chloride concentrations, and prolonged heating of the reaction mixture. No reaction occurred when Mg turnings were substituted for powdered Mg. This procedure gave a fairly high yield of acid **1** (80–90%)[5] in the crude reaction mixture, indicating no apparent difficulties from involvement of the Si–H bond. However, decomposition of **1** during the vacuum distillation resulted in a lower yield of the pure compound.

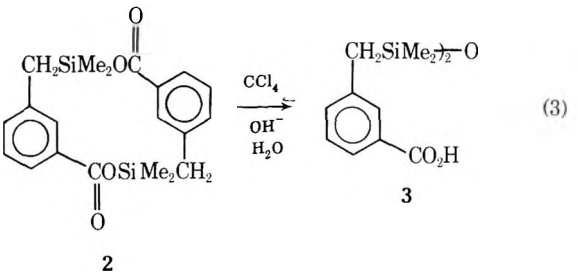
During the distillation of **1** the first time it was prepared, relatively high pot temperatures (>200°) were reached and partial solidification of the pot mixture occurred. On further investigation into the nature of the solid, which showed spectroscopically the absence of a Si–H linkage, we were able to determine that heating acid **1** with base results in formation of a novel silalactone dimer, **2**.[6] Several silalactones with silyl ester linkages and one example of a dimer have been reported in the literature;[7-10] however, none have been prepared in this manner. Disilalactone **2** is unusual in several respects. It is the largest dimer reported in the literature, it reacts differently than previously reported silalactones, and it is the only silalactone that contains phenyl groups in the heterocyclic ring. Owing to the novelty of this system, we decided that it merited further study.

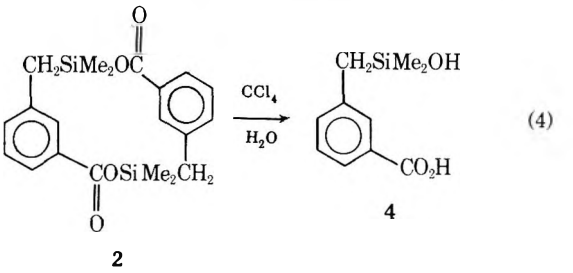
In the absence of base, the conversion of acid **1** to disilalactone **2** proceeded very slowly at 180°. Under these conditions, approximately 10% of **1** had been converted to **2** after heating for 4 hr. Upon addition of methanolic KOH, complete conversion of the acid was achieved after heating at 180° for 2 hr.



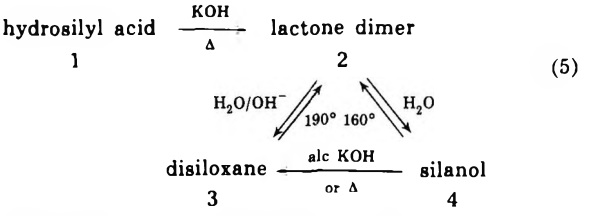
The product mixture contained 78% of **2** and 22% of (3-carboxybenzyl)dimethyldisiloxane (**3**). The silalactone dimer could be readily purified by subliming it directly from the latter reaction mixture at 170° (0.5 mm). A white, crystalline solid was obtained which became a viscous oil when exposed to atmospheric moisture.

When the reaction mixture from eq 2 was dissolved in hot CCl_4 and exposed to moisture, **3**, the disiloxane, crystallized out of the solution (eq 3). This reaction was not surprising, since disiloxanes have been observed to form from silalactones upon the addition of moisture.[7,9] Mironov, *et al.*, also observed that a disiloxane was converted to a silalactone on heating. Indeed, heating compound **3** at 190° for 1 hr gave 20% of the disilalactone with 80% of **3** unconverted. Further heating caused no appreciable change in the composition of the product mixture. Since other workers reported that silalactones could be converted to disiloxanes by moisture alone, the sublimed disilalactone was dissolved in hot CCl_4 and exposed to moisture in the absence of any base. Instead of the expected disiloxane, (3-carboxybenzyl)dimethylsilanol (**4**), was obtained (eq 4).





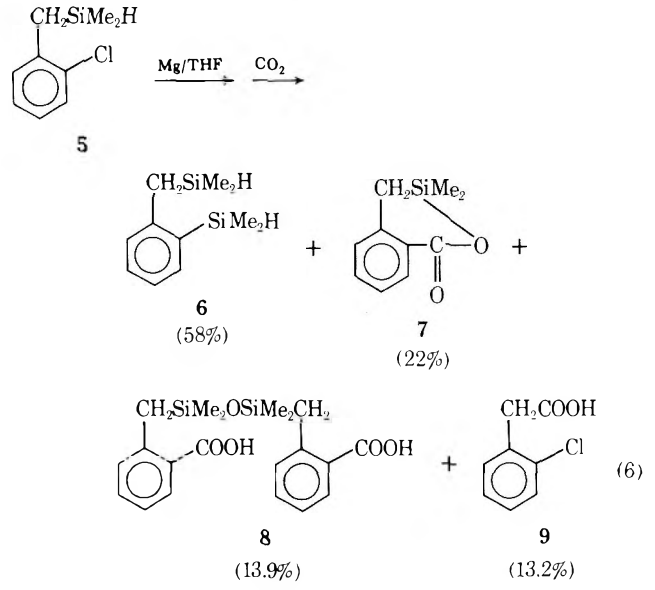
The formation of a silanol from a silalactone has not been previously reported, and we are somewhat surprised at the reluctance of **4** to yield disiloxane in protic media. Silanol **4** did react in the usual manner with base to give disiloxane **3**. However, heating the silanol in the absence of base gives disilalactone **2** and disiloxane **3** in approximately equal quantities. The interconversions involving all of the species mentioned so far are summarized in eq 5. The system is, so



far as we are aware, unique in allowing the formation of all of these related compounds under conditions where any one can be obtained as the almost exclusive product by appropriate minor adjustment of reaction conditions.

The literature with respect to preparation of ω-silalactones is very sparse, and the present work gives promise of affording a general method for their preparation from readily available starting materials. The essence of a preparative method for ω-silalactones is the generation of silanol and carboxylic acid functions together; then, if ring size is appropriate, silalactone formation should follow. The present method involves generation of the acid function by a Grignard route in the presence of Si–H, followed by hydrolysis of hydride to silanol. In order to have some evidence of the generality of the synthesis, and also because we were still interested in the spectroscopic properties of the hydrosilyl acids, we extended our investigations to the corresponding ortho and para derivatives.

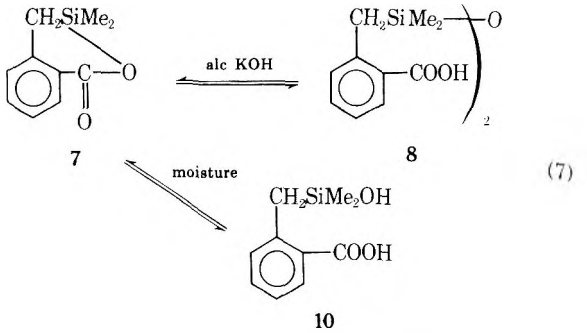
o-Carboxybenzyldimethylsilane could be expected to be a precursor for a six-membered ring silalactone or conceivably a 12-membered ring dimer which could be compared with **2**. The Grignard reagent of (2-chlorobenzyl)dimethylsilane (**5**) was prepared using the method developed for compound **1**. The usual carbonation and work-up with mild acid hydrolysis gave a crude reaction mixture which apparently, from its nmr spectrum, contained none of the expected o-hydrosilyl acid. Careful fractional distillation afforded the components of the mixture shown in eq 6. The silalactone **7** is obtained (in impure form) on distillation of the reaction mixture which has been subjected to hydrolysis in the presence of mild acid. Such conditions are normally not sufficient to result in Si–H hydrolysis, so that we presume that lactone is formed immediately on carbonation, with carboxylate anion displacing hydride. Simple propinquity



(6)

plus the reasonable stability of the silalactone apparently afford sufficient driving force to make the displacement proceed.

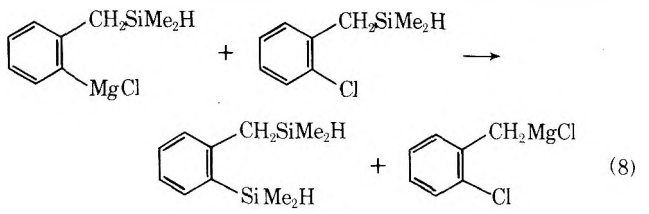
Pure disiloxane 8 was obtained only after distillation fractions were extracted with mild base. The yield quoted is derived from nmr spectra of the first distillation products. It is possible that some 8 may have been formed on hydrolysis of 7. Indeed, in a separate experiment, silalactone 7 in CCl_4 was treated with alcoholic KOH to reach an equilibrium mixture containing 7 and 8 in a 5:3 ratio, respectively. Exposing silalactone 7 to moisture gave an equilibrium mixture of 7 and a compound that could not be isolated in pure form but was tentatively identified as (2-carboxybenzyl)dimethylsilanol (**10**, eq 7). The reactions of



(7)

compound 7 were consistent with those observed for the silalactone dimer, **2**; however, in contrast to the behavior of **2**, **7** reacted more slowly and formed equilibrium mixtures that contained appreciable quantities of itself. The greater *stability of 7 is probably due to the favorable six-membered* ring geometry, while the macrocycle, **2**, is more like a normal silyl ester.

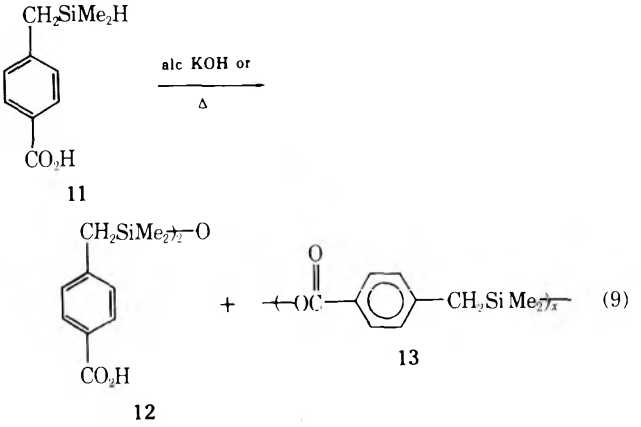
The main product in eq 6 was a considerable surprise. The disilyl derivative, **6**, was easily isolated by distillation and identified as the same compound previously prepared[11] by a standard procedure. The disilyl compound was apparently formed when one molecule of Grignard attacked the Si atom of another molecule of starting material, displacing the benzyl anion (eq 8). Cleavage of a benzyl



(8)

group from Si by a Grignard reagent has in fact been previously observed.[12] In agreement with eq 8, *o*-chlorophenylacetic acid, the carbonation product from the benzyl fragment, was also isolated. The observation of benzyl anion displacement with the ortho Grignard reagent, but not with the meta reagent, might be attributed to some kind of electronic effect. However, this seems unlikely, particularly since it is also not observed with the para reagent (*vide infra*). Perhaps Grignard and starting chloride complex with one another but only in the case of the ortho derivatives is there a reasonable steric disposition for nucleophilic attack on Si.

The Grignard reagent of p-chlorobenzyldimethylsilane was prepared and carbonated to obtain a good yield of the expected para hydrosilyl acid, **11**. This acid could not be anticipated to be the precursor for a monomeric silalactone, and models of the lactone dimer seem significantly strained. When the acid was heated in the presence of alcoholic KOH, a complex product mixture was formed. However, *the most prominent Si–Me peak in the nmr spectrum* of the mixture was a singlet at δ 0.4 ppm which (*vide infra*) we tentatively ascribe to a polymeric silyl ester. Also in agreement with this assignment is the observation that the peak eventually disappears on exposure to moisture. When the acid is heated without base, only two main products are formed, which we tentatively identify as polymer and disiloxane (eq 9).



(9)

Spectral Properties. The nmr spectra of the compounds described are quite simple (see Experimental Section), a *fact which made it possible to follow spectrally* some of the complex hydrolysis equilibria encountered. In the hydrosilyl acids and their precursors, the Si–H proton appeared with the septet pattern from coupling with Si–Me protons, but further broadened by coupling with the benzylic protons. Disappearance of the Si–H signal was one major clue to the transformations taking place. The lactone dimer[12] had several notable features. As is well known and was observed throughout our series of compounds, aromatic protons ortho to a carbonyl function are shifted downfield. the dimer **2**, however, showed a resonance even further downfield in the aromatic region (δ 8.4) which we assign to the aromatic proton contained in the heterocyclic ring. Models indicate that this proton can come quite near the aromatic nucleus across the ring, thus being further deshielded. The second feature of interest in **2** is the chemical shift of the Si–Me protons. At δ 0.4 they are substantially further downfield than the Si–Me protons of the silanol **4** (δ 0.2), or disiloxane **3** (δ 0.1), which also have Si attached to oxygen.[13] We suggest that this chemical shift will be found to be characteristic of Si–Me protons in silyl esters, as an identical position is observed for the ortho silalactone **7**. The Si–Me chemical shift also serves as one basis for our assignment of the polymeric silyl ester structure to

the product, **13**, of pyrolysis of the para hydrosilyl acid **11**.

Determination of the variable-temperature nmr spectral properties of the meta hydrosilyl acid **1** was one of the original goals of the research. At temperatures as low as −80° in acetone-d_6, however, no splitting of either benzylic or Si–Me signals could be observed. The observation is, of course, no direct proof against the existence of a hyperconjugative or other interaction. We simply cannot see evidence of one in this system using this technique.

We have not yet been able to obtain good mass spectra of all of the products identified, but both lactone dimer **2** and lactone **7** gave spectra in which the parent peak is prominent. The tentatively identified silanol, **10**, and the disiloxane, **8**, in the ortho series both gave mass spectra essentially identical with that of the lactone **7**, indicating quite facile dehydration, perhaps occurring thermally, prior to ionization. The disiloxane in the para series, **12**, also shows the fragment at *m/e* 192, $O_2CC_6H_4CH_2SiMe_2$, and this peak grows as inlet temperature is raised, again indicating the possibility of pyrolysis.

Experimental Section

Unless otherwise stated, all Grignard reagents were prepared in three-neck round-bottom flasks equipped with a reflux condenser, a magnetic stirrer, and an addition funnel. The glassware was flame dried and flushed with nitrogen prior to conducting the reaction under a nitrogen atmosphere. Tetrahydrofuran (THF) was dried by distilling from calcium hydride and then shaking with Linde 5A molecular sieves. The low-temperature nmr study was run on a Varian HA-100 and routine nmr spectra were recorded using a Varian A-60A spectrometer. Chemical shifts reported are relative to internal TMS. Infrared spectra were obtained using a Perkin-Elmer 137 Infracord spectrophotometer. Mass spectra were obtained using a Hitachi Perkin-Elmer RMS-4 mass spectrometer operating at 70 eV, and data are reported as *m/e* (relative intensity). Melting points are corrected.

Preparation of (3-Carboxybenzyl)dimethylsilane (1). Magnesium powder (0.16 mol, 3.9 g) and 50 ml of dry THF were placed in a round-bottom flask. The magnesium was activated by the addition of 1 ml of dibromoethane and refluxing for 15 min. (3-Chlorobenzyl)dimethylsilane (0.11 mol, 20.4 g) was added dropwise while refluxing the reaction mixture. An additional 25 ml of dry THF was added to the reaction vessel about 4 hr later. After refluxing for 24 hr, the Grignard reagent was poured into a slurry of Dry Ice in 50 ml of THF and stirred with a mechanical stirrer until the Dry Ice had sublimed. The organic layer was then hydrolyzed with dilute HCl, separated, and washed with H_2O. The solvent was removed using a rotary evaporator. Dry ether (25 ml) was added to the remaining material and this solution was dried over anhydrous $MgSO_4$ for several hours. The solvent was removed and the remaining material was vacuum distilled to yield 9.55 g (31%) of **1**: bp 109–110° (0.3 mm); nmr (CCl_4) δ 0.05 (d, J = 4 Hz, 6 H), 2.15 (d, J = 3 Hz, 2 H), 3.9 (broadened septet, 1 H), 7.2–7.8 (m, 4 H), 11.7 (s, 1 H); ir (neat) 3000, 2600, 2100, 1675, 1600, 1400, 1260, 1240, 1200, 1150, 1060, 900, 850, 820, 780, 760, 750, and 680 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}SiO_2$: C, 61.81; H, 7.26. Found: C, 61.81; H, 7.38.

Preparation of Silalactone Dimer (2). (3-Carboxybenzyl)dimethylsilane (0.0078 mol, 1.52 g) and 0.6 ml of 0.46 *M* KOH in anhydrous methanol were placed in a round-bottom flask and heated at 170° for 2 hr under a nitrogen atmosphere. An nmr spectrum indicated that approximately 78% of the acid had been converted to the disilalactone. The disilalactone was then sublimed from the product mixture at 170° (0.5 mm) to yield 1.00 g (67%) of **2**: mp 152–155°; nmr ($CDCl_3$) δ 0.4 (s, 6 H), 2.4 (s, 2 H), 7.2–7.5 (m, 2 H), 7.7–8.0 (m, 1 H), 8.4 (s, 1 H); ir (Nujol) 1600, 1280, 1240, 1210, 1110, 1080, 930, 920. 840, 815, 790, 775, 755, and 690 cm^{-1}; mass spectrum m/e (rel intensity) 384 (30), 192 (18), 179 (13), 165 (14), 149 (18), 119 (16), 118 (70), 90 (100), 89 (25). *Anal.* Calcd for $C_{20}H_{24}Si_2O_4$: C, 62.46; H, 6.29. Found: C, 62.30; H, 6.37.

Preparation of (3-Carboxybenzyl)dimethylsilanol (4). The purified silalactone dimer obtained in the previous procedure was dissolved in hot CCl_4 and left open to atmospheric moisture.[14] After 2 days, the silanol, a white, fluffy solid, precipitated from the solution. An nmr spectrum indicated that greater than 95% of the disilactone had been converted to the silanol. The silanol was recrystallized from hot $CHCl_3$ to give 0.6 g (50%) of **4**: mp 115–117°; nmr ($CDCl_3$) δ 0.2 (s, 6 H), 2.3 (s, 2 H), 6.8 (s, 2 H), 7.2–7.4 (m, 2 H), 7.7–7.9 (m, 2 H); ir (Nujol) 3300, 2800, 2700, 1650, 1600, 1350, 1150, 1125, 1060, 1050, 900–750, and 680 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}SiO_3$: C, 57.11; H, 6.71. Found: C, 56.96; H, 6.80.

Preparation of (3-Carboxybenzyl)dimethyldisiloxane (3). (3-Carboxybenzyl)dimethylsilane (1.27 g, 0.0067 mol) and 0.4 ml of 0.46 *M* potassium hydroxide in anhydrous methanol were placed in a round-bottom flask. The mixture was heated at 166° for 3 hr. The product mixture was then dissolved in hot CCl_4 and left open to moisture. After 2 days, the disiloxane, a white, crystalline solid, precipitated from the solution. An nmr indicated that greater than 95% of the disilalactone had been converted to the disiloxane. After recrystallization from hot CCl_4, 0.70 g (54%) of pure disiloxane, mp 143–145°, was collected: nmr ($CDCl_3$) δ 0.1 (s, 6 H), 2.2 (s, 2 H), 7.2–7.4 (m, 2 H), 7.7–7.9 (m, 2 H), 10.2 (s, 1 H); ir (Nujol) 2800, 2600, 1650, 1575, 1400, 1260, 1240, 1200, 1150, 1060, 950, 900, 840–780, 750, and 685 cm^{-1}. *Anal.* Calcd for $C_{20}H_{26}Si_2O_5$: C, 59.67; H, 6.51. Found: C, 59.22; H, 6.53.

Preparation of (2-Chlorobenzyl)dimethylsilane (5). Magnesium turnings (0.68 mol, 16.5 g) and 400 ml of dry ether were placed in a round-bottom flask. The magnesium was activated by the addition of 2 ml of dibromoethane and stirring for 15 min. A mixture of 2-chlorobenzyl chloride (0.62 mol, 98.5 g) and 400 ml of dry ether was added dropwise. After all of the mixture had been added, the solution was refluxed for 1 hr. The Grignard reagent was then added dropwise to a mixture of dimethylchlorosilane (0.62 mol, 60.2 g) and 200 ml of dry ether. After the addition was completed, the solution was refluxed for 2 hr. The solution was then hydrolyzed with dilute HCl, separated, and washed with H_2O. The organic layer was dried over anhydrous $MgSO_4$, and then the ether was removed using a rotary evaporator. The remaining material was vacuum distilled to yield 67.6 g (59%) of **5**: bp 59° (2 mm); nmr (CCl_4) δ 0.0 (d, J = 4 Hz, 6 H), 2.25 (d, J = 3 Hz, 2 H), 3.95 (broadened septet, 1 H), 6.8–7.3 (m, 4 H); ir (neat) 3000, 2130, 1470, 1440, 1250, 1220, 1160, 1050, 1030, 900, 840, 785, 770, 750, 700 cm^{-1}. *Anal.* Calcd for $C_9H_{13}SiCl$: C, 58.51; H, 7.09; Si, 15.20. Found: C, 58.27; H, 7.12; Si, 15.15.

Preparation of α,*o*-Bis(dimethylsilyl)toluene (6). The preparation was accomplished by using the procedure outlined in the preparation of (3-carboxybenzyl)dimethylsilane. The product was vacuum distilled to yield 7.46 g (65%) of **6**: bp 57° (0.3 mm); nmr (CCl_4) δ 0.0 (d, J = 4 Hz, 6 H), 0.25 (d, J = 4 Hz, 6 H), 2.25 (d, J = 3 Hz, 2 H), 3.95 (broadened septet, 1 H), 4.55 (septet, J = 3 Hz, 1 H), 6.8–7.4 (m, 4 H); ir (neat) 3000, 2150, 1600, 1460, 1450, 1260, 1200, 1150, 1120, 900, 840, 790, 750, 715, 680 cm^{-1}. *Anal.* Calcd for $C_{11}H_{20}Si_2$: C, 63.38; H, 9.67; Si, 26.95. Found: C, 63.43; H, 9.61; Si, 27.04.

The residue from the vacuum distillation was further distilled at 85–105° (0.3 mm) and three fractions were collected. The fraction collected at 85–95° was dissolved in ether and washed twice with 5% $NaHCO_3$. The ether layer was dried over anhydrous $MgSO_4$ and the ether was evaporated. The residue was vacuum distilled at 91° (0.3 mm) to yield pure lactone **7**: nmr ($CDCl_3$) δ 0.4 (s, 6 H), 2.31 (s, 2 H), 7.1–7.5 (m, 3 H), 8.0–8.4 (m, 1 H); mass spectrum *m/e* (rel intensity) 192 (25), 133 (74), 118 (67), 90 (100), 89 (68), 63 (20). *Anal.* Calcd for $C_{10}H_{12}SiO_2$: C, 62.45; H, 6.29. Found: C, 62.65; H, 6.14.

The fraction collected at 100–105° was dissolved in ether and washed twice with 5% $NaHCO_3$ solution. The aqueous layer was acidified and washed with ether. The ether was removed and the residue was recrystallized from an ethanol–water solution, and a white powder precipitated that was identified as disiloxane **8**: mp 87–89°; nmr ($CDCl_3$) δ 0.0 (s, 6 H), 2.8 (s, 2 H), 7.0–8.2 (m, 4 H), 9.5 (s, 1 H). *Anal.* Calcd for $C_{20}H_{26}Si_2O_5$: C, 59.67; H, 6.51. Found: C, 59.92; H, 6.75.

The filtrate from the previous crystallization was washed with ether. The ether solution was concentrated and petroleum ether was added until the solution became cloudy. A white crystalline precipitate was collected and identified as (*o*-chlorophenyl)acetic acid (**9**): mp 94–96°; nmr ($CDCl_3$) δ 3.85 (s, 2 H), 7.2–7.5 (m, 4 H), 11.4 (s, 1 H); mass spectrum *m/e* (rel intensity) 172 (18), 170 (51), 135 (69), 127 (35), 125 (100), 91 (61), 90 (22), 89 (31).

Preparation of (4-Carboxybenzyl)dimethylsilane (11). The preparation was accomplished using the procedure outlined in the preparation of **1**. The product was obtained by dissolving the reaction mixture in diethyl ether, adding petroleum ether until the solution became cloudy, and then cooling. The product precipitated as a white, fluffy solid to yield 16.49 g (78%): mp 121–124°; nmr ($CDCl_3$) δ 0.05 (d, J = 4 Hz, 6 H), 2.3 (d, J = 3 Hz, 2 H), 3.9

(broadened septet, 1 H), 7.1–7.4 (m, 2 H), 7.9–8.2 (m, 2 H), 12.1 (s, 1 H); ir (Nujol) 3000, 2100, 1700, 1630, 1430, 1310, 1290, 1250, 1220, 1190, 1080, 950, 900, 870, 840, 750 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}SiO_2$: C, 61.81; H, 7.26. Found: C, 61.71; H, 7.12.

Preparation of (4-Carboxybenzyl)dimethyldisiloxane (12). (4-Carboxybenzyl)dimethylsilane (0.87 g, 0.0046 mol) and 0.4 ml of 0.46 *M* KOH in anhydrous methanol were placed in a round-bottom flask. The mixture was heated at 150° for 1 hr. An nmr of the mixture indicated that about 50% of the acid had reacted. The reaction mixture was dissolved in ether and exposed to moisture for a few days. Petroleum ether was added to the ether solution until the solution became cloudy. A powdery precipitate was collected. The filtrate was concentrated and the disiloxane precipitated from solution yielding 0.1 g (10%) of pure product, mp 108–110°, after several recrystallizations: nmr (acetone-d_6) δ 0.0 (s, 6 H), 2.0 (s, 2 H), 6.1 (s, 1 H), 7.0–7.2 (m, 2 H), 7.7–8.0 (m, 2 H). *Anal.* Calcd for $C_{20}H_{26}O_5Si_2$: C, 59.67; H, 6.51. Found: C, 59.63; H, 6.72.

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Registry No.—**1**, 51801-42-4; **2**, 51801-43-5; **3**, 51801-44-6; **4**, 51801-45-7; **5**, 51801-46-8; **6**, 17867-29-7; **7**, 51801-47-9; **8**, 51801-48-0; **9**, 2444-36-2; **11**, 51801-49-1; **12**, 51801-50-4; (3-chlorobenzyl)dimethylsilane, 27856-35-5; 2-chlorobenzyl chloride, 611-19-8; dimethylchlorosilane, 1066-35-9; (4-chlorobenzyl)dimethylsilane, 27856-36-6.

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(5) Estimated from an nmr spectrum of the crude reaction mixture.

(6) 4,4,13,13-Tetramethyl-3,12-dioxa-4,13-disilatricyclo[13.3.1.$1^{6,10}$]eicosa-1(19),6,8,10(20),15,17-hexaene-2,11-dione.

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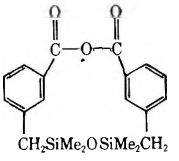
(13) This feature of the nmr spectrum of **2**, along with the absence of the very characteristic Si–O–Si band in the infrared spectrum of **2**, led us to exclude the possibility that **2** could be the isomeric disiloxy anhydride.



(14) The reaction occurred during a period of very high humidity. With lower humidity, the dimer (**2**) may precipitate from solution.

Notes

Radicals from 2-Nitrofuran

C. Maurizio Camaggi, Lodovico Lunazzi,* and Giuseppe Placucci

Laboratorio CNR dei Composti del Carbonio Contenenti Eteroatomi, Institute of Organic Chemistry, University of Bologna, Risorgimento, 4, 40136 Bologna, Italy

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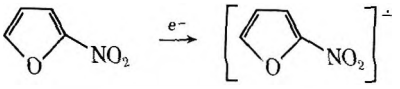
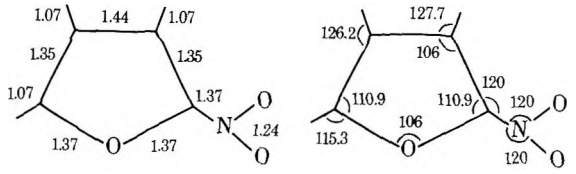
The electrochemical reduction of 2-nitrofuran in acetonitrile affords the corresponding radical anion (I).[1] Its esr



spectrum has been recorded and interpreted in terms of three nonequivalent a_H and one a_N splitting constants (Table I).

Whereas the assignment of a_N is straightforward, some doubt might arise as far as the assignment of the three a_H values is concerned. The 5-methyl-2-nitrofuran radical anion (II) allowed us to show that the 4.12 G splitting belongs to position 5; in fact in II this value is substituted by an a_{Me} splitting of similar magnitude (4.05 G) whereas the other two couplings are almost unaffected.[2] The largest splitting (5.65 G) has been assigned to position 3 and the smallest (1.00 G) to position 4 on the ground that the conjugation of five-membered aromatic rings with substituents in position 2 is expected to be more effective[3] in the 3,5 positions than in the 4 position. To check such an hypothesis theoretical calculations have been carried out by the self-consistent molecular orbital (INDO) method.[4]

The geometrical parameters employed are as follows.



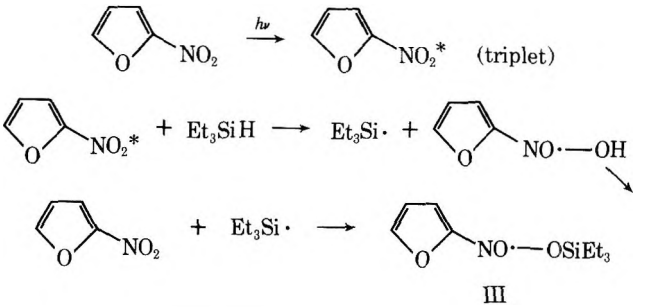
The theoretical splittings for the hydrogen atoms, given in parentheses in Table I, are in agreement with the experiment, thus supporting the tentative assignment for what concerns positions 3 and 4.

This theoretical approach also allowed us to estimate the energy barrier to the internal rotation in the nitrofuran radical anion as a difference between the planar and the 90° twisted structures. The values of the total energies were calculated to be −93.53292 and −93.51702 au, respectively, and the rather large ΔE value (10 kcal mol^{-1}) would indicate that the rotation of the NO_2 group is expected to be slow in the esr time scale.

In order to test experimentally such a possibility it would be necessary to differentiate in some way the two oxygen atoms, so that two conformational isomers would appear if the rotation rate around the furan–nitrogen bond is slower than the reciprocal lifetime of the spin of the unpaired electron.

A possible way to reach such a goal is the transformation of the nitrogen group into an alkoxy nitroxide. This modification would completely change the chemical character of the molecule; since, however, the conjugative power of the nitroxide moiety with the aromatic ring is expected to be lower than that of the nitro group, the existence of rotational isomers in the alkoxy nitroxide would be a very strong support in favor of a restricted rotation also in the corresponding nitro derivative.

Sutcliffe, *et al.*,[5,6] demonstrated that the photolysis of nitroaromatics in hydrogen donor solvents affords the corresponding alkoxy nitroxides. Therefore we photolyzed the 2-nitrofuran within the cavity of an esr spectrometer in a solution of triethylsilane. The following reactions are believed[5,6] to occur, yielding the 2-(triethylsiloxy)nitroxyfuran (III).



III

The radical ArNOOH decays too fast than required to build up a steady-state concentration allowing the esr detection. That ArNOOH is not responsible for the signal reported in Figure 1 is proved by the fact that with hydrogen donor solvents having $-CH_2-$ groups (such as tetrahydrofuran) an additional splitting is observed,[5,6] whereas no such a feature is apparent when the solvent has -CH- groups.

Et_3SiH was found even more convenient than the previously employed solvents,[5,6] as it affords larger concentrations of radicals and avoids (as the -CH- containing solvents) additional couplings from the -OR moiety in the spectrum.

At room temperature a spectrum analogous to that of

Table I
Hyperfine Splitting Constants (Gauss) of the Radical Anions of 2-Nitrofuran (I), 5-Methyl-2-nitrofuran (II), and the Neutral Radical 2-(Triethylsiloxy)nitroxyfuran (III)[a]

		a_{H-3}	a_{H-4}	a_{H-5}	a_N	a_{Me}
I		5.65 (−5.21)	1.00 (2.06)	4.12 (−3.63)	11.25 (7.28)	
II		6.00	0.85		11.60	4.05
III	70%	5.80	0.90	4.50	13.25	
	30%	5.65	0.85	4.30	13.80	

[a] Values in parentheses refer to the calculated (INDO) splittings of I.

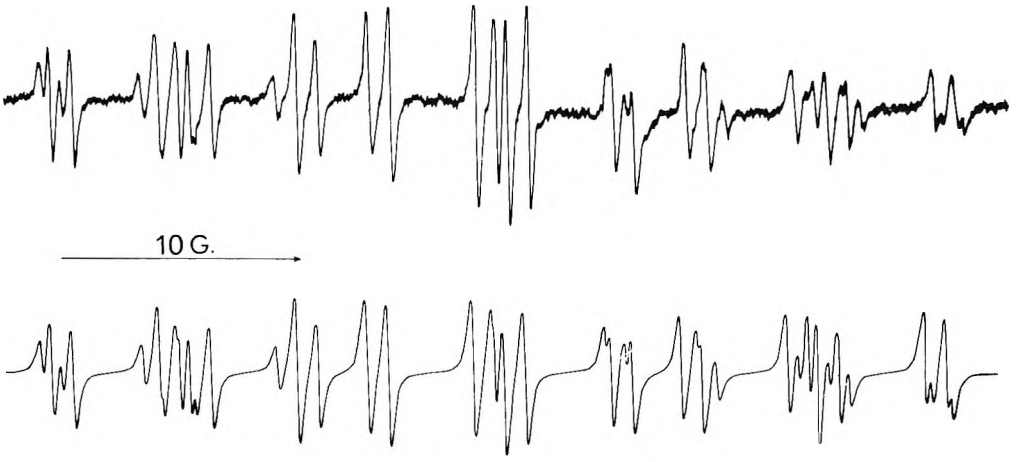
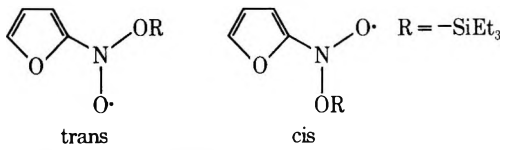


Figure 1. Experimental (upper) and computed esr spectrum of III at −60° showing the existence of two rotational isomers. The hyperfine splitting constants are given in Table I, the intensity ratio of the two species is 7:3, the line width is 0.23 G, and the difference between the two centers of the spectra is 0.10 G.

nitrofuran anion (I) (*i.e.*, one a_N and three a_H couplings) was observed. By lowering the temperature, however, a line width broadening effect was observed and at −60° two well-resolved spectra, corresponding to two different radicals, were detected, their relative intensity being 7:3 (Figure 1).

As the phenomenon appears to be reversible, the two groups of signals were attributed to rotational isomers having respectively the -OR group trans or cis with respect to the heterocyclic oxygen.



The two rotamers have rather similar proton splittings and g values, the more stable having the center of its spectrum shifted downfield with respect to that of the less stable by only 0.10 G. As the a_H values are not too different from those of the nitro anion (I), the assignment to the various positions has been made assuming af analogous trend.

It is clear that a restricted rotation exists in aromatic alkoxy nitroxides, as already observed in phenyl nitroxide,[7] and that most likely the same can be inferred for the radical anions of nitro aromatics.

The study is being pursued on the more stable thiophene analog which give the same effect.[8]

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Registry No.—I, 34480-16-5; II, 34480-15-4; III, 51108-28-2.

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Vapor-Phase Introduction of Vinyl Ketones in Michael Additions

Charles D. DeBoer

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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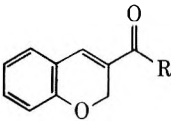
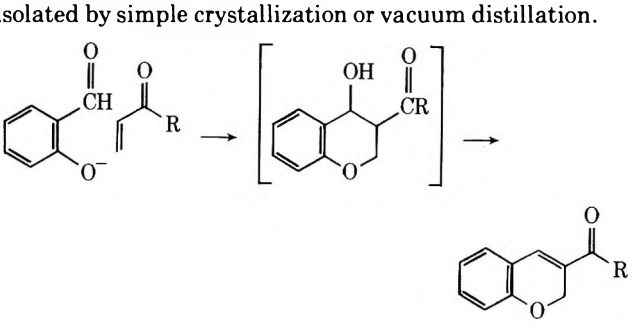
In a study of the photochemistry of some structurally related, unsaturated ketones,[1] the chromenes **1** were needed.



1a, R = H
b, R = CH_3
c, R = Ph
d, R = OH
e, R = OCH_3

Although chromenes **1d** and **1e** have been prepared[2] by the slow addition of sodium hydroxide to a refluxing mixture of salicylaldehyde and acrylonitrile (followed by hydrolysis), **1a-c** have never been reported. Attempts to prepare **1a-c** by the method of Taylor and Tomlinson[2] gave only polymeric mixtures. Attempts to convert **1d** to **1a**, **1b**, or **1c** by conventional reactions (Friedel-Crafts, Grignard, reduction, etc.) also failed, or at best gave poor yields with many side-products. It was then discovered that **1a** and **1b** can be prepared in good yield by stirring a mixture of salicylaldehyde and water with 0.1 equiv of base and introducing 1 equiv of the vinyl ketone (acrolein or methyl vinyl ketone) in the vapor phase in a stream of nitrogen. Apparently this dilution method of adding vinyl ketone prevents polymerization. The chromene is then isolated by simple crystallization or vacuum distillation.



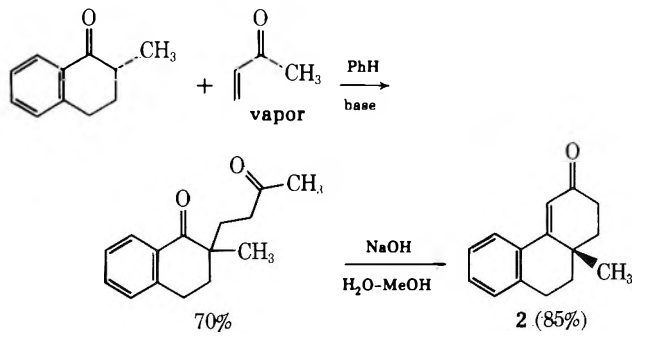
1

The 5-chloro- and 5-bromosalicylaldehydes have also been used successfully in this preparation, but 5-nitrosalicylaldehyde and 2,4-dihydroxybenzaldehyde failed to give isolable products. Use of *o*-hydroxyacetophenone with methyl vinyl ketone did not give an isolable amount of product, but silica gel thin layer chromatography showed a spot having the highly characteristic green fluorescence of the 3-ketobenzopyran system, so it is possible that a trace of the product, 3-acetyl-4-methyl-5,6-benzopyran, may have been formed.

The vapor-phase introduction of vinyl ketones is useful in C-Michael as well as O-Michael additions. For example, a considerably higher yield of 3-phenylcyclohexenone can be obtained from ethyl benzoylacetate and methyl vinyl ketone if the vinyl ketone is introduced as a vapor rather than as a liquid.[3]

This method of introducing a vinyl ketone to a reaction mixture in a dilute form offers an alternative to the widely used Robinson method using the Mannich base methiodide and 1 equiv of base.[4]

Although the Robinson method gives excellent results, the vapor-phase method, when applicable, may be a simpler and easier procedure. For example, the condensation of 2-methyl-1-tetralone with methyl vinyl ketone was carried out by bubbling a stream of nitrogen saturated with methyl vinyl ketone into a benzene solution of 2-methyl-1-tetralone with diazabicyclononene as the base. Cyclization with 2% NaOH in methanol–water then gave the tricyclic compound in good yield.[5]



Experimental Section

Preparation of 5,6-Benzopyran-3-carboxaldehyde. Salicylaldehyde (122 g, practical grade, Eastman No. P225) was stirred with 850 ml of water and 4 g of sodium hydroxide. A stream of nitrogen (about 50 ml/min) was bubbled through 67 g of acrolein (Eastman No. 2037) and then into the salicylaldehyde–water mixture through a fritted disk. This assembly was left overnight, and by morning all the acrolein had evaporated into the reaction mixture. The mixture was acidified with 25 ml of concentrated HCl and the lower layer was separated, washing the water layer with CH_2Cl_2. The organic layer was dried and distilled under vacuum. At ~1 Torr, the first cut was 42.5 g of salicylaldehyde, bp 58–62°, followed by 88.2 g of **1a**, bp 128–135°. The bright yellow product solidified when a seed crystal was introduced. The yield was 85%, based on salicylaldehyde consumed.

Preparation of 3-Acetyl-5,6-benzopyran. Salicylaldehyde (122 g, Eastman No. 225), was stirred with 1700 ml of water, and 4 g of sodium hydroxide dissolved in 15 ml water was added. A stream of nitrogen was bubbled through 82 g of methyl vinyl ketone (Aldrich No. M8, 750-9, used without purification after 2 years of storage), and then into the salicylaldehyde–water mixture through a coarse fritted disk. When the ketone had evaporated into the mixture, 25 ml of concentrated HCl was added and the organic material was extracted with CH_2Cl_2. Distillation gave 37 g of salicylaldehyde, bp 58–62°, followed by 87 g of **1b**, bp 130–135°, mp 50–53°. The yield was 72% based on salicylaldehyde consumed.

Preparation of 3-Benzoyl-5,6-benzopyran. Salicylaldehyde (122 g), 1000 ml of 50:50 ethanol–water, and 8 g of sodium hydroxide were stirred while 132 g of phenyl vinyl ketone in 400 ml of ethanol was slowly dripped into a 2000-ml vessel at a temperature of 25°. Then a seed crystal was formed and when the product, 3-benzoyl-5,6-benzopyran, had crystallized it was collected and recrystallized from methanol, mp 60–61°.

Preparation of 3-Phenylcyclohexen-1-one. Ethyl benzoylacetate (40 g, Eastman No. 2731) was stirred with 2 g of sodium hydroxide and 300 ml of methanol while 15 g of methyl vinyl ketone was evaporated into the solution in a stream of nitrogen. In the morning, the mixture was solid. The solid was filtered, washed with methanol, and recrystallized from alcohol, mp 148–149°, yield 41 g (82%) of the methyl ester of 3-phenyl-3-hydroxycyclohexanone-4-carboxylic acid. This was converted to the enone by refluxing in aqueous sodium hydroxide.

Preparation of 2. A stream of nitrogen saturated with methyl vinyl ketone was bubbled through a solution of 2-methyl-1-tetralone (10 g, Aldrich No. 16,322-8), 20 ml of benzene, and 2 ml of 1,5-diazabicyclo[4.3.0]non-5-ene (Aldrich No. 13,656-1) until gas chromatographic analysis showed that the tetralone was 95% reacted. The mixture was diluted with 1% HCl and extracted with methylene chloride, the organic layer was dried and evaporated, and the residue was distilled under vacuum, bp 157° (~1 Torr), to give 10.1 g of the Michael adduct, which was cyclized by refluxing with 2% NaOH in 400 ml of 50:50 water–methanol for 3 hr. The product was extracted with CH_2Cl_2, filtered through 2 in. of alumina, and crystallized from 50 ml of hexane, yield 8.0 g (60% overall), mp 54°.

Registry No.—**1a**, 51593-69-2; **1b**, 51593-70-5; **1c**, 51593-71-6; **2**, 51593-72-7; salicylaldehyde, 90-02-8; acrolein, 107-02-8; methyl vinyl ketone, 78-94-4; phenyl vinyl ketone, 768-03-6; 3-phenylcyclohexen-1-one, 10345-87-6; ethyl benzoylacetate, 94-02-0; methyl 3-phenyl-3-hydroxycyclohexanone-4-carboxylate, 51593-73-8; 2-methyl-1-tetralone, 1590-08-5.

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Acid-Catalyzed Ketone Rearrangements. Synthesis of Decalins and Spiro[4.5]decanes

Peter Bakuzis,* G. C. Magalhães, H. Martins, and M. L. F. Bakuzis

Departamento de Química, Universidade de Brasília, Brasília, D. F., Brasil 70.000

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As part of a project to develop new routes to hydroazulenic sesquiterpenoids, we examined the photochemical and acid-catalyzed behavior of the β,γ-unsaturated ketone **1**. As the photochemical properties of **1** have recently been reported by other workers,[1] we would like to communicate our acid-catalyzed rearrangement studies which, surprisingly, led to compounds having a decalin or spirodecane skeleton.

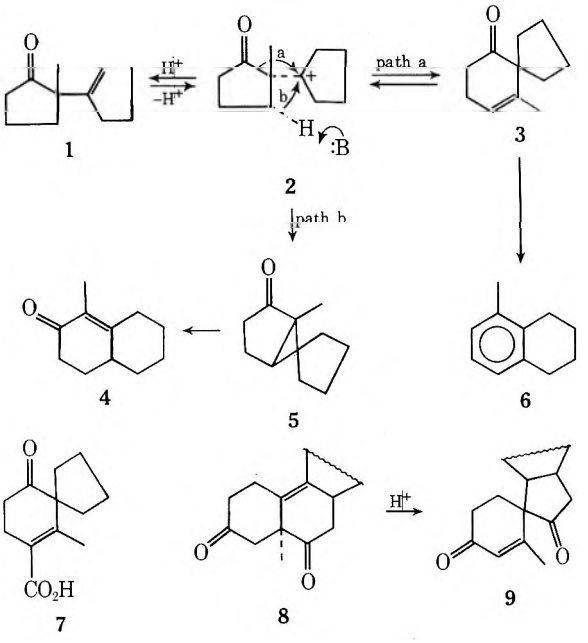
Treatment of enone **1**[1] for 3 hr with boron trifluoride etherate in refluxing benzene resulted in the preparation of the tetrahydronaphthalene[2] **6** and octalone **4** in 46 and 51% yields, respectively. The structure of hydrocarbon **6** was apparent from its spectra and the facile aromatization to 1-methylnaphthalene,[3] while the enone[4] **4** was compared with an authentic sample.[3]

Partially reacted mixtures allowed the isolation of an intermediate **3** whose structure is supported by the spectral data, but different from that reported for the same compound.[5] Confirmation of the assigned structure came from chemical correlation *via* the Kochi decarboxylation[6] of spiro acid **7**[7] in the presence of lead tetraacetate or *via* the thermal decomposition of the corresponding *tert*-butyl

perester in refluxing decalin. Submission of the spiro ketone to the original rearrangement conditions for 25 min resulted in the isolation of approximately equal quantities of 1, 6 and 4, while the reaction run to completion gave the hydrocarbon 6 and enone 4 in 46 and 44% yields, respectively.

While acid-catalyzed ketone rearrangements are not rare,[8] there is a paucity of quantitative and qualitative data that permits a satisfying interpretation of this reaction. Most acid-catalyzed rearrangements of β,γ-unsaturated ketones[8,9a,b] proceed by initial protonation of the more basic site, the carbonyl oxygen. Such a mechanism seems unlikely in the present case and we propose that the equilibration of 1 and 3 is catalyzed by electrophilic attack on the double bond followed by a 1,2-acyl shift (path a in Scheme I) in a mechanism reminiscent of the heterolytic rearrangements of α,β-epoxy ketones[10] and of steroid 8 to 9.[9c] The hydrocarbon 6 probably arises by rearrangement of the conjugate acid of spiro ketone 3, since an alternative pathway, enone 4 → 6, was found to be too slow under the reaction conditions.

Scheme I



More intriguing is the transformation of 1 to 4. Since we did not find glpc evidence for the presence of one or more intermediates, the pathway must proceed *via* a compound which would be expected to be quite reactive. Accordingly, we propose that the key intermediate may be the spiro ketone 5, formed by the loss of a proton at C-3 of cation 2 (path b in Scheme I). Examination of molecular models shows a remarkable steric similarity of cation 2 and the 2-methyl-2 norbornyl cation, which is known to be able to lose a proton to give nortricylene derivatives, *e.g.*, in the acid-catalyzed isomerization of sativene to cyclosativine.[11]

Attempted synthesis by sensitized photolysis[12] of spiro ketone 3 failed to yield 5, a result which might have been expected[12] from the λ_{max} of 4 (289 nm).

Experimental Section

Acid-Catalyzed Rearrangement of 2-Methyl-2-(1-cyclopent-1-yl)cyclopentanone (1). A solution of 1.0 g of ketone 1 in 25 ml of benzene (under N_2) was brought to reflux and then 1.0 ml of freshly distilled boron trifluoride etherate was added *via* a syringe. Stirring was continued at reflux for 6 hr, the disappearance of starting material 1 and appearance of products 3, 4, and 6 being monitored by glpc using 1-methylnaphthalene as internal standard (2 m × 0.25 in. 15% FFAP on Chromosorb P). The yield of spiro ketone 3 reached a maximum of 19% after 45 min, thereafter decreasing to zero, wile the hydrocarbon 6 and enone 4 reached 46 and 51% yields, respectively, after 3 hr, not changing significantly (<1%) thereafter. The cooled mixture was poured onto ice and the organic layer was washed with water and then with 5% NaOH. After drying over Na_2SO_4, the solvent was distilled off and the residue was chromatographed on 30 g of silica gel. Elution with petroleum ether gave hydrocarbon 6, nmr (CCl_4) δ 6.82 (m, 3 H), 2.86-2.38 (m, 4 H), 2.13 (s, 3 H), 1.95-1.53 (m, 4 H), which was oxidized by DDQ in 80% yield to 1-methylnaphthalene. Continued elution with benzene gave octalone 4.[3,4] The rate of reaction increased, but the yields decreased, when less care was used to dry the system. Acids, presumably derived from acid-catalyzed ketone cleavage, became important products under these conditions.

Isolation of 10-Methylspiro[4.5]dec-9-en-6-one (3). To a solution of 23.9 g of ketone 1 in 600 ml of benzene at reflux under N_2 was added 25 ml of freshly distilled boron trifluoride etherate. After the mixture was stirred at reflux for 120 min, it was poured onto crushed ice and worked up as above. Two chromatographies of the residue on 600 g of silica gel using petroleum ether–benzene mixtures as solvents resulted in the isolation of 11.0 g of starting material 1 and 4.7 g (37% yield, based on unrecovered starting material) of spiro ketone 3: ir (neat) 5.83 μ; uv λ_{max} (EtOH) 289 nm (ϵ 49); nmr δ 5.5 (m, 1 H), 2.4 (m, 4 H), 1.75 (m, 11 H).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.41; H, 9.78.

Preparation of Spiro Ketone 3 by Kochi Decarboxylation[6] of Spiro Keto Acid 7. A mixture of 0.208 g of keto acid 7 and 0.50 g of dry (KOH vacuum) lead tetraacetate in 15 ml of acetonitrile (distilled from P_2O_5) was photolyzed at 3000 Å (Rayonet photoreactor) for 40 min. The resulting light yellow solution was filtered and 1-methylnaphthalene was added as internal standard. Analysis on two glpc columns (FFAP at 230° and DCC550 at 160°) showed the presence of only one volatile compound in 32.5% yield, based on unrecovered starting material. The mixture was separated by the usual procedures to give 69 mg of starting keto acid 7 and 33 mg of spiro ketone 3, identical in all respects (ir, nmr, glpc, and column chromatography behavior) with material isolated above.

Preparation of Spiro Ketone 3 by Thermolysis of the *tert*-Butyl Perester of Spiro Keto Acid 7. To 1.3 g of dicyclohexylcarbodiimide in 35 ml of ether was added 6.0 ml of *tert*-butyl hydroperoxide, and the resulting solution was cooled to 0° and 1.04 g of keto acid 7 added during 2 min. Stirring at 0° was continued for 3 hr followed by 16 hr at room temperature. The mixture was filtered and the organic phase was washed successively with 2% NaOH, 2% H_2SO_4, and H_2O until neutral and then dried over Na_2SO_4. Chromatography of the residual oil on 50 g of Florisil with 2% Et_2O–petroleum ether gave 1.13 g of *tert*-butyl perester, ir (neat) 5.65 and 5.81 μ. The perester, 198 mg in 12 ml of decalin, was refluxed for 35 min. Glpc analysis of the reaction mixture using 1-methylnaphthalene as internal sample showed the presence of spiro ketone 3 (56% yield) as the only volatile component. The ketone 3 was isolated by passing the reaction mixture through a column of silica gel (20 g) and eluting the adsorbed material with benzene.

Acid-Catalyzed Rearrangement of Spiro Ketone 3. A mixture of 0.202 g of spiro ketone 3 and 5.0 ml of benzene, under N_2, was brought to reflux and 0.2 ml of boron trifluoride etherate was added. After refluxing for 25 min, the mixture was worked up as above and the resulting oil was chromatographed on 10 g of silica gel. Elution with petroleum ether gave 44 mg of hydrocarbon 6. Continued elution with benzene gave 32 mg of cyclopentanone 1 and 58 mg of octalone 4. A second reaction run to completion and analyzed by glpc using an internal standard gave 46% hydrocarbon 6 and 44% octalone 4.

Acknowledgment. We are grateful to Professor Hart for spectral data and thank CNP_q (Brasil) for partial support of this work.

Registry No.—1, 43011-75-2; 3, 6684-92-0; 4, 5164-37-4; 6, 2809-64-5; 7, 20006-95-5; 7 *tert*-butyl perester, 51472-62-9; dicyclohexylcarbodiimide, 538-75-0.

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Heterogeneous Catalytic Asymmetric Hydrogenation

L. H. Gross[6] and P. Rys*

Department of Industrial and Engineering Chemistry, Eidgenössische Technische Hochschule, Zürich, Switzerland

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Previous studies by Izumi, *et al.*,[1] of the asymmetric hydrogenation of methyl acetoacetate to yield optically active methyl 3-hydroxybutyrate using Raney nickel catalysts (R-Ni) modified with optically active (2*R*,3*R*)-tartaric acid were limited to the effects which various modification conditions (and other modification agents) had on the stereoselectivity of the overall reaction. Hubbell and Rys[2] showed, however, that the optical yield was dependent on conversion. Difficulties with their analytical procedure prohibited the accurate measurement of the optical activities of the alcohol products below 25% conversion, a region shown to be of interest in this study.

Initial experiments showed that no racemization or asymmetric transformation occurred after 100% conversion was attained, that the stirring speed was sufficiently fast to eliminate macroscopic diffusion problems, and that the initial pH of the (2*R*,3*R*)-tartaric acid solution used to modify the R-Ni was 4.9. Because the activity of R-Ni catalysts affects the rate of hydrogenation to such a large extent, it was felt that it might also affect the stereoselectivity of the reaction.

The hydrogenation of methyl acetoacetate was performed with modified R-Ni catalysts (of various premodification hydrogenation activities) to yield methyl 3-hydroxybutyrate with good stereoselectivity. Although the rate of the hydrogenations after the modification reaction was carried out was nearly the same for all the catalysts used (owing to the necessity of heating and the presence of water in the modification reaction), Figure 1 shows that the catalyst's premodification hydrogenation activity had a large influence on the optical yield of the alcohol product and on the shapes of the curves. As the W-scale (Wisconsin) activity of the catalyst changes, the optical activity of the alcohol product is altered from yielding a very flat maximum at about 70% conversion (W-6, the most active catalyst used) to a very sharp maximum at about 25% conversion (>W-1). Although the alcohol produced by the catalyst of W-1 activity does not appear to have a maximum, this may be due to the fact that no samples were taken below 10% conversion. Between the W-1 and the still less active W-0 catalyst, the pattern is broken and the optical activity of the product obtained from using the W-0 catalyst is much lower than expected. In addition,

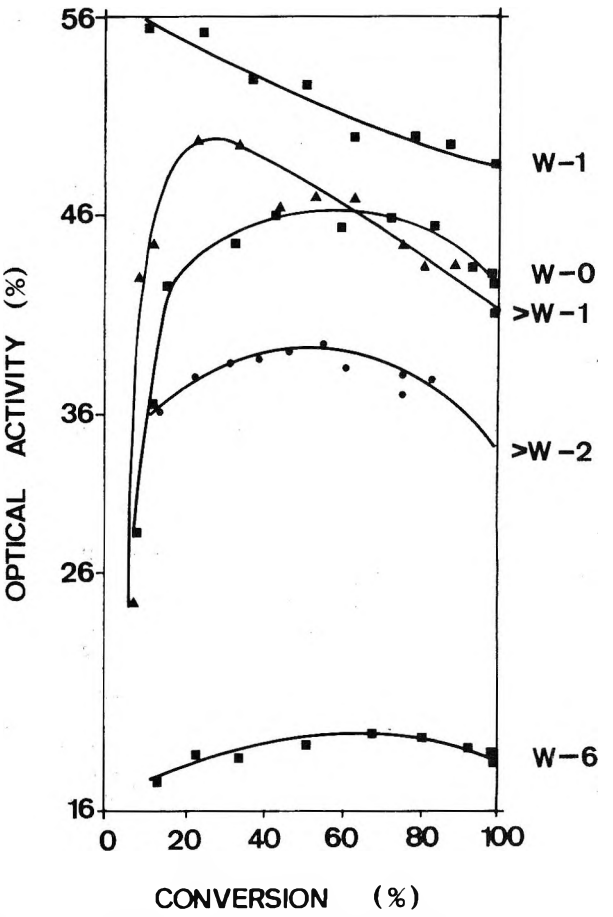

Figure 1. Optical activity of the alcohol product *vs.* conversion of the reaction (per cent alcohol) for the five R-Ni catalysts with various premodification (W scale) activities.

the shape of the curves, in particular the decrease beyond the maximum, was shown not to have been caused by an irreversible catalyst poisoning. This was verified by the use of Hubbell and Rys'[2] rerun procedure in which reused catalysts gave similar optical activity *vs.* conversion curves to their initial experimental curves.

Also noteworthy is that for all of the hydrogenations the maximum optical activity of the alcohol product does not occur at 100% conversion. Rather, the maximum stereoselectivity for a given catalyst moves to lower conversions as the overall stereoselectivity increases.

The maximum optical activity obtained was 55.4% (77.7% *R* to 22.3% *S* alcohol) at approximately 10% conversion for the W-1 catalyst. Although Knowles, Sabacky, and Vineyard[3] have obtained 90% stereoselectivity for homogeneous catalytic asymmetric hydrogenations, and Tanabe and Izumi[4] have been able to achieve 66% optical yield for methyl propionylacetate with a R-Ni catalyst (with a change in the usual modification procedures), the experiments presented here represent some of the highest stereoselectivities found for heterogeneous catalytic asymmetric hydrogenation reactions. The fact that the optical yields are so dependent on conversion and catalyst activity must be carefully considered in future work done in this area.

Experimental Section

Preparation of Raney Nickel Catalysts. A 30-g portion of the Ni-Al alloy (50:50) was slowly added to 500 ml of a 20% NaOH aqueous solution. The addition was carried out at 5–10° for the catalysts W-0, W-1, and >W-1, at 80° for >W-2, and at 50° for the preparation of W-6. After the addition of the alloy, the digestion reaction was allowed to proceed at reflux for 24 hr (W-0), 4 hr (W-1), and 75 min (>W-1), at 80° for 50 min (>W-2), and at

50° for 50 min (W-6). Their activity ratings on the W scale were obtained from comparisons with the known ratings of the W-1 and W-6 catalysts as described by Augustine.[5] In this way Hubbell and Rys'[2] catalyst preparation procedure yielded the ">W-2" catalyst, the procedure of Izumi, *et al.*,[1] yielded the ">W-1" catalyst, and one was prepared for this study, with the lowest hydrogenation activity, as the "W-0" catalyst.

Modification of Raney Nickel Catalyst. In each case the modification reaction was carried out by adding 1 l. of a 2% aqueous solution of optically active (2*R*, 3*R*)-tartaric acid (initial pH adjusted to 4.9 by addition of NaOH) to the washed catalyst and refluxing for 1 hr.

Hydrogenation of Methyl Acetoacetate. All reactions were carried out in stirred autoclaves at 60°, 90 atm H_2, and catalyst concentrations of 0.05 g of untreated Ni–Al alloy per milliliter of reactant.

Low-Conversion Calibration Curve. Samples taken during the low-conversion part of the reaction were extremely difficult to separate into their optically active alcohol product and nonoptically active ketone reactant. In addition, large volumes were required to get sufficient alcohol to fill the polarimeter cell. The use of a calibration curve allowed the determination of the optical activity of the pure alcohol product by measurement of the optical activity of the ketone–alcohol mixture.

A methyl 3-hydroxybutyrate of known optical activity was diluted with varying amounts of methyl acetoacetate (to give between 100 and 5% alcohol solutions) and the optical activities of the mixtures were measured. The same procedure was done with two other methyl 3-hydroxybutyrates of different optical activities and it was found that for the entire concentration range one curve of percentage decrease in optical activity from the pure alcohol *vs.* concentration would suffice. This curve was then used to determine the optical activity for the samples taken during the reaction.

Acknowledgment. We would like to thank the Schweizerischer Nationalfonds zur Förderung der Wissenschaften for financial support of this study (Project 2.437.71), and for the travel grant given to one of us (L. H. G.) by Hoffmann-La Roche Inc.

Registry No.—Methyl acetoacetate, 105-45-3; methyl 3-hydroxybutyrate, 1487-49-6.

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Friedel–Crafts Chemistry. IX.[1] Aluminum Chloride and Antimony Pentafluoride Catalyzed Desulfonylative Alkylation of Aromatics with Isopropyl, *tert*-Butyl, and Benzylsulfonyl Halides and Related Sulfones

George A. Olah,* Jun Nishimura,[2] and Yorinobu Yamada[2]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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In the study of the Friedel–Crafts reactions of *tert*-alkylcarbonyl halides, such as pivaloyl chloride, it was observed that they readily decarbonylate, thus can also act as alkylating agents.[3] Consequently, alkylsulfonyl halides also may desulfonylate and alkylate aromatics, although these systems so far were reported to act exclusively as sulfonylating agents in Friedel–Crafts reactions.[4] In fact, however, desulfonylation of alkylsulfonyl chlorides is known to take place under various conditions.[5]

tert-Butylsulfonyl chloride, for example, can easily undergo homolytic decomposition to yield *tert*-butyl radical chlorine atom, and sulfur dioxide.[6] The attempted Friedel–Crafts cyclization of ω-arylalkylsulfonyl chlorides was reported to give only unidentified decomposition products.[7]

We considered it of interest to undertake a study of the Friedel–Crafts reactions of sulfonyl halides potentially capable of undergoing desulfonylation and thus give alkylated product. As the formation of *tert*-butyl cation and protonated benzylsulfinic acid has been reported in the protolysis of *tert*-butyl benzyl sulfone in "magic acid,"[8] we also extended our investigation to related Friedel–Crafts reactions of sulfones potentially capable of alkyl–sulfur cleavage. We would like to report now the observation of the novel Friedel–Crafts desulfonylative alkylation of aromatics, namely benzene and toluene, with several sulfonyl chlorides and sulfones.

Results and Discussion

Isopropyl, *tert*-butyl-, benzyl-, and *p*-methylbenzylsulfonyl chloride gave ready alkylation of aromatics in the presence of aluminum chloride–nitromethane catalyst at 25°. The reaction with *p*-nitrobenzylsulfonyl chloride needed to be carried out at 60° using aluminum chloride, not complexed with nitromethane, in excess of aromatic hydrocarbon as solvent.

$$ArH + RSO_2Cl \xrightarrow{AlCl_3} ArR + SO_2 + HCl$$

Isopropyl *p*-tolyl sulfone, *tert*-butyl *p*-tolyl sulfone, and benzyl *p*-tolyl sulfone similarly gave alkylation in excess aromatic as solvent in the presence of aluminum chloride.

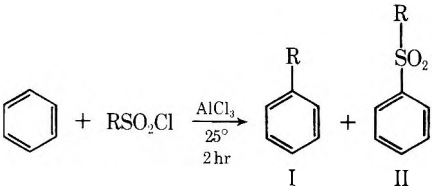
$$ArH + RSO_2\text{-}p\text{-}Tol \xrightarrow{AlCl_3} ArR + p\text{-}TolSO_2H$$

tert-Butyl benzyl sulfone did not alkylate in the presence of aluminum chloride at 80°, but reacted with antimony pentafluoride in 1,1,2-trichloro-1,2,2-trifluoroethane solution (Freon 113) to give *tert*-butylbenzene and -toluene from benzene and toluene, respectively. Generally, the alkylation with sulfones necessitates more severe conditions than that with sulfonyl chlorides.

Methyl- and ethylsulfonyl chlorides and sulfones did not give alkylation products, indicating that the desulfonylative cleavage has no driving force in these primary systems.

The results of desulfonylative alkylations are summarized in Table I.

We have also determined whether in the studied desulfonylative alkylations competing sulfonylation also takes place. In the case of the reaction of benzene with benzyl-



sulfonyl chloride and *tert*-butylsulfonyl chloride only alkylation products were obtained. Isopropylsulfonyl chloride gave 94.3% alkylation products and 5.7% isopropyl phenyl sulfone, the competing sulfonylation product. All reactions with anisole gave exclusively alkylation products.

Considering the remarkable difference in conditions needed to achieve alkylations with sulfonyl chlorides and sulfones (the latter react only with neat aluminum chlo-

Table I

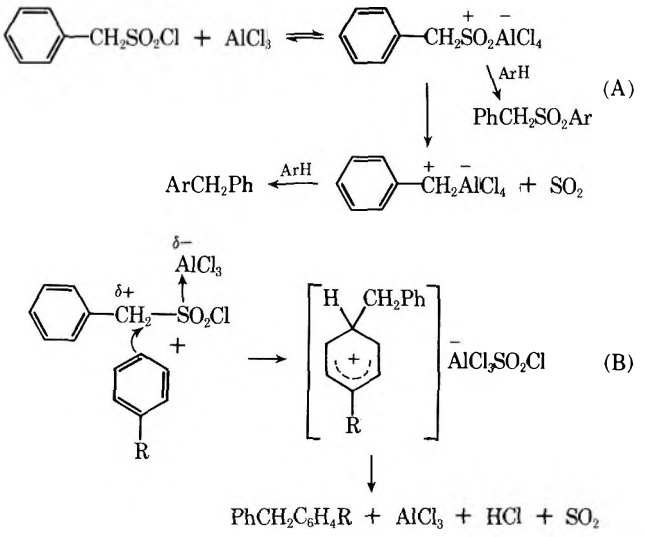
Alkylation of Benzene and Toluene with Alkylsulfonyl Chlorides and Sulfones (RSO_2X)

Registry no.	R	X	Solvent	Catalyst	Temp, °C	Time, hr	k_T/k_B	Isomer ratio of alkyltoluene, % o-	m-	p-
51751-71-4	*i*-Pr	*p*-Tol		$AlCl_3$[a]	60	1.0	0.5	2.2	65.1[e]	32.5[f]
10147-37-2	*i*-Pr	Cl	CH_3NO_2	$AlCl_3$	25	4.0	1.5	46.7[g]	22.6	30.7
5324-90-3	*t*-Bu	*p*-Tol		$AlCl_3$	60	1.0	0.6		33.2[h]	66.8[i]
20282-89-7	*t*-Bu	$PhCH_2$	Freon 113	SbF_5[b]	20	0.25	0.8		68.0	32.0
	t-Bu	$PhCH_2$		$AlCl_3$[c]	80	24.0				
10490-22-9	*t*-Bu	Cl	CH_3NO_2	$AlCl_3$[a]	25	0.16	16.1		8.7	91.3
51419-59-1	*p*-$CH_3C_6H_4CH_2$	Cl	CH_3NO_2	$AlCl_3$	25	1.0	30.8	30.3[j]	3.1	66.7[k]
1939-99-7	$PhCH_2$	Cl	CH_3NO_2	$AlCl_3$	25	1.0	4.2	34.4[l]	3.3	62.4[m]
	$PhCH_2$	Cl		$AlCl_3$[d]	Room	2.0		47.1		52.9
4025-75-6	*p*-$NO_2C_6H_4CH_2$	Cl		$AlCl_3$[a]	60	2.0	1.2			
	p-$NO_2C_6H_4CH_2$	Cl	CH_3NO_2	$AlCl_3$[c]	25	3.5				
3112-88-7	$PhCH_2$	Ph		$AlCl_3$[a]	60	1.0	2.5	37.5	10.1	52.4
	$PhCH_2$	Ph	CH_3NO_2	$AlCl_3$[c]	Room	48.0				

[a] Reaction conditions: 1:1 (mol/mol) benzene–toluene mixture, 10 g; solvent, 10 ml; aluminum chloride, 0.01 mol; alkylating agent, 0.005 mol. [b] Reaction conditions: 1:1 (mol/mol) benzene–toluene mixture, 10 g; 1,1,2-trichloro-1,2,2-trifluoroethane, 10 ml; antimony pentafluoride, 0.02 mol; *tert*-butyl benzyl sulfone, 0.02 mol. [c] No reaction occurred. [d] The reaction of anisole (50 ml), the chloride (0.01 mol), and aluminum chloride (0.01 mol) was carried out at room temperature for 2 hr. [e] Registry no., 535-77-3. [f] Registry no., 99-87-6. [g] Registry no., 1595-06-8. [h] Registry no., 1075-38-3. [i] Registry no., 98-51-1. [j] Registry no., 21895-17-0. [k] Registry no., 4957-14-6. [l] Registry no., 713-36-0. [m] Registry no., 620-83-7.

ride in hydrocarbon media, but not like the sulfonyl chlorides in nitromethane solution), there is little possibility for the formation of sulfones as intermediates during desulfonylative alkylations with sulfonyl chlorides.

There are two possible mechanisms for the studied Friedel–Crafts reactions with sulfonyl chlorides. The first (A) involves a stepwise formation of an alkyl cation *via* fragmentation of the corresponding sulfonyl cation, *i.e.*, SN1 type reaction involving initial ionization of the sulfonyl chloride by the catalyst. The second (B) involves displacement of the alkyl group from the polarized sulfonyl chloride–catalyst complex, *via* R–S fission, *i.e.*, SN2 type reaction. The experimental data obtained do not allow a differentiation, although there is little evidence for ionization of sulfonyl halides.[9]



Experimental Section

Melting points are not corrected. *tert*-Butylsulfonyl chloride (mp 95°, lit.[6] mp 95–95.5°), *p*-methylbenzylsulfonyl chloride[6] (mp 80–81°), *p*-nitrobenzylsulfonyl chloride (mp 93°, lit.[10] mp 89–90°), isopropyl *p*-tolyl sulfone (mp 83°, lit.[11] mp 80°), *tert*-butyl *p*-tolyl sulfone (mp 121°, lit.[12] mp 120°), and benzyl *p*-tolyl sulfone (mp 145°, lit.[13] mp 146–147°) were prepared by known methods. Other materials were commercially available. Glc analyses were carried out on Perkin-Elmer Models 226 and F-11 gas chromatographs, the former equipped with a nitrogen flame ionization detector, and using an electronic printing integrator. MBMA [*m*-bis(*m*-phenoxyphenoxy)benzene] and Apiezon L coated 150 ft × 0.01 in. open tubular stainless steel columns were used for analyses of isopropylations and *tert*-butylations, a purified Apiezon L coated column for that of benzylation, and a butanediol succinate coated column for that of *p*-nitrobenzylation, respectively. Sulfones were analyzed using Chromosorb (RAW 80/100 mesh) coated with 590 SE-30 oil (Chemical Research Services, Inc.).

General Procedure for Alkylation with Sulfonyl Chlorides. *Into* a mixture of benzene (10 ml) and aluminum chloride (2.66 g, 0.02 mol), benzylsulfonyl chloride (1.9 g, 0.01 mol) was slowly added at 25° with vigorous stirring under nitrogen for 2 hr. The reaction mixture was poured into 50 ml of ice–water and the aqueous layer was extracted with 50 ml of ether. The combined ether solution was washed with water, aqueous NaOH, and water, and then dried over $MgSO_4$. The evaporation of benzene and ether gave 1.21 g (72% yield) of diphenylmethane. It was analyzed by nmr and ir spectroscopy, in comparison with an authentic sample. The formation of benzyl phenyl sulfone was not observed.

The reaction of benzene (10 ml), *p*-nitrobenzylsulfonyl chloride (2.2 g, 0.01 mol), and aluminum chloride (0.03 mol) was carried out under reflux for 18 hr and gave 1.0 g (38% yield) of 4-nitrophenyl phenyl sulfone.

Acknowledgment. Partial support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; diphenylmethane, 101-81-5; nitrophenyl phenyl sulfone, 1146-39-0.

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1,3-Bridged Aromatic Systems. X. Stereospecific Reductions with Lithium Aluminum Deuteride[1]

William E. Parham,* Paul E. Olson, and K. Ratnammal Reddy

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

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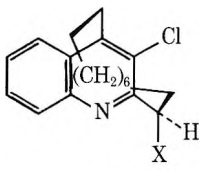
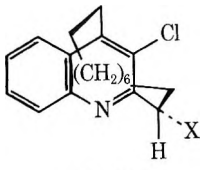
Although meta cyclophanes of type **1a, 1b, 2a,** and **2b** are quite resistant to nucleophilic substitution reactions,[2] we have observed that they are readily reduced to **1c** by



1(syn)

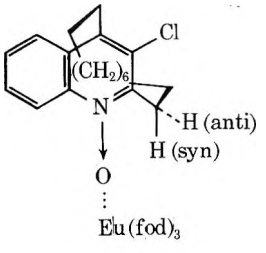


2 (anti)

a, X = Br
b, X = *p*-$CH_3C_6H_4SO_3$
c, X = H
d, X = D

$LiAlH_4$. In a preliminary experiment we observed that **1b** did not react with 1 equiv (0.25 molar equiv) of $LiAlH_4$ in dry ether, but gave **1c** in 54% yield when an excess (3.5 molar equiv) of $LiAlH_4$ was employed. Since we wished to prepare the monodeuterated cyclophanes **1d** or **2d** for other studies, we have examined the reaction of **1a, 1b, 2a,** and **2b** with $LiAlD_4$. In each case a monodeuterated product (99% monodeuterio by pmr and/or mass spectral analysis) was obtained (62, 74, 66, and 21%[3] yields, respectively), and in every case the product was the syn isomer **1d.** Thus, complete retention of configuration occurred with **1a** and **1b** and complete inversion of configuration occurred with **2a** and **2b.** While displacement reactions of this type normally[4] occur with inversion of configuration, reductions with retention of configuration as well as nonselective reduction have been reported.[5]

Assignment of the syn and anti hydrogens in **1c** by comparison of their pmr signals at 60 MHz with those of the derived *N*-oxide, as used successfully for other derivatives in the system,[2a] was not possible, since the four benzylic protons in **1c** and in the corresponding *N*-oxide of **1c** are not sufficiently resolved at 60 MHz. Definite assignments were possible, however, for the *N*-oxide of **1c** by pmr (100 MHz) using the chemical shift reagent $Eu(fod)_3$-d_{27}.[6] A plot of the pmr signals of **3** *vs.* *R* in which the ratio *R*

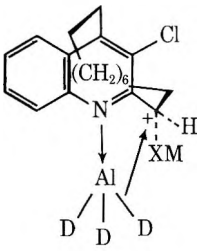


3

([$Eu(fod)_3$-d_{27}]/[*N*-oxide]) was varied at constant volume (*i.e.*, [*N*-oxide] was constant) is shown in Figure 1. This model predicts that the syn proton (and the peri H) should show larger downfield shifts with larger *R* values than the anti proton, since the syn proton not only occupies a position closer to europium, but is also expected to have an angle ϕ_{syn} (defined by the europium–substrate bonding axis and the syn proton) which is smaller than ϕ_{anti}.[7] These predictions are corroborated by the slopes of the lines shown in Figure 1. The syn proton (c) exhibits a slope of 8.9 ± 0.6 and the peri hydrogen (a) 11.3 ± 0.4, while the anti proton exhibits a slope of 2.6 ± 0.2. Applying this same technique to the monodeuteriocyclophane **1d,** obtained from **1a, 1b, 2a** and **2b,** showed complete absence of syn H; the anti proton was present and integrated for one proton compared with the four aromatic protons.

Additional evidence for the syn structure **1d** (obtained from **1b**) was obtained by pmr studies at 100 and 270 MHz. At 100 MHz the four benzylic protons of **1c** appear as a multiplet at δ 3.8–2.8; the corresponding spectrum of **1d** shows a three-proton absorption at δ 3.8–3.2, with loss of the upfield component observed for **1c.** The 100-MHz spectrum of the *N*-oxide of **1c** shows a four-proton absorption at δ 3.9–3.2, while the *N*-oxide of **1d** shows a three-proton absorption at δ 3.7–3.2 with loss of the downfield component observed for the *N*-oxide of **1c.** By analogy to previously reported[2a] examples of large chemical shift changes of syn protons in going from the free base to the corresponding *N*-oxide, the upfield proton in **1c** and the downfield proton in the *N*-oxide of **1c** are assigned to the syn proton, which is absent in **1d.** At 270 MHz the pmr spectrum of the unlabeled *N*-oxide of **1c** was well resolved and showed the syn proton centered at δ 3.71 (octet, $J_{AB(gem)}$ = 12–13, $J_{AC(cis)}$ = 4, $J_{AD(trans)}$ = 3 Hz, all *J*'s first order), one proton at the other benzylic position centered at δ 3.45 (octet, $J_{AB(gem)}$ = 13–14, $J_{AC(cis)}$ = 10, $J_{AC(trans)}$ = 4 Hz, all *J*'s first order), and two benzylic protons centered at δ 3.3 (multiplet). The downfield absorption at δ 3.71 was completely absent in the labeled *N*-oxide derived from **1d** which is consistent with the conclusion that all of the deuterium was at the syn position as shown in **1d.** The anti proton has been assigned resonance at δ 3.3, since the splitting pattern in that region is simplified in the labeled compound.

While we can make no definitive statement concerning the mechanism[8] and stereoselectivity of the reduction process, the requirement of excess $LiAlH_4$ suggests that a complex of reagent with nitrogen prior to reduction is possible, as illustrated in **4** and **5.**



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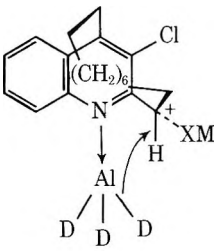

5

Experimental Section

Reductions with $LiAlD_4$. A. In a typical experiment a solution of syn tosylate **1b**[2a] (6.43 g, 13.6 mmol) in dry diethyl ether (120 ml) was heated under nitrogen at reflux for 24 hr with $LiAlH_4$ (17.4 mmol).[12] The reaction mixture was quenched with D_2O (3 ml) and then acidified with 5% hydrochloric acid (150 ml). The extract was washed (saturated sodium bicarbonate) and then dried ($MgSO_4$) and concentrated. The resulting oil (4.4 g) was chromatographed [260 of g alumina, 0.5% diethyl ether–petroleum ether (bp 60–90°) to 100% ether as eluent] to give **1d:** 3.08 g (75% yield); mp 81–82° from ethyl acetate; mmp[9] 81–82°; mass spectral analysis showed 99+% monodeuterio species.

The *N*-oxide of **1d** was prepared by oxidation of **1d** with *m*-chloroperbenzoic acid:[2,10] 74% yield; mp 122.5–123.5° (from acetone) (lit.[11] mp 125–127°); mmp 122.5–123.5°.

B. In an alternate procedure used for **1a, 2a,** and **2b**[2a] dry (distilled from $LiAlH_4$) tetrahydrofuran (10–15 ml) was used as solvent (16 hr, 66.5 hr for **2a**). The reduced cyclophane **1d** was purified by preparative tlc [silica gel, 25% diethyl ether–petroleum ether (bp 30–60°)].

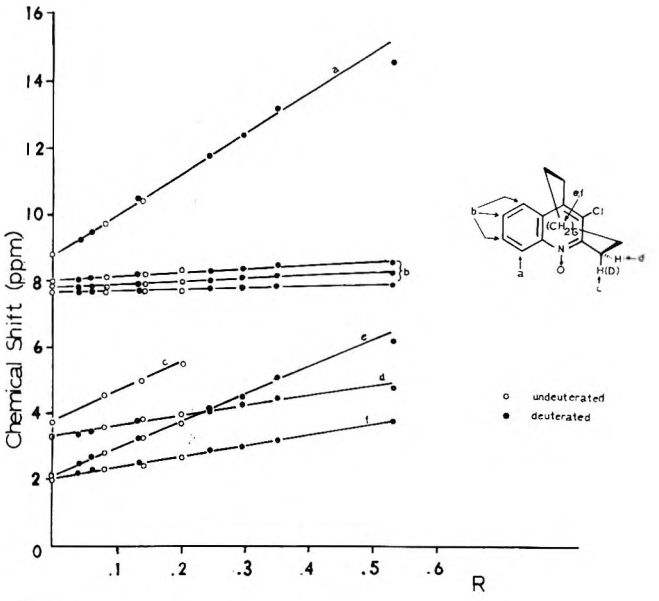

Figure 1.

Registry No.—**1a,** 25859-37-4; **1b,** 37781-25-2; **1c,** 22200-39-1; **1c** *N*-oxide, 25907-81-7; **1d,** 51794-47-9; **1d** *N*-oxide, 51820-05-4; **2a,** 42880-45-5; **2b,** 37781-31-0; $LiAlD_4$, 14128-54-2.

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Carbenium Ion Rearrangements in the Alkylation of Tertiary Halides with Trimethylaluminum

Earl G. Melby

Union Carbide Corporation, Chemicals and Plastics, Bound Brook, New Jersey 08805

Joseph P. Kennedy*

Institute of Polymer Science, The University of Akron, Akron, Ohio 44325

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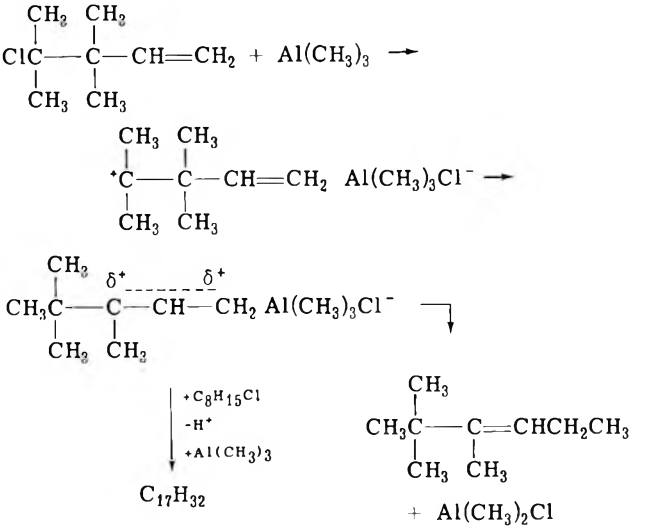
In the course of our fundamental studies on cationic isomerization polymerization we were interested in the synthesis of 3,3,4,4-tetramethyl-1-pentene, which we hoped to obtain by methylating 4-chloro-3,3,4-trimethyl-1-pentene with Me_3Al. The rapid, quantitative methylation with Me_3Al of tertiary chlorines to quaternary carbons has recently been described.[1]

Interestingly, instead of the desired product we obtained 2,2,3-trimethyl-3-hexene, most likely by the following route.

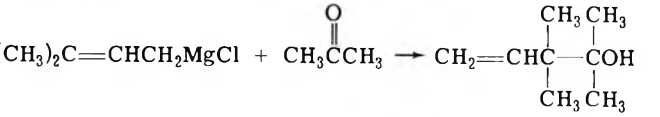


The initially formed carbenium ion rearranges to the more stable tertiary, allylic ion. This carbenium ion subsequently reacts with the counterion to give the thermodynamically more stable internal olefin.

In addition to 2,2,3-trimethyl-3-hexene, a second product of overall composition $C_{17}H_{32}$ was also obtained. While conclusive structural analysis could not be carried out, it is presumed that this product is a methylated dimer.

According to these findings allylic rearrangement by methide shift and dimerization is faster than methylation of the carbenium ion by the Me_3AlCl^- counteranion. The relatively slow methylation of carbenium ions with Me_3AlCl^- is important in cationic polymerization and might account for the formation of high molecular weight polymers by the faster propagation (dimerization) step.

The tertiary chloride used in the above scheme was prepared from the corresponding tertiary alcohol; no evidence for rearrangement during this step has been detected. The tertiary alcohol in turn was obtained by an unusual Grignard (rearrangement) synthesis found in our laboratory. Thus the reaction between γ,γ-dimethylallylmagnesium chloride and acetone yields 4-hydroxy-3,3,4-trimethyl-1-pentene. Evidently the internal C of the allylic system rather than the C bonded to the -MgCl reacts with the carbonyl function. Similar rearrangements during Grignard reactions of allylmagnesium halides have been described.[2,3]



Experimental Section

General. Gas chromatographic analysis was carried out with an HP-5750 gas chromatograph. Molecular weights were determined using a Chromalytics MC-2 mass chromatograph. Nmr analysis was done using a Varian T-60 spectrometer. Microanalysis was done by Galbraith Laboratories, Knoxville, Tenn. Distillations were carried out using a Nester-Faust adiabatic spinning band column.

Synthesis of 4-Hydroxy-3,3,4-trimethyl-1-pentene. To synthesize this previously unknown alcohol, we adapted the procedure of Dreyfuss[4] for the Grignard reaction. To 0.50 mol of magnesium turnings in 100 ml of ether was added γ,γ-dimethylallyl chloride (0.05 mol) in 25 ml of ether. After the reaction was proceeding vigorously, a solution of the remaining chloride (0.45 mol)

and acetone, 0.55 mol in 400 ml of ether, was added dropwise. The reaction was quenched using saturated aqueous NH_4Cl solution and filtered. After removal of the ether, distillation of the product mixture gave 4-hydroxy-3,3,4-trimethyl-1-pentene: 40% yield; bp 53–54° (10 mm); nmr (CCl_4) δ 0.92 [s, 6 H, $C(CH_3)_2$], 1.02 [s, 6 H, $C(CH_3)_2$], 4.9–6.1 (m, 3 H, $CH=CH_2$). The aldol condensation of acetone accounted for the major by-product, diacetone alcohol.

Synthesis of 4-Chloro-3,3,4-trimethyl-1-pentene. To 4-hydroxy-3,3,4-trimethyl-1-pentene (25 g) was added 200 ml of concentrated HCl at 0°. The mixture was stirred for 30 min and the organic layer was removed and neutratized with K_2CO_3. The product, 4-chloro-3,3,4-trimethyl-1-pentene, which previously has not been reported in the literature, was distilled: 100% yield; bp 55° (20 mm); mp 22–26°; nmr (CCl_4) δ 1.10 [s, 6 H, $C(CH_3)_2$], 1.48 [s, 6 H, $C(CH_3)_2$], 4.82–6.30 (m, 3 H, $CH=CH_2$).

Reaction of 4-Chloro-3,3,4-trimethyl-1-pentene with Trimethylaluminum. To a stirred solution of $AlMe_3$ (0.115 mol) in 200 mol of CH_2Cl_2 at 25° was added 4-chloro-3,3,4-trimethyl-1-pentene (0.10 mol) in 200 ml of CH_2Cl_2. After 30 min, the reaction was quenched by slowly adding 50 ml of methanol and extracted with saturated aqueous potassium sodium tartrate solution. Removal of the CH_2Cl_2 yielded an organic phase containing two products which were separated by distillation. The lower boiling component was identified[5] as 2,2,3-trimethyl-3-hexene: 69% yield; bp 56° (55 mm); mol wt 125.0 (calcd for C_9H_{18}, 126.2); nmr (CCl_4) δ 1.01 [s, 9 H, $C(CH_3)_3$], 0.98 (t, 3 H, CCH_3), 1.55 (m, 3 H, CCH_3), 1.98 (m, 2 H, CH_2–), 5.18 (t, 1 H, –CH=). The second component (31% yield) had bp 106° (3 mm), mol wt 238.0 (calcd for $C_{17}H_{32}$, 236.6). *Anal.* Calcd for $C_{17}H_{32}$: C, 86.5; H, 13.5. Found: C, 86.47; H, 13.50.

Acknowledgment. Partial financial support by the National Science Foundation (Grant GH-37985) is gratefully acknowledged.

Registry No.—Trimethylaluminum, 75-24-1; 4-hydroxy-3,3,4-trimethyl-1-pentene, 36934-19-7; γ,γ-dimethylallyl chloride, 503-60-6; acetone, 67-64-1; 4-chloro-3,3,4-trimethyl-1-pentene, 51751-72-5; 2,2,3-trimethyl-3-hexene, 51751-73-6.

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A Comment on the Acetoxythallation-Induced Lactonization of 2-*endo*-Norbornenecarboxylic Acids

Alexander McKillop* and Michael E. Ford

School of Chemical Sciences, University of East Anglia, Norwich, England

Edward C. Taylor*

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

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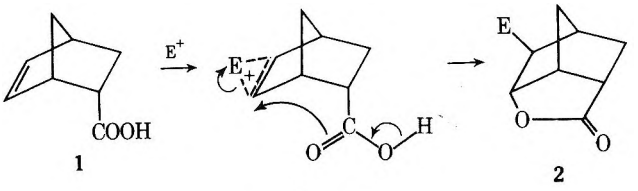
Electrophile-induced lactonization of 5-norbornene-2-*endo*-carboxylic acid (**1**) and related substrates is well known (Scheme I), and stable lactones **2** have been obtained when E is hydrogen,[1] halogen,[2] or acetoxymercury(II).[3] Neighboring-group participation has also been invoked to account for the formation of **4** when **1** is oxidized with lead(IV) acetate (Scheme II).[4,5] In this case, electrophile-induced lactonization presumably gives the oxymetalation adduct **3** as an unstable intermediate, and rapid conversion of **3** into **4** is fully consistent with the known lability of carbon–lead bonds in alkyllead(IV) triacetates.[6]

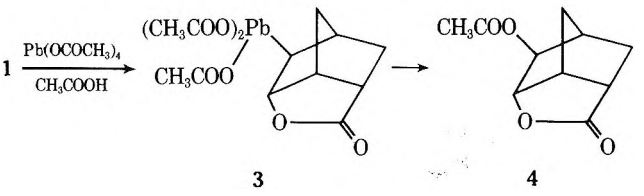
Oxidation of **1** with thallium(III) acetate has recently been reported by Moriarty and Gopal to give a mixture of **5** and **6** (Scheme III), formation of which was explained on

Scheme I



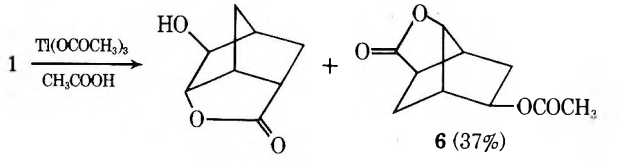
1 2

Scheme II



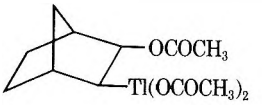
3 4

Scheme III



5 (24%) 6 (37%)

the basis of the sequence (i) neighboring-group participation during acetoxythallation; (ii) generation of a norbornylthallium(III) diacetate; and (iii) facile heterolysis of this latter species to give the corresponding carbonium ion from which **5** and **6** are ultimately derived.[7] In principle this explanation is quite reasonable. Most oxythallation adducts are notoriously unstable, very few have ever been isolated, and their decomposition in solution is believed to involve heterolysis of the carbon–thallium bond and generation of carbonium ions.[8] Nevertheless, we were surprised by Moriarty and Gopal's comment *vis à vis* Scheme III that "Attempts were made, to no avail, to isolate the proposed organothallium intermediate in the present examples." Some 10 years ago Pande and Winstein showed that treatment of norbornene and norbornadiene with thallium(III) acetate gave the cis,exo-acetoxythallation adducts **7** and **8** as relatively stable, isolable solids,[9] and



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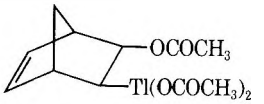


8

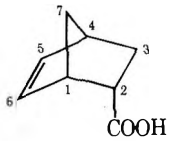
we have confirmed these results on a number of occasions in our own laboratories. As there appeared to us to be no obvious reason why the oxythallation adduct of **1** should be significantly less stable than compounds **7** or **8**, we have reinvestigated the reaction of **1** and some related compounds with thallium(III) acetate.

Oxidation of **1** with thallium(III) acetate in glacial acetic acid proceeded smoothly at room temperature to give the oxythallation adduct **9** in 88% yield as an easily handled, relatively stable, colorless, crystalline solid. The presence of the five-membered lactone ring was evident from the ir spectrum ($\nu_{C=O}$ 1780 cm^{-1}), while the nmr spectrum exhibited the expected large ^1H–$^{203/205}Tl$ coupling constants characteristic of organothallium compounds (Table I).[10,11] Similar treatment of the dicarboxylic acids **10** and **12** provided the analogous crystalline lactones **11** and **13** in virtually quantitative yield. As with compound **9**, the ir spectra of **11** and **13** showed characteristic, strong lactone absorptions at 1780–1800 cm^{-1}; the presence of the covalent carbon–thallium bond was again confirmed by nmr spectroscopy (Table I).

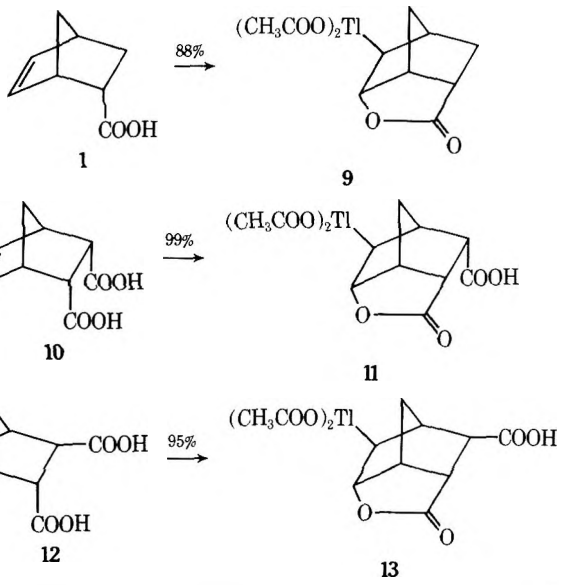
Table I
^1H–$^{203/205}Tl$ Coupling Constants (Hertz) in Norbornylthallium Diacetates[a,b]

Compd	$J_{Tl-H-3(exo)}$	J_{Tl-H-4}	J_{Tl-H-5}	J_{Tl-H-6}
9	208	630	1200	909
11	223	515	1197	911
13		545	1204	898

[a] The numbering system used is that of the corresponding precursor norbornenecarboxylic acid, *viz.*



[b] Coupling constants are accurate to ±5 Hz.



The stability of the oxythallation adducts **9**, **11**, and **13** is comparable to that of **7** and **8**; all of these compounds can be handled easily in the atmosphere and do not decompose to any significant extent over a period of several days when stored in closed bottles. They do undergo slow decomposition during storage for several weeks, and are, predictably, completely destroyed when they are heated in acetic acid. Thus, heating of a solution of freshly made **9** in acetic acid at 60–65° [12] for 14 hr resulted in total destruction of the organothallium compound and gave the acetoxy lactone **4** in poor (19%) yield. A similar result was obtained when a mixture of **1** and thallium(III) acetate was heated in acetic acid at 60–65° for 16 hr; no **9** was obtained, and the acetoxy lactone **4** was again formed in very low (13%) yield.

The above results thus confirm and extend Pande and Winstein's earlier observations that certain norbornene derivatives react readily with thallium(III) acetate to give oxythallation adducts which, in comparison with those derived from almost all other types of olefinic substrate, show a remarkable degree of stability.

Experimental Section[13]

Acetoxythallation of 1. Thallium(III) acetate (4.1 g, 0.01 mol) was dissolved in a solution of 1.36 g (0.01 mol) of **1** in 30 ml of glacial acetic acid; the resulting mixture was stirred at room temperature for 4 hr, during which time a colorless solid precipitated. Addition of 25 ml of dry benzene, followed by 200 ml of petroleum ether (bp 40–60°), resulted in precipitation of more of this colorless solid, which was removed by filtration, washed with diethyl ether, and dried at room temperature to give 4.3 g (88%) of pure **9** as the dihydrate, mp 144° dec. *Anal.* Calcd for $C_{12}H_{15}O_6Tl \cdot 2H_2O$: C, 29.09; H, 3.84. Found: C, 28.91; H, 3.72. The infrared spectrum showed $\nu_{C=O\ lactone}$ 1780 cm^{-1}, $\nu_{C=O\ acetate}$ 1730 cm^{-1}, and a weak ν_{OH} at 3150 cm^{-1}. Details of the nmr spectrum are listed in Table I.

Acetoxythallation of 10. Thallium(III) acetate (4.1 g, 0.01 mol) was dissolved in a solution of 1.82 g (0.01 mol) of **10** in 35 ml of glacial acetic acid; the resulting mixture was stirred at room temperature for 24 hr, during which time a colorless solid precipitated. This was removed by filtration, washed with diethyl ether, and dried at room temperature to give 5.0 g (99%) of pure **11**, mp 200° dec. *Anal.* Calcd for $C_{13}H_{15}O_8Tl$: C, 30.83; H, 2.98. Found: C, 31.00; H, 3.26. The infrared spectrum showed $\nu_{C=O\ lactone}$ 1790 cm^{-1} and $\nu_{C=O\ acetate}$ 1730 cm^{-1}. Details of the nmr spectrum are listed in Table I.

Acetoxythallation of 12. Acetoxythallation of **12** (1.82 g, 0.01 mol) was carried out in the same manner as described for **10**, and gave 4.8 g (95%) of **13**, mp 138° dec. *Anal.* Calcd for $C_{13}H_{15}O_8Tl$: C, 30.83; H, 2.98. Found: C, 30.90; H, 3.14. The infrared spectrum showed $\nu_{C=O\ lactone}$ 1790 cm^{-1} and $\nu_{C=O\ acetate}$ 1725 cm^{-1}. Details of the nmr spectrum are listed in Table I.

Oxidation of 1 with Thallium(III) Acetate–Acetic Acid. A solution of 1.36 g (0.01 mol) of **1** and 4.1 g (0.01 mol) of thallium(III) acetate in 30 ml of glacial acetic acid was heated at 60–65° (bath temperature) with stirring for 16 hr. The reaction mixture was then cooled to room temperature and partitioned between ether and saturated aqueous sodium chloride solution; the ethereal extract was washed twice with distilled water, once with 10% aqueous sodium hydroxide solution, and twice more with distilled water. Subsequent drying ($MgSO_4$), filtration, and evaporation of the solvent gave 0.25 g (13%) of a colorless solid, **4**, mp (after washing with petroleum ether, bp 40–60°) 92–94° (lit.[14] mp 95–96°). The infrared spectrum of the product showed $\nu_{C=O\ lactone}$ 1800 cm^{-1} and $\nu_{C=O\ acetate}$ 1740 cm^{-1}.

Treatment of 9 with Hot Acetic Acid. A solution of 1.36 g (0.01 mol) of **1** and 4.1 g (0.01 mol) of thallium(III) acetate in 30 ml of glacial acetic acid was stirred at room temperature for 4 hr (during which time **9** precipitated from solution), and then heated at 60–65° (bath temperature) for 14 hr. Isolation of the product in the manner described immediately above gave 0.35 g (19%) of a white solid identical in melting point (after washing with petroleum ether, bp 40–60°) and infrared spectrum with the acetoxylactone **4** obtained above.

Acknowledgment. One of us (M. E. F.) acknowledges receipt of a Marshall Commission Scholarship.

Registry No.—**1**, 1195-12-6; **4**, 16479-66-6; **9**, 51510-07-7; **10**, 3853-88-1; **11**, 51510-08-8; **12**, 1200-88-0; **13**, 51606-65-6; thallium(III) acetate, 2570-63-0.

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(1) See, *inter alia*, (a) J. S. Meek and W. B. Trapp, *J. Amer. Chem. Soc.*, **79**, 3903 (1957); (b) S. Beckmann and H. Geiger, *Chem. Ber.*, **94**, 48 (1961); (c) H. Geiger, *Tetrahedron*, **27**, 165 (1971).
(2) See, *inter alia*, (a) ref 1a; (b) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959); (c) K. Takeda, K. Kitahonoki, M. Sigiura, and Y. Takano, *Chem. Ber.*, **95**, 2344 (1963), and references cited therein.
(3) (a) Reference 2b; (b) M. Malaiyandi and G. F. Wright, *Can. J. Chem.*, **41**, 1493 (1963); (c) A. Factor and T. G. Traylor, *J. Org. Chem.*, **33**, 2607 (1968).
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(8) For a full discussion see A. McKillop and E. C. Taylor, *Advan. Organometal. Chem.*, **11**, 147 (1973).
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(10) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Organometal. Chem.*, **24**, 77 (1970), and references cited therein.
(11) F. A. L. Anet, *Tetrahedron Lett.*, 3399 (1964).
(12) Reaction was carried out at 60–65° as it is known that, at higher temperatures, thallium(III) acetate oxidizes acetic acid to give thallium(I) acetoxyacetate in excellent yield: E. C. Taylor, H. W. Altland, G. McGillivray, and A. McKillop, *Tetrahedron Lett.*, 5285 (1970).
(13) Melting points were determined on a Kofler hot-stage microscope melting point apparatus and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders of the University of East Anglia. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer using the normal Nujol mull technique. Nuclear magnetic resonance spectra were obtained with a Perkin-Elmer R12 60-MHz spectrometer using deuteriochloroform or DMSO-d_6 as solvents and TMS as internal standard.
(14) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959).

Base Rearrangement of Chromone-3-carboxylic Esters to 3-Acyl-4-hydroxycoumarins

Sylvester Klutchko,* John Shavel, Jr., and Maximilian von Strandtmann

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey 07950

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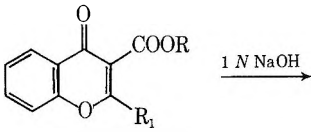
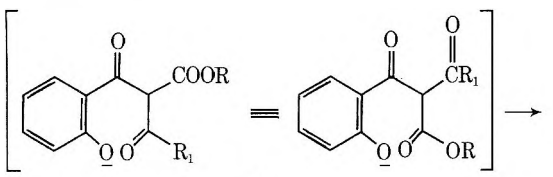
In the course of our work in chromone chemistry[1] the hydrolysis of chromone-3-carboxylic esters **1a** and **1b** was studied. It was found that acid condition gave the expected chromone-3-carboxylic acids **5a** and **5b** in good yields. Basic condition, however, resulted in facile rearrangement in high yields to the known 3-acyl-4-hydroxycoumarins[2,3] **3a** and **3b**.

This reaction may be looked upon as a "reverse" acyllactone rearrangement.[4] Its probable course would involve opening of the chromome ring system by base with subsequent ring closing through lactonization of the postulated triacyl intermediate **2**. In one experiment the sodium salt



1a, R = C_2H_5; R_1 = H
b, R = CH_3; R_1 = CH_3
c, R = CH_3; R_1 = C_2H_5



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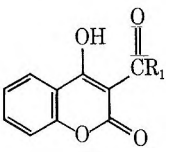


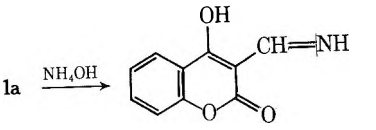
3a, R_1 = H
b, R_1 = CH_3
c, R_1 = C_2H_5

of the coumarin **3a** precipitated directly from solution, indicating that rearrangement occurred under basic conditions and before acidification of the reaction solution.

The two types of products, 3-acyl-4-hydroxycoumarins and chromone-3-carboxylic acids, could not be readily distinguished by ir or on the basis of their acidity, since both were found to be equally soluble in sodium bicarbonate. Differentiation was made by consideration of the following spectral data. Ultraviolet spectra of the coumarins **3a–c** displayed a band at about 300 nm with an intensity of ϵ 14,000 whereas the intensity of the corresponding bands for the acids **5a** and **5b** was less than half of this value. Nmr spectra showed signals for the methyl protons of **3b** and **5b** at δ 2.76 and 3.04 ($CDCl_3$), respectively. The broad signal for the OH proton of **3b** appeared at δ 17.70 ($CDCl_3$) whereas the carboxylic acid proton of **5b** appeared at δ 14.33. Mass spectra proved to be most useful for structure proof by showing the elimination of CO_2 (m/e 190 → 146 for **5a** and m/e 204 → 160 for **5b**) from the carboxylic acid molecular ions.

The rearrangement was seen also under conditions other than that of basic hydrolysis. Preparation of the 2-alkyl esters **1b** and **1c** under the basic conditions of a Kostanecki-type reaction on the recently reported methyl salicyloylacetate[5] with acetic or propionic anhydride resulted in rearrangement in varying degree. In the case of cyclization to **1b**, which was isolated in good yield, a minor amount of **3b** was obtained, whereas the attempted preparation of **1c** by the same method resulted mainly in rearrangement to 3c in good yield.

An analogous transformation was observed when 3-carbethoxychromone **1a** was heated with concentrated ammonium hydroxide, giving rise to the known 3-(formimidoyl)-4-hydroxycoumarin (**4**).[6]



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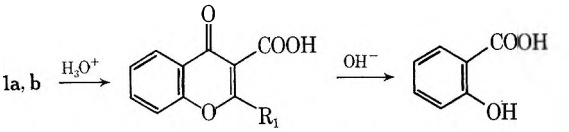
Rearrangement did not occur on treatment of the free carboxylic acid **5b** with base. There was either no reaction at 20° or degradation on warming to give a good yield of salicylic acid (**6**).



5a, R_1 = H
b, R_1 = CH_3

6

These observations may explain the scarcity of chromone-3-carboxylic acids and esters in the literature, since most known methods of preparation are base catalyzed. The similarity of some physical and chemical properties between chromone-3-carboxylic acids and 3-acyl-4-hydroxycoumarins indicates that caution should be exercised in structure assignments in this area.

Experimental Section[7]

Base Rearrangement of Ethyl 4-Oxo-4*H*-1-benzopyran-3-carboxylate (1a) to 4-Hydroxy-2-oxo-2*H*-1-benzopyran-3-carboxaldehyde (3a). A mixture of 6.4 g (0.029 mol) of **1a**[1] and 100 ml of 1 *N* NaOH was stirred at room temperature for 15 min. Partial solution took place as the sodium salt of **3a** separated. Water (800 ml) was added to dissolve all solid and the solution was acidified with concentrated HCl to precipitate **3a**, 4.6 g (83%), mp 135–137°. Recrystallization from 2-propanol gave pure **3a**: mp 137–139° (reported[2] mp 136–137°); ir (Nujol) 1715 (formyl C=O), 1615 cm^{-1} (2-pyrone C=O); uv max (95% EtOH) 238 nm (ϵ 15,100), 304 (14,250); mass spectrum m/e (rel intensity) 190 (50), 162 (100), 121 (50), 120 (70), 92 (30).

In one run the insoluble sodium salt of **3a** was filtered in 58% yield. Recrystallization from methanol–water gave the pure sodium salt: mp 375° dec; ir (Nujol) 1690 (formyl C=O), 1615 cm^{-1} (2-pyrone C=O).

Anal. Calcd for $C_{10}H_5O_4Na$: C, 56.62; H, 2.38; Na, 10.84. Found: C, 56.90; H, 2.55; Na, 10.59.

Methyl 2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxylate (1b). A stirred mixture of 22.0 g (0.112 mol) of methyl salicyloylacetate,[5] 600 ml of xylene, 60 g of powdered anhydrous potassium carbonate, and 60 ml of acetic anhydride was heated to 80°. After evolution of CO_2 was complete the temperature was raised to 125–130° for 1 hr. The mixture was filtered (filter cake was retained for isolation of **3b**) and the filtrate was stirred for 2 hr with 200 ml of water, washed well with water, dried (Na_2SO_4), and concentrated to give 15 g (62%) of crude ester. Recrystallization from ethyl acetate gave pure **1b**: mp 116–118°; ir (Nujol) 1725 (ester C=O), 1640 cm^{-1} (pyrone C=O); nmr ($CDCl_3$) δ 8.22 (q, 1, H-5), 7.3–7.8 (m, 3, H-6, -7, -8), 3.97 (s, 3, $COOCH_3$), 2.53 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.03; H, 4.59.

3-Acetyl-4-hydroxy-2*H*-1-benzopyran-2-one (3b). A. Isolated in the Preparation of 1b. The above K_2CO_3 filter cake from the xylene reaction mixture was dissolved in 500 ml of water and aci-

dified with concentrated HCl to precipitate 1.1 g (5%) of **3b**, mp 133–135° (reported[3] mp 134°).

B. From Base Rearrangement of 1b. A mixture of 1.0 g (0.005 mol) of **1b** and 100 ml of 1 *N* NaOH was warmed on the steam bath for 5 min or until complete solution took place. The cooled solution was acidified with concentrated HCl to precipitate **3b**: 0.80 g (86%); mp 133–135°; ir (Nujol) 1730 (acetyl C=O), 1615 cm^{-1} (2-pyrone C=O); uv max (95% EtOH) 212 nm (ϵ 23,000), 300 (14,000), 320 sh (9600); mass spectrum *m/e* (rel intensity) 204 (60), 189 (40), 162 (20), 121 (60), 120 (60), 105 (10), 93 (15), 92 (50), 77 (25), 43 (100).

4-Hydroxy-3-(1-oxopropyl)-2*H*-1-benzopyran-2-one (3c). A mixture of 5.5 g (0.028 mol) of methyl salicyloylacetate, 150 ml of xylene, 19.5 g (0.15 mol) of propionic anhydride, and 30 g of powdered potassium carbonate was heated with stirring at 135° for 0.5 hr. Ether (300 ml) was added to the cooled mixture and the solids were filtered and washed with ether. The filter cake was stirred with 500 ml of water, the insoluble portion was filtered, and the filtrate was acidified with concentrated HCl to precipiate 4.8 g (78%) of **3c**: mp 122–124° (reported[3] mp 123°); ir (Nujol) 1720 (acyl C=O), 1610 cm^{-1} (2-pyrone C=O); uv max (95% EtOH) 226 nm sh (ϵ 15,200), 301 (13,300); mass spectrum *m/e* (rel intensity) 218 (50), 200 (15), 189 (100), 162 (17), 121 (50), 120 (25), 105 (12), 93 (12), 92 (25), 77 (25), 43 (5).

In this reaction the 3-carbomethoxy-2-ethylchromone **1c** could not be isolated from work-up of the above xylene–ether reaction filtrate as was the case in the preparation of **1b**.

4-Oxo-4*H*-1-benzopyran-3-carboxylic Acid (5a). A solution of 1.09 g (0.005 mol) of **1a**[1] and 100 ml of concentrated HCl was heated at 100° for 1 hr. Ice water (100 ml) was added and the mixture was filtered to give **5a**, 0.90 g (95%), mp 198–200°. Recrystallization was effected by dissolution in 100 ml of ethyl acetate and concentration to 25-ml volume to give pure crystals of **5a**: mp 199–201° (reported[1] mp 199–201°); ir (Nujol) 1740 (carboxylic C=O), 1620 cm^{-1} (pyrone C=O); uv max (95% EtOH) 213 nm (ϵ 18,000), 238 sh (11,000), 300 (5600); mass spectrum *m/e* (rel intensity) 190 (10), 173 (5), 146 (100), 120 (20), 104 (30), 92 (15), 63 (15), 53 (20).

2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxylic Acid (5b). A solution of 10.0 g (0.046 mol) of **1b** in 100 ml of concentrated HCl was heated at 80–90° for 20 min. Ice (400 g) was added to precipitate a tacky solid. The crude product was dissolved in 300 ml of 5% $NaHCO_3$ and the insoluble portion was extracted away with ether. The aqueous phase was acidified with concentrated HCl to give 6.4 g (68%) of **5b**, mp 120–135°. Recrystallization from 2-propanol gave pure **5b**: mp 145–147°; ir (Nujol) 1725 (carboxylic C=O), 1618 cm^{-1} (pyrone C=O); uv max (95% EtOH) 232 nm (ϵ 21,300), 298 (5660); mass spectrum *m/e* (rel intensity) 204 (57), 186 (22), 160 (100), 131 (5), 120 (98), 92 (32); nmr ($CDCl_3$) δ 14.33 (broad, 1, COOH), 8.35 (q, 1, H-5), 7.3–8.0 (m, 3, H-6, -7, -8), 3.04 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_8O_4$: C, 64.70; H, 3.95. Found: C, 64.79; H, 4.11.

Base Degradation of 5b to Salicylic Acid (6). A solution of 2.5 g (0.012 mol) of **5b** in 100 ml of 1 *N* NaOH was heated at 100° for 1 min. The cooled solution was acidified with concentrated HCl to precipitate **6**, 1.5 g (88%), mp 157–159° [reported (Lange Handbook) mp 158.3°].

4-Hydroxy-3-(iminomethyl)-2*H*-1-benzopyran-2-one (4). A mixture of 2.0 g (0.009 mol) of **1a** was heated with 5 ml of concentrated NH_4OH on the steam bath. The ester soon dissolved and after 5 min crude **4** separated, 1.5 g (81%), mp 223–225°. Recrystallization from ethanol gave pure **4**, mp 236–238° (reported[6] mp 240–242°).

Acknowledgment. We wish to thank Dr. Clive Greenough, Mr. Robert Saville, and Mr. Ka To Ng for spectral data and Mrs. Unni Zeek for microanalyses. We also thank Mr. Freeman McMillan and Mr. Gerald Kanter of the Chemical Development Department for assistance.

Registry No.—**1a**, 51085-94-0; **1b**, 51751-33-8; **3a**, 51751-34-9; **3a** sodium salt, 51751-35-0; **3b**, 2555-37-5; **3c**, 4139-73-5; **4**, 51751-36-1; **5a**, 39079-62-4; **5b**, 51751-37-2; **6**, 69-72-7; methyl salicyloylacetate, 20349-86-4.

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(7) Melting points were determined with the Thomas-Hoover capillary melting point apparatus, which was calibrated against known standards. Infrared spectra were determined with a Baird Model 455 double-beam instrument. Nmr spectra were measured with a Varian A-60 spectrophotometer.

Selective Demethylation of 2,5-Dimethoxybenzaldehyde to 5-Hydroxy-2-methoxybenzaldehyde

Henri Ulrich,* D. V. Rao, B. Tucker, and A. A. R. Sayigh

The Upjohn Company, Donald S. Gilmore Research Laboratories, North Haven, Connecticut 06473

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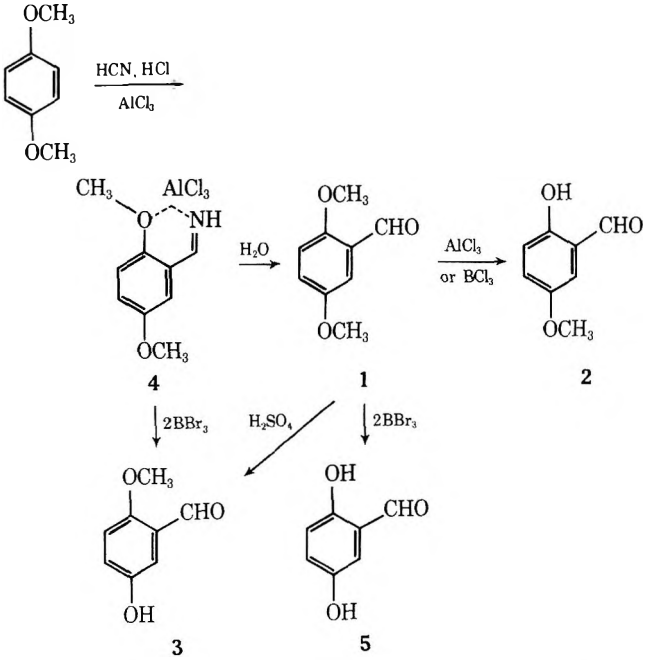
The selective demethylation of 2,5-dimethoxybenzaldehyde (**1**) with boron trichloride to give 2-hydroxy-5-methoxybenzaldehyde (**2**) is well known.[1] This reaction proceeds by a cyclic process involving the boron trichloride complex of 2,5-dimethoxybenzaldehyde. However, 5-hydroxy-2-methoxybenzaldehyde (**3**), the isomer of **2**, has not been synthesized previously.

Utilization of the complexing ability of the aldehydic group with the *o*-methoxy group could be used to advantage to block the approach of the demethylating agent, providing that the complexing agent does not cleave the neighboring ether group as observed with boron trichloride or aluminum trichloride. In the Gattermann reaction of 1,4-dimethoxybenzene with hydrogen cyanide in the presence of aluminum chloride, an iminium complex **4** is produced in which the aluminum chloride in fact could coordinate with the neighboring methoxy group. A cyclic ether cleavage process analogous to the boron trichloride demethylation is not operative, as evidenced by the fact that **2** was not isolated on hydrolysis of **4**. The approach of a



sterically bulky ether cleavage reagent, such as boron tribromide, to the o-methoxy group ought to be prevented in **4**.

In order to test this hypothesis 1,4-dimethoxybenzene was treated with hydrogen cyanide, aluminum chloride, and hydrogen chloride in methylene chloride to produce a soluble iminium complex **4**. Treatment of this complex with 2 equiv of boron tribromide gave exclusively 5-hydroxy-2-methoxybenzaldehyde (**3**), mp 114–116°. Hydrolysis of **4** gave **1**, which on treatment with 2 equiv of boron tribromide afforded 2,5-dihydroxybenzaldehyde (**5**) in excellent yield.

Since the 5-methoxy group in **1** is more nucleophilic than the 2-methoxy group, a certain degree of selectivity should also be achieved on treatment of **1** with concentrated sulfuric acid. Thus, heating of **1** with concentrated sulfuric acid at 50–54° for 46 hr indeed gave a 42% yield of **3**; the only other product isolated was **1** (20%).[2]

Experimental Section

5-Hydroxy-2-methoxybenzaldehyde (3). A. From the Iminium Complex 4 and Boron Tribromide. To 27.6 g (0.2 mol) of 2,5-dimethoxybenzene in 200 ml of methylene chloride with ice cooling and stirring, 28.4 g (0.22 mol) of aluminum chloride and 8.1 g (0.3 mol) of hydrogen cyanide were added. The cooling bath was removed and 21 g of hydrogen chloride was added slowly at room temperature over a period of 4 hr. After stirring for 40 hr one-quarter of the reaction mixture (85 ml) was stirred with 25 g (0.1 mol) of boron tribromide for an additional 20 hr. After hydrolysis with dilute hydrochloric acid (100 ml), 6.65 g of a mixture of hydroquinone and **3**, mp 145–155°, precipitated. Extraction of this solid with two 200-ml portions of methylene chloride and evaporation of the combined methylene chloride portions gave 4.55 g (60%) of **3**, mp 112–115°. Hydrolysis of the remaining reaction mixture (255 ml) with dilute hydrochloric acid, extraction of the methylene chloride layer with 5% sodium hydroxide, drying with magnesium sulfate, evaporation, and vacuum distillation of the residue gave a first fraction of 2,5-dimethoxybenzene and 20.2 g (91.5%) of **1**, bp 98° (0.1 mm), mp 49–52°.

B. From 2,5-Dimethoxybenzaldehyde (1) and Concentrated Sulfuric Acid. To 20.75 g (0.125 mol) of **1** with ice cooling, 112.5 ml of concentrated sulfuric acid was added and the mixture was heated at 50–54° for 46 hr. The reaction mixture was poured onto ice and the precipitated oil was extracted with diethyl ether. Extraction of the solvent with 200 ml of 5% sodium hydroxide, acidification, extraction with diethyl ether, drying over anhydrous $MgSO_4$, and evaporation of the solvent gave 8.15 g (42.3%) of **3**: mp 114–116° after recrystallization from aqueous alcohol; ir ($CHCl_3$) 1672 cm^{-1} (C=O); nmr (acetone-d_6) δ 3.88 (s, 3, OCH_3), 3.0–4.0 (s, 1, OH), 6.9–7.3 (m, 3, aromatic), 10.38 (s, 1, CHO).

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.93; H, 5.31.

From the neutral diethyl ether layer 4.3 g (20.7%) of **1** was recovered.

2,5-Dihydroxybenzaldehyde (5). To 7 g (0.028 mol) of boron tribromide in 40 ml of methylene chloride, 3.32 g (0.02 mol) of 2,5-dimethoxybenzaldehyde was slowly added and the mixture was stirred at room temperature for 20 hr. Addition to ice water (70 ml), separation of the organic layer, and evaporation of the dried methylene chloride layer gave **5**, 0.8 g, mp 100–102° (lit.[3] mp 100–101°). Extraction of the aqueous layer with 100 ml of ethyl acetate produced another 1.8 g of **5**, total yield 2.6 g (92.2%).

Registry No.—**1**, 93-02-7; **3**, 35431-26-6; **4**, 51801-41-3; **5**, 1194-98-5.

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Light-Induced Reaction of 3,3′,5,5′-Tetramethyldiphenoquinone in Benzene

Shigeru Tsuruya*[1] and Teijiro Yonezawa

Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

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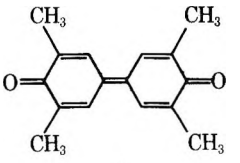
The irradiation of substituted *p*-benzoquinones, as solids or in solution, has been reported to yield photoaddition products as well as various types of dimers. These dimers include cyclobutanes,[2] spirooxetanes,[3] cage-like structures,[4] and unidentified products.[5]

In contrast to the photoinduced reactions of benzoquinone derivatives, no dimer was detected when **1** was irradiated in benzene in a nitrogen atmosphere. The products were 2,2′,6,6′-tetramethyl-*p*,*p*′-biphenol (**2**) and biphenyl (**3**).



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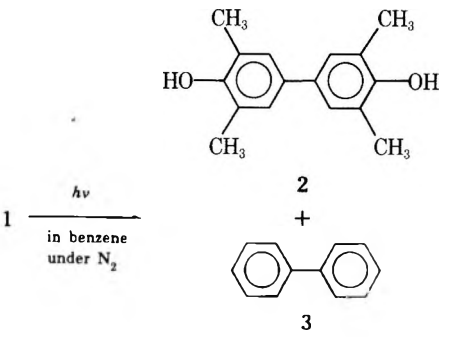


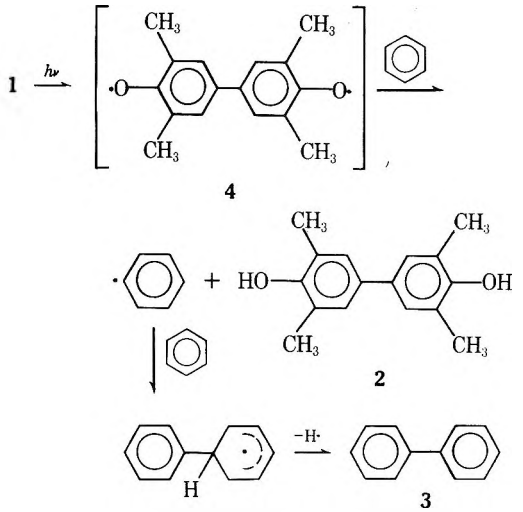
This result is surprising, since biphenyl formation is not common when benzoquinones are irradiated in benzene, which has been widely used as an inert solvent for photochemical reactions of benzoquinones.[6] For example, irradiation of 1,4-naphthoquinone in benzene gave only the dimer and no reduction products or biphenyl while 1,4-naphthoquinone in isopropyl alcohol gave the corresponding hydroquinone.[7]

The photolysis of iodoaromatic or bromoaromatic compounds in benzene solution results in a good yield of biphenyl or the result of the generation of an intermediate phenyl radical by the following photoinduced primary process.[8] The formation of biphenyl in the present work

$$PhX \xrightarrow{h\nu} Ph\cdot + \cdot X \quad X = \text{halogen atom}$$

indicates that here, too, a phenyl radical is generated as a reactive intermediate and that a benzene molecule may function as a hydrogen donor in the present photoinduced reaction of diphenoquinone.

Hay[9] has found that the thermolysis of molten 3,3′,5,5′-tetraphenyldiphenoquinone gave the corresponding biphenol as one of the products and demonstrated that diphenoquinones such as 3,3′,5,5′-tetraphenyldiphenoquinone were powerful oxidizing agents. Hence it appears reasonable to assume that species such as **4** are participating in the light-induced reaction. One possible route to the two products is the abstraction of a hydrogen atom from solvent benzene by the excited biradical (**4**)[10,11] followed by reaction of the resulting phenyl radical with a benzene molecule as follows, even though the possibility



of a dipolar transition state[6] consisting of diphenoquinone and benzene in place of **4** cannot be ruled out at present.

Experimental Section

Melting points are uncorrected. Infrared spectra were run on a Hitachi Model 215 grating spectrophotometer. Nmr spectra were recorded on a Varian HR-220 apparatus. Chemical shifts of the nmr spectra are reported in parts per million downfield from internal TMS. Mass spectra were obtained on a double-focusing mass spectrometer, Model JMS-01SG.

3,3′,5,5′-Tetramethyldiphenoquinone (**1**) was prepared by the oxidation of 2,6-xylenol with a copper(I) chloride–acetonitrile system. A solution of 0.5 g (0.005 mol) of copper(I) chloride in 50 ml of acetonitrile was stirred under an oxygen atmosphere, followed by addition of 1.22 g (0.01 mol) of 2,6-xylenol to the resulting homogeneous solution. The mixture was stirred for 2 hr at 30° while oxygen was being bubbled in and was chilled with an ice–water mixture. The resulting red crystals were filtered to yield 0.7 g of **1**, mp 207–208° (lit.[12] mp 208–210°). The elementary analysis, ir, and nmr spectra were all in agreement with the reported structure. Reduction of **1** with zinc dust in acetic acid gave the corresponding biphenol (**2**): mp 220–223° (lit.[12] mp 223–225°); mass spectrum M^+ m/e 242 (calcd for $C_{16}H_{18}O_2$, 242); nmr ($CDCl_3$) 8.15, 8.26 (CH_3, s), 6.63 (OH, s), and 3.14 and 3.25 ppm (ring H, s); ir (KBr) 3380 (OH), 860 cm^{-1} (phenyl).

Irradiation of 3,3′,5,5′-Tetramethyldiphenoquinone. A solution of 0.4 g of diphenoquinone (**1**) in 1000 ml of benzene was purged with nitrogen for 2 hr and then irradiated by means of a 200-W high-pressure mercury arc surrounded by a quartz filter for 100 hr under a stream of nitrogen gas. After removal of the solvent *in vacuo*, the chloroform solution of the reaction mixture was chlomatographed over silica gel (300 g) using chloroform as eluent. The first fraction (50 ml of eluent) obtained contained 0.02 g of **3**, whose ir (KBr) and nmr spectra were completely identical with those of authentic diphenyl. The second fraction (0.072 g, 75 ml of eluent) was identified as biphenol (**2**) by comparison with spectra of an authentic specimen. Starting material (0.250 g) was recovered as the third fraction by elution with 250 ml of chloroform.

Registry No.—**1**, 4906-22-3; **2**, 2417-04-1; **3**, 92-52-4; 2,6-xylenol, 576-26-1.

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Atomic Oxygen. III. Reaction of 1,3-Butadiene with Oxygen(^{3}P) Atoms[1]

James J. Havel* and Kam H. Chan

Department of Chemistry, Rice University, Houston, Texas 77001

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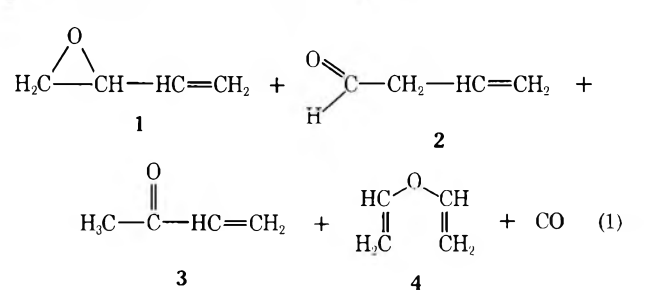
Atomic oxygen in its ground (triplet) state is produced by the gas-phase mercury-photosensitized decomposition of nitrous oxide.[2] The reaction of oxygen atoms with organic compounds is accomplished by photolysis of a mixture of mercury vapor, organic acceptor, and a large excess of nitrous oxide.[3] The generation of oxygen atoms by this technique produces one molecule of nitrogen per oxygen atom. Yields given below were calculated on the basis of nitrogen evolved during photolysis. Reactions were stopped with less than 25% of the reactant diene converted to products.

The reaction of 1,3-butadiene with O(^{3}P) has been studied by Cvetanovic and Doyle.[4] The oxygenated products that they isolated were carbon monoxide, 3,4-epoxy-1-butene, and crotonaldehyde. Crotonaldehyde may have been produced by rearrangement of 3-butenal during work-up.

We have examined the reaction of 1,3-butadiene with O(^{3}P) and have determined the product composition with very mild analytical techniques (*vide infra*). The oxygen-containing products of the reaction were carbon monoxide (14% yield); 3,4-epoxy-1-butene (**1**, 41%); 3-butenal (**2**, 23%); 3-buten-2-one (**3**, 1.5%); and vinyl ether (**4**, 0.5%) (eq 1). Total recovery of oxygenated material was 80%.



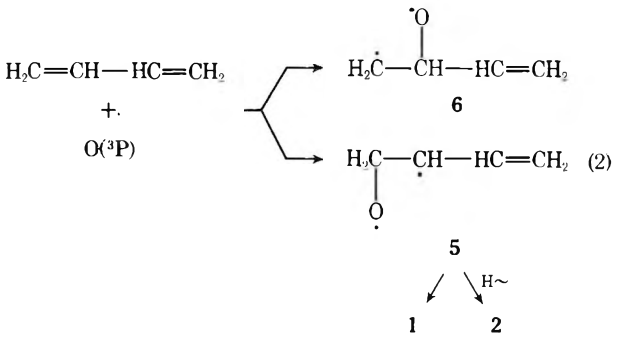
(1)

The hydrocarbons produced by formation of carbon monoxide were not quantitatively analyzed; however, propene was the major product of low molecular weight. Cvetanovic and Doyle[4] have shown that at a constant total pressure, product yields from the reaction of 1,3-butadiene with O(^{3}P) are independent of reactant ratio in the range nitrous oxide:1,3-butadiene = 9.6:137.

A search was made for the presence of 2,5-dihydrofuran in the product mixture. None of this product was detected upon injection of the product mixture on a vpc column known to separate an authentic sample of 2,5-dihydrofur-

an from products 1–4. 5 would be the product of a 1,4-cycloaddition of atomic oxygen to the diene. 1,4-Cycloaddition products have been reported from the reactions of atomic sulfur[5] and nitrogen[6] with 1,3-butadiene.

The initial reaction of atomic oxygen with a conjugated diene is addition of the atom to a double bond to form 1,3 biradicals.[7] This process is illustrated in eq 2. Addition

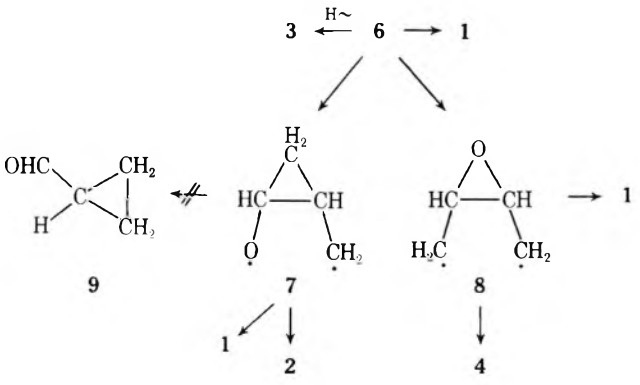


(2)

can occur either to an external carbon atom to produce biradical **5**, or to an internal carbon atom to make biradical **6**. Of these two competing processes, production of biradical **5** is favored over production of **6**. The carbon radical site of **5** is both secondary and allylic, whereas the carbon radical of **6** is primary and without allylic stabilization. The addition of O(³P) to olefins also shows preferential formation of the more stable biradical.[7] Product formation from **5** is accomplished by either ring closure to yield epoxide **1** or rearrangement of a hydrogen atom to give aldehyde **2**.

The transformation of biradical **6** to products is more complex (Scheme I). Ring closure and hydrogen migration produce epoxide **1** and ketone **3**, respectively. Another mode of reaction of **6** is intramolecular addition of the carbon and oxygen radical sites to the double bond to produce new 1,4 biradicals, **7** and **8**. The intermediates formed in this process are similar to those produced in triplet di-π-methane rearrangements. Photoinduced oxadi-π-methane rearrangements of β,γ-unsaturated carbonyl compounds appear to take place solely from the triplet state.[8]

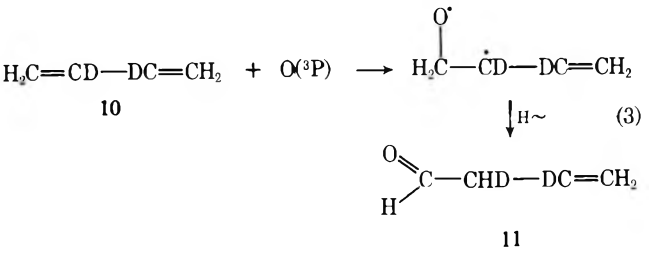
Scheme I



Possible reactions of biradical **7** include rearrangement either by β-cleavage to 3-butenal (**2**), or by a di-π-methane-like process to give epoxide **1** and cyclopropanecarboxaldehyde (**9**). However, no trace of **9** was detected among the products from the reaction of 1,3-butadiene with oxygen atoms.[9] Biradical **8** can decompose to the ether **4** (an observed product) or to epoxide **1**.

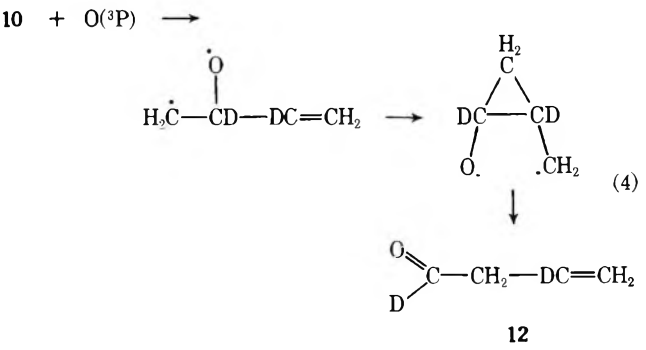
The β-cleavage reactions of 1,4 biradicals **7** and **8** (yielding **2** and **4**, respectively) are not without precedent. Pitts and Hess[10] have generated an analogous biradical by photolytic decarbonylation of bicyclo[3.1.0]hexan-3-one.

As is seen from the preceding discussion, epoxide product **1** can be made from four separate intermediates, while aldehyde **2** can arise by two pathways. It is possible to determine how much 3-butenal arises from each of the biradicals **5** and **7** by studying the reaction of 1,3-butadiene-*2,3-d*$_2$ (**10**) with oxygen atoms. 3-Butenal formed from intermediate **5** would be labeled at carbons 2 and 3 (eq 3),



(3)

while aldehyde from intermediate **7** would have deuterium in positions 1 and 3 (eq 4).



(4)

The ratio of 3-butenal-*2,3-d*$_2$ (**11**) to 3-butenal-*1,3-d*$_2$ (**12**) was determined by mass spectrometry. At 70 eV, the mass spectrum of undeuterated 3-butenal shows a large HCO^+ ion (m/e 29) and a small H_2CO^+ ion (m/e 30). The intensity of the ion at m/e 30 is only 1% of that of HCO^+ (corrected for the natural abundance of carbon-13 in HCO^+). This observation makes it possible to determine the ratio of **11** to **12** from the reaction of deuterated butadiene by measuring the intensities of the HCO^+ and DCO^+ ions. The corrected[11] ratio of HCO^+ to DCO^+ was 19:1. Thus, 95% of the 3-butenal arises by the mechanism of eq 3. No more than 5% is made by the di-π-methane process (eq 4).

In conclusion, it should be noted that 3-butenal is difficult to prepare by other methods. Isomerization to the conjugated isomer can be catalyzed by acid or base[12] or can occur under some vpc conditions.[4] 3-Butenal has been made in unspecified yields by the chromium trioxide oxidation of 3-buten-1-ol[13] and by the thermolysis of vinyl ether.[14] The reactions of other dienes with O(³P) and the independent production of biradicals **5** and **6** are currently being examined in these laboratories.

Experimental Section

Materials. All reactants were purified by trap-to-trap distillation before reaction. 1,3-Butadiene-*2,3-d*$_2$ (**10**) was prepared by the method of Craig and Fowler.[15] Mass spectrometric analysis at 10 eV indicated that the sample of **10** contained 9% monodeuterated and 1% undeuterated butadiene. Integration of the nmr spectrum of **10** showed that the area of absorptions in the region of the internal protons (τ 3.3–4.1) was <3% of the area of the terminal protons (τ 4.6–5.2).[16] This observation is consistent with specific deuteration in the 2 and 3 positions and with the isotopic purity determined by mass spectrometry.

Cyclopropanecarboxaldehyde (**9**) was made by the method of

Young and Trahanovsky.[17] Comparison samples of products **1**, **3**, and **4** and 2,5-dihydrofuran were obtained commercially.

Reaction Procedures. The apparatus and techniques used for the reactions of hydrocarbons with $O(^3P)$ have been described previously.[3] Reactions were run to less than 25% completion to avoid secondary oxidation of products. A high ratio of nitrous oxide to diene reactant (>25) was used in all reactions. Under these reaction conditions, no products of the direct[18] or mercury-sensitized[19] photorearrangement of the diene were observed (0.3% conversion could have been detected). The product composition from the reaction of 1,3-butadiene with $O(^3P)$ is not affected by the duration of photolysis.[4]

During photolysis, a thin, pale-yellow polymer formed on the surface of the immersion lamp. Irradiation of a mixture of nitrogen (586 Torr), 1,3-butadiene (24 Torr), and mercury vapors resulted in the loss of 2% of the butadiene by polymerization on the lamp.

Vpc analysis of the product mixture from the reaction of 1,3-butadiene was performed by injection of gas-phase aliquots onto either a 5-ft column of 10% dinonyl phthalate or an 11-ft column of 20% tricresyl phosphate in polyethylene tubing at 25°. Double vpc purification of individual products gave samples of >98% purity.

Spectra of products **1**, **3**, and **4** closely corresponded to spectra of authentic commercial samples of these compounds. Spectrometric data on 3-butenal (2) include ir (vapor phase) 3110, 3020, 2910, 2830, 2740, 1740, 1645, 1405, 1300, 1125, 990, and 915 cm^{-1}; uv (vapor phase) λ_{max} 300 mμ (ϵ 22); nmr ($CDCl_3$ solvent) 0.21 (1 H, triplet, J = 1.8 Hz), 3.9–5.0 (3 H, multiplet), 6.8 (2 H, multiplet); mass spectrum (70 eV) m/e (rel intensity) 70 (54), 69 (9), 42 (88), 41 (100), 40 (53), 39 (96), 38 (34), 29 (60), 27 (60), 26 (19); high-resolution mass spectrum of parent peak, observed mass 70.0421 (calcd for C_4H_6O, 70.0418).

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Registry No.—1, 930-22-3; 2, 7319-38-2; 1,3-butadiene, 106-99-0.

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Multipathway Bromination of Stilbenes. Competition between Carbonium and Bromonium Ion Intermediates

Marie-Françoise Ruasse and Jacques-Emile Dubois*

Laboratoire de Chimie Organique Physique de l'Université Paris VII associé au CNRS rue Guy de la Brosse, 75005 Paris, France

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A recent thermodynamic–kinetic approach to the transition state structure of the electrophilic bromination of olefins[1] leads to the conclusion that tensions in the ground state are preserved or even enhanced in the activated complex whatever the structure, bromonium or carbonium, of the intermediate. Therefore, it was proposed that bridged transition states are involved in all cases and that they lead to either bridged or open cationic intermediates. These results prompt us to report an extension of our study on the bromination of substituted stilbenes[2] which confirms that carbonium ion like and bromonium ion like transition states differ in their charge distribution.

We have shown elsewhere[2] that the bromination of stilbenes, $XC_6H_4C_xH{=}C_yHC_6H_4Y$, in methanol is a dual-path addition leading competitively to carbonium ions C_x^+ and C_y^+ through transition states where the charge is on one of the olefinic carbon atoms, without significant participation of the bromine atom. In this note, we investigate a new series of substituted stilbenes to determine how bromine participation modifies the carbonium pathway mechanism and to measure the differences between carbonium and bromonium ion like transition states. To establish the carbonium ion mechanism, we had selected stilbenes where one substituent at least was electron donating, favoring thus charge development on the benzylic carbon atom, α to the donor ring. Here, we attempt to determine whether bromonium ions occur in the bromination of stilbenes where both rings contain deactivating groups which disfavor formation of benzyl cations.

Bromination rate constants for X,Y-disubstituted stilbenes where X and Y are both electron attracting are given in Table I. The elementary rate constants for molecular bromine addition, k_{Br_2}, were measured in methanol at 25° either by the conventional method[3] (kinetic effects of the bromide ion concentration) or by an empirical equation established previously.[2a]

The reactivities of the deactivated stilbenes are first calculated as if the addition proceeds *via* the dual-path mechanism: the overall rate constant is the sum of the two partial rate constants k_x and k_y. Each partial rate constant follows the two-parameter equation $\log (k_x/k_0) = \rho_\alpha\sigma_X^+ + \rho_\beta\sigma_Y$ (eq 1) and $\log (k_y/k_0) = \rho_\alpha\sigma_Y^+ + \rho_\beta\sigma_X$ (eq 2), where ρ_α and ρ_β are −5.07 and −1.41, respectively. Comparison of the calculated and experimental values (Table II) reveals that the two carbonium ion scheme is inadequate for strongly deactivated stilbenes and that these latter react more rapidly than expected by the dual-carbonium path mechanism.

Bromonium Ion Intermediates. The attenuation of the effects of strongly electron-attracting substituents can most reasonably be interpreted in terms of an increase in the substituent–charge distance, so that the charge is on the bromine atom, *i.e.*, the transition states resemble bromonium ions **3**. In this case, the two substituents X and Y should have identical kinetic effects and there should be a linear free energy relationship between the reactivities, $\log k$, and the sum of the Hammett constants: $\log k = \rho_{Br^+}(\sigma_X + \sigma_Y) + \log k_0'$. For the four stilbenes which deviate most

Table I
Bromination Rate Constants of Stilbenes Substituted by Strongly Electron-Attracting Groups

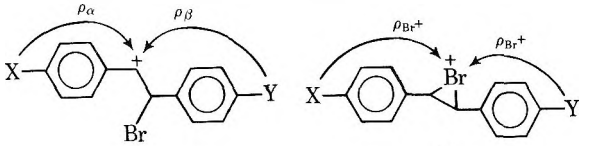
No.	X	Y	k_{exptl},[a] l. mol^{-1} min^{-1}: 0.2 *M*	0.1 *M*	0.05 *M*	0.025 *M*	k_{Br_2}[c]	$k_{Br_3^-}$	Log k_{Br_2}[d]
1	*p*-NO_2	*m*-CF_3	0.18	0.22	0.32		1.8	0.13	0.25
2	*p*-NO_2	*m*-Cl	0.15	0.20	0.25		1.6	0.11	0.21
3	*p*-NO_2	*p*-Cl	0.34						0.60[e]
4	*p*-NO_2	H[b]	1.05	1.30	1.90		11.9	0.64	1.07
5	*m*-CF_3	*m*-CF_3		0.30	0.40	0.65	3.0	0.16	0.48
6	*m*-CF_3	H[b]	3.4						1.70[e]
7	*m*-Cl	*m*-Cl	0.40						0.70[e]
8	*m*-Cl	*p*-Cl[b]	1.80						1.40[e]
9	*m*-Cl	H[b]	5.2						1.90[e]

[a] Experimental rate constants measured in methanol at various sodium bromide concentrations at 25°. [b] Rate constants previously obtained (ref 2). [c] Elementary rate constants obtained by extrapolation to zero bromide ion concentration using the equation $k_g[1 + K(Br^-)] = k_{Br_2} + Kk_{Br_3^-}(Br^-)$.[3] [d] The precision of the experimental rate constants smaller than 1 is only 8–10%. The error on the extrapolated value can be in the range of 20%. However, the structural effects are discussed on the reactivities log k_{Br_2} and not on the rate constants. A maximum error of 30% on k_{Br_2} would lead to an error of 0.3 l.u. on log k_{Br_2}. Thus, variations of log k_{Br_2} smaller than 0.3 l.u. are not significant. [e] These values are obtained by extrapolation from empirical relationships between (log $k_{exptl})_{0.2\ M\ NaBr}$ and log k_{Br_2}. For experimental rate constants higher than 1, there exists a linear relationship established in ref 2a. For smaller constants, the extrapolation has been made in each subpopulation *with X constant and Y variable: for the p-nitro Y-substituted stilbenes,* (log $k_{exptl})_{0.2\ M\ NaBr}$ = 0.97 log k_{Br_2} − 1.02 (r = 0.999, s = 0.007); for *m*-chloro Y-substituted stilbenes, (log $k_{exptl})_{0.2\ M\ NaBr}$ = 0.90 log k_{Br_2} − 1.01 (r = 0.999, s = 0.0003). This method leads to extrapolated elementary rate constants whose precision is of the same order as that of the experimental values.

markedly from the dual-path mechanism predictions (Table II, compounds 1, 2, 5, and 7), eq 3 is valid.

$$\log k = -1.0(\sigma_X + \sigma_Y) + 1.3 \qquad (3)$$

Although the correlation coefficient is only fair (r = 0.96, s = 0.038), deviations of the defining compounds from eq 3 are small, less than 0.1 l.u. (Compare Tables I and III). However, the errors on ρ_{Br^+} and log k_0' of eq 3 are about 0.5. Therefore, we can consider that the value of ρ_{Br^+} is rather similar to ρ_β (−1.4), which is the reaction constant for the substituent Y on the ring β to the carbonium ion **1**.



1 **3**

This is expected, since the substituents X and Y are in the same position with respect to the charge in the ion **3** as the substituent Y is in the ion **1**. In contrast, the values of log k_0 in eq 1 and 3, corresponding to the bromination of the unsubstituted stilbene *via* carbonium or bromonium ion intermediates **1** and **3**, are significantly different, +2.2 and +1.3, respectively.

General Scheme for the Bromine Addition to Aromatic Conjugated Olefins. The structure–reactivity relationships for bromination *via* bromonium ions and carbonium ions correspond to a scheme in which each type of intermediate is generated in a discrete pathway and imply thus three distinct transition states where the charge is either developed on the carbon atom C_x, on the atom C_y, or on the bromine atom. This description is rather different from the generally accepted mechanism[4] which features a single intermediate[5] with the charge distributed more or less equally between the three atoms. The multipathway scheme is, however, a good mathematical description of the results, whereas kinetic treatment of the usual model is im-

Table II
Failure of the Carbonium Ion Mechanism for Strongly Electron-Attracting Stilbenes

No.	Log k_x[a]	Log k_y[a]	Log k_{calcd}	Δ log k[b]
1	−2.39	−1.54	−1.54	−1.80
2	−2.32	−0.90	−0.90	−1.10
3	−2.12	0.57	0.57	−0.07
4	−1.80	1.10	1.10	0.03
5	−1.06	−1.06	−0.76	−1.20
6	−1.60	1.61	1.61	−0.10
7	−0.36	−0.36	−0.06	−0.75
8	0.15	1.10	1.10	−0.30
9	−0.17	1.68	1.68	−0.20

[a] These values are calculated from eq 1 and 2 with $k_{calcd} = k_x + k_y$ (see ref 2a). [b] Δ log k = log k_{calcd} − log k_{exptl}.

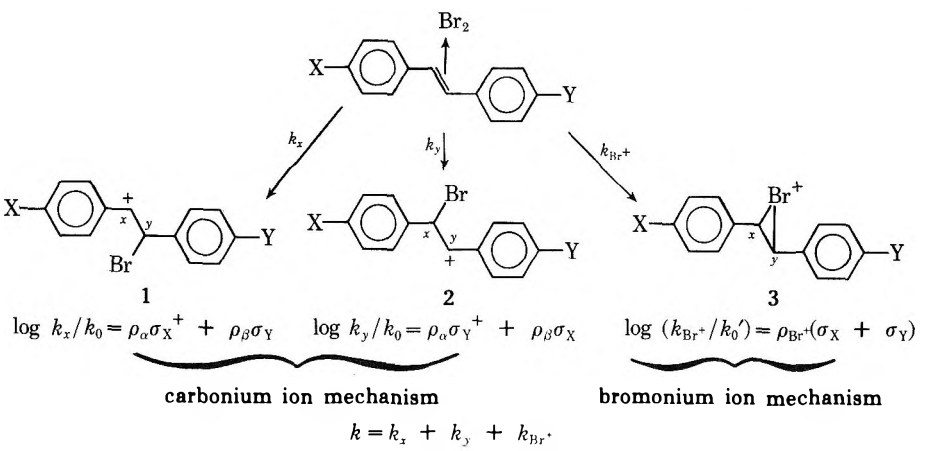
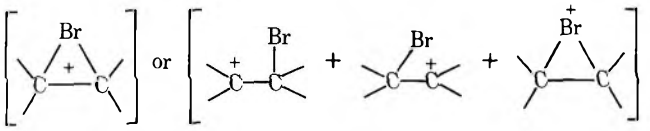


Table III
Competition between Bromonium and Carbonium Ion Pathways in Stilbene Bromination

Registry no.	No.	X	Y	Elementary calculated reactivities: Log k_x[a]	Log k_y[a]	Log k_{Br^+}[b]	Predominant intermediate[e]: C_x^+	C_y^+	Br^+[f]	Overall calculated and experimental reactivities: Log k_{calcd}[c]	Δ[d]
51751-38-3	1	*p*-NO_2	*m*-CF_3	−2.90	−2.05	+0.15			+	0.15	+0.10
51751-39-4	2	*p*-NO_2	*m*-Cl	−2.86	−1.31	+0.20			+	0.20	+0.01
3757-16-2	3	*p*-NO_2	*p*-Cl	−2.64	+0.14	+0.34		+	+	0.55	+0.05
4003-94-5	4	*p*-NO_2	H	−2.27	+0.75	+0.57		+	+	0.96	+0.25
27892-96-2	10	*p*-NO_2	*m*-Me	−2.15	+1.13	+0.64		+	+	1.25	+0.20
7560-35-2	11	*p*-NO_2	*p*-Me	−1.99	+2.42	+0.74		+		2.42	−0.14
1472-68-0	12	*p*-NO_2	*p*-OMe	−1.83	+4.96	+0.84		+		4.96	−0.01
51751-40-7	5	*m*-CF_3	*m*-CF_3	−1.47	−1.47	+0.51			+	0.51	−0.03
28495-61-6	6	*m*-CF_3	H	−0.80	+1.33	+0.93		+	+	1.47	+0.24
3240-26-4	7	*m*-Cl	*m*-Cl	−0.75	−0.75	+0.61			+	0.61	−0.10
51751-41-8	8	*m*-Cl	*p*-Cl	−0.53	+0.80	+0.75		+	+	1.08	+0.32
24942-77-6	9	*m*-Cl	H	−0.16	+1.41	+1.00		+	+	1.55	+0.24
51751-42-9	13	*m*-Cl	*p*-Me	+0.11	+3.08	+1.15		+		3.08	−0.07
5415-08-7	14	*m*-Cl	*p*-MeO	+0.27	+5.62	+1.25		+		5.62	+0.13
5121-74-4	15	*p*-Cl	*p*-Cl	+1.02	+1.02	+0.89	+	+	+	1.46	+0.28
4714-23-2	16	*p*-Cl	H	+1.39	+1.63	+1.12	+	+	+	1.89	+0.18
22692-73-5	17	*p*-Cl	*p*-Me	+1.66	+3.30	+1.30		+		3.30	−0.13
5043-91-4	18	*p*-Cl	*p*-MeO	+1.82	+5.84	+1.40		+		5.84	+0.03
588-59-0	19	H	H	+2.00	+2.00	+1.30	+	+	+	2.34	+0.33
28495-59-2	20	*m*-Me	H	+2.38	+2.11	+1.42	+	+		2.60	+0.30
4714-21-0	21	*p*-Me	H	+3.67	+2.27	+1.52	+	+		3.69	−0.03

[a] Calculated by eq 1′ and 2′. [b] Calculated by eq 3. [c] $k_{calcd} = k_x + k_y + k_{Br^+}$. [d] $\Delta = \log k_{exptl} - \log k_{calcd}$. [e] Owing to imprecision of the bromonium equation (eq 3), we give only the nature of the intermediate, although the relative importance of each intermediate could be calculated by $(k_x \times 100)/(k_x + k_y + k_{Br^+})$ for C_x^+ and similarly for C_y^+ and Br^+. [f] Br^+ is the bromonium ion.

possible in the absence of a quantitative relationship between charge magnitude and the ρ value.[9]



However, the equivalence of the two descriptions is questionable only in borderline cases where several pathways compete. This does not discredit our conclusion regarding the differences between carbonium and bromonium ion-like transition states, since there are compounds (1, 2, 11, 12, 13, 14, or 17 of Table III) whose bromination passes through only one transition state which can be either **1**, **2**, or **3**.

Competition between Bromonium and Carbonium Ion Pathways. Since we have now identified a discrete pathway for bromonium ion formation, we shall examine the competition between bromonium and carbonium ion pathways. From data for stilbenes with at least one electron-donating substituent, we had concluded that bromine participation was unimportant. However, substituent effects on the bromonium ion pathway are weaker than on the carbonium ion one, since ρ_α (−5.0) is considerably higher than ρ_{Br^+} and the existence of pathway 3 could have been neglected in the carbonium treatment. We have, therefore, reexamined the previous data[2b] and recalculated the parameters of the carbonium ion mechanism from the elementary rate constants k_{Br_2} of only those stilbenes with at least one strongly electron-donating substituent, namely, *p*-hydroxy, *p*-methoxy, or *p*-methyl. In this way, we obtain the following equations ($r = 0.981$, $s = 0.005$).

$$(\log k_x)_{Br_2} = -5.4\sigma_X^+ - 1.6\sigma_Y + 2.00 \quad (1')$$

$$(\log k_y)_{Br_2} = -5.4\sigma_Y^+ - 1.6\sigma_X + 2.00 \quad (2')$$

The parameters ρ_α and ρ_β, −5.4 and −1.6, are approximately identical with those obtained previously, −5.1 and −1.4, respectively. From eq 1′, 2′, and 3, we have calculated the relative importance of each pathway for a number of stilbenes (Table III). Differences between experimental and calculated overall rates are also given only for guidance, since the bromonium equation (eq 3) is too rough to allow any quantitative conclusion. For the same reasons, we give only the structure of the existent intermediate and not the exact value of its contribution. The results confirm the predominance of the carbonium and bromonium mechanism for stilbenes with strongly electron-donating (11, 12, 13, 14, 17, and 18) or electron-attracting groups (1, 2, 5, and 7), respectively. For some electron-attracting substituents (3, 4, 8, 9, 15, and 16), the bromonium ion pathway competes with the carbonium one. This intervention does not lead to significant accelerations with respect to the carbonium ion predictions. Typical examples are given by the *p*-nitro- or *p*-nitro-*m*′-methylstilbenes,for which the neglect of the third pathway induces an error on the reactivity of about 0.2 l.u. In the same way, it must be noted that for stilbene itself, the results of Table III indicate a slight preference for the carbonium ion pathway. However, the difference between calculated and experimental reactivities is particularly high. Therefore, we can only assume that this compound is a borderline case for which carbonium and bromonium intermediates are of comparable stability.

In short, once parameters for the linear free energy relationship describing reactivity in the absence of assistance have been determined with precision, it is possible to discern cases where there are significant deviations and to determine the parameters of the assisted reaction. Thereafter, the small contribution of the assisted pathway can be calculated for compounds previously considered to be unassisted. It turns out that these small contributions for an assisted pathway do not affect the linearity of the original equation. The long controversy[12] on the assistance or absence of assistance by the phenyl ring in solvolysis of secondary tosylate, $PhCH_2CH(OTs)CH_3$, has been largely settled by an extensive investigation of substituent effects,[10] which has revealed that there is, in fact, competition between the two mechanisms and that the importance of assistance depends on the ring substituent.

Our results concerning substituent effects on the forma-

Table IV

Stilbene X	Stilbene Y	Mp, °C
p-NO_2	m-CF_3[a]	123
p-NO_2	m-Cl[b]	118
p-NO_2	p-Cl[b]	185
m-CF_3	m-CF_3[c]	112
m-Cl	m-Cl[d]	95

[a] *Anal.* Calcd: C, 61.43; H, 3.41; N, 4.77. Found: C, 61.08; H, 4.09; N, 5.40. [b] Reference 15. [c] *Anal.* Calcd: C, 60.76; H, 3.18. Found: C, 61.25; H, 3.52. [d] D. E. Bissings and A. J. Speziale, *J. Amer. Chem. Soc.*, **87**, 2683 (1965).

tion of carbonium and bromonium ion intermediates in stilbene bromination show that the transition states which lead to these intermediates are significantly different in their charge distributions. This confirmation of our previous work is apparently contradictory with the arguments of Yates, *et al.*,[1] who proposed a single transition state structure regardless of the intermediate. In reality, the thermokinetic data signify only that the magnitude of the interactions is retained or slightly increased in passing from the initial to the transition states, *i.e.*, no rotation occurs at this stage.[13] In our opinion, bromine bridging is not the only explanation consistent with strain conservation; counterion effects, interactions between the C–Br bond and the p orbital,[14] or some compensation of substituent–substituent interactions of the ground state by the bromine–substituent interactions of the transition state cannot as yet be excluded.

Experimental Section

Synthesis of Stilbenes. The p-nitro, Y-substituted stilbenes (Table IV) were prepared by condensation of Y-substituted benzaldehydes with p-nitrophenylacetic acid in the presence of piperidine.[15]

The di-m,m'-trifluoromethyl-and di-m,m'-chlorostilbenes were synthesized by pyrolysis of azines obtained from benzaldehydes and hydrazine.[16]

Kinetic Measurements. The bromination rate constants were measured in methanol at 25° for various bromide ion concentration by amperometric titration, as described previously.[17]

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(3) J. E. Dubois and F. Garnier, *Bull. Soc. Chim. Fr.*, 4512 (1967); J. E. Dubois and X. Q. Huyn̈h, *Tetrahedron Lett.*, 3369 (1971).
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(9) An identical problem exists for the solvolysis of secondary systems where the assistance by a neighboring aryl group is possible: the widely accepted[10] scheme of Winstein[11] implies two discrete transition states for the assisted and unassisted pathways.
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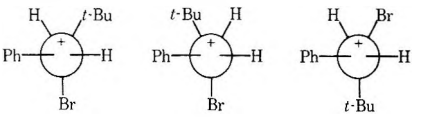
(13) The discussion of Yates, *et al.*, is based on comparison of thermodynamic parameters of ground and transition states, for cis and trans pairs of olefins selected as models for carbonium or bromonium ion intermediates. The conclusions for the carbonium ion brominations are inferred from stilbenes and β-*tert*-butylstyrenes. Our results for stilbene itself strenghten doubts expressed by Yates as to the free carbonium structure of the intermediate. The β-*tert*-butylstyrenes are sterically congested both in the initial state and in the intermediate. Conformational analysis of the intermediate reveals that the bromine–phenyl and *tert*-butyl–phenyl interactions are high for all conformations. In particular, rotation in b, which is directly generated from the cis olefin, requires eclipsing of the phenyl ring with bromine or *tert*-butyl, involving thus a non-negligible energy barrier.



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On the Absolute Configuration of Two *trans*-*p*-Menthane-2,3-diols

Jeffrey I. Seeman‡ and Herman Ziffer*

Laboratory of Chemical Physics, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

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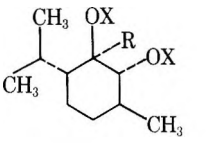
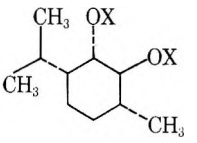
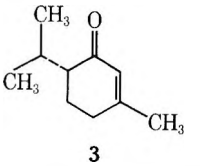
In order to determine the absolute configuration of substituted benzene dihydrodiols obtained in small quantities from enzymatic reactions,[1] it is necessary to employ spectroscopic methods rather than chemical correlations. We have recently applied the dibenzoate chirality rule of Nakanishi[2] (DCR) to ascertain the absolute configuration of a substituted *cis*-cyclohexane-1,2-diol and have verified this assignment by X-ray analysis.[3] Although the dibenzoate chirality rule has been applied to a wide variety of compounds,[2] its extension to the monocyclic *trans*-cyclohexane-1,2-diol system has not previously been reported. The diols **1a** and **2a** were selected for this study, since they can be prepared by hydroboration[4] of piperitone (**3**) whose absolute stereochemistry is known and therefore provides a check of the dibenzoate chirality rule.



1a, R = X = H
b, R = D; X = H
c, R = H; X = COPh



2a. X = H
b. X = COPh



3

Although Klein and Dunkelblum[4] had assigned the relative stereochemistry of **1a** and **2a** from 60-MHz nmr spectra and mechanistic consideration, their published data for **2a** were inconclusive.[5] In our hands, the absorption for carbinol hydrogens in **2a** at 60 MHz overlapped and could not be analyzed. However, these absorptions were separated in the 220-MHz nmr spectrum and the coupling constants so determined (Table I) confirmed the assigned configurations

‡ Philip Morris Research Center, Richmond, Va.

Table I[a]

Compd	δ_{C-2}	δ_{C-3}	$J_{2,3}$	$J_{3,4}$	$J_{1,2}$
1a	2.94	3.18	9	9	9
1b	2.94			9	
2a	3.37	3.68	8	8	4

[a] Coupling constants given in hertz.

1a and **2a**. The chemical shifts of the carbinol protons for **2a** were assigned from the observed coupling constants, but a similar assignment was not possible for **1a**. The deuterio derivative **1b** was prepared by lithium aluminum deuteride reduction of **3** followed by hydroboration of the resulting allylic alcohol. The disappearance of the multiplet at δ 3.18 in the nmr spectrum of **1b** established the chemical shifts of the carbinol protons.

Since the absolute configuration of (−)-piperitone is known to be 6*R*,[6] the relative stereochemistry of the diols can be used to assign their absolute configurations. From these considerations, (+)-**1a** is (1*S*,2*R*,3*R*,4*R*)-2,3-dihydroxy-*p*-menthane while (+)-**2a** is (1*R*,2*S*,3*S*,4*R*)-2,3-dihydroxy-*p*-menthane.

The dibenzoate chirality rule predicts that the sign of the first Cotton effect around 230 nm is in accordance with the chirality of the dibenzoate groups of a vicinal diol.[2] This chirality is negative for **1** and positive for **2**. The dibenzoates **1c** and **2b**, prepared by treatment of the corresponding diols with excess benzoyl chloride–pyridine, have strong Cotton effects (Figure 1) whose sign is in agreement with that predicted by the rule. The molar ellipticities given in Figure 1 differ by an order of magnitude, although the curves clearly bear a mirror image relationship. The differences in the magnitude of the two effects are probably ascribable to deviations from the parallel alignment of the carbinol carbon–oxygen bond and the long axis transition moment of the benzoate, as well as differences in the relative orientation and separation of the aromatic rings.

In conclusion, the absolute configurations deduced from the CD measurements correspond with those assigned from the known absolute configuration of (−)-piperitone and the relative stereochemistry obtained from the proton nmr spectra. These results coupled with earlier studies[1] support the use of the dibenzoate chirality rule in assigning the absolute configuration of other substituted 1,2-cyclohexanediols.

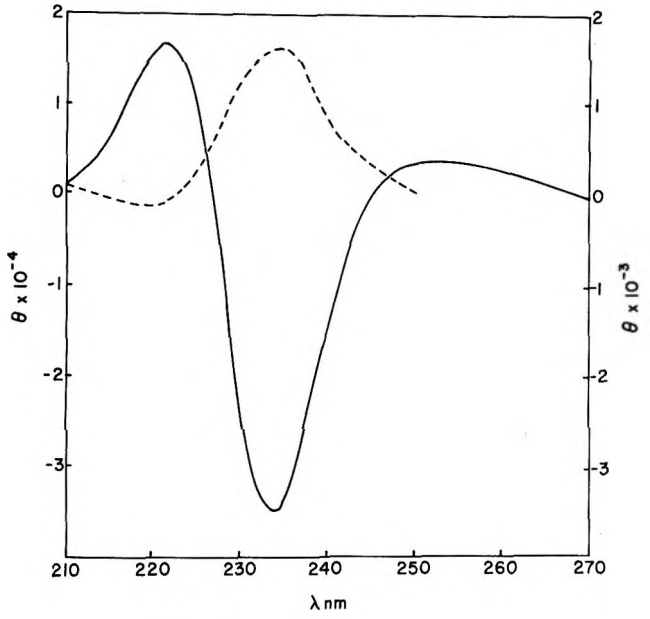


Figure 1. CD curves of diol dibenzoates. The solid line is **1c** legend on left and the dashed line is **2b** legend on right. Optical purity of dibenzoates ~40%.

Experimental Section

(−)-Piperitone, $[\alpha]_D$ −21.1° (reported[7] $[\alpha]_D$ −51.5°, *i.e.*, ~41% optically pure), was hydroborated and oxidized as described by Klein and Dunkelblum.[4] The reaction mixture was distilled and the diol fraction, bp 110–115° (0.1 mm), was collected. Chromatography on silica gel, using ethyl acetate–hexane (1:4) separated the mixture into a faster moving oil (**2a**) and a slower moving oil (**1a**). The specific rotations at the D line in chloroform for **1a** and **2a** were 47.2 and 13.3°, respectively. When these rotations are corrected for the optical purity of (−)-piperitone they become 115 and 32.4°, respectively. The dibenzoate of each diol was prepared by treating the diol in pyridine with excess benzoyl chloride, and the reaction products were purified by preparative thick layer chromatography on silica gel using ethyl acetate in hexane (1:9). The dibenzoates **1c** and **2b** were oils, $[\alpha]_D$ −74° and 42° ($CHCl_3$), respectively. The CD curves of the dibenzoates were determined in isooctane using a Cary 60 spectropolarimeter and are shown in Figure 1. The 220-MHz spectrum of **1c** in $CDCl_3$ showed absorption at δ 5.305 (t, 1 H) and 5.091 (t, 1 H) and complex aromatic absorption (10 H). The spectrum of **2b** showed absorption at δ 5.418 (d, 1 H) and 5.327 (q, 1 H) and complex aromatic absorption (10 H).

Registry No.—**1a**, 51745-19-8; **1b**, 51745-20-1; **1c**, 51705-86-3; **2a**, 51745-21-2; **2b**, 51705-87-4; **3**, 4573-50-6.

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Preparation and Purification of 18-Crown-6[1]

George W. Gokel and Donald J. Cram*

Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024

Charles L. Liotta,* Henry P. Harris, and Fred L. Cook

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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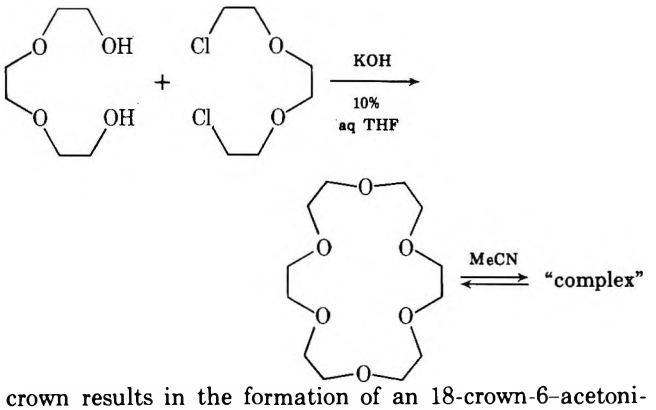
Of the many crown ethers which have been prepared[2] since the pioneering work of Pedersen[3] first appeared, 18-crown-6 is probably the simplest and most synthetically useful. Its synthesis in low yield was reported by Pedersen in his first paper.[3] Greene[4] and Dale and Kristiansen[5] have reported syntheses of 18-crown-6 from triethylene glycol and the corresponding ditosylate. A variety of bases was examined by Greene[4] but in both cases potassium *tert*-butoxide was favored. We report here a simple synthesis of 18-crown-6 from triethylene glycol and the commercially available (Eastman) 3,6-dioxa-1,8-dichlorooctane (triethylene glycol dichloride) using potassium hydroxide as base in 10% aqueous tetrahydrofuran and purification of the crown *via* its acetonitrile complex.

The Williamson ether synthesis yields crude crown in about 40% yield after a rapid distillation under high vacuum. The distilled material contains an impurity believed to be a vinyl ether and some open-chain, hydroxyl-containing material. Addition of acetonitrile to the crude



crown results in the formation of an 18-crown-6–acetonitrile adduct (complex)[6] of variable stoichiometry depending on conditions. Evaporation of the acetonitrile leaves crown of high purity. Evidence on the nature of this and other complexes of 18-crown-6 will be published elsewhere.

Experimental Section

A 3-l., three-neck flask equipped with mechanical stirrer, reflux condenser, and addition funnel was charged with triethylene glycol (112.5 g, 0.75 mol) and tetrahydrofuran (600 ml). Stirring was commenced and a 60% KOH solution (109 g of 85% KOH in 70 ml of water) was poured in. The solution warmed but did not boil. After *ca.* 15 min of stirring (the solution darkened) a solution of 3,6-dioxa-1,8-dichlorooctane (140.3 g, 0.75 mol) in THF (100 ml) was added in a stream. After the addition was complete, the solution was heated at reflux and stirred vigorously for 18 hr. The solution was allowed to cool and the bulk of the THF was evaporated under reduced pressure. The resulting thick brown slurry was diluted with 500 ml of dichloromethane and filtered. The salts removed by filtration were washed with more dichloromethane to remove adsorbed crown, and the combined organic solution was dried over $MgSO_4$, evaporated to minimum volume (aspirator vacuum), and then distilled under high vacuum. The distillation should be carried out at the lowest possible pressure; a typical fraction contained 80 g and was collected at 100–160° (0.2 mm).

To 50 g of crude 18-crown-6, bp 125–160° (0.2 mm), in a 250-ml erlenmeyer flask was added 125 ml of acetonitrile. The resulting slurry was heated on a hot plate to effect solution. A magnetic stirring bar was added and the neck was equipped with a $CaSO_4$ drying tube. The solution was stirred vigorously as it was allowed to cool to ambient temperature, and fine white crystals of crown–acetonitrile complex were deposited. The flask was finally cooled in an ice–acetone bath to precipitate as much complex as possible, and the solid was then collected by rapid filtration. The hygroscopic crystals were transferred to a 500-ml round-bottom flask equipped with a magnetic stirring bar and vacuum take-off. The acetonitrile was removed from the complex under high vacuum (0.1–0.5 mm) with gentle heating (≤40°) over 2–3 hr. The pure, colorless crown (20–30 g, 40–60%) crystallized on standing and showed no ions above m/e 265 in the mass spectrum and no significant hydroxyl vibration in the 3500-cm^{-1} region of the infrared. The pure crown had mp 36.5–38.0° (lit.[4] mp 39–40°); nmr (60 MHz, CCl_4) 3.56 ppm (singlet); ir (neat) 2875 (alkane CH), 1450 and 1350 (alkane CH), and 1120 cm^{-1} (ether link); mass spectrum M and M + 1 at m/e 264 and 265, other fragments at m/e 89, 87, 59, 45, 44, 43, and 31.

Registry No.—18-Crown-6, 17455-13-9; triethylene glycol, 112-27-6; 3,6-dioxa-1,8-dichlorooctane, 112-26-5.

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Fluorescence Properties of a Meisenheimer Complex[1]

Sutton Farnham and Ronald Taylor*

Laboratory for Biophysical Chemistry, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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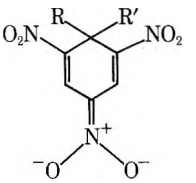
Meisenheimer complexes (below), the σ complexes which are formed as a result of the attack of nucleophilic agents on polynitroaromatic compounds, have been of interest to chemists for over 70 years.[2] Their spectroscopic



R = H, OH, OCH_3; R′ = H, OCH_3, CN, SO_3^-, etc.

(uv–visible, ir, nmr)[3,4] properties have been extensively studied, but the fluorescence behavior of these complexes has been overlooked. In view of the similarity of these complexes to the polynitrophenyl haptens used in many immunochemistry studies,[5] we decided to investigate the possibility of using these complexes as fluorescent biophysical probe molecules.[6] We report here the results of our preliminary investigations of the fluorescence properties of a Meisenheimer complex (where R = R′ = H, tetramethylammonium 1,1′-dihydro-2,4,6-trinitrocyclohexadienate) under differing environmental conditions. We believe that these results represent the first reported observations of Meisenheimer complex fluorescence.

The 1,1′-dihydro-2,4,6-trinitrocyclohexadienate anion fluoresces in acetronitrile with an emission maximum at about 670 nm. The quantum efficiency, which because of instrumental limitations must be considered only an estimate, is about 0.09. The measured lifetime is 1.8 ± 0.4 nsec. These data give a radiative lifetime of about 20 nsec.

In water, the emission maximum is shifted to the red (Figure 1) and the intensity is greatly diminished from that in acetonitrile. However, in the presence of an excess of human serum albumin (HSA) the emission spectrum (Figure 1) is similar to that in acetonitrile, although the quantum efficiency is somewhat less.

It is well known that serum albumins act as nonspecific binding agents for hydrophobic anions[7] and apparently the binding of the 1,1′-dihydro-2,4,6-trinitrocyclohexadienate anion to HSA[8] places it in a sufficiently nonaqueous environment that its emission spectrum more closely resembles that observed in acetonitrile. The lifetimes of

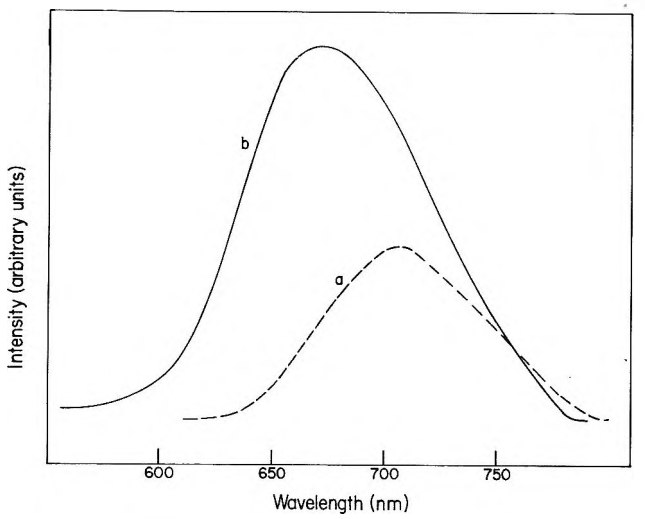


Figure 1. Emission spectra of 10^{-5} *M* tetramethylammonium 1,1′-dihydro-2,4,6-trinitrocyclohexadienate in (a) 0.05 *M* pH 6 phosphate buffer and in (b) the same buffered solution containing 10^{-4} *M* HSA. Excitation wavelength: 478 nm.

this anion in nondeoxygenated aqueous solutions both with and without HSA were less than in acetonitrile, probably near 1 nsec.

The theoretical aspects of the fluorescence of this compound are quite interesting. A general rule in fluorescence spectroscopy states that most electron-withdrawing groups, and nitro groups in particular, rather effectively decrease or eliminate fluorescence in aromatic compounds.[9] We could detect no fluorescence for trinitrobenzene (TNB). Other related compounds such as trinitrotoluene (TNT) likewise exhibit no observable fluorescence.[10] It should be noted, however, that 1,1′-dihydro-2,4,6-trinitrocyclohexadienate is *nonaromatic*, and considerable electron delocalization is possible within the pentadienate anion moiety. This fact, coupled with the observation of low-lying excited states for the molecule,[11] may hold the key to the observed fluorescence. It is likely that these results on 1,1′-dihydro-2,4,6-trinitrocyclohexadienate, the prototype Meisenheimer complex, can be generalized to other related species. The σ complexes formed when amines are added to acetone solutions of TNB[12] exhibited fluorescence properties similar to those we have reported.

We note in passing the resemblance of these systems to the NADH–NAD^+ pair.[13] The nonaromatic NADH molecule has rather intense fluorescence while the aromatic NAD molecule shows little, if any, detectable fluorescence.

These preliminary studies indicate that there is a possibility of using anions such as 1,1′-dihydro-2,4,6-trinitrocyclohexadienate as fluorescent biophysical probe molecules. Compared with its fluorescence in aqueous solution, the relative increase in intensity in the presence of HSA is considerable, but on an absolute basis the yields in these systems are quite low. It may be that immunoglobulins *specific* for the trinitrophenyl moiety will bind this anion in environments which exclude water more efficiently than does HSA. It has been suggested that displacement of bound water from both haptens and immunoglobulins plays a decisive role in the antibody–hapten binding reaction.[14,15] If this is the case it is possible that the fluorescence yield observed under these latter circumstances will be sufficiently enhanced to facilitate their use for physical studies or trinitrophenyl specific antibodies in solution.

There is one other potential application in this work. The fluorescence properties of Meisenheimer complexes might be very useful in analyses for TNT. Though TNT itself is nonfluorescent, it can easily be converted to a Meisenheimer complex by reaction with borohydride[16] or hydropolyborate anions.[17] We have found that sodium cyanoborohydride can be used to prepare the sodium salt of 1,1′-dihydro-2,4,6-trinitrocyclohexadienate from TNB,[16] and we suggest that this milder reducing agent could also be used to convert TNT to a fluorescent species. In this way it should be possible to detect small quantities of TNT (*ca.* 10–100 μg) and related derivatives.

Experimental Section

Tetramethylammonium 1,1′-dihydro-2,4,6-trinitrocyclohexadienate was prepared by previously published methods.[18] Acetonitrile was Aldrich spectrophotometric grade. Human serum albumin was fraction V obtained from Sigma.

The instrument on which the fluorescence spectra were recorded has been described before.[19] It was modified for this study to use a 250-mm Bausch and Lomb emission monochromator (blazed at 750 nm) and an E. M. I. 9558B photomultiplier tube. Spectra were corrected for instrumental response. Quantum yields were estimated using the method of Parker and Rees[20] with fluorescein as the standard.

Fluorescence lifetimes were measured with an instrument based on the single photon timing technique.[21] The excitation beam from a gated deuterium discharge lamp passed through a Jarrell-Ash 0.25-m monochromator. The emission was detected through interference or cutoff filters by an RCA 7265 photomultiplier tube. START and STOP pulses were transmitted to the time to pulse height converter (Ortec 437A) by Ortec NIM modules 417 and 454-453, respectively. The time-correlated signals, after bias amplification (Ortec 444), were analyzed with a Nuclear Data 1100 Series data-handling system. Decay curves were deconvoluted by numerical convolution.[21]

Samples were generally 10^{-5} *M* or less. Samples which were deoxygenated by nitrogen bubbling showed no apparent differences from those which were air saturated. All data were taken at room temperature.

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Registry No.—Tetramethylammonium 1,1′-dihydro-2,4,6-trinitrocyclohexadienate, 27554-58-1.

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Urea Dissociation. A Measure of Steric Hindrance in Secondary Amines

John C. Stowell* and Stanley J. Padegimas

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70122

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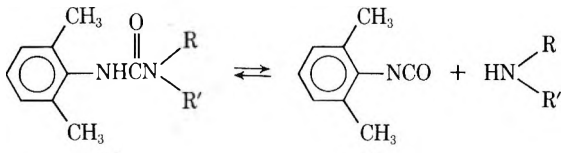
Most ureas are very stable compounds, sometimes used as characterizing derivatives of amines. Thermal dissociation may require high temperatures; *e.g.*, *N,N'*-diphenylurea was 99% dissociated into phenyl isocyanate and aniline at 370° in the gas phase.[1] Sufficient dissociation of some ureas occurs at 175° to give measurable rates of reaction with alcohols to give urethanes.[2] Similarly at 240–280° *N,N*-diphenyl-*N'*-methylurea dissociates enough to allow distillative removal of methyl isocyanate.[3] The possibility that lower temperature dissociation occurs in hindered cases is suggested by the room temperature rearrangement of *N*-*tert*-butyl-*N*-hydroxyureas to urethanes,[4] and the room temperature decomposition of 1,2-di-*tert*-butyl-4-isopropylsemicarbazide.[5]

We have found that ureas 1–8 dissociate appreciably in the range of 20–140° and that the equilibrium constants



1-8 9

1, R = R' = *sec*-butyl
2, R = cyclohexyl; R' = 3-pentyl
3, R = R' = cyclohexyl
4, R = *tert*-butyl; R' = isopropyl
5, R = *tert*-butyl; R' = 3-pentyl
6, R = *tert*-butyl; R' = cyclohexyl
7, R = 2,4,4-trimethyl-2-pentyl; R' = isopropyl
8, NRR' = 2,2,6,6-tetramethylpiperidyl

are readily measured by nmr spectroscopy. The equilibrium constants at two temperatures are given in Table I, and the thermodynamic values for variable-temperature measurements are given in Table II.

These equilibrium constants are a good indication of steric hindrance in secondary amines.[6,7] Polar effects should be very slight since we are not comparing relative rates, *i.e.*, stabilities of charged transition states, as in esterifications and hydrolyses.[8] It is interesting to note the very large difference between the disecondary alkyl amines and the secondary tertiary alkyl amines. This dramatic effect is similar to the one found in hydroboration of hindered olefins where the *tert*-butyl group exerts an extraordinary rate-retarding effect.[9] A scale of E^*_s values based on the hydroboration rates[10] was similar to the Taft E_s scale[8] except for the *tert*-butyl group, which showed greater hindrance in hydroboration.

Table I
Urea Dissociation Equilibrium Constants

	40°		127°	
Urea	K[a]	% dissociation[c]	K[a]	% dissociation[c]
1			0.017	12
2			0.032	16
3	2.6×10^{-5} [b]	0.52[b]	0.044	19
4	0.20	36	72.[b]	99[b]
5	0.34	42		
6	1.4	67	117.[b]	99[b]
7	2.1	74		
8	(15.)[d]	(95)[d]		

[a] K = [isocyanate][amine]/[urea]; ±10% of value. [b] Extrapolated values. [c] Calculated for 1 *M* initial urea concentration. [d] At 22°.

Table II
Thermodynamic Values for Urea Dissociation

Urea	$\Delta H°$, kcal/mol	$\Delta S°$, cal/deg mol
3	21.6 ± 0.5	48 ± 1
4	17.2 ± 0.4	51 ± 1
6	12.8 ± 0.2	41 ± 1

Our equilibria showed several inversions of order of steric hindrance in alkyl groups, compared to those indicated by E_s values. For example, we find the 3-pentyl group (E_s = −1.98) less hindering than the cyclohexyl group (E_s = −0.79).[11] In kinetic terms however, we find that urea formation for this pair is qualitatively in line with E_s values. At 40° the reaction of *tert*-butylcyclohexylamine with **9** (0.7 *M*) is at equilibrium (27% associated) in less than 1.5 hr, at which time the reaction of *tert*-butyl-3-pentylamine with **9** is only 14% associated. Even after 2 days, equilibrium is not yet reached (final value after 4 days is 47% associated). Similarly in the reverse direction, **2** required about 20 min to reach equilibrium at 140° by dissociation while **3** required only about 5 min.

Experimental Section

3-Pentylcyclohexylamine was prepared by a modification of the method of Skita and Keil.[12] Platinum oxide (25 mg) and one drop of concentrated HCl were added to 9.9 g (0.10 mol) of cyclohexylamine and 17.2 g (0.20 mol) of 3-pentanone. This was hydrogenated in a Parr shaker at 50 psi initial pressure for 2 days. The solution was decanted, about 200 mg of Na_2CO_3 was added, and then the solution was distilled on a spinning band column to give 11.0 g (65%) of the secondary amine, bp 95° (13 mm) (lit. yield 31%, bp 208–209°).

Di-*sec*-butylamine was prepared similarly from *sec*-butylamine and 2-butanone.

Commercial dicyclohexylamine was purified by distillation.

The secondary alkyl tertiary alkyl amines were prepared as described previously.[13]

All amines were dried over 4A molecular sieves before use.

2,6-Dimethylphenyl isocyanate[14] was prepared by phosgenation of 2,6-dimethylaniline hydrochloride and purified by spinning band distillation, bp 112–113° (35 mm) [lit.[14] bp 90–91° (13 mm)].

Anisole was purified by distillation and dried over 4A molecular sieves. Anisole was chosen as solvent for the higher boiling point (155°). Moreover, the difference in nmr chemical shift between the methyl groups on the isocyanate and those on the ureas (Table IV) were greater than in, *e.g.*, o-dichlorobenzene.

Equilibrium Measurements. 2,6-Dimethylphenyl isocyanate (303 mg, 2.06 mmol) was added to a solution of *tert*-butylisopropylamine (217 mg, 0.189 mmol) in 2 ml of pentane under nitrogen. The resulting white solid (**4**) was filtered, washed with pentane, and dried under nitrogen in a glove bag. A sample of the dry urea (97.4 mg) was dissolved in 307.2 mg of anisole under nitrogen in a well-dried nmr tube equipped with a tight cap. The tube was heated in the variable-temperature probe of an A-60 nmr spectrometer at each temperature until the ratio of isocyanate to urea remained constant. The peaks for the benzylic methyl

Table III
Equilibrium Constants for Variable-Temperature Dissociation of Ureas

Urea 6		Urea 4		Urea 2	
Temp, °C	K	Temp, °C	K	Temp, °C	K
32	0.70	44.5	0.31	103	8.3×10^{-3}
34.5	0.89	48.5	0.40	109	1.25×10^{-2}
39	1.10	52.5	0.55	120.5	2.8×10^{-2}
50	2.4	61	0.94	127	4.1×10^{-2}
55	2.6	65	1.57	134	7.0×10^{-2}
59	4.0	69	2.1	138	1.0×10^{-1}
65.5	5.5	73.5	2.7	143	1.3×10^{-1}
		81.5	4.5		

Table IV
Chemical Shift Values[a] of the Benzylic Methyl Groups in Each Urea and the Isocyanate at 34°

Compd	δ	Compd	δ
1	1.29	**6**	1.23
2	1.27	**7**	1.24
3	1.26	**8**	1.22
4	1.26	**9**	1.36
5	1.26		

[a] In parts per million upfield from anisole OCH_3.

groups of the isocyanate and the urea were recorded at 100-Hz sweep width and measured with a planimeter. In the case of this particular urea, the concentration of the amine could be measured as well. The *tert*-butyl groups and the methyls of the isopropyl groups were at δ 2.44 and 2.51. The corresponding peaks in the urea were at δ 2.12 and 2.25 ppm upfield from anisole OCH_3.

The equilibrium constants (Table I) were calculated using a correction for the density of anisole at each temperature.[15] The thermodynamic values (Table II) were obtained by a least-squares treatment of log K *vs.* $1/T$. The temperatures could be measured quickly after each equilibration if a very fine sealed capillary of ethylene glycol was placed in the nmr tube with the sample. The ethylene glycol peaks occur in an otherwise clear area of the spectrum.

Urea **6** was prepared similarly, although the pentane solution required cooling for crystallization of the product.

Urea **3** gave no precipitate; so it was prepared by transferring the amine, isocyanate, and anisole with syringes in a glove bag under nitrogen to the nmr tube, weighing after each addition.

Equilibrium constants (Table III) were determined from solutions of each of the above ureas at two different concentrations to check reproducibility.

Ureas **1**, **2**, **5**, **7**, and **8** were measured at only one temperature owing to very slow equilibration, or their dissociating near the upper limit of the usable temperature range. They were each prepared in the nmr tubes as described above for **3**. See Table IV for chemical shift values.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corporation for the support of this research.

Registry No.—**1**, 51608-96-9; **2**, 51608-97-0; **3**, 51608-98-1; **4**, 51608-99-2; **5**, 51609-00-8; **6**, 51609-01-9; **7**, 51609-02-0; **8**, 51609-03-1; **9**, 28556-81-2; di-*sec*-butylamine, 626-23-3; cyclohexyl-3-pentylamine, 51609-04-2; dicyclohexylamine, 101-83-7; *tert*-butylisopropylamine, 7515-80-2; *tert*-butyl-3-pentylamine, 51609-05-3; *tert*-butylcyclohexylamine, 51609-06-4; isopropyl(2,4,4-trimethyl-2-pentyl)amine, 51609-07-5; 2,2,6,6-tetramethylpiperidine, 768-66-1; cyclohexylamine, 108-91-8; 2-butanone, 78-93-3; 2,6-dimethylaniline hydrochloride, 21436-98-6.

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Heterodienophiles. VI.[1] The Structure of Protonated Aldimines

Grant R. Krow,* C. Pyun, C. Leitz, and J. Marakowski
Temple University, Philadelphia, Pennsylvania 19122
Kermit Ramey
ARCO Chemical Company, Glenolden, Pennsylvania 19036

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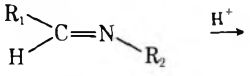
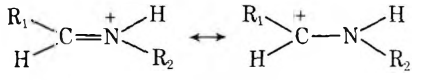
A nuclear magnetic resonance study[2] of protonated aldimines **1–3** with fluorosulfonic acid–antimony pentafluoride in sulfur dioxide solution has indicated a predominance of *E*-immonium structure **I**, with only limited contribution of aminocarbonium ion form **II**. We have extended this study in strongly acidic solution to aldimines having electron-withdrawing *N*-carbamyl, acyl, and *p*-toluenesulfonyl substituents.

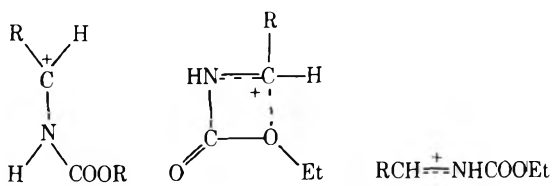


1, $R_1 = Ph; R_2 = CH_3$
2, $R_1 = Ph; R_2 = Ph$
3, $R_1 = Ph; R_2 = Ph\text{-}p\text{-}Cl$



I **II**

A literature survey indicates that reactions of *N*-carbethoxyl imines have been variously described as polar cycloadditions,[3] Diels–Alder reactions,[4] pseudo-Diels–Alder reactions,[5] α-amidoalkylations,[6] or stabilized carbonium ion reactions.[7] The reactive species in these reactions has been depicted as an azacarbonium ion[3] **4**, an



4 **5** **6**

azacarbonium ion stabilized by ester oxygen[8] **5**, a resonance-stabilized carbonium ion[7,9] **6**, an N-protonated *Z*-immonium ion[5] **7**, and a carbonyl-oxygen protonated *E*-iminourethane **9**. One might in addition postulate an *E*-immonium ion **8** similar to **7**, as well as significant contri-

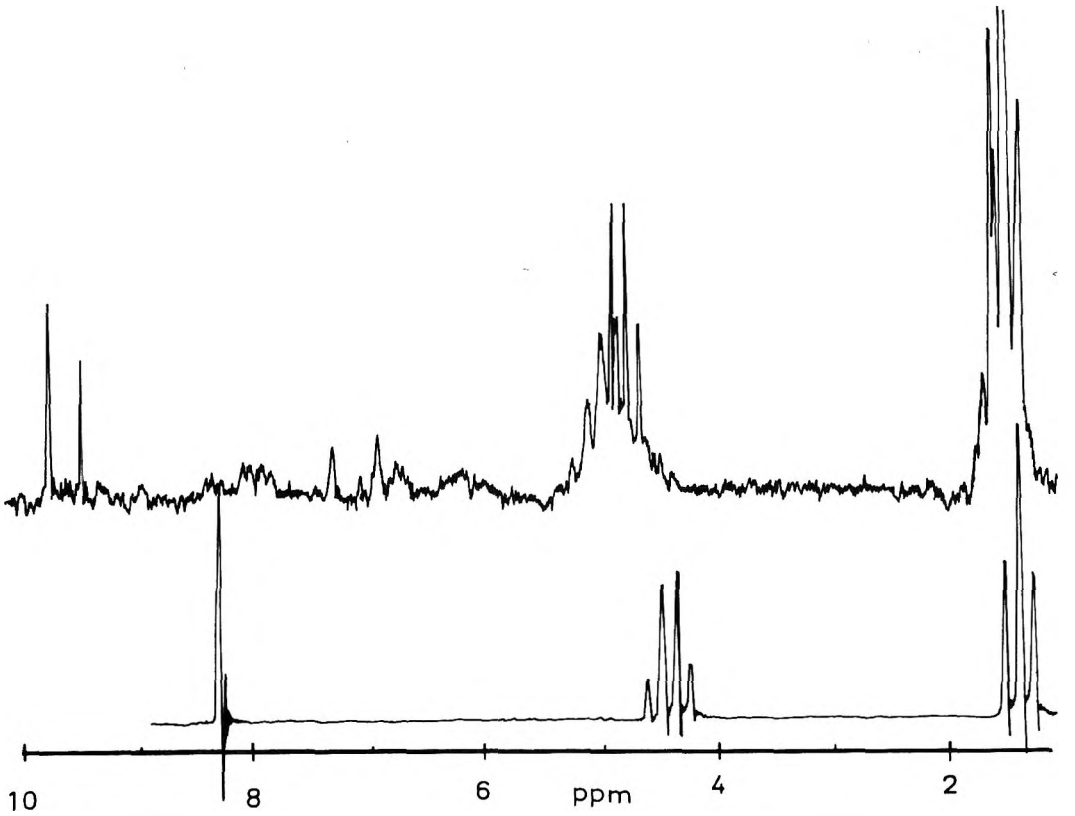
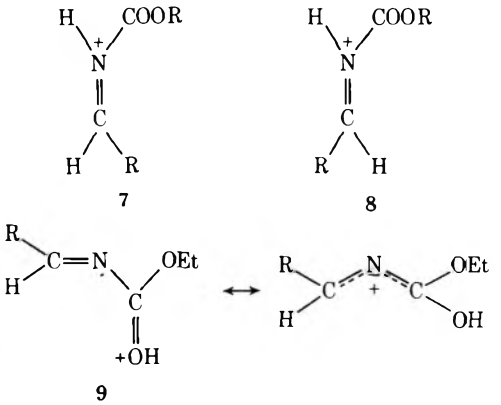


Figure 1. $CCl_3CH{=}NCOOEt$ (SO_2): lower, free imine; upper, SbF_5–$HFSO_3$ added, imine doublet at δ 9.40.

bution from a hydroxyazaallyl cation resonance contributor to **9**. The various structural possibilities for protonated iminocarbamates are associated with differing steric and electronic properties. Accordingly, determination of the site of protonation is crucial if Lewis acid catalyzed heterodienophilic imine cycloadditions are to be understood and best utilized in synthesis.[10]



7 **8**

9

Results and Discussion

The nmr spectral data for the methine hydrogen of trichloromethyl-*N*-carbethoxylimine[11] (**10**) in sulfur dioxide solution at −20° both with and without fluorosulfonic acid–antimony pertafluoride added is shown in Figure 1 and summarized in Table I. The methine proton of **10** appears as a singlet which upon protonation of the imine is shifted downfield δ 1.10 and is split by an NH proton into a doublet, J = 17 Hz.

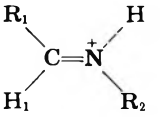
It previously has been noted[2] that the magnitude of trans-coupling constants through a double bond does not change much in isoelectronic molecules; so the nmr coupling data is in best agreement with an *E*-immonium ion structure **8** for protonated imine **10**, rather than with structures **4**, **5**, **7**, or **9**. Although some contribution from structure **6** may be present, the coupling information and the small deshielding observed for the methine hydrogen indicates little charge delocalization away from nitrogen. Consistent with this interpretation, the magnitudes of both the small downfield shift of the methine resonance position upon imine protonation and of the methine to NH proton coupling are similar to those observed for *N*-alkyl and *N*-aryl immonium ion species **1**–**3** (Table I), for which azacarbonium ion structures have been largely precluded.[2]

The preferential N-protonation of iminocarbamate **10** can be contrasted with carbonyl-oxygen protonation of *N*-alkyl carbamates,[12] of α,β-unsaturated aldehydes and ketones,[13] whose conjugate acids are hydroxyallyl cations in nature, and of α,β-unsaturated acids.[14]

E-Immonium ions have also been observed (Table I) upon N-protonation of phenyl-*N*-*p*-toluenesulfonylimine[15a] (**11**), trichloromethyl-*N*-*p*-toluenesulfonylimine[15b] (**12**), and the immonium ions **14**, formed from *N*-benzoyl-α-methoxybenzylamine[16] (**13**), and **17**, formed from benzaldehyde bisurethane[4] (**15**). For all imines studied, the NH proton could not be observed because of broadening due to quadrupole interaction of the nitrogen and contributions of coupling to NH broadening. Failure to observe coupling is not due to rapid exchange, since splitting of the methine proton by the NH proton is observed.[2] Methylenebisurethane[4] **16** failed to eliminate urethane, *N*-hydroxymethylbenzamide[17] failed to dehydrate, and α-methoxy-*N*-phenylhydantoin[18] decomposed in the strongly acidic solutions used; so protonated imines were not observed with these compounds.

The observation of N-protonated immonium ions as the thermodynamically most stable isomeric species[13] suggests a reinterpretation of the reactivity course of Lewis acid catalyzed reactions involving alkylidenebisurethane **15**.[10] Lewis acid decomposition of **15** results in formation of a protonated immonium ion **17**. In the synthesis of bicyclic moieties[10] **18**, using **17** and cyclo-

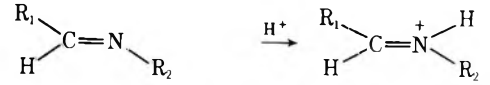
Table I
Nmr Chemical Shifts and Coupling Constants of the Methine Hydrogen (H_1) of Aldimines



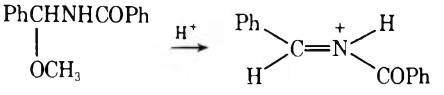
Structure	R_1	R_2	Solvent	Temp, °C	H_1, δ	Protonated[a] H_1, δ	Δδ	J_{H_1-NH}, Hz
1[b]	Ph	Me	$CDCl_3$	−30	7.99			
			SO_2	−30		8.70	−0.71	16.9
2[b]	Ph	Ph	SO_2	−20	8.17			
			SO_2	−40		9.35	−1.18	18
3[b]	Ph	Ph-*p*-Cl	SO_2	−30	8.32			
			SO_2	−30		9.27	−0.95	17.2
10	CCl_3	CO_2Et	SO_2	−20	8.30			
			SO_2	−20		9.40	−1.10	17
11	Ph	SO_2Ph-*p*-Me	SO_2	−20	8.80			
			SO_2	−20		9.34	−0.54	17
12	CCl_3	SO_2Ph-*p*-Me	SO_2	−20	8.25			
			SO_2	−20		9.40	−1.15	17
14	Ph	COPh	SO_2	−20		9.83		17
17	Ph	CO_2Et	SO_2	−20		9.05		17

[a] SO_2–HSO_3F–SbF_5. [b] G. Olah and P. Kreienbühl, *J. Amer. Chem. Soc.*, **89**, 4756 (1967).

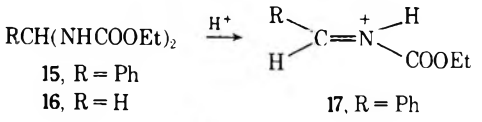
hexa-1,3-diene,exo-*R* stereoselectivity was observed to be a function of solvent and Lewis acid catalyst. Although



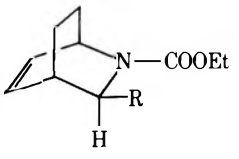
10, $R_1 = CCl_3$; $R_2 = COOEt$
11, $R_1 = Ph$; $R_2 = SO_2Ph$-*p*-CH_3
12, $R_1 = CCl_3$; $R_2 = SO_2Ph$-*p*-CH_3



13 **14**



15, R = Ph
16, R = H
17, R = Ph



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stereochemical differences could be rationalized by assuming carbonyl-oxygen Lewis acid coordinated imines as reactive species, it now appears likely that N-protonated imines are formed in the decomposition of alkylidenebisurethanes regardless of the Lewis acid employed. N-Coordination of a wide variety of sterically different Lewis acid catalysts would certainly have been expected to result in wider stereochemical variation than the 73–91% range in exo-phenyl selectivity observed.[10] Stereochemical differences are more likely the result of temperature, solvent polarity, and medium acidity effects. Preliminary studies of Lewis acid effects on the stereochemistry of cycloadditions with independently synthesized imines are in progress to confirm this suggestion.

Experimental Section

Trichloromethyl-*N*-carbethoxy-,[11] trichloromethyl-*N*-*p*-toluenesulfonyl-,[15b] and phenyl-*N*-*p*-toluenesulfonylimine[15a] were synthesized according to literature procedures, as were *N*-benzoyl-α-methoxybenzylamine,[16] *N*-hydroxymethylbenzamide,[17] methylenebisurethane,[4] benzalbisurethane,[4] and α-methoxy-*N*-phenylhydantoin.[18]

Protonation of Imines. The samples were prepared by condensing SO_2 directly into an nmr tube containing the sample *via* liquid nitrogen. Acidification took place by the addition of small amounts of FSO_3H–SbF_5 accompanied by vigorous stirring as the sample was warmed to −20°.

Nmr spectra. Spectra were obtained using a Varian A-60 spectrometer equipped with V-6040 variable-temperature probe and accessories. Temperatures were measured using the methanol standard supplied by Varian. The Van Geet[19] correction was incorporated.

Acknowledgment. This investigation was supported by Public Health Service Research Grant CA-12020.

Registry No.—**1**, 25521-74-8; **2**, 1750-36-3; **3**, 1613-89-4; **10**, 51608-59-4; **11**, 51608-60-7; **12**, 51608-61-8; **14**, 51608-62-9; **17**, 51608-63-0.

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Rates of Protonation of Aromatic Radical Anions in Dimethyl Sulfoxide

Albert J Fry* and Alexander Schuettenberg

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

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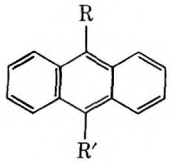
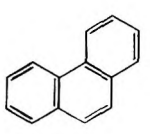
The electrochemical behavior of aromatic hydrocarbons has been the subject of a large number of investigations.[1] In aprotic solvents, two polarographic waves are observed, associated with initial reduction of the hydrocarbon to the corresponding radical anion and subsequent reduction of this to the dianion, at potentials E_1 and E_2, respectively. When increasing amounts of a proton source, *e.g.*, phenol, are added, the first wave grows at the expense of the second, the total height remaining constant, until a point is reached where one merely observes a single two-electron wave. It is now generally accepted that this response to added proton donors is associated with the fact that protonation of the initially formed radical anion (ArH·) forms a neutral radical (ArH_2·) which is *easier* to reduce than the starting hydrocarbon, and hence immediately accepts a second electron.[1] These features are summarized in Scheme I, where E_3 is positive of E_1. Although some exceptions have been noted, *e.g.*, where ArH_2· dimerizes at a rate competitive with its reduction, or where the dihydroaromatic ArH_3 is itself reducible, this so-called "ECE" behavior is exhibited by a surprisingly large number of aromatic hydrocarbons.[1] A model for studies of this type is the behavior of 9,10-diphenylanthracene (**1e**) in dimethylformamide (DMF), reported by Santhanam and Bard.[2] Figure 1 illustrates the observed behavior. The solid and dotted lines represent the polarographic behavior of **1e** before and after addition of a 50-fold excess of phenol.

The solvents most often employed in such studies have been DMF, acetonitrile, and 96% dioxane. Dimethyl sulfoxide (DMSO) seems, however, to have been used only infrequently.[3] In the course of experiments designed to explore the electrochemical behavior of *trans*-15,16-dimethyldihydropyrene[4] and cyclooctatetraene[5] in DMSO, we had occasion to examine the polarographic response of **1e** to proton donors in DMSO. We were surprised to observe that addition of 30-fold excess of 2,4,5-trimethyphenol (TMP)[6] to the solution resulted in a negligible increase (<2%) in the height of the first wave of **1**, in contrast to the marked increase noted in DMF.[2] Anthracene (**1a**), on the other hand, behaved much as expected, although the first wave did not appear to grow as rapidly as has been



1a, R = R′ = H
b, R = CH_3; R′ = H
c, R = C_6H_5; R′ = H
d, R = R′ = CH_3
e, R = R′ = C_6H_5



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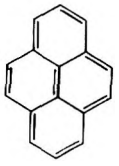

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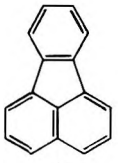

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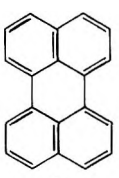

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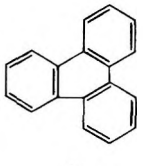

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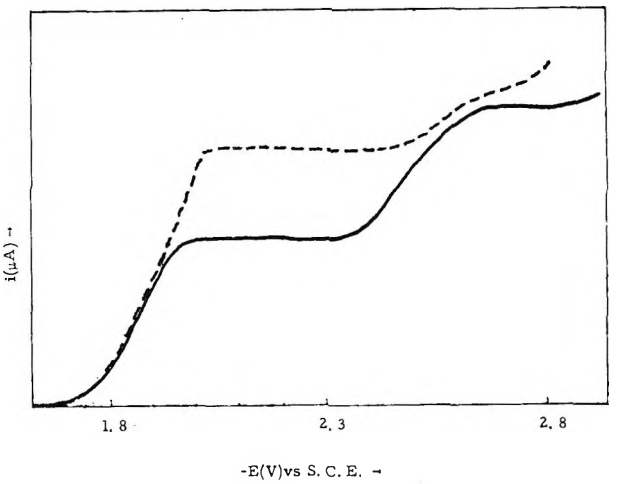

Figure 1. Solid line: polarographic behavior of 9,10-diphenylanthracene (1 m*M*) in dimethylformamide containing tetrabutylammonium iodide (0.1 *M*). Dashed line: same, with 50 m*M* phenol added. From K. S. V. Santhanam and A. J. Bard, *J. Amer. Chem. Soc.*, 88, 2669 (1966).

Scheme I

$$ArH \xrightarrow[E_1]{e} ArH\cdot^- \xrightarrow[E_2]{e} ArH^{2-} \rightarrow\rightarrow ArH_3$$

$$ArH\cdot^- \xrightarrow{k_p,\ HX} ArH_2\cdot \xrightarrow[E_3]{e} ArH_2^- \xrightarrow{HX} ArH_3$$

reported for anthracene in DMF.[7] In order to understand this phenomenon better, the response of the polarographic behavior of a number of hydrocarbons to added proton donors in DMSO was then examined. Most hydrocarbons were examined in the presence of TMP; with others, phenol, resorcinol, or 9-phenylfluorene were also used as proton donors. 9-Phenylfluorene (9-PF) was selected because its pK_a in DMSO (16.4) is exactly the same as that of phenol,[8] thus permitting comparison of the relative effectiveness of a carbon acid *vs.* oxygen acid in protonation of aromatic radical anions. Comparisons of the relative efficiency of various radical anions by the same proton donor, or of a given radical anion by different proton donors, were made using measured values of k_p, the bimolecular rate constant for protonation (Scheme I). Values of k_p were estimated using polarographic theory for the ECE process as developed by Nicholson and coworkers.[9] Values of k_p could also be calculated by the method of Mark and Janata,[10] but these values were generally two or more orders of magnitude higher than those computed by the Nicholson procedure. This is presumably because of certain approximations involved in the computational method, based upon reaction-layer theory, used by Mark.[10] It is now recognized that numerical procedures, such as that used by Nicholson,[9] are more valid than reaction-layer theory for such calculations[11] and indeed more recent work by Mark has been based upon the Nicholson procedure.[3] Table I tabulates values of (a) i_k/i_d, the ratio of currents for the first polarographic curve in the presence and absence of added proton donors, respectively; (b) protonation rate constants, k_p, calculated using measured polarographic drop times, the concentration of added proton donor, and a working curve constructed from data computed by Nicholson and coworkers;[9] and (c) for some hydrocarbons, electron densities at the carbon of highest electron density in the radical anion, as computed by simple Hückel MO theory. Some data for DMF taken from the literature are shown in Table II for comparison purposes. Because some measurements were made at the ends of the working curve, the data must be regarded as

Table I
Polarographic Response of Hydrocarbons to Added Proton Donors

Hydrocarbon[a]	Proton donor[b]	i_k/i_d[c]	k_p, M^{-1} sec^{-1}	Electron density[g]
COT[d]	TMP	1.7	~3000	0.125
2	TMP	1.5	~900	0.17
3	TMP	1.2	130	0.14
1a	TMP	1.1	75	0.19
4	TMP	1.0[e]	≤1	0.12
5	TMP	1.0[e]	≤1	0.11
6	TMP	1.3	400	0.06
7	TMP	1.4	630	0.06
1b	TMP	1.1	80	
1c	TMP	1.1	75	
1d	TMP	1.2	125	
1e	TMP	1.0[e]	≤1	
1a	Resorcinol[f]	1.4	250	
1a	9-PF	1.03	22	
3	9-PF	1.03	23	

[a] Proton donor concentrations 1 m*M*; hydrocarbon concentration 0.5–1 m*M*. [b] 1 m*M*; TMP = 2,4,5-trimethylphenol; 9-PF = 9-phenylfluorene. [c] Defined as in ref 9. [d] COT = cyclooctatetraene. [e] $i_k = (0.97 \pm 0.02)i_d$ for these compounds. This may be an electrocapillary effect of phenol. [f] 2.8 m*M*. [g] A. Streitweiser and J. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Pergamon Press, Oxford, 1965.

Table II
Solvent and Proton Donor Effects upon Protonation Rates

Hydrocarbon	Proton donor	k_p, M^{-1} sec^{-1} DMSO	DMF
1a	2,4,5-Trimethylphenol	75	
	Phenol		390[a]
	Resorcinol	250	1300[b]
	9-Phenylfluorene	22	
1e	2,4,5-Trimethylphenol	<1	
	Phenol		30[c]
3	2,4,5-Trimethylphenol	130	
	9-Phenylfluorene	23	

[a] Computed from data in ref 1c, p 137. [b] Reference 10. [c] Reference 2.

approximate, but the trends evident in the data are clear enough for qualitative interpretations to be made.

Several comments may be made upon the data in Table I. With the exception of coronene (**6**) and triphenylene (**7**), there is a rough correlation between the protonation rate and the electron density at the position of highest electron density (presumably the site of protonation) in the radical anion. The correlation is qualitatively reasonable, but in view of the simplified nature of the MO calculations employed, and the neglect of steric and other factors, one would probably not expect agreement any better than that observed. The qualitative correlation between protonation rates and electron densities revealed by the data is probably real and not fortuitous, however. A similar correlation has in fact been observed between reaction rates of aromatic radical cations and the extent of charge dispersal in the radical cation.[12] In that study it was noted that two types of radical cations tend to react relatively slowly toward nucleophiles: (a) those with highly dispersed charge and (b) those in which the reactive sites of a ring system with a substantial degree of charge localization happen to bear blocking groups. Thus, the anthracene (**1a**) radical cation is very reactive toward nucleophiles, since the positive charge is localized largely on atoms 9 and 10, while the perylene (**5**) radical cation is much less reactive because the charge is spread rather evenly over the whole system. The radical cation of **1e** is also relatively stable because of the presence of the two phenyl groups.[12] The same generalizations seem to be true for the radical anions listed in Table I. The low reactivity of **1e** is apparently associated with an electronic effect (rather than steric) since **1a–d** all react rather rapidly with added proton donors. It appears that the radical anions of COT, **6**, and **7** are protonated at rates considerably higher than would have been anticipated from electron densities. This could be because the apparent correlation for the other compounds is not real, or because the two compounds may be deviating because of some other effect. In this connection, it may be noted that in all three substances the unpaired electron in the radical anion enters either of a pair of degenerate molecular orbitals. A number of such species, including in fact the radical anions of **6** and **7**, have been found previously to exhibit a range of anomalous properties.[13]

Mark and coworkers have examined the polarographic behavior of **4** in DMF.[14] They reported that the first wave does not increase in height upon addition of proton donors, but that the wave does shift toward more positive potentials. They concluded that the radical anion is protonated under these conditions, and that the resulting radical undergoes a rapid following chemical reaction rather than reduction. This cannot be true for **4** in DMSO. The half-wave potential, height, and log-plot slope of the first wave are all unchanged upon addition of TMP (the second wave does grow and move to more positive potentials), and furthermore, the reversible couple observed for **4** by cyclic voltammetry (100 mV/sec) at a platinum electrode is unchanged upon addition of TMP. In DMSO, therefore, the radical anion of **4** is not protonated on the voltammetric time scale.

Rates of protonation by the carbon acid 9-phenylfluorene (9-PF) can be seen to be slower than by the oxygen acids of similar pK_a (phenols). The data also demonstrate a difference between kinetic and thermodynamic acidities for several substances. For example, 2,4,5-trimethylphenol must have a higher pK_a than 9-PF in DMSO;[15] yet it protonates the radical anions of **1a** and **3** *faster* than does the latter. A similar contrast may be noted between data taken in DMF *vs.* that in DMSO. Most acids,[16] including phenol,[17] have smaller pK_a's in DMSO than in DMF, yet proton transfers to radical anions can be seen (Table II) to be higher in DMF than in DMSO.

It was noted at the outset that while Scheme I accounts for the polarographic behavior of a large number of hydrocarbons, occasional exceptions are encountered. Two such cases were observed in this study. The first wave for phenanthrene (**2**) does increase in height with added TMP, but simultaneously a new wave appears between the original two. As has been pointed out previously, this behavior appears to be associated with dimerization of the radical $ArH_2\cdot$ (Scheme I) at a rate competitive with reduction, followed by reduction of the dimer.[1a,b] The reduced dimer has in fact been obtained from a preparative-scale electrolytic reduction of phenanthrene in DMF.[19] The behavior of 9,10-dimethylanthracene (**1d**) is harder to explain. All of the other anthracenes studied exhibited the usual increase in height of the first wave, at the expense of the second, with added TMP; even **1e** exhibited this behavior in the presence of the stronger acid, benzoic acid, or of large excesses of TMP. In contrast, *both* waves of **1d** increased with added proton donor. This may be because (unlike anthracene itself) the radical anion of **1d** is protonated partly at positions other than 9 or 10 as a consequence of the electronic and steric effects of the two methyl groups. If this occurred, the resulting material, a 2,3-dihydroanthracene, would be expected to be reducible further.

Experimental Section

Polarographic and cyclic voltammetric measurements were carried out with the aid of a Princeton Applied Research Model 170 electrochemical instrument. Polarograms were measured in the conventional manner before and after addition of known amounts of proton donor.

Cyclooctatetraene was purified by vacuum distillation under nitrogen. Purity of the other hydrocarbons was assessed by thin layer chromatography. If more than one spot was observed, the hydrocarbon was purified by column chromatography, sublimation, and/or recrystallization. Dimethyl sulfoxide (Matheson Coleman and Bell) was used as received. Tetrabutylammonium perchlorate (Southwestern Analytical Labs), the supporting electrolyte, was dried in an Abderhalden drying pistol.

Acknowledgment. Financial support was provided by the National Science Foundation. The Uniroyal Corp. provided a summer research assistantship for A. S. Miss Ling Ling Chung made the initial observations upon 9,10-diphenylanthracene and anthracene which led to this study.

Registry No.—**1a**, 120-12-7; **1b**, 779-02-2; **1c**, 602-55-1; **1d**, 781-43-1; **1e**, 1499-10-1; **2**, 85-01-8; **3**, 129-00-0; **4**, 206-44-0; **5**, 198-55-0; **6**, 191-07-1; **7**, 217-59-4; COT, 629-20-9.

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Preparation of Some Thiovulpinic Acids

Joseph Weinstock,* Judith E. Blank, and Blaine M. Sutton

Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

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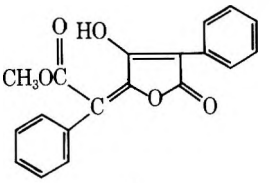
Recent findings of anti-inflammatory activity in the vulpinic acid series[1] prompted us to undertake the investigation of some thio analogs of this interesting series of lichen metabolites.[2] One thio analog of vulpinic acid (**1**) is the thiol ester **2**. Since the dilactone **3** is converted to **1** by



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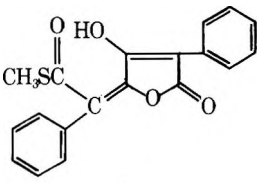

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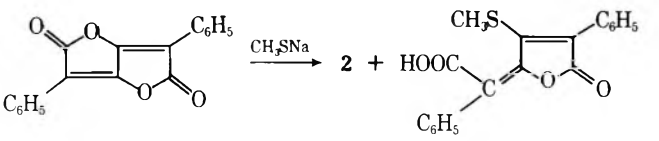
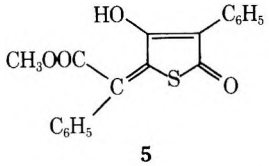
reaction with sodium methoxide,[2] the reaction of **3** with the sodium salt of methyl mercaptan was studied. Two products were isolated from this reaction in about 50% yield each, both of which analyzed for the expected product.



3 **4**

The structure of **2** was established by comparison of its nmr and mass spectra with that of **1**. Both **1** and **2** have very similar characteristic aromatic proton peaks at δ 7.4 (8 protons) and 8.2 (2 protons) and enolic protons at δ 13.8 and 13.65, respectively. The latter indicate chelate-type hydrogen bonding between the enol and the ester carbonyl, and provide strong evidence for the stereochemistry about the exocyclic double bond. The mass spectra of both **1** and **2** show molecular ion peaks, and also strong peaks at *m/e* 290 corresponding to the *m/e* for **3** formed by the primary elimination of the elements of methanol and methyl mercaptan, respectively.[3] The nmr of **4** showed a one-proton peak at δ 10.90 characteristic of a carboxylic acid, and the mass spectrum, in addition to the molecular ion peak, showed a strong peak at *m/e* 294 which is consistent with the loss of CO_2 from the molecular ion. Only a weak peak at *m/e* 290 was present.

Another thiovulpinic acid is **5**, in which the lactone is replaced by a thiolactone. Since, as shown above, sulfur anions can displace the ring oxygen of **3**, we attempted to prepare **6**, which could conceivably be converted to **5** *via* the monothiodilactone **7** by processes analogous to those used for the preparation of **1**. However, although reaction of **3** with hydrogen sulfide in the presence of sodium methoxide gave a base-soluble product, on attempted recrystallization from methanol of the crude product obtained by acidification of the basic solution, only **3** was isolated. This suggested that **3** was opened to give the



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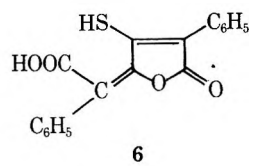

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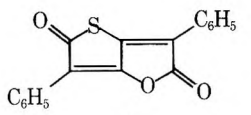

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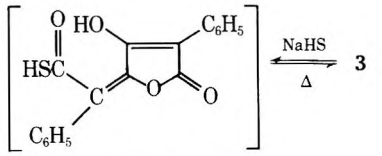
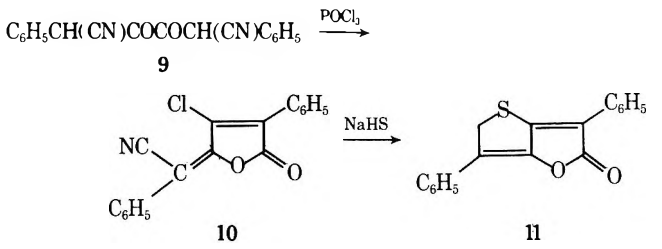


8

thiol acid 8, which behaves like a mixed anhydride to thermally re-form 3.

In another approach to 6, we repeated (and confirmed) the 1894 preparation[4] of 10 from 9. We hoped to react 10 with sodium hydrosulfide in order to displace the chlorine with a mercaptan. Reaction of 10 with H_2S and sodium methoxide gave a single product in 85% yield which has been assigned the structure 11. Thus the mass spectrum



had a molecular ion at m/e 292 containing (by isotope ratios) only one sulfur, the nmr showed as the only nonaromatic protons a single two-proton peak at δ 4.6, and the elemental analysis (C, H, S) was correct for $C_{18}H_{12}SO_2$. Apparently sulfur did displace the chlorine either before or after reaction with the nitrile. The resultant bicyclic product presumably was reduced by the excess hydrogen sulfide to the observed product. The reducing properties of H_2S and its conjugate anions are well known.[5]

The successful preparation of 7 was suggested by the report[6] that thiolacetic acid and pyridine convert certain simple butenolides to the corresponding thiolactones. Treatment of 3 with 1 mol of thiolacetic acid and pyridine in chloroform gave the desired monothiolactone 7; excess thiolacetic acid gave the dithiolactone 12. A rationalization of this reaction may be that thiolacetate attacks 3 to give both 13 and 14 in a manner similar to the reaction of 3 with methylmercaptide ion. Since 13 is able to revert readily to 3 by loss of thioacetate, no net reaction results. However, 14 is unable to re-form 3 readily, and the carboxylate anion can be acylated either by the adjacent thioacyl group or by thiolacetic acid. The mixed anhydride 15 now can form 7 by a sterically favored cyclization.

Reaction of 7 with methanolic sodium methoxide gave the desired thiovulpinic acid 5. The thiolactone structure for 5 was suggested by the presence of carbonyl peaks in the ir at 5.94 and 6.03 μ and the absence of a strong peak near 5.65 μ characteristic of vulpinic acids due to the lactone carbonyl. The cis relationship of the ester and enol is most clearly indicated by the chelated OH peak in the nmr at δ 13.97. Prolonged refluxing of 5 during attempted recrystallization from methanol or melting at 110° converted 5 back to 7. Lactonization of 1 to give 3 is not observed under such mild conditions; so the presence of sulfur in the thiolactone ring greatly increases the rate of ring formation of the adjacent five-membered ring, possibly because the larger size of sulfur in comparison to oxygen decreases strain energy. Treatment of 12 with sodium methoxide formed a soluble salt, presumably 16, but acidification even at 0° caused recyclization to 12. Presumably ring formation is aided by the low strain energy of two thiolactone rings and the nucleophilicity of the mercapto group.

Experimental Section

Melting points (uncorrected) were determined using a Thomas-Hoover capillary melting point apparatus. Mass spectra were determined using a Hitachi Perkin-Elmer RMN-6E spectrometer. Nmr spectra were obtained on a Varian T-60 instrument, and ir on a Perkin-Elmer 137 Infracord.

Thiolpulvinic Acid Methyl Ester (2) and 2,5-Diphenyl-4-hydroxy-3-methylthio-2,4-hexadienedioic Acid γ-Lactone (4). Pulvinic acid lactone (16.0 g, 0.055 mol) was added to a suspension of 2.88 g (0.06 mol) of 50% sodium hydride in oil in 100 ml of glyme. Methyl mercaptan was bubbled through the solution until a clear brown solution was obtained and tlc indicated that no dilactone remained. The reaction mixture was diluted with about 400 ml of water and extracted with ether, and the aqueous layer was acidified with hydrochloric acid to give an oily solid. Recrystallization from acetone–water gave 7.0 g (37%) of 2 as orange needles, mp 156–158°. A second recrystallization from the same solvent mixture gave 3.87 g of orange needles: mp 165–168°; ir (Nujol) 4.3 (broad, chelate OH), 5.65, 6.20, 6.30 μ; nmr ($CDCl_3$) δ 2.36 (s, 3, SCH_3), 7.40 (m, 8 H, 3′-, 4′-, 5′-, 2-, 3-, 4-, 5-, 6-phenyl H), 8.14 (m, 2 H, 2′-, 6′-phenyl H), 13.65 (s, 1, OH); mass spectrum m/e 338 (M^+), 290 ($M^+ - CH_3SH$), 263 ($M^+ - COSCH_3$), 235, 207, 178, 145.

Anal. Calcd for $C_{19}H_{14}O_4S$: C, 67.44; H, 4.17; S, 9.48. Found: C, 67.53; H, 4.30; S, 9.28.

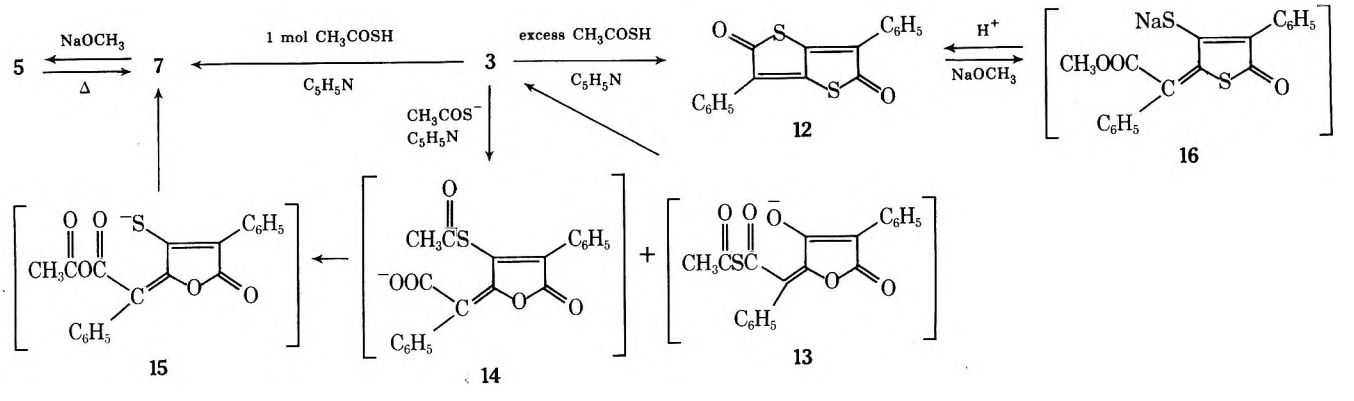
Evaporation of the mother liquor of the first crystallization above gave a red oil which on drying under vacuum and trituration with cyclohexane gave 5.0 g of a yellow solid. Recrystallization from benzene gave 1.4 g of 4 as yellow needles: mp 166.5–167°; ir (Nujol) 5.7 and 6.0 μ; nmr ($CDCl_3$) δ 2.08 (s, 3, SCH_3), 7.55 (m, 10, phenyl H), 10.90 (s, 1, OH); mass spectrum m/e 338 (M^+), 294 ($M^+ - CO_2$), 290, 279, 148 ($C_6H_5C{=}CSCH_3^+$).

Anal. Calcd for $C_{19}H_{14}O_4S$: C, 67.44; H, 4.17; S, 9.48. Found: C, 67.53; H, 4.25; S, 9.38.

3,6-Diphenyl-2*H*,5*H*-thieno[3.2-*b*]furan-2-one (11). A suspension of 0.174 g (0.00325 mol) of sodium methoxide in 20 ml of dry glyme was saturated with hydrogen sulfide gas and a slurry of 1.0 g (0.00325 mol) of 4-chloropulvinonitrile in glyme was added in portions. After 1 hr a yellow solid had formed. The reaction mixture was diluted with water and the solid was collected by filtration and washed with water to give 0.85 g (90%) of brown-yellow needles. Recrystallization from methanol–chloroform and then chlorobutane gave golden needles: mp 208.5–210° dec; ir (Nujol) 5.8 μ; nmr ($CDCl_3$) δ 4.56 (s, 2, CH_2S), 7.37 (m, 6, phenyl H), 7.76 (m, 4, phenyl H); mass spectrum m/e 292 (M^+, isotope peak indicates 1 S), 291, 263, 247, 235.

Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14; S, 10.97. Found: C, 73.89; H, 3.96; S, 10.78.

3,6-Diphenyl-2*H*,5*H*-thieno[3,2-*b*]furan-2,5-dione (7). A mixture of 2.90 g (0.01 mol) of pulvinic acid lactone, 0.76 g (0.01 mol) of thiolacetic acid, and 1.01 g (0.01 mol) of triethylamine in 15 ml of dry pyridine was stirred at room temperature for 30 min. The reaction mixture was chilled, diluted with water, and acidified to give red crystals which were recrystallized from chlorobutane. Since previous experience indicated that this product, although mostly the desired 7, was contaminated with both pulvinic acid



lactone 3 and the dithiolactone 12, it was dissolved in methanolic sodium methoxide, cooled, diluted with water, and acidified. The crude 5 thus obtained was dissolved in 5% sodium carbonate, the insoluble fraction was removed by filtration, and the solution was extracted with ether. Acidification gave pure 5, which was dissolved in 50 ml of methanol and refluxed for 35 min to give 1.5 g of 7 as long yellow needles: mp 175–176.5°; ir (Nujol) 5.6, 5.9, 6.2 μ; nmr ($CDCl_3$) δ 7.30 (m, 6, phenyl H), 7.80 (m, 4, phenyl H); mass spectrum m/e 306 (M^+), 278, 250.

Anal. Calcd for $C_{18}H_{10}O_3S$: C, 70.57; H, 3.29; S, 10.47. Found: C, 70.89; H, 3.41; S, 10.23.

5-Carbomethoxy-2,5-diphenyl-3-hydroxy-4-mercapto-2,4-pentadienoic Acid γ-Thiolactone (*E*) (5). A solution of 1.6 g (0.00523 mol) of 7 and 1.6 g (0.03 mol) of sodium methoxide in 35 ml of methanol was kept at 0–5° for 30 min. The solution was treated with charcoal and diluted with water, and the chilled solution was acidified with HCl to give a yellow solid. This was dissolved in about 200 ml of 5% Na_2CO_3 and extracted twice with ether, and the aqueous layer was acidified in the cold with acetic acid to give 1.50 g (84%) of a yellow-orange, flocculent solid: mp 115–116° (resolidified and remelted at 173–175°); ir (Nujol) broad peak at 3.9–4.4 (chelated OH), 5.94 and 6.03 μ; nmr ($CDCl_3$) δ 3.76 (s, 3, OCH_3), 7.31 (m, 8, phenyl H), 7.72 (m, 2, phenyl H), 13.97 (br s, 1, OH); mass spectrum m/e 338 (M^+), 306 ($M^+ - CH_3OH$), 278.

Anal. Calcd for $C_{19}H_{14}O_4S$: C, 67.44; H, 4.17; S, 9.48. Found: C, 67.74; H, 4.29; S, 9.19.

3,6-Diphenyl-2*H*,5*H*-thieno[3,2-*b*]thiophene-2,5-dione (12). A mixture of 5.0 g (0.0172 mol) of pulvinic acid lactone, 4 ml of thiolacetic acid, 8 ml of chloroform, and 22 ml of dry pyridine was refluxed for 3 hr. Then another 4 ml of thiolacetic acid was added, the refluxing was continued for an additional 1 hr, and the reaction mixture was allowed to stand at room temperature for 18 hr. This gave 0.90 g (16%) of an orange solid, mp 219–221.5°. For purification this was dissolved in warm methanolic sodium methoxide to give a red solution. The chilled solution was diluted with water and acidified to give a yellow solid, which was slurried with sodium carbonate and washed with water to give 0.65 of a yellow solid: mp 221–222.5° dec; ir 5.9 μ; mass spectrum m/e 322 (M^+).

Anal. Calcd for $C_{18}H_{10}O_2S_2$: C, 67.06; H, 3.13; S, 19.89. Found: C, 67.08; H, 3.32; S, 19.55.

Acknowledgments. We are indebted to our Analytical and Physical Chemistry Section personnel for analytical and physical data: Miss Edith Reich for elemental analysis and Dr. Edward White and Mr. Gerald Roberts for mass spectra.

Registry No.—2, 51751-95-2; 3, 6273-79-6; 4, 51751-96-3; 5, 51751-97-4; 7, 51751-98-5; 10, 51751-99-6; 11, 51751-00-2; 12, 51751-01-3.

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An Improved Synthesis of Tetrathiafulvalene

L. Russell Melby,* Harris D. Hartzler, and William A. Sheppard

Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898[1]

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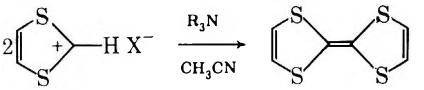
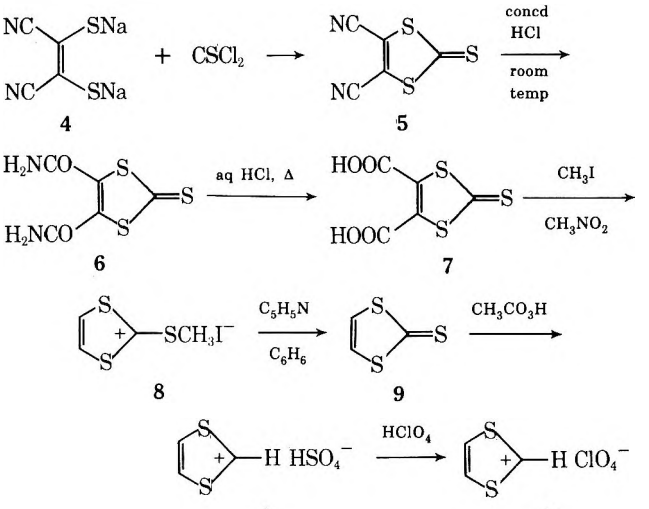
The phenomenon of metallic electrical conductivity in the complex of tetrathiafulvalene (TTF, 3) with tetracyanoquinodimethane has recently been a subject of intense interest.[2-4] Extensive physical study of this complex depends, among other things, upon a reliable source of TTF, which must be unusually pure.[5] In our hands existing routes to TTF proved to be tedious and difficult to reproduce, and often gave product of dubious or unsatisfactory purity. We now report an improved synthesis of TTF.

Typical preparative procedures for TTF ultimately rely on coupling the 1,3-dithiolium hydrogen sulfate (1) or perchlorate (2)[2,6-8] with a tertiary amine, the thiolium salts



1, X = HSO_4^-
2, X = ClO_4^-

being obtained by the method of Klingsberg.[9] The latter entails the multistep sequence depicted in transformations 4 through 9.



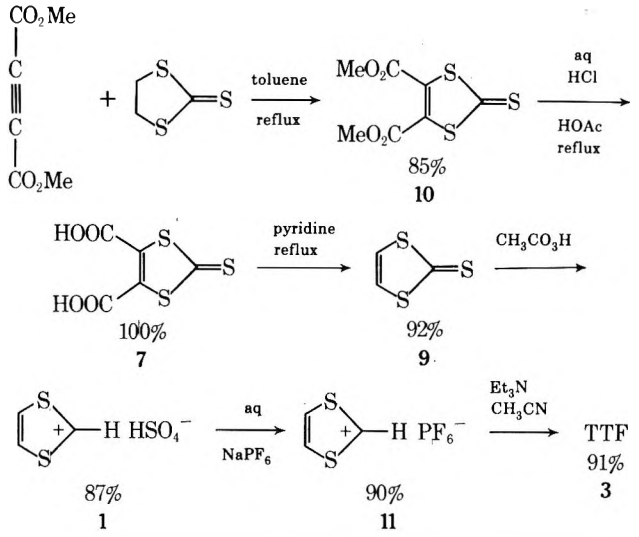
In this sequence we encountered particular difficulty in obtaining reasonable yields of thione 9 by demethylation of the methiodide 8. This in turn complicated preparing pure hydrogen sulfate 1. Furthermore, although the hydrogen sulfate can be directly coupled to TTF without conversion to an intervening salt form, the fact that it is hygroscopic and difficult to purify seriously compromises its use as a coupling substrate. The hydrogen sulfate can be readily converted to very pure perchlorate 2, which is chemically satisfactory for coupling, but which entails a serious explosion hazard particularly if large quantities are to be used.

Our improved procedure begins with the diester 10 prepared according to the directions of O'Connor and Jones.[10]

By this means we have reproducibly obtained recrystallized TTF of very high purity in 65% yields based on diester 10, or 55% overall yields based on commercially available dimethyl acetylenedicarboxylate and ethylene trithiocarbonate; the yields cited are reproducible to within ±2%.

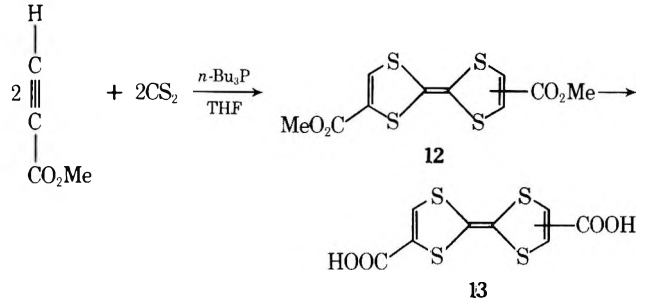
In addition to high yields, the main points of advantage and novelty in this sequence are (1) a simplified route to diacid 7, (2) direct decarboxylation of the diacid to thione 9 in high yield and purity and consequent improved accessibility of the hydrogen sulfate 1, (3) formation of analytically pure PF_6^- salt 11, which is an ideal coupling substrate both with respect to the chemistry of coupling and safety of handling even on a large scale.[11]

For spectral studies we also required highly deuterated TTF. By hydrolyzing the ester 10 with a mixture of DCl and DOAc in D_2O (from acetyl chloride and D_2O), and

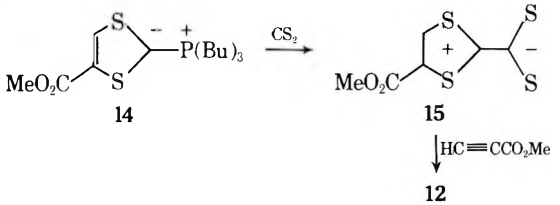


continuing the series as above, we obtained TTF deuterated to the extent of 96% and in 64% yield based on the diester.

In examining other routes to TTF it was found that 4,4′(5′)-bis(carbomethoxy)-$\Delta^{2,2'}$-bi-1,3-dithiole (12) was formed in modest yield by the reaction of methyl propiolate, tributylphosphine, and carbon disulfide in tetrahydrofuran (THF) at −30°. Alkaline hydrolysis of the diester and decarboxylation of the resulting diacid (13) afforded TTF in 13% overall yield based on methyl propiolate.



The formation of the diester 12 is somewhat difficult to rationalize, but is presumably mediated by the phosphorane 14;[12] if the latter were a sufficiently potent nucleophile it could attack carbon disulfide to form an intermediate of type 15 which could further react with methyl propiolate.



Experimental Section

Dimethyl 1,3-Dithiole-2-thione-4,5-dicarboxylate (10).[10] The reaction of dimethyl acetylenedicarboxylate with ethylene trithiocarbonate in refluxing toluene was conducted on a 5-mol scale. After refluxing for a minimum of 6 hr the solution was chilled and the first crop was collected, yield 742 g (59%), mp 86–87° (lit.[10] mp 72–72.5). Successive concentration of the liquors gave additional crops of material which was less pure, but adequate for subsequent hydrolysis. Combined total yields amounted to 80–85%, nmr (DMSO-d_6) δ 3.83.

1,3-Dithiole-2-thione-4,5-dicarboxylic Acid (7). A mixture of 100 g (0.4 mol) of the diester **10**, 600 ml of water, 430 ml of concentrated hydrochloric acid, and 200 ml of glacial acetic acid was boiled under reflux for 2 hr and then chilled in an ice bath. The solid was collected without washing, sucked dry under a stream of nitrogen, and dried in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide, yield 72 g (81%), mp 165–167° dec (lit.[9] mp *ca.* 160° dec). The motho. liquor was evaporated to dryness to obtain a second crop, 17 g, mp 164–167°. The combined total yield was quantitative, nmr (DMSO-d_6) δ 15.48.

1,3-Dithiole-2-thione (9). A mixture of 22.2 g (0.1 mol) of the diacid **7** in 100 ml of pyridine was boiled under reflux for 3 hr. The mixture was concentrated to a thick black oil on a vacuum rotary evaporator with gentle heating (40–50°) until the thione began to show as a thin yellow film in the neck of the flask. To the oil was added 500 ml of hexane which was refluxed under nitrogen for 0.5 hr. The hot hexane was decanted into a flask and chilled in a Dry Ice–acetone mixture to obtain the thione as long, yellow, silky needles. The residual oil was subjected to four such extractions to obtain a total of 12.3 g of thione (93% yield), mp 48–49° (lit.[9] mp 50–51°), nmr ($CDCl_3$) δ 7.17.

1,3-Dithiolium Hydrogen Sulfate (1). A solution of 12.7 g (0.095 mol) of thione **9** in 250 ml of acetone was cooled to −50° in a Dry Ice–acetone bath and a solution of 73 g (0.38 mol) of 40% peracetic acid and 150 ml of acetone was added dropwise, with stirring at such a rate that the temperature did not rise above −40° (about 15 min). The cooling bath was removed and, with continued stirring, the mixture was allowed to warm spontaneously. Within 15–20 min the reaction became rapidly exothermic and when the temperature had risen to 15° the cooling bath was immediately replaced. When the temperature had again reached −50° the bath was removed and the mixture was again allowed to warm spontaneously. No further exotherm occurred and when the temperature reached 5–10° the solid was collected, washed with 100 ml of cold acetone, and sucked dry under a nitrogen stream, yield 16.6 g (87%), mp 123–125° dec (lit.[9] mp *ca.* 125° dec).

1,3-Dithiolium Hexafluorophosphate (11). In 200 ml of deaerated water was dissolved 42 g (0.21 mol) of the hydrogen sulfate **1**, Darco was added, and the soluton was filtered through a Celite pad directly into a previously filtered solution of 38 g (0.23 mol) of sodium hexafluorophosphate in 100 ml of water. The flask was flushed with nitrogen, capped, swirled gently, and refrigerated at 5–10° for 4 hr. The white solid was collected, washed with 50 ml of cold water, and sucked dry under a stream of nitrogen, yield 46 g (90%), mp *ca.* 150–200° dec. *Anal.* Calcd for $C_3H_3S_2PF_6$ (248.17): C, 14.5; H, 1.2; S, 25.8. Found: C, 14.8; H, 1.5; S, 25.9.

Tetrathiafulvalene (3). A solution of 45 g (0.18 mol) of the thiolium hexafluorophosphate (**11**) in 800 ml of anhydrous acetonitrile was filtered through a medium-frit funnel directly into a 5-l. flask equipped with a nitrogen inlet, dropping funnel, and magnetic stirrer. After purging with nitrogen for 15 min, 28 ml (0.2 mol) of triethylamine was added dropwise during about 15 min with stirring at room temperature.[13] Stirring was continued for 15 min more and then 3 l. of deaerated water was added to precipitate the TTF as a flocculent, dull orange solid. After 10 min of stirring the solid was collected, washed with water, and sucked dry under a stream of nitrogen. The crude yield was 18.2 g (98%), mp 118–119° (lit.[6] mp 120°). The crude product was dissolved in 1 l. of boiling cyclohexane, treated with Darco, filtered hot, and immediately diluted with 400 ml of *n*-hexane. After cooling overnight at 5–10° the product crystallized as long, orange needles, yield 14.7 g (81% recovery), mp 119–119.5°. The mothor liquor was evaporated under a nitrogen stream to a volume of 150 ml, and the mixture was reheated to dissolve the solid and chilled as before to obtain a second crop, yield 2.1 g, mp 119–119.5°. The total yield was thus 16.8 g (91%), nmr ($CDCl_3$) δ 6.32, ir (Nujol) 1530, 1250, 1090, 795, 780, and 730 cm^{-1}.

Tetrathiafulvalene-d_4. A hydrolysis medium was prepared by carefully adding 100 ml of redistilled acetyl chloride to 280 ml of D_2O contained in a flask with a Dry Ice condenser. Beginning with this mixture and 30 g of diester **10** and carrying each intermediate through the above sequence appropriately scaled, there was obtained 8.0 g (64%) of recrystallized product, mp 119–119.5°. *Anal.* Calcd for $C_6D_4S_4$: C, 34.6; S, 61.6. Found: C, 34.6; S, 61.5.

Mass spectral analysis showed 0% d_0, 0% d_1, 1% d_2, 13% d_3, and 86% d_4 species corresponding to 96% deuterium exchange; ir (Nujol) 2290, 1500, 1160, 1040, 780, and 700 cm^{-1}.

Ordinary reagents were used throughout except for the hexafluorophosphate metathesis, where D_2O was used as the solvent.

4,4′(5′)-Bis(carbomethoxy)-$\Delta^{2,2'}$-bi-1,3-dithiole (12). Tributylphosphine (20.2 g, 0.1 mol) was added dropwise to a solution of 10 ml of carbon disulfide in 50 ml of tetrahydrofuran under nitrogen. The deep maroon solution was cooled to −30° and a solution of 8.4 g (0.1 mol) of methyl propiolate in 50 ml of tetrahydrofuran was added dropwise. The temperature was maintained be-

tween −20 and −30° during addition. The system was warmed to room temperature and volatiles were removed through the rotary evaporator. The residue was stirred with a little ether and filtered to give 3.3 g (21%) of the red, crystalline product which melted at 238–240°. Recrystallization from glyme gave material which melted at 244–245°: ir (Nujol) 3080 (w), 2950 (w), 1720 (s), 1550 (s), 1440 (m), 1250 (s), 1200 (m), 1160 (m), 1050 (m), 940 (m), 830 (m), 820 (m), 765 (m), 730 cm^{-1} (m); uv (CH_2Cl_2) λ 444 nm (ε 2470), 315 (11,000), 302 (10,600) and 290 (sh, 10,000).

Anal. Calcd for $C_{10}H_8O_4S_4$: C, 37.48; H, 2.52; S, 40.03. Found: C, 37.28; H, 2.54; S, 39.88.

$\Delta^{2,2'}$-Bi-1,3-dithiole-4,4'(5')-dicarboxylic Acid (13). A heterogeneous system consisting of 3.2 g (0.01 mol) of the diester, 25 ml of 1 *N* sodium hydroxide, and 100 ml of tetrahydrofuran was heated at reflux for 45 min. The mixture was then homogeneous. It was acidified with 1 *N* hydrochloric acid and filtered to give 2.6 g (89%) of the red, crystalline acid. The acid did not melt under 350°: uv (0.01 *N* NaOH) λ_{max} 407 nm (ε 2570), 313 (13,000), 302 (12,600), 285 (sh); ir (Nujol) 3100–2500 (w), 1660 (s), 1540 (s), 1420 (s), 1290 (s), 1195 (m), 1040 (m), 840 (m), 825 (w), 775 (w), and 730 cm^{-1} (w).

Anal. Calcd for $C_8H_4O_4S_4$: C, 32.9; H, 1.4; S, 43.9. Found: C, 33.0; H, 1.6; S, 43.7.

Tetrathiafulvalene.[14] A mixture of 292 mg of the diacid and 10 ml of pyridine was sealed in a heavy-walled glass tube under vacuum after flushing with argon while freeze–thawing. The tube was heated at 240° for 1.5 hr. The tube was cooled and opened and the solvent was evaporated. The dark residue was extracted twice with 10-ml portions of acetonitrile. The extracts were evaporated and the residue was sublimed at 105° (0.1 Torr) to give 140 mg (69%) of the orange product. The sublimate melted at 114–116°.

Acknowledgment. We are indebted to Eleanor G. Applegate for expert technical assistance.

Registry No.—**1**, 51751-15-6; **3**, 31366-25-3; **3**-d_4, 51751-16-7; **7**, 1008-62-4; **9**, 930-35-8; **10**, 7396-41-0; **11**, 51751-17-8; **12**, 51751-18-9; **13**, 51751-19-0; dimethyl acetylenedicarboxylate, 762-42-5; ethylene trithiocarbonate, 822-38-8; tributylphosphine, 998-40-3.

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(13) When reaction is complete the mixture abruptly changes color from greenish-black to deep amber. If this change is not observed, additional drops of amine are added until it occurs.
(14) We are indebted to Dr. W. R. Hertler for this experiment.

Synthesis of Optically Active Sulfoximines from Optically Active Sulfoxides[1]

Carl R. Johnson,* Robert A. Kirchhoff, and H. Glenn Corkins

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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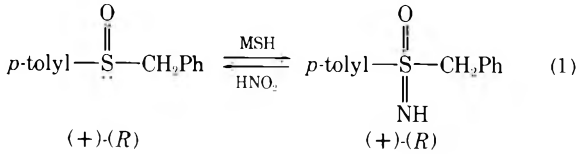
Optically active sulfoximines are useful synthetic intermediates.[2] There are, however, only a few methods available for their preparation. One, involving resolution with (+)-10-camphorsulfonic acid, has been found useful only in the case of *S*-phenyl-*S*-methylsulfoximine.[3a,b] A resolution has been achieved by separation of *N*-(+)-10-camphorsulfonylsulfoximine diastereomers followed by removal of the resolving group by acid hydrolysis.[3c] The reaction of an optically active sulfoxide with tosyl azide in the presence of copper catalyst[4] results in optically pure *N*-tosylsulfoximines.[3b] Hydrolysis with strong acid is required to remove the *N*-tosyl group; the hydrolysis often fails and/or results in extensive decomposition. The direct preparation of optically active "free" sulfoximines using the hydrazoic acid method[5] is not applicable, since racemization of the starting sulfoxide occurs.[3b] This note describes a simple one-step method for the production of optically active sulfoximines in good yield and high enantiomeric purity.

Reaction of *O*-mesitylsulfonylhydroxylamine (MSH) with sulfides and sulfoxides has been reported to produce sulfilimines and sulfoximines, respectively.[6] In exploring the scope of this sulfoximine preparation we have found that the reaction of optically active sulfoxides with MSH results in sulfoximines of high optical purity. Table I shows the various optically active "free" sulfoximines prepared. By the nature of the various sulfoxides shown here and earlier[6] it can be seen that the imidation reaction is quite general.

When 99% pure (+)-(*R*)-methyl *p*-tolyl sulfoxide was treated with MSH, (−)-(*R*)-*S*-methyl-*S*-*p*-tolylsulfoximine was obtained in 98.5% optical purity. Likewise, (−)-(*S*)-methyl phenyl sulfoxide with 94% optical purity was converted to (+)-(*S*)-*S*-methyl-*S*-phenylsulfoximine of 93.5% purity. Since the absolute configurations of these sulfoximines are known[7,8] as well as the absolute configuration of the starting sulfoxides,[9,10] it can be stated that these reactions occur with retention of configuration at the sulfur atom. Deimidation of (+)-benzyl-*p*-tolyl sulfoximine with nitrous acid (eq 1) resulted in (+)-benzyl *p*-tolyl



(1)

sulfoxide, which is known to have the *R* configuration.[9] Cram and coworkers have shown this reaction to occur with retention of configuration.[11]

Experimental Section

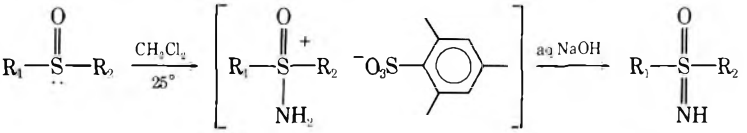
Optical rotations were measured on a Perkin-Elmer 141 polarimeter using a 1-dm cell.

The alkyl aryl and diaryl sulfoxides were obtained by the Anderson method in which the corresponding Grignard reagent was treated with (−)-menthyl *p*-toluenesulfinate;[12] for information concerning the assignment of their absolute configuration see ref 9. The preparation of (−)-(*R*)-methyl *n*-butyl sulfoxide as well as its configurational assignment has been described.[13]

***O*-Mesitylsulfonylhydroxylamine (MSH).**[14] Ethyl *O*-(mesitylsulfonyl)acetohydroxamate (7.5 g) was dissolved in dioxane (5 ml) and cooled to 0° with stirring. To this was added 70% perchloric acid (3 ml) dropwise at a rate so as to maintain the temperature below 10°. The resulting mixture was added to ice water (300 ml), the crude MSH was filtered off, washed well with water, and dissolved in ether (30 ml). The ether solution wash washed with water (25 ml), treated with anhydrous potassium carbonate (5 g) for 30 sec and filtered. The ether solution was poured into cold pentane (300 ml) to precipitate the MSH as small crystals which were collected and dried under vacuum for 5 min at room temperature. Caution, this material may explode;[15] it should be stored in a plastic container sealed with plastic or wax film.

Optically Active Sulfoximines. Compounds **1a–h** were prepared by treating the corresponding optically active sulfoxide (2

Table I
Reactions of Sulfoxides with MSH



la-h

		Sulfoxide				Sulfoximine				
R_1	R_2	$[\alpha]^{25}D$, deg (c, acetone)	Absolute config	Optical purity, %	Registry no.	$[\alpha]^{25}D$, deg (c, acetone)	Absolute config	Optical purity, %	Reaction yield, %	Registry no.
CH_3	*p*-Tolyl	+145.0 (1.00)	*R*	99	1519-39-7	−31.9 (3.00)	*R*	98.5	80	20414-85-1
C_2H_5	*p*-Tolyl	+188.0 (1.10)	*R*	100	1519-40-0	−22.9 (1.00)	*R*	99[c]	70	51774-51-7
$CH(CH_3)_2$	*p*-Tolyl	+191.1 (1.255)	*R*	100[a]	1517-74-4	−17.1 (1.005)	*R*	99[c]	79	51774-52-8
$(CH_2)_3CH_3$	*p*-Tolyl	+193.8 (1.430)	*R*	100[b]	20288-49-7	−17.2 (1.530)	*R*	99[c]	77	51774-53-9
$C_6H_5CH_2$	*p*-Tolyl	+234 (1.00)	*R*	93	4820-07-9	+4.7 (1.26)	*R*	92[c]	60	51774-54-0
C_6H_5	*p*-Tolyl	+21.0 (1.090)	*R*	99.5	16491-20-6	+5.0 (1.075)	*R*	99[c]	19	51774-55-1
C_6H_5	CH_3	−137.0 (1.20)	*S*	94	18453-46-8	+34.1 (2.00)	*S*	93.5	70	33903-50-3
CH_3	$(CH_2)_3CH_3$	−110.3 (1.985)	*R*	92	51795-48-3	−5.00 (1.209)	*R*	91.5[c]	78	51774-56-2

[a] Highest rotation previously reported: +176.5° (ref 9). [b] Highest rotation previously reported: +187.0° (ref 9). [c] Assumed based on 99.5% retention of optical purity.

g) with a 40% excess of *O*-mesitylsulfonylhydroxylamine in methylene chloride (25 ml) at room temperature. After 2 hr the reaction mixture was poured into cold aqueous 10% NaOH (25 ml) solution, stirred for 10 min, and extracted with methylene chloride. The extracts were then washed with two 25-ml portions of 10% HCl solution and 5 ml of H_2O. If desired, unreacted sulfoxide (partially racemized) can be recovered by drying ($MgSO_4$) and concentrating the methylene chloride layer. Pure sulfoximine can be isolated as a colorless liquid or white solid by neutralizing the acidic aqueous layer with solid Na_2CO_3, extracting with methylene chloride, drying ($MgSO_4$), and concentrating. The solids were recrystallized from hexane.

Spectral data (ir and nmr) were consistent with the assigned structures. The most characteristic spectral feature indicative of the sulfoximine is noted in the infrared, where bands for the N-H (3270 cm^{-1}) and N=S=O (1110 and 1218 cm^{-1}) stretching are observed.

Registry No.—MSH, 36016-40-7.

References and Notes

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Sulfonation of 1-Butenes with Sulfur Trioxide

M. D. Robbins* and C. D. Broaddus

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

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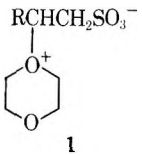
The sulfonation of α-olefins can provide a variety of products ranging from sultones to alkanesulfonic acids[1] depending largely upon the sulfonating agent chosen. The reagents used most commonly are the sulfur trioxide–dioxane complex introduced by Suter[2] in 1938 and the sulfur trioxide–pyridine complex of Terent'ev,[1,3] although very nearly the entire range of ethers and amines have been investigated. These complexes have sufficient activity to react with most organic substrates but reduce substantially the charring of products observed historically with sulfur trioxide. Unfortunately, yields are often quite low and serious side reactions from stabilization of intermediates by the complexing agent are encountered. For example, it has been suggested[4] that dioxonium ions such as 1 are responsible for the formation of β-substituted al-



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kanesulfonic acids in reactions of sulfur trioxide–dioxane with olefins. Attempts have been made to mitigate such complications by introducing sulfur trioxide as a gas, liquid, or solid[5] to long-chain 1-olefins with no real success. We have found, however, that liquid sulfur trioxide introduced to a dilute solution of an olefin at −78° has none of the problems discussed and report here details of the synthesis of several 1,3-sultones in high yields. We also present evidence for the general mechanism of sulfonation of 1-olefins.

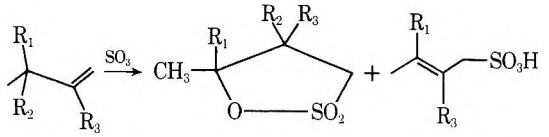
The addition of 1 equiv of liquid sulfur trioxide to 1-butenes in dichloromethane at −78° resulted in the formation of 1,3-propanesultones in at least 75% yield (Table I, examples 1, 3, 4, 5, and 6). Minor side products were 2-butene-1-sulfonic acids in 10–15% yield. An exception to

Table I
Yields of Sultones and 2-Butenesulfonic Acids from 1-Butenes and Sulfur Trioxide

	Olefin[a]	Rel yield, % 1,3-Sultone	Rel yield, % 2-Butene-1-sulfonic acid[b]	Absolute yield, %
1	1-Butene[c] $R_1 = R_2 = R_3 = H$	87	13	90
2	2-Methyl-1-butene[d] $R_1 = R_2 = H$; $R_3 = CH_3$		100	90
3	3-Methyl-1-butene[d] $R_1 = CH_3$; $R_2 = R_3 = H$	89	11	73
4	2,3-Dimethyl-1-butene[d] $R_1 = R_3 = CH_3$; $R_2 = H$	90	10	80
5	3,3-Dimethyl-1-butene[d] $R_1 = R_2 = CH_3$; $R_3 = H$	100		83
6	2,3,3-Trimethyl-1-butene[d] $R_1 = R_2 = R_3 = CH_3$	100		98

[a] Concentration of the olefin was 0.1 *M* in dichloromethane at −78°. [b] Cis–trans isomerization of the double bond is not known. [c] Analytical data is by gc. [d] Analytical data is by nmr.

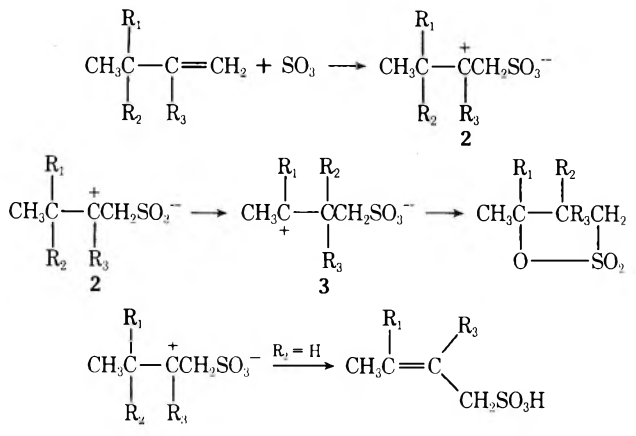
predominant sultone formation was 2-methyl-1-butene, where 2-methyl-2-butene-1-sulfonic acid is the sole product (Table I, example 2). Careful tlc and gc examination



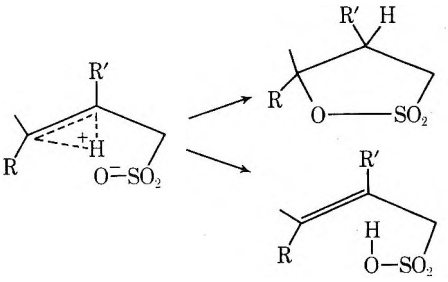
of the reaction mixtures showed only traces of unidentified hydrocarbons. The sultones were isolated either by distillation or crystallization, procedures simplified greatly by lack of the usual acid-catalyzed decomposition. The 2-butene-1-sulfonic acids can be separated by preparative tlc but are not stable for more than several hours. The methyl esters are quite stable and can be isolated directly by distillation. Nmr analysis of the reaction mixtures and the isolated acids and esters shows that only the 2-alkene isomers are present. Brouwer and van Doorn[6] have found that 6–7% 1-butene-1-sulfonic acid can be observed in 2-butene-1-sulfonic acid; so we assume that no more than that can be present in our reactions.

These data support electrophilic addition of sulfur trioxide to double bonds and the intermediacy of carbonium ions (see Scheme I). The hydride and methide migration pattern is typical of cationic species involved in electrophilic addition of olefins.[7] As implied by Bordwell[4] and other early workers,[1] it is clear now that the controlling factor in sultone *vs.* sulfonic acid formation is the relative stability of the carbonium ions formed at the β and γ carbons, *i.e.*, of **2** *vs.* **3**. For example, 2-methyl-1-butene (**2**, $R_1 = R_2 = H$; $R_3 = CH_3$) yields only elimination products whereas 3-methyl-1-butene (**2**, $R_1 = CH_3$; $R_2 = R_3 = H$) exhibits almost complete 1,2-hydride migration and 1,3-sultone formation. The former involves tertiary–secondary carbonium ions (no hydrogen rearrangement) and the latter secondary–tertiary. Furthermore, unpublished work on 1-pentenes indicates that high yields of 1,4-sultones may be obtained if the carbonium ion on the δ carbon is more stable than that on the γ.

Scheme I



The factor(s) responsible for exclusive formation of 2-butene-1-sulfonic acids are not so obvious and may involve a facile intramolecular transfer of a γ proton to the sulfonate moiety in **2**. Sulfonic acids are found only where the starting olefin had a γ hydrogen (*cf.* 2,3-dimethyl-1-butene and 3,3-dimethyl-1-butene) and no 1-butene-1-sulfonic acids were observed (loss of an α hydrogen). Rearranged carbonium ions apparently do not give rise to elimination, as both 2,3-dimethyl- and 3,3-dimethyl-1-butene ultimately yield the same carbonium ion after hydride or methide migration (Scheme I), but only 2,3-dimethyl-1-butene yields any trace of a butenesulfonic acid. Indeed, the fact that no elimination is observed into a methyl branch (*e.g.*, 2-methyl-1-butene) may suggest that the relative position of the proton and the sulfonate group in the transition state leading to elimination is not too dissimilar from that leading to sultone formation.



One major difference in this study from other sulfonation studies is the absence of β-substituted products. This may be due to the lack of formation of intermediates such as **1** or to a lack of β-sultones, as have occasionally been suggested[4] in connection with **1**. We presently have no evidence requiring the intermediacy of β-sultones. Low-temperature nmr of 3-methyl-1-butene and sulfur trioxide reaction mixtures shows immediate formation of 3,3-dimethyl-1,3-propanesultone and discounts the presence of a stable, observable intermediate. Work is currently in progress to determine the cyclic *vs.* noncyclic nature of the initial addition of sulfur trioxide to the double bond in an attempt to resolve this conflict.

Experimental Section

Materials and Methods. Pmr spectra were determined on a Varian T-60 or HA-100 spectrometer. Infrared spectra were obtained from a Perkin-Elmer Model 257. Melting points and boiling points are uncorrected. Gc measurements were made on an Aerograph Model 202 gas chromatograph using a 20 ft × 0.25 in. 10% Silicone SE-30 on Chromosorb P column.

Dichloromethane and sulfur trioxide were used as obtained from commercial sources. All olefins were obtained from Chemical Samples Co. except 1-butene (J. T. Baker Specialty Gas, 99.0%) and used without further purification after confirmation of purity by gc and nmr analyses.

General Procedure for the Sulfonation of Olefins. The same general method was used for all the olefins. To a quantity of 0.02 mol of the olefin dissolved in 200 ml of dichloromethane at −78° was added slowly from a syringe 1 equiv of liquid sulfur trioxide. The mixture was then allowed to come slowly to room temperature and the solvent was removed on a rotary evaporator at *ca.* 20°. Infrared analysis at this point showed the presence of the hy-

dronium ion [3000 (br, s), 1700 (br, s), and 900 cm^{-1} (br, s)] for all examples except 3,3-dimethyl- and 2,3,3-trimethyl-1-butene. The sultones were isolated by distillation (1-butene) or by crystallization from ethanol. The 2-butene-1-sulfonic acids were isolated by preparative tlc on silica gel using 50:50 chloroform–pentane. Quantitative nmr analyses were prepared by addition of the internal standard, diphenyl ether, after the reaction mixture had warmed to room temperature followed by the usual work-up. Comparison of the integral at δ 7.1 (m, Ph_2O) to the one at δ 6.0–5.0 (olefinic hydrogens of 2-butenesulfonic acids) and 2.2 (1,3-propanesultone β hydrogens) provided relative and absolute yields for entries 2–6 in Table I. Analysis for the products from 1-butene was by gc using diphenyl ether as internal standard.

The esters of 2-butene-1-sulfonic acids were prepared by addition of ethereal diazomethane to the reaction mixture at room temperature until a pale yellow color persisted and no further evolution of bubbles was noted. The esters were then separated by tlc (50:50 chloroform–pentane), by gc collection, or by distillation. Analytical data were difficult to obtain owing to decomposition during isolation and insufficient amounts of pure samples were obtained to include sulfur analysis. Where combustion analysis was outside accepted limits, assignments were confirmed by high-resolution mass spectra.

1-Butene. The reaction product was a dark oil from which could be distilled 1,3-butanesultone: bp 125° (0.1 mm) [lit.[8] bp 150° (12 mm)]; nmr[9] ($CDCl_3$, TMS) δ 5.0 (m, 1 H, CH_3CHO–), 3.3 (m, 2 H, $>CH_2CH_2SO_2$–), 2.2 (m, 2 H, $>CHCH_2CH_2SO_2$–), and 1.4 (d, J = 6 Hz, 3 H, $CH_3CH<$); ir 1350 (s), 1160 (s), 1030 (m), 920 (m), and 830 cm^{-1} (s). From a typical reaction mixture treated with ethereal diazomethane, a fraction was isolated and shown to be methyl 2-butene-1-sulfonate: bp 70–80° (0.1 mm); nmr[6] ($CDCl_3$, TMS) δ 5.8 (m, 2 H, $CH_3CH{=}CH$–), 3.9 (m, 5 H, $CH_2SO_3CH_3$), and 1.9 (m, 3 H, $CH_3CH{=}$); ir 1660 (vw, 1380 (s), 820 (m), and 770 cm^{-1} (m); mass spectrum M^+ m/e 150.0353 (calcd for $C_5H_{10}SO_3$, 150.0351).

Anal. Calcd for $C_5H_{10}SO_3$: C, 39.99; H, 6.91. Found: C, 40.44; H, 6.86.

2-Methyl-1-butene. Upon removal of the solvent from the reaction mixture, a brown, unstable oil was obtained, partially purified by tlc: nmr ($CDCl_3$, TMS) δ 5.5 (m, 1 H), 3.8 (m, 2 H), and 1.5 (m, 6 H); ir 3000, 1700, and 900 cm^{-1}, all very broad. Addition of ethereal diazomethane to the reaction mixture and subsequent distillation gave methyl 2-methyl-2-butene-1-sulfonate: bp 75–80° (0.4 mm); nmr ($CDCl_3$, TMS) δ 5.7 (m, 1 H, $CH_3CH{=}C<$), 3.8 (m, 5 H, $-CH_2SO_3CH_3$), and 1.8 (m, 6 H, $CH_3CH{=}CCH_3$); ir 1650 (vw), 1360 (s), 1160 (s), 1000 (s), 830 (m), and 770 cm^{-1} (m). Gc analysis of the methyl ester on SE-30 or Carbowax 20 M showed only one peak.

Anal. Calcd for $C_6H_{12}SO_3$: C, 43.89; H, 7.34. Found: C, 44.23; H, 7.48.

3-Methyl-1-butene. Recrystallization of the reaction mixture after evaporation of the solvent gave colorless needles of 3,3-dimethyl-1,3-propanesultone, mp 72–73° (lit.[10] mp 71.5–78°). Addition of ethereal diazomethane and separation by preparative tlc afforded a small amount of methyl 3-methyl-2-butene-1-sulfonate; nmr ($CDCl_3$, TMS) δ 5.3 (m, 1 H, $>C{=}H$–), 3.8 (m, 5 H, $-CH_2SO_3CH_3$), and 1.8 [m, 6 H, $(CH_3)_2C{=}CH$–]; ir 1650 (vw), 1360 (s), 1000 (s), 830 (m), and 770 cm^{-1} (m); mass spectrum M^+ m/e 164.050 (calcd for $C_6H_{12}SO_3$, 164.048).

Anal. Calcd for $C_6H_{12}SO_3$: C, 43.89; H, 7.34. Found: C, 44.58; H, 7.25.

2,3-Dimethyl-1-butene. Crystallization of the reaction mixture from ethanol gave colorless crystals of 2,3,3-trimethyl-1,3-propanesultone, mp 59–62° (lit.[4c] mp 61–63°). Formation of the methyl ester with diazomethane and collection from the gc gave methyl 2,3-dimethyl-2-butene-1-sulfonate: nmr ($CDCl_3$, TMS) δ 3.8 (s, 5 H, $-CH_2SO_3CH_3$) and 1.8 [m, 9 H, $(CH_3)_2C{=}C(CH_3)$–]; ir 1660 (vw), 1360 (s), 1160 (s), 1000 (s), and 830 cm^{-1} (m).

Anal. Calcd for $C_7H_{14}SO_3$: C, 47.17; H, 7.92. Found: C, 47.55; H, 8.00.

3,3-Dimethyl-1-butene. Crystallization from ethanol gave 2,3,3-trimethyl-1,3-propanesultone: mp 58–59°; ir 1340 (s), 1170 (s), 1050 (m), and 850 cm^{-1} (s). The ir of the reaction solution (CH_2Cl_2) and of the reaction mixture after evaporation of the solvent were identical with that of the sultone ($CHCl_3$ or CH_2Cl_2). The reaction mixture did not react with ethereal diazomethane. Tlc separation afforded only the sultone and trace amounts of a hydrocarbon.

2,3,3-Trimethyl-1-butene. Removal of solvent immediately gave a solid, 2,2,3,3-tetramethyl-1,3-propanesultone, recrystallized from ethanol, mp 142–143° (lit.[3] mp 145–146°). There was no evidence for sulfonic acids in the ir of the crude material.

Registry No.—Sulfur trioxide, 7446-11-9; 1-butene, 106-98-9; 1,3-butanesultone, 3289-23-4; methyl 2-butene-1-sulfonate, 51774-45-9; 2-methyl-1-butene, 563-46-2; 2-methyl-1,3-butanesultone, 51774-46-0; methyl 2-methyl-2-butene-1-sulfonate, 51774-47-1; 3-methyl-1-butene, 563-45-1; 3,3-dimethyl-1,3-propanesultone, 19028-67-2; methyl 3-methyl-2-butene-1-sulfonate, 51774-48-2; 2,3-dimethyl-1-butene, 563-78-0; 2,3,3-trimethyl-1,3-propanesultone, 51774-49-3; methyl 2,3-dimethyl-2-butene-1-sulfonate, 51801-40-2; 3,3-dimethyl-1-butene, 558-37-2; 2,3,3-trimethyl-1-butene, 594-56-9; 2,2,3,3-tetramethyl-1,3-propanesultone, 51774-50-6.

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Reaction of 2-Chloromethylpyridine with Sodium Acetylide[1]

Albert E. Zune,[2] Ulrich Hollstein,* and William M. Litchman

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

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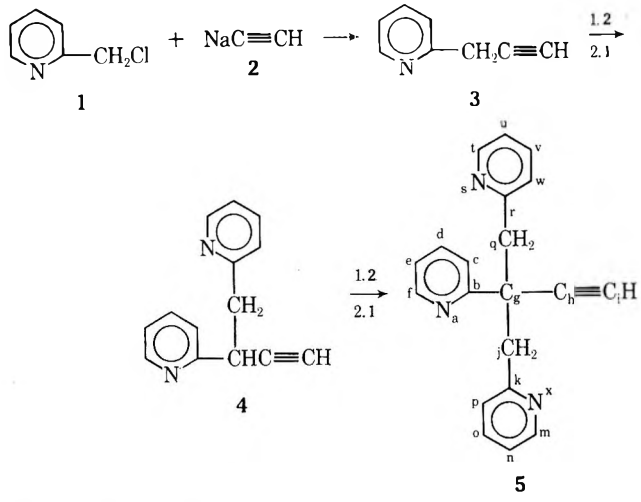
Several alkenyl- and alkynylpyridines with chain end unsaturation are known; among them are 2-vinylpyridine, 2-allylpyridine,[3] (2-pyridyl)-4-butene-1, and (2-pyridyl)-4-butyne-1. Troyanowsky[5] discussed these products, and, in attempts to synthesize other members in this series, notably 2-propargylpyridine, studied the reaction of propargylmagnesium bromide with 2-bromopyridine, and 2-pyridylmagnesium bromide with propargyl bromide.[4] Reportedly, no new product was obtained from the first of these reactions, whereas the second one yielded 3-(α-pyridyl)hexyn-5-one-2. During studies of the preparation of propargylpyridine, coupling reactions between 2-chloromethylpyridine and sodium acetylide were investigated in this laboratory. Reaction between equivalent amounts of these two reagents in liquid ammonia resulted in the formation of two new compounds.

A white solid was isolated by filtration during the work-up. Extensive use of chromatographic techniques yielded only one other new product in the reaction mixture, and helped purify it as a yellow thick oil. Other products, such as the intermediates proposed in this paper, may have been present in trace amounts, but none of them could be isolated by column or thin layer chromatography. The yellow oil was analyzed by ir, uv, pmr, and cmr, and identified as 1′-ethynyl-1′,1′-di-α-picolyl-α-picoline (5). Absorbtions at 3300 and 2200 cm^{-1} in the ir spectrum indicate the presence of a terminal acetylenic moiety; uv absorption was consistent with the presence of three pyridine rings in the molecule; the pmr features an acetylenic

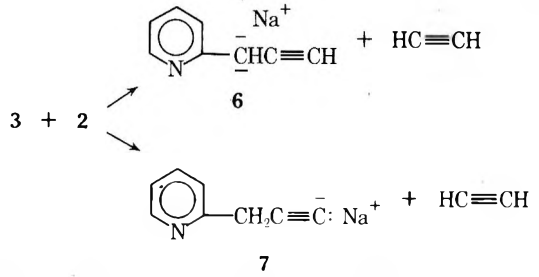
proton signal along with aromatic protons and an AB quartet centered at δ 3.65. This quartet was attributed to the signal of the protons of the methylene groups.

A model of **5** showed that a hydrogen atom of carbon atom j can form a hydrogen bond to nitrogen atom s. Similarly, a hydrogen atom of carbon q can form a hydrogen bond to nitrogen x. These two hydrogen bonds close two six-atom rings. Consequently, the two hydrogen atoms of each methylene group (j and q) become nonequivalent, and present different chemical shifts. In groups j and q the hydrogen involved in a hydrogen bond is more deshielded than one with a similar environment which is not hydrogen bonded. An AB quartet is therefore produced. Because of the thermal instability of **5**, elemental analytical results were poor and a mass spectrum, for which the sample had to be heated, indicated only fragments belonging to the pyridine moiety. Cmr, however, provided as expected signals for the 14 different types of carbons,[6] and those were unequivocally assigned.

It is proposed that **5** was formed by the following pathway. Because of resonance stabilization with the ring and

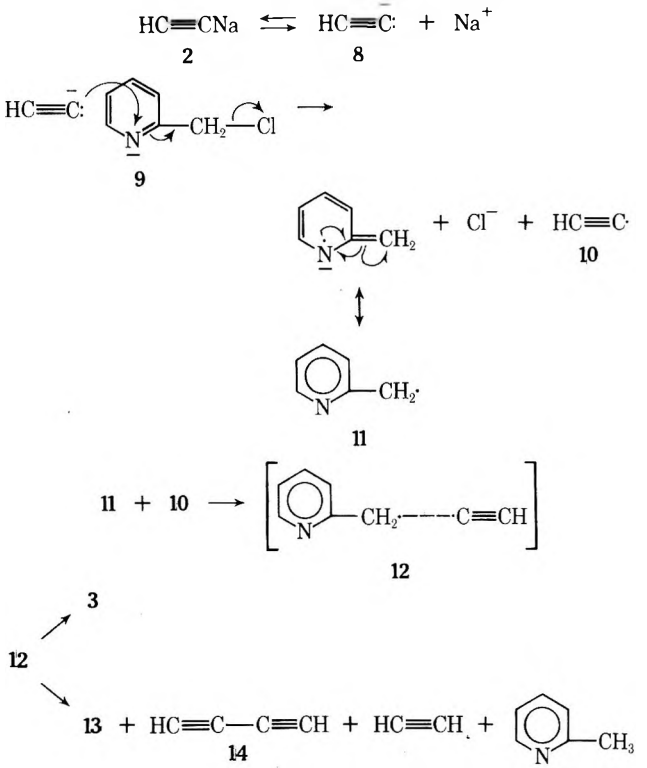


the inductive effect of the acetylenic linkage, the anion **6** is possibly more stable than anion **7**. Assuming that the



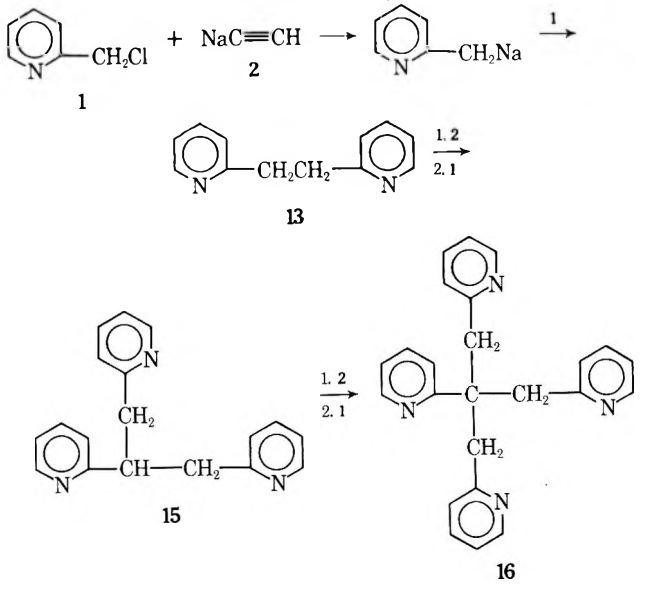
transition state for the reaction forming an anion of **3** partly resembles the products, one can expect the activation energy for the process leading to **6** to be lower than in the case of formation of **7**. Species **6** is thus formed faster than **7**, and, reacting immediately with **1**, forms **4**. The isolation of **5** as reaction product does not by itself necessarily imply that **6** is more stable than **7**. Indeed, a less stable anion will react faster. It can be argued that since **5** is obtained as product, **6** must be the faster reacting, and thus the least stable species. Metalation, however, has been shown to occur preferentially at the most acidic site in a molecule.[7] The site of metalation is clearly the methylene group. This indicates that in **3**, the methylenic protons are more acidic than the acetylenic one. Accordingly, we propose that **6** is, in fact, more stable than **7**. A similar discussion can be proposed about the reactions leading to **5**, **15**, and **16**.

Even though the reactions were run in an ionic solvent, a small proportion of intermediates **3** and **13** might have been formed by an alternative radical anion mechanism.

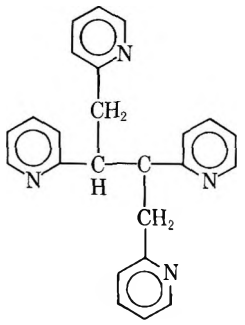


Caged radical pair **12** can yield **3** by coupling within the solvent cage or, when the cage breaks down, can go to **13** and **14**. *Via* proton abstraction from the solvent, acetylene and α-picoline can also be produced.

The solid product, isolated during the work-up of the same reaction, was analyzed by ir, pmr, and cmr. The infrared spectrum revealed the absence of acetylenic linkage, and this was confirmed by the absence of a pmr signal at δ 2.5. In the nmr, an AB quartet is found, similar to the one observed in the spectrum of **5**. The other signals belong to the aromatic region of the spectrum. These features suggest structure **16** for the analyzed solid. Hydrogen bonding can occur between three methylene hydrogens and three ring nitrogens in six different combinations. A dynamic equilibrium between those bonding combinations results in one AB quartet in the nmr. The proposed structure was confirmed by cmr[6] and elemental analysis. The following pathway is suggested for the formation of 1′,1′,1′-tri-α-picolyl-α-picoline (**16**). Halogen-



metal exchange yields 2-picolylsodium, which can couple with 1 to form 13. A first metalation and coupling with 1 leads to 15, where the methine group is a site of choice for further metalation, because of the inductive effect of the picolyl groups. Subsequent coupling forms 16. The increased acidity at the methine group therefore overweighs steric hindrance, since no formation of 17 was observed.



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The total yield of 5 and 16 is quantitative.

Experimental Section

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 instrument, using KBr plates for the liquid sample and pressed KBr pellets for the solid. The nmr spectra were recorded on Varian A-60 and XL-100 spectrometers. The mass spectrum was obtained using a Du Pont 21-491 spectrometer. The uv spectra were recorded on a Cary 14 instrument.

Sodium Acetylide (2) and 2-Chloromethylpyridine (1). Ammonia was condensed into a three-neck flask fitted with a stopper, a potassium hydroxide drying tube, and a Dry Ice condenser. After 150 ml of liquid ammonia had been obtained, the condenser was disconnected from the gas cylinder and fitted with a potassium hydroxide drying tube. The contents of the flask were stirred magnetically. The stopper was replaced by a gas dispersing tube through which a stream of purified acetylene was passed. In the course of 15 min 2.3 g (0.1 mol) of sodium was added in small parts. The ammoniacal solution turned dark blue after each addition of sodium, but this color was soon discharged as a result of the reaction with acetylene. After completion of the sodium addition, the mixture was stirred for 5 min. The potassium hydroxide drying tube was replaced by a pressure-equalizing addition funnel containing 11.76 g (0.092 mol) of 1. This reagent was added in the course of 5 min, causing the formation of a white precipitate. The mixture was stirred for 3 hr while the ammonia slowly evaporated. Water and ice were then cautiously added to the obtained dark, pasty residue. Suction filtration of the resulting mixture removed a white precipitate. This compound was recrystallized from di-*n*-butyl ether to yield 1.51 g (17.8%) of 16, with a sharp melting point of 196°: ir 1590 (s), 1570 cm^{-1} (s); nmr ($CDCl_3$) δ 8.8–6.5 (m, 16 H, ring protons), 3.75 (d, 3 H, HCH···, J = 13 Hz), 3.45 (d, 3 H, HCH···, J = 13 Hz); cmr ($CDCl_3$) δ −34.07, −31.10, −21,14, −21.03, −8.03, −7.48, +2.65, +4.13, +6.21, +6.53, +77.95, +78.45 (shifts relative to benzene, used as an external reference).

Anal. Calcd for $C_{24}H_{22}N_4$: C, 78.66; H, 6.05; N, 15.29. Found: C, 79.03; H, 5.79; N, 15.16.

The filtrate was extracted with ether. After evaporation of the solvent, 8.0 g (86%) of a dark liquid was obtained, placed on an alumina column, and eluted with ether. A yellow liquid was collected, which decomposed when submitted to heat, thus rendering distillation or analysis by mass spectrometry impossible. A sample was analyzed by proton and ^{13}C nmr, and was identified as 5: nmr (chloroform-*d*) δ 8.8–6.7 (m, 12 H, ring protons), 3.82 (d, 2 H, HCH···, J = 13 Hz), 3.5 (d, 2 H, HCH···, J = 13 Hz), 2.55 (s, 1 H, C≡CH); cmr (chloroform-*d*) δ −32.70, −30.07, −21.22, −20.92, −8.26, −7.62, +2.90, +4.87, +5.94, +6.32, +42.12, +50.76, +78.35, +78.74 (shifts relative to benzene, used as an external reference).

Anal. Calcd for $C_{20}H_{17}N_3 \cdot 1.3H_2O$: C, 74.4; H, 6.1; N, 13.0. Found: C, 74.65; H, 5.91; N, 11.73.

Registry No.—1, 4377-33-7; 2, 1066-26-8; 5, 51510-19-1; 16, 51510-20-4.

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A Hammett Relationship Study for the Thermal Decomposition of Sterically Hindered Hydrogen Phthalate Esters in Solution

Raphael M. Ottenbrite* and James W. Brockington[1]

Department of Chemistry and Pharmaceutical Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284

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The presently accepted mechanism for the thermal decomposition of acetate, xanthate, and related esters involves a concerted six-membered cyclic transition state. An exception to this generalization is the pyrolysis of tertiary hydrogen phthalate esters, which decompose at relatively low temperatures (less than 150°) to yield exclusively olefinic products and phthalic acid.[2]

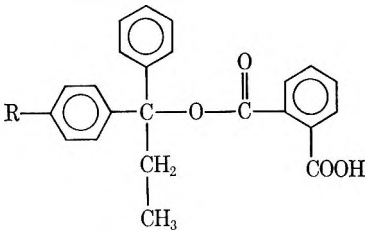
It has been found that considerable trans-elimination products are obtained from tertiary hydrogen phthalate decompositions.[2,3] To account for these products, it was suggested that carbonium ion character was apparent in the transition state. Further evidence of carbonium ion participation was obtained by partial decomposition of ^{18}O-enriched carbonyl oxygen labeled *trans*-1,2-dimethylcyclohexyl hydrogen phthalate ester which resulted in the enrichment of ^{18}O in the alkyl portion of the undecomposed ester.[4] A kinetic study of the decomposition of *cis*- and *trans*-1,2-dimethylcyclohexyl and *cis*- and *trans*-2-methyl-1-phenylcyclohexyl hydrogen phthalate esters[5] indicated that ion-pair formation was involved in the rate-determining step of the reaction.

More recently we reported that the thermal decomposition of 1,1-diphenylpropyl hydrogen phthalate ester followed first-order kinetics in DMSO solution.[6] The positive entropy of activation (7.3 eu) obtained precluded a cyclic transition state for this decomposition and gave support to the previously postulated mechanism involving heterolytic cleavage. Although homolytic decomposition of these esters has not been observed, this mode of decomposition could not be entirely ruled out. We wish to report in this paper a Hammett relationship study of the effect of substituents on the decomposition on a series of 1-aryl-1-phenylpropyl hydrogen phthalate esters which supports the concept of carbonium ion formation rather than radical pair formation in the rate-determining step.

Results and Discussion

The para 1-aryl-1-phenylpropyl alcohols were prepared by the Grignard method using the appropriate arylmagnesium halides and ketones (Table I). The hydrogen phthalate esters were prepared from the sodium salt of these alcohols and phthalic anhydride (Table I). A preparative-scale decomposition of the hydrogen phthalate esters in DMSO solution gave near-quantitative yields (>95%) of the corresponding olefin II and phthalic acid III. Kinetic decomposition studies of these esters were car-

Table I
1-Aryl-1-phenylpropyl Alcohols and Hydrogen Phthalate Esters



Substituent	Alcohol: Yield, %	Alcohol: Mp, °C	Alcohol: Registry no.	Hydrogen phthalate esters: Yield, %	Hydrogen phthalate esters: Mp,[a] °C	Hydrogen phthalate esters: Registry no.
H	91.5[b]	90–92[b]		46[b]	119[b]	
Cl	96[c]	Oil	51608-64-1	46.5	117	51608-68-5
Me	94[c]	Oil	51608-65-2	48	115.5	51608-69-6
Br	90[c]	Oil	51608-66-3	51	117	51608-70-9
Ph	58	102–104	51608-67-4	64.5	100	51608-71-0

[a] These decomposed on melting. [b] These data have been published [R. M. Ottenbrite, J. W. Brockington, and K. G. Rutherford, *J. Org. Chem.*, **38,** 1189 (1973)] and are included for comparison. [c] The compound did not crystallize and yields are based on purified oil. [d] The hydrogen phthalate esters all gave acceptable C, H analyses (±0.4%). Ed.

Table II
Rate Constants for the Decomposition of a Series of 1-Arylphenyl Hydrogen Phthalates in Dimethyl Sulfoxide at 65°

Compd	$k \times 10^5$, sec^{-1}	σ^+ [a]	σ [b]
Ia[c]	2.46 ± 0.01	0.00	0.00
Ib	0.679 ± 0.018	+0.11	+0.24
Ic	21.6 ± 0.7	−0.31	−0.13
Id	0.581 ± 0.033	+0.15	+0.27
Ie	7.22 ± 0.02	−0.17	+0.01

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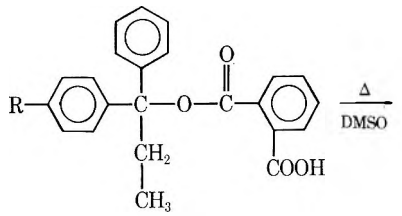
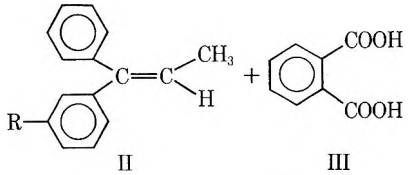


Ia, R = H
b, R = Cl
c, R = CH_3
d, R = Br
e, R = Ph



II III

ried out in DMSO solution at 65°. The rates of reaction were followed using nmr techniques previously described.[6]

Plots of log $H_a/(H_a + H_b)$ *vs.* time for the decomposition were obtained, where H_a and H_b are the height of the integrations of peaks due to the methyl group of the ester and the olefin, respectively. First-order kinetics was observed in each case. The individual rate constants for each aryl-substituted ester are listed in Table II. Hammett relationships using these rate data *vs.* σ constants and σ^+ constants were determined. The ρ value with σ was −3.74 (correlation coefficient 0.955) and with σ^+ −3.44 (correlation coefficient 0.995).

Taylor, *et al.*,[7] reported that for the pyrolysis of a series of 1-arylethyl acetates that their kinetic data correlated better with σ^+ than with σ and gave a ρ value of −0.66. From this, they concluded that the transition state was ionic in character with some charge separation. Further, free-radical reactions on the average have ρ values that are closer to zero than do ionic reactions.[8] The magnitude of the ρ values obtained for our ester decomposition study (−3.74 for σ and −3.44 for σ^+) are comparable to the ρ value (−3.97) obtained for the equilibrium between triarylmethanol and triarylcarbonium ion[9] in dilute sulfuric acid. Consequently, the large ρ values that we obtained for the hydrogen phthalate ester decomposition indicate that a substantial charge separation is taking place in the transitions, therefore substantiating ion-pair formation and precluding free-radical involvement in this reaction.

$$Ph_3COH \rightleftharpoons Ph_3C^+ + {}^-OH$$

Experimental Section

All melting points are uncorrected and were determined in a Thomas-Hoover melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer 257. Kinetic studies were performed in a mineral bath, maintained at ±0.1° by means of a Haake E-51 temperature controller. Kinetic measurements were made on a Varian A-60 nmr spectrometer in precision nmr tubes (507-PP-7 and 504-PP-7) obtained from Wilmad Glass Co. The deuterated solvents were obtained from Merck Sharp and Dohme. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

General Kinetic Procedure. Ester was analytically weighed and a 0.75 *M* solution was prepared in dimethyl sulfoxide-d_6. At the beginning of each run, 0.4 ml of this solution was placed into each of six nmr tubes which immediately were sealed with pressure caps. The tubes were placed simultaneously in the constant-temperature bath. Tubes were withdrawn at appropriate intervals and quenched by plunging the tube into a beaker of crushed ice and water. The tube was allowed to return to room temperature and the nmr analysis was performed. Each nmr signal was integrated six times. The averaged value for $H_a/(H_a - H_b)$ had a mean deviation of less than 1%.

Preparation of Alcohols. The alcohols were prepared by the method previously described[7] using the appropriate para-substituted phenylmagnesium halide with propiophenone. All gave similar spectral data: ir (thin film) 3560 (free O–H stretch), 3460 (broad peak, bonded O–H stretch), 1395 (O–H bend), and 1165 cm^{-1} (C–O stretch); nmr ($CDCl_3$, TMS internal standard) δ 0.80–0.82 (t, 3, J = 7 Hz, CH_3CH_2) 2.22 (q, 2, J = 7 Hz, CH_2CH_3), 2.26 (s, 1, OH), and 7.1–7.5 ppm (m, 9, aromatic). The peak at δ 2.26 disappeared upon the addition of D_2O.

Preparation of Hydrogen Phthalate Esters. These compounds were prepared according to the procedure previously described.[7] All gave similar spectral data: ir (KBr) 3420 (broad peak, bonded O–H stretch), 2650 and 2540 (O–H stretch characteristic of hydrogen-bonded carboxylic acids), 1734 and 1705 (C=O stretch), and 1300, 1270, 1125, and 1070 cm^{-1} (C–O

stretch); nmr (dimethyl sulfoxide-d_6, TMS internal standard) δ 0.85 (t, 3, J = 7 Hz, CH_3CH_2), 2.95 (q, 2, J = 7 Hz, CH_2CH_3), and 7.0–8.0 ppm (m, 13, aromatic).

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6-Methyl-2-naphthalenesulfonate (Menasylate). A New and Useful Leaving Group for Trifluoroacetolysis

Takashi Ando,* Yoshimasa Saito, Junko Yamawaki, Hisao Morisaki, Masami Sawada, and Yasuhide Yukawa

The Institute of Scientific and Industrial Research, Osaka University, Suita, Osaka, Japan

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Recently, trifluoroacetic acid has become an important solvolyzing solvent because of its very low nucleophilicity and relatively high ionizing power. Its strong acidity, however, restricts the method for measurement of solvolysis rates so that only the ultraviolet spectroscopic method has been the one for general use.[1] This method, developed originally by Swain and Morgan for following the reactions of arenesulfonates,[2] takes advantage of the differences in the absorptions of alkyl tosylates and tosylate anion at 261 or 272 nm; at 261 nm methyl tosylate has ϵ 671 and tosylate anion has ϵ 344 both in water. For the reactions of aralkyl arenesulfonates, whose aralkyl groups absorb in the same region as arenesulfonate groups do, extraction techniques were recommended by the original authors.[2] Although this technique has been successfully utilized by Bentley and Dewar[3] and by us[4,5] for trifluoroacetolysis of 2-arylethyl tosylates and nosylates, the experimental procedure is tedious and the accuracy of the results is limited. We report now that 6-methyl-2-naphthalenesulfonate, abbreviated as "menasylate (OMns)," is a useful leaving group for following the reactions in trifluoroacetic acid without extraction techniques.

Although menasyl chloride is commercially unavailable, it can be prepared easily from 2-methylnaphthalene.[6,7] Any indication of the presence of an isomer could not be observed for the chloride and all the menasylates prepared from it. The ultraviolet spectrum of ethyl menasylate in 95% ethanol showed maxima at 282 nm (ϵ 5650), 311 (1240), 318 (782), and 326 (936). On the other hand, the spectrum of menasylic acid in the same solvent showed maxima at 278 nm (ϵ 5470), 308 (393), and 318 (194); ϵ was only 56 at 326 nm and no maximum was observed around there. Addition of trifluoroacetic acid and sodium trifluoroacetate to the solutions did not cause any change in the spectra at all. This remarkable difference in the absorptions at 326 nm (*ca.* 20-fold) facilitated the measurement of the trifluoroacetolysis rates of several menasylates whose alkyl groups have absorptions at a longer wavelength region. Thus, the trifluoroacetolysis rates of 2-phenylethyl and 2-(*p*-methoxyphenyl)ethyl menasylate (**1** and **2**) were determined (Table I). In a typical run, the absorbance at 326 nm changed from 0.733 (at zero point) to 0.060 (at "infinity" after more than 10 half-lives). This large variation in the absorbance resulted in much improved accuracy and reproducibility without a great deal of skill such as necessary for extraction techniques. Correlation coefficients were better than 0.9999 in most cases. The presence of even a nitrophenyl group in the substrate (**3**) did not interfere with the measurement, although the background absorbance was relatively high in this case; the absorbance changed from 0.582 to 0.339 in one run. Application of a high temperature (>130°) caused desulfonation from the leaving group, and a small amount of 2-methylnaphthalene was detected in the products of trifluoroacetolysis of **3**.

It is apparent that menasylates can be used conveniently in any solvent other than trifluoroacetic acid; their reactions can be followed accurately and their melting points are usually high. Comparison of the present data with those reported by Nordlander and Deadman[8] revealed that the reactivity of a menasylate was almost the same as that of a tosylate.

Experimental Section

Menasylic Acid. A mixture of 71 g of 2-methylnaphthalene and 71 g of *concentrated* sulfuric acid (*d* 1.84) was stirred for 6 hr at 90–100°. At the end of this period the hot reaction solution was poured into 250 ml of water while stirring. The unreacted 2-methylnaphthalene and the sulfone produced as a by-product were extracted twice with 50 ml each of benzene. To the water layer was added 400 ml of aqueous solution saturated with sodium chloride. After stirring for several hours the sodium salt thus precipitated was filtered and dried at 120–150° *in vacuo*. The crystals were suspended in acetone and warmed under reflux for 2 hr. After filtration sodium menasylate recrystallized twice from water. The yield was 25–40%.

Sodium menasylate was dissolved in 3 *N* hydrochloric acid at 60°. Upon cooling to room temperature colorless crystals precipitated. Menasylic acid was obtained as a monohydrate after recrystallization from 3 *N* hydrochloric acid and then from ethyl acetate, mp 118–121°.

Anal. Calcd for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.03; S, 13.34. Found: C, 55.22; H, 4.83; S, 13.23.

Menasyl Chloride. To a stirred suspension of 20 g of sodium

Table I
Trifluoroacetolysis Rates of 2-Arylethyl Arenesulfonates

Substrate	Temp, °C	$10^5 k_t$, sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
$PhCH_2CH_2OMns$ (**1**)[a,b]	50	8.08 ± 0.01	19.9	−15.9
	60	21.1 ± 0.1		
p-$MeOPhCH_2CH_2OMns$ (**2**)[a,b]	24	6.38 ± 0.03		
p-$NO_2PhCH_2CH_2OMns$ (**3**)[b,c]	130	2.64 ± 0.00	25	−19
	150	11.9		
$PhCH_2CH_2OTs$[b,d]	50	7.75	20.8	−13.1
$PhCH_2CH_2ONs$[e]	50	26.0	19.5	−14.7

[a] 0.05 *M* in menasylate. [b] With 0.125 *M* sodium trifluoroacetate. [c] 0.025 *M* in menasylate. [d] Interpolated from data in ref 8. 0.05 *M* in tosylate. [e] Reference 5; 0.02 *M* in nosylate.

menasylate in 80 ml of dimethylformamide was added dropwise over a 15-min period 9 ml of thionyl chloride at room temperature. After stirring for an additional 5 min, the reaction solution was poured into ice–water. Precipitates were filtered and dried. Recrystallization from ligroin gave 15.7 g of the pure chloride, mp 98.0–99.0° (lit.[6] mp 97–98°).

Preparation of Menasylates. Menasylates were prepared by standard procedures from menasyl chloride and alcohols at 0° in pyridine as a solvent.

2-Phenylethyl menasylate (1) had mp 101.9–102.5° (from ligroin).

Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56; S, 9.82. Found: C, 69.98; H, 5.29; S, 9.71.

2-(*p*-Methoxyphenyl)ethyl menasylate (2) had mp 112.8–113.3° (from ligroin–benzene).

Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66; S, 9.00. Found: C, 67.30; H, 5.46; S, 8.80.

2-(*p*-Nitrophenyl)ethyl menasylate (3) had mp 135.0–135.8° (from carbon tetrachloride–chloroform).

Anal. Calcd for $C_{19}H_{17}NO_5S$: C, 61.44; H, 4.61; N, 3.77; S, 8.63. Found: C, 61.31; H, 4.47; N, 3.58; S, 8.78.

Trifluoroacetolysis Media. Trifluoroacetic acid and its 2 vol % of trifluoroacetic anhydride were refluxed for 2 hr. The solution was then distilled through a 85-cm vacuum-jacketed column packed with glass helices. The middle cut (bp 71.5–72.0°) was redistilled through the same column. To this middle cut (bp 71.5–72.0°) was added 1 wt % of freshly distilled trifluoroacetic anhydride. Sodium trifluoroacetate (17.0 g, 0.125 mol) was dissolved with the previous solution in a 1000-ml volumetric flask to prepare buffered medium.

Kinetic Procedure. The required amount of menasylate for making a 0.05 *M* solution was weighed in a volumetric flask and diluted with the trifluoroacetolysis media prepared as above. For the reactions above 50°, 1.5-ml portions of this solution were sealed in 5-ml glass ampoules, which were placed together in a thermostatic bath at the desired temperature (±0.02°). At the appropriate intervals, the tubes were quenched in ice–water successively. Each was warmed to room temperature and opened, and 1.00 ml of the solution was pipetted into *ca.* 48 ml of 95% ethanol in a 50-ml volumetric flask, followed by 95% ethanol up to the mark. The absorbance of the resulting solution was measured at the maximum of 326 nm, using a Hitachi Perkin-Elmer 139 uv-visible spectrophotometer. A Beer's law for the concentration of ethyl menasylate was shown to be linear over the range used for the kinetics.

The reaction of 3 was followed using a 0.025 *M* solution. For the reaction of 2 at 24°, 1-ml aliquots were pipetted out from a reaction flask placed in a thermostatic bath.

Registry No.—1, 51751-79-2; 2, 51751-80-5; 3, 51751-81-6; menasylic acid, 29181-96-2; 2-methylnaphthalene, 91-57-6; menasyl chloride, 1875-72-5; sodium menasylate, 13035-04-6; 2-phenylethanol, 60-12-8; 2-(*p*-methoxyphenyl)ethanol, 702-23-8; 2-(*p*-nitrophenyl)ethanol, 100-27-6; trifluoroacetic acid, 76-05-1.

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Friedel–Crafts Alkylations with Aromatic Aldehydes

Paul R. Stapp

Phillips Petroleum Company, Bartlesville, Oklahoma 74004

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Friedel–Crafts reactions of benzaldehyde with aromatic substrates have been reported to produce either triarylmethanes or anthracene derivatives depending on the catalyst, substrate, and reaction conditions.[1] In the reaction of substituted benzaldehydes with benzene in the presence of aluminum chloride to produce anthracenes it was found that the aldehyde served only to supply the meso carbon atoms in the anthracene molecule[2] *via* decarbonylation to carbon monoxide. Benzoic acid[3] and "traces" of diphenylmethane[4] have also been reported as products of the reaction of benzaldehyde with benzene in the presence of aluminum chloride.

During the course of a study of Tishchenko reactions catalyzed by boron compounds[5] a new modification of the Friedel–Crafts reaction of benzaldehydes with aromatics has been found. When boron trifluoride etherate is used as catalyst at elevated temperatures the major products are diphenylmethane derivatives along with low yields of the corresponding benzoic acids. If the assumption is correct that the initial reaction step is disproportionation of the aldehyde to benzyl benzoate, the following reaction stoichiometry would be expected.

$$2\mathrm{ArCHO} \xrightarrow{BF_3} \mathrm{ArCO_2CH_2Ar} \xrightarrow[BF_3]{\mathrm{Ar'H}} \mathrm{ArCH_2Ar'} + \mathrm{ArCO_2H}$$

Table I summarizes the results observed under typical conditions using excess aromatic hydrocarbon as solvent.

Although good yields of diphenylmethane derivatives were usually obtained, the corresponding carboxylic acid was generally found in only 10–15% yield by basic extraction. In addition to the products isolated there were rather substantial quantities of heavy tars produced. Dibenzylated materials were found in some cases but there was no indication of incorporation of the bulk of the benzoic acid in the form of volatile carbonyl-containing compounds; however, minor quantities of ethyl benzoate were detected (control experiments showed that benzoic acid in benzene solution reacted with boron fluoride etherate to give ethyl benzoate at 150°). Benzylation of benzene and toluene with benzyl benzoate in the presence of catalytic quantities of boron fluoride etherate was found to give high yields of both diphenylmethane and benzoic acid. Treatment of benzaldehyde with boron fluoride etherate in cyclohexane gave no reaction at reflux and tars under more forcing conditions. Pure benzyl benzoate when refluxed with boron fluoride in cyclohexane was converted to polymer (polybenzyl) and benzoic acid. Benzene did not react with carbon monoxide at 200° and 1800 psig in the presence of boron fluoride. Stannic chloride was completely ineffective as a catalyst for the reaction using method B; the starting materials were recovered unchanged. Because of the differences in reaction products between benzaldehyde and benzyl benzoate cited the equation above undoubtedly represents an oversimplification. Although mechanisms can be written which would account for the observed products, they would be speculative at this time; a competition between other routes and a Tishchenko disproportionation, followed by alkylation, may also be occurring.

Isomer distributions of the benzyltoluenes from the reaction of benzaldehyde with toluene were determined by capillary glc and found to be substantially the same for all three methods of preparation: 49–51% para, 7–8% meta, and 41–43% ortho. Reaction of *p*-tolualdehyde with benzene gave *p*-benzyltoluene of >99.5% purity and *p*-chlorobenzaldehyde with benzene gave 4-chlorodiphenylmethane, also in very high purity. Where the requisite aldehydes are available this method may provide a useful synthetic procedure for the preparation of substituted diphenylmethanes,[6] since the experimental procedure, par-

Table I

$$2ArCHO + Ar'H \xrightarrow{BF_3} ArCH_2Ar' + ArCO_2H$$

Registry no. ArCHO′	Registry no. Ar′H	Ar	Mol	Ar′	Ml	Method[a]	Aldehyde conversion, %	Diphenylmethane[b] yield, %	$ArCH_2Ar'$ registry no.
100-52-7	71-43-2	C_6H_5	1.89	C_6H_5	400	A	8	85	101-81-5
		C_6H_5	1.89	C_6H_5	400	B	16	91	
		C_6H_5	1.89	C_6H_5	300	C	47	55	
	108-88-3	C_6H_5	1.89	$CH_3C_6H_4$	400	A	16	81	
		C_6H_5	1.89	$CH_3C_6H_4$	400	B	36	82	
		C_6H_5	1.89	$CH_3C_6H_4$	300	C	51	57	
	108-38-3	C_6H_5	1.89	m-$(CH_3)_2C_6H_3$	300	C	53	67	38094-29-0
104-87-0		p-$CH_3C_6H_4$	1.89	C_6H_5	300	C	48	33	620-83-7
104-88-1		p-ClC_6H_4	1.00	C_6H_5	300	C	66	79	14310-22-6

[a] In method A the indicated quantities were refluxed under nitrogen with 25 ml of boron fluoride etherate for 24 hr, method B used 48-hr reflux, and in method C the reaction mixtures were heated for 6 hr at 150° in an autoclave. [b] Based on reacted aldehyde.

ticularly using method B, is simple and product isolation is easily accomplished by distillation.

Experimental Section[7]

Reaction of Benzaldehyde with Toluene (Method B). A mixture of 200 g (1.89 mol) of benzaldehyde, 25 ml of boron fluoride etherate, and 400 ml of toluene was refluxed for 48 hr. After cooling, the reaction mixture ws washed with water (100 ml) and extracted with saturated sodium carbonate solution. The organic layer was dried ($MgSO_4$) and filtered, and the toluene was removed on a 36-in. column. Distillation of the residue through the same column gave 127.3 g (64% recovery) of benzaldehyde, bp 80–82° (20 mm), and 51.1 g (82%) of a mixture of benzyltoluenes, bp 160–164° (18 mm), which was found to contain 42% ortho, 7% meta, and 51% para isomer by glc analysis (150 ft × 0.01 in. Carbowax 20M column programmed from 150 to 200° at 5°/min). The sodium carbonate extracts were filtered, acidified with concentrated HCl, collected on a filter, and air dried to give 5.4 g (13%) of benzoic acid, mp 119–120°, identified by its infrared spectrum.

Reaction of p-Chlorobenzaldehyde with Benzene (Method C). A 1-l. Magnedrive autoclave[9] constructed of Hastelloy C was charged with 140.5 g (1.0 mol) of p-chlorobenzaldehyde, 300 ml of benzene, and 25 ml of boron fluoride etherate. The autoclave was flushed with nitrogen and heated at 150° for 6 hr. After work-up as in method B there was obtained 48.2 g (34%) of unreacted p-chlorobenzaldehyde, bp 98–100° (15 mm), and 52.9 g (79%) of 4-chlorodiphenylmethane, bp 116–117° (3 mm).

Anal. Calcd for $C_{13}H_{11}Cl$: C, 77.04; H, 5.43; Cl, 17.5. Found: C, 76.88; H, 5.35; Cl, 17.4.

Acidification of the sodium carbonate extracts gave 10.3 g (10%) of p-chlorobenzoic acid, mp 232–234°, identified by comparison of the infrared spectrum with that of an authentic sample.

Registry No.—o-Benzyltoluene, 713-36-0.

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(2) (a) D. H. Hey, *J. Chem. Soc.*, 72 (1935); (b) H. Ellison and D. H. Hey, *ibid.*, 1847 (1938).
(3) J. Dewar and H. O. Jones, *J. Chem. Soc.*, 212 (1904).
(4) A. Schaarschmidt, L. Herman, and B. Szemzo, *Ber.*, **58B**, 1914 (1925).
(5) P. R. Stapp, *J. Org. Chem.*, **38**, 1433 (1973).
(6) Aromatic aldehydes may be used to prepare diphenylmethanes *via* a three-step procedure involving 1-aryl-2,2,2-trichloroethanes. See, for example, (a) A. B. Galun, A. Kaluszyner, and E. D. Bergmann, *J. Org. Chem.*, **27**, 1426 (1962); (b) A. B. Galun and A. Kalir, "Organic Syntheses," Collect. Vol. V, Wiley, New York, N. Y., 1973, p 130.
(7) The aldehydes and aromatic hydrocarbons were the best commercial grades and were used as received. Boron fluoride etherate was Eastman White Label material and was used as received. Reduction of 4-methylbenzophenone and 2-methylbenzophenone (Aldrich) to p- and o-benzyltoluene was carried out by the Huang-Minlon modification of the Wolff-Kishner procedure.[8] 3-Methylbenzophenone was prepared by reaction of 3-methylphenylmagnesium bromide with benzonitrile followed by reduction to m-benzyltoluene.
(8) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2847 (1946).
(9) Autoclave Engineers, Inc., Erie, Pa.

Reaction of Carbon Disulfide with 4-Hydrazinoquinazoline

Gary M. Coppola and Goetz E. Hardtmann*

Medicinal Chemistry Department, Sandoz-Wander, Inc., Research and Development Section, East Hanover, New Jersey 07936

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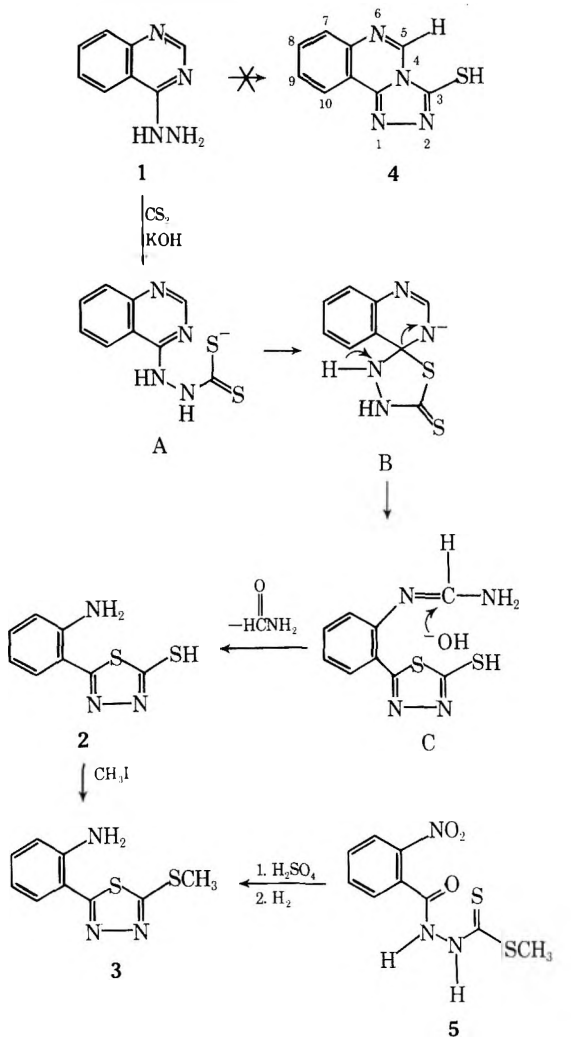
During the course of our studies on quinazolines we observed an unusual reaction between carbon disulfide and 4-hydrazinoquinazoline.



Iyengar, Naqui, and Sidhu[1] reported that the treatment of 1-hydrazinoisoquinoline with carbon disulfide in the presence of base led to the formation of 3-mercapto-*s*-triazolo[3,4-*a*]isoquinoline. When 4-hydrazinoquinazoline (1) was allowed to react with carbon disulfide under the same conditions, we observed that the expected [4,3-c]triazoloquinazoline (4) was not formed. Instead, 2-(2-aminophenyl)-5-mercapto-1,3,4-thiadiazole (2) was isolated as indicated by the presence of $-NH_2$ absorptions at 3410 and 3300 cm^{-1} in the infrared and by the absence of the expected proton in the 5 position of 4 in the nmr.

As the mechanism of the formation of 2 under these conditions, we stipulate the first intermediate to be A, which should be formed by a nucleophilic attack of the hydrazino group of carbon disulfide. An intramolecular attack of the dithiocarbazate anion may then occur at the 4 position and the spiro intermediate B is formed. Following the abstraction of a proton from the solvent, the quinazoline ring opens and C is produced. This, in turn, is attacked by hydroxide ion to produce 2 with concomitant loss of formamide.

The structure of 2 was also confirmed by the independent synthesis of 3. Using the procedure of Young and Wood,[2] 2-nitrobenzoylhydrazide was treated with carbon disulfide in the presence of potassium hydroxide followed by alkylation of the intermediate with methyl iodide to form methyl-3-(2-nitrophenyl)dithiocarbazate (5) in 25% yield (mp 174–178°). Compound 5 cyclized in concentrated sulfuric acid to 5-methylmercapto-2-(2-nitrophenyl)1,3,4-thiadiazole in 85% yield (mp 90–93°), which was then hydrogenated over palladium on carbon at 3.5 atm to 3 in 28% yield. All physical constants and spectra were identical with those of 3 isolated by the previous route.

Experimental Section[3]

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. All compounds gave satisfactory elemental analyses and their spectra (ir, obtained on Perkin-Elmer Models 257 and 457 spectrophotometers, and nmr, on Varian Models A-60 and T-60) were in full accord with the proposed structures.

2-(2-Aminophenyl)-5-mercapto-1,3,4-thiadiazole (2). A mixture of 10.0 g of 4-hydrazinoquinazoline,[4] 10 ml of carbon disulfide, 3.6 g of potassium hydroxide (85%), and 30.0 g of water in 200 ml of ethanol was refluxed for 3 hr. All insoluble materials were filtered from the reaction mixture and the solvent was removed under reduced pressure. To the residue was added 200 ml of 5% potassium hydroxide solution and any insoluble material was filtered off. The resulting solution was neutralized with 50% aqueous acetic acid, and the yellow precipitate was filtered and washed well with water. Recrystallization from ethanol furnished 6.1 g (48%) of 2, mp 214–216°.

Anal. Calcd for $C_8H_7N_3S_2$: C, 45.9; H, 3.4; N, 20.1. Found: C, 45.5; H, 3.4; N, 19.8.

2-(2-Aminophenyl)-5-methylmercapto-1,3,4-thiadiazole (3). To a solution of 2 in 125 ml of 1 *N* potassium hydroxide was added 2.2 ml of methyl iodide. The mixture was stirred at 25° for 30 min (precipitation occurred after 5 min). The resulting precipitate was filtered and recrystallized from ether to yield 6.0 g (87%) of 3, mp 91–92°.

Anal. Calcd for $C_9H_9N_3S_2$: C, 48.4; H, 4.1; N, 18.8. Found: C, 48.3; H, 4.1; N, 18.6.

Acknowledgment. The authors wish to thank Dr. Sandor Barcza and his associates for measuring the ir and nmr spectra and Mr. William Bonkoski and associates for performing the microanalyses.

Registry No.—1, 36075-44-2; 2, 51805-88-0; 3, 51805-89-1; carbon disulfide, 75-15-0.

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(4) T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960).

Oxidation of Hydrocarbons. V. Oxidation of Naphthalenes by Ruthenium Tetroxide[1]

Udo A. Spitzer* and Donald G. Lee

Department of Chemistry, University of Saskatchewan, Regina Campus, Regina, Saskatchewan, Canada S4S 0A2

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It is known that ruthenium tetroxide will readily oxidize aromatic rings to yield either mono- or dicarboxylic acids.[2-5] This ability has found particular application in the degradation of steroids.[6] Ruthenium tetroxide is an attractive reagent for these processes, since it is a vigorous oxidant which is soluble in a variety of organic solvents.[5] Furthermore it is not costly, since it can be used catalytically in conjunction with inexpensive cooxidants such as aqueous sodium hypochlorite (household bleach). Despite these advantages little was known about the directive effect of ring substituents in fused polyaromatic systems prior to this study.

From the data contained in Table I it can be seen that the substituents exert a substantial directive effect on the oxidation of substituted naphthalenes. In those cases where the substituent is electron donating it activates the ring and increases the yield of phthalic acid. When electron-withdrawing groups are present the overall reaction time is increased, the substituted ring is protected, the observed yield is reduced, and a mixture of products is obtained. The application of these observations to organic synthesis is straightforward; if it is desirable to use this reaction in an oxidative degradation procedure, the introduction of an activating group such as hydroxy or methoxy will greatly increase the rate of oxidation, thus preventing side reactions. Conversely, an aromatic ring may be protected simply by introduction of an electron-withdrawing group such as nitro.

In the case of methyl-substituted naphthalenes no evidence could be found for side-chain oxidation. In this respect ruthenium tetroxide differs in its reactions from those of several other common oxidants, particularly aqueous sodium dichromate, which is known to attack side chains preferentially.[7]

Experimental Section

All successful reactions were carried out using a two-phase system composed of carbon tetrachloride and water along with catalytic amounts of ruthenium dioxide and an excess of cooxidant. [Several experiments which were performed using stoichiometric amounts of ruthenium tetroxide were found to give extremely low yields (<10%) possibly because of absorption of the organic products on the resulting inorganic product, ruthenium dioxide.]

A typical reaction was initiated by combining 50 ml of carbon tetrachloride and 100–200 ml of bleach (enough cooxidant to ensure that phthalic acid would be the product). Then 0.01 g of $RuO_2 \cdot 2H_2O$ was added while stirring. When all of the black ruthenium dioxide had been converted to yellow ruthenium tetroxide, 0.5 g of the particular naphthalene was added. The reaction mixture was well stirred and allowed to react until no further ruthenium tetroxide was generated. Typically this time varied from hours for activated naphthalenes to several days for those compounds with electron-withdrawing groups present.

The products were separated by ether extractions and identified by glc (after esterification), ir, and tlc.

Table I
Products from Ruthenium Tetroxide Oxidation of Substituted Naphthalenes

Compd[a]	Registry no.	Reaction time[b]	Products	Yield, %
Naphthalene (3)	91-20-3	60 hr	Phthalic acid	70
α-Naphthol (3)	90-15-3	1 hr	Phthalic acid	82
β-Naphthol (2)	135-19-3	1 hr	Phthalic acid	60
1-Methylnaphthalene (7)	90-12-0	24 hr	Phthalic acid	24
			3-Methylphthalic acid	6
2-Methylnaphthalene (5)	91-57-6	24 hr	Phthalic acid	50
			4-Methylphthalic acid	5
1-Methoxynaphthalene (3)	2216-69-5	4 days	Phthalic acid	85
2-Methoxynaphthalene (1)	93-04-9	4 days	Phthalic acid	72
			4-Methoxyphthalic acid	6
2,3-Dimethylnaphthalene (2)	581-40-8	3 days	Phthalic acid	25
1,4-Dimethylnaphthalene (2)	571-58-4	3 days	Phthalic acid	10
			3,6-Dimethylphthalic acid	15
2-Chloronaphthalene (2)	91-58-7	5 days	Phthalic acid	7
			4-Chlorophthalic acid	70
1-Fluoronaphthalene (3)	321-38-0	3 days	Phthalic acid	44
			3-Fluorophthalic acid	11
1-Nitronaphthalene (4)	86-57-7	7 days	Phthalic acid	7
			3-Nitrophthalic acid	63
1-Naphthoic acid (2)	86-55-5	36 hr	Phthalic acid	38
			1,2,3-Tricarboxybenzene	16
2-Naphthoic acid (3)	93-09-4	48 hr	Phthalic acid	28
			1,2,4-Tricarboxybenzene	24
2-Naphthaldehyde (2)	66-99-9	48 hr	Phthalic acid	29
			1,2,4-Tricarboxybenzene	29
			2-Naphthoic acid	2
Tetralin (6)	119-64-2	60 hr	Adipic acid[c]	36
3-Hydroxy-2-naphthoic acid (2)	92-70-6	48 hr	Phthalic acid	85

[a] Numbers in parentheses indicate number of trials. [b] The reaction time can be reduced if more $RuO_2 \cdot 2H_2O$ is used, but this causes large decreases in yields. [c] Large amounts of tars present.

All materials were available commercially; the substituted naphthalenes were purified prior to use by crystallization and/or sublimation.

Acknowledgments. The authors are grateful to Mrs. L. Dabeka for skillful technical assistance and to the National Research Council for financial support.

Registry No.—Ruthenium tetroxide, 20427-56-9.

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(2) J. A. Caputo and R. Fuchs, *Tetrahedron Lett.*, 4729 (1967).
(3) S. Wolfe, S. K. Hasan, and J. R. Campbell, *J. Chem. Soc. D*, 1420 (1970).
(4) D. C. Ayres and A. M. M. Hossain, *J. Chem. Soc., Chem. Commun.*, 428 (1972).
(5) D. G. Lee in "Oxidation in Organic Chemistry," Part B, S. W. Trahanovsky, Ed., Academic Press, New York, N. Y., 1973, pp 194–196.
(6) D. M. Piatak, G. Herbst, S. Wicha, and E. Caspi, *J. Org. Chem.*, **34**, 116 (1969).
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Dominance of an Ionic Mechanism over a Cyclic Concerted Process in a Hydrocarbon Solvent

F. M. Menger[1] and L. E. Glass

Department of Chemistry, Emory University, Atlanta, Georgia 30322

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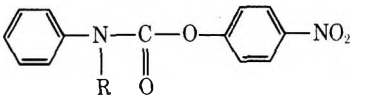
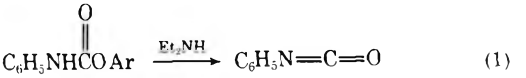
We have investigated the mechanism for the aminolysis of *p*-nitrophenyl *N*-phenylcarbamate (Ia) in toluene.[2] As will be shown below, Ia reacts in the nonpolar solvent through an ionic mechanism to the exclusion of a cyclic six-center process that generates little or no charge.



Ia, R = H
b, R = CH_3

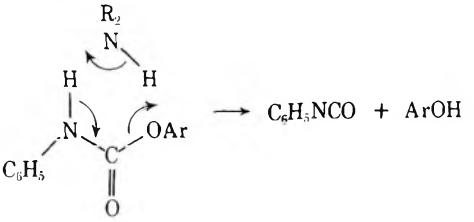
The observed rate constant (as measured by *p*-nitrophenol release) for the reaction of 0.053 *M* diethylamine with 8.7×10^{-5} *M* Ia in toluene at 25.0° was found to equal 1.50×10^{-3} sec^{-1}. This is at least 10^4 faster than that between diethylamine and Ib.[3] If the amine attacked the carbamate carbonyl (to eject *p*-nitrophenol and form a urea *via* a BAC2 mechanism), then Ia and Ib would not differ so widely in their rates.[4] The requirement of an N proton for a facile reaction demands that Ia eliminate to give an isocyanate intermediate (eq 1).[5,6] The intermediate subsequently reacts with amine to produce a urea.



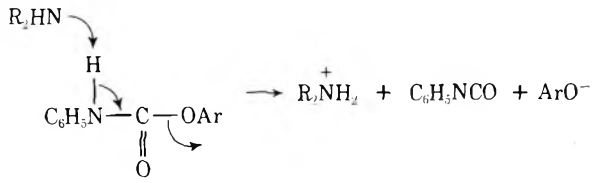
(1)

Formation of the isocyanate in toluene could conceivably occur by one of three mechanisms.

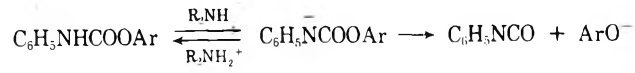
(1) Six-membered cyclic concerted process



(2) E2 mechanism



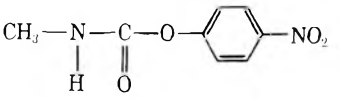
(3) E1cB mechanism



The following results remove the cyclic concerted mechanism as an acceptable possibility. Both diethylamine and triethylamine were found to catalyze the formation of isocyanate from Ia. The triethylamine-catalyzed elimination is first order in amine below 0.1 *M* amine ($k_2 = 4.5 \times 10^{-2}$ M^{-1} sec^{-1}, toluene, 25.0°).[7] The diethylamine reaction is *both first order and second order in amine with the former* predominating below 0.1 *M* amine ($k_2 = 2.2 \times 10^{-2}$ M^{-1} sec^{-1}, toluene, 25.0°). Comparison of the corresponding bimolecular rate constants for the secondary and tertiary amines shows that triethylamine is a twofold better catalyst than diethylamine. Of the three mechanisms above, only the first is inconsistent with this comparison. Triethylamine lacks the necessary N proton to participate in the cyclic pathway. We conclude that the concerted mechanism is incorrect.

Both of the remaining mechanisms entail charge formation. One would predict, therefore, that carbamate aminolysis should be subject to a sizable solvent effect, and this was found to be the case. The reaction of triethylamine with Ia is three orders of magnitude faster in acetonitrile than in toluene.

No evidence was collected which distinguishes the E2 from the E1cB-type mechanism. There does seem, however, to be considerable N–H breakage in the transition state, because Ia reacts over 200 times faster than *p*-nitrophenyl *N*-methylcarbamate (II) with triethylamine in toluene.



II

In conclusion, we have found that the aminolysis of Ia prefers an ionic mechanism despite the nonpolar medium and despite the availability of a seemingly feasible concerted pathway. The lack of a concerted proton transfer from a secondary amine to the "ether" oxygen of Ia during the proton abstraction suggests that there is little carbonyl carbon–oxygen bond cleavage in the transition state. If bond cleavage were appreciable, then the cyclic mechanism would be favored because *p*-nitrophenoxide is undoubtedly a stronger base than an aliphatic amine in a hydrocarbon solvent.[8,9] Our results can also be viewed in terms of the postulate that intramolecular proton transfer is most probable when a cyclic transition state can accommodate a linear arrangement of the donor atom, proton, and acceptor atom.[10] The absence of a cyclic mechanism for aminolysis of Ia might, therefore, stem from the inability of a six-membered ring to attain such a relationship.

Experimental Section

Materials. *p*-Nitrophenyl *N*-phenylcarbamate was prepared by refluxing equimolar amounts of *p*-nitrophenol and phenyl isocyanate in dry toluene for 3 hr. Recrystallization and drying gave pale yellow crystals, mp 148–150° (lit. mp 153–155°,[11] 149–150° [12]).

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.50; H, 3.91; N, 10.87.

p-Nitrophenyl *N*-methyl-*N*-phenylcarbamatewas prepared from *p*-nitrophenol, *N*-methyl-*N*-phenylcarbamoylchloride, and triethylamine in toluene. The product was purified by liquid chromatography and by crystallization to give a 6% yield of product melting at 62–64°.

Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.83; H, 4.50; N, 10.36.

p-Nitrophenyl *N*-methylcarbamate was obtained by mixing *p*-nitrophenol and methyl isocyanate in anhydrous diethyl ether with a trace of triethylamine, mp 162–163° (lit.[2a] mp 157.5–159°).

Kinetics. A stoppered cuvette containing 3.00 ml of a toluene solution of an aliphatic amine (0.01–0.1 *M*) was equilibrated at 25.0° within the thermostated cell comparment of a Cary 14 spectrophotometer. A small amount (25 μl) of a toluene solution of Ia was then added to the cuvette such that the initial substrate concentration was 8.7×10^{-5} *M*. The production of *p*-nitrophenol (measured by the increase in absorbance at 322 nm) was then traced as a function of time.[13] Pseudo-first-order rate constants were secured by processing the absorbance–time data in the usual manner.

Acknowledgment. This work was supported in part by the National Science Foundation.

Registry No.—Ia, 6320-72-5; Ib, 49839-35-2; II, 5819-21-6; diethylamine, 109-89-7; triethylamine, 121-44-8.

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(2) For information on the mechanism of carbamate hydrolyses, see (a) M. L. Bender and R. B. Homer, *J. Org. Chem.*, **30**, 3975 (1965); (b) A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 808 (1972); (c) L. N. Frost and A. F. Hegarty, *J. Chem. Soc., Chem. Commun.*, *82* (1973).
(3) The reaction of Ib is too slow to measure under our reaction conditions; therefore 10^4 is only a *minimum* rate difference.
(4) The rate difference cannot be attributed to steric effects on a BAC2 mechanism because diisopropylamine reacts with Ia nearly as rapidly as does diethylamine.
(5) The same argument has been used in a study of the alkaline hydrolysis of carbamates (ref 2a).
(6) Y. Furuya, *et al.*, *Tetrahedron*, **24**, 2367 (1968), studied the mechanism of aminolysis of *p*-nitrophenyl *N*-phenylcarbamate by aniline in dioxane at 80°. Since they did not consider the possibility of an isocyanate intermediate, we feel that their work ought to be reexamined in the light of our results.
(7) At concentrations well above 0.1 *M* triethylamine, the k_{obsd} vs. [amine] plot curves downward. The origin of this effect has not yet been established.
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(13) Analysis of the infinity spectra of the triethylamine-catalyzed reaction showed that the production of *p*-nitrophenol is quantitative.

Selectivity in the Free-Radical Reduction of Lactones with Trichlorosilane[1]

S. W. Baldwin,* R. J. Doll, and S. A. Haut

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

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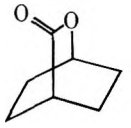
Each of the generally recognized methods for converting lactones to cyclic ethers suffers from distinct structural limitations. For instance, Adams catalyst in an acidic medium will reduce δ-lactones to the corresponding ethers but fails completely with γ- and ε-lactones.[2] Pettit's reagents derived from complex metal hydrides and boron trifluoride are very effective when the alcohol portion of the lactone is tertiary, but the yields of ethers decrease

dramatically as substitution at the alcohol portion is decreased.[3] Published results suggest a further limitation to the Pettit procedure when the lactone is part of an otherwise flexible system that can adopt a more favorable conformation by ring opening. For instance, Bruice[4] has reported that no ether is formed on reduction of 2-oxabicyclo[2.2.2]octan-3-one (1) with BF_3–B_2H_6 and we have encountered a similar failure with 6-oxabicyclo[3.2.1]octan-7-one (2). Each of these lactones are esters of secondary



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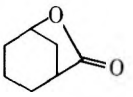

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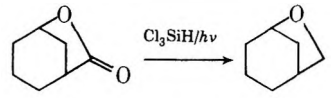
alcohols and would normally be expected to afford moderate amounts of ether. Failure to do so presumably indicates that the preferred conformations of ring-opened intermediates derived from 1 and 2 are such as to preclude ready recyclization to the desired ethers.[5] Thus the successful applications of the Lewis acid–metal hydride reagents have generally occurred when the lactone ring was either part of a strain-free or conformationally restricted system. We wish to report here that the radical-induced reduction of lactones by trichlorosilane circumvents many of the problems previously mentioned and further that the reaction can exhibit remarkable selectivity.

There have been several recent reports describing the reduction of simple esters and lactones with trichlorosilane on ultraviolet irradiation.[6] Tsurugi's thorough work has established that the reduction proceeds by a radical chain process, greatly diminishing the opportunity for ring opening *via* ionic intermediates. We anticipated that the application of Tsurugi's method to more complex lactones might well be of value.

In practice this prediction was realized when lactones 2 and 4 were smoothly converted to the cyclic esters by irra-



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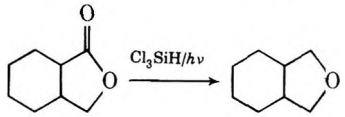
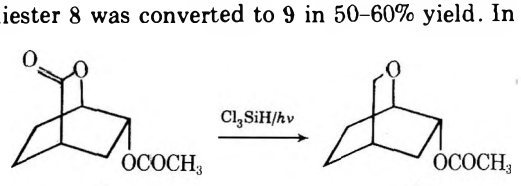


4 5

diation in the presence of excess trichlorosilane. Perhaps of greater interest was the selectivity shown when the lactone contained additional ester groupings. For instance, reaction of lactone acetate 6 with 2 equiv of trichlorosilane afforded ether 7 in 73% yield.[7] In a similar manner lactone diester 8 was converted to 9 in 50–60% yield. In each



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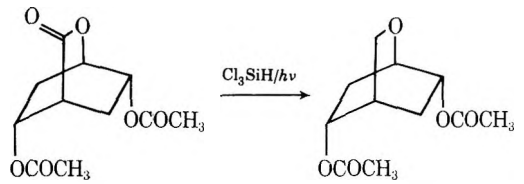

8 9

case the lactone carbonyl was selectively reduced. Current observations suggest that the observed selectivity is steric in origin, although this remains to be rigorously demonstrated.

Although the work reported herein describes the direct one-step conversion of lactones to polycyclic ethers, there is some question as to other fuctionality which may be present. For instance, Tsurugi[6a] has noted the inhibitory effect of added aromatic compounds to the reaction medium and the propensity for reaction between $\cdot SiCl_3$ and other unsaturated centers is known. We are currently examining the scope of this reaction in detail.

Experimental Section

The ir spectra were recorded on Perkin-Elmer 137 and 237 spectrophotometers. Nmr spectra were determined on a Varian A-60 spectrometer or a Jeol MH-100 spectrometer and are reported in δ units downfield from TMS. Gas chromatographic analyses were performed on a Hewlett-Packard Model 700 laboratory gas chromatograph equipped with dual flame ionization detectors. A flow rate (N_2) of 35 ml/min through 6 ft × 0.125 in. columns (5% SE-30 on Chromosorb P) was employed. Microanalyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga., and M-H-W Laboratories, Garden City, Mich. Yields have not been optimized.

6-Oxabicyclo[3.2.1]octane (3). A. A solution of 478 mg (3.80 mmol) of lactone 2 and 29 mg (0.04 ml, 0.2 mmol) of di-*tert*-butyl peroxide in 2.06 g (1.60 ml, 15.2 mmol) of trichlorosilane was degassed (0.01 mm) with three freeze–pump–thaw cycles, sealed in a Pyrex tube, and irradiated for 2.5 hr with a Hanovia 450-W medium-pressure ultraviolet lamp. The resulting clear solution was diluted with 50 ml of CH_2Cl_2 and then the excess trichlorosilane was destroyed by the careful addition (0°, stirring) of 10 ml of water and 2.5 ml of 10% NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 ml) and the combined organic layer was washed with saturated brine (50 ml) and dried ($MgSO_4$). Gas chromatographic analysis of this dilute solution showed a single peak identical with authentic material prepared in B. Careful removal of the solvent and distillation (sublimation) of the residue in the Kugelrohr manner (110°, 33 mm) afforded 126 mg (27.5%)[8] of semisolid residue, spectroscopically identical with the ether prepared in B.[9]

B. An ether solution of 204 mg (2.42 mmol) of lactone 2 was reduced with excess lithium aluminum hydride. The resulting crude diol and 2 mg of *p*-toluenesulfonic acid were distilled (sublimed) as above (110°, 33 mm) to give 160 mg (59.4%) of a waxy solid, which exhibited a single peak on gas chromatographic analysis (100°, 2.3 min), identical with the ether prepared in A: nmr (CCl_4) δ 1.43–2.50 (broad, 9 H), 3.78 (m, 2 H, $-CH_2O-$), 4.25 (broad, 1 H, –CHO).

***trans*-8-Oxabicyclo[4.3.0]nonane (5).**[10] **A.** A solution of 500 mg (3.57 mmol) of lactone 4 (prepared by the method of Bloomfield[11]), 26 mg (0.033 ml, 0.18 mmol) of di-*tert*-butyl peroxide, and 1.94 g (1.44 ml, 14.3 mmol) of trichlorosilane was degassed and sealed in a Pyrex tube as described above. Irradiation as before for 2 hr followed by a similar work-up (CH_2Cl_2, NaOH, NaCl, $MgSO_4$) and concentration at 200 mm led to 410 mg of mobile oil which was distilled in the Kugelrohr manner (85°, 33 mm) to give 373 mg (83%) of colorless liquid identical with that produced in B. Occasionally the presence of minor amounts (10–20%) of cis ether was apparent from the nmr spectrum, which showed complex absorption centered at δ 3.64.

B. A solution of trans diol [derived from reducing 5.0 g (35.7 mmol) of trans lactone 4 with excess lithium aluminum hydride], 20 ml of water, and 1 ml of concentrated H_2SO_4 was steam distilled, additional water being added as necessary to maintain the original volume. When organic material stopped collecting, the distillate was saturated with potassium carbonate and extracted with ether (3 × 10 ml). The combined ether layers were washed with brine (50 ml), dried ($MgSO_4$), and concentrated at 200 mm. Distillation of the residue afforded 3.5 g (78%) of pure ether, bp 73–77° (20 mm) [lit.[10] bp 70° (20 mm)], homogeneous by gas chromatography (150°, 1.3 min): nmr (CCl_4) δ 0.84–1.63 (broad, 8 H), 1.81 (broad, 2 H), 2.09 (m, 2 H), 3.64 (m, 4 H).

6-*endo*-Acetoxy-2-oxabicyclo[2.2.2]octan-3-one (6). A. A solution of 10.3 g (65.0 mmol) of 3α,4β-dihydroxycyclohexane-1α-carboxylic acid (**13**)[12] in 200 ml of acetic anhydride was slowly heated under nitrogen to 180–185° and maintained at that temperature for 1 hr. Removal of the acetic anhydride *in vacuo* gave 13 g of a light yellow oil, vacuum distillation of which afforded 4.72 g

(40%) of a colorless liquid: bp 111–120° (0.05 mm); ir (CCl_4) 1774 and 1755 cm^{-1} (C=O); nmr (CCl_4) δ 1.90 (broad, 5 H), 2.10 (s, 3 H, $COCH_3$), 2.50 (broad, 2 H), 4.55 (broad, 1 H), 5.00 (m, 1 H).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.61; H, 6.41.

B. Oxidation of Ether 7 with Ruthenium Tetroxide.[13] To a solution of 200 mg (1.28 mmol) of ether **7** in 50 ml of carbon tetrachloride was added 2 ml of a carbon tetrachloride solution of ruthenium tetroxide [prepared by stirring 0.1 g (0.49 mmol) of ruthenium trichloride and 0.5 g (2.32 mmol) of sodium periodate in 25 ml of carbon tetrachloride and 10 ml of water for 20 hr] and a solution of 0.5 g (2.32 mmol) of sodium periodate in 25 ml of water. After the mixture was stirred vigorously for 2 days, isopropyl alcohol was added and the mixture was filtered. Concentration of the organic layer afforded 129 mg (55%) of lactone **6**, identical with material prepared in A.

6-*endo*-**Acetoxy-2-oxabicyclo[2.2.2]octane (7). A.** A solution of 5.59 g (30.0 mmol) of lactone **6**, 8.31 g (61 mmol) of trichlorosilane, and 0.22 g (1.5 mmol) of di-*tert*-butyl peroxide in a Pyrex tube (35 × 1.5 cm) was degassed by four freeze–pump–thaw cycles (0.01 mm). The tube was sealed and then irradiated as before for 4 hr. The contents of the tube were then poured into 200 ml of ether and 10% sodium hydroxide was added carefully until no further reaction occurred. After filtration, the filtrate was washed with saturated sodium bicarbonate (25 ml) and brine (25 ml), dried ($MgSO_4$), and concentrated. Distillation of the resulting oil in the Kugelrohr manner afforded 3.78 g (73%) of a light oil (70–80°, 0.01 mm): ir (CCl_4) 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.30–2.50 (broad, 7 H), 2.08 (s, 3 H, $COCH_3$), 3.70 (broad, 3 H, H_2COCH), 4.90 (m, 1 H, HCOCOCH$_3$).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.66; H, 8.06.

5-*endo*-**Carbomethoxy-7-*endo*-acetoxy-2-oxabicyclo[2.2.2]octane (9).** A solution of 5.0 g (21.0 mmol, freshly recrystallized) of lactone 8,[14] 7.01 g (52.0 mmol) of trichlorosilane, 0.241 g (1.65 mmol) of di-*tert*-butyl peroxide, and 30 ml of tetrahydrofuran (doubly distilled from $LiAlH_4$) was placed in a Pyrex tube (35 × 1.5 cm) and degassed by eight freeze–pump–thaw (0.01 mm) cycles. The tube was sealed and irradiated as before for 12 hr at 50° (heat lamp) and at a distance of 11.5 cm from the lamp. Volatile material was removed by vacuum distillation (30°, 20 mm) and the residue was dissolved in a slurry of 100 ml of ethyl ether and 3 g of sodium bicarbonate. Water was added dropwise until gas evolution ceased. After stirring for 0.5 hr the mixture was dried ($CaCl_2$), filtered, and concentrated to give a light residue. Distillation afforded 2.40 g (50%) of product, bp 95–100° (0.04 mm), that was homogeneous by gas chromatography (160°, 5.0 min):[15] ir (CCl_4) 1745 cm^{-1} (C=O); nmr (CCl_4) δ 1.5–2.4 (broad, 6 H), 2.05 (s, 3 H, $COCH_3$), 3.65 (s, 3 H, $COOCH_3$), 3.75 (broad, 3 H, H_2COCH), 4.90 (m, 1 H, HCOCOCH$_3$).

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.64; H, 6.86.

Registry No.—**2**, 4350-83-8; **3**, 279-87-8; **4**, 7702-72-9; **5**, 10479-79-5; **6**, 51608-92-5; **7**, 51608-93-6; **8**, 51608-94-7; **9**, 51608-95-8; **13**, 23477-88-5; *trans*-1,2-cyclohexanedimethanol, 25712-33-8.

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(7) When the reduction of **6** was carried out with 4 equiv of trichlorosilane, the major product (60% yield) was the ethyl ether formed by further reduction of the acetate of **7**.
(8) Gas chromatographic analysis of the crude reaction mixture showed that ether **3** was the only volatile product present and that it had been formed in 67% yield (*p*-xylene internal standard). The low isolated yield is ascribed to its extreme volatility and resultant loss during work-up.
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(14) Details of the synthesis of triester **8** from *trans*-1,2,3,6-tetrahydrophthalic anhydride (75% yield) will be reported at a later date.
(15) The major contaminant in the reduction of **8** resulted from attack at the acetate carbonyl and ranged randomly from 15 to 35%.

Methoxymethyl Isocyanate from Thermal Rearrangement of 5-Methoxymethyldioxazolone

W. J. Kauffman

Armstrong Cork Company, Research and Development Center, Lancaster, Pennsylvania 17604

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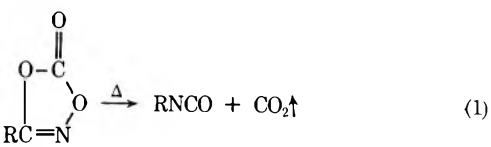
The acid-catalyzed reactions[1] of *N*-methylol and *N*-methoxymethyl derivatives have been utilized industrially. The formation of resins and modifications of cellulose employing urea–formaldehyde and melamine–formaldehyde chemistry are examples. Interst has developed in methoxymethyl isocyanate (MMI) as a modifying agent for incorporating *N*-methoxymethyl sites onto reactive polymers.[2-5] Such modifications have resulted in thermosetting lacquers, coatings, and resins suitable for industrial applications. Our efforts in this area were initially complicated by problems encountered in the synthesis of MMI.

The reported[3] synthesis of MMI involves the reaction of chloromethyl methyl ether with sodium cyanate in a mixed solvent system composed of DMF and a hydrocarbon, and isolation of the MMI by distillation (90°, 760 mm). We found the yields of MMI by this method to be low and variable. The highest yield of MMI we have realized by this procedure is 45%. The MMI was codistilled with toluene from the reaction mixture containing DMF–toluene as solvents. The utilization of this MMI–toluene solution was previously reported.[6] We would like to report a superior synthetic route for the generation of MMI in excellent yields in a hydrocarbon solvent.

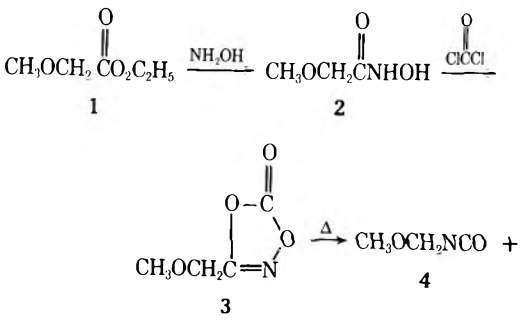
The thermal rearrangement of dioxazolones (nitrile carbonates) to aliphatic and aromatic isocyanates has been well documented.[7-12] The nature and scope of the rearrangement have not, however, been thoroughly investigated. We have applied the aforementioned thermal rearrangement of nitrile carbonates to the synthesis of MMI. The precursor dioxazolone (**3**) was prepared as shown in eq 2.



(1)

Ethyl methoxyacetate (**1**) was treated with hydroxylamine in methanol to produce methoxyacetohydroxamic acid (**2**). The hydroxamic acid **2** was then treated with excess phosgene, which resulted in the isolation of methoxymethyldioxazolone (**3**) in excellent yield.

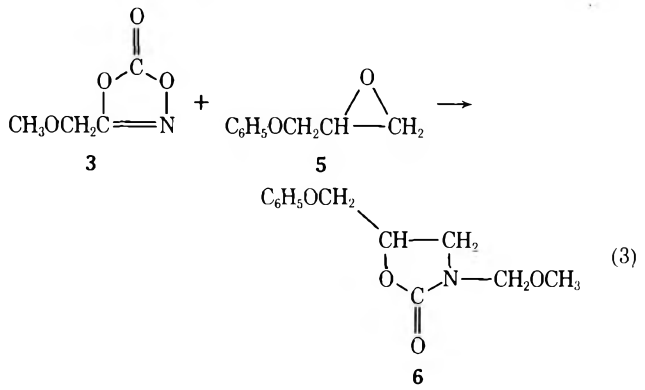
The dioxazolone **3** could be easily handled and was not a lachrymator. Analysis (neat) by differential scanning calo-



rimetry (DSC) indicated an initial decomposition point of 150° with rapid decomposition occurring at 170°. The decomposition of the dioxazolone **3** in solution could be easily followed by ir owing to its characteristic[6] carbonyl bands. The rearrangement of a 10% solution of dioxazolone **3** in DMF occurred at 130° with the appearance of the isocyanate band at 2250 cm^{-1}. Most of the dioxazolone **3** had decomposed after 1 hr, but the isocyanate band dropped in intensity and new bands appeared corresponding to the trimer (1,2,5-trimethoxymethyleneisocyanurate). This is consistent with the exclusive formation of trimer from the chloromethyl methyl ether and sodium cyanate reaction in DMF.[3] The decomposition of dioxazolone **3** in refluxing xylene (140°) was also investigated. After 16 hr, most of the dioxazolone **3** remained unreacted; however, a weak isocyanate band had developed at 2250 cm^{-1}.

The dioxazolone **3** was observed to decompose rapidly in refluxing xylene solution containing 2.5 mol % of a hydrocarbon-solubilized adduct of tributylphosphine oxide and lithium bromide. After 15 min, the infrared spectrum indicated the disappearance of dioxazolone **3** and the appearance of an intense isocyanate band at 2250 cm^{-1}. A conventional isocyanate (NCO) analysis[14] indicated 95% conversion to MMI.

As previously reported,[6,15] the MMI can be trapped with phenyl glycidyl ether under these conditions. Equimolar



quantities of methoxymethyldioxazolone (**3**) and phenyl glycidyl ether (**5**) in xylene were added dropwise (15 min) to a refluxing solution of hydrocarbon-solubilized catalysts (2.5 mol %) in xylene. After the addition was completed, ir analysis indicated a trace of isocyanate, no dioxazolone, and an intense band at 1760 cm^{-1} (2-oxazolidone). Work-up of the reaction mixture resulted in the isolation of 90% *N*-methoxymethyl-5-phenoxym ethylene-2-oxazolidone (**6**) that was identical with the known sample.[15] The thermal rearrangement of the dioxazolone (3) under these conditions produces excellent yields of MMI in xylene solution.

Experimental Section

General. Phosgene was obtained from Air Products and Chemicals, Inc., and was utilized without further purification. All other chemicals were obtained from Aldrich Chemical Co. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared absorption spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. The nmr spectra were determined on a Japan Electron Optics Lab 4H-100 spectrometer using TMS as internal standard and solvents were as indicated. The DSC data were obtained on a Du Pont 900 Thermal Analyzer in the DSC mode.

Methoxyacetohydroxamic Acid (2). The procedure of Jones and Powers[13] was employed. A solution of hydroxylamine hydrochloride (140 g, 2.0 mol) in methanol (750 ml) was prepared by heating to reflux. The solution was allowed to cool to 30° and a solution of potassium hydroxide (112 g, 2.0 mol) in methanol (300 ml) was added. The temperature of the resulting mixture was kept below 40° by the use of an ice bath. After 5 min the ethyl methoxyacetate was added and the flask was stoppered and allowed to stand overnight. The mixture was filtered and the filtrate was concentrated on a rotary evaporator. The resulting solid was recrystallized from ethyl acetate–ligroin, yielding 71 g of methoxyacetohydroxamic acid: mp 83–84° (lit.[13] mp 85.5°); nmr (DMSO-d_6) δ 10.58 (s, 1 H), 8.80 (s, 1 H), 3.76 (s, 2 H), 3.25 (s, 3 H).

5-Methoxymethyldioxazolone (3). The recrystallized methoxyacetohydroxamic acid (**2**, 30 g, 0.28 mol) was slurried with 400 ml of anhydrous ether and cooled to 0°. Excess phosgene (180 g, 1.8 mol) was bubbled into the stirred ether slurry. After the phosgene had been added, the clear solution was warmed to room temperature and flushed with dry nitrogen (8 hr) to remove the excess phosgene. The ether was removed on a rotary evaporator and the residue was distilled, yielding 34.0 g (92%) of methoxymethyldioxazolone (**3**): bp 52–54° (0.85 mm); ir (neat) 1825 and 1875 cm^{-1} (dioxazolone ring); nmr ($CDCl_3$) δ 4.39 (s, 2 H), 3.45 (s, 3 H).

Anal. Calcd for $C_4H_5NO_4$: C, 36.65; H, 3.84; N, 10.69. Found: C, 36.72; H, 3.79; N, 10.67.

Trapping of Methoxymethyl Isocyanate with Phenyl Glycidyl Ether. A xylene solution (100 ml) containing the hydrocarbon-solubilized adduct of tributylphosphine oxide (0.8 mmol, 3.5 mol %) and lithium bromide (0.57 mmol, 2.5 mol %) was prepared and dried as previously reported.[6] A xylene solution (10 ml) containing methoxymethyldioxazolone (3.0 g, 22.9 mmol) and phenyl glycidyl ether (3.4 g, 22.9 mmol) was added dropwise (15 min) to the refluxing solution of the hydrocarbon-solubilized catalyst. The reaction was judged complete by ir analysis and the solution was allowed to cool to room temperature. The xylene was removed on a rotary evaporator under vacuum and the solid product was recrystallized from carbon tetrachloride–hexane, yielding 90% of *N*-methoxymethylene-5- phenoxymethylene-2-oxazolidone (5.6 g, 20.6 mmol). This material was identical with a known sample previously prepared.[6]

Registry No.—**1**, 3938-96-3; **2**, 51821-07-9; **3**, 51821-08-0; **4**, 6427-21-0; **5**, 122-60-1; **6**, 34277-53-7.

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The Synthesis of 9-*epi*-Leucomycin A_3. The Revised Configurational Assignment of C-9 in Natural Leucomycin A_3

Summary: The configurational assignment of C-9 in leucomycin A_3 has been revised, based on spectral data obtained with 9-*epi*-leucomycin A_3 and the natural material, which were synthesized from niddamycin.

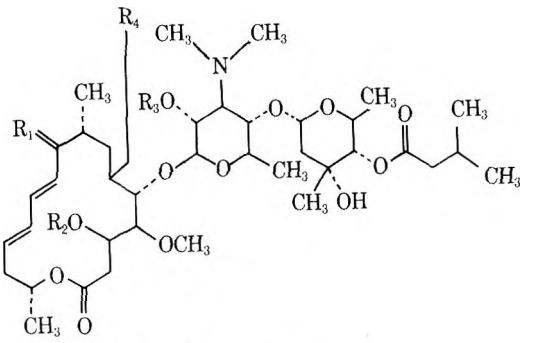
Sir: The absolute configuration of the lactone ring of the antibiotic leucomycin A_3, except for C-9, has been established by X-ray spectroscopy of an acid degradation product.[1] The absolute configuration at C-9 has been assigned independently by the application of the benzoate or Mills' rule to 3,5-dinitrobenzoate derivatives.[2] We now wish to report the synthesis and characterization of the two C-9 epimers of leucomycin A_3 and present spectral evidence which suggests the configuration at C-9 in the natural material is *R, epimeric to the previous assignment.*[3]

The initial synthetic step was the selective protection of the aldehyde group of niddamycin (**1**)[5,6] by acid-catalyzed dimethyl acetal formation. A methanol solution of **1** (0.085 *M*) and difluoroacetic acid (10 equiv) on standing for 66 hr at 25° gave 6b-niddamycin dimethyl acetal (**2**) in 50% yield: mp 208–211° (ethyl acetate–hexane); $[\alpha]^{25}D$ −39.3°.[7] Under these mild conditions, dimethyl acetal formation is found to proceed at a much faster rate than acid-catalyzed methanolysis of glycosidic bonds.[8] Next, the required 3-(*O*)-acetyl group was introduced by exhaustive acetylation of **2** with acetic anhydride–pyridine at 25° to give the diacetate **3** [mp 176–181° (ethyl acetate–hexane), $[\alpha]^{25}D$ −32.7°], followed by removal of the 2′-(*O*)-acetyl group by hydrolysis with $NaHCO_3$ in MeOH–H_2O to give 3-(*O*)-acetyl-6b-niddamycin dimethyl acetal (**4**): mp 202–208° (MeOH–H_2O); $[\alpha]^{25}D$ −10.5°; λ_{max}^{MeOH} 278 nm (ε 21,800).

Studies on the sodium borohydride reduction of **4** showed the ratios of C-9 epimeric alcohols obtained were markedly sensitive to the solvent employed. Thus, reduction of **4** in dioxane at 25° provided a 4:1 (epi:natural) mixture of isomers (tlc) from which the major product was isolated by column chromatography on silica gel [benzene–methanol (2%)] to give a 35% yield of pure 9-*epi*-leucomycin A_3 dimethyl acetal (**5**): amorphous; $[\alpha]^{25}D$ −36.2°; λ_{max}^{MeOH} 232 nm (ε 25,800). In contrast, reduction of **4** in methanol at 25° provided a 1:4 (epi:natural) mixture, which gave after chromatography (silica gel) a 57% yield of leucomycin A_3 dimethyl acetal (**6**): amorphous; $[\alpha]^{25}D$ −64.0°; λ_{max}^{MeOH} 232 nm (ε 28,200).

Finally, the acetal protecting groups were removed by acid hydrolysis in 50% acetonitrile–water. Treatment of an 0.075 *M* solution of **5** with 2.5 equiv of difluoroacetic acid at 25° for 4 hr gave 9-*epi*-leucomycin A_3 (**7**) in quantitative yield: amorphous; $[\alpha]^{25}D$ −38.7°; λ_{max}^{MeOH} 232 nm (ε 26,600). Under identical conditions **6** required 24 hr for complete hydrolysis, giving after chromatography a 50% yield of leucomycin A_3 (**8**): mp 125–127° (benzene); $[\alpha]^{25}D$ −69.1°; λ_{max}^{MeOH} 231 nm (ε 28,100).[9] Similarly, hydrolysis of **4** gave carbomycin B (**9**): mp 193–200° (prisms, acetone–water); $[\alpha]^{25}D$ −37° (c 1.00, $CHCl_3$); λ_{max}^{MeOH} 278 nm (ε 23,200).[10]

Proton nmr and high dilution differential ir spectral data were employed to establish the configurations at C-9 in **5**–



1, R_1 = O; R_2 = R_3 = H; R_4 = CHO
2, R_1 = O; R_2 = R_3 = H; R_4 = $CH(OCH_3)_2$
3, R_1 = O; R_2 = R_3 = Ac; R_4 = $CH(OCH_3)_2$
4, R_1 = O; R_2 = Ac; R_3 = H; R_4 = $CH(OCH_3)_2$
5, R_1 = HO, H; R_2 = Ac; R_3 = H; R_4 = $CH(OCH_3)_2$
6, R_1 = H, HO; R_2 = Ac; R_3 = H; R_4 = $CH(OCH_3)_2$
7, R_1 = HO, H; R_2 = Ac; R_3 = H; R_4 = CHO
8, R_1 = H, HO; R_2 = Ac; R_3 = H; R_4 = CHO
9, R_1 = O; R_2 = Ac; R_3 = H; R_4 = CHO

8. Since the C-9 and double-bond region of the molecule had not been defined by the X-ray structure, these proton resonances were of particular interest. The coupling constants of $J_{10,11}$ and $J_{12,13}$ = 15 Hz indicate that the double bonds are trans[11] and the value of $J_{11,12}$ = 10 Hz that the diene systems are in a nearly planar *S* (trans) conformation.[12] In the natural series (**6** and **8**) $J_{9,10}$ = 9.0 Hz, indicating that H-9 lies nearly in the plane of the diene system.[13] In the epi series (**5** and **7**), however, H-9 forms an appreciable angle with this plane as shown by the values of $J_{9,10}$ = 4.0 Hz[13] and the 4-bond allylic coupling $J_{9,11}$ = 1.8 Hz.[14] In both epimers and their derivatives, coupling between H-8 and H-9 is small ($J_{8,9}$ = 3–4 Hz), indicating a dihedral angle of $\phi \simeq 60°$ between these protons. Anticipating that the plane of the diene system is approximately perpendicular to the general plane of the lactone ring,[1,15] the nmr data are consistent with the configurational assignments as shown in Figure 1.

Evidence that these assignments are correct was obtained from ir spectral studies. Corey–Pauling–Koltun (CPK) molecular models of the C-9 leucomycin A_3 epimers were constructed to fit the observed lactone ring coupling constants and X-ray structure. These models reveal the 9-hydroxyl group of the *S* epimer **7** is in close proximity (~3.2 Å) to the 3-(*O*)-acetyl carbonyl oxygen and should form an intramolecular hydrogen bond. Furthermore, in **5** (the dimethyl acetal derivative) a second hydrogen bond accepting site (an OMe group) is available. However, the CPK model of the *R* epimer **8** shows the 9-hydroxyl group to be 5 Å or greater from any potential intramolecular hydrogen bonding site. This situation is not changed by any reasonable conformation reorganization of the model.

High dilution differential ir spectra of the epimeric alco-

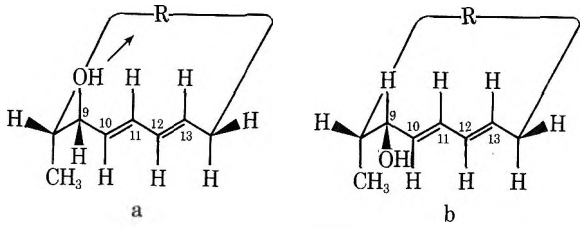


Figure 1. Projection view of the C-8 to C-14 portion of the lactone ring of (a) 9-*epi*-leucomycin A_3 (7) and (b) leucomycin A_3 (8) (R = remainder of lactone ring).

hols, employing the ketones **4** or **9** in the reference beam, were obtained for the hydroxyl region. The spectral data obtained at 2×10^{-3} *M* in CCl_4 were exactly reproduced at tenfold dilution, showing the intramolecular nature of the H-bonding patterns observed. The 9-epi derivative **7** showed bands at 3618 and 3550 cm^{-1} while the corresponding dimethyl acetal derivative **5** showed bands at 3618, 3535, and 3482 cm^{-1} providing clear evidence of intramolecular hydrogen bonding of the C-9 hydroxyl to oxygen electron pair donors. However, in agreement with results reported by Omura,[15] the C-9 hydroxyl groups of leucomycin A_3 [and the dimethyl acetal derivative (**6**)] show single strong hydroxyl bands at 3618 cm^{-1}. Therefore, we conclude that the configuration at C-9 of leucomycin A_3 is *R*, as shown in Figure 1b, which is epimeric to the previous assignment.

The configuration at C-9 in spiramycin has been shown to be the same as leucomycin A_3 by chemical interrelation[16] and should also be revised. The recently reported value of $J_{9,10}$ = 9.0 Hz for maridomycin II[17] suggests that the configuration at C-9 of this antibiotic is also *R*.

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Supplementary Material Available. Tables of nmr and ir spectral data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2474.

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Division of Antibiotics and Natural Products
Abbott Laboratories
North Chicago, Illinois 60064

Leslie A. Freiberg*
Richard S. Egan
William H. Washburn

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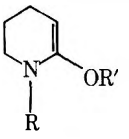
New Synthetic Reactions. Alkylation of Lactam Derivatives

Summary: Alkylation of the enolate equivalent of 1-methyl-2-piperidone (**1a**) and2-methoxy-3,4,5,6-tetrahyd ropyridine (**1b**) gave only substitution at carbon; with methyl vinyl ketone, **1a** gave carbonyl addition but **1b** gave conjugate addition.

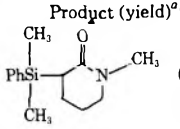
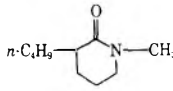
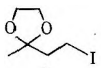
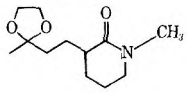
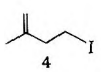
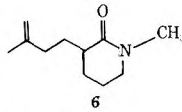
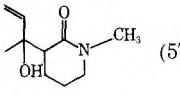
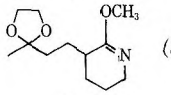
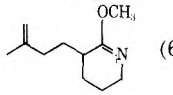
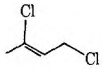
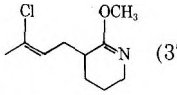
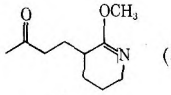
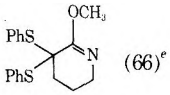
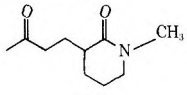
Sir: The direct alkylation of carboxylic acid derivatives has rapidly become a very useful method in organic synthesis.[1-5] More recently, this methodology has been extended to lactones.[3] For alkaloid synthesis, direct alkylation of lactams has great potential for developing molecular architecture. We want to report a study comparing the reactivity of various lactam derivatives **1a–c**, which is, in many respects, in marked contrast to the behavior of lactone enolates.



1a, R = CH_3; R′ = Li
b, R = Li; R′ = CH_3
c, R = R′ = CH_3

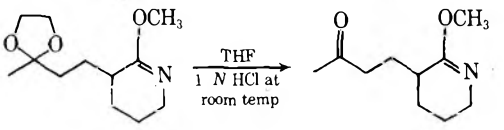
The enolate **1a** was generated by the treatment of 1-methyl-2-piperidone with lithium diisopropylamide or *N*-cyclohexyl-*N*-isopropylam ide in THF at −78°. After 15-min generation time, silylation with dimethylphenylchlorosilane produced a quantitative yield of the C-silylated product **2**[6] [ir 1626 cm^{-1}; nmr δ 2.40 (3 H, s) and 0.10 (6 H, s); see Chart I]. "O" rather than "C" silylation normally predominates with ester enolates.[7] The higher bond energy of the amide carbonyl group rationalizes the opposite regioselectivity observed here. In contrast to lactone enolates, the unactivated alkylating agents **3** and **4** react smoothly in THF to produce **5**[6] [ir 1635 cm^{-1}; nmr δ 3.96 (4 H, s) and 2.83 (3 H, s)] and **6**[6] [ir 1639 cm^{-1}; nmr δ 4.67 (2 H, br s), 2.84 (2 H, s), and 1.72 (3 H, br s)], respectively. It is interesting to note that methyl vinyl ketone reacts highly regioselectively by carbonyl addition to produce **7**[6] [ir 3378 and 1616 cm^{-1}; nmr δ 5.5 (3 H, ABC), 2.82 (3 H, s), and 1.15 (3 H, s)] with no detectable amount of conjugate addition.

Chart I
Reaction of Lactam Derivatives

Derivative	Electrophile	Product (yield)[a,b]	Time[c,d]	Temp, °C[c,d]
1a	CH_3, PhSiCl, CH_3	 (100)	15 min 1 hr	0 −78
1a	C_4H_9I	 (78)	12 hr	−15
1a		 (68)	8 hr	−15
1a		 (72)	14 hr	−15
1a		 (57)	15 min	−78
1b	3	 (56)	4 hr	Room temp
1b	4	 (60)	3 hr 20 min	−78 22
1b		 (37)	2 hr 12 hr	−78 Room temp
1b		 (31)	5 min 20 min	−78 Room temp
1b	PhSSPh	 (66)[e]	3 min 30 min	−78 Room temp
1c		 (29)	22 hr	Room temp

[a] The yields are for isolated pure product except as otherwise noted. [b] See ref 6. [c] The enolate derivatives were normally generated at −78° for 2 hr. [d] Times and temperatures given represent variables after addition of electrophiles. [e] Mp 93–94°.

The metalated lactim **1b** offers a simple approach to α-substituted secondary lactams. Again metalation proceeds readily with lithium diisopropylamide (but not *n*-butyllithium[5]) at −78°. Alkylation of the less reactive **1b** with **3** or **4** requires room temperature to produce **8** [ir 1669 cm^{-1}; nmr δ 3.82 (4 H, s), 3.50 (3 H, s), and 1.20 (3 H, s)] and **9** [ir 1672 and 1655 cm^{-1}; nmr δ 4.63 (2 H, br s, 3.50 (3 H, s), and 1.70 (3 H, br s)], respectively (see Chart I), whereas alkylation of **1a** proceeded at −15° for comparable times. In contrast to **1a**, addition of methyl vinyl ketone to **1b** led to isolation of only the conjugate addition product **10** [ir 1724 and 1675 cm^{-1}; nmr δ 3.50 (3 H, s) and 2.05 (3 H, s)]. Comparison of the spectral properties of the product of hydrolysis of **8** to those of **10** confirmed the structure of the latter. This discrepancy in behavior can be rationalized by assuming that, with the less reactive lactim derivative, delocalization of charge in the transition state of addition becomes more important. In agreement with this concept, the ketene aminal **1c** only yielded the product of conjugate addition with methyl vinyl ketone, **11**[6] [ir 1721 and 1642 cm^{-1}; nmr δ 2.92 (3 H, s) and 2.10 (3 H, s)], albeit in low yield.



8 **10**

In an ancillary experiment, sulfenylation of 1b proceeded to produce the bissulfide **12**.[6] This reaction is indeed general for enolates of carboxylic acid derivatives and should become a useful entry into α-ketocarboxylic acid derivatives.[8]

Acknowledgment. We wish to thank the National Institutes of Health and the National Science Foundation for their generous support of our programs.

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(9) Camille and Henry Dreyfus Teacher Scholar Grant Recipient.

Department of Chemistry
University of Wisconsin,
Madison, Wisconsin 53706

Barry M. Trost*[9]
Robert A. Kunz

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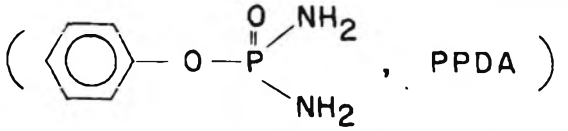
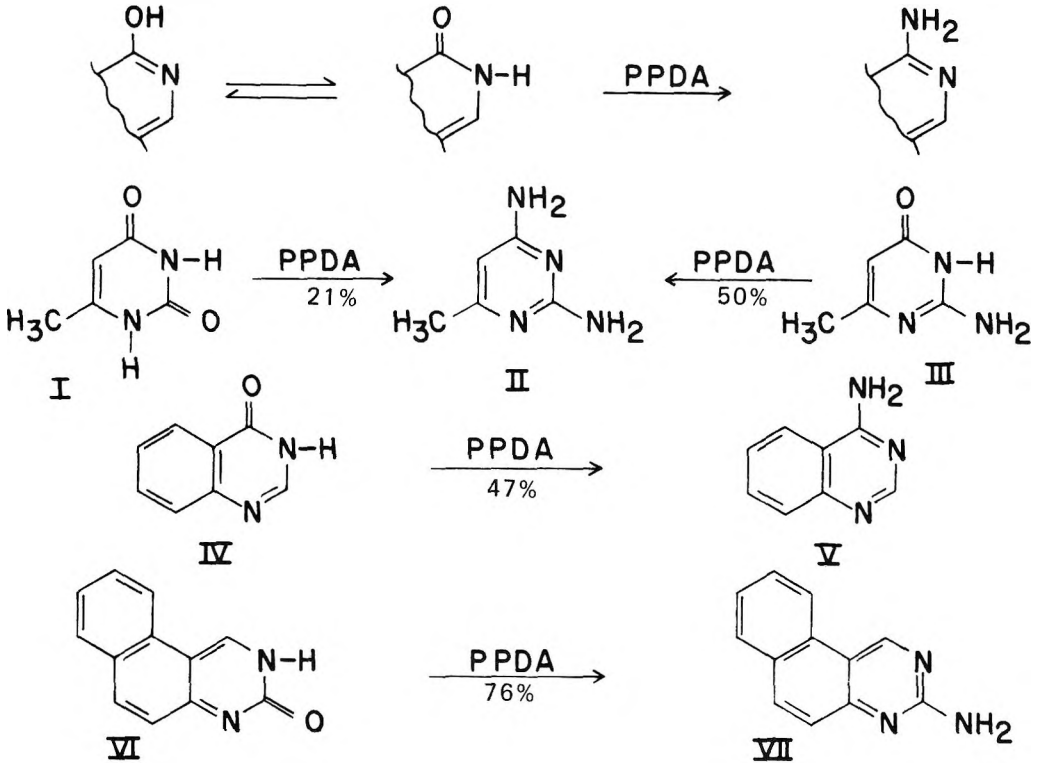
PHENYL PHOSPHORODIAMIDATE



PPDA Converts Tautomeric Oxo-hydroxy Groups Directly to Amino Groups



OXO DIRECTLY TO AMINO

The classic conversion of oxo groups to amino groups is generally carried out in two steps. First, the oxo group is converted to a halo group by treatment with phosphorous tri- or pentahalide in phosphorous oxyhalide mixtures. The labile halo group is then replaced by amination. While this procedure has been applied successfully to a wide variety of nitrogen heterocycles, undesireable side reactions, functional group displacement, low yields, ring cleavage, and overt failure to react are not uncommon occurrences.

Recently, Arutyunyan and co-workers have reported the direct formation of 2,4-diamino-6-methylpyrimidine (II) by simply heating either 6-methyluracil (I), or 6-methylisocytosine (III) briefly with phenyl phosphorodiamidate (PPDA).[1,2] Similar reactions with N-substituted and N,N-disubstituted phenyl phosphorodiamidates were also reported[3,4,5] and analogous procedures applied to the amination of purines,[3,6,7] N-alkyluracils,[3,8] and s-triazines[1,2]. It was also reported that catalytic amounts of phosphorous oxychloride or amine salts greatly improved the yields.[5,6] More recently, PPDA has been used to convert oxo groups in several fused pyrimidine derivatives directly to the corresponding amino groups.[9] For example, 4-quinazolinone is converted to the corresponding 4-aminoquinazoline in 47% yield, and 3-benzo[f]quinazolinone is converted to 3-aminobenzo[f]quinazoline in 76% yield.

The new PPDA procedure for converting oxo groups to amino groups is potentially as useful as the old classic two step procedure. Furthermore, PPDA is much easier to use and the overall yields are often much improved over the old two step procedure. We think PPDA will prove a useful reagent for converting oxo groups to amino groups in a wide variety of nitrogen heterocycles. In addition, we think PPDA may prove useful for other novel reactions such as converting amides to amidines, or ureas to guanidines. We are just waiting for somebody to give it a try.

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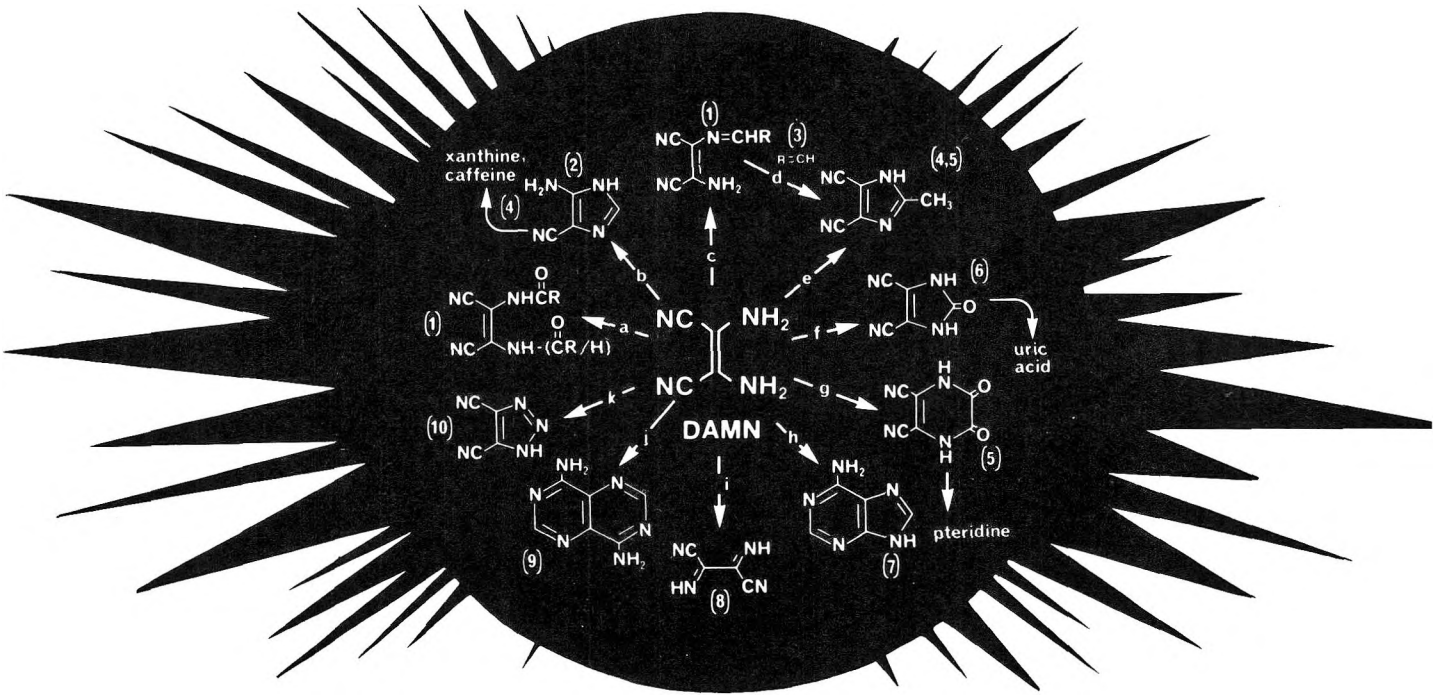
In the beginning . . .

Hydrogen cyanide, which was surely present during the creation of the world, yields DAMN at high pressure and temperature. Many imidazoles and purines are easily made from DAMN. Hence, it appears likely that DAMN was the bridge between the inorganic universe and life as we know it.

But DAMN is more than just a curiosity on the road to life.



Reagents:
a = carboxylic anhydride; b = uv photolysis; c = aryl/alkyl aldehyde; d = N_2O; e = triethyl orthoacetate or $CH_3C(=NH)OEt \cdot HCl$; f = phosgene; g = oxalyl chloride; h = formamidine acetate, 130°; i = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; j = formamidine acetate, liquid NH_3, 130°; k = HONO.

Many heterocyclic systems may be synthesized easily from DAMN. For example, substituted imidazoles are obtained from DAMN by photolysis,[2] by oxidative condensation with an aldehyde,[1,3] and by reaction with an ortho ester[4] or imino ester hydrochloride.[5] Pyrazines, which serve as starting materials for pteridines, are obtained from the reaction of DAMN with oxalyl chloride.[5] Adenine is formed from the reaction of DAMN and formamidine acetate at 130°, whereas 4,8-diaminopyrimido[5,4-*d*]pyrimidine is obtained from DAMN and formamidine acetate in liquid ammonia at 130°.[9]

These selected reactions indicate that the organic chemist will find DAMN an extremely useful synthetic building block for compounds of biological interest.

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