VOLUME 43 JUNE 23, 1978 NUMBER 13 JOCEAH

THE JOURNAL OF Organic Chemistry

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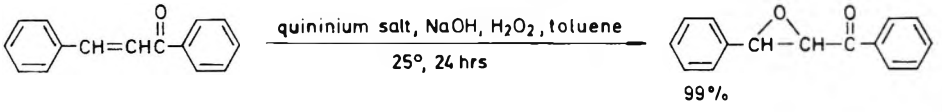
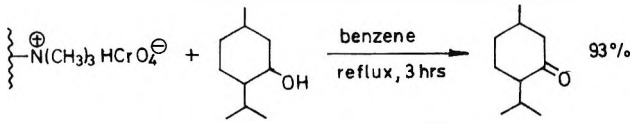
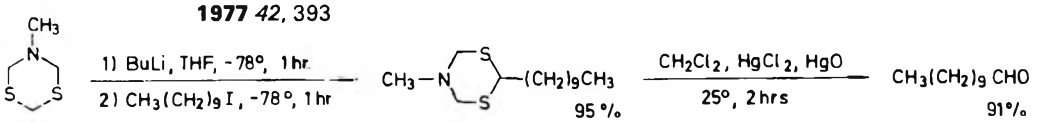
13265 **N-Benzyl quininium chloride purum** >97%(Cl); MP 177.5° (dec.); $[\alpha]_D^{20}$-223.5 (c=1.5 in H_2O) . . . 5 g sFr. 21.— US$ 10.50
$C_{27}H_{31}ClN_2O_2$ MW 451.01 25 g sFr. 90.— US$ 45.00
Chiral phase-transfer catalyst for the asymmetric induction in oxidation reactions: R. Helder, J.C. Hummelen, R.W.P.M. Laane, J.S. Wiering, Hans Wynberg, Tetrahedron Lett. **1976** 1831; J. C. Hummelen, H. Wynberg ibid. **1978** 1089



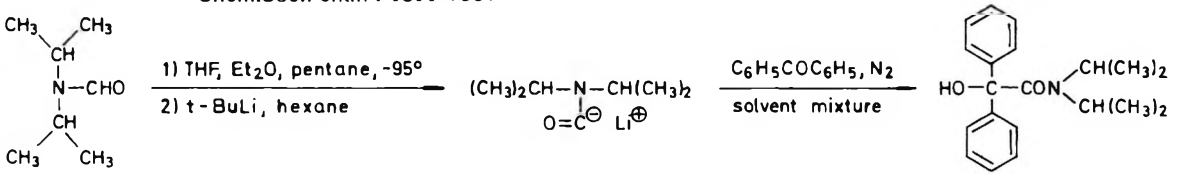
27175 **Chromic acid polymer supported** contains ~2.5 mmol CrO_3/g resin (Amberlyst A-26 $HCrO_4$-form, Polymer supported chromic acid) . . . 25 g sFr. 24.— US$ 12.00
Ⓟ-$C_6H_4CH_2N(CH_3)_3HCrO_4$ 100 g sFr. 90.— US$ 45.00
Polymer supported reagent for the clean oxidation of primary and secondary alcohols to carbonyl compounds in high yields: G. Cainelli et al., J. Am. Chem. Soc. **1976** *98*, 6737; reagent for the synthesis of aldehydes and ketones from allylic and benzylic halides: G. Cardillo et al., Tetrahedron Lett. **1976** 3985



37335 **4,5-Dihydro-5-methyl-1,3,5-dithiazine purum** >98%(GLC); MP 63-65° (Methylthioformaldine) . . . 10 g sFr. 25.— US$ 12.50
$CH_3NCH_2SCH_2SCH_2$ $C_4H_9NS_2$ MW 135.25 50 g sFr. 105.— US$ 52.50
Formaldehyde anion equivalent with several advantages over 1,3-dithiane (higher reactivity in the alkylation and hydrolysis step): R.D. Balanson et al., J.Org.Chem. **1977** *42*, 393



38401 **N,N-Diisopropylformamide purum** >98%(GLC); BP_{11} 83-86°; n_D^{20} 1.4371 1 lt ≈ 0.89 kg 10 ml sFr. 25.— US$ 12.50
$(CH_3)_2CHN(CHO)CH(CH_3)_2$ $C_7H_{15}NO$ MW 129.20 50 ml sFr. 105.— US$ 52.50
Intermediate for the synthesis of highly branched aliphatic compounds; reagent for the preparation of lithium-diisopropylformamide which reacts with carbonyl compounds to give high yields of α-hydroxyamides: K. Smith, K. Swaminathan, J. Chem.Soc.Chem.Comm. **1976** 387; A.S. Fletcher, K. Smith, K. Swaminathan, J. Chem.Soc.Perkin I **1977** 1881



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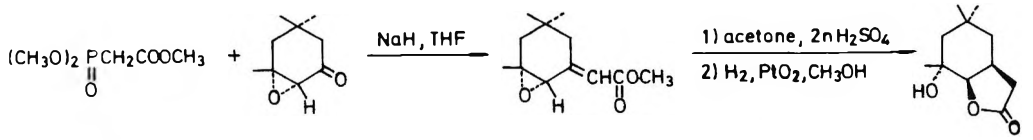
$(CH_3O)_2P(O)CH_2COOCH_3$ $C_5H_{11}O_5P$ MW 182.12 50 ml sFr. 90.— US$ 45.00
A Horner-Wittig reagent: N. Bensel, H. Marschall, P. Weyerstahl, Tetrahedron Lett. **1976** 2293



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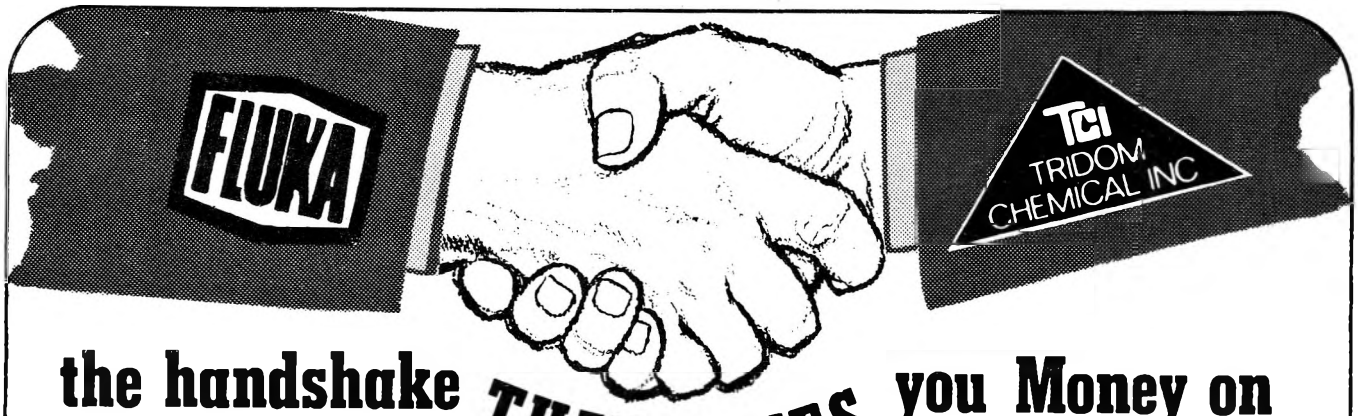

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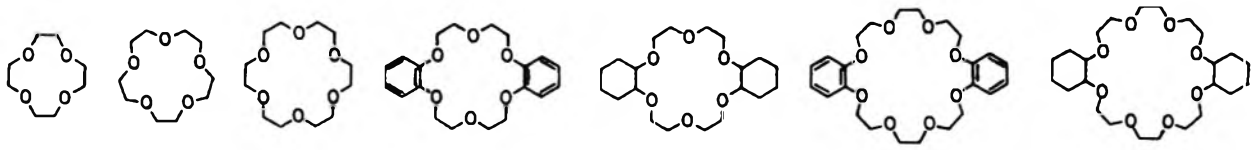

28122	28123	28125	33531	36665/6	33539	36668

28122	**12-Crown-4 purum** >98%(GLC); $BP_{0.1}$ 68-70°; n_D^{20} 1.462		1 lt ≈ 1.11 kg	5 ml	—	$12.80
	$C_8H_{16}O_4$ MW 176.22			25 ml	—	54.00
28123	**15-Crown-5 purum** >98%(GLC); $BP_{0.1}$ 93-95°; n_D^{20} 1.465		1 lt ≈ 1.11 kg	5 ml	—	11.00
	$C_{10}H_{20}O_5$ WM 220.27			25 ml	—	36.00
28125	**18-Crown-6 purum** >98%(GLC); MP 37-39°			5 g	—	6.00
	$C_{12}H_{24}O_6$ MW 264.32			25 g	—	26.00
33531	**Dibenzo-18-crown-6 purum** >98%(GLC); MP 161-163°			5 g	—	6.00
	$C_{20}H_{24}O_6$ MW 360.41			25 g	—	17.00
33539	**Dibenzo-24-crown-8 pract.** >98%(GLC); MP 102-107°			1 g	—	8.40
	$C_{24}H_{32}O_8$ MW 448.52			5 g	—	35.00
36665	**Dicyclohexyl-18-crown-6 cryst. purum** >98%(GLC); MP 48-58°			5 g	—	11.60
	$C_{20}H_{36}O_6$ MW 372.51			25 g	—	48.00
36666	**Dicyclohexyl-18-crown-6 techn.** >70%(GLC); contains less than 2% Dibenzo-18-crown-6 (UV)			10 g	—	14.00
	$C_{20}H_{36}O_6$ MW 372.51			50 g	—	56.00
36668	**Dicyclohexyl-24-crown-8 pract.** >96%(GLC); contains less than 2% Dibenzo-24-crown-8 (UV); MP −23- +27°; n_D^{20} 1.488		1 lt ≈ 1.10 kg	1 ml	—	12.60
	$C_{24}H_{44}O_8$ MW 460.61			5 ml	—	49.00

REVIEWS ON CROWN ETHERS

C.J. Pedersen, H.K. Frensdorff, "Makrocyclische Polyaether und ihre Komplexe", Angew. Chem. **1972**, *84*, 16–26; Angew. Chem. Int. Ed. **1972**, *11*, 16–26
G.W. Gokel, H.D. Durst, "Principles and Synthetic Applications in Crown Ether Chemistry", Synthesis **1976**, 168–184
J.J. Christensen, D.J. Eatough, R.M. Izatt, "The Synthesis and Ion Binding of Synthetic Multidentate Macrocyclic Compounds", Chem. Rev. **1974**, *74*, 351-384

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NOTES

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JUNE 23, 1978

Syntheses of 1-, 2-, 3-, 4-, 6-, 9-, and 10-Hydroxy-7,12-dimethylbenz[*a*]anthracenes

Melvin S. Newman,* J. M. Khanna,[1] K. Kanakarajan,[1] and S. Kumar[1]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received November 25, 1977

The condensation of 8-methyoxy-1-naphthyllithium with phthalic anhydride produced 2-(8-methoxy-1-naphthoyl)benzoic acid (**4**), which was converted by two routes into 1-methoxy-7,12-dimethylbenz[*a*]anthracene (**2**). Similarly, 7-methoxy-1-naphthylmagnesium iodide and 5-methoxy-1-naphthylmagnesium iodide were reacted with phthalic anhydride to produce 2-(7-methoxy-1-napthoyl)benzoic acid (**12**) and 2-(5-methoxy-1-napthoyl)benzoic acid (**13**), respectively. These were converted into 2-methoxy- (**20**) and 4-methoxy-7,12-dimethylbenz[*a*]anthracene (**21**). Reaction of 3-methoxy-7,12-benz[*a*]anthraquinone (**24**) with methyllithium yielded 7,12-dimethyl-7,12-dihydroxy-7,12-dihydrobenz[*a*]anthracene (**25**), which was converted to 7-chloromethyl-3-methoxy-12-methylbenz[*a*]anthracene (**26**), in turn reduced to 3-methoxy-7,12-dimethylbenz[*a*]anthracene (**27**). Reaction of the Grignard reagent prepared from 2-(o-bromophenyl)-4,4-dimethyl-2-oxazoline with 3-methoxy-2-napthyl methyl ketone followed by hydrolysis afforded the lactone of 2-[1-hydroxy-1-(3-methoxy-2-naphthyl)ethyl]benzoic acid (**32**), which was converted into 6-methoxy-7,12-dimethylbenz[*a*]anthracene (**29**). Ring closure of 2-(4-methoxybenzyl)-1-naphthoic acid (**42**) yielded 12-acetoxy-10-methoxybenz[*a*]anthracene (**43**), readily oxidized to 10-methoxy-7,12-benz[*a*]anthraquinone (**44**), from which 10-methoxy-7,12-dimethylbenz[*a*]anthracene (**38**) was synthesized. All of the methoxy-7,12-dimethylbenz[*a*]anthracenes were cleaved to the corresponding hydroxy compounds by heating with sodium ethyl mercaptide.

The arene oxide concept concerning the metabolism of polycyclic aromatic hydrocarbons has long been advanced.[2] Since arene oxides are very prone to rearrange into a mixture of the two related isomeric phenols,[2] the isolation of epoxides from in vitro or in vivo metabolism studies might be difficult. Accordingly, the synthesis of all of the nuclear monohydroxylated 7,12-dimethylbenz[*a*]anthracenes was undertaken in order that known compounds, or suitable derivatives thereof, would become available to use as standards, the carcinogenicity and mutagenicity of each could be determined, and the tendency of each to react with methanolic HCl as its ketonic isomer could be assessed.[3]

Although the synthesis of 1-hydroxy-7,12-dimethylbenz[*a*]anthracene (**1**) and the corresponding methoxy compound (**2**) was accomplished, as shown in Scheme I, these compounds were extremely unstable; the hydroxy compound (**1**) turned into a dark brown material even when protected from light and air, and the methoxy compound (**2**) polymerized to a large extent during the final step of its synthesis (although when pure, it is stable). The synthetic routes shown in Scheme I seem straightforward, but experimental difficulties (owing to the steric effect of the methoxy group in the 8 position of the naphthalenic intermediates) were severe.

Since 8-methoxy-1-iodonaphthalene[4] (**3**) would not form a Grignard reagent, lithiation yielded a reagent which condensed with phthalic anhydride to yield **4** (71%). As **4** was recovered unchanged on attempted reaction with methylmagnesium iodide, it was reacted with excess methyllithium to yield the desired lactone which was reduced directly to **5** (overall yield from **4** was 96%). Under the usual conditions **5** was inert to the action of CH_3Li. However, when tetramethylethylenediamine (TMEDA) was added, reaction occurred to yield the ketone **6** (70%). Cyclization with polyphosphoric acid (PPA) afforded 1-methoxy-DMBA[5] (**2**) in fair yield accompanied by high molecular weight material.

In an alternate synthesis, **5** was cyclized to the anthrone **7**, which on treatment with CH_3Li afforded, unexpectedly, the relatively stable adduct **8**, which could be dehydrated to a mixture of the methylene compound **9** and **2**. Under certain conditions more **9** was formed than **2**. However, **9** readily changes to **2**. When **8** or **2** was heated with sodium ethylmercaptide reagent[6] followed by acidification, **1** was produced.

The syntheses of 2-hydroxy- (**22**) and 4-hydroxy-DMBA (**23**) are outlined in Scheme I.

The required 1-iodo-7-methoxynaphthalene[7] (**10**) was prepared from 7-methoxy-1-tetralone[8] via the oxime which on treatment with acetic anhydride and PPA at 65–70 °C for 6 min yielded 1-acetylamino-7-methoxynaphthalene in 85% yield. This intramolecular oxidation–reduction reaction occurred much more readily than the conversion of the oxime of 1-tetralone to 1-acetylaminonaphthalene, which required[9] heating for 30 min at 80 °C. Diazotization of the corresponding amine hydrochloride led to **10**. The remaining steps from **10** to **20** were accomplished in about 50% overall yield. In a similar way, 1-iodo-5-methoxynaphthalene[10] (**11**) was converted into **21** in about 36% overall yield.

We had planned to synthesize **28** by a route similar[11] to that shown in Scheme I starting from 6-methoxy-1-iodonaphthalene. However, all attempts to convert the oxime of 6-methoxy-1-tetralone into 1-acetylamino-6-methoxynaphthalene failed,[9] and the alternate route shown in Scheme II worked

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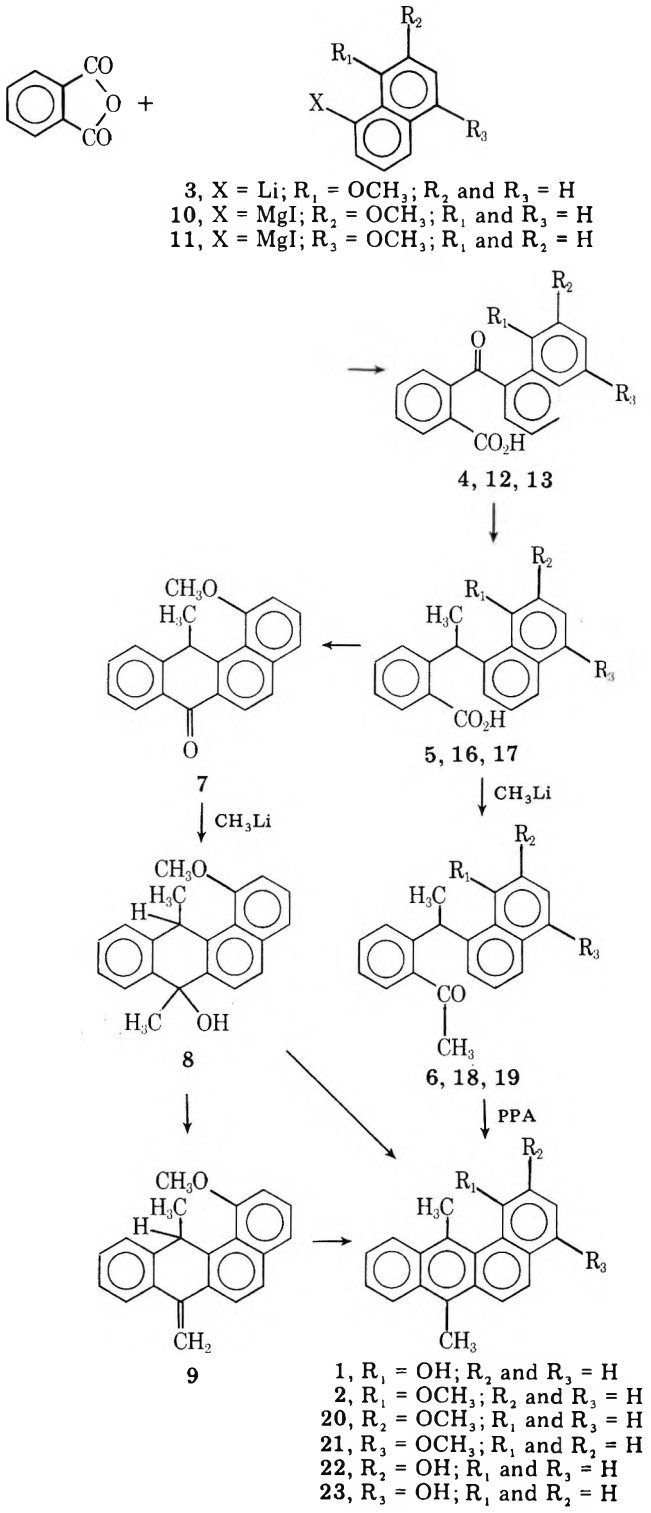
Scheme I

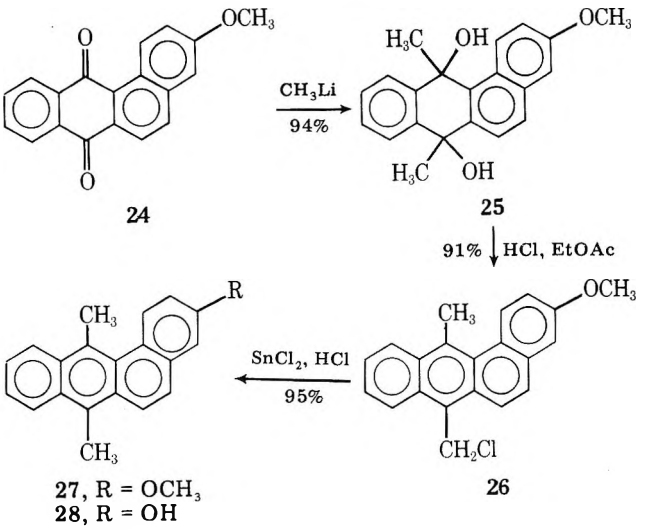


extremely well.

An improved synthesis of 6-methoxy-DMBA[12] (**29**) has been developed by reacting the Grignard reagent of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline[13] (**30**) with 3-methoxy-2-naphthyl methyl ketone[14] (**31**) followed by appropriate treatment[15] to yield, after three steps, **29**, as shown in Scheme III.

Hydrolysis of the condensation product of the Grignard reagent[13] prepared from **30** and **31**[14] yielded **32** (60%), which was converted into **34** (84% overall from **32**). Attempted cyclization of **34** to **29** with polyphosphoric acid as described for a similar case[3] gave poor results, which undoubtedly stemmed from the facts that ring closure must occur meta to a methoxy group and demethylation of the ether function occurred.

Scheme II



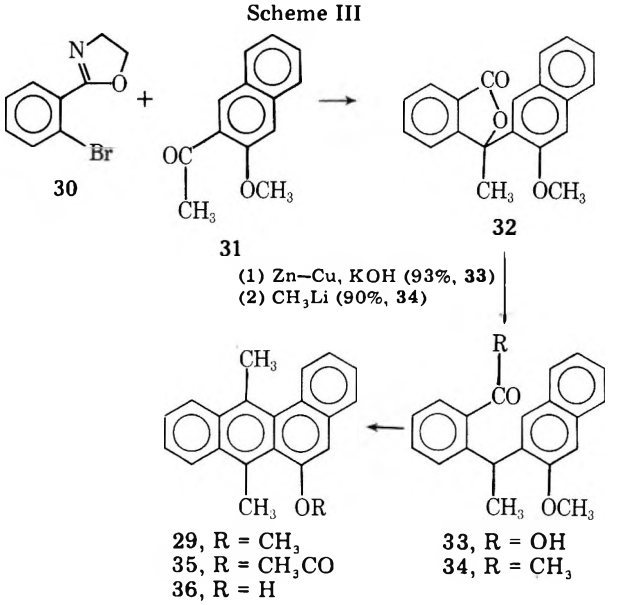
Cyclization of **34** with HBr–acetic acid followed by acetylation of the crude product afforded 63% of **35**. This treatment was necessary because demethylation occurred during the cyclization. Treatment of **35** with methanolic HCl afforded **29**, identical with that synthesized by an alternate route.[3]

The attempted coversion of **29** to **36** as described[6] proved difficult because of the great instability[3] of **36**. However, the acetate **35** was readily obtained.[3] In the IR spectra of crude samples of **36**, ketonic as well as hydroxylic bands were observed (compare with ref 3).

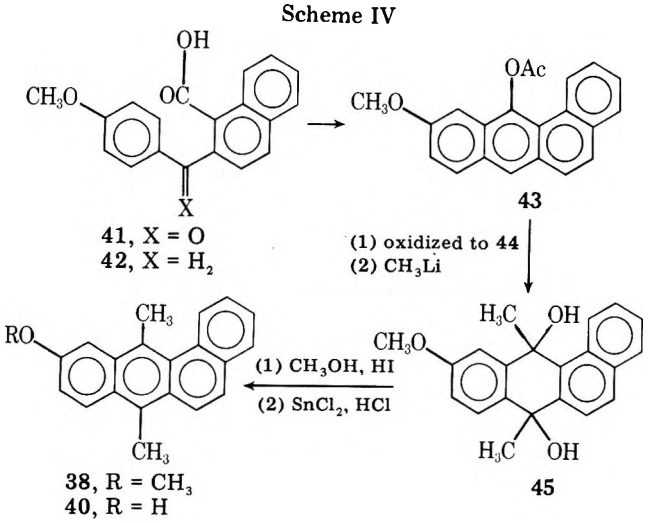
The syntheses of 9-methoxy- (**37**) and 10-methoxy-DMBA (**38**) by a sequence of reactions starting with 4-methoxyphthalic anhydride and 1-naphthylmagnesium bromide have been reported.[16] However, the synthesis of **37** by this route uses 2-(1-naphthoyl)-5-methoxybenzoic acid, formed in less than 10% yield.[16] We have synthesized **37** and **38** by a route[15] which does not require the separation of the isomeric acids formed in the above-mentioned Grignard reaction. We have also synthesized **38** by an alternate route,[18] shown in Scheme IV, which allows for functionalization at the 7-methyl group if desired.

All of the methoxy-DMBA compounds (**2, 20, 27, 21, 29, 37,** and **38**) were converted into the corresponding hydroxy-DMBA compounds (**1, 22, 28, 23, 36, 39,** and **40**) essentially as described.[6,12] Of the phenols, only **36** and 5-hydroxy-DMBA[12] gave ketonic IR bands and were converted in high yield to the corresponding methyl ethers on treatment, under

Scheme III



Scheme IV



standard conditions, with 0.1 N methanolic HCl at room temperature for 7 h.[12] The other phenols gave only 0–6% of methyl ethers under these conditions. Thus, the steric strain in the DMBA derivatives results in abnormal reactivity involving the ketonic isomer only when the oxygenated moiety is in the 5 and 6 positions (compare with other results[12]).

Experimental Section[19]

2-(8-Methoxy-1-naphthoyl)benzoic Acid* (4). To a stirred solution of 15.0 g of **3**[4] in 250 mL of ether was added 40 mL of a 1.6 M ethereal butyllithium solution. After 0.5 h at room temperature, this solution was added to a stirred solution of 8.0 g of phthalic anhydride in 100 mL of freshly distilled THF. After being held at reflux for 72 h, the cooled mixture was treated with dilute HCl and the acidic component was crystallized once from $CHCl_3$–benzene to produce 11.5 g (71%) of **4**, mp 228–230 °C.

2-[α-(8-Methoxy-1-naphthyl)ethyl]benzoic Acid* (5). To a solution of 20.0 g of **4** in 350 mL of ether was added 140 mL of 1.6 M methyllithium. After 48 h at reflux, the cooled mixture was acidified with HCl and most of the THF was removed on a rotary evaporator. To the neutral portion of the reaction product, isolated as usual, was added 100 g of zinc, 1.5 g of $CuSO_4$, 75 mL of pyridine, and 1 L of 10% KOH. The vigorously stirred mixture was heated at reflux for 20 h, cooled, and filtered. The filtrate was acidified with HCl, and the acid product, after crystallization from benzene–petroleum ether, amounted to 19.2 g (96%) of **5**, mp 194–195 °C.

2-[α-(8-Methoxy-1-naphthyl)ethyl]acetophenone* (6). In the best of several runs, 35 mL of 1.84 M methyllithium was added dropwise to a solution of 5.0 g of **5** in 200 mL of ether containing 5 g of TMEDA. After a 24-h reflux the neutral fraction was crystallized from ethanol to yield 3.5 g (70%) of **6**, mp 119–121 °C. From the acid portion was recovered 1.2 g (24%) of **5**.

7,12-Dimethyl-7-hydroxy-1-methoxy-7,12-dihydrobenz[a]anthracene* (8). A mixture of 2.40 g of **5**, 0.5 g of $ZnCl_2$, and 50 mL of CF_3CO_2H was held at reflux for 3 h, cooled, and poured on ice. The reaction product was chromatographed over silica gel (benzene) to yield 1.70 g (75%) of an oil (anthrone **7** from IR analysis), which was treated with excess CH_3Li in ether for 20 h at room temperature. The reaction product on crystallization from benzene–petroleum ether yielded 1.35 g (56% from **5**) of **8**, mp 191–195 °C dec. By TLC analysis the material in the mother liquor contained **8**, **9**, and **2**.

1-Methoxy-12-methyl-7-methylene-7,12-dihydrobenz[a]anthracene (9). A solution of 1.00 g of **5** in 25 mL of anhydrous HF was poured on ice after 1 h. To the crude anthrone **7**, isolated as usual, was added excess CH_3Li in ether at room temperature. After 20 h the mixture was acidified with dilute HCl and the dried product was chromatographed over alumina (benzene–petroleum ether, ca. 1:3) to yield 450 mg (48%) of **9**, *m/e* 286,[20] from the first 5 fractions and then 200 mg (21%) of **2**: mp 138–140 °C; *m/e* 286. The remaining material was of high molecular weight. The NMR[21] spectrum of **9** [δ 1.50 (d, 3, OCH_3), 4.05 (s, 3, OCH_3), 5.70–5.75 (m, 3, $=CH_2$, 12-H), and 7.3 (m, 9, ArH)] and an IR band at 1620 cm^{-1} indicate the methylene feature. Because of the ready rearrangement of **9** to **2**, no elemental analysis was attempted.

1-Methoxy-7,12-dimethylbenz[a]anthracene* (2). Method A. A stirred mixture of 1.50 g of **6**, and 30 mL of PPA was heated on a steam bath for 40 min and poured on ice. Mass spectral analysis of the crude reaction product isolated in the usual way showed high molecular weight impurities. Chromatography over basic alumina using benzene–petroleum ether (1:3) afforded 800 mg of pale yellow **2** from the first 10 fractions (25 mL each): mp 138–140 °C; NMR δ 2.80 (s, 3, 7-CH_3), 3.00 (s, 3, 12-Me), 3.85 (s, 3, OCH_3), 7.3 (m, 9, ArH).

Method B. A solution of 225 mg of **8** and 10 mg of *p*-toluenesulfonic acid in 10 mL of benzene was held at reflux for 1 h, cooled, washed with dilute NaOH, and dried over Na_2SO_4. The product was chromatographed as in method A to yield 100 mg (47%) of pure **2**.

1-Hydroxy-7,12-dimethylbenz[a]anthracene (1). A mixture of 500 mg of **2** in 10 mL of dimethylformamide with the sodium ethyl mercaptide formed[6] from 500 mg of ethyl mercaptan and NaH in 5 mL of dimethylformamide was heated at 155 °C for 2 h and poured on ice. The crude product was chromatographed over silica gel using ether to yield a homogeneous fraction which did not solidify on removal of solvent (all saturated with N_2 in this work). The pale yellow viscous **1**, *m/e* 272, obtained in 75% yield (350 mg) could not be obtained crystalline. It was hygroscopic, and a solid sample, mp 60–70 °C (unsharp), was obtained. Analysis indicated 0.5 molecule of water of hydration. The solid rapidly turned dark brown. No **2** was obtained on standard treatment[3] with CH_3OH–HCl.

2-(7-Methoxy-1-naphthoyl)benzoic Acid* (12). A solution of 9.4 g of ethylene dibromide in 200 mL of ether[22] was added during 3 h to a stirred mixture of 14.2 g of **10**[5] and 2.4 g of sublimed Mg in 200 mL of ether. After 1 h this Grignard reagent was added to a stirred solution of 8.8 g of phthalic anhydride in 100 mL of THF. After 20 h at room temperature, a conventional workup yielded 11.0 g (68%) of **12**, mp 154–155 °C, after one crystallization from benzene–petroleum ether (bp 35–55 °C).

2-[α-(7-Methoxyl-1-naphthyl)ethyl]benzoic Acid* (16). A Grignard reagent prepared from 21.3 g of CH_3I, 3.6 g of Mg, and 450 mL of ether was added dropwise to a solution of 17.5 g of **12** in 500 mL of ether. After being held at reflux for 24 h, the cooled mixture was worked up as usual to yield 16.0 g of lactone **14**, which was stirred at reflux with 840 mL of 10% KOH, 84 mL of pyridine, and 105 g of Zn dust (activated with 1 g of $CuSO_4$) for 24 h. The acidic fraction of the product was crystallized from benzene–petroleum ether to yield 12.0 g (69%) of **16**, mp 170–172 °C.

2-[α-(7-Methoxyl-1-naphthyl)ethyl]acetophenone* (18). To a solution of 5.0 g of **16** in 200 mL of ether was added 35 mL of 1.8 M CH_3Li. After 20 h at reflux the mixture was worked up as usual to yield **18** as colorless crystals, mp 104–105 °C. in almost quantitative yield. No unreacted **16** was recovered.

2-Methoxy-7,12-dimethylbenz[a]anthracene (20). A mixture of 6.0 g of **18** and 120 mL of PPA was heated on a steam bath for 45 min. A conventional workup afforded 5.3 g of **20**, mp 131–132 °C (lit.[23] mp 131–132.5 °C), after crystallization from benzene–petroleum ether or methanol.

2-Hydroxy-7,12-dimethylbenz[a]anthracene* (22). Demethylation of 2.4 g of **20** by heating at 155–160 °C for 3 h with C_2H_5SNa[6] afforded 1.7 g (89%) of **22**, mp 115–117 °C. A freshly vacuum sublimed sample melted at 122–124 °C and was pale yellow. On standing, the color darkens and the melting point becomes lower and broader.

2-(5-Methoxy-1-naphthoyl)benzoic Acid* (13). By reacting 5-iodo-1-methoxynaphthalene[10] (**11**) with phthalic anhydride essentially as described for the synthesis of **12**, **13** was obtained, mp 184–185 °C, on crystallization from benzene in 70% yield.

2-[1-Hydroxy-1-(5-methoxy-1-naphthyl)ethyl]benzoic Acid Lactone* (15). The Grignard reagent prepared from 4.2 g of Mg and MeI in ether was added to a solution of 15.0 g of **13** in 300 mL of benzene and 300 mL of ether. After 20 h at reflux a conventional workup yielded 14.0 g (93%) of **15**, mp 159–161 °C, on crystallization from ether–petroleum ether.

2-[α-(5-Methoxy-1-naphthyl)ethyl]benzoic Acid* (17). Reduction of 15.0 g of **15** as described for **14** afforded 11.5 g (77%) of **17**, mp 170–171 °C, on crystallization from benzene–petroleum ether.

2-[α-(5-Methoxy-1-naphthyl)ethyl]acetophenone* (19). Treatment of 7.65 g of **17** in ether with 65 mL of 1.4 M methyllithium as described for **16** yielded 6.80 g (89%) of **19**, mp 132–134 °C, on crystallization from ethanol.

4-Methoxy-7,12-dimethylbenz[a]anthracene (21). After heating a solution of 6.08 g of **19** in 105 mL of PPA on a steam bath for 35 min, a conventional workup followed by chromatography over alumina yielded 94% of **21**, mp 120–121 °C (lit.[24] mp 121 °C), on crystallization from methanol.

4-Hydroxy-7,12-dimethylbenz[a]anthracene (23). On treatment of 1.00 g of **21** with C_2H_5SNa as described above for **20**, 0.80 g (84%) of **23** was obtained, mp 164–154 °C (lit.[24] mp 164–165 °C), on crystallization from benzene. All solvents used in the preparation of **23** were saturated with N_2.

3-Methoxy-7,12-benz[*a*]anthraquinone* (24). A solution of 2.50 g of 12-acetoxy-3-methoxybenz[*a*]anthracene (mp 165–167 °C), prepared as described[11] (mp 166–167 °C), and 3.3 g of $Na_2Cr_2O_7$ in 60 mL of acetic acid was boiled for 15 min, cooled, and diluted with 60 mL of dilute H_2SO_4. The precipitate was chromatographed over basic alumina eluting with $CHCl_3$ to yield 2.25 g (95%) of **24**, mp 162–163 °C, on crystallization from benzene–petroleum ether.

7,12-Dimethyl-7,12-dihydroxy-3-methoxy-7,12-dihydrobenz[*a*]anthracene* (25). A solution of CH_3Li (0.04 mol) in ether was added to a suspension of 2.88 g (0.01 mol) of **24** in 150 mL of 1:1 benzene–ether at room temperature. After being held at reflux for 15 h, the mixture was treated with aqueous NH_4Cl and the product isolated as usual. After recrystallization from benzene–petroleum ether, 3.00 g (94%) of **25** was obtained, mp 135–140 °C, as a mixture of isomers suitable for the next step.

7-Chloromethyl-3-methoxy-12-methylbenz[*a*]anthracene* (26). Dry HCl was passed into a solution of 2.30 g of **25** in 30 mL of dry ethyl acetate at 0 °C. After 5 h at 0 °C, 2.10 g (91%) of **26**, mp 149–150 °C, before and after recrystallizaion from benzene–petroleum ether, was collected by filtration.

3-Methoxy-7,12-dimethylbenz[*a*]anthracene* (27). A solution of 2.0 g of **26** in 50 mL of dioxane containing 10 g of stannous chloride and 10 mL of concentrated HCl was heated on a steam bath for 1 h. The crude product obtained as usual was chromatographed over a short column of basic alumina to yield 1.7 g (95%) of **27**, mp 128–129 °C, suitable for demethylation. A pale yellow analytical sample, mp 131–132 °C, was obtained with little loss on crystallization from benzene–petroleum ether.

3-Hydroxy-7,12-dimethylbenz[*a*]anthracene* (28). Demethylation of 1.00 g of **27** was carried out as described for the preparation of **22** to yield 0.90 g of **28**, mp 165–166 °C, on crystallization from N_2-saturated chloroform–petroleum ether. A colorless analytical sample, mp 167–168 °C, was prepared by sublimation at 160 °C and 1 mm.

3-Methoxy-2-naphthyl Methyl Ketone (31). To a stirred suspension at room temperature of 20.2 g of 2-methoxy-3-naphthoic acid, prepared in 71% yield essentially as described,[14] in 400 mL of ether was added 108 mL of 1.84 M methyllithium during 1 h. After being stirred at reflux for 16 h, the reaction mixture was worked up as usual to yield 13.0 g (86% based on recovery of 5.0 g of starting acid by alkaline extraction) of **31**: bp 134–136 °C (0.2 mm); mp 42–44 °C (lit.[25] mp 48 °C).

2-[1-Hydroxy-1-(3-methoxy-2-naphthyl)ethyl]benzoic Acid Lactone (32). To the Grignard reagent prepared from 5 g of 2-(*o*-bromophenyl)-4,4-dimethyl-2-oxazoline[13] (**30**) in THF using sublimed magnesium was added a solution of 4.4 g of **31** in THF at room temperature. After being stirred for 16 h at 15–20 °C and at reflux for 1 h, a conventional workup afforded a crude oil which was heated at reflux for 18 h with 100 mL of 8% ethanolic H_2SO_4. After dilution with water the mixture was worked up as usual to yield an oil from which 3.2 g (53%) of colorless crystals of **32**, mp 159–162 °C, was obtained. An analytical sample, mp 165–165.5 °C, was obtained on crystallization from ethanol with little loss.

***o*-[1-(3-Methoxy-2-naphthyl)ethyl]benzoic Acid* (33).** On reduction by refluxing a stirred mixture of 3.0 g of **32**, 20 g of Zn (activated by acid washing and treatment with 200 mg of $CuSO_4$), 130 mL of 10% KOH, and 12 mL of pyridine for 20 h, 2.8 g (93%) of colorless **33** was obtained, mp 177–179 °C, by a conventional workup. An analytical sample, mp 179–180 °C, was obtained by recrystallization from benzene–petroleum ether.

***o*-[1-(3-Methoxy-2-naphthyl)ethyl]acetophenone* (34).** As in the case of the above synthesis of **31**, **33** was converted to pure **34**, mp 127–128 °C, in 90% yield.

6-Acetoxy-7,12-dimethylbenz[*a*]anthracene (35). A mixture of 0.6 g of **34**, 6 mL of acetic acid, and 6 mL of 48% HBr was held at reflux for 15 min. Isolation of the product as usual gave 0.5 g of a light yellow solid which was dissolved in 10 mL of pyridine and 5 mL of acetic anhydride. After 18 h at room temperature, water was added and the product, isolated by ether extraction as usual, was crystallized twice from ether to yield 400 mg (63%) of **35**, mp 138–139 °C. A mixture melting point with 138–139 °C material prepared as described[3] was not depressed. The IR and NMR spectra were identical.

6-Methoxy-7,12-dimethylbenz[*a*]anthracene* (29). In one experiment the crude product obtained by treating **34** with HBr as described above was treated with 0.1 M methanolic HCl at room temperature for 24 h to yield 40% of pure **29**: melting and mixture point with another sample,[3] 140–141 °C; IR and NMR spectra were identical.

In as much as the experiment describing the synthesis of **29** was inadvertently omitted,[3] it is given here. A mixture of 3.0 g of *o*-[α-(3-methoxy-1-naphthyl)ethyl]acetophenone (**27**) (numbering is the same as that in ref 3) and 60 g of PPA was stirred at 85 °C for 2 h. Workup, including chromatography over neutral alumina, afforded 1.4 g (50%) of **29**, mp 140–141 °C.

A solution of 0.337 g of pure **35** in 20 mL of 0.1 N methanolic HCl was allowed to stand at room temperature for 7 h. The volatile matter was removed under reduced pressure, and the product was taken up in ether. After three washings with 3% KOH (no material recoverable from the aqueous washings), the dried ether solution afforded 0.308 g (ca. 100%) of light yellow solid, mp 135–137 °C. One recrystallization from ether afforded 0.273 g (90%) of pure **29**, mp 140–141 °C.

4-Methoxy-2-(1-naphthoyl)benzoic Acid. When an ether–benzene solution of 1-naphthylmagnesium bromide was added to a solution of 4-methoxyphthalic anhydride in ether, a mixture of ketoacids was obtained. When an aqueous alkaline solution of these acids was just acidified with acetic acid, 4-methoxy-2-(1-naphthoyl)benzoic acid, mp 191–193 °C, was obtained in 61% yield. Recrystallization from benzene afforded pure acid, mp 198–199 °C (lit.[16] mp 199–201 °C), with little loss. The dilute acetic acid filtrate on acidification with HCl yielded a solid which on recrystallization from benzene afforded 5-methoxy-2-(1-naphthoyl)benzoic acid, mp 158–159 °C (lit.[16] mp 178–180 °C; a sample sent by Dr. Pataki melted at 172–178 °C alone and mixed with our 158–159 °C acid, a polymorphic form, as seeding with Dr. Pataki's sample raised the melting point to 172–178 °C).

2-[1-Hydroxy-1-(1-naphthyl)ethyl]-4-methoxybenzoic Acid Lactone. To a solution at 0 °C of lithiated 2-(*p*-methoxyphenyl)-4,4-dimethyl-2-oxazoline, prepared as described[15] from 10.25 g (0.05 mol) of oxazoline in 150 mL of ether, was added a solution of 8.5 g (0.05 mol) of methyl 1-naphthyl ketone in 50 mL of ether during 5 min. After 18 h at room temperature and 10 h at reflux, the cooled mixture was treated with 50 mL of water and worked up as usual. A solution of the product in 300 mL of 8% ethanolic H_2SO_4 was refluxed for 18 h, after which time the ethanol was removed under reduced pressure. The product, isolated after the usual workup, was heated at reflux with 100 mL of 20% aqueous NaOH and 100 mL of ethanol. From the neutral portion of the reaction products was isolated 3.5 g (41%) of starting ketone by vacuum distillation. Acidification of the aqueous alkaline layer afforded 8.2 g (53%; 90% based on recovered 4-methoxybenzoic acid) of lactone, mp 195–203 °C, after trituration with $NaHCO_3$ solution to remove *p*-methoxybenzoic acid. Recrystallization from methanol yielded pure lactone; mp and mmp 205–206 °C with lactone prepared as described.[16] The crude lactone was suitable for reduction to 4-methoxy-2-(1-naphthylethyl)benzoic acid as described.[16]

Reaction of 4-Methoxyphenylmagnesium Bromide with 1,2-Naphthalic Anhydride. This reaction was carried out essentially as described[23] except that pure sublimed magnesium was used. An 80% yield of a mixture of **41** and its isomer was obtained (lit.[23] 58%). Separation began by refluxing in methanolic HCl for 12 H (1.2 L of methanol for 74 g of acids). A conventional workup afforded 74 g of a mixture of methyl esters. A solution of the esters in 350 mL of concentrated H_2SO_4 was held at room temperature for 2 h and then poured on ice. By treatment of the organic products with 2% KOH, 42 g (45% based on 1,2-naphthalic anhydride) of 2-(4-methoxybenzoyl)-1-naphthoic acid (**41**), mp 169–173 °C, was obtained which on one crystallization from benzene–acetone yielded pure **41**, mp 176–178 °C (lit.[23] mp 179.5–181 °C), with little loss. From the neutral fraction 20.0 g (21%) of methyl 1-(4-methoxybenzoyl)-2-naphthoate, mp 135–136 °C, was obtained. Alkaline hydrolysis yielded pure 1-(4-methoxybenzoyl)-2-naphthoic acid, mp 216–217 °C (lit.[23] mp 212–216 °C), in high yield.

2-(4-Methoxybenzyl)-1-naphthoic Acid* (42). Reduction of 18.1 g of **41** as described for *o*-benzoylbenzoic acid[26] yielded 13.7 g (93% based on recovery of 2.5 g of **41**) of the lactone of 2-(1-hydroxy-4-methoxyphenylmethyl)-1-naphthoic acid, mp 133–134 °C. Reduction of 13.5 g of the lactone with 60 g of activated zinc dust (washing with 10% HCl followed by treatment with ammoniacal $CuSO_4$), 200 mL of 30% KOH, and 300 mL of ethylene glycol by boiling for 48 h afforded 12.9 g (96%) of **42**, mp 150–152 °C, suitable for the next step. An analytical sample, mp 155–156 °C, was obtained with little loss by crystallization from benzene–petroleum ether.

12-Acetoxy-10-methoxybenz[*a*]anthracene* (43). A solution of 12.0 g of **42**, 0.7 g of $ZnCl_2$, 240 mL of HOAc, and 90 mL of Ac_2O was boiled for 90 min, and the cooled solution was poured into 1 L of water. The solid which separated was collected by filtration and washed with water and dilute $NaHCO_3$ to yield 12.0 g (92%) of **43**, mp 180.5–181.5 °C. An analytical sample, mp 183–184 °C, was obtained with little loss by crystallization from benzene–petroleum ether.

A solution of 12.0 g of **43** and 16.3 g of $K_2Cr_2O_7$ in 280 mL of HOAc

was refluxed for 45 min, cooled, and added to 1 L of 10% H_2SO_4. The yellow solid which separated was collected, washed with water, and dried to give 10.0 g (92%) of 10-methoxy-7,12-benz[*a*]anthraquinone* (**44**), mp 168–169 °C, suitable for further use. Recrystallization from acetic acid yielded pure **44**, mp 171.5–172.0 °C, with little loss.

7,12-Dihydroxy-7,12-dimethyl-10-methoxy-7,12-dihydrobenz[*a*]anthracene* (45). To a solution of 9.0 g (0.03 mol) of **44** in 270 mL of benzene was added 65 mL (0.09 mol) of 1.4 M CH_3Li in ether during 5 min. After 18 h at reflux, saturated NH_4Cl solution was added and the mixture worked up as usual to yield 9.2 g (95%) of **45**, which showed no carbonyl group in the IR spectrum. A colorless analytical sample, mp 175.5–176.5 °C, was obtained by crystallization from benzene–petroleum ether and benzene alone with little loss.

10-Methoxy-7,12-dimethylbenz[*a*]anthracene (**38**) was obtained by adding a solution of 7.0 g of **45** in 400 mL of methanol dropwise during 25 min to a solution at 0 °C of 75 mL of 70% HI in 100 mL of methanol. After 1 h at 5 °C the solid which had separated was collected and dissolved in 400 mL of dioxane and 30 mL of concentrated HCl. This solution was added to a solution of 70 g of $SnCl_2$ in 300 mL of dioxane and 210 mL of concentrated HCl. On holding at reflux for 30 min the color changed from dark orange-yellow to light yellow. The cooled reaction mixture was added to 3 L of water. The crude solid obtained was dissolved in 70 mL of hexamethylphosphoramide (HMPA) containing a solution of 2 g of NaOH in 5 mL of water and 2 mL of methyl iodide. After 7 h the mixture was diluted with water and the product extracted with ether to yield 4.3 g of solid. Chromatography over basic alumina afforded 4.0 g (62% from **45**) of **38**, mp 135–136 °C (lit.[23] mp 136–137 °C), identical with the **38** produced by the alternate synthesis.

9-Hydroxy-7,12-dimethylbenz[*a*]anthracene* (39) and 10-Hydroxy-7,12-dimethyl-benz[*a*]anthracene (40). Demethylation of **37** and **38** as described[6] afforded 79% of **39** as pale yellow crystals, mp 197–198 °C, and 87% of **40** as pale yellow crystals, mp 133–134 °C (lit.[17] mp 122–123 °C; light tan), respectively, after chromatography and recrystallization.

Registry No.—**1**, 66240-13-9; **2**, 66240-14-0; **3**, 51179-24-9; **4**, 66240-15-1; **5**, 66240-16-2; **6**, 66240-17-3; **7**, 66240-1-4; **8**, 66240-19-5; **9**, 66240-20-8; **10** halide derivative, 66240-21-9; **11** halide derivative, 61735-51-1; **12**, 66240-22-0; **13**, 66240-23-1; **14**, 66240-24-2; **15**, 66240-25-3; **16**, 66240-26-4; **17**, 66240-27-5; **18**, 66240-28-6; **19**, 66240-29-7; **20**, 66240-30-0; **21**, 16277-49-9; **22**, 66240-31-1; **23**, 14760-53-3; **24**, 63216-11-5; *cis*-**25**, 66239-99-4; *trans*-**25**, 66240-00-4; **26**, 66240-01-5; **27**, 66240-02-6; **28**, 57266-83-8; **29**, 53306-04-0; **30**, 32664-13-4; **31**, 17056-94-9; **32**, 66240-03-7; **33**, 66240-04-8; **34**, 66240-05-9; **35**, 53306-06-2; **37**, 62078-52-8; **38**, 62064-35-1; **39**, 66240-06-0; **40**, 62064-38-4; **41**, 66240-07-1; **42**, 66240-08-2; **43**, 66240-09-3; **44**, 66240-10-6; **45**, 66240-11-7; 12-acetoxy-3-methoxybenz[*a*]anthracene, 66240-12-8; 2-methoxy-3-naphthoic acid, 883-62-5; 1-naphthyl bromide, 90-11-9; 4-methoxyphthalic anhydride, 28281-76-7; 4-methoxy-2-(1-naphthoyl)benzoic acid, 62064-28-2; 5-methoxy-2-(1-naphthoyl)benzoic acid, 62064-27-1; 2-[1-hydroxy-1-(1-naphthyl)ethyl]-4-methoxybenzoic acid lactone, 62064-30-6; oxazoline, 504-77-8; methyl 1-naphthyl ketone, 1333-52-4; 4-methoxyphenyl bromide, 104-92-7; 1,2-naphthalic anhydride, 5343-99-7; methyl 1-(4-methoxybenzoyl)-2-naphthoate, 66239-96-1; 1(4-methoxybenzoyl)-2-naphthoic acid, 66239-97-2; 2-(1-hydroxy-4-methoxyphenylmethyl)-1-naphthoic acid lactone, 66239-98-3.

References and Notes

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(19) All melting points are uncorrected. The term "worked up as usual" means that an ether–benzene solution of the products was washed with dilute HCl and/or alkali and then with saturated NaCl and dripped through a cone of anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator, and the residue was treated as indicated. All compounds gave NMR and IR spectra consistant with the formula, and the mass spectra were performed by C. R. Weisenberger on an MS9 instrument made by A.E.I. All new compounds marked with an asterisk gave analyses (by M-H-W Laboratories, Garden City, Mich., and the Galbraith Laboratory, Knoxville, Tenn.) within ±0.30% of theory.
(20) We thank Mr. R. Weisenberger for the mass spectra.
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Structure Relation of Conjugated Cycloalkenones and Their Ketals

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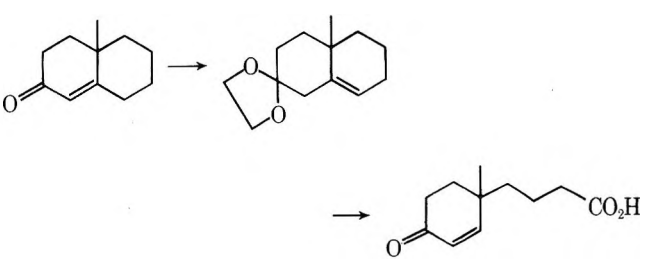
The degree of double bond shift during ketalization was studied on cycloalkenone systems. It was found that the shift was dependent on ring size and the location of substituents.

Introduction

In the framework of research carried out in our laboratory,[1] we attempted to develop a new and efficient method for the synthesis of 4,4-disubstituted cycloenones according to Scheme I.

A necessary requirement for success is the shift of the double bond to the β,γ position during the conversion of the ketone into the ketal. The fact that the double bond migrates on ketalization was discovered by Fernholz and Stavely[2] in 1937 and applied in syntheses of natural products.[3,4] Although

Scheme I



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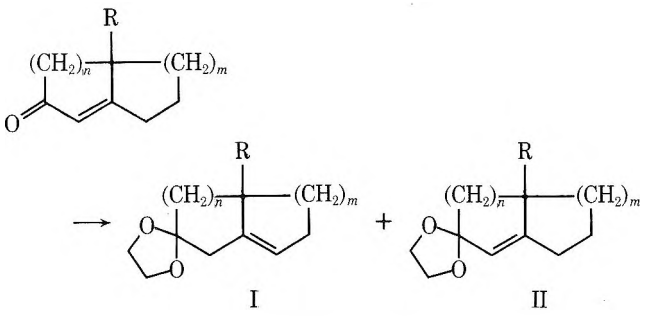


I II

ketalization of conjugated enones is a well-established method of protection, the mechanism is not yet fully understood.[5-7] The position of double bonds in substituted cyclic systems is affected mainly by the degree of substitution, conjugation, ring strain, and steric effects.[8,9] This problem has drawn attention for years and is still being studied.[10]

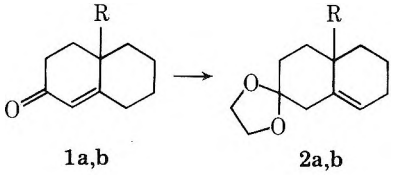
Two additional factors which must be taken into account when discussing the position of the double bond in the ketal are the ketalizing agent, e.g., 1,2-thiol vs. 1,2-diol,[6] and the nature of the acid catalyst.[7,11]

Since the many parameters involved frustrated predictions of the ketal structure we undertook a more systematic study of ketalization of bicyclic enones.

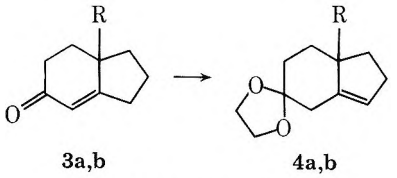
Results and Discussion

In order to facilitate the use of Scheme I as a synthetic method, we studied the ratio of the two isomers potentially formed during ketalization and its dependence upon ring size and substitution. The progress of the reaction was followed by IR and the isomer ratio was determined by NMR.

In bicyclo[4.x.0] frameworks, where x = 3 or 4, when the enone is in the six-membered ring and substituted at the β position, the double bond shift on ketalization was complete, as reported by Marshall in 1a[12] and as found in this work[1] for **1b**,[13] **3a**,[14] and **3b**.[15]



1a,b **2a,b**

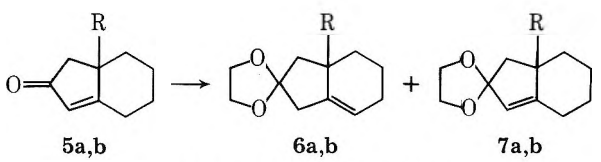


3a,b **4a,b**

a, R = Me; b, R = CO_2Et

This process was carried out in high yield and replacement of the methyl group by a carboethoxy group had no effect on the position of the double bond in the ketals **2b,4b**. This observation enabled us to carry out Scheme I satisfactorily.[16]

Compounds **5a,b**,[15] in which the enone function is located

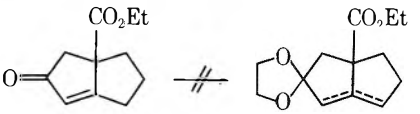


5a,b **6a,b** **7a,b**

a, R = Me; b, R = CO_2Et

in a five-membered ring, were prepared in order to study the effect of ring size on the double bond shift.

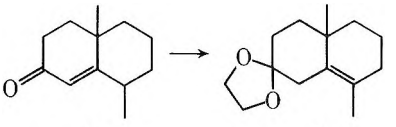
In comparing the cyclopentenone systems to the cyclohexenone systems, we soon learned that the cyclopentenones underwent ketalization more slowly. In order to obtain optimal results refluxing for 48 h was required and the product was always contaminated by starting material. Extending reaction times up to two weeks did not affect the ratio of ketals formed. Bauduin[17] has shown that formation of the ketal of cyclopentanone is less favored than that of cyclohexanone. We emphasize that ketal isomer II is very sensitive to acid hydrolysis, which may even occur when drying a benzene solution of the ketal over anhydrous magnesium sulfate.[11] In fact, we could hydrolyze isomer II with magnesium sulfate in wet benzene in the presence of isomer I and isolate the latter from the starting material by chromatography over basic alumina. Workup of the ketalization mixture under basic conditions, e.g., drying over anhydrous sodium carbonate, enabled us to prepare the ketals free of starting material. Although the structure of the ketal of **5a,b** could not be determined by NMR, we believe the product is **7a,b** based on 10% conversion to the same ketal with catalysis by oxalic acid, which is known to give predominantly α,β-unsaturated ketals, and on analogy.[18] The vinylic proton of the ketal appeared at δ 5.27, which is characteristic of a vinylic proton adjacent to the dioxolane in five-membered rings as seen in Table I. To further observe the influence of the bicyclic system on the location of the double bond in a six-membered ring vs. a five-membered ring, compound 8 was synthesized. To our disappointment we failed to obtain the appropriate ketal.[19]



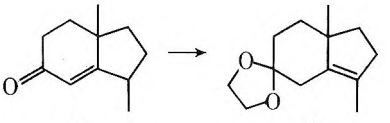
8

It is well known that substituents can influence the location of the double bond in cyclic systems. In order to determine the effect of a γ-methyl substituent on the isomer ratio, the following systems were studied.

In view of previous results for systems **1** and **3**, it was not surprising to observe that compounds **9**[20] and **11** gave ketals

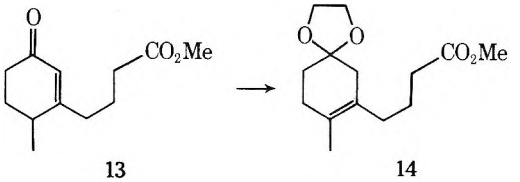


9 **10**



11 **12**

in high yield with complete double bond shift to the more substituted position, as shown unequivocally by NMR spectroscopy. The same behavior was found in monocyclic systems such as Hagemann's ester[21] and **13**[22] in which the double bond shifted completely to the more substituted β,γ position.

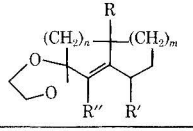
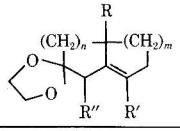


13 **14**

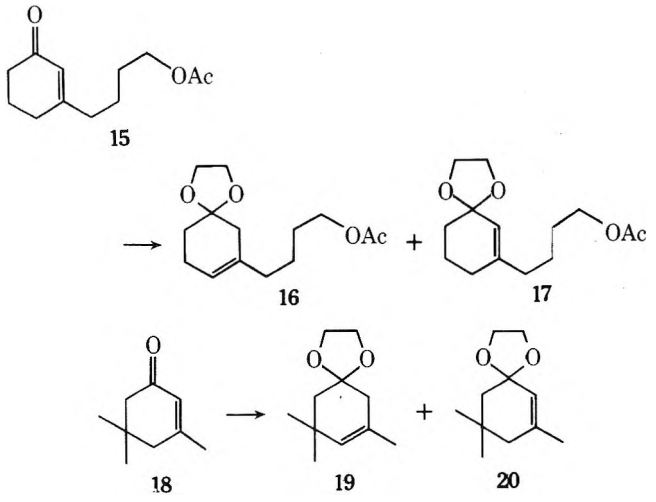
In the absence of a stabilizing γ substituent the double bond shift was found to be partial as observed in **15**[23] and **18**.

Compounds **16** and **17** were obtained in a 1:1 ratio and were separated by chromatography over Florisil. The identity of

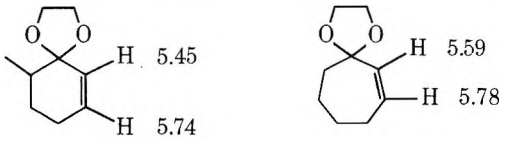
Table I

	Registry no.	 R″	(–OCH₂–)₂	R		 R′	(–OCH₂–)₂	R	Ketal (s) obtained	Ratio
$n = m = 2$ R = Me; R′ = R″ = H		5.27	3.96	1.1[a]	**2a** 3287-60-3	5.84	3.97	1.1	**2a**	
$n = 2; m = 1$ R = Me; R′ = R″ = H		5.19	3.85	0.98[a]	**4a** 59586-82-2	5.3	3.95	1.07	**4a**	
$n = m = 2$ R = –CO_2Et; R′ = R″ = H					**2b** 65898-58-0	5.65	3.97		**2b**	
$n = 2; m = 1$ R = –CO_2Et; R′ = R″ = H					**4b** 65898-59-1	5.58	3.93		**4b**	
$n = 1; m = 2$ R = R′ = Me; R″ = H	**30** 65898-52-4	5.25	3.95	1.18	**29** 65898-60-4	1.55	3.93 (d)	1.13	**30/29**	3:7
		R′ = 1.08 (d, 6 Hz)				R″ = 1.01 (d, 7 Hz)				
$n = 1; m = 2$ R = R′ = Me; R″ = H	**37** 65898-57-9	5.6		1.19[b]	**36** 65898-61-5	1.58		1.10[b]	**37/36**	3:7
$n = m = 1$ R = R′ = Me; R″ = H	**35** 65898-53-5	5.22	3.92	1.20	**34** 65898-62-6	1.63	3.92	1.1	**35/34**	2:8
$n = 1; m = 2$ R = Me; R′ = R″ = H	**7a** 65898-54-6	5.27	3.93	1.17					**7a**	
$n = 1; m = 2$ R = CO_2Et; R′ = R″ = H	**7b** 65898-55-7	5.5	3.95						**7b**	
$n = m = 2$ R = R′ = Me; R″ = H					**10** 65898-63-7	1.63	3.97	1.1	**10**	
$n = 2; m = 1$ R = R′ = Me; R″ = H					**12** 65898-64-8	1.62	3.98	1.03	**12**	
$n = m = 2$ R = R″ = Me; R′ = H	**27** 65898-56-8	1.63	4.05	1.1	**26** 65898-65-9	5.46	4.0 (d)	1.13	**27/26**	5:5
						R″ = 1.01 (d, 7 Hz)				

[a] Reference 7a, solvent $CDCl_3$. [b] 1,3-Dioxane.

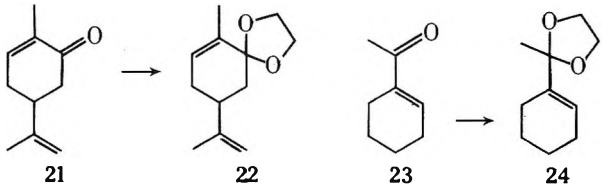


the isomers was determined by the number of allylic protons in the NMR spectra. It is worth noting that the vinylic proton adjacent to the ketal is shielded. The same effect can be seen in the following ketals prepared by Reich.[24]

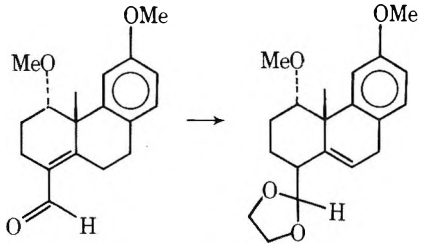


Upon ketalization of isophorone **18**, a mixture of two isomers, **19** and **20**, in the ratio 2:1 was obtained. The structure of the ketals was determined by partial decomposition of one isomer with magnesium sulfate in wet benzene and preparation of the same isomer, **20**, from **18** with fumaric acid[7a] as catalyst. We noticed that in contrast to other cases, the vinylic proton of ketal **19** appeared at higher field than the vinylic proton of isomer **20**, apparently due to the neighboring *gem*-dimethyl group.[25]

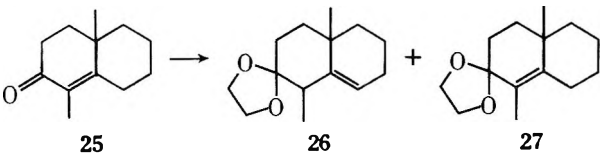
The effect of an α substituent was determined in the following monocyclic systems and it was observed that after ketalization the double bond does not shift and is located at the α,β position.



In more complex systems, additional factors may be more important than α substitution and the double bond may migrate during ketalization as reported by Wiesner[26] in the following example.

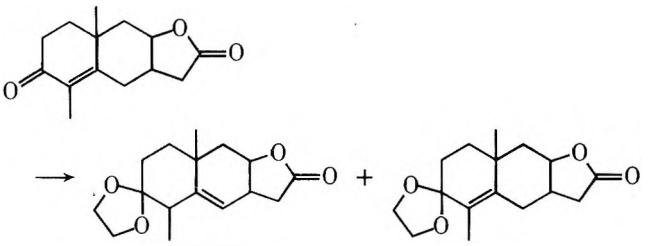


It was interesting to examine bicyclic system **25**[27] in which the enone group is substituted in α and β positions. In this case it was found that two isomers were formed in a 1:1 ratio as determined by NMR.



Treatment of the mixture with magnesium sulfate in wet benzene brought about selective deketalization of **27**, enabling isolation of **26** by chromatography on basic alumina. These results are consistent with Caine's report on a similar system.[28]

From the results discussed so far, it is clear that substituents affect the degree of double bond migration in cyclohexenone



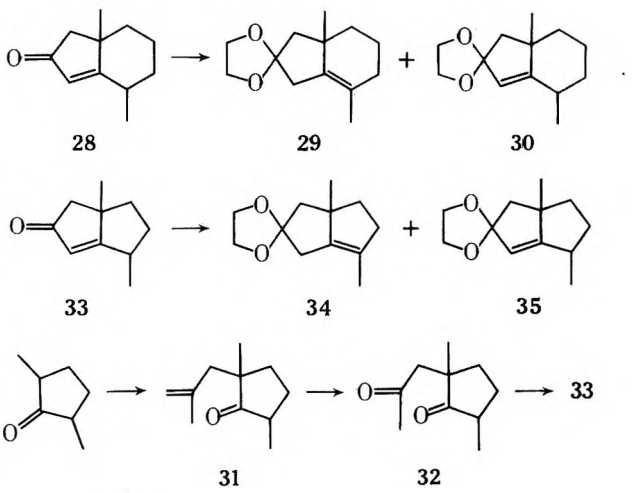
systems during ketalization. In the following bicyclic cyclopentenones the importance of a γ-methyl substituent was studied further.

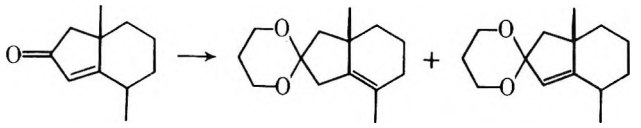
It was found that 70% of the ketal formed from **28**[29] had undergone double bond migration, in contrast to system **5a** in which no migration took place. The ring size effect was seen by comparing ketalization of systems **28** and **33** (Scheme II). Double bond shifted isomer **34** was 80% of the ketal mixture. These findings are in accord with empirical results for bicyclic [4.3.0] systems that double bonds prefer to be endocyclic to five-membered rings and exocyclic to six-membered rings rather than vice versa.[30]

We found that replacing the 1,3-dioxolane ring by a 1,3-dioxane ring had no effect on the degree of migration of the double bond based on the fact that the ratio of the isomers was not affected, although in the NMR spectrum a significant shift was observed, the vinylic proton of **37** appearing at δ 5.60 as opposed to **30** in which it appears at δ 5.25.

In view of the results presented here we can conclude that in bicyclic systems containing enones in a six-membered ring

Scheme II





28 36 37

the double bond has a strong tendency to shift to the β,γ position on ketalization with a strong acid catalyst.

In order to prevent this shift a stabilizing substituent must be introduced in the α position. On the other hand, in systems containing cyclopentenones the tendency to form the ketal is lower, the double bond does not tend to migrate, and only stabilizing groups in the γ position can cause partial migration.

Experimental Section

Infrared spectra were recorded on Perkin-Elmer 237 in chloroform. The ultraviolet spectra were measured on a Cary 15. The NMR spectra were recorded on a Varian A-60 and Varian T-60 using tetramethylsilane as internal standard.

Mass spectra were determined on an Atlas CH4.

The gas-liquid chromatography was carried out using a Varian Aerograph Model 90-P, carrier gas helium; column 15% XE-60 on Chromosorb Q, 1/4 in. × 10 ft, 60–80 mesh.

Materials. 1-Acetyl-1-cyclohexene (Aldrich Chemical) was used without further purification.

2-Acetonyl-2-methylcyclohexanone. A solution of 4.9 g of 2-methyl-2-(2-methylallyl)cyclohexanone[31] was oxidized as described for **32**, yielding 4.9 g of crude oil. After short-path distillation at 65°C (0.1 mm), 3.48 g in 61% yield was collected.

5,6,7,7a-Tetrahydro-4,7a-dimethylindan-2(4*H*)-one (5a).[32] To a solution of 26.6 g of potassium hydroxide in 530 mL of absolute ethanol 3.5 g of 2-acetonyl-2-methylcyclohexanone was added and refluxed under nitrogen for 3 h. The solution was cooled and acidified with 90 mL of 3 N hydrochloric acid diluted with 130 mL of water, and the ethanol was removed under reduced pressure. The oily layer was extracted by four 30-mL portions of ether. The organic layers were combined, washed with 20 mL of brine, and dried over magnesium sulfate and the solvents were removed under reduced pressure to yield 2.8 g of crude **5a**. The crude oil was distilled at 50–60 °C (0.3 mm) to yield 1.3 g of **5a** in 48% total yield.

3,7a-Dimethyl-1,2,3,6,7,7a-hexahydro-5*H*-indan-5-one (11). A sodium methoxide solution was obtained from 7.8 g of sodium and 130 mL of methanol. To the ice-cooled solution was added dropwise 8 g of 2,5-dimethylcyclopentanone and afterwards 8 g of methyl vinyl ketone diluted with 10 mL of methanol was added over 4 h. The solution was allowed to stand overnight under nitrogen. Acidification was carried out with 10% hydrochloric acid, methanol was removed in vacuo, and the product was extracted with three 40-mL portions of methylene chloride. The organic phase was washed with 5% sodium bicarbonate solution and dried over magnesium sulfate. After filtration, the solvent was removed in vacuo, leaving a yellow oil which was distilled at 70 °C (0.1 mm). The 6 g of oil obtained were purified on a 150-g Florisil column, most of the material coming out when the solvent ratio was 1:4 hexane/methylene chloride; 4.8 g of pure compound was obtained: IR 1665 cm^{-1} (α,β-unsaturated ketone); NMR ($CDCl_3$) δ 1.20 (s, 3H, CH_3), 1.33 (d, 3 H, CH_3), 5.82 (m, 1 H, –CO-CH=C–).

Ethyl 2,3,4,5-Tetrahydro-5-oxo-3a-(1*H*)pentalenecarboxylate (8). To a stirred mixture of 0.45 g (19 mmol) of sodium hydride in 30 mL of dry toluene under nitrogen in a three-neck flask was added 0.8 g (3.8 mmol) of ethyl 1-acetonyl-2-oxocyclopentanecarboxylate[33] in 30 mL of toluene during 0.5 h and the reaction was refluxed overnight.

The mixture was cooled and acidified with 5 mL of 2 N hydrochloric acid. The water layer was separated and extracted by four 10-mL portions of ether. The organic layers were combined, washed with 10 mL of brine, and dried over magnesium sulfate. The solvents were removed under reduced pressure to yield 0.6 g of crude **8**.

In bulb-to-bulb distillation of 0.56 g of the crude oil at 50 °C (0.02 mm), 0.45 g was collected containing 55% of **8** according to VPC; the total yield was 57%: IR 1715 (C=O; COO), 1635 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.03 (t, 1 H, J = 1.5 Hz, vinylic), 4.18 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 2.89, 2.31 (AB, 2 H, J = 17 Hz, $COCH_2$), 1.25 (t, 3 H, J = 7 Hz, CH_3CH_2–); MS M^+ 194, calcd 194; main *m/e* 77, 91, 121, 165; UV λ_{max} (CH_3OH) 232 (ϵ 9.7 × 10^3), 295 nm (ϵ 35). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.21; H, 7.50.

2-(2-Methylallyl)-2,5-dimethylcyclopentanone (31). To 4.37 g (0.039 mol) of potassium *tert*-butoxide in 80 mL of dry benzene in a 250 mL three-neck flask equipped with a mechanical stirrer, an addition funnel, and a condenser was added 3.56 g (0.31 mol, 4 mL) of 2,5-dimethylcyclopentanone in 10 mL of dry benzene during 10 min.

The mixture was heated to boiling and cooled to room temperature. Methallyl chloride (7.4 g, 0.082 mol) diluted in 10 mL of dry benzene was added during 1.5 h and the mixture stirred overnight at room temperature. The flask was cooled with ice and 20 mL of water and 8.5 mL of hydrochloric acid were added. The aqueous layer was extracted with three 15-mL portions of ether. The combined organic layers were washed with 10 mL of 10% sodium bicarbonate solution and 10 mL of brine and dried over anhydrous magnesium sulfate. After filtration the solvents were removed, yielding 4.7 g of oil.

The product was used in the next step without further purification.

The product was short-path distilled at 78–80 °C (10 mm); the first fraction of 1.4 g was pure **31** as shown by VPC and the second fraction of 7.49 g contained 43% of **31** (total yield 46%): IR 1730 (C(=O)C), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.87 (m, 1 H, vinylic), 4.73 (m, 1 H, vinylic), 1.7 (br s, 3 H, CH_3C=C), 0.97 (s, 3 H, $-CCH_3$); MS M^+ 166, calcd 166; main characteristic *m/e* 41, 55, 81, 96, 111.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.08; H, 10.77.

2-Acetonyl-2,5-dimethylcyclopentanone (32). **31** (1.99 g, 0.012 mol) was ozonolyzed in 150 mL of methylene dichloride at −78 °C. The excess of ozone was removed by a stream of nitrogen and the solvent was removed at 0 °C under reduced pressure on a rotary evaporator. To the oily ozonide were added 40 mL of acetone and 1.7 mL of Jones reagent at 0 °C with vigorous stirring. The excess of the oxidizing reagent was decomposed by 2-propanol, and the acetone was removed under reduced pressure. The product was extracted by five 20-mL portions of methylene chloride and washed with 20 mL of sodium bicarbonate and 20 mL of brine. The solvent was removed under reduced pressure, yielding 1.88 g of **32** which was used without further purification in the next step. Short-path distillation, at 80–85 °C (0.8 mm), of the crude product yielded 0.74 g of pure **32** and 0.56 g of a fraction containing 40% of **32** according to VPC (total yield 46%): IR 1735 (cyclic C=O), 1720 cm^- (C=O); NMR ($CDCl_3$) δ 2.7–2.9 (m, 2 H), 2.08 (s, 3 H, $-CCH_3$), 1.02 (d, 3 H, $-CHCH_3$, J = 7 Hz); MS M^+ 168, calcd 168; main *m/e* 41, 43, 55, 110, 111.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.62; H, 9.51.

4,5,6,6a-Tetrahydro-4,6a-dimethyl-2(1*H*)-pentalenone (33). Crude **32** (0.5 g, 0.003 mol) and 0.41 g of pyrrolidine were dissolved in 30 mL of dry benzene in a 100-mL flask equipped with a Dean Stark trap. Water removal took place for 24 h under nitrogen, the solvent was evaporated, and 25 mL of benzene, 0.55 g of sodium acetate, 1.1 mL of water, and 1.1 mL of acetic acid were added. The mixture was refluxed for 4 h under nitrogen and cooled to room temperature. The organic layer was separated, washed with 10 mL of 10% hydrochloric acid, 10 mL of 10% sodium bicarbonate, and 10 mL of brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield 0.4 g of crude **33**. Purer **33** was obtained in 30% yield by chromatography over Florisil, eluting with methylene chloride/hexane (1:9): IR 1705 (C=O), 1615 cm^{-1} (C=C); NMR ($CDCl_3$) δ 5.77 (d, 1 H, vinylic), 2.37 (s, 2 H, CH_2C(=O)–), 1.23 (d, 3 H, J = 7 Hz, CH_3CH–), 1.22 (s, 3 H, CH_3); MS M^+ 150, calcd 150; main *m/e* 41, 43, 79, 80, 108, 135; UV λ_{max} (CH_3OH) 232 (ϵ 1.19 × 10^4), 290 nm (ϵ 160).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.39; H, 8.94.

General Ketalization Procedure. Into a flask fitted with a Dean–Stark trap and a reflux condenser with a calcium chloride drying tube were added 2 mmol of ketone, 0.04 g (0.2 mmol) of *p*-toluenesulfonic acid monohydrate, 70 mL of dry benzene, and 2.5 g (40 mmol) of ethylene glycol. The reaction mixture was refluxed overnight or several days. After cooling, anhydrous sodium bicarbonate was added. The mixture was transferred to a separatory funnel containing 20 mL of saturated sodium bicarbonate solution. The aqueous layer was separated and extracted with two 15-mL portions of hexane. The combined organic layers were dried (anhydrous $NaHCO_3$), filtered, and concentrated in vacuo to give an oil in nearly quantitative yield.

Registry No.—**5a**, 16508-51-3; **8**, 65898-66-0; **11**, 65898-67-1; **31**, 65898-68-2; **32**, 65898-69-3; **33**, 65898-70-6; 2-methyl-2-(2-methylallyl)cyclohexanone, 65898-71-7; 2-acetonyl-2-methylcyclohexanone, 27943-50-6; 2,5-dimethylcyclopentanone, 4041-09-2; methyl

vinyl ketone, 78-94-4; ethyl 1-acetonyl-2-oxocyclopentanecarboxylate, 61771-77-5; methallyl chloride, 563-47-3.

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New Approach to the Synthesis of 4,4-Disubstituted Cycloalkenones

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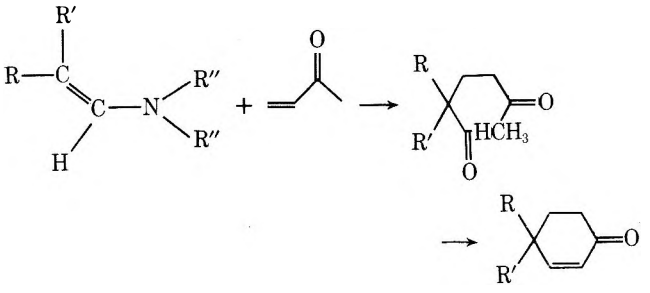
4,4-Disubstituted cycloalkenones were synthesized from appropriate bicyclic systems. The ozonide of each bicyclic system was treated by either the oxidative or the reductive route, giving products which were easily transformed to monocyclic enones. The advantages and limitations of the two routes are described.

Introduction

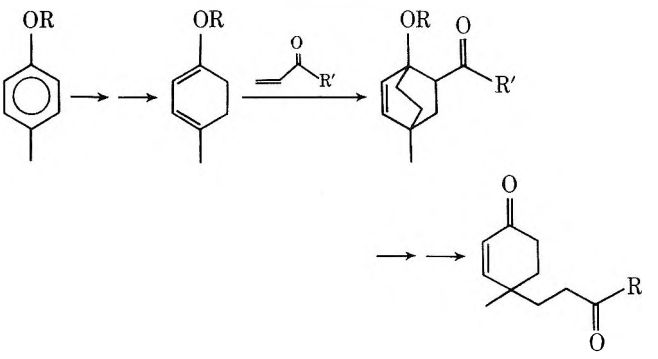
Conjugated cycloalkenone systems are very useful intermediates in synthesis, and therefore, much effort has been invested in developing methods for their preparation. The most common method is annelation, which has been improved and adapted to a wide variety of syntheses.[1] Conjugated 4,4-disubstituted cyclohexenones may be synthesized by many routes, but most of those were tailored to specific problems. Stork[2] has developed a general method consisting of condensation of the enamine with methyl vinyl ketone to produce the desired compound.



This method was applied by Yamada[3] to the synthesis of optically active 4,4-disubstituted cyclohexenones using optically active enamines.

Recently Martin[4] has described a new route to a suitable enamine for this type of annelation, starting with the appropriate ketone and diethyl lithiomorpholinomethyl phosphonate.

Another approach to conjugated cyclohexenones is based on the cleavage of bicyclic systems. For example, the starting material for the synthesis of (±)-Trichodermin was prepared by cleavage of an appropriate bicyclo[4.1.0]heptane by Raphael.[5] Birch[6] suggested a more general method based on the cleavage of bicyclo[2.2.2]octenes which were prepared by Diels–Alder addition to cyclic dienes.



In this report we summarize work in which conjugated 4,4-disubstituted cycloalkenones were prepared from conjugated bicyclic enones. The method consists basically of three steps, the first of which is the shift of the double bond induced by ketalization. The next step is cleavage of the double bond

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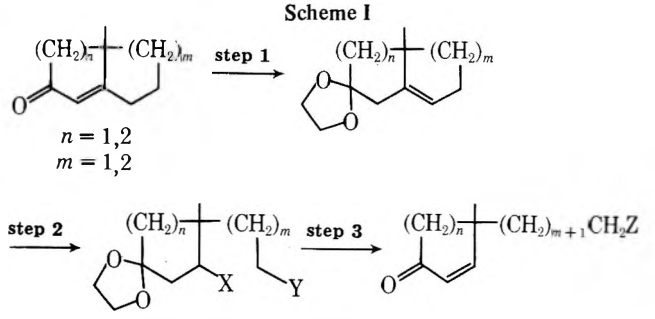
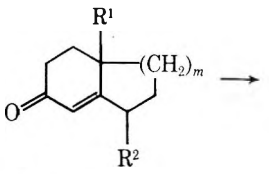
Scheme I

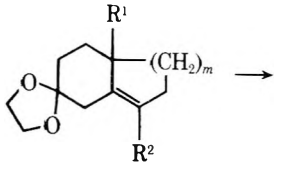


in its new position by ozonolysis to an intermediate which is easily transformed in the third step by mild acid catalysis to the desired 4,4-disubstituted cycloalkenone as described in Scheme I.

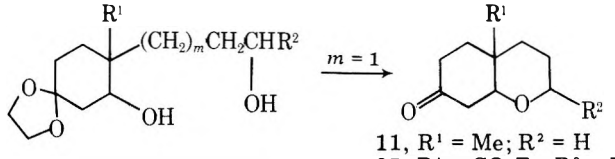
Scheme II. Reductive Route



1, R^1 = Me; R^2 = H; m = 2
17, R^1 = CO_2Et; R^2 = H; m = 2
8, R^1 = Me; R^2 = H; m = 1
24, R^1 = CO_2Et; R^2 = H; m = 1
29, R^1 = Me; R^2 = Me; m = 2
37, R^1 = Me; R^2 = Me; m = 1

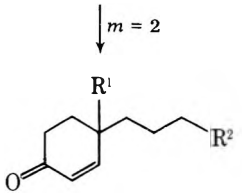


2, R^1 = Me; R^2 = H; m = 2
18, R^1 = CO_2Et; R^2 = H; m = 2
9, R^1 = Me; R^2 = H; m = 1
25, R^1 = CO_2Et; R^2 = H; m = 1
30, R^1 = Me; R^2 = Me; m = 2
38, R^1 = Me; R^2 = Me; m = 1



3, R^1 = Me; R^2 = H; m = 2
19, R^1 = CO_2Et; R^2 = H; m = 2
10, R^1 = Me; R^2 = H; m = 1
26, R^1 = CO_2Et; R^2 = H; m = 1
31, R^1 = Me; R^2 = Me; m = 2
39, R^1 = Me; R^2 = Me; m = 1

11, R^1 = Me; R^2 = H
27, R^1 = CO_2Et; R^2 = H
40, R^1 = Me; R^2 = Me



4, R^1 = Me; R^2 = CH_2OH
5, R^1 = Me; R^2 = CH_2OAc
20, R^1 = CO_2Et; R^2 = CH_2OH
21, R^1 = CO_2Et; R^2 = CH_2OAc
6, R^1 = Me; R^2 = CO_2H
7, R^1 = Me; R^2 = CO_2Me
22, R^1 = CO_2Et; R^2 = CO_2H
23, R^1 = CO_2Et; R^2 = CO_2Me
32, R^1 = Me; R^2 = CH(Me)OH
33, R^1 = Me; R^2 = CH(Me)OAc
34, R^1 = Me; R^2 = C(=O)Me

Results and Discussion

The fact that a double bond conjugated to a ketone may shift during ketalization has been known for some time.[7,8] For this work we synthesized a series of appropriate bicyclic enone systems which were ketalized in the usual manner. However, results described in the literature did not enable us to predict the position of the double bond in every case. In the accompanying paper[9] we have summarized some of the factors determining the position of the double bond in these bicyclic systems.

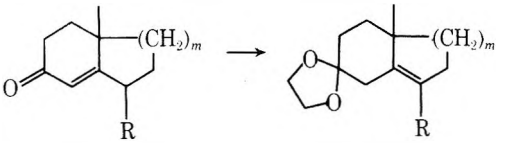
The first compound studied was **1**, since it was known that the double bond shifts to the β,γ position.[10] Ketalization was carried out with ethylene glycol using *p*-toluenesulfonic acid as catalyst in refluxing benzene with continuous removal of water. The ketal **2** was ozonized in methylene chloride at −78 °C followed by reduction with excess sodium borohydride (reductive method, Scheme II). The resulting crude ketal diol **3** was isolated in 90% yield and treated with oxalic acid solution to give hydroxycyclohexenone, which was then oxidized with Jones' reagent to the corresponding acid **6** in good yield. The fact that compound **6** was obtained in a few simple steps and in good yield encouraged us to study the scope and limitation.

We wished to determine whether the above pathway could be used to synthesize the known acid **14**.[6] The appropriate starting material was **8**,[11] which was ketalized in good yield with full shift of the double bond.[9] However, upon completing the above sequence of reactions, we found that the sole product was the ketone ether (perhydrochromanone) **11**. All our efforts to prevent formation of the ether ring by methods such as use of milder acidic or basic conditions or protection of the primary alcohol failed. Attempts to cleave **11** to **14** were also unsuccessful.

The tendency of 1,5-diols to form cyclic ethers is well known,[12] and this sequence is recommended as a simple and high-yield route to 7-perhydrochromanones.

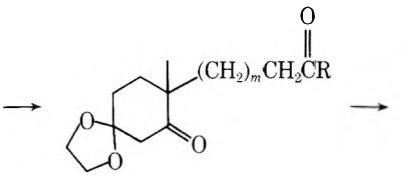
Since the corresponding acid **14** had been prepared and isolated under strongly acidic conditions from its ester without lactone formation,[13] we based our solution on early oxidation of the terminal carbon atom to a carboxylic acid (oxidative route, Scheme III) in order to prevent cyclization, in the following manner.

Scheme III. Oxidative Route

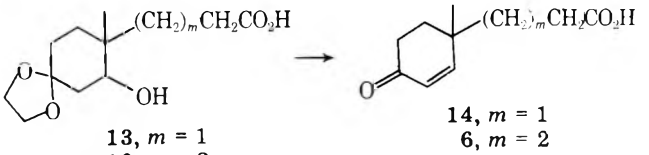


8, R = H; m = 1
1, R = H; m = 2
37, R = Me; m = 1

9, R = H; m = 1
2, R = H; m = 2
38, R = Me; m = 1



12, R = OH; m = 1
15, R = OH; m = 2
41, R = Me; m = 1



13, m = 1
16, m = 2

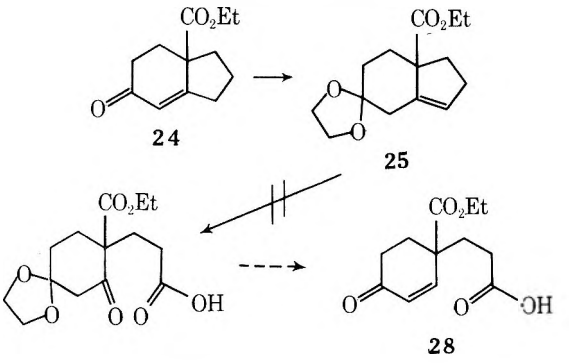
14, m = 1
6, m = 2

The ketal **9** was ozonized at −78 °C and oxidized[14] at 0 °C with Jones' reagent to the ketal acid **12**, which was isolated by a special technique (see Experimental Section) to prevent hydrolysis of the ketal function. This sequence provides a versatile intermediate **12** containing three functional groups which may be utilized selectively. In order to achieve our goal keto acid **12** was converted by sodium borohydride to alcohol **13**, which was transformed easily under mildly acidic conditions to **14** in moderate yield. Isolation of keto acid **14** prepared by the oxidative route met with some difficulty from accompanying byproducts. In order to determine whether the difficulty may be attributed to the oxidative route itself or to the particular starting material, ketal **2** was treated similarly yielding keto acid **6** via the ketal acid **15**. Since byproducts lowered the yield in this case also, the reductive approach is recommended, as will be shown later.

Another group of compounds which we studied were bicyclic compounds containing a carboethoxy group in the angular position. Treatment of ketal ester **18**, prepared from **17**[15] by the reductive route, enabled isolation of **22** in high yield.

Attempts to decarboxylate keto acid ester **22** by methods described in the literature[16,17] for 4-carboethoxycyclohexenone to form a cyclohexenone monosubstituted with a hydrocarbon chain at the 4 position failed.

In order to study the generality of the synthesis of perhydrochromanones, ketal ester **25** was prepared from **24**[18] and

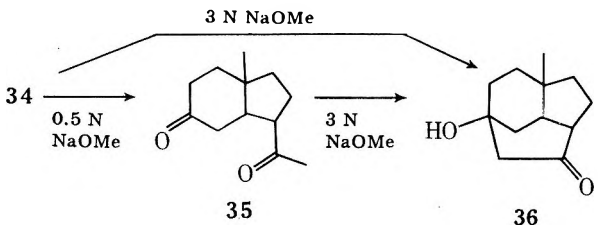


its subjection to the reductive route led to **27** as expected. The alternative preparation of **28** by the oxidative route led to a mixture of products from which the desired keto acid ester **28** could not be isolated.

Replacement in the starting material of a hydrogen atom in the γ position by an alkyl group enables preparation of side chains containing a keto function. For example, the 4-oxopentyl chain was prepared from compound **29**.[19]

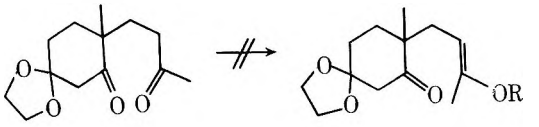
Ketal **30** was synthesized and cleaved as described, giving keto alcohol **32** in good yield; from this, ketocyclohexenone **34** was prepared. In this case the reductive method was found to be efficient, whereas using the oxidative route the same difficulties as mentioned above were encountered.

Ketocyclohexenone **34**, which is readily available by this method, may serve as a useful intermediate to certain polycyclic systems. Thus treating **34** with 3 N sodium methoxide



resulted in transformation to the tricyclic compound **36** in high yield. Double cyclizations of this type are known[20] in similar systems and have been used by Yamada[21] for the total synthesis of (±)-derbrobine. We then found that on treating **34** under milder conditions, such as 0.5 N sodium methoxide, intermediate bicyclic system **35** could be obtained. The high tendency of the 4-oxopentyl chain to cyclize and form a five-membered ring, in preference to a seven-membered ring, is known in the literature.[22,23]

Attempts to apply the reductive route to the synthesis of the corresponding 3-oxobutyl side chain from **37**[9] failed and led to formation of the keto ether **40** in high yield. Applying the oxidative route to the synthesis of the 3-oxobutyl chain is conditional on selective protection of one carbonyl group. For this ketal, dione **41** was prepared in good yield and found to be acid sensitive. However attempts at selective protection,



41

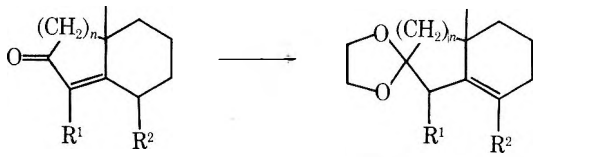
for example, by enol acetate formation, were unsuccessful.

In the accompanying paper it was shown that the shift of the double bond upon ketalization is affected by ring size and the degree of substitution at the α and γ positions. Although certain systems gave mixtures of isomeric ketals, these mixtures were investigated without separation, hoping they would serve per se as starting materials. Ketalization of compound **42**[24] gave two ketals **43** and **44** in a 1:1 ratio (Scheme IV) due to the presence of the α-methyl substituent, in contrast to the unsubstituted compound **1** in whose ketal the double bond had shifted completely.

The reductive method was applied to the mixture of **43** and **44** and the desired acid, **48**, was separated in good yield based on ketal **43**. In the course of the preparation of **46**, the products from ketal **44** did not interfere, since they probably dissolved in the aqueous phase during workup. Furthermore, ketal **43** could be isolated from the mixture by selective deketalization of ketal **44**.

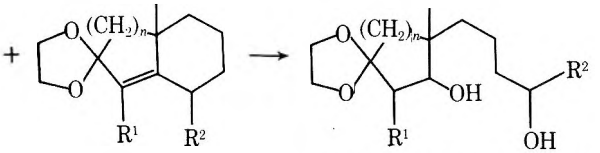
Upon ketalization of **50**[25] we found that the effect of the γ substituent was not sufficient to cause complete migration of

Scheme IV



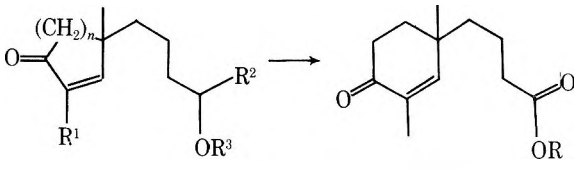
42, R¹ = Me; R² = H; *n* = 2
50, R¹ = H; R² = Me; *n* = 1

43, R¹ = Me; R² = H; *n* = 2
51, R¹ = H; R² = Me; *n* = 1



44, R¹ = Me; R² = H; *n* = 2
52, R¹ = H; R² = Me; *n* = 1

45, R¹ = Me; R² = H; *n* = 2
53, R¹ = H; R² = Me; *n* = 1



46, R¹ = Me; R² = R³ = H; *n* = 2
47, R¹ = Me; R² = H; R³ = Ac; *n* = 2
54, R¹ = H; R² = Me; R³ = H; *n* = 1
55, R¹ = H; R² = Me; R³ = Ac; *n* = 1

48, R = H
49, R = Me

the double bond, and the ratio of **51** to **52** was 7:3. The mixture was cleaved as usual by the reductive method and cyclopentenone alcohol **54** could be separated in moderate yield.

In summary, it may be concluded that in cases in which the double bond shifts into a six-membered ring, cycloalkenones substituted in the 4 position with long chains may be synthesized in high yield by the reductive method. When the double bond is located in a five-membered ring, the reductive method leads to keto ethers in very high yields, and only the oxidative method enables preparation of the desired substituted cycloalkenones.

Experimental Section

Infrared spectra were recorded on Perkin-Elmer 237 in chloroform. The ultraviolet spectra were measured on Cary 15. The NMR spectra were recorded on Varian A60 and Varian T60 using tetramethylsilane as internal standard. Mass spectra were determined on an Atlas CH_4. The gas–liquid chromatography was carried out using Varian Aerograph Model 90-P, carrier gas was helium, column 15% Xe-60 on Chromosorb Q, 9 ft.

4-(4-Hydroxybutyl)-4-methyl-2-cyclohexen-1-one (4). Ozonolysis of 0.6 g (2.88 mmol) of **2** dissolved in 50 mL of 3:1 methylene chloride/methanol at −78 °C under nitrogen was carried out with ozone until a light blue color was stable for 5 min. The ozonide was reduced with 300 mg of sodium borohydride at −78 °C for 3 h. The reaction mixture was warmed to room temperature and quenched with 30 mL of water. The organic layer was separated and the water was extracted with three 30-mL portions of ether and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and 0.66 g (90%) of **3** was isolated as a crude oil: IR 3500 (OH), 1100 cm^{-1} (ketal); NMR ($CDCl_3$) δ 3.96 [s, 4 H, $(-OCH_2)_2$], 3.66 (m, 3 H), 3.55 (br, 2 H, OH), 0.95 (s, 3 H, CH_3).

To a solution of 1.38 g (5.65 mmol) of **3** in 180 mL of 1:1 tetrahydrofuran/water was added 20 g of oxalic acid and the solution was refluxed for 3 h. To the cooled solution sodium chloride was added to saturation and the tetrahydrofuran was removed under reduced pressure. The solution was extracted by three 60-mL portions of methylene chloride, washed with 5% sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was removed by reduced pressure to give 0.80 g (80%) of oil **4**: IR 3450 (OH) 1675 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 6.64, 5.77 (AB, 2 H, J_{AB} = 10 Hz, vinylic), 4.73 (br s, 1 H. OH), 3.56 (m, 2 H, $-CH_2OH$), 1.13 (s, 3 H, CH_3).

It was found that **4** was unstable in GC. The acetate was prepared according to Bayless[26] and **5** was purified for analysis: IR 1720 ($-C(=O)CH_3$), 1680 cm^{-1} [c-$C(=O)CH=CH(C_2)_3$]; UV λ_{max} (MeOH) 227 nm (ϵ 9.5 × 10^3); NMR ($CDCl_3$) δ 6.72, 5.83 (AB, 2 H, J = 10 Hz, vinylic), 4.10 (t, 2 H, J = 6 Hz, $-CH_2OAc$) 2.05 (s, 3 H $-CCH_3$), 1.13 (s, 3 H, CH_3); MS M^+ 224, calcd 224.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.46; H, 8.99.

4-(1-Methyl-4-oxo-2-cyclohexenyl)butanoic Acid (6). (a) **4** (3.0 g, 0.16 mmol) dissolved in 150 mL of acetone was oxidized with Jones' reagent at 0 °C. The excess of reagent was quenched by 2-propanol and the acetone was removed under reduced pressure. The product was extracted with three 40-mL portions of chloroform and dried over anhydrous magnesium sulfate. The solvent was removed and 1.9 g (60%) of **6** was obtained: IR 3500–3200 (–COOH), 1720 (–COOH), 1680 cm^{-1} [c-$C(=O)CH=CH(CH_2)_3$]; NMR ($CDCl_3$) δ 8.4 (br, s, 1 H, $-CO_2H$) 6.72, 5.83 (AB, 2 H, J = 10 Hz, vinylic), 1.13 (s, 3 H, CH_3).

The methyl ester **7** was prepared by treatment with excess diazomethane in order to enable purification by GC for analysis: MS M^+ 210, calcd 210; UV λ_{max} (MeOH) 227 nm (ϵ 8.5 × 10^3).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.29; H, 8.23.

(b) Ozonolysis of 1.1 g (5.3 mmol) of ketal **2** was carried out in 50 mL of 3:1 methylene chloride/methanol at −78 °C with excess ozone. The solvents were removed at 0 °C under reduced pressure and the ozonide was dissolved in 40 mL of acetone and added via an addition funnel to 20 mL of Jones' reagent at 0 °C. Excess oxidizing reagent was destroyed with 2-propanol and the reaction mixture was filtered over Celite and sodium carbonate. The acetone was removed, the water layer was acidified to pH 5, extracted by three 50-mL portions of chloroform, and dried over anhydrous magnesium sulfate. The solvents were removed and 0.94 g of crude **15** was obtained: IR 3500–3300 (–COOH), 1715 cm^{-1} (–COOH).

Reduction of 0.94 g (3.6 mmol) of **15** in 100 mL of tetrahydrofuran was carried out with 0.35 g of sodium borohydride at 0 °C for 2 h. To the cooled stirred solution 100 mL of 10% hydrochloric acid was added and the solution refluxed for 18 h. The reaction mixture was saturated with sodium chloride and the solvent was removed under reduced pressure. The water layer was extracted with three 60-mL portions of chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give 0.7 g of crude acid **6** (50% pure by GC).

Octahydro-4a-methyl-7*H*-1-benzopyran-7-one (11). Ketal **9** was prepared from 3 g of **8** as usual[9] and 3.3 g (85%) were obtained: IR 1100 cm^{-1}; NMR ($CDCl_3$) δ 5.30 (m. 1 H, vinylic), 3.95 (s, 4 H, ketal), 1.07 (s, 3 H, CH_3).

Ozonolysis was carried out on 1.0 g (5.1 mmol) as described for **3** and 1.0 g (84%) of **10** was obtained: IR 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 3.95 (s, 4 H, $-OCH_2CH_2O-$), 3.65 (m, 3 H, $-CH_2OH$, >CHOH), 2.6 (m, 2 H, –OH), 0.93 (s, 3 H, CH_3).

To a solution of 0.9 g (3.9 mmol) of **10** in 180 mL of 1:1 tetrahydrofuran/water was added 20 g of oxalic acid. The solution was refluxed for 3 h, cooled to room temperature, and saturated with sodium chloride. The tetrahydrofuran was removed under reduced pressure and the water layer was extracted with three 80-mL portions of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 0.54 g (77%) of crude **11** (95% according to GC).

11 was purified for analysis by GC to yield crystals: mp 42.5–44 °C; IR 1715 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 4.0 (m, 1 H, HCO–), 3.53 (m, 2 H, $-H_2CO-$), 1.15 (s, 3 H, CH_3); MS M^+ 168, calcd 168.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.39; H, 9.64.

3-(1-Methyl-4-oxo-2-cyclohexene)propionic Acid (14). On ozonolysis of 0.36 g (1.8 mmol) of ketal **9** cleaved as described for **15**, 0.45 g (80%) of **12** was isolated as a crude oil: IR 3500–3200 (–COOH), 1720 cm^{-1} (–COOH); NMR ($CDCl_3$) δ 6.20 (m, 1 H, OH), 3.95 (s, 4 H, $-OCH_2CH_2O-$), 1.1 (s, 3 H, CH_3).

A solution of 0.32 g (1.3 mmol) of **12** in 15 mL of tetrahydrofuran was treated with 0.4 g of sodium borohydride as described for **16** to give 0.26 g (80%) of **13** as a crude oil: IR 3500 (–COOH), 1730 cm^{-1} (–COOH).

13 (0.26 g, 1.3 mmol) was dissolved in 8 mL of tetrahydrofuran and 8 mL of 5% hydrochloric acid in water and refluxed overnight. The solution was cooled to room temperature and neutralized with sodium carbonate. The tetrahydrofuran was removed under reduced pressure and the water layer washed with methylene chloride. The aqueous solution was acidified with concentrated hydrochloric acid and extracted four times with 20-mL portions of methylene chloride. The solvent was dried over magnesium sulfate and removed under reduced pressure to give 0.12 g (40%) of crude acid **14**.

4-(4-Hydroxybutyl)-4-carboethoxy-2-cyclohexen-1-one (20). Ketalization of 0.48 g (2.1 mmol) of **17** was carried out as usual. **18** (0.6 g) was obtained as a crude oil: IR 1725 cm^{-1} [$-C(=O)OC_2H_5$]; NMR ($CDCl_3$) δ 5.65 (m, 1 H, vinylic), 4.2 (q, 2 H, OCH_2CH_3), 3.97 (s, 4 H, $-OCH_2CH_2O-$), 1.27 (t, 3 H, CH_3CH_2-).

Ozonolysis of 2.66 g (10 mmol) of **18** dissolved in 130 mL of methylene chloride and 20 mL of methanol with an excess of ozone was carried out as described for **3**. **19** (2.34 g; 77%) was obtained: IR 3500 (OH), 1720 cm^{-1} (–COOEt).

Deketalization and dehydration of 0.45 g (1.47 mmol) of **19** in 100 mL of 1:1 tetrahydrofuran/water and 10 g of oxalic acid was carried out as described for **4**. After removal of the solvent 0.28 g (85%) of the keto alcohol ester **20** was obtained: IR 3600–3400 (OH), 1730 (–COOEt), 1680 cm^{-1} [$-C(=O)C=Cl$]; NMR ($CDCl_3$) δ 6.97, 6.02 (AB, 2 H, J = 10 Hz, vinylic), 4.28 (q, 2 H, $-CH_2CH_3$), 3.70 (m, 3 H, $-CH_2OH$), 1.30 (t, 3 H, CH_3CH_2-).

In order to obtain an analytical sample the acetate **21** was prepared in pyridine with acetyl chloride as usual: IR 1730 [–COOEt, $-OC(=O)CH_3$], 1680 cm^{-1}; NMR ($CDCl_3$) δ 6.97, 6.02 (AB, 2 H, J = 10 Hz, vinylic), 4.30 (q, 2 H, OCH_2CH_3) 2.07 (s, 3 H, $CH_3C(=O)-$), 1.03 (t, 3 H, CH_3CH_2-).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.82; H, 7.81.

4-[1-Carboethoxy-4-oxo-2-cyclohexene]butaonic Acid (22). Oxidation of 1 g (4.45 mmol) of hydroxyketo acid **20** with 20 mL of Jones' reagent in 30 mL of acetone was carried out at 0 °C and quenched with 5 mL of 2-propanol. The solvents were removed under reduced pressure and the water layer was extracted with five 40-mL portions of chloroform. From the organic phase the acid was extracted with five 10-mL portions of 5% sodium bicarbonate. The combined aqueous layers were acidified with concentrated hydrochloric acid to pH 2 and extracted with five 50-mL portions of chloroform. The organic layers were combined and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 0.70 g (60%) of

the keto acid **22**: IR 3500-3000 (-COOH) 1730 (-COOH, -COOEt), 1680 cm^{-1} [c-C(=O)CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.97, 6.02 (AB, 2 H, J = 10 Hz, vinylic), 4.25 (q, 2 H, OCH_2CH_3) 1.30 (t, 3 H, CH_3CH_2-).

In order to purify this compound the methyl ester **23** was prepared with excess diazomethane: IR 1735 (-COOR), 1685 cm^{-1} [c-C(=O)-CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.97, 6.02 (AB, 2 H, J = 10 Hz, vinylic), 4.23 (q, 2 H, OCH_2CH_3), 3.7 (s, 3 H, CH_3O-), 1.3 (t, 3 H, CH_3CH_2-); UV λ_{max} (MeOH) 223 (ϵ 7.2 × 10^3).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67, H, 7.51. Found: C, 62.15, H, 8.08.

Octahydro-4a-carboethoxy-7*H*-1-benzopyran-7-one (27). Ketalization of 4.0 g (1.9 mmol) of **24** was carried out as usual to give in quantitative yield the ketal **25**: IR 1716 (-COOEt) 1090 cm^{-1} (ketal); NMR ($CDCl_3$) δ 5.58 (m, 1 H, vinylic), 4.17 (q, 2 H, $-CH_2O$), 3.13 (s, 4 H, $-OCH_2CH_2O$-), 1.23 (t, 3 H, CH_3CH_2-).

Ozonolysis of 2.0 g (7.9 mmol) of **25** dissolved in 50 mL of methylene chloride and 10 mL of methanol was carried out as usual to yield 1.4 g of crude diol **26**: IR 3480 (-OH), 1720 cm^{-1} (-COOEt).

Hydrolysis of 0.2 g (0.69 mmol) of **26** was carried out in 60 mL of 1:1 tetrahydrofuran/water and 7 g of oxalic acid. The reaction mixture was refluxed for 3 h. At room temperature the solution was saturated with sodium chloride and the tetrahydrofuran was removed under reduced pressure. The water was extracted with three 40-mL portions of methylene chloride. The organic layer was washed with 5% sodium carbonate and dried over anhydrous magnesium sulfate. The solvent was removed and 0.13 g of **27** in 50% overall yield was obtained: IR 1725 cm^{-1} (-COOR); NMR ($CDCl_3$) δ 4.25 (q, 2 H, CH_3CH_2O-), 3.50 (m, 3 H, >$CHOCH_2$-), 1.30 (t, 3 H, CH_3CH_2-); MS M^+ 226, calcd 226.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.88; N, 8.17.

4-Methyl-4-(4-pentanol)-2-cyclohexenone (32). Ketalization was carried out on 3.7 g (19.6 mmol) of **29** dissolved in 150 mL of dry benzene as usual. The yield was 4.15 g (95%) of **30**: IR 1100 cm^{-1} (ketal); NMR ($CDCl_3$) δ 3.97 (s, 4 H, $-OCH_2CH_2O$-), 1.63 (s, 3 H, CH_3C=C-), 1.1 (s, 3 H, CH_3-).

Ozonolysis of 2.03 g (9.15 mmol) of **30** dissolved in 100 mL of methylene chloride and 20 mL of methanol at −78 °C was carried out as described for **2**.

After removal of the solvents 2.35 g (93%) of crude diol **31** was isolated: IR 3500 (-OH), 1100 cm^{-1} (ketal); NMR ($CDCl_3$) δ 3.97 (s, 4 H, $-O(CH_2)_2O$-), 2.47 (m, 2 H, HCOH), 1.17 (d, 3 H, J = 6 Hz, CH_3CH-) 0.93 (s, 3 H, CH_3-).

Crude diol **31** (0.9 g, 3.49 mmol) was dissolved in 140 mL of 1:1 tetrahydrofuran/water, 15 g of oxalic acid was added and the solution was refluxed for 3 h. Workup as usual yielded 0.625 g (85%) of **32**: IR 3600 (OH), 1660 cm^{-1} [c-C(=O)CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.7, 5.96 (AB, 2 H, J = 10 Hz, vinylic), 3.80 (m, 1 H, >CHOH) 1.08 (s, 3 H, CH_3); MS M^+ 196, calcd 196.

The acetate **33** was prepared in the usual way with acetyl chloride in pyridine: IR 1720 [OC(=O)CH_3], 1665 cm^{-1} [c-C(=O)-CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.70, 5.96 (AB, 2 H, J = 10 Hz, vinylic), 2.05 (s, 3 H, $-OCOCH_3$), 1.23 (d, 1 H, J = 6 Hz, HCOH), 1.08 (s, 3 H, CH_3); UV λ_{max} (MeOH) 227 mm (ϵ 1.2 × 10^4).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.60; H, 8.91.

4-Methyl-4-(4-oxopentyl)-2-cyclohexenone (34). Oxidation of 0.18 g (9.18 mmol) of hydroxy ketone **32** was carried out in a solution of 0.3 g of chromium trioxide, 0.2 mL of water, and 3 mL of pyridine. The mixture was stirred overnight at room temperature. To the reaction mixture was added 10 mL of water and the solids were removed by filtration with Celite. The water layer was extracted with four 30-mL portions of ether. The organic layers were combined and washed with 5% hydrochloric acid and brine. The solution was dried over anhydrous magnesium sulfate and the solvents were removed under reduced pressure to give 0.163 g (91%) of diketone **34**: IR 1715 (>C=O), 1675 cm^{-1} [c-C(=O)CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.70, 5.96 (AB, 2 H, J = 10 Hz, vinylic), 2.17 (s, 3 H, CH_3CO) 1.17 (s, 3 H, CH_3); UV λ_{max} (MeOH) 226 nm (ϵ 6.9 × 10^3); MS M^+ 194, calcd 194.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.14; H, 9.34. Found: C, 73.84; H, 9.20.

3-Acetyl-7a-methyl-3a,6,7,7a-tetrahydro-5-(4*H*)-indanone (35). Sodium methoxide (0.5 N) in methanol was prepared from 0.17 g of sodium and 15 mL of anhydrous methanol. Diketone **34** (0.1 g, 0.51 mmol) dissolved in 1 mL of methanol was added at 0 °C and stirred for 2 h. Brine was added and the methanol was removed under reduced pressure. The water layer was extracted with three 25-mL portions of methylene chloride. The organic layers were washed with water and dried over anhydrous magnesium sulfate and the solvent was removed to give 0.095 g (90%) of **35**: IR 1715 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 2.20 (s, 3 H, CH_3C-); MS M^+ 194, calcd 194.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.22; H, 9.27.

1-Hydroxy-7-methyltricyclo[5.2.2.$0^{4,8}$]undecan-3-one (36). Sodium methoxide (2.5 N) in methanol was prepared from 5 g of sodium and 100 mL of methanol. Diketone **34** (1.05 g, 5.4 mmol) dissolved in 2 mL of methanol was added dropwise at 0 °C and stirred overnight under nitrogen at room temperature. To the reaction mixture was added 25 mL of brine and the solvent was removed under reduced pressure. The water layer was extracted with three 40-mL portions of methylene chloride. The organic layers were combined, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed and 0.9 g (86%) of crude oil was isolated. The crude oil was crystallized from hexane to give **36** in high yield: mp 116–118 °C; IR 3580 (OH), 1700 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 1.08 (s, 3 H, CH_3); MS M^+ 194, calcd 194.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.76; H, 9.29.

Octahydro-2,4a-dimethyl-(7*H*)-1-benzopyran-7-one (40). Ketal **38** was prepared from 1 g (6.1 mmol) of **37** as usual. **38** (1.25 g) was obtained as a crude oil: IR 1090 cm^{-1} (ketal); NMR ($CDCl_3$) δ 3.98 (s, 4 H, $-OCH_2CH_2O$-), 1.62 (s, 3 H, CH_3C=C), 1.03 (s, 3 H, CH_3).

Ozonolysis of 0.18 g (0.86 mmol) of **33** was carried out as described for **2**, followed by sodium borohydride treatment. The crude diol **39** (0.17 g) was dissolved in 90 mL of 1:1 tetrahydrofuran/water and 10 g of oxalic acid was added and refluxed for 3 h. The reaction mixture was worked up as usual to give 0.14 g (89%) of **40**: IR 1715 (>C=O), 1100 cm^{-1} (-O-); NMR ($CDCl_3$) δ 3.60 (m, 2 H, >CHO-), 1.25 (d, 3 H, CH_3CO), 1.17 (s, 3 H, CH_3); MS M^+ 182, calcd 182.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.81; H, 9.79.

Ketalization of 4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-2(3*H*)-naphthalenone (42). Ketone **42** (2.09 g, 11.2 mmol) was ketalized in 60 mL of dry benzene, 1.5 g of ethylene glycol, and 60 mg of *p*-toluenesulfonic acid and the solution was refluxed for 4 days with constant removal of water. Hexane (100 mL) was added and the acid was quenched with sodium carbonate. The organic layer was washed three times with 30 mL of 5% sodium bicarbonate and dried over anhydrous sodium carbonate. The solvent was removed. A 2.1-g (84%) mixture of two ketals **43** and **44** in a 1:1 ratio was obtained: IR 1090 cm^{-1} (ketal); MS M^+ 222, calcd 222.

In order to isolate isomer **43** 50 mg of a mixture of 1:1 **43**/**44** was dissolved in 2 mL of benzene and 1 mL of tetrahydrofuran. A solution of 0.5 g of magnesium sulfate in 5 mL of water was added and the mixture was stirred overnight at room temperature. The solvents were removed under reduced pressure and the water extracted with three 10-mL portions of methylene chloride. The organic layers were combined and dried over anhydrous magnesium sulfate. Crude oil (50 mg) was isolated. The crude oil was chromatographed over basic alumina plate eluting with 1:12 acetone/hexane to yield 20 mg (80%) of clean **43**: NMR ($CDCl_3$) δ 5.46 (m, 1 H, vinylic), 4.0 (d, 4 H, $-OCH_2CH_2O$-), 1.13 (s, 3 H, CH_3), 1.0 (d, 3 H, J = 7 Hz, CH_3CH<).

2,4-Dimethyl-4-(4-butanol)-2-cyclohexenone (46). A mixture of 1 g (4.5 mmol) of **43**/**44** in a 1:1 ratio was dissolved in 50 mL of methylene chloride and ozonized at −78 °C as usual. Crude oil (0.82 g) was isolated and was used in the next step without further purification: NMR ($CDCl_3$) δ 4.0 (m, 4 H, $-OCH_2CH_2O$-), 3.70 (m, 3 H, -OCH-), 1.1 (d, 3 H, CH_3CH), 0.91 (s, 3 H, CH_3).

Crude diol **45** was dissolved in 50 mL of 1:1 tetrahydrofuran/water and 5 g of oxalic acid was added and refluxed overnight. The reaction was worked up as usual and 0.45 g of crude oil was obtained (84% yield based on one isomer): IR 3450 (-OH), 1670 cm^{-1} [c-C(=O)-CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.5 (br s, 1 H, vinylic), 3.60 (m, 2 H, $-CH_2O$-), 1.77 (d, 3 H, J = 2 Hz, CH_3C=CH), 1.13 (s, 3 H, CH_3).

Acetate **47** was prepared as usual with pyridine–acetyl chloride: IR 1730 (acetate), 1670 cm^{-1} [c-C(=O)CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.47 (br s, 1 H, vinylic), 4.10 (t, 2 H, $-CH_2OH$), 2.07 [s, 3 H, CH_3C(=O)-] 1.77 (d, 3 H, J = 2 Hz, CH_3CH=C), 1.13 (s, 3 H, CH_3); MS M^+ 238, calcd 238; UV λ_{max} (MeOH) 236 mm (ϵ 8.8 × 10^3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.66; H, 9.18.

4-(1,3-Dimethyl-4-oxo-2-cyclohexene)butanoic Acid (48). Oxidation of 0.44 g (2.2 mmol) of crude keto alcohol **46** was carried out with 6 mL of Jones' reagent at 0 °C in 30 mL of acetone. 2-Propanol was added to quench the excess reagent and the acetone was removed under reduced pressure. The water layer was extracted with three 30-mL portions of chloroform. The solvent was dried over an-

hydrous magnesium sulfate and removed to give 0.30 g (65%) acid **48**, and the corresponding methyl ester **49** was prepared with excess diazomethane: IR 1735 (-COOR), 1675 cm^{-1}. [c-C(=O)-CH=CH$(CH_2)_3$]; NMR ($CDCl_3$) δ 6.49 (br s, 1 H, vinylic), 3.72 (s, 3 H, -OMe) 1.73 (d, 3 H, J = 2 Hz, CH_3CH=C), 1.13 (s, 3 H, CH_3); UV λ_{max} (MeOH) 236 mm (ϵ 5.5 × 10^3); MS M^+ 224, calcd 224.

Ketalization of 5,6,7,7a-tetrahydro-4,7a-dimethylindan-2(4*H*)-one (50). Ketalization of 0.31 g (1.9 mmol) of **50** was carried out in 70 mL of dry benzene, 2.4 mL of ethylene glycol, and 31 mg of *p*-toluenesulfonic acid for 5 days and worked up as usual. Oil (0.43 g) was obtained in quantitative yield. According to the NMR the ratio **51/52** was 7:3. **51**: NMR ($CDCl_3$) δ 3.93 (br, 4 H, J = 3 Hz, -OCH_2CH_2O-), 2.63 (bs, 2 H, O_2CCH_2C=), 1.87 (s, 2 H, O_2CCH_2-), 1.55 (bs, 3 H, CH_3C=C), 1.13 (s, 3 H, CH_3). **52** NMR ($CDCl_3$) δ 5.25 (bd, 1 H, J = 2 Hz, CH=C), 3.95 (s, 4 H, -OCH_2CH_2O-), 2.00 (s, 2 H, CCH_2-), 1.18 (s, 3 H, CH_3C=C), 1.08 (d, 3 H, J = 6 Hz, CH_3C-).

Isomer **51** was isolated from the mixture following the procedure described for **43**.

4-(4-Hydroxypentyl)-4-methyl-2-cyclopenten-1-one (54). Ozonolysis of 1.08 g (5.2 mmol) of a mixture of **51** and **52** in 100 mL of methylene chloride and 20 mL of methanol at −78 °C was performed as described before. The crude diol (0.81 g; 64%) was isolated: IR 3400 (-OH), 1070 cm^{-1} (ketal); NMR ($CDCl_3$) δ 3.9 (s, 4 H, -OCH_2CH_2O-), 1.18 (d, 3 H, J = 6 Hz, CH_3CH 1.03 (s, 3 H, CH_3).

Crude diol **53** (0.18 g) was dissolved in 140 mL of 1:1 tetrahydrofuran/water and 15 g of oxalic acid and refluxed for 3 h. The reaction mixture was worked up as usual and 0.44 g (74%) of **54** as crude oil was isolated: IR 3460 (OH), 1710 cm^{-1} [c-C(=O)CH=CH$(CH_2)_2$]; NMR ($CDCl_3$) δ 7.52, 6.10 (AB, 2 H, J = 6 Hz, vinylic), 1.25 (s, 3 H, CH_3), 1.08 (d, 3 H, CH_3CH).

The corresponding acetate **55** was prepared from 0.33 g of **54** in 5 mL of pyridine and 0.25 mL of acetyl chloride. The keto acetate **54** was purified on basic alumina plates and elated with 3:7 acetone/hexane in 61% yield: IR 1725 ($OCCH_3$), 1700 cm^{-1} [c-C(=O)-CH=CH$(CH_2)_2$]; NMR ($CDCl_3$) δ 7.45, 6.05 (AB, 2 H, J = 6 Hz, vinylic), 2.03 (s, 3 H, CH_3C-); MS M^+ 224, calcd 224.

Registry No.—**2**, 3287-60-3; **3**, 65969-91-7; **4**, 33948-33-3; **5**, 65969-92-8; **6**, 33919-22-1; **7**, 33919-23-2; **8**, 17299-55-7; **9**, 59586-82-2; **10**, 65969-94-0; **11**, 33948-34-4; **12**, 65969-95-1; **13**, 65969-96-2; **14**, 33948-32-2; **15**, 65969-93-9; **17**, 7478-39-9; **18**, 65898-58-0; **19**, 65969-97-3; **20**, 65969-68-8; **21**, 65969-69-9; **22**, 33919-24-3; **23**, 65969-70-2; **24**, 65969-71-3; **25**, 65898-59-1; **26**, 65969-72-4; **27**, 65969-73-5; **29**, 4071-63-0; **30**, 65898-63-7; **31**, 65969-74-6; **32**, 65969-75-7; **33**, 65969-76-8; **34**, 65969-77-9; **35**, 65969-78-0; **36**, 65969-79-1; **37**, 65898-67-1; **38**, 65898-64-8; **39**, 65969-80-4; **40**, 65969-81-5; **42**, 878-55-7; **43**, 65898-65-9; **44**, 65898-56-8; **45**, 65969-82-6; **46**, 65969-83-7; **47**, 65969-84-8; **48**, 65969-85-9; **49**, 65969-86-0; **50**, 65969-87-1; **51**, 65898-60-4; **52**, 65898-52-4; **53**, 65969-88-2; **54**, 65969-89-3; **55**, 65969-90-6.

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Selective Reduction of Alkenes and Alkynes by the Reagent Lithium Aluminum Hydride–Transition-Metal Halide

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The reactions of alkenes and alkynes with $LiAlH_4$ in admixture with first-row transition-metal halides have been studied in detail. When $LiAlH_4$ and $TiCl_3$, VCl_3, $CrCl_3$, $FeCl_2$, $FeCl_3$, $CoCl_2$, or $NiCl_2$ were mixed in equimolar quantities, alkenes were reduced in quantitative yield to the corresponding alkanes. However, when the transition-metal halide was used in catalytic amount, only $CoCl_2$, $NiCl_2$, and $TiCl_3$ were effective in reducing olefins to alkanes in high yield. 1-Methylcyclohexene (a trisubstituted olefin), which is reduced only poorly by hydrozirconation or $LiAlH_4$–$TiCl_3$, was reduced in quantitative yield by $LiAlH_4$–$CoCl_2$ and $LiAlH_4$–$NiCl_2$. The following olefins were reduced to the corresponding alkanes in quantitative yield by one or more transition-metal halides in admixture with $LiAlH_4$: 1-octene, 1-hexene, *cis*-2-hexene, *trans*-2-hexene, styrene, cyclohexene, and 2-ethylhexene. Phenylacetylene was reduced quantitatively to styrene using $LiAlH_4$–$FeCl_2$ or to ethylbenzene when $LiAlH_4$–$NiCl_2$ was used. Diphenylacetylene could be reduced to *cis*-stilbene in the absence of *trans*-stilbene by $LiAlH_4$–$NiCl_2$. 1-Octyne could be reduced to octane in quantitative yield by $LiAlH_4$–$FeCl_2$ or to 1-octene by $LiAlH_4$–$NiCl_2$. Deuterium incorporation studies indicate that the intermediate transition-metal alkyls formed in these reactions are not stable, as only 12–47% deuterium incorporation is observed except when $TiCl_3$ is used as the catalyst.

Application of transition-metal hydrides in organic synthesis has been an area of considerable interest in recent years. Although the ability of transition-metal hydrides to add to olefins to form C–M bonds has been known for some years,[1] the synthetic utility of this reaction is still under development.

Recently, hydrozirconation of alkenes and alkynes has been shown to yield a versatile intermediate for useful synthetic

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Table I. Reactions of 1-Octene with $LiAlH_4$–Transition-Metal Halides in 1.0:1.0:0.5 Molar Ratio for $LiAlH_4$–Metal Halide–1-Octene[a]

Expt	Metal halide	Registry no.	Reaction time, h	1-Octene recovery, %	Octane,[b] %
1	$TiCl_3$	7705-07-9	1	0	98
2	VCl_3	7718-98-1	1	100	0
			8	0	93
3	$CrCl_3$	10025-73-7	1	0	100
4	$MnCl_2$	7773-01-5	1	71	25
			8	53	40
5	$FeCl_2$	7758-94-3	1	0	98
6	$FeCl_3$	7705-08-0	1	0	98
7	$CoCl_2$	7646-79-9	1	0	100
8	$NiCl_2$	7718-54-9	1	0	100
9	CuI	7681-65-4	8	95	~5
10	$ZnBr_2$	7699-45-8	8	100	0

[a] Reactions were carried out in THF at room temperature. [b] Yield was determined by GLC using an internal standard.

Table II. Reactions of 1-Octene with $LiAlH_4$–Transition-Metal Halides in 1.0:0.10:1.0 Ratio for $LiAlH_4$–Metal Halide–1-Octene[a]

Expt	Metal halide	1-Octene recovery, %	Octane, %
11	VCl_3	64	42
12	$CrCl_3$	80	19
13	$MnCl_2$	100	0
14	$FeCl_2$	95	5
15	$FeCl_3$	95	5
16	$CoCl_2$	0	98
17	$NiCl_2$	5	94
18	$TiCl_3$	0	95

[a] Reactions were carried out in THF at room temperature for 18 h.

Table III. Reactions of 1-Octene with $LiAlH_4$–Transition-Metal Halides in 1.0:1.0:4.0 Ratio for $LiAlH_4$–Metal Halide–1-Octene[a]

Expt	Metal halide	1-Octene recovery, %	Octane, %
19	VCl_3	8	90
20	$CrCl_3$	6	91
21	$FeCl_2$	0	96
22	$FeCl_3$	18	80
23	$CoCl_2$	17	80
24	$NiCl_2$	17	82
25	$TiCl_3$	0	96

[a] Reactions were carried out in THF at room temperature for 18 h.

Table IV. Reactions of 1-Methylcyclohexene with $LiAlH_4$–Transition-Metal Halides[a]

Expt	Metal halide	Molar ratio, $LiAlH_4$–metal halide–substrate	1-Methylcyclohexene recovery, %	Methylcyclohexane, %
26	VCl_3	1:1:2	100	0
27	$CrCl_3$	1:1:2	100	0
28	$MnCl_2$	1:1:2	100	0
29	$FeCl_2$	1:1:2	67	27
30	$FeCl_2$	1:1:0.5	70	30
31	$CoCl_2$	1:0.1:2	98	2
32	$CoCl_2$	1:1:0.5	0	96
33	$CoCl_2$	1:1:1	0	91
34	$NiCl_2$	1:0.1:2	100	0
35	$NiCl_2$	1:1:1	0	94
36	$TiCl_3$	1:0.1:2	100	0
37	$TiCl_3$	1:1:1	94	2

[a] Reactions were carried out in THF at room temperature for 24 h.

transformations.[2] In addition to $Cp_2Zr(H)Cl$, $LiAlH_4$–catalytic $ZrCl_4$[3] has been reported to reduce terminal alkenes to alkanes and $LiAlH_4$–stoichiometric $TiCl_4$[4] was found to be useful for the reduction of alkynes and monosubstituted alkenes. The applicability of these reagents is limited by their low reactivity with higher substituted or strained olefins as well as the need for stoichiometric amounts of the transition-metal reagent. At this stage of development, it would seem important to investigate other transition-metal halides which might be more reactive or generally more attractive than those of zirconium and titanium.

Results and Discussion

Reactions of 1-Octene. The monosubstituted olefin 1-octene was chosen for initial studies of the reaction of olefins with $LiAlH_4$ in the presence of first-row transition-metal halides. The results are shown in Table I. High yields of octane are obtained using $TiCl_3$, $CrCl_3$, $FeCl_2$, $FeCl_3$, $CoCl_2$, and $NiCl_2$ in admixture with $LiAlH_4$. $LiAlH_4$–VCl_3 and $LiAlH_4$–$MnCl_2$ both had lower activities, and $LiAlH_4$–CuI and $LiAlH_4$–$ZnBr_2$ showed no activity at all toward olefin reduction. The transition-metal halide and $LiAlH_4$ were employed in stoichiometric ratio, and the reactive species is presumed to be a transition-metal hydride (eq 1–3). The addition of the transition-metal hydride to the olefin is believed to be due to d orbital overlap between the metal atom and the unsaturated carbon–carbon bond. Under this assumption, Cu(I) (d^{10}) and Zn(II) (d^{10}) have no empty d orbitals to overlap with the olefin and Mn(II) (d^5), with its d orbitals half filled, should exhibit a lower activating ability. This explanation is consistent with the results obtained.

$$MH + M'X \longrightarrow [M'H] + MX \quad (1)$$

$$= + [M'H] \longrightarrow \overset{M'}{\underset{H}{}} \longrightarrow \overset{H}{\underset{M'}{}} \quad (2)$$

$$\overset{H}{\underset{M'}{}} + MH \longrightarrow \overset{H}{\underset{M}{}} + [M'H] \quad (3)$$

M = Al; M' = first-row transition metal

In order to investigate the catalytic properties of the first-row transition-metal halides, a 1.0:0.10:1.0 ratio of $LiAlH_4$–metal halide–1-octene was used in experiments 11–18 (Table II). The results show clearly that 1-octene can be reduced to *n*-octane by the combination of $LiAlH_4$ with a catalytic amount of $CoCl_2$, $NiCl_2$, or $TiCl_3$. The same reaction was partially catalyzed by VCl_3 or $CrCl_3$, but little or no catalytic behavior was observed with $MnCl_2$, $FeCl_2$, or $FeCl_3$. It is clear from a comparison of experiments 8 and 17 that the use of catalytic amounts of transition-metal halide ($NiCl_2$ in this case) decreases the rate of reaction. Using a catalytic amount of $NiCl_2$, 5% of 1-octene remains unreacted after an 18-h reaction time, whereas no octene remains after 1 h when a stoichiometric amount of transition-metal halide is used.

Reactions were also carried out using a 1.0:1.0:4.0 ratio of $LiAlH_4$–metal halide–1-octene, and the results are given in Table III.

Table V. Reactions of Other Alkenes with $LiAlH_4$–Transition-Metal Halides

Expt	Metal halide	Alkene[c]	Reaction time, h	Substrate recovery, %	Alkane[c]	Yield of alkane, %
38	$FeCl_2$[a]	Styrene	24	0	Ethylbenzene	95
39	$CoCl_2$[b]			5		92
40	$NiCl_2$[b]			0		92
41	$TiCl_3$[b]			0		94
42	$FeCl_2$[a]	1-Hexene	24	2	Hexane	97
43	$CoCl_2$[b]			0		97
44	$NiCl_2$[b]			0		97
45	$TiCl_3$[b]			0		96
46	$FeCl_2$[a]	*cis*-2-Hexene	24	0	Hexane	98
47	$CoCl_2$[b]			70		32
48	$CoCl_2$[a]			0		98
49	$NiCl_2$[b]			70		28
50	$NiCl_2$[a]			3		95
51	$TiCl_3$			80		18
52	$FeCl_2$[a]	*trans*-2-Hexene	24	0	Hexane	99
53	$CoCl_2$[a]			0		96
54	$NiCl_2$[a]			0		95
55	$TiCl_3$[a]			10		90
56	$FeCl_3$[a]	2-Ethyl-1-hexene	24	20	3-Methyl-	80
			48	0	heptane	95
57	$CoCl_2$[b]		48			35
58	$CoCl_2$[a]		24	0		98
59	$NiCl_2$[b]		48			15
60	$NiCl_2$[a]		24	18		82
			48	0		95
61	$TiCl_3$[b]		48			10
62	$TiCl_3$[a]		24	10		88
			48	2		94
63	$FeCl_2$[a]	Cyclohexene	24	0	Cyclohexane	96
64	$CoCl_2$[b]		48	45		55
65	$CoCl_2$[a]		24	0		96
66	$NiCl_3$[b]		48	60		40
67	$NiCl_2$[a]		24	2		94
68	$TiCl_3$[b]		48	95		0
69	$TiCl_3$[a]		24	60		45
			48	0		95

[a] The molar ratio of $LiAlH_4$–metal halide–olefin is 1.0:1.0:2.0. [b] The molar ratio of $LiAlH_4$–metal halide–olefin is 1.0:0.1:2.0. [c] Registry no.: styrene, 100-42-5; 1-hexene, 592-41-6; *cis*-2-hexene, 7688-21-3; *trans*-2-hexene, 4050-45-7; 2-ethyl-1-hexene, 1632-16-2; cyclohexene, 110-83-8; ethylbenzene, 100-41-4; hexane, 110-54-3; 3-methylheptane, 589-81-1; cyclohexane, 110-82-7.

Reactions of 1-Methylcyclohexene. The trisubstituted olefin 1-methylcyclohexene was allowed to react with $LiAlH_4$ in admixture with first-row transition-metal halides. The purpose of studying this particular olefin is that it is sterically hindered and does not react by hydrozirconation.[2] Table IV shows that this olefin can be transformed into the saturated hydrocarbon by $LiAlH_4$–$FeCl_2$ (1:1) in 27–30% yield and also reduced by either $LiAlH_4$–$CoCl_2$ (1:1) or $LiAlH_4$–$NiCl_2$ (1:1) in high yields (91–96%). These results with 1-methylcyclohexene reveal that cobalt(II) and nickel(II) salts, when allowed to react with $LiAlH_4$, are better reducing agents than iron(II) or other first-row transition-metal halides in hydrometalation reactions. It is also important to note that this same reaction cannot be carried out catalytically using $CoCl_2$, $NiCl_2$, or $TiCl_3$ or even using a stoichiometric amount of $TiCl_3$.

Reactions of Styrene, 1-Hexene, *cis*-2-Hexene, *trans*-2-Hexene, 2-Ethyl-1-hexene, and Cyclohexene. The monosubstituted olefins styrene and 1-hexene were reduced to ethylbenzene and *n*-hexane in high yield by $LiAlH_4$–equiv/molar ratio of $FeCl_2$ or by catalytic $CoCl_2$, $NiCl_2$, or $TiCl_3$ at room temperature for 24 h (Table V). The disubstituted olefins 2-ethyl-1-hexene, *cis*- and *trans*-2-hexene, and cyclohexene were also reduced by $LiAlH_4$–$FeCl_2$ (1:1 ratio). On the other hand, catalytic amounts of $CoCl_2$, $NiCl_2$, or $TiCl_3$ affected the reduction of the disubstituted olefins at a much slower rate than that of the monosubstituted olefins. However, when stoichiometric amounts of $CoCl_2$, $NiCl_2$, or $TiCl_3$ were used, the rate of reaction accelerated and high yields of products were obtained in 24 h.

Reaction of Phenylacetylene. The terminal alkyne phenylacetylene was allowed to react with $LiAlH_4$–transition-metal halides. When the transition-metal halide was VCl_3, $CrCl_3$, or $MnCl_2$, phenylacetylene was reduced to yield styrene and ethylbenzene without selectivity. Both products appeared from the beginning of the reaction (experiments 70, 72, and 74 in Table VI), showing the competition between alkyne and alkene reduction. In addition, the ratio of $LiAlH_4$–metal halide–substrate seems to be important in suppressing side reactions. For example, the ratio of 1:1:2 exhibited an improved mass balance compared to the ratio of 1:1:3.5. The reaction of $LiAlH_4$–$FeCl_2$ with phenylacetylene was studied carefully (experiments 75–78). The mass balance was increased by decreasing the substrate–reagent ratio as observed in the other transition-metal halide cases. When the ratio is 1:1:2 ($LiAlH_4$–metal halide–substrate), either product can be obtained in high yield. Styrene is obtained by early quenching (10-min reaction time at −40 °C) in 92% yield with no ethylbenzene present. On the other hand, late quenching of the same reaction mixture (24 h at room temperature) produces 85% ethylbenzene in the presence of only 1% styrene. However, 94% ethylbenzene can be obtained when the ratio is 1:1:1 after a 24-h reaction time at room temperature.

Table VI. Reactions of Phenylacetylene with $LiAlH_4$–Transition-Metal Halides

Expt	Metal halide	Molar ratio $LiAlH_4$–metal halide–substrate	Reaction time, h	Phenylacetylene recovery, %	Styrene, %	Ethylbenzene, %
70	VCl_3	1:1:3.5	0.5	92	5	2
			3.0	50	21	13
			24.0	7	40	20
71	VCl_3	1:1:2	1.0	88	11	5
			24.0	0	71	32
72	$CrCl_3$	1:1:3.5	0.5	19	33	27
73	$CrCl_3$	1:1:2	1.0	0	25	62
			24.0	0	7	74
74	$MnCl_2$	1:1:3.5	3.0	53	38	8
			24.0	0	21	53
75	$FeCl_2$	1:1:3.5	0.5	0	37	35
76	$FeCl_2$	1:1:2	1.0	0	14	68
			24.0	0	~1	85
77	$FeCl_2$	1:1:2	10 min[a]	~0	92	~0
78	$FeCl_2$	1:1:1	10 min	0	10	86
			24.0	0	0	94
79	$FeCl_3$	1:1:3.5	0.5	0	37	51
80	$FeCl_3$	1:1:2	1.0	0	10	56
			24.0	0	~1	72
81	$CoCl_2$	1:0.1:3.5	24.0	10	63	13
82	$CoCl_3$	1:0.1:2.0	10 min[a]	55	35	8
			24.0	15	60	21
83	$NiCl_2$	1:0.1:3.5	0.5	0	86	5
			3.0	0	77	16
			24.0	0	62	26
84	$NiCl_2$	1:0.1:2	1.0	0	55	45
85	$NiCl_2$	1:0.1:2	10 min[a]	32	62	0
			30 min[a]	10	88	0
			1.0[a]	0	94	0
			24.0	0	35	65
86	$NiCl_2$	1:0.1:1	10 min	0	45	52
			24.0	0	0	99
87	$TiCl_3$	1:0.1:2	24.0	42	34	5

[a] At −40 °C.

Ferric chloride behaved in a similar fashion to $FeCl_2$, but with a lower mass balance (experiments 77–80). It is also important to note that a catalytic amount of $NiCl_2$ produced the same results as a stoichiometric amount of $FeCl_2$, selectively producing a 94% yield of styrene when the reaction was carried out at −40 °C for 1 h (experiment 85) or ethylbenzene in 99% yield when the reaction was carried out at room temperature for 24 h (experiment 86). The reactions of $LiAlH_4$ with phenylacetylene in the presence of a catalytic amount of $TiCl_3$ or $CoCl_2$ were comparably slower than those employing $NiCl_2$, and they also exhibited inferior selectivities.

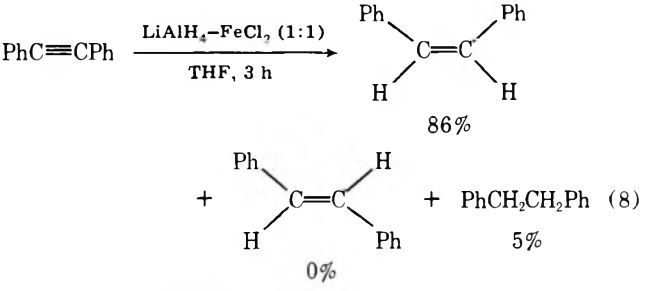
$$PhC{\equiv}CH \xrightarrow[-40\ °C,\ 10\ min]{LiAlH_4\text{–}FeCl_2\ (1:1)} PhCH{=}CH_2 \quad (92\%) \quad (4)$$

$$PhC{\equiv}CH \xrightarrow[room\ temp,\ 24\ h]{LiAlH_4\text{–}FeCl_2\ (1:1)} PhCH_2CH_3 \quad (94\%) \quad (5)$$

$$PhC{\equiv}CH \xrightarrow[-40\ °C,\ 60\ min]{LiAlH_4\text{–}NiCl_2\ (1:0.1)} PhCH{=}CH_2 \quad (94\%) \quad (6)$$

$$PhC{\equiv}CH \xrightarrow[room\ temp,\ 24\ h]{LiAlH_4\text{–}NiCl_2\ (1:0.1)} PhCH_2CH_3 \quad (99\%) \quad (7)$$

Reactions of Diphenylacetylene. Three products are observed in the reaction of $LiAlH_4$–transition-metal halides with diphenylacetylene, i.e., *cis*-stilbene, *trans*-stilbene, and 1,2-diphenylethane (Table VII). Reactions of $LiAlH_4$–VCl_3, –$CrCl_3$, or –$MnCl_2$ with diphenylacetylene are similar to the reactions with phenylacetylene; i.e., no selectivity in product distribution is observed. However, *cis*-stilbene (100% stereoselectivity and 86% yield) was obtained by the reaction of $LiAlH_4$–$FeCl_2$ with diphenylacetylene.



Both $CoCl_2$ and $NiCl_2$ were also studied by varying the ratio of reagent–substrate, reaction temperature, and reaction time. In general, cis reduction was observed when lower reaction temperatures (−20 or −40 °C) and shorter reaction times were employed. Slight isomerization to the more stable *trans*-stilbene did occur with longer reaction times at room temperature. However, $NiCl_2$ produced 75% *cis*-stilbene with 100% stereoselectivity with only 15% 1,2-diphenylethane after a 24-h reaction time at room temperature. $CoCl_2$ showed less promise as a catalyst, always producing some of the trans olefin or else very low yields of the cis olefin. The reaction using $TiCl_3$ at either room temperature or −40 °C was much slower than the rate of reaction using either $NiCl_2$ or $CoCl_2$.

It is clear from these results that $FeCl_2$ is the best catalyst with $NiCl_2$ the next best in converting alkynes to cis olefins and that cis olefins are the initial products in the reaction. It

Table VII. Reactions of Diphenylacetylene with $LiAlH_4$–Transition-Metal Halides

Expt	Metal halide	Molar ratio, $LiAlH_4$–metal halide-substrate	Reaction time, h	Stilbene, % Cis	Stilbene, % Trans	1,2-Diphenylacetylene, %
88	VCl_3	1:1:1	24	26	33	13
89	$CrCl_3$	1:1:1	24	10	47	37
90	$MnCl_2$	1:1:1	24	15	6	2
91	$FeCl_3$	1:1:1	24	17	0	81
92	$FeCl_2$	1:1:1	24	8	8	79
93	$FeCl_2$	1:1:1	1[a]	42	0	6
94	$FeCl_2$	1:1:4	1[a]	12	0	0
			3	86	0	5
95	$CoCl_2$	1:0.1:1	24	14	14	7
96	$CoCl_2$	1:0.1:1	4[b]	24	0	0
			24	18	10	~0
97	$CoCl_2$	1:1:1	1[a]	50	Trace	35
98	$CoCl_2$	1:1:4	1[a]	52	4	0
			12	72	12	5
99	$NiCl_2$	1:0.1:1	24	13	16	5
100	$NiCl_2$	1:0.1:1	4[b]	8	0	0
			24	75	0	15
101	$NiCl_2$	1:1:1	1[a]	23	0	52
102	$NiCl_2$	1:1:4	1[b]	40	0	0
			12	75	4	5
103	$TiCl_3$	1:0.1:1	24	24	9	18
104	$TiCl_3$	1:1:1	1[a]	0	0	0

[a] At −40 °C. [b] At −20 °C.

Table VIII. Reactions of Other Alkynes with $LiAlH_4$–Transition-Metal Chlorides

Expt	Metal halide	Alkyne	Conditions[c]	1-Octene, %	Octane, %
105	$FeCl_2$[a]	1-Octyne	−40 °C, 10 min	80	16
			−40 °C, 1 h	60	37
			RT, 48 h	0	98
106	$CoCl_2$[b]		−40 °C, 1 h	70	17
			RT, 48 h	73	23
107	$NiCl_2$[b]		−40 °C, 1 h	96	1
			RT, 48 h	99	1

Expt	Metal halide	Alkyne	Conditions[c]	2-Hexene, % Cis	2-Hexene, % Trans	Hexane, %
108	$FeCl_2$[a]	2-Hexyne	−40 °C, 1 h	55	11	4
			RT, 48 h	16	14	63
109	$CoCl_2$[b]		RT, 2 h	40	5	4
			RT, 48 h	82	4	6
110	$CoCl_2$[a]		−40 °C, 1 h	32	62	0
			RT, 24 h	12	18	62
111	$NiCl_2$[b]		RT, 2 h	40	0	6
			RT, 24 h	91	0	4
112	$NiCl_2$[a]		−40 °C, 1 h	85	0	3
			−40 °C, 2 h	92	0	5
			RT, 24 h	18	20	58

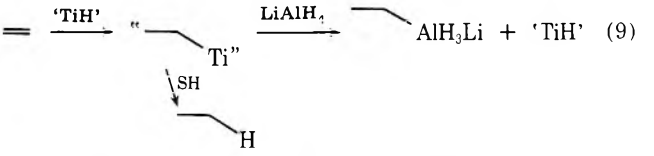
[a,b] See footnotes *a* and *b* in Table V. [c] RT = room temperature.

also appears that with time and higher temperatures the cis olefins isomerize to the trans olefins, which are reduced to the alkanes just like the cis olefins, except at a slower rate. It is also clear from these data that alkynes can be reduced to alkanes directly by using $FeCl_2$ or $FeCl_3$ in admixture with $LiAlH_4$ at room temperature for at least 48 h [for example, 1-octyne is reduced to octane in 98% yield using $FeCl_2$ at room temperature for 48 h (Table VIII)].

Reactions of 1-Octyne and 2-Hexyne. The aliphatic alkynes 1-octyne and 2-hexyne were allowed to react with $LiAlH_4$–$FeCl_2$ (1:1) in THF to produce 1-octene and octane and *cis*- and *trans*-2-hexene and hexane, respectively. The results (Table VIII) show little selectivity on the part of $FeCl_2$ to stop at the octene or *cis*-2-hexene stage. Reactions involving $LiAlH_4$–$CoCl_2$ (1:0.1) showed somewhat better results, but still the reaction is not particularly selective. However, excellent selectivity in reduction was obtained using the reagent $LiAlH_4$–$NiCl_2$ (1:0.1), which reduced 1-octyne to 1-octene in 99% yield with only 0–1% octane formed and reduced 2-hexyne to *cis*-2-hexene in 91% yield with 0% *trans*-2-hexene and 4% hexane formed. It is clear from these results that $LiAlH_4$–$FeCl_2$ is a more powerful agent than $LiAlH_4$–$NiCl_2$ and that both reagents can be used to advantage depending on the ease of reduction of the alkyne or olefin.

Deuterium Incorporation. In order to determine the nature of the reaction intermediate of alkene reduction by $LiAlH_4$ with transition-metal halides, deuterium incorporation experiments were carried out by quenching the reaction

mixtures with deuterium oxide. The products were isolated by preparative GLC, and the deuterium content was measured by the molecular ion peak ratio of deuterated–nondeuterated product in the mass spectrum. In reactions involving stoichiometric amounts of $FeCl_2$ or catalytic amounts of $CoCl_2$ or $NiCl_2$, the content of octane-*d* was only 12–26% based on total octane product. The only experiments yielding high amounts of deuterium incorporation involved those reactions with $TiCl_3$ (94% deuterium incorporation). These results imply that the hydrometalation intermediate "—Ti" is not stable under the conditions studied except in the case of $TiCl_3$. Presumably homolytic dissociation takes place, producing a radical —· which abstracts hydrogen from the solvent (this aspect is being studied further). In other words, the trans metalation reaction from transition-metal alkyl to alkylaluminum intermediate proceeds only in the case of $TiCl_3$ (eq 9).



(9)

Several experiments were attempted to stabilize the carbon–transition-metal bond by varying the ligands attached to the transition metal. It is expected that ligands are capable of stabilizing the transition-metal compounds by dispersing the d orbitals of the transition metal through the attached ligands. A 2-equiv amount of triphenylphosphine was added to $NiCl_2$, which resulted in higher deuterium incorporation (34–42%) and lower rates of reduction. Other nickel halides such as cyclopentadienylnickel chloride and bis(cyclooctadienyl)nickel in the presence of 2 equiv of triphenylphosphine gave 27 and 47% deuterium incorporation, respectively. Although the maximum deuterium incorporation has only reached 47%, the significant improvement compared to $NiCl_2$ shows that the stability of the transition-metal intermediate can be increased by using ligands. We are continuing to study this question.

In conclusion, reactions of $LiAlH_4$–first-row transition-metal halides ($TiCl_3$, VCl_3, $CrCl_3$, $MnCl_2$, $FeCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$, CuI, and $ZnBr_2$) with monosubstituted alkenes (1-octene, 1-hexene, and styrene), disubstituted alkenes (2-ethyl-1-hexene, *cis*-2-hexene, *trans*-2-hexene, and cyclohexene), and trisubstituted alkenes (1-methylcyclohexene), as well as terminal alkynes (phenyacetylene and 1-octyne) and internal alkynes (diphenyacetylene and 2-hexyne), have been studied. The ability of alkenes to be reduced by $LiAlH_4$–transition-metal halide reagents was found to be in the following order: Co(II) > Ni(II) > Fe(II) > Fe(III) > Ti(III) > Cr(III) > V(III) > Mn(II) > Cu(I) > Zn(II). Admixtures of $LiAlH_4$–CuI and $LiAlH_4$–$ZnBr_2$ were not effective in alkene reduction. $CoCl_2$, $NiCl_2$, and $TiCl_3$ can catalyze the $LiAlH_4$ reduction of monosubstituted alkenes. VCl_3 and $CrCl_3$ have partial catalytic ability, and no catalytic activity was observed for $MnCl_2$, $FeCl_2$, and $FeCl_3$. Catalysis is slower for disubstituted and trisubstituted alkenes than for the corresponding monosubstituted compounds.

Reduction of alkynes can be carried out quantitatively to give alkenes and alkanes, depending on the transition-metal halide used as a catalyst, the ratio of reagent to substrate, and the reaction conditions. The best reagent is $LiAlH_4$–$NiCl_2$ from the point of view of product selectivity. A cis reduction mechanism is indicated from cis olefin product formation studies.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[5] GLC analyses were performed on F and M Model 720 and 700 gas chromatographs. NMR spectra were obtained on a Varian T-60 spectrometer. Mass spectra were obtained on a Varian Model M-66 mass spectrometer.

Materials. Tetrahydrofuran (Fisher certified reagent grade) was distilled under nitrogen over $NaAlH_4$. $LiAlH_4$ solutions were prepared by stirring $LiAlH_4$ (Alfa Inorganics) in THF overnight followed by filtration through a fritted glass funnel in a drybox.[6] The concentration was determined by aluminum analysis (EDTA). Transition-metal halides [$TiCl_3$, $CrCl_3$, $MnCl_2$, $ZnBr_2$ (Fisher), VCl_3, $FeCl_3$, $CoCl_2$, and $NiCl_2$ (Alfa)] were opened only in a drybox and used without further purification. All organic substrates were purchased commercially and used without further purification. 1-Octene, 1-methylcyclohexene, styrene, *cis*-2-hexene, *trans*-2-hexene, 2-ethyl-1-hexene, cyclohexene, phenylacetylene, diphenylacetylene, 1-octyne, and 2-hexyne were obtained from Chemical Samples Co. or Aldrich.

General Reactions of Alkenes and Alkynes. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush. Transition-metal halide (ca. 3-mmol scale for stoichiometric reaction and ca. 1 mmol for catalytic reaction) was transferred to the flask in a drybox; it was sealed with a rubber septum, removed from the box, and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil filled bubbler. A 1–2 mL amount of THF was introduced into the reaction vessel, and then the olefin or alkyne was added. The resulting solution was cooled by means of a dry ice–acetone bath before adding the desired amount of $LiAlH_4$. After 10 min, the reaction was warmed to the desired temperature (−40 °C, −20 °C, or room temp). The reaction was quenched by water, the mixture worked up by extraction with THF, and the resulting solution dried over $MgSO_4$. Most products were separated by GLC using a 6 ft 10% Apiezon L 60–80 S column: 1-octene (110 °C, oven temperature), 1-methylcyclohexene (50 °C), 2-ethyl-1-hexene (50 °C), and cyclohexene (50 °C). A 20 ft 10% TCEP column was used for 1-hexene, *cis*-2-hexene, *trans*-2-hexene, and 2-hexyne (50 °C), and a 10 ft 5% Carbowax 20M column was used for phenylacetylene (90 °C) and diphenylacetylene (200 °C). The yields were calculated by using a suitable hydrocarbon internal standard for each case, and the products were identified by comparing their retention times with those of authentic samples. Yields of *cis*-stilbene [δ 6.60 (vinyl H)], *trans*-stilbene [δ 7.10 (vinyl H)], and 1,2-diphenylacetylene [δ 2.92 (benzyl H)] were determinated by NMR integration and are based on total phenyl protons. However, the ratio of *cis*-stilbene to *trans*-stilbene was also checked by GLC. The yield of adamantane (δ 1.88 and 1.77) was determined by NMR spectroscopy and GLC (Apiezon column). The adamantane was isolated and characterized by its melting point, mp 206–210 °C (lit. 205–210 °C), and mass spectrum, *m/e* 136.5 (M^+) (expected, *m/e* 136.24).

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Registry No.—$LiAlH_4$, 16853-85-3; 1-octene, 111-66-0; octane, 111-65-9; 1-methylcyclohexene, 591-49-1; methylcyclohexane, 108-87-2; phenylacetylene, 536-74-3; *cis*-stilbene, 645-49-8; *trans*-stilbene, 103-30-0; 1,2-diphenylacetylene, 501-65-5; 1-octyne, 629-05-0; 2-hexyne, 764-35-2.

References and Notes

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Photochemical Oxidation of Selected Nucleosides and Related Carbohydrates[1]

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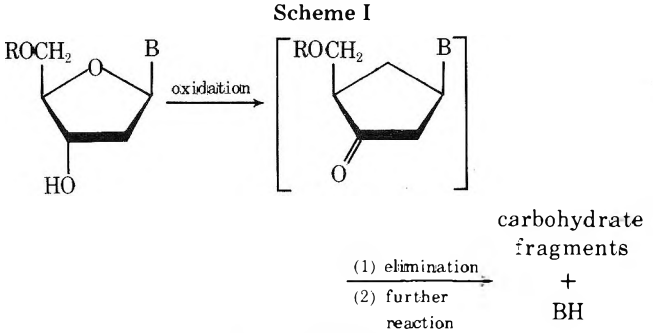
A recently developed photochemical oxidation technique has been used to convert four nucleoside derivatives, 5′-*O*-tritylthymidine (**8**), 5′-*O*-benzoylthymidine (**10**), 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**9**), and 1-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**11**), into the corresponding 3′-keto compounds. The conditions for these oxidations were sufficiently mild that the 3′-ketonucleosides, relatively unstable structures which easily experience β elimination, were isolated and characterized. A fifth compound, 3′-*O*-acetylthymidine (**16**), was oxidized to 3′-*O*-acetylthymidine-5′-aldehyde (**18**). In addition to these five nucleoside derivatives, four related carbohydrates (**1**–**4**) have been successfully oxidized using the photochemical oxidation technique.

Aldehydo- and ketonucleosides are types of compounds whose significance has become increasingly apparent in recent years. These structures represent key intermediates in the laboratory synthesis of such biologically important molecules as cyclonucleosides,[2] antiviral and antifungal nucleosides and related structures,[3–5] derivatives of adenosine 3′,5′-cyclic phosphate,[6] and adenosine 5′-phosphate and 5′-triphosphate.[7] Also, certain ketonucleosides are known to inhibit cancerous cell growth.[8] The significance of these compounds is evident.

Several years ago Pfitzner and Moffatt noted in their pioneering work on nucleoside oxidation that a severe limitation existed to the successful synthesis of certain ketonucleosides and ketonucleotides, particularly the 3′-keto compounds.[9] Hydroxyl to carbonyl oxidation, a logical process for obtaining keto derivatives, resulted in molecular decomposition of many compounds[10] (e.g., thymidine 5′-phosphate, adenosine 5′-phosphate, uridine 5′-phosphate, 5′-*O*-acetylthymidine, and 5′-*O*-*p*-nitrobenzoylthymidine). (To account for this instability, the reaction sequence shown in Scheme I was proposed.[11]) It was clear that a significant need existed for an oxidation process which was sufficiently mild to permit general hydroxyl to carbonyl oxidation in nucleosides and their derivatives without further reaction.

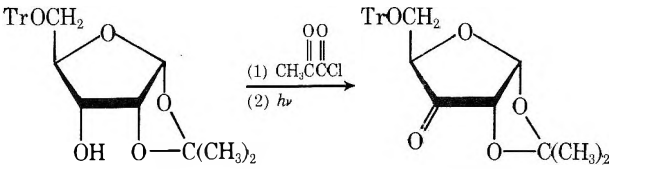
Two years ago we reported a photochemical process for oxidation of carbohydrates which was conducted under quite mild reaction conditions.[13] This process seemed well suited for situations in which oxidation products were known to be relatively unstable. Recently, successful photochemical oxidation of three tetraacetates of D-glucopyranose[14] demonstrated that, in fact, this technique was useful in preparing relatively unstable carbonyl compounds.[15] Such a finding suggested that similar transformations producing reactive aldehydo- and ketonucleosides also might be successful. In preparation for nucleoside oxidation, four model systems, 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranose (**1**), 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-xylofuranose (**2**), methyl 2-deoxy-5-*O*-trityl-α-D-*erythro*-pentofuranoside (**3**), and methyl 2-deoxy-5-*O*-trityl-β-D-*erythro*-pentofuranoside (**4**), were investigated.

Scheme I

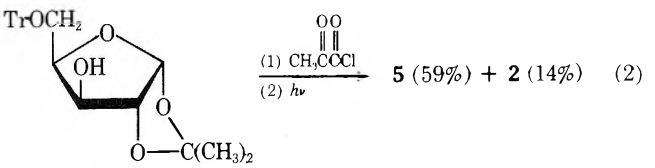


R = H, PO_3H_2, OAc, ETC; B = nitrogenous base

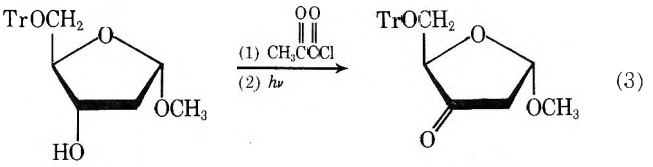
The same general procedure was used for the oxidation of all four alcohols **1**–**4**. Pyruvoyl chloride was added to a benzene solution of the alcohol and pyridine, resulting in ester formation which was immediate and quantitative. Each pyruvate ester (3.00 mmol) in 350 mL of benzene was irradiated for 1 h under nitrogen through a Pyrex filter with a 450-W mercury vapor lamp. The solvent was removed in vacuo below 25 °C and the resulting material was chromatographed on silica gel to afford the products in percent yields shown in eq 1–4.



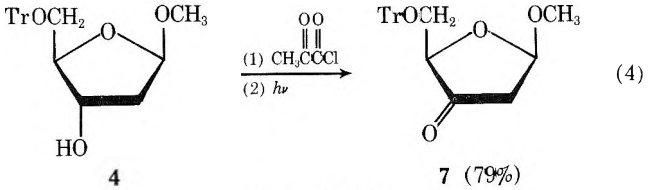
1 **5** (38%) + **1** (37%) + **2** (8%) (1)



2 **5** (59%) + **2** (14%) (2)



3 **6** (80%) (3)



4 **7** (79%) (4)

Tr = $C(C_6H_5)_3$

Product identities were established by comparison with authentic samples. The alcohols recovered from photochemical reactions of **1** and **2** were not simply unreacted starting materials since pyruvate ester formation was complete prior to

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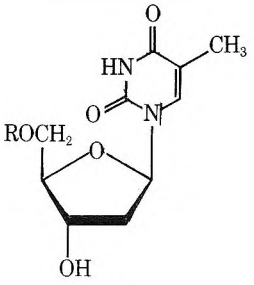
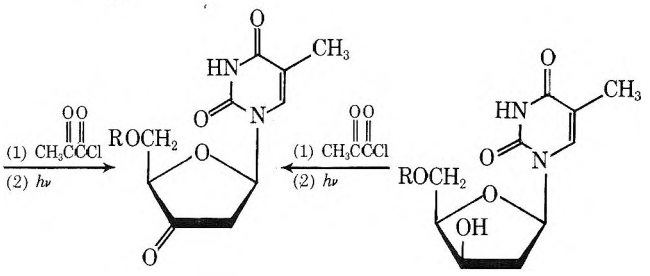
irradiation; further, product alcohols did not arise from hydrolysis of unreacted esters during workup since the starting esters were consumed totally during photolysis.

Following successful oxidation of compounds 1–4, four nucleoside derivatives (8–11) were studied. Reaction of the first of these, 5′-*O*-tritylthymidine (8), resulted in the formation of a single product from the oxidation process. Chromatography was unnecessary since after solvent removal, the photoproduct crystallized from chloroform–carbon tetrachloride. The IR spectrum of the photoproduct showed a carbonyl absorption at 1778 cm^{-1} (carbonyl in a five-membered ring). The ^1H-NMR spectrum of the photoproduct was similar to the starting alcohol (8) except that absorptions due to the hydroxyl proton and the proton on C_3' were absent; also, the patterns exhibited by the hydrogens attached to C_2' and C_4' were simplified. These data and the elemental analysis indicated the 3′-keto-5′-*O*-tritylthymidine (12) structure for



8

10



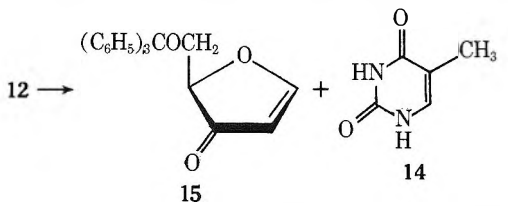
12 9

13 11

8, 9, 12, R = $C(C_6H_5)_3$ 10, 11, 13, R = $C(=O)C_6H_5$

the photoproduct. This structure (12) was confirmed by reduction of the photoproduct with sodium borohydride to yield 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (9). The yield of crystalline 12 from oxidation of 8 was 61%.

The work of Pfitzner and Moffatt correctly suggested that compounds such as 12 should be unstable under certain mild conditions. That the ketonucleoside 12 was unstable under rather mild conditions was evidenced by the fact that dissolving it in triethylamine at 25 °C or chromatographing it on silica gel resulted in immediate formation of thymine (14) and an unsaturated sugar. (Pyridine caused a similar change over a period of 2 days.) The enone 15 seemed the most reasonable possibility for the structure of the unsaturated sugar. This possibility was clearly supported by the quite simple ^1H NMR spectrum of the new sugar, in particular the coupled doublet absorptions for H_1 and H_2 (δ 8.24 and 5.54 ($J_{1,2}$ = 3 Hz)). In-



15 14

dependent synthesis of 15 by silica gel catalyzed elimination of methanol from 6 made certain the structural assignment.

Three related nucleoside derivatives were oxidized successfully using the photochemical oxidation procedure. Compound 9 reacted to give 12 in 57% yield. 5′-*O*-Benzoylthymidine (10) was oxidized to a compound, mp = 87–92 °C, for which the structure 5′-*O*-benzoyl-3′-ketothymidine (13) was tentatively assigned on the basis of elemental and ^1H NMR analysis and analogy to the oxidation of compound 8. The assignment of structure 13 to the oxidation product from 10 was confirmed by oxidation of 1-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (11) to the same product (13) under identical conditions. The yields of 13 from 10 and 11 were 68 and 57%, respectively.

Photochemical oxidation of two additional nucleoside derivatives (3′-*O*-acetylthymidine (16) and 2′,3′-*O*-isopropylidineuridine (17)) was undertaken in order to study the formation of aldehydonucleosides. Oxidation of 3′-*O*-acetylthymidine (16) was successful; however, oxidation of 17 was thwarted by its extreme insolubility in benzene, the normal irradiation solvent. Photolysis of 17 was attempted in other solvents such as acetone, chloroform, and dichloromethane; unfortunately, TLC analyses of the crude reaction mixtures indicated them to be complex and ^1H NMR analyses of these mixtures gave no indication of aldehyde formation. The irradiation products from 17 were not further characterized.

When the results from the present study are combined with those from previous investigations,[1,13,14] it is clear that the photochemical oxidation procedure can be useful in the oxidation of a variety of carbohydrates and appears to be a promising technique for oxidation of the carbohydrate portions of nucleosides. This process should be particularly valuable in forming products which are themselves relatively unstable.

Experimental Section

General Information. Two esterification procedures were used. For compounds 1–4 procedure I was used while for 8–11 procedure II was employed. The photolysis of all compounds was carried out in the same manner. These procedures are described in a general form below. ^1H NMR spectra were obtained ($(CH_3)_4Si$, δ 0 ppm) from a Varian T-60 spectrometer (coupling constants, J, are given in hertz; s, d, t, and m indicate singlet, doublet, triplet, and multiplet, respectively). Mass spectra were measured on a Finnigan 1015-D mass spectrometer using both electron impact (ionizing voltage of 70 eV) and chemical ionization with methane as the reagent gas at a pressure of 1.00 Torr and an ionizing voltage of 110 eV. Column chromatography effluents were monitored with an ISCO UA-2 ultraviolet analyzer.

Esterification Procedure I. The alcohol to be esterified (0.03 mol) and dry pyridine (0.033 mol) were dissolved in 25 mL of anhydrous benzene. Pyruvoyl chloride[16] (0.04 mol) in 10 mL of dry benzene was added in a dropwise manner with stirring. Precipitation of pyridinium hydrochloride was immediate. Cooling with cold water was necessary to keep the reaction mixture below 10 °C. After stirring for 15 min, the pyridinium hydrochloride was removed by filtration and the benzene was distilled in vacuo to yield the pyruvate ester contaminated with pyridinium hydrochloride. The contaminant could be removed by shaking the reaction mixture in 25 mL of carbon tetrachloride, allowing it to stand for a few hours, and filtering the insoluble material. When the carbon tetrachloride was evaporated from the filtrate, the resulting ester (^1H NMR analysis showed each alcohol to be completely esterified) was subjected immediately to irradiation.

Esterification Procedure II. A solution of 0.5 g of pyruvoyl chloride[16] in 5 mL of benzene was added dropwise to a stirred solution of 1.0 mmol of alcohol in 10 mL of anhydrous pyridine. After 15 min, 50 mL of chloroform was added and the solution was extracted with two 50-mL portions of water and dried over anhydrous sodium sulfate. Distillation of the chloroform and pyridine in vacuo left a yellow oil (^1H NMR analysis showed that esterification was complete in each case) which was irradiated without further purification.

Irradiation Procedure. The pyruvate ester was dissolved in 350 mL of dry benzene and the solution was purged with nitrogen for 2.0 h. The nitrogen purge was continued during Pyrex-filtered irradiation with a 450-W medium-pressure Hanovia mercury lamp. After 1 h, the

irradiation was stopped, the reaction mixture was analyzed by TLC, the benzene was removed by distillation, and ^{1}H NMR analysis was conducted prior to chromatography or crystallization.

Oxidation of 1,2-*O*-Isopropylidene-5-*O*-trityl-α-D-ribofuranose[17] (1). After esterification of 1 according to procedure I followed by irradiation and solvent removal, the residual material was chromatographed on a 90 × 2.5 cm silica gel (60–200 mesh) column slurry packed in 1:9 ether–hexane; 60 mL fractions were collected. The column was eluted as follows: 0.5 L of 1:9 ether–hexane, 1.0 L of 1:4 ether–hexane, and 1.0 L of 1:1 ether–hexane.

Fractions 10–18 afforded 489 mg (1.14 mmol, 38%) of 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentofuranos-3-ulose[17] (**5**), identical in NMR, mass, and IR spectra with a known sample. Fractions 20–26 gave 495 mg (1.11 mmol, 37%) of 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranose (**1**), and fractions 27–32 yielded 104 mg (0.24 mmol, 8%) of 1,2-isopropylidene-5-*O*-trityl-α-D-xylofuranose[17] (**2**). Compounds **1** and **2** were identified by comparison with known samples.

Oxidation of 1,2-*O*-Isopropylidene-5-*O*-trityl-α-D-xylofuranose[17] (2). After esterification of **2** according to procedure I and irradiation and solvent removal, the residual material was chromatographed in a manner identical to the chromatography of the reaction mixture from the oxidation of **1**. Fractions 10–18 afforded 776 mg (1.77 mmol, 59%) of **5** while fractions 27–35 gave 181 mg (0.42 mmol, 14%) of **2**.

Oxidation of Methyl 2-Deoxy-5-*O*-trityl-α-D-*erythro*-pentofuranoside[18] (3). After esterification of **3** according to procedure I, irradiation, and solvent removal, a material remained which by ^{1}H NMR analysis appeared to be at least 90% methyl 2-deoxy-5-*O*-trityl-α-D-*glycero*-pentofuranosid-3-ulose (**6**).

Chromatography of the reaction mixture on a 4.0 × 20 cm column of 200–300 mesh silica gel with 500 mL of 60% ether–hexane produced **6** in 80% yield. The identity of the photoproduct was established as methyl 2-deoxy-5-*O*-trityl-α-D-*glycero*-pentofuranosid-3-ulose (**6**) by comparison with an authentic sample.[18]

Oxidation of Methyl 2-Deoxy-5-*O*-trityl-β-D-*erythro*-pentofuranoside[18] (4). The oxidation and isolation procedure for **4** was the same as used for **3**. A 79% yield of methyl 2-deoxy-5-*O*-trityl-β-D-*glycero*-pentofuranosid-3-ulose (**7**), identified by comparison with an authentic sample,[18] was obtained.

Oxidation of 5′-*O*-tritylthymidine[19] (8). After esterification of **8** according to procedure II and irradiation, the cloudy reaction mixture was filtered and the benzene was distilled in vacuo to leave a residue which was dissolved in 10 mL of chloroform. Carbon tetrachloride (20 mL) was slowly added, and after standing for 12 h 305 mg of crystals formed, mp 171–4 °C. The photoproduct had ^{1}H NMR (60 MHz) absorptions ($CDCl_3$) at δ 8.55 (NH, broad s), 7.47–7.11 (aromatic and H_6, m), 6.55, 3.04, 2.85 ($H_{1'}$, $H_{2'}$, $H_{2''}$, ABX pattern, $J_{1',2'}$ = 7 Hz, $J_{1',2''}$ = 9.5 Hz), 4.14, 3.64, 3.36 ($H_{4'}$, $H_{5'}$, $H_{5''}$, ABX pattern $J_{4',5'} = J_{4',5''}$ = 3 Hz, $J_{5',5''}$ = 10 Hz), and 1.52 (CH_3, s). Also, the photoproduct exhibited an IR absorption at 1778 cm^{-1}.

Anal. Calcd for $C_{29}H_{26}O_5N_2$: C, 72.18; H, 5.43; N, 5.80. Found: C, 72.00; H, 5.49; N, 5.71.

The spectral evidence and the elemental analysis indicated the photoproduct to be 3′-keto-5′-*O*-tritylthymidine (**12**). Sodium borohydride reduction of it to compound **9** confirmed this structural assignment.

Photoproduct (200 mg) was dissolved in 15 mL of ethanol and 100 mg of sodium borohydride was added. After 1 h at room temperature, the solution was partitioned between chloroform (25 mL) and water (25 mL) and the chloroform layer was extracted with water (25 mL) and dried over sodium sulfate. Evaporation of the chloroform left 160 mg of 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymidine[20] (**9**).

The yield of crystalline **12** from the oxidation of **8** was 61%.

Oxidation of 1-(2-Deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine[20] (9). The oxidation of **9** was conducted in the same manner as that of **8**. The yield of the oxidation product **12** was 57%.

Reaction of 3′-Keto-5′-*O*-tritylthymidine (12) with Triethylamine. 3′-Keto-5′-*O*-tritylthymidine (100 mg) was dissolved in 5 mL of methanol and 1 mL of triethylamine was added. After 1 h the solvent was removed in vacuo and the residue was partitioned between water (5 mL) and ethyl ether (10 mL). Evaporation of the dried ether layer (sodium sulfate) produced 55 mg of colorless oil which showed ^{1}H NMR absorptions (C_5D_5N) at δ 8.24 ($H_{1'}$, d, $J_{1,2}$ = 3 Hz), 7.50–6.76 (aromatic, m), 5.54 ($H_{2'}$, d), 4.43 ($H_{4'}$, t, $J_{4,5} = J_{4,5'}$ = 4 Hz), 3.33 ($H_{5'}$, $H_{5''}$, d). The mass spectrum (electron impact) showed a small parent peak at *m/e* 256. These spectral data indicated **15** as the structure of the colorless oil.

Compound **15** was independently synthesized from methyl 2-deoxy-5-*O*-trityl-α-D-*glycero*-pentofuranosid-3-ulose (**6**) by stirring 100 mg of **6** for 1 h in 25 mL of ethyl ether in which 1 g of silica gel was suspended. Washing the silica gel with an additional 25 mL of ether followed by evaporation of the ether yielded 80 mg of **15**.

Oxidation of 5′-*O*-Benzoylthymidine[21] (10) and 1-(5-*O*-Benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine[22] (11). Following esterification of **10** according to procedure II and irradiation, the cloudy reaction mixture was filtered and the benzene was distilled in vacuo to leave a residue which was dissolved in 5 mL of chloroform. Addition of carbon tetrachloride (15 mL) caused precipitation of 270 mg of a material which was reprecipitated in the same manner to yield 232 mg of a solid, mp 87–92 °C. This product had ^{1}H NMR (60 MHz) absorptions at δ 8.94 (NH, broad s), 8.13–7.75 (ortho aromatic, m), 7.65–7.11 (meta and para aromatic, H_6, m), 6.30, 3.04, 2.68 ($H_{1'}$, $H_{2'}$, $H_{2''}$, ABX pattern, $J_{1',2'}$ = 7 Hz, $J_{1',2''}$ = 6.5 Hz, $J_{2',2''}$ = 10 Hz), 5.03–4.24 ($H_{4'}$, $H_{5'}$, $H_{5''}$, m), and 1.62 (CH_3, s). Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.13. Found: C, 59.51; H, 4.67; N, 8.21.

The analytical and spectral data suggested the 5′-*O*-benzoyl-3′-ketothymidine (**13**) structure for the photoproduct. Confirmation of this structure was obtained from oxidation of 1-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine[22] (**11**) in the same manner as **10** to yield the same material (**13**). The yield of **13** from **10** was 68% and from **11** it was 57%.

Oxidation of 3′-*O*-acetylthymidine[23] (16). After esterification according to procedure II and irradiation (only 75 mg of **16** was irradiated), the benzene was distilled to leave 50 mg of residue which was identified as 3′-*O*-acetylthymidine-5′-aldehyde[9] (**18**) by ^{1}H NMR and TLC comparison with a known sample.

Attempted Oxidation of 2′,3′-*O*-Isopropylideneuridine[23] (17). Photochemical oxidation of 2′,3′-*O*-isopropylideneuridine (**17**) was unsuccessful because although esterification took place (procedure II), the resulting ester was insoluble in benzene. Photolysis of the pyruvate ester of **17** in solvents in which it was soluble (acetone, chloroform, dichloromethane) resulted in quite complex reaction mixtures (by TLC analysis); further ^{1}H NMR and IR analyses showed no evidence of aldehyde formation. These reactions were not studied further.

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Registry No.—**1**, 20590-57-2; **2**, 20590-53-8; **3**, 16801-99-3; **4**, 16802-00-9; **5**, 20590-54-9; **6**, 51885-24-6; **7**, 51921-34-7; **8**, 7791-71-1; **9**, 55612-11-8; **10**, 35898-29-4; **11**, 65475-51-6; **12**, 65475-49-2; **13**, 65475-50-5; **15**, 65475-52-7; **16**, 21090-30-2; **18**, 5983-15-3.

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Approach to the Use of Benzylpenicillinacylase for Configurational Correlations of Amino Compounds

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Benzylpenicillinacylase (BPA) from *Escherichia coli* ATCC 9637 was found capable of hydrolyzing, in addition to the *N*-acyl derivatives of α-amino acids, the *N*-phenylacetyl derivatives of a variety of primary amino compounds. An approach to the use of the stereospecific action of BPA for correlating the absolute configurations of amino compounds is described. For this purpose enzymatic hydrolysis of several *N*-phenylacetylamino derivatives with known absolute configuration was examined. Reference to a single stereomodel was made to analyze hydrolytic data. The substituents at the asymmetric carbon atoms of the preferred enantiomers were then classified in terms of position occupied inside groups of priority sequences. The priority relations found constitute an empirical guide for stereochemical predictions. For some of the substrates examined the absolute configuration was determined, in the course of the present work, by chemical methods.

The stereospecific action of enzymes of the class of the acylases, amidases, decarboxylases, and oxidases is a long-established and reliable method of determining the absolute configuration of α-amino acids. More recently, benzylpenicillinacylase (BPA) from *Escherichia coli* ATCC 9637 has been reported to show L-directed stereochemical preference in hydrolyzing *N*-phenylacetylamino acids.[2-4] In accordance with this observation we have used BPA to define and confirm the absolute configuration of some amino acids.[3,4]

On further investigation[5] BPA was found capable of (i) hydrolyzing (in addition to the *N*-phenylacetylamino acids) a variety of *N*-phenylacetylamino compounds with a primary amino group and (ii) reacting at different rates on both the enantiomers of racemic mixtures.

On the basis of these properties it seems interesting to examine the potentiality of this enzyme in the field of enzymatic hydrolysis, particularly for the resolution of racemates and for configurational correlations.

Although in the case of the enzymatic hydrolysis of *N*-acylamino acids, the configurational correlations can be defined by referring the results to the D/L system, it is evident that this assumption cannot be retained in the more general case of the enzymatic hydrolysis of *N*-acylamino compounds. As a continuation of previous work,[5] this paper presents an attempt to correlate the absolute configuration of amino compounds, by using the BPA-catalyzed hydrolysis of the amide linkage. For this purpose several *N*-phenylacetylamino compounds having known absolute configuration were tested with the acylase. Hydrolysis results of all examined substrates were then analyzed by using a single model, corresponding to the more rapidly hydrolyzed enantiomer. The relative positions of the substituents at the asymmetric carbon atom of the preferred enantiomer were examined, in order to define a method for correlating the absolute configurations.

Results and Discussion

All substrates subjected to enzymatic hydrolysis with BPA are reported in Table I (the more rapidly hydrolyzed enantiomers are also shown). Experimental details relative to the hydrolysis of compounds **1–25** were reported in previous communications.[3-6] Hydrolysis conditions and results relative to substrates examined here are summarized in Table II. *N*-Phenylacetyl derivatives were generally prepared following known methods. In the case of *N*-phenylacetylserinonitrile (**29**) and *N*-phenylacetyl-4-cyano-4-phenylacetamidobutyric acid (**32**), the syntheses were accomplished starting from (2-tetrahydropyranyloxy)acetaldehyde and 2-ketoglutaric acid, respectively. Hydrolysis experiments were performed with a purified preparation of BPA. The reactions were carried out limiting the time to avoid the complete hydrolysis of racemic substrates. The unaltered portion of the *N*-phenylacetyl derivatives was isolated from the reaction mixture and the optical activity examined (Table II). The progress of the hydrolysis was followed by determining the phenylacetic acid produced by GC.

In order to establish the stereochemical preference of the enzyme, we have determined the absolute configuration of the substrates through chemical correlation. In the case of the *N*-phenylacetyl derivatives **28, 30, 34,** and **35,** whose corresponding amino compounds have known absolute configuration, the configurational correlations were simply established by preparing the *N*-phenylacetyl derivatives of the optical active amino compounds. In the case of substrates **26, 27, 29,** and **32,** the corresponding amino compounds have unknown absolute configuration. The optically active *N*-phenylacetyl derivatives recovered from the enzymatic hydrolyses were then transformed by chemical methods into compounds having known absolute configuration, as reported in Table III. In the case of the methyl esters **31** and **33,** the absolute configurations of the corresponding acids **8** and **32** are known (the configuration of **32** was defined by us, as reported in Table III). Corresponding optically active acids were then esterified to establish the desired correlation.

To define a method for stereochemical correlations, the following approach was adopted. A single model,[7] reported in Figure 1, was defined and used to represent the configuration at the chiral center of the more rapidly hydrolyzed enantiomers. Since the absolute configuration of the enantiomer

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Table I. Compounds Subjected to Enzymatic Hydrolysis and Absolute Configuration of the Preferred Enantiomers

Compd[h]	Registry no.	Preferred enantiomer: Absolute[a] config	Registry no.	Positions of substituents in model of Figure 1: A	B
N-PA-alanine (**1**)	17966-65-3	(*S*)-(−)[b]	718-07-0	COOH	CH_3
N-PA-2-aminobutyric acid (**2**)	65451-16-3	(*S*)-(−)[c]	836-32-8	COOH	C_2H_5
N-PA-valine (**3**)	2752-50-3	(*S*)-(−)[b]	725-67-7	COOH	$CH(CH_3)_2$
N-PA-leucine (**4**)	65415-00-1	(*S*)-(−)[b]	730-15-4	COOH	$CH_2CH(CH_3)_2$
N-PA-phenylalanine (**5**)	54582-05-7	(*S*)-(+)[b]	738-75-0	COOH	$CH_2C_6H_5$
N-PA-norvaline (**6**)	65415-01-2	(*S*)-(−)[c]	34337-08-1	COOH	$(CH_2)_2CH_3$
N-PA-phenylglycine (**7**)	35039-72-6	(*S*)-(+)[c]	24003-71-2	COOH	C_6H_5
N-PA-serine (**8**)	2752-41-2	(*S*)-(+)[b]	2752-53-6	COOH	CH_2OH
N-PA-aspartic acid (**9**)	17079-41-3	(*S*)-(+)[b]	2752-32-1	COOH	CH_2COOH
N-PA-glutamic acid (**10**)	2752-35-4	(*S*)-(−)[b]	2752-33-2	COOH	$(CH_2)_2COOH$
N-PA-alaninamide (**11**)	65415-02-3	(*S*)-(−)[c]	65451-29-8	$CONH_2$	CH_3
N-PA-2-aminobutyramide (**12**)	65415-03-4	(*S*)-(−)[c]	65451-30-1	$CONH_2$	C_2H_5
N-PA-alaninonitrile (**13**)	31962-96-6	(*S*)-(−)[d]	65451-31-2	CN	CH_3
N-PA-2-aminobutyronitrile (**14**)	34096-57-6	(*S*)-(−)[d]	65451-32-3	CN	C_2H_5
N-PA-valinonitrile (**15**)	31962-95-5	(*R*)-(+)[d]	65451-33-4	$CH(CH_3)_2$	CN
N-PA-alaninol (**16**)	34084-11-2	(*S*)-(−)[d]	65451-13-0	CH_2OH	CH_3
N-PA-2-aminobutanol (**17**)	34114-57-3	(*S*)-(−)[d]	65451-14-1	CH_2OH	C_2H_5
N-PA-3-aminobutyric acid (**18**)	65451-17-4	(*S*)-(−)[e]	65414-81-5	CH_2COOH	CH_3
N-PA-3-aminovaleric acid (**19**)	65451-18-5	(*S*)-(−)[e]	65414-82-6	CH_2COOH	C_2H_5
N-PA-3-amino-3-phenylpropionic acid (**20**)	65451-19-6	(*S*)-(+)[e]	65414-83-7	CH_2COOH	C_6H_5
N-PA-4-aminovaleric acid (**21**)	65451-20-9	(*S*)-(−)[e]	65414-84-8	$(CH_2)_2COOH$	CH_3
N-PA-5-aminohexanoic acid (**22**)	65451-21-0	(*S*)-(−)[e]	65414-85-9	$(CH_2)_3COOH$	CH_3
N-PA-6-aminoheptanoic acid (**23**)	65451-22-1	(*S*)-(−)[e]	65414-86-0	$(CH_2)_4COOH$	CH_3
N-PA-2-aminobutane (**24**)	56649-69-5	(*S*)-(+)[f]	56572-16-8	C_2H_5	CH_3
N-PA-*p*-hydroxyamphetamine (**25**)	34096-54-3	(*S*)-(−)[d]	65451-15-2	$CH_2C_6H_4$-*p*-OH	CH_3
N-PA-norleucinonitrile (**26**)	65451-23-2	(*S*)-(−)[f]	65414-87-1	CN	$(CH_2)_3CH_3$
N-PA-leucinonitrile (**27**)	65451-24-3	(*S*)-(−)[f]	65414-88-2	CN	$CH_2CH(CH_3)_2$
N-PA-valinol (**28**)	65451-25-4	(*S*)-(−)[f]	65414-89-3	CH_2OH	$CH(CH_3)_2$
N-PA-serinonitrile (**29**)	65451-26-5	(*S*)-(+)[f,g]	65414-90-6	CH_2OH	CN
N-PA-serinamide (**30**)	27826-53-5	(*S*)-(+)[f]	27820-89-9	$CONH_2$	CH_2OH
N-PA-serine methyl ester (**31**)	65415-04-5	(*S*)-(−)[f]	65414-91-7	$COOCH_3$	CH_2OH
4-Cyano-4-phenylacetamidobutyric acid (**32**)	65451-27-6	(*R*)-(+)[f]	65414-92-8	$(CH_2)_2COOH$	CN
Methyl 4-cyano-4-phenylacetamidobutyrate (**33**)	65451-28-7	(*R*)-(+)[f]	65414-93-9	$(CH_2)_2COOCH_3$	CN
N-PA-aspartic acid α-methyl ester (**34**)	65415-05-6	(*S*)-(−)[f]	65414-63-3	$COOCH_3$	CH_2COOH
N-PA-glutamic acid α-methyl ester (**35**)	65415-06-7	(*S*)-(−)[f]	65414-94-0	$COOCH_3$	$(CH_2)_2COOH$

[a] The sign of the optical rotations is referred to the sodium D line and methanol or ethanol as solvent. [b] T. Suyama, T. Toyoda, and S. Kanao, *Yakugaku Zasshi*, **85**, 279 (1965). [c] Specific rotation has been determined in the course of the present work since previously not reported: **2**, $[\alpha]^{20}_D$ −20.0° (c 4.5, ethanol); **6**, $[\alpha]^{20}_D$ −17.5° (c 4.0, ethanol); **7**, $[\alpha]^{20}_D$ +143° (c 1.0, ethanol); **11**, $[\alpha]^{20}_D$ −27.8° (c 4.0, methanol; **12**, $[\alpha]^{20}_D$ −28.3° (c 2.0, methanol). [d] See ref 5. [e] See ref 4. [f] See Table II. [g] In relation to the use of *R*/*S* and D/L nomenclatures, notice that for all the compounds in the table, the *S* configuration corresponds to L except for compound **29**. [h] PA = phenylacetyl.

preferred by the enzyme is known, the A and B position can be assigned to each pair of substituents (Table I). By examining A and B positions relative to the different substrates, substituents can be classified according to the decreasing tendency to occupy position A, i.e., priority sequences A > B can be defined. Positions A and B found for the substituents of each compound are reported in Table I. Analysis of these results, by using internal comparisons,[8] allowed three priority sequences to be defined.

By examining the results relative to *N*-phenylacetylvalinonitrile (**15**), to *N*-phenylacetylbutyronitrile (**14**), and to *N*-phenylacetyl-2-aminobutane (**24**), respectively, the relations $(CH_3)_2CH > CN$, $CN > C_2H_5$, and $C_2H_5 > CH_3$ can be obtained; see sequence I. One of the three possible priority relations between the noncontiguous terms of sequence I can be verified by examining hydrolytic data for *N*-phenylacetylalaninonitrile (**13**); the $CN > CH_3$ relation is found, as indicated in sequence I:

$$CH(CH_3)_2 > CN > C_2H_5 > CH_3$$

By examining hydrolytic results of substrates **8**, **31**, **30**; **28**; **15**; **13**, **14**, **26**, and **27** sequence II can be defined:

$$\left.\begin{matrix}COOH\\COOCH_3\\CONH_2\end{matrix}\right\} > CH_2OH > CH(CH_3)_2 > CN$$

$$> \begin{cases}CH_2CH_3 > CH_3\\CH_2CH(CH_3)_2\\CH_2(CH_2)_2CH_3\end{cases}$$

From the hydrolysis data of compounds **9**, **10**, **34**, **35**; **32** and **33** sequence III can be analogously defined. Hydrolysis data

$$\left.\begin{matrix}COOH\\COOCH_3\end{matrix}\right\} > \left\{\begin{matrix}CH_2COOH\\CH_2CH_2COOH\\CH_2CH_2COOCH_3\end{matrix}\right\} > CN$$

Table II. Hydrolytic Data Relative to *N*-Phenylacetylamino Compounds[a]

Substrate No.	mg	Buffer, mL	Enzyme, mg	Incubn time, h	Hydrolysis, %	$[\alpha]_D$, deg,[b] of substrates: Recovered	$[\alpha]_D$, deg,[b] of substrates: *S* isomers
(±)-**26**	200	370[c]	0.50	20	70	+30 (*c* 4.0)	
(±)-**27**	200	370[c]	0.50	20	42	+33 (*c* 4.0)	
(±)-**28**	150	30[c]	3.50	240[d]	49	+5.8 (*c* 6.0)	−30 (c 3.0)
(±)-**29**	600	120[c]	0.70	5	57	−2.1 (*c* 7.0)	
(±)-**30**	300	60[c]	0.50	24	50	−3.0 (*c* 7.0)	+4.0 (*c* 4.0)
(±)-**31**[e]	150	40[c,f]	1.10	24	66	+11 (*c* 1.5)	−13 (*c* 1.5)
(±)-**32**	500	100	0.35	18	75	−12 (*c* 2.0)	
(±)-**33**	200	50[c,f]	0.20	24	46	−1.4 (*c* 6.0)	−15.7 (c 2.0)[g]
(±)-**9**[h]	300	70[f]	0.30	20	48	−9.0 (*c* 5.0)[i]	+10.4 (c 2.0)[i]
(±)-**34**	600	150[f]	0.60	14	52	+3.0 (*c* 5.0)	−14.5 (*c* 4.0)
(*S*)-**34**	600	150[f]	0.60	18	70		
(*R*)-**34**	600	150[f]	0.60	18	65		
(±)-**35**	500	100[f]	0.60	24	47	+19 (*c* 2.0)	−31.5 (*c* 1.0)
(*S*)-**35**	850	170[f]	0.85	16	65		
(*R*)-**35**	500	100[f]	0.50	20	10		
(±)-**16**[h]	150	20	0.50	24[d]	52	+12 (*c* 4.0)	−15.2 (*c* 3.0)
(±)-**17**[h]	150	30	1.00	24[d]	50	+9.2 (*c* 4.0)	−34 (*c* 4.0)
(±)-**24**[h]	200	45	2.00	24[d]	53	−9.2 (*c* 3.0)	+17 (*c* 3.0)

[a] Hydrolysis experiments were carried out in 0.1 M phosphate buffer, pH 7.0, and at a temperature of 30 °C unless otherwise indicated. [b] All values were determined in methanol at 20 °C unless otherwise specified. [c] Because of the low solubility of the substrate, methanol was added (8% v/v). [d] Incubation temperature 37 °C. [e] A. Romeo and G. Di Maio, *Ann. Chim. (Rome)*, **47**, 675 (1957). [f] pH 6.2. [g] Obtained as an oil by treating (−)-**32** with diazomethane. [h] Hydrolysis experiments on this substrate were previously reported. See ref 5 and 6. [i] Solvent ethanol.

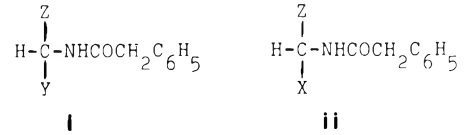
Table III. Substrates with Unknown Absolute Configuration. Configurational Correlation by Chemical Methods

Compd[a]	$[\alpha]^{20}_D$, deg[b]: Reaction product	$[\alpha]^{20}_D$, deg[b]: *S* isomer
N-Phenylacetylnorleucine methyl ester (**36**) from (+)-**26**	+16.3 (*c* 1.0)	−31 (*c* 4.0)
N-Phenylacetylleucine methyl ester (**37**) from (+)-**27**	+3.3 (*c* 4.0)	−41 (*c* 4.0)[c]
N-Phenylacetylserinamide (**30**)[d] from (−)-**29**	Δε −0.1 (220 nm)	Δε −1.4 (220 nm)
Glutamic acid from (−)-**32**	+26.4 (*c* 1.5, 5 N HCl)	+31 (*c* 1.5, 5 N HCl)

[a] Compounds into which the recovered substrates (+)-**26**, (+)-**27**, (−)-**29**, and (−)-**32** were transformed (see Experimental Section). [b] Solvent methanol unless otherwise specified. [c] Lit. $[\alpha]^{20}_D$ −13° (*c* 2.0, ether); cf. H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin", Princeton University Press, Princeton, N.J., 1949, p 786. [d] Because of the low value of the $[\alpha]_D$, CD_{max} in methanol are reported.

of *N*-phenylacetylserinonitrile (**29**), of *N*-phenylacetylamino alcohols **16** and **17**, of *N*-phenylacetylamino amides **11** and **12**, and of the *N*-phenylacetylamino acids are in accordance with sequence II which was defined (as for sequence I) by using the indicated internal comparisons between contiguous terms.

In order to further analyze priority relations and to better define sequences II and III, hydrolytic results have been examined by making use of external comparisons.[8] The following general procedure was adopted; a priority relation between two substituents Y and X was established by comparing the stereoselectivity of the hydrolysis of two substrates, i and ii,



i ii

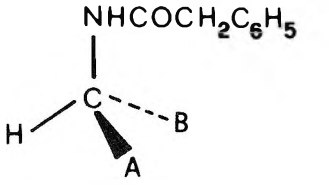


Figure 1. Configuration of the more rapidly hydrolyzed enantiomer.

containing the common substituent Z. Two cases have been considered.

(1) The Z group is in position A with respect to the two groups under examination [Z > (Y; X)]. Priority is then assigned to that substituent (Y or X) which confers lower stereoselectivity to the hydrolysis (e.g., Y > X if the hydrolysis of i is found to be less stereoselective than that of ii).

(2) The two groups Y and X are both in position A with respect to the common group [(Y; X) > Z]. Priority is assigned to that substituent (Y or X) which confers higher stereoselectivity to the hydrolysis (e.g., Y > X if the hydrolysis of i is more selective than that of ii).

Priority relations deduced by using the above described external comparisons are given in Table IV. The data show that for all the substrates examined, the relations obtained through external comparison agree with the relations already defined by using internal comparison. A direct confirmation of this accordance can be found by comparing the relations $C_2H_5 > CH_3$ and $CH_2OH > CH_3$, given in Table IV, with the corresponding ones based on the hydrolysis of *N*-phenylacetyl-2-aminobutane (**24**) and of *N*-phenylacetylalaninol (**16**), respectively. The relation $CH_2COOH > CH_2CH_2COOH$ was confirmed by performing separate hydrolysis experiments (Table II) on the two enantiomers of *N*-phenylacetylaspartic acid α-methyl ester, (*S*)-**34** and (*R*)-**34**, and on those of *N*-phenylacetylglutamic acid α-methyl ester, (*S*)-**35** and (*R*)-**35**. In accordance with the assigned priority, the data given in Table II show that the difference between the hydrolysis rates of the two enantiomers is clearly lower for **34** than for **35**. The following relations, $COOH > COOCH_3 > CONH_2$ and $CH_2COOH > CH_2CH_2COOH$, found by external comparison, can then be introduced into sequences II and III, respectively, and some of the unresolved priorities can be defined.

Table IV. Priority Relations Based on External Comparisons

Compd	Positions of substituents in model of Figure 1 A	B	Optical purity, %[a]	Priority relation
16	CH_2OH	CH_3	79	$C_2H_5 > CH_3$
17	CH_2OH	CH_2CH_3	27	
28	CH_2OH	$CH(CH_3)_2$	19	$CH(CH_3)_2 > CH_3$
16	CH_2OH	CH_3	79	
28	CH_2OH	$CH(CH_3)_2$	19	$CH(CH_3)_2 > C_2H_5$
17	CH_2OH	CH_2CH_3	27	
16	CH_2OH	CH_3	79	$CH_2OH > CH_3$
24	CH_2CH_3	CH_3	54	
9	COOH	CH_2COOH	87	$COOH > COOCH_3$
34	$COOCH_3$	CH_2COOH	21	
35	$COOCH_3$	$(CH_2)_2COOH$	60	$CH_2COOH > (CH_2)_2COOH$
34	$COOCH_3$	CH_2COOH	21	
30	$CONH_2$	CH_2OH	75	$COOCH_3 > CONH_2$
31	$COOCH_3$	CH_2OH	85	

[a] $100 \times [\alpha]_D$ obsd/$[\alpha]_D$ max.

The priority relations found in the present investigation clearly indicate that relative arrangement of the substituents in the A > B sequence is controlled by different factors whose contribution is, at the present, difficult to evaluate. In the series of the *N*-phenylacetyl-α-amino acids, the COOH group is found in position A for all the substrates examined and a progressive decrease of the hydrolysis rate[3] is observed as the size of the substituents at the chiral center increases. On the other hand, data relative to the hydrolysis of the other series of *N*-phenylacetylamino compounds lead to priority relations which are, in some cases, anomalous in terms of the usual concepts of the sizes of the groups concerned, e.g., $CN > C_2H_5$, $CH_2OH > CH(CH_3)_2$, $CN > CH_2CH(CH_3)_2$. In this context, the inversion of the steric course of the hydrolysis found on passing from *N*-phenylacetylalaninonitrile (**13**) and *N*-phenylacetyl-2-aminobutyronitrile (**14**) to *N*-valinonitrile (**15**) and *N*-phenylacetylserinonitrile (**29**) is of note. Steric hindrance as well as polarity of the substituents is then to be considered among the most effective factor regulating the steric course of the hydrolysis.

Given the absence of information on the active site, the data reported here constitute a contribution to elaborate empirical guidelines for stereochemical predictions in the BPA-catalyzed hydrolyses of the amide bond. Further studies are in progress to unify the proposed priority sequences and to extend the analysis to new substituents.

Experimental Section

General. Melting points were determined in capillary tubes and are uncorrected. Preparative layer chromatography (PLC) was carried out with Merck HF_{254} silica gel on 0.5 mm thick plates. Optical rotations were taken at 20 °C with a Schmidt & Haensch 16065 polarimeter. IR spectra were recorded on a Perkin-Elmer 521 spectrophotometer. The mass spectrum was determined with an A.E.I. MS 12 spectrometer.

Enzyme. Hydrolysis experiments were performed using BPA prepared as follows. *Escherichia coli* cells were grown at 24 °C for 24 h in a medium containing 1.0% peptone, 1.0% meat extract (Acas, A. Costantino, Italy), 0.5% NaCl, and 0.2% phenylacetic acid. The pH was adjusted to 7.0 with sodium hydroxide. Cells were separated from the medium by centrifugation, disintegrated with the X-Press (AB Biox, Sweden), and extracted with 0.3 M phosphate buffer, pH 7.0. After centrifugation, 30% v/v of 1% protamine sulfate in 0.1 M phosphate buffer, pH 7.0, was added to the solution, and nucleic acids were removed by centrifugation. Cold ammonium sulfate was then added to the supernatant, and proteins precipitating between 30 and 60% saturation were collected. The precipitate was dissolved with 0.02 M phosphate buffer, pH 7.0, and dialyzed overnight against the same buffer. The protein solution was then fractionated on a DEAE-Sephadex A50 column equilibrated with the same buffer. Fractions with highest hydrolytic activity were collected and concentrated on a UM10 DIAFLO membrane (Amicon, USA). This solution contained 30 mg of protein/mL with a specific activity of 2000 units[9] per milligram; further steps of fractionation did not result in significant improvement of this value.

Substrate Recovery. General Procedure. Hydrolysis experiments were carried out in 0.1 M phosphate buffer at the pH and temperature reported in Table II. The time course of production of phenylacetic acid was followed by gas chromatography (internal standard methyl benzoate) by esterifying with diazomethane aliquots at suitable intervals. Neutral *N*-phenylacetyl derivatives were separated from the phenylacetic acid and from the amino compounds released by the enzyme, following usual fractionation with solvents. Acidic *N*-phenylacetyl derivatives were separated from phenylacetic acid by column chromatography on silica gel (3 g of silica per 100 mg of residue). Elution with benzene–ethyl acetate (8:2) gave phenylacetic acid. On subsequent elution with ethyl acetate, the unreacted *N*-phenylacetyl derivative was recovered in practically quantitative yield.

(±)-*N*-Phenylacetylnorleucinonitrile (26). This was obtained by acylating the corresponding aminonitrile[10] with phenylacetyl chloride in aqueous sodium bicarbonate solution containing 20% tetrahydrofuran: mp 71–72 °C from ether–petroleum ether (65% yield). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.97; H, 7.90; N, 12.07.

(±)-*N*-Phenylaeetylleucinonitrile (27). The procedure adopted for **26** was followed. Leucinonitrile was prepared according to the literature.[10] **27** was crystallized from ethyl acetate–petroleum ether: mp 96 °C (60% yield). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.92; H, 7.97; N, 12.17.

(±)-*N*-Phenylacetylvalinol (28). Phenylacetyl chloride (2.79 g, 18.15 mmol) was added dropwise (1 h) at 0 °C to a stirred solution of 1.25 g (12.1 mmol) of (±)-valinol[11] in 10 mL of 20% sodium hydroxide. After an additional 0.5 h of stirring at room temperature the mixture was extracted with ether. The extract, washed with 0.5 N hydrochloric acid and water and dried, gave a residue which was crystallized from ether: 1.06 g (40%); mp 91–92 °C; IR ($CHCl_3$) 3410, 2940, 1645, 1590 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.63; H, 8.58; N, 6.27.

From the mother liquors of the crystallization of **28** the *N*,O-diphenylacetyl derivative of the starting amino alcohol was isolated: mp 87–88 °C from ether. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.40; H, 7.42; N, 4.07.

(*S*)-*N*-Phenylacetylvalinol [(*S*)-28] was prepared from (*S*)-valinol as described above for **28**: mp 72 °C from ether (37% yield);

$[\alpha]^{25}_D$ −30° (c 3.0, methanol). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.55; H, 8.72; N, 6.35.

(±)-*N*-Phenylacetylserinonitrile (29). (2-Tetrahydropyranyloxy)acetaldehyde[12] (5.0 g, 34.7 mmol) in 15 mL of ether was saturated with ammonia at 10 °C. The solution was then evaporated and the residue carefully dried under vacuum to give *O*-(2-tetrahydropyranyl)-2-iminoethanol. To the crude imino derivative, 3.5 mL of dry hydrogen cyanide was added and the solution was allowed to stand overnight at 18 °C. After evaporation of the hydrogen cyanide the residue was dissolved in 120 mL of dry benzene containing 2.74 g of pyridine. Phenylacetyl chloride (5.34 g, 34.7 mmol) in 50 mL of dry benzene was added under stirring, during a 20-min period, at room temperature. After an additional 15 h of stirring, the solution was washed with cooled 1 N hydrochloric acid (40 mL), aqueous sodium bicarbonate, and water. The organic layer was dried over Na_2SO_4 and evaporated to give 6.5 g of an oily residue. Purification by PLC (eluent, 1:1 ether–petroleum ether) gave 2.25 g (23%) of 2-phenylacetamido-3-(2-tetrahydropyranyloxy)propanenitrile. The mass spectrum taken at 70 eV gave a molecular ion peak at *m/e* 288; IR ($CHCl_3$) 3405, 2935, 2860, 2245, 1680, 1600, 1495 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.35; H, 6.83; N, 9.48.

Hydrochloric acid (150 mL, 2 N) was added, at room temperature, to a stirred solution of 1.44 g (5.0 mmol) of the above product in 50 mL of methanol over a period of 15 min. After an additional 30 min of stirring, a slight excess of solid sodium bicarbonate was added. After removal of the methanol under vacuum at room temperature, the aqueous solution was extracted with ethyl acetate. Drying and evaporation of the solvent gave a residue which was crystallized from chloroform: 0.930 g of **29** (91%); mp 126–127 °C; IR ($CHCl_3$) 3405, 2925, 2245, 1670, 1600, 1485 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.61; H, 5.93; N, 13.64.

***N*-Phenylacetyl-(±)-serinamide (30)** was obtained by treating (±)-serinamide hydrochloride in saturated aqueous sodium bicarbonate with phenylacetyl chloride at 0 °C: mp 144–145 °C (methanol–ethyl acetate); 37% yield. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.38; H, 6.38; N, 12.47.

***N*-Phenylacetyl-(*S*)-serinamide [(*S*)-30]** was prepared from (*S*)-serinamide hydrochloride as described above for **30**: mp 137–138 °C (methanol–ethyl acetate); 30% yield; $[\alpha]^{20}_D$ + 4.0° (c 4.0, methanol). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.49; H, 6.40; N, 12.51.

***N*-Phenylacetylserinamide (30) Starting from (−)-*N*-Phenylacetylserinonitrile (29).** The solid-phase catalysis of the hydrolysis of nitriles to amides reported by Cook[13] was utilized. Manganese dioxide (2 g) was added to a solution of 100 mg (0.49 mmol) of *N*-phenylacetylserinonitrile, $[\alpha]^{20}_D$ −2.0° (c 7.0, methanol), recovered from enzymatic hydrolysis of **(±)-29.** The mixture was stirred for 15 h at room temperature. The dioxide was filtered and repeatedly washed with 7:3 ethyl acetate–methanol. The combined solutions were evaporated under vacuum and the residue was purified by PLC (eluent, 93:7 ethyl acetate–methanol; 35 mg (32%) of *N*-phenylacetylserinamide was obtained. The optical data of this compound are reported in Table III.

(±)-4-Cyano-4-phenylacetamidobutyric Acid (32). 2-Ketoglutaric acid (21.9 g, 150 mmol) was added to a stirred solution containing 9.78 g (150 mmol) of KCN, 8.64 g (160 mmol) of NH_4Cl in 36 mL of water, and 36 mL of aqueous (25%) NH_3, over 20 min at 20 °C. The reaction mixture was allowed to stir for another hour at room temperature and for 4 h at 60 °C. NaOH (60 mL, 20%) was added to the cooled solution and the ammonia was removed under vacuum at room temperature. The aqueous alkaline solution was then treated, at 5 °C under stirring, with 30 g (195 mmol) of phenylacetyl chloride. During the acylation, portions of 20% NaOH were added to keep the pH at 8.5. The resulting solution was washed with ether and acidified (pH 2.5) at 5 °C with hydrochloric acid. The separated solid was crystallized from methanol–ethyl acetate to give 10.4 g (23%) of (±)-2-cyano-2-phenylacetamidoglutaric acid. The compound did not show a definite melting point but began to decompose, starting at 120 °C. Because of its thermal lability, this compound was analyzed as the dimethyl ester obtained by treatment with diazomethane in ether. The diester melted at 132–133 ° C (ethyl acetate–petroleum ether). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.21; H, 5.71; N, 8.82.

(±)-2-Cyano-2-phenylacetamidoglutaric acid (9.0 g, 30.4 mmol) was heated under vacuum (0.1 mm) at 145 °C for 10 min. The glass obtained was purified by silica-gel (240 g) column chromatography. After washing the column with ethyl acetate, 30.2 g (43%) of **32** was eluted. The compound was crystallized from ethyl acetate–petroleum ether: mp 138–139 °C; IR (KBr) 3275, 2240, 1965, 1665 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.16; H, 5.76; N, 11.21.

(±)-Methyl-4-cyano-4-phenylacetamidobutyrate (33). This compound was obtained by treating **32** with diazomethane in ether: mp 72–73 °C (ethyl acetate–petroleum ether); IR (KBr) 3260, 2240, 1725, 1650 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.60; H, 6.22; N, 10.82.

Preparation of *N*-Phenylacetyl Derivatives of α-Methyl Esters of Aspartic and Glutamic Acids [(±)-34, (*S*)-34, (*R*)-34, (±)-35, (*S*)-35, and (*R*)-35]. The amino derivatives corresponding to the title compounds were prepared according to general procedure reported by Kovacs and co-workers.[14] The *N*-phenylacetyl derivatives were prepared according to the following procedure relative to **(±)-34.** Phenylacetyl chloride (680 mg, 4.4 mmol) was added dropwise (1 h) to a stirred solution of 285 mg (3.4 mmol) of $NaHCO_3$ and 500 mg (3.4 mmol) of (±)-aspartic acid α-methyl ester in 5 mL of water at 0 °C. The solution was carefully maintained at pH 7.5 by adding 1 N NaOH. After washing with ether, the solution was acidified and extracted with ethyl acetate. The oily residue (890 mg) was purified by column chromatography on silica gel (23 g). After elution of phenylacetic acid with 6:4 benzene–ethyl acetate, the *N*-phenylacetyl derivative **(±)-34** was eluted with 9:1 ethyl acetate–acetic acid: 785 mg (67%); mp 111–113 °C (ethyl acetate–petroleum ether). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.59; H, 5.80; N, 5.15.

***N*-Phenylacetyl-(*S*)-aspartic acid α-methyl ester [(*S*)-34]** was obtained as an oil (60% yield): $[\alpha]^{20}_D$ −14.5° (c 4.0, methanol). For elemental analysis the dicyclohexylamine salt was prepared: mp 165–166 °C (dry ethyl ether); $[\alpha]^{20}_D$ +5.8° (c 3.0, methanol). Anal. Calcd for $C_{25}H_{38}N_2O_5$: C, 67.23; H, 8.58; N, 6.27. Found: C, 67.32; H, 8.63; N, 6.29.

***N*-Phenylacetyl-(*R*)-aspartic acid α-methyl ester [(*R*)-34]** was obtained as an oil (70% yield): $[\alpha]^{20}_D$ +14.0° (c 4.0, methanol). For elemental analysis the dicyclohexylamine salt was prepared: mp 165 °C (dry ethyl ether); $[\alpha]^{20}_D$ −5.5 ° (c 3.0, methanol). Anal. Calcd for $C_{25}H_{38}N_2O_5$: C, 67.23; H, 8.58; N, 6.27. Found: C, 67.04; H, 8.71; N, 6.21.

***N*-Phenylacetyl-(±)-glutamic acid α-methyl ester [(±)-35]** was crystallized from ethyl acetate–petroleum ether (65% yield): mp 79–80 °C. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.13; H, 6.05; N, 4.95.

***N*-Phenylacetyl-(*S*)-glutamic acid α-methyl ester [(*S*)-35]** was crystallized from ethyl acetate–petroleum ether (60% yield): mp 103–104 °C; $[\alpha]^{20}_D$ −31.5° (c 1.0, methanol). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.10; H, 6.10; N, 4.93.

***N*-Phenylacetyl-(*R*)-glutamic acid α-methyl ester [(*R*)-35]** was crystallized from ethyl acetate–petroleum ether (65% yield): mp 103 °C; $[\alpha]^{20}_D$ +32.0° (c 1.0, methanol). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 59.94; H, 6.20; N, 4.89.

***N*-Phenylacetyl-(*S*)-norleucine Methyl Ester [(*S*)-36].** (*S*)-Norleucine was treated in aqueous sodium hydroxide (20%) at 0 °C with phenylacetyl chloride. Usual workup gave a 55% yield of *N*-phenylacetyl-(*S*)-norleucine: mp 92–93 °C (ethyl acetate–hexane); $[\alpha]^{20}_D$ −12.0° (c 4.0, methanol). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.38; H, 7.65; N, 5.58.

The *N*-phenylacetylamino acid was then treated with diazomethane in ether to give *N*-phenylacetyl-(*S*)-norleucine methyl ester: mp 56–57 °C (ethyl acetate–hexane); $[\alpha]^{20}_D$ −31.0° (c 4.0, methanol). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.50; H, 8.06; N, 5.22.

***N*-Phenylacetylnorleucine Methyl Ester (36) Starting from (+)-*N*-Phenylacetylnorleucinonitrile (26).** A solution of 0.26 g (1.13 mmol) of *N*-phenylacetylnorleucinonitrile, $[\alpha]^{20}_D$ +30.0° (c 4.0, methanol), recovered from enzymatic hydrolysis of (±)-**26**, in 45 mL of dry methanol was saturated at room temperature with gaseous hydrogen chloride. The solution was refluxed for 1.5 h. After removal of the solvent, the residue was taken up with ether and the resulting solution washed with sodium bicarbonate solution and water. Usual workup gave an oily residue. PLC (eluent, 1:1 benzene–ether) afforded 50 mg of the compound: pure by TLC examination; the IR spectrum ($CHCl_3$) was identical with those of the above reported *S* isomer; $[\alpha]^{20}_D$ +16.3° (c 1.0, methanol).

***N*-Phenylacetylleucine Methyl Ester (37).** This was prepared from (+)-*N*-phenylacetylleucinonitrile, $[\alpha]^{20}_D$ +33.0° (c 4.0, methanol), recovered from the enzymatic hydrolysis of (±)-**27.** The method reported for the preceding compound was followed. A compound which resulted, identical with an authentic specimen of *N*-phenylacetylleucine methyl ester (see footnote c in Table III), was obtained (20% yield): $[\alpha]^{20}_D$ +3.3° (c 4.0, methanol).

Glutamic Acid from (−)-4-Cyano-4-phenylacetamidobutyric

Acid. This transformation (Table III) was performed by refluxing (−)-4-cyano-4-phenylacetamidobutyric acid, $[\alpha]^{20}_D$ −12.0° (c 2.0, methanol), recovered from the enzymatic hydrolysis of (±)-**32**, with 3 N hydrochloric acid.

Registry No.—(*R*)-**26**, 65414-95-1; (*R*)-**27**, 65414-96-2; **28** PA ester, 65414-97-3; (*R*)-**29**, 65414-98-4; **29** THP ether, 65414-99-5; (*S*)-**32**, 65414-60-0; (*R*)-**34**, 65414-61-1; (*R*)-**34** salt, 65414-62-2; (*S*)-**34** salt, 65414-64-4; (*R*)-**35**, 65414-65-5; (*S*)-**36**, 65414-66-6; (*R*)-**36**, 65414-67-7; (*R*)-**37**, 65414-68-8; norleucinonitrile, 65414-69-9; phenylacetyl chloride, 103-80-0; leucinonitrile, 65451-12-9; valinol, 16369-05-4; (*S*)-valinol, 22464-36-4; (2-tetrahydropyranyloxy)acetaldehyde, 65414-70-2; *O*-(2-tetrahydropyranyl)-2-iminoethanol, 65414-71-3; 2-amino-3-(2-tetrahydropyranyl)propionitrile, 65414-72-4; (±)-serinamide hydrochloride, 65414-73-5; (*S*)-serinamide hydrochloride, 65414-74-6; (±)-2-cyano-2-phenylacetamidoglutaric acid, 65414-75-7; (±)-2-cyano-2-phenylacetamidoglutaric acid dimethyl ester, 65414-76-8; diazomethane, 334-88-3; (±)-aspartic acid α-methyl ester, 65414-77-9; (*S*)-aspartic acid α-methyl ester, 17812-32-7; (*R*)-aspartic acid α-methyl ester, 65414-78-0; (±)-glutamic acid α-methyl ester, 65414-79-1; (*S*)-glutamic acid α-methyl ester, 6384-08-3; (*R*)-glutamic acid α-methyl ester, 26566-13-2; (*S*)-norleucine, 327-57-1; *N*-phenylacetyl-(*S*)-norleucine, 65414-80-4; benzylpenicillinacylase, 9014-06-6.

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Reactions of Protonated Diamino Acids in the Gas Phase

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The methane chemical ionization mass spectra of series of α,ω-diamino acids, ω-amino acids, cyclic and acyclic α-amino acids, and methyl esters have been obtained. Protonated α,ω-diamino acids react in the gas phase through the competitive cycloelimination of water or ammonia, decarboxylation, or collision stabilization of the intramolecularly hydrogen bonded protonated molecular ion. Structural factors which select between decarboxylation and lactam, lactone, and cyclic amino acid formation are determined by comparison of spectra of these related compounds. The prevalence of reactions correlates with the product ion stability and not with the site of protonation, the thermodynamically preferred site of protonation, or the stability of the intramolecularly hydrogen-bonded complex.

Reactions of protonated diamino acids in the gas phase may be studied under conditions of chemical ionization mass spectrometry. Under these conditions the diamino acid is protonated on a single site by way of an exothermic proton transfer reaction with reagent gas ions CH_5^+ or $CH_3CH_2^+$. The protonated molecular ions may undergo collision stabilization while in the ion source[1] or react through elimination of water, ammonia, or carbon monoxide.[2] In many ways these conditions are analogous to those in solution. The reactions of protonated molecules which occur in the gas phase but are not observed in solution demonstrate the influence of solvent effects on molecular reactivity.

Protonated molecules such as the diamino acids, 2,3-diaminopropionic to 2,6-diaminohexanoic acid (lysine), may react in the gas phase through simple S_E1 elimination analogous to reactions in strongly acid solution[3,4] or neighboring group displacement reactions involving three- to seven-membered cyclic transition states.[5-7] While gas phase reaction mechanisms may be analogous to solution chemistry, the charge on a protonated site is not distributed through solvation so that internal effects such as substituent polarizability,[6] hydrogen bonding,[8,9,10] and ion–dipole interactions[11,12,13] are relatively more important.

The reactions of protonated diamino acids are related to the interfunctional distance between the terminal amine and the α-amino acid moiety which indicates that neighboring group interactions may be involved. Lactam, lactone, and cyclic amino acid formation as well as decarboxylation reactions are believed to occur in the gas phase.

Our investigation of these reactions has centered on determining which intramolecular interactions (amine–amine or amine–carboxyl) are involved in diamino acid fragmentation and the structural features which regulate the probability of their occurrence. Although reaction product structures cannot be determined directly, supporting evidence may be obtained by comparing product ion reactivities to the reactivity of ions generated from other sources. For example, the subsequent fragmentation of the $MH-NH_3$ ion products, reactions 1–3, may be compared to protonated cyclic amino acid reactions.

The general features of 2,5-diaminopentanoic acid (ornithine) and 2,6-diaminohexanoic acid (lysine) methane chemical ionization mass spectra have been reported previously. Milne et al.[2] noted the selective initial elimination of ammonia from the 6 position of lysine, reaction 1. The cyclization mechanism postulated was supported by studies of diaminoalkanes,[5] $NH_2(CH_2)_nNH_2$, in which the probability of ammonia loss paralleled the rate of cyclization of $Br(CH_2)_nNH_2$ in solution.[14] An additional sequence leading to the cyclic iminium ion with loss of ammonia from the 2 position was also indicated.[2] Leclercq and Desiderio[15] noted the facile loss of water from ornithine and suggested that this

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Table I. Diamino Acid Chemical Ionization Mass Spectra (Methane, 200 °C)

	$NH_2(CH_2)_{n-2}CH(NH_2)COOH$,[c] n =			
	3	4	5	6
M + C_3H_7	0.6			0.7
$-NH_3$	1.7			0.7
$-H_2O$		2.4	1.3	
$-H_2O$, CO				0.3
M + C_2H_5				0.6
$-NH_3$	3.9		0.2	1.3
$-H_2O$		1.2	0.4	
MH	26.6	0.8	0.7	28.0
$-NH_3$	27.6	1.2	3.0	23.9
$-H_2O$[a]	0.8	49.0	40.3	3.4
$-H_2O$, NH_3	1.7	1.6	3.1	1.6
$-H_2O$, CO	25.9	17.6	3.0	2.2
$-NH_3$, H_2O, CO	1	7.8	30.7	29.0
M − H				.2
$-NH_3$	0.3	4.1	3.7	4.2
$-H_2O$	0.9	6.9	2.3	
Misc	6.6			
ΣI	93.6	91.4	88.6	96.0

[a] Isobaric with M 29–46. [b] *(m/e, % ΣI)* 76, 38; 58, 0.7; 30, 2.3. [c] Registry No.—$C_3H_8N_2O_2$, 515-94-6; $C_4H_{10}N_2O_2$, 305-62-4; $C_5H_{12}N_2O_2$, 70-26-8; $C_6H_{14}N_2O_2$, 56-87-1.

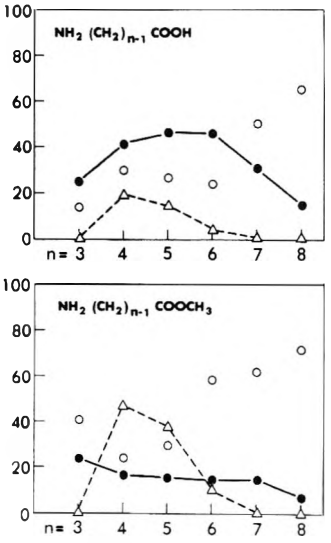


Figure 1. Chemical ionization mass spectra of ω-amino acids and methyl esters (methane, 200 °C) showing the variation in abundance of MH^+ (○), MH − HOR (●), R = H, CH_3, and MH − NH_3 (△) with interfunctional separation.

may involve lactam formation. Loss of water from simple amino acids is always accompanied by the subsequent loss of carbon monoxide.[16] In this study the properties of model compounds have been investigated in an effort to obtain experimental evidence in support of fragmentation reaction mechanisms.

Experimental Section

Amino acids were obtained from commercial sources. Mass spectra were obtained using an Associated Electrical Industries MS-902 double focusing mass spectrometer which had been modified to operate under chemical ionization conditions[17] and in the ion kinetic energy scan mode.[18] Samples were introduced using a direct insertion probe. Methane was used as the reagent gas at 0.7 Torr. All spectra were taken under similar conditions of sample partial pressure, source temperature, 200–210 °C, and instrumental parameters.

Table II. Diamino Acid Methyl Ester Chemical Ionization Mass Spectra (Methane, 200 °C)

	$NH_2(CH_2)_{n-2}CH(NH_2)COOCH_3$,[e] n =			
	3	4	5	6
M + C_3H_7	0.4	0.4		1.1
$-NH_3$	1.0	.3		0.5
$-HOCH_3$		.3	0.4	
$-HOCH_3$, CO	0.4	.4	0.1	0.1
M + C_2H_5				1.0
$-NH_3$	2.9	0.4		1.2
$-H_2O$		0.4	0.7	
$-HOCH_3$		0.7	0.7	0.6
MH	15.4	13.6	18.6	34.3
$-NH_3$	35.9	22.1	34.4	28.2
$-H_2O$[a]	3.3	16.6	3.1	1.6
$-HOCH_3$[b]	1.4	22.8	10.6	2.1
$-H_2O$, NH_3		0.6	0.1	0.1
$-HOCH_3$, NH_3		1.4	1.8	1.7
$-H_2O$, $HOCH_3$		1.8	1.3	1.2
$-HOCH_3$, CO	15.9	10.9	1.5	1.8
$-HOCH_3$, CO, NH_3	c	1.5	22.4	18.2
M − H	1.0			
$-NH_3$			1.6	2.7
$-H_2O$		0.4		
$-HOCH_3$			0.2	0.2
Misc	12.3[d]			
ΣI	94.7	94.3	98.3	96.2

[a] Isobaric with M + 29–46. [b] Isobaric with M + 29–60. [c] m/e 42 concealed by reagent gas ions, assumed to be zero. [d] *(m/e, % ΣI)* 30, 9.0; 58, 1.8; 88, 1.5. [e] Registry No.—$C_3H_{10}N_2O_2$, 20610-20-2; $C_4H_{12}N_2O_2$, 37529-96-7; $C_5H_{14}N_2O_2$, 6384-10-7; $C_6H_{16}N_2O_2$, 687-64-9.

Ion intensities are corrected for ^{13}C natural abundance. The formulas for ions in the 2,6-diaminohexanoic acid spectra were determined from accurate mass measurements and are consistent with the structures shown.

Results

The methane chemical ionization mass spectra of four diamino acids, 2,3-diaminopropionic to 2,6-diaminohexanoic acid, are shown in Table I. Each of these compounds fragment following protonation by the loss, or successive losses, of ammonia, water, and carbon monoxide. The relative abundance of these ions varies over a wide range even within this limited series. Ions formed by association of $C_2H_5^+$ or $C_3H_7^+$ are of low intensity at the source pressure used[19] (0.7 Torr) and their fragmentation parallels that of the protonated molecular ion. The ions derived from $(M - H)^+$ are also of low intensity in these spectra.

The spectra for the methyl ester of each of these diamino acids are shown in Table II. The differences in the acid and methyl ester spectra can be attributed to the fact that loss of methanol from an alkyl methyl ester (MH = 100, MH − $HOCH_3$ = 13) is less facile than loss of water from an acid (MH = 100, MH − H_2O = 65).[11] As a consequence all of the fragmentation reactions which involve loss of methanol are less abundant than the corresponding acid fragment ions and the percent abundance of the remaining ions is increased. The close parallel between the acid and methyl ester spectra tend to confirm that pyrolysis of the diamino acids has been avoided. Elimination of water from the diamino acid methyl esters implicates a reaction mechanism through which either water or methanol may be lost from the ester function.

Table III shows the spectra of ω-amino acids and methyl esters which were taken under the same conditions as the α,ω-diamino acids and esters of Tables I and II. These spectra are similar to the two previously reported ω-amino acid

Table III. Terminal Amino Acid and Methyl Ester Chemical Ionization Mass Spectra (Methane, 200 °C)

	$NH_2(CH_2)_{n-1}COOH$,[a,2] n =						$NH_2(CH_2)_{n-1}COOCH_3$,[b,h] n =					
	3	4	5	6	7	8	3	4	5	6	7	8
M + C_3H_7	1.0	1.0	1.1	1.8	0.2	2.4	0.5	0.8	2.0	1.3	1.8	1.7
-HOR		1.1	1.9									
M + C_2H_5	0.1	0.3	0.9	4.1	5.6	4.9		0.2	0.9	3.6	8.1	9.3
-HOR		1.4	2.8	1.3	1.3	0.8		1.3	0.4	0.7	0.5	0.4
M + H	14.0	29.6	26.9	24.3	49.9	64.5	41.1	24.0	29.6	57.5	61.9	71.6
$-NH_3$	0.9	18.9	14.5	4.3	0.4	0.1	0.5	47.2	38.3	10.4	1.1	0.4
$-H_2O$[c]	24.8	41.5	46.2	46.0	30.6	15.1		1.0	1.0	0.3	0.3	0.6
$-HOCH_3$[d]							24.5	17.4	16.3	14.9	16.1	7.8
$-NH_3$, HOR	1.6	1.4	0.5	7.1	2.2	1.0		1.3	1.4	3.2	2.3	1.4
-HOR, CO	0.9	0.2	0.2	2.1	0.2	0.9			1.7			
$-NH_3$, HOR, CO			1.0	4.3	2.2				1.5	2.5	2.1	0.9
M − H	0.9	1.0	0.6	1.6	1.8	2.8		0.7	0.8	0.9	1.9	3.0
$-NH_3$		0.5	1.1	0.3	0.7						0.3	
-HOR		0.7	0.9	1.0	0.9	0.6	0.9	0.4	0.3	0.4	0.3	
Misc	47.0[e]	1.0[f]					26.1[g]					
ΣI	91.2	97.6	98.6	98.2	96.0	93.1	93.6	94.3	92.2	95.7	96.7	97.1

[a] R = H. [b] R = CH_3. [c] An isobar of M + 29–46. [d] An isobar of M + 29–60. [e] (*m/e*, % ΣI) 30, 17.9; 58, 3.7; 102, 4.7. [f] (*m/e*, % ΣI) 44, 1.0. [g] 30, 33.6; 48, 6.0; 58, 7.4; 70, 0.9. [h] Registry No.—$C_3H_7NO_2$, 107-95-9; $C_4H_9NO_2$, 56-12-2; $C_5H_{11}NO_2$, 660-88-8; $C_6H_{13}NO_2$, 60-32-2; $C_7H_{15}NO_2$, 929-17-9; $C_8H_{17}NO_2$, 1002-57-9. [h] Registry No.—$C_4H_9NO_2$, 4138-35-6; $C_5H_{11}NO_2$, 3251-07-8; $C_6H_{13}NO_2$, 63984-02-1; $C_7H_{15}NO_2$, 2780-89-4; $C_8H_{17}NO_2$, 39979-08-3; $C_9H_{19}NO_2$, 59080-49-8.

Table IV. Cyclic and Acyclic α-Amino Acid Chemical Ionization Mass Spectra (Methane, 200 °C)

	$CH_3(CH_2)_{n-2}CH(NH_2)COOH$,[c] n =		$CH_2NHCHCOOH$,[d] n = $(CH_2)_{n-3}$		
	2	3	4	5	6
M + C_3H_7	1.3	2.2	2.2	2.1	1.5
$-H_2$			0.4	0.1	0.4
$-H_2O$, CO	0.8	0.3	0.2	0.3	1.9
M + C_2H_5	1.2	2.4	1.2	2.0	2.1
$-H_2$			0.4	0.1	1.2
$-H_2O$, CO[a]	8.0	4.5	2.0	2.3	2.5
MH	20.4	6.4	63.2	59.6	35.3
$-H_2O$, CO	65.7	75.7	24.1	27.0	35.3
M − H	0.7	2.4	0.4	5.8	7.7
$-H_2O$, CO	0.8	2.8	0.2	0.2	3.1
gly[b]	0.4	2.6			
ΣI	99.2	99.3	94.3	99.2	91.0

[a] Isobaric with MH − H_2O. [b] gly = $(NH_2{=}CHCOOH)^+$. [c] Registry No.—$C_3H_7NO_2$, 56-41-7. [d] Registry No.—$C_4H_7NO_2$, 2517-04-6; $C_5H_9NO_2$, 147-85-3; $C_6H_{11}NO_2$, 3105-95-1.

Table V. Diamino Alkane, $NH_2(CH_2)_nNH_2$, Chemical Ionization Mass Spectra (Methane, 200 °C)

	Percent total ionization,[a] n =			
	3	4	5	6
M + C_3H_7				1.0
$-NH_3$	1.3	1.8	1.5	0.4
M + C_2H_5	0.06	0.07	0.1	3.5
$-NH_3$	4.1	5.1	3.5	4.1
MH	22.5	6.0	6.6	20.1
$-NH_3$	68.4	72.0	69.4	63.3
$-CH_2NH_2$	1.2	2.7	0.8	0.3
M − H	0.5	0.5	0.6	0.5
$-NH_3$	0.8	8.9	11.8	4.3
ΣI	98.8	97.0	95.2	97.5

[a] Registry No.—$C_3H_{10}N_2$, 109-76-2; $C_4H_{12}N_2$, 110-60-1; $C_5H_{14}N_2$, 462-94-2; $C_6H_{16}N_2$, 124-09-4.

spectra.[16] The ω-amino acids and esters are bifunctional molecules in which the terminal amino and carboxyl interactive reactions may occur without influence of the α-amino group. Decarboxylation is a minor process in these compounds due to the absence of the α-amino group. Elimination of water or methanol and ammonia are facilitated relative to monofunctional *n*-alkyl amines[10] and acids[11] which suggests the presence of bifunctional interactions. These elimination reactions are dependent on the number of methylene groups, *n*, separating the terminal functions $NH_2(CH_2)_nCOOR$, as shown in Figure 1. Structural dependence of the MH − H_2O and MH − $HOCH_3$ reactions is similar to that observed for the elimination of water and methanol from dicarboxylic acids and methyl esters.[11] Elimination of H_2O from the ω-amino acid methyl esters is also observed in these compounds.

Presence of the amino group increases the extent of decarboxylation in acyclic α-amino acids relative to ω-amino acids, Table IV. This is probably due to the stability of the product iminium ion.[16] Decarboxylation of cyclic α-amino acids is less facile than that observed in the acyclic α-amino acids. The extent of decarboxylation is inversely proportional to the ring size of the cyclic iminium product ion, Table IV.

Spectra of diamino alkanes have been discussed previously.[5] Table V shows the methane CI spectral data for those diamino alkanes which have amine–amine orientations related to the diamino acids of this study.

Discussion

Ion intensity data available from mass spectrometry reflect the steady state reaction products formed during the average ion residence time within the source (10^{-5} to 10^{-6} s).[1] The rate of each initial fragmentation reaction affects the intensity of the protonated molecular ions, MH^+, while fragment ion intensity is determined by the probability of competitive reactions of the parent ion and secondary reactions of the fragment ion. The transitions which occur in the diamino acids are apparent from the ion kinetic energy scan of lysine, Table VI. Losses of water and ammonia from the parent ion are observed but the minor decarboxylation transition (MH − H_2O, CO

Table VI. Ion Kinetic Energy and Metastable Chemical Ionization Scans of Lysine (Methane, 205 °C)[a]

Transition ion (*m/e*)	Calcd		Obsd	
	m_2/m_1	m_2^2/m_1	E_i/E	M*
MH(147) → MH − NH_3(130)	0.884	115.0	0.881	114.8
MH(147) → MH − H_2O(129)	0.878	113.2	0.881	113.8
MH − H_2O,CO(101) → MH − H_2O,CO,NH_3(84)	0.831	69.9	0.832	70.6
MH − NH_3(130) → MH − NH_3,H_2O,CO(84)	0.646	54.3	0.648	54.7

[a] Slow transitions $M_1 \rightarrow M_2$ with metastable ions M* are observed on the ion monitor at normal accelerating voltage, V, by lowering the normal electric sector voltage E to E_i when $E_1/E = M_2/M_1$. A magnet scan at V and E_i shows M* at mass M_2^2/M_1.

2.2% ΣI) was not detectable. Two secondary fragments, (MH − H_2O,CO) − NH_3 and (MH − NH_3) − H_2O,CO, were also observed. These transitions account for more than 80% of the diamino acid fragments.

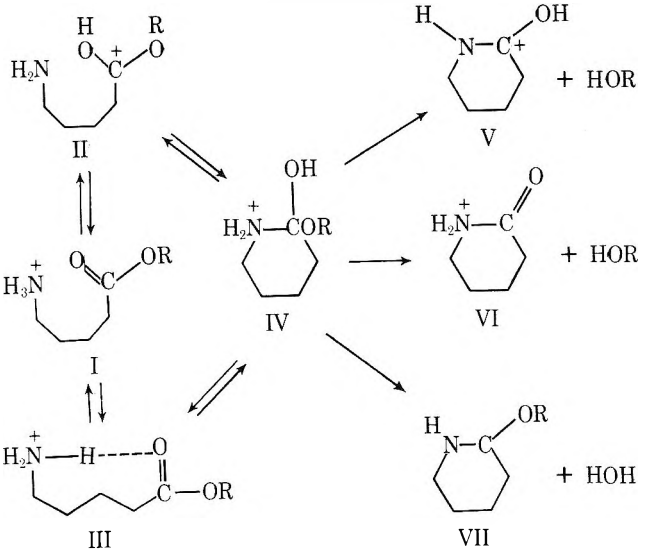
If proton transfer were directed toward the single most basic site of a polyfunctional molecule then this factor would increase the probability of fragmentation of that function. This, however, does not appear to occur in polyfunctional compounds. Although proton transfer efficiency to different functional groups is not well understood any exothermic proton transfer reaction should be facile.[20] Proton transfers from CH_5^+ and $C_2H_5^+$ (PA_{CH_4} = 128, $PA_{CH_2CH_2}$ = 158 kcal/mol) to amino and carboxyl groups ($PA_{RNH_2} \approx 217$, $PA_{RCOOH} \approx 192$ kcal/mol) of diamino acids are all exothermic so that collision probability rather than the amount of energy transfer would determine the extent of initial protonation of distal ω-amino and α-amino acid moieties.

An isolated protonated site within a polyfunctional molecule may undergo an S_Ni type elimination reaction;[3,4] however, the frequency of intramolecular interactions is competitive with unifunctional fragmentations even for very facile reactions.[5] For example: 1-decanol, MH = 0, MH − H_2O = 100%; 1,10-decanediol, MH = 59, MH − H_2O = 100%[10] and 1-acetoxydecane, MH = 68, MH − HOAc = 100%; 10-diacetoxydecane, MH = 100, MH − HOAc = 9%.[11] When amino acids are ionized with deuterated reagent gases (CD_4, D_2) extensive exchange with labile amino acid protons was observed prior to fragmentation.[16] These observations support the fact that intramolecular interactions including hydrogen bond formation and proton transfer between accessible functions may occur before fragmentation. The enthalpy of hydrogen bond formation increases the internal energy of the protonated molecular ion until collision stabilization[19] with a reagent gas molecule occurs (10^{-7} to 10^{-8} s at 1.0 Torr).[1] This internal energy may facilitate some fragmentation reactions as well as reversible proton transfer between functional groups within MH^+. Neighboring group reactions involving 3- to 7-membered transition states also occur prior to complete collision stabilization of MH^+ and localization of the proton on the thermodynamically preferred site.[5]

The thermodynamics and kinetics implicit in these observations do not support the fact that protons are localized at a single site within a molecular ion[21] before collision stabilization is complete. While this does not justify the assumption that the site of protonation is evenly distributed within the molecular ion our discussion is consistent with the fact that product ion stability rather than the site of protonation determines the extent of fragmentation of the protonated molecular ion.

Initial Reactions. Loss of water from MH^+ is a major process for 2,4- and 2,5-diamino acids (Table I). Elimination of water is not observed for simple α-amino acids[16] so the

Scheme I

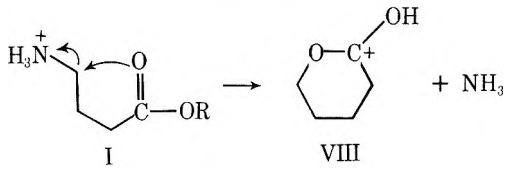


prevalence of MH − H_2O must involve participation of the ω-amino group. In order to focus on the amine–carboxyl interaction, a series of ω-amino acids and methyl esters were studied (Table III). All of these compounds show facile loss of water and/or methanol but the reaction is not critically dependent on interfunctional separation, Figure 1. When the influence of competitive reactions is considered it appears that there is a gradual decrease in MH − HOR from n = 3 to 8. This is analogous to the gradual decrease in MH − HOR observed in dicarboxylic acids and methyl esters[11] and contrasts to the highly specific elimination of ammonia from ω-amino acids and methyl esters (Table III). These contrasts may be explained if carboxyl compounds, such as 5-aminopentanoic acid, can react from the intramolecular hydrogen bonded structure[13] of Scheme I, (III → IV) as well as by direct association (II → IV) of the carbonyl protonated molecular ion. Direct association reactions are dependent on interfunctional separation and collision frequency[5] while hydrogen bond formation in the gas phase may precede fragmentation even for larger molecules in which the distal functions are separated by more than ten methylene units. For this reason elimination reactions which occur prior to collision stabilization of III, Scheme I, would not be highly dependent on the interfunctional distances between the amine and carboxyl function. If, however, no reaction pathway were accessible to the hydrogen-bonded complex, III, this exothermic bond (I → III ≈ −20 kcal/mol) would be stabilized through collision with reagent gas molecules and no further reactions would occur.

Evidence for the tetrahedral carbon intermediate[22] (IV) comes from the observation that water as well as methanol is lost from ω-amino and diamino acid methyl esters (Tables II and III). Loss of methanol from IV may occur following proton transfer from nitrogen (V) or oxygen (VI); water loss may occur only from NH proton transfer (VII). This may explain the preferential loss of methanol from the ω-amino esters. The presence of the α-amino group greatly facilitates elimination of water from the diamino acid methyl esters (Table II).

Loss of ammonia from the ω-amino acids and methyl esters is highly dependent on interfunctional separation and prominent only for n = 4 and 5, Figure 1. This structural dependence suggests a cyclization step, Scheme II, leading to formation of 5- and 6-membered lactones through direct displacement of the terminal amine. This reaction is in competition with lactam formation, Scheme I. The relative abundance of this reaction correlates with the rate of ring closure in cyclization reactions and not with differences in the site of protonation or with the stability of intramolecular

Scheme II

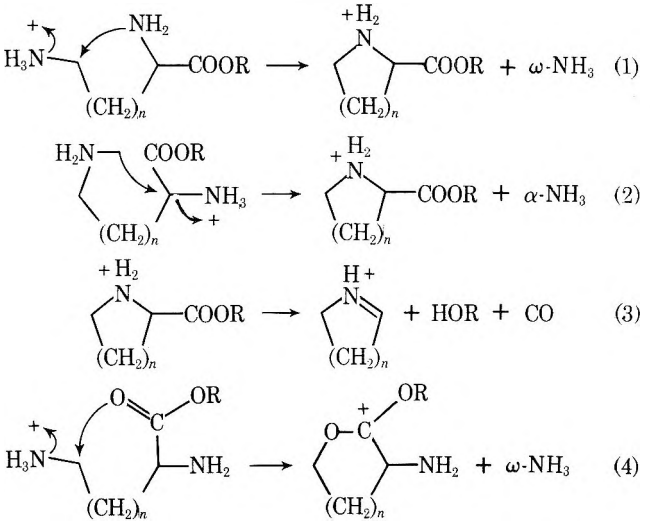


I VIII

hydrogen bonding which should be maximal in the gas phase for $n \geq 5$.[8,9]

Elimination of ammonia may also occur through an amine–amine interaction as in diamino alkanes (Table V). Loss of ammonia in compounds where $n = 3$ to 6 is faciliated relative to monofunctional amines and long-chain diamino alkanes.[5] There is apparently no favorable elimination mechanism for intramolecularly hydrogen bound diamines, diols, and dithiols[10] so that collision stabilization of these species results in stabilization of the protonated molecular ion. Facile loss of ammonia is observed in these diamino alkanes and ω-amino acids when the elimination rate is rapid relative to collision stabilization and/or competitive reactions.

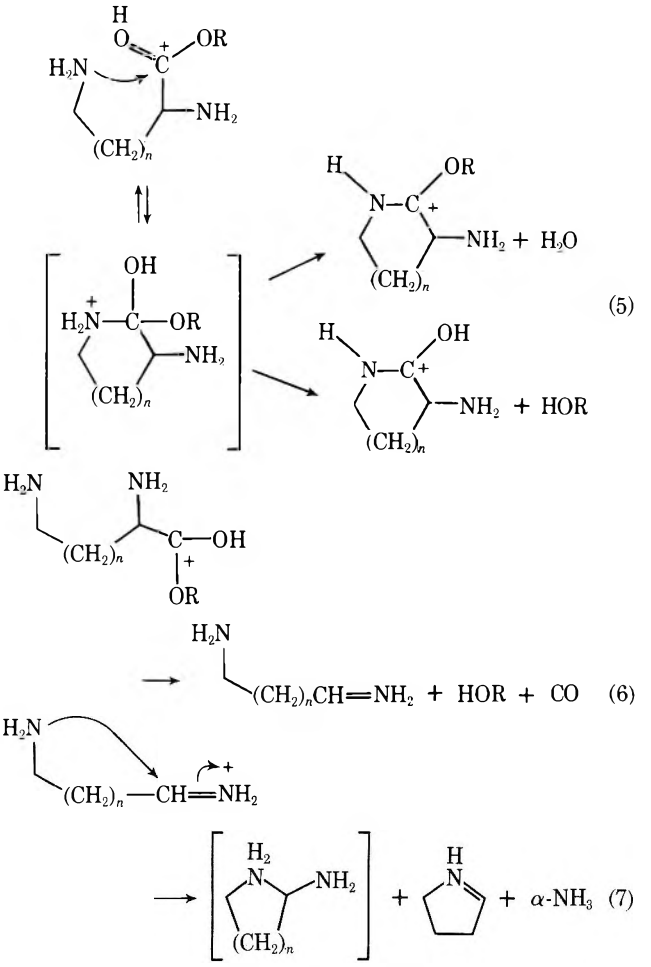
Elimination of ammonia from diamino acids may proceed by the same reaction pathways that occur in the diaminoalkanes and ω-amino acids, reactions 1, 2, and 4. Displacement



of the α-amino group, reaction 2, is reduced in the diamino acids by the influence of the carboxyl group adjacent to the α-amino function. The remaining initial diamino acid fragmentation reaction is decarboxylation, or rapid sequential loss of water and carbon monoxide, reaction 6. Alkyl carboxylic acids eliminate water (10–20% ΣI) with little subsequent loss of CO under methane CIMS conditions.[11] The presence of the α-amino function facilitates loss of CO from $(MH - H_2O)^+$ to give an iminium ion. Decarboxylation of simple amino acids, Table IV, is a facile process, $MH - H_2O,CO$ = 65–75% ΣI. The corresponding reaction of the diamino acids is less abundant, $MH - H_2O,CO$ < 25% ΣI, so that there is no reason to postulate participation of the ω-amino group in the decarboxylation reaction.[2] This reaction is a unifunctional process so that its occurrence should be independent of structural variation. Rapid competitive reactions of MH^+ would, however, decrease the relative abundance of the decarboxylation reaction.

The relative abundance of these initial reactions varies over a wide range in the 2,3- to 2,6-diamino acid series of Table I. These spectra do not directly reflect the prevalence of these reactions since some of the initial products may react further.

Secondary Reactions. Two of the initial diamino acid reaction products undergo subsequent fragmentation. The proposed reactions 1 and 2 lead to formation of a protonated cyclic amino acid. Protonated cyclic amino acids are found to



(5)

(6)

(7)

fragment through decarboxylation, reaction 3, where the extent of H_2O,CO loss is a function of ring size. Presumably strain and bond angle distortion of small rings destabilizes the cyclic iminium product ion of reaction 3, R = H.

Reaction 6 leads to the formation of an acylic iminium ion through an initial decarboxylation reaction. This same ion may be generated as $(M - H)^+$ from diamino alkanes, Table V. The homologous series of $NH_2(CH_2)_{n-1}CH{=}NH_2^+$ ions shows a pronounced loss of NH_3 for n = 4, 5, and 6. Higher homologues $n \geq 8$ and $n = 3$ show much less fragmentation.[5] These data, and the fact that there is no apparent driving force for elimination of ammonia from the acyclic iminium ion, suggest a cyclization step preceding loss of NH_3, as in reaction 7. Both reactions 3 and 7 yield the same cyclic iminium ion. The influence of ring size observed in the decarboxylation of protonated cyclic amino acids of reaction 3 would also operate to reduce elimination of ammonia through reaction 7 for the lower diamino acid homologues. The abundance of this $(MH - H_2O,CO,NH_3)^+$ ion is low (1 to 8% ΣI) for the 2,3- and 2,4-diamino acids, respectively.

Other initial diamino acid reactions, 4 and 5, yield either α-amino lactams, which do not fragment significantly under these conditions,[15] or α-amino lactones. By analogy to acyclic esters, these lactones should ring open on protonation, i.e., alcohol elimination, and then lose carbon monoxide. This product ion, $MH - NH_3,CO$, is not observed in any of the diamino acid spectra. Since $MH - NH_3$ is a minor ion for 2,5-diaminopentanoic acid, none of the lactone fragment ions are observed, and since this is the optimal steric arrangement for the competitive formation of the lactam, one must conclude that lactone formation is not an important process in the diamino acids. The absence of lactone formation in the diamino acids may also be due to competitive amine–amine interactions, which are possible in these compounds, reactions 1 and 2.

Table VII. Ion Abundance[a] for Initial Reaction Processes of Diamino Acids (Methane, 200 °C)

	$NH_2(CH_2)_{n-2}CH(NH_2)COOH$, n =			
	3	4	5	6
MH	30	1	1	32
$-H_2O$	1	63	50	4
$-NH_3$	31	5	38	57
$-H_2O,CO$	29	27	7	6

[a] Ion abundance calculated as percent of total MH related ions only.

The prevalence of initial reaction processes can be approximated by assigning secondary reaction products to their respective precursor ions. The significant secondary reactions follow initial loss of NH_3 and H_2O,CO from 2,5- and 2,6-diamino acids. Assignment of precursor ions for the latter compound may be made from the spectra of the α-^{15}N-labeled analogue. This spectra shows 13% of the initial NH_3 loss occurs from the α position, reaction 2, and 19% of the ammonia lost in formation of the $(MH - H_2O,CO,NH_3)^+$ ion is from the α position. This increase in the percent of α-NH_3 loss is due to the contribution of reaction 7 which involves elimination only from the α position. The maximum amount of initial decarboxylation from 2,6-diamino acid MH^+ is 9%, reaction 6. This should approximately be true for 2,5-diaminopentanoic acid if one assumes that reactions involving 5- and 6-membered cyclic products occur at a similar rate. Precursor ions may then be assigned as shown in Table VII.

Table VII shows MH^+ ion intensity to be 1% for $n = 4$ and 5 indicating very rapid initial reactions. This correlates with the high abundance of $MH - H_2O$, reaction 5, resulting in formation of 5- and 6-membered lactams. A high abundance of $MH - NH_3$ is observed for $n = 3$, 5, and 6 involving formation of 3-, 5-, and 6-membered cyclic amino acids by way of reaction 1. Decarboxylation is abundant only for $n = 3$ and 4 and is less prevalent than in simple α-amino acids. The factors which determine the abundance of $MH - H_2O,CO$ may be complex and relate to the rate of competitive processes and inductive effects in this case of 2,3-diaminopropionic acid.

Conclusion

Protonated diamino acids undergo a variety of reactions which may be correlated with bifunctional model compounds. Reactions are highly dependent on interfunctional separation and appear to involve neighboring group interactions. The diamino acids show a hierarchy of reactions with water loss more rapid than ammonia loss which is more rapid than decarboxylation. The prevalence of each cyclization reaction, as in solution, follows the order 5 > 6 > 3 > 7 for ring formation rates.

The gas phase reaction conditions give rise to a number of products, lactones and cyclic amino acids, which are not observed in solution. The most facile reaction, lactam formation, is common in solution for 2,5- and 2,6-diamino acids, however. Reaction products can be rationalized on the bases of product ion stability and neighboring group reaction rates and do not appear to correlate with preferred sites of protonation, proton affinity of functional groups, or the stability of intramolecular hydrogen bonds.

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Regiospecific Substituent Effects in 6-Substituted Purines As Measured by Proton Magnetic Resonance[1]

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The ^{1}H NMR spectra showed the H-2 signal at lower field than that of H-8 for purines **1–13**, but a crossover of the two proton peaks was observed for the 6-phenoxypurines **14–16**. Correlations of δ(H-2) and δ(H-8) with substituent constants σ_m, σ_p, σ_p^+ (calcd), F, and R were determined for **1–14**, and with Brown's σ_p^+ and Taft's σ_R^0 and σ_I for fewer compounds. For correlation with both δ(H-2) and δ(H-8), the σ_p set is the best, yielding correlation coefficients of 0.931 and 0.933, respectively. These δ(H)–σ correlations are impractical for predicting proton chemical shifts of 6-substituted purines. However, they are useful in sorting out the regiospecific effects and proportions of the field and resonance components of the 6-substituent, i.e., 65% resonance and 35% field for H-2, 44% resonance and 56% field for H-8, as derived from the polynomial equations 2 and 3, respectively. These observations are rationalized by considering contributions of the mesomeric structures a–e. Furthermore, because of the uniquely large resonance and field effects of the phenoxy group, the apparent crossover of H-2 and H-8 in **14–16** can be accounted for in the same manner using structures f and g.

Coburn et al.[2] reported the first linear correlation of the chemical shifts of the 8- and 2-hydrogen of eight 6-substituted purines plus purine itself with Brown's σ_p^+ and Taft's σ_R substituent constant, respectively. They also reported[3] similar relations for the ^{13}C chemical shifts of carbons 8 and 5 but not for the carbons at other positions for a variety of 6- and 2,6-substituted purines. In the course of our studies[4] of the electronic aspects and reactivities of purines and pyrimidines, we have examined the relationship between the proton chemical shifts (δ(H)) of 16 6-substituted purines and various sets of substituent constants (σ). We have found: (1) the δ(H)–σ correlations are impractical for predicting proton chemical shifts of 6-substituted purines; (2) the correlation coefficients (r) obtained are useful in sorting out the regiospecific effects and proportions of the field and resonance components of the 6-substituent; and (3) these effects are consistent with certain mesomeric contributions to the purine structure.

Results and Discussion

The chemical shifts of H-2 and H-8 of 16 purine compounds at 0.1–0.2 M in dimethyl sulfoxide are shown in Table I. The ^{1}H NMR peak assignments were made by virtue of partially 8-deuterated samples. The 6-phenoxypurines **14, 15,** and **16,** and trimethylpurin-6-yl ammonium chloride **13** were prepared by nucleophilic substitution of 50% 8-deuterated 6-chloropurine (**8**), whereas other 6-substituted purines were partially deuterated selectively at the 8-position upon heating in D_2O.[5] The relative order of H-8 at high field and H-2 at low field was obtained for purines **1–13,** but a crossover of the two proton peaks was shown by the phenoxypurines **14–16.**

Correlation of the proton chemical shifts with the substituent constants was accomplished by means of the regression equation

$$\delta(\mathrm{H}) = a + b\sigma \qquad (1)$$

The ^{1}H NMR chemical shift δ(H) reflects the electron density at that proton, whereas the substituent constant measures the ability of the 6-substituent to attract or repel electrons by virtue of its resonance and field effect. Since H-2 is meta to the 6-substituent and H-8 occupies the para-equivalent site, the five σ sets which are particularly meaningful in this correlation study are σ_m, σ_p, σ_p^+, F, and R. The σ_m and σ_p are the most venerable of the substituent constants and experimentally the two most complete and accurate sets of data available. The σ_p^+ values for all the substituents in this study are taken from the calculated σ_p^+ set derived by Swain and Lupton[6] based on 23 experimental data values. The first three σ sets have been analyzed by Swain et al.[6a] to contain % resonance of 22 ± 0%, 53 ± 0%, and 70 ± 0%, respectively. The F and R field and resonance constants proposed by the same group to gauge only the individual effects have 0 ± 0% and 100 ± 0% resonance. The δ(H-2) and δ(H-8) data of compounds **1–14** were fit into the above equation using a standard linear least-square routine with σ values of the five sets obtained from the Swain paper.[6] The corresponding σ constants for the p-methoxyphenoxy substituent in **15** and the p-nitrophenoxy in **16** are unknown; hence they are not included in the correlation. In addition, correlations for a smaller set of compounds were obtained with other popular substituent constants, e.g., the experimental σ_p^+ of Brown[7] (which lacks isopropoxy, methylsulfinyl, and methylsulfonyl), and Taft's[8] σ_R^0 and σ_I (both of which lack isopropoxy and trimethylammonium). The values for the parameters a and b for the five sets on a 14 compound base as well as those of the three smaller sets are given in Table II. Also shown are the correlation coefficients r for each of the constants. An r value close to unity implies that a high degree of correlation exists and that the proportions of field and resonance effects which constituted the given σ set are properly weighted. For correlation with both δ(H-2) and δ(H-8), the σ_p set is the best giving r values of 0.931 and 0.933, respectively. These parameters predict δ(H-2) 8.35 (obsd 8.20) and δ(H-8) 8.26 (obsd 8.17) for adenine, indicating the correct relative field position of H-2 and H-8, but do not predict the crossover in 6-phenoxypurine: δ(H-2) 8.56 (obsd 8.60) and δ(H-8) 8.34 (obsd 8.66). The calculated σ_p^+ correlates equally well with δ(H-2) but not with δ(H-8). Although Coburn et al.[2] obtained excellent correlation with r = 0.991 for δ(H-8) vs. σ_p^+, their study was done on nine purines (**1, 2, 3, 5, 6, 7, 8, 9, 11**), and the H-2, H-8 assignments were reversed for adenine (**2**) and 6-iodopurine (**5**).[9] After correcting for the latter, we have found that r is reduced slightly to 0.986 (or 0.984 with σ_p^+ calcd). However, inclusion of the trimethyl N^+ cation and the phenoxy group has led to r = 0.951 for the 11 purines, which further deteriorates to 0.897 for the entire 14 compound correlation. Thus, our present observation of r = 0.950 for σ_R^0 vs. δ(H-2) on the basis of 12 compounds should not be generalized in the absence of the isopropoxy and trimethylammonium derivatives.

From the five complete sets of correlation in Table II, it is apparent that the H-2 data correlate better than the H-8 data at >53% resonance and the reverse is true for <53% resonance. These trends are supported by the change in chemical shifts of the series of compounds in Table I relative to purine ($\Delta\delta$ = $\delta(\mathrm{H_{6\text{-substituted}}}) - \delta(\mathrm{H_{purine}})$). Thus, in **1** where the dimethylamino group has a large resonance effect (R = −0.848) but a

0022-3263/78/1943-2587$01.00/0

Table I. ^{1}H NMR Chemical Shifts of 6-Substituted Purines in Dimethyl Sulfoxide

Registry no.	Compd	6-Substituent	H-2	H-8
938-55-6	1	$-N(CH_3)_2$	8.19	8.07
73-24-5	2	$-NH_2$	8.20	8.17
1074-89-1	3	$-OCH_3$	8.57	8.40
66085-16-3	4	$-OCH(CH_3)_2$	8.62	8.49
2545-26-8	5	$-I$	8.63	8.60
50-66-8	6	$-SCH_3$	8.75	8.47
2004-03-7	7	$-CH_3$	8.80	8.55
87-42-3	8	$-Cl$	8.80	8.73
120-73-0	9	$-H$	9.00	8.67
19769-31-4	10	$-SOCH_3$	9.05	8.75
2036-13-7	11	$-CN$	9.12	8.93
19769-32-5	12	$-SO_2CH_3$	9.19	8.95
13020-83-2	13	$-{}^+N(CH_3)_3Cl^-$	9.28	9.03
66085-17-4	14	$-O-C_6H_5$	8.60	8.66
5546-38-8	15	$-O-C_6H_4-p-OCH_3$	8.56	8.61
66085-18-5	16	$-O-C_6H_4-p-NO_2$	8.67	8.71

negligible field effect ($F = 0.031$), the $\Delta\delta$(H-2) of -0.81 ppm is greater than the $\Delta\delta$(H-8) of -0.60 ppm. For the ammonium salt 13 where the substituent has a large field effect only ($R = 0, F = 1.46$), the $\Delta\delta$'s are +0.28 ppm for H-2 and +0.36 ppm for H-8. In order to estimate the maximum correlation of δ(H) with the most optimum weighting of the resonance and field effects of the 6-substituent, the r values (y) vs. % resonance contribution (x) to the five σ sets were examined in terms of $y = f(x)$. The equations for H-2 and H-8 are best defined by the polynomials derived from a computer least-square routine as shown in eq 2 and 3, and they are plotted in Figure 1.

$$\text{H-2: } y = 0.163x^3 - 0.841x^2 + 0.914x + 0.654 \quad (2)$$

$$y_{max} = 0.938 \text{ at } x = 65\%$$

$$\text{H-8: } y = 0.315x^3 - 1.020x^2 + 0.720x + 0.787 \quad (3)$$

$$y_{max} = 0.934 \text{ at } x = 44\%$$

The $y_{max} < 1$ at any x value suggests that the δ(H) vs. σ should not be expected to be completely linear. The σ constants provide a good account of the 6-substituent effect on the excess charge densities at H-2 and H-8 which constitute major contribution to chemical shift values. However, they do not assess the perturbation of the ring current and magnetic anisotropy in the 6-substituted compounds which also affect chemical shifts. To test this, 6-hydroxypurine (hypoxanthine, δ(H-2) 8.03, δ(H-8) 8.17) and 6-mercaptopurine (δ(H-2) 8.23, δ(H-8) 8.42) which exist in the 6-keto form were used to replace 6-methoxy- and 6-methylthiopurine in the σ_p correlation. The r value for δ(H-2) drops from 0.931 to 0.815 and that for δ(H-8) from 0.933 to 0.900, showing the sensitivity of the correlation coefficients to the 6-keto nonbenzenoid structure. Another uncertainty is the solvent effects on the intermolecular interactions of the purine compounds, e.g., base stacking and hydrogen bonding. The purine chemical shifts were determined in dimethyl sulfoxide for solubility reason but the σ constants are based in aqueous media. Within such limitation, eq 2 indicates that δ(H-2) correlates best with 65% resonance and 35% field contribution of the 6-substituent, whereas eq 3 suggests that δ(H-8) fits best with 44% resonance and 56% field. Thus, the conclusion arrived at earlier by Coburn et al.[2] that "the mechanism of transmission of substituent effects is purely resonance from the 6- to the 2-position in the pyrimidine ring and a combination of induction and enhanced resonance from the 6- to the 8-position, across both rings" is now modified.

These regiospecific substituent effects can be rationalized by mesomeric contributions as shown in Scheme I.

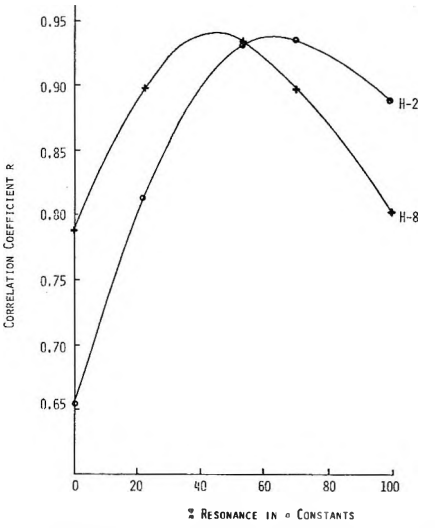


Figure 1. A plot of correlation coefficient r obtained from δ(H)–σ correlations vs. % resonance in σ constants for H-2 (O) and H-8 (+). The solid lines are generated from eq 2 and 3.

Although the 2-position, unlike the 8-position, is not in direct resonance with the 6-substituent, the larger resonance effect at the 2- than that at the 8-position implies that structures a and b contribute to the resonance hybrid to a greater extent than does c. This is reasonable since the negative charge is on nitrogen instead of carbon and since less charge separation is required in a and b vs. c. On the other hand, greater field effect is experienced at the more distant 8-position than at the closer 2-position by virtue of structure e. It has been found by Grant et al.[10] that this quinone type structure is the major contributing form to the resonance hybrid of 1-methylpurine and N-1 protonated purine. Its contribution places a positive charge on the imidazole ring and a negative charge on the pyrimidine ring, hence the increase in electron withdrawal from 8 relative to 2. The bond dipole effect as depicted in structure d accentuates electron withdrawal more at 2 than

Scheme I. Regiospecific 6-Substituent Effects

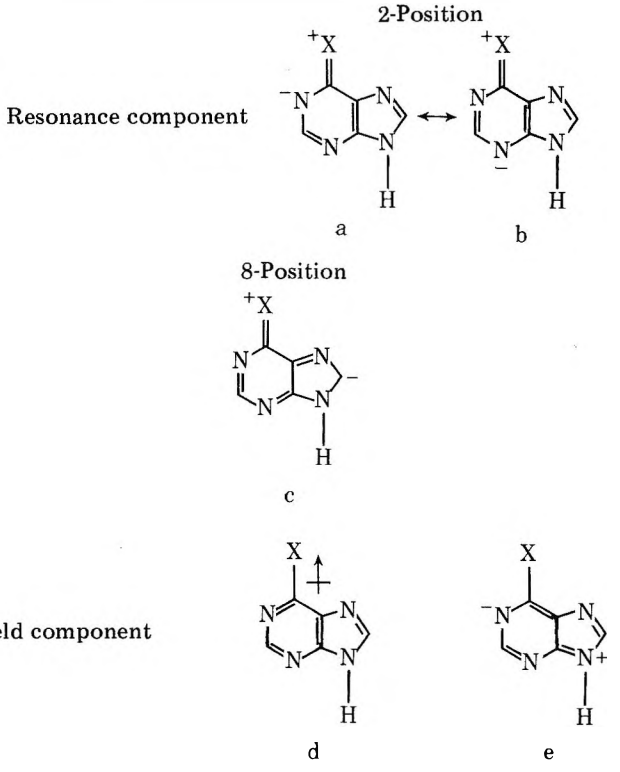
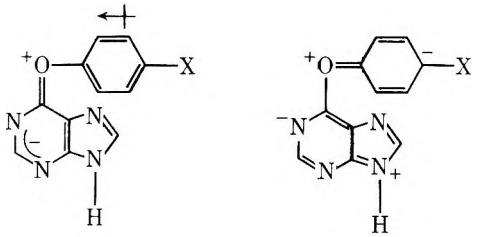


Table II. Linear Least-Square Parameters for Proton Chemical Shifts vs. Substituent Constants for 6-Substituted Purines 1–14

Compd	σ substituent constant	% resonance for σ	2-Hydrogen a	2-Hydrogen b	2-Hydrogen Correlation coefficient r	8-Hydrogen a	8-Hydrogen b	8-Hydrogen Correlation coefficient r
14 (1–14)	σ_m	22 ± 0	8.55	0.860	0.814	8.41	0.785	0.898
14 (1–14)	σ_p	53 ± 0	8.75	0.605	0.931	8.59	0.501	0.933
14 (1–14)	σ_p^+ (calcd)	70 ± 0	8.87	0.448	0.934	8.68	0.356	0.897
14 (1–14)	R	100 ± 0	8.99	0.829	0.890	8.77	0.618	0.803
14 (1–14)	F	0 ± 0	8.50	0.504	0.655	8.34	0.502	0.788
11 (except 4, 10, 12)	σ_p^+ (exptl)	66 ± 5	8.87	0.427	0.901	8.71	0.383	0.951
12 (except 4, 13)	σ_R^0	84 ± 10	9.00	1.371	0.950	8.78	1.051	0.882
12 (except 4, 13)	σ_I	0 ± 5	8.51	0.779	0.525	8.33	0.858	0.700

at 8 due to proximity, but its effect is not expected to be the dominant one compared to the charge effects of structure e.

Of the 6-substituted purines shown in Table I, only in the case of 6-phenoxypurines does H-2 resonate at higher field strength than H-8. Indeed, the phenoxy group is unique in having the largest resonance constant ($R = -0.740$) among the 42 substituents whose resonance effects are calculated by Swain et al.[6] It also has a very large field effect ($F = 0.747$), thus giving it the largest combination σ values ($F + R = 1.487$) of the 6-substituent groups in compounds **1–14.** These large resonance and field constants of the phenoxy substituent can be manifested on the basis of structures f and g. Thus, the



f g

electron-donating resonance effect as well as the electron-withdrawing field effect of the phenoxy oxygen are both facilitated by the phenyl ring acting as an electron donor and electron sink, respectively. The regiospecificity of these two component effects follows the same trend as above. The resonance effect, felt more strongly at H-2, tends to shift the H-2 peak to higher field relative to purine. The resonance effect felt at H-8 is weaker, hence a lesser displacement of H-8 to higher field. At the same time the large electron-withdrawing field effect, felt more strongly at the 8-position, shifts the H-8 peak to lower field. The smaller field effect at the 2-position shifts H-2 to lower field but to a lesser extent than H-8. The final result is a crossover of H-2 and H-8.

In the case of the para-substituted 6-phenoxypurines **15** and **16,** the H-2 peak also appears at higher field than that of H-8. These data are compatible with structures f and g. The *p*-methoxy group in **15** will increase the contribution of **f** at the expense of g. This will increase the electron donating resonance effect of the phenoxy group by stabilizing the oxygen cation in f. The increased resonance effect will be felt more strongly at H-2 than at H-8. This will, therefore, cause a greater upfield shift for H-2 than H-8. The electron withdrawing field effect is diminished relative to 6-phenoxypurine since g contributes to a lesser extent. Nevertheless, the diminished field effect will be felt at H-8 to a greater extent than H-2 and will cause a greater downfield shift of H-8. Again, H-8 occurs at lower field. With the *p*-nitro group present in **16,** the above argument, although reversed, leads to the same conclusion. A greater contribution of structure g relative to f is expected for **16** relative to 6-phenoxypurine (**14**). This will lower the electron donating resonance effect more at H-2 but raise the electron-withdrawing field effect more at H-8. The net effect is that H-2 is moved upfield to a lesser extent than that of **14,** while H-8 is moved downfield to a greater extent, thereby maintaining the original crossover in 6-phenoxypurine.

Experimental Section

The ^1H NMR spectra were obtained using a Varian A-60A spectrometer or a Perkin-Elmer R-12 spectrometer. NMR samples were prepared at 0.1–0.2 M solutions in dimethyl sulfoxide containing 1% sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Ultraviolet spectra were obtained with a Cary 14 spectrophotometer. The 6-substituted purines **1–13** as well as hypoxanthine and 6-mercaptopurine are known compounds, and most are available from Cyclo, Aldrich, and Sigma Chemical Co. The partially 8-deuterated samples of the above were prepared according to published procedures.[5] The preparations of the three 6-phenoxypurines **14, 15,** and **16** are shown below. Melting points are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Garden City, Mich.

6-Phenoxypurine (14), 6-*p*-Methoxyphenoxypurine (15), and 6-*p*-Nitrophenoxypurine (16). A phenol melt containing 200 mg of 6-chloropurine (**8**) (or 50% 8-deuterated) was stirred at 110 °C for 3.5 h. To the cooled mixture was added 25 mL of ether and 5 mL of water, and the pH of the aqueous layer was adjusted to 5. The resulting suspension was cooled, filtered, and the residue recrystallized from 2-propanol to yield 192 mg (70%) of 6-phenoxypurine (**14**): mp 217–218 °C; λ_{max} (EtOH) 254 nm (ε 17 000).

Anal. Calcd for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.50; H, 3.98; N, 26.56.

By using *p*-methoxyphenol in the above procedure, 6-*p*-methoxyphenoxypurine (**15**) was obtained: mp 201–202 °C, λ_{max} (EtOH) 257 nm (ε 11 300).

Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.42; H, 4.16; N, 23.21. Found: C, 59.22; H, 4.10; N, 23.13.

By using *p*-nitrophenol in the above procedure, 6-*p*-nitrophenoxypurine (**16**) was obtained: mp 206–207 °C dec; λ_{max} (EtOH) 271 nm (ε 15 000).

Anal. Calcd for $C_{11}H_7N_5O_3$: C, 51.36; H, 2.74; N, 27.23. Found: C, 51.09; H, 2.54; N, 27.48.

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Registry No.—Phenol, 108-95-2; *p*-methoxyphenol, 150-76-5; *p*-nitrophenol, 100-02-7.

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in Table I. Their respective values of −1.385, −0.848, and 0.031 are calculated from the known σ_m and σ_p using the coefficients in Table IV.

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(8) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).
(9) For unequivocal assignment of 2- and 8-proton signals in adenine and others, see J. R. Fox, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1965. The current work using 8-deuterated 6-chloro and 6-iodopurine established both of their ^{1}H NMR spectra to be H-2 at lower field than H-8. This is further corroborated by the ^{13}C NMR spectra of the 6-halopurines (ref 2).
(10) R. J. Pugmire, D. M/ Grant, L. B. Townsend, and R. K. Robins, *J. Am. Chem. Soc.*, **95**, 2791 (1973), and pertinent references cited.

Substituent and Medium Effects on Nitrogen-15 Shieldings of Compounds with >C=N Bonds (Imines, Oximes, and Phenylhydrazones)[1a]

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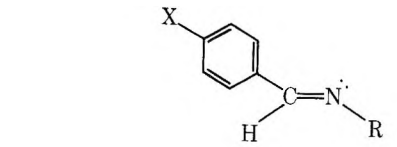
The ^{15}N chemical shifts of 13 *N*-(arylmethylidene)alkanamines, seven *N*-(arylmethylidene)azanols, five 1-(arylmethylidene)-2-phenyldiazanes, and 11 *N*-(arylmethylidene)arenamines have been determined at the natural-abundance level of ^{15}N in several solvents. The shifts of several of the *N*-(phenylmethylidene)alkanamines with different alkane groups have been analyzed in terms of α-, β-, and γ-methyl substituent effects. For those *N*-(arylmethylidene)azanes substituted at the para position, linear correlations with Hammett σ parameters having negative slopes are found for the ^{15}N chemical shifts. However, the ^{15}N shifts of *N*-(phenylmethylidene)arenamines (substituted at the para position of the arenamine moiety) are essentially insensitive to the nature of the substituent. The slopes of the Hammett correlations become more negative with increasing proton-donating power of the solvent for most series of compounds studied. In general, the ^{15}N shifts were found to be 5–12 ppm toward higher fields in methanol compared to chloroform, and except for the alkylidenazanols (oximes), about the same in dimethyl sulfoxide as in chloroform. In contrast, the alkylidenazanol resonances move 13–16 ppm downfield for the change from chloroform to dimethyl sulfoxide.

Systematic nitrogen nuclear magnetic resonance (NMR) studies, which were previously limited by inaccuracies of the ^{14}N NMR data and the expense and difficulties of using ^{15}N-enriched materials,[2] can now be carried out easily with ^{15}N isotope at the natural-abundance level and are expected to lead to a more complete understanding of the factors which contribute to the shieldings of nitrogen nuclei.

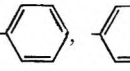
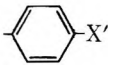
Previous studies of structural effects on ^{15}N shifts largely have been confined to systems containing sp^3-hybridized nitrogen atoms.[3-6] Both saturated systems in which inductive and steric effects should dominate and unsaturated systems containing aromatic groups capable of conjugative interaction have been investigated. Thus, the ^{15}N shifts in alkanamines have been found to change with alkyl substituents in much the same manner as ^{13}C shifts in structurally related compounds.[3] Such correlations further substantiate the belief that substituent-induced shielding changes result from external perturbations which are common to several nuclei.[7-9] Investigations of ^{15}N shifts of the amine nitrogens of substituted benzenamines[4-6] have revealed the importance of the inductive and resonance effects of the individual substituents. The basic assumption in all of these correlations is that substituents may be expected to alter the electron density at the nitrogen atom and the C–N bond order, thus causing changes in the paramagnetic part of the Ramsey shift equations.

We report here further evaluation of steric, electronic, and medium effects on ^{15}N chemical shifts for the specific case of imino nitrogens. The bonding in these types of nitrogen can be usefully regarded as involving a C–N σ and a C–N π bond with a lone electron pair on nitrogen which, to the first approximation, is not considered to be involved with the π-bonding orbitals.

In this work, we have chosen to study a number of arylmethylidenamines, azanols, and diazanes with the general structure **1**. These substances, in principle, will allow for conjugation of the unsaturated nitrogen with the *C*-aryl group



1

R = alkyl,  , -OH, -NH-  ,  -X′

through the C=N π bond and/or of the unshared pair on nitrogen with an *N*-aryl group. The importance of such conjugation was expected to be revealed by the variation of the nitrogen shieldings with the nature of the substituent group (X or X′) on the aryl groups from *p*-N(CH$_3$)$_2$ to *p*-NO$_2$.

Experimental Section

The natural-abundance ^{15}N spectra were recorded on a Bruker WH-180 spectrometer operating at 18.25 MHz in the Fourier-transform mode employing quadrature detection and complete noise–proton decoupling. Samples were run as 20 or 36 mol % solutions in chloroform, dimethyl sulfoxide, or methanol contained in 25-mm o.d. precision-ground sample tubes, with 17–22-mL sample volumes. Chemical shifts are reported in parts per million (ppm) upfield with respect to 1.0 M ^{15}N-enriched nitric acid in deuterium oxide contained in a 5-mm o.d. NMR tube. The deuterium oxide was used to produce the field lock signal. The optimum conditions for observation of the imino nitrogen signals of the compounds studied here were found to have a pulse width of 55 μs (70° pulse angle), a repetition rate of 30 s, and gated proton decoupling for which the decoupler was on only during acquisition of data (no NOE). Under these conditions, the sample remained at ambient probe temperature (25 °C), and typical spectra required 200 accumulations to provide an adequate signal-to-noise ratio. Gated proton decoupling during acquisition is preferable to no decoupling to ensure removal of any nitrogen–proton couplings which might broaden the signal and thus reduce the signal-to-noise ratio. For measurement of the shifts of the amino nitrogen signals in the phenyldiazanes, continuous proton decoupling was

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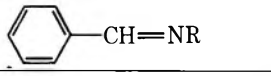
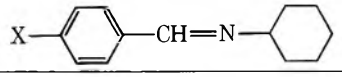
Table I. ^{15}N Chemical Shifts of *N*-(Phenylmethylidene)alkanamines[a]



R	Registry no.	Chemical shift
CH_3	622-29-7	55.9
CH_2CH_3	6852-54-6	40.6
$CH(CH_3)_2$	6852-56-8	28.5
$C(CH_3)_3$	6852-58-0	20.6
$CH_2CH_2CH_3$	6852-55-7	42.9
$CH_2CH(CH_3)_2$	6852-57-9	43.0
$CH_2C(CH_3)_3$	7731-35-3	43.1
$C(CH_3)_2CH_2CH_3$	65815-57-8	21.8

[a] All chemical shifts are given in ppm upfield of external 1.0 M $D^{15}NO_3$. Measured as 36 mol % solutions in chloroform.

Table II. ^{15}N Chemical Shifts of *N*-(Arylmethylidene)cyclohexanamines[a]



X	Registry no.	σ_P[b]	^{15}N chemical shift: Chloroform	Methanol
CH_3O	56644-00-9	−0.268	38.5	50.8
CH_3	65815-58-9	−0.170	33.9	45.0
H	2211-66-7	0.0	30.2	41.0
Cl	24431-14-9	+0.226	28.1	36.6
NO_2[c]	42974-61-8	+0.778	14.7	21.7

[a] All chemical shifts are given in ppm upfield from external $D^{15}NO_3$. Measured in 20 mol % solutions. [b] Taken from ref 41. [c] $\delta_{^{15}N}(NO_2)$ = 6.8 ppm ($CHCl_3$); 5.3 ppm (MeOH).

employed with a pulse width of 25 μs (40° pulse angle) and a 3-s repetition rate.

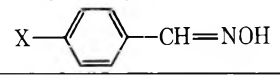
Substituted *N*-(arylmethylidene)arenamines were prepared from the appropriately substituted benzenamines and benzenecarbaldehydes according to the method of Law,[11] or of Roe and Montgomery.[12] Physical and spectral parameters were consistent with reported data.[11-14] The arylmethylidenazanols and diazanes were synthesized from 4-substituted benzenecarbaldehydes and purified by recrystallization from ethanol. Melting points were identical with reported values.[15] *N*-(Phenylmethylidene)alkanamines were prepared by heating the appropriate alkanamines at reflux for 30 min with an equimolar amount of benzenecarbaldehyde in benzene. The solvent was removed under reduced pressure and the crude product purified by distillation. Boiling points were in agreement with those reported.[15-18] *N*-Phenylmethylidenemethanamine was commercially available.

Results

The nuclear Overhauser effect (NOE) resulting from proton decoupling is extremely important in ^{13}C and ^{15}N NMR spectroscopy. The magnetogyric ratio is negative for the ^{15}N nucleus, and thus, when dipole–dipole interactions between the nitrogen and directly bonded protons dominate the relaxation mechanism, irradiation over the range of proton frequencies generally causes inversion of the ^{15}N resonances. A maximum NOE of −3.93[19a] is theoretically possible for the case of pure dipolar relaxation. For nitrogens having no directly bonded protons, dipole–dipole interactions may not dominate the relaxation mechanism, and, consequently, proton irradiation may lead to a decrease in signal intensity or even complete disappearance of the signal.[19b] We have found that, for compounds containing imino nitrogens, continuous proton–noise decoupling does not generally give useful natural-abundance ^{15}N signals.

The ^{15}N chemical shifts of *N*-(phenylmethylidene)alkanamines are given in Table I, and those of *N*-(arylmethylidene)cyclohexanamines in Table II.

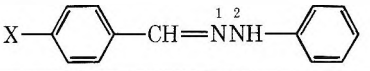
Table III. ^{15}N Chemical Shifts of *N*-(Arylmethylidene)azanols[a]



X	Registry no.	σ_p[b]	^{15}N chemical shift: Chloroform	Dimethyl sulfoxide
$N(CH_3)_2$	2929-84-2	−0.600	32.2	16.9
OCH_3	3235-04-9	−0.268	24.7	11.0
CH_3	3235-02-7	−0.170	23.1	7.0
H	932-90-1	0.0	20.1	4.5
F	459-23-4	+0.062	20.5	5.7
Cl	3848-36-0	+0.226	17.3	2.9
NO_2[c]	1129-37-9	+0.778	*d*	−7.6

[a] All chemical shifts are given in ppm upfield from external $D^{15}NO_3$. Measured in 20 mol % solutions. [b] Taken from ref 41. [c] $\delta_{^{15}N}(NO_2)$ = 6.5 ppm (Me_2SO). [d] Insufficiently soluble to obtain spectrum.

Table IV. ^{15}N Chemical Shifts in 1-(Arylmethylidene)-2-phenyldiazanes[a]



X	Registry no.	σ_p[b]	^{15}N chemical shift: N-1	N-2
CH_3O	622-73-1	−0.268	53.8	232.8
CH_3	2829-25-6	−0.170	50.2	231.7
H	588-64-7	0.0	47.8	230.8
Cl	2829-26-7	+0.226	46.6	229.9
NO_2[c]	2829-27-8	+0.778	37.2	224.1

[a] All chemical shifts are given in ppm upfield from external $D^{15}NO_3$. Measured as 20 mol % solution in dimethyl sulfoxide. [b] Taken from ref 41. [c] $\delta_{^{15}N}(NO_2)$ = 5.1 ppm.

Table III and IV give the shifts for para-substituted *N*-(arylmethylidene)azanols and 1-(arylmethylidene)-2-phenyldiazanes, respectively. Both resonance lines of the diazane derivatives were narrow, which indicate that quadrupole relaxation of the adjacent ^{14}N nucleus (I = 1) is rapid.[5] There is no ambiguity in the assignment of the two signals because of the large characteristic shift difference between imine- and amine-like nitrogens. For the nitrogen bonded directly to hydrogen (N-2), continuous proton irradiation gave a strong, inverted ^{15}N signal only after 50–100 transients.

The shifts for the nitro and imino nitrogens of the *p*-nitro derivatives in Tables III and IV are not very far apart, and the assignments were based on ^{14}N data reported for aromatic nitro compounds.[2d]

Chemical shifts for *N*-(arylmethylidene)arenamines in several different solvents are listed in Tables V and VI.

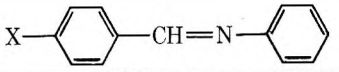
Discussion

Alkyl Substituent Effects. Theoretical considerations of nitrogen chemical shifts[20] have largely focused on the expression for the "paramagnetic" screening contribution which, for second-row elements, appears to dominate the total screening of these nuclei. Contributions from the diamagnetic term appear to be small by comparison.[21] In Pople's LCAO–MO treatment,[22] the paramagnetic term can be approximated by the equation

$$\sigma \frac{\text{para}}{A} = -\frac{e^2h^2}{2m^2c^2}\langle r^{-3}\rangle_{2p}\frac{1}{\Delta E_{av}}\sum_B Q_{AB} \qquad (1)$$

where ΔE_{av} is the average excitation energy for transitions

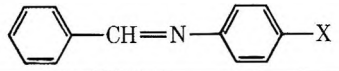
Table V. ^{15}N Chemical Shifts in *N*-(Arylmethylidene)benzenamines[a]



X	Registry no.	σ_p[b]	^{15}N chemical shift: Chloroform	Dimethyl sulfoxide	Methanol
$N(CH_3)_2$	889-37-2	−0.600	66.7[c]	*d*	*d*
OCH_3	836-41-9	−0.268	56.4	55.6	65.6
CH_3	2362-77-8	−0.170	51.9	50.6	*d*
H	538-51-2	0.0	47.9	47.5	53.5
F	5676-81-3	+0.062	49.3	48.8	*d*
Cl	2362-79-0	+0.226	46.6	46.0	51.9
NO_2[e]	785-80-8	+0.778	35.1	36.6	*d*

[a] All chemical shifts are given in ppm upfield from external $D^{15}NO_3$. Measured as 20 mol % solutions. [b] Taken from ref 41. [c] $\delta_{15N}(N(CH_3)_2)$ = 321.9 ppm. [d] Insufficiently soluble to observe signals. [e] $\delta_{15N}(NO_2)$ = 7.1 ($CHCl_3$); 5.7 (Me_2SO).

Table VI. ^{15}N Chemical Shifts in *N*-(Phenylmethylidene)arenamines[a]



X	Registry no.	σ_p[b]	^{15}N chemical shift: Chloroform	Dimethyl sulfoxide
OCH_3	783-08-4	−0.268	51.4	49.9
CH_3	2272-45-9	−0.170	49.0	48.0
H		0.0	47.9	47.5
Cl	780-21-2	+0.226	52.0	51.5
NO_2	785-81-9	+0.778	51.7	*c*

[a] All chemical shifts are given in ppm upfield from external $D^{15}NO_3$. Measured as 20 mol % solutions. [b] Taken from ref 41. [c] $\delta_{15N}(NO_2)$ = 4.4 ppm (Me_2SO); NO_2 signal not observed when chloroform was solvent.

involving σ or nonbonding electrons, $\langle r^{-3}\rangle_{2p}$ is the orbital expansion term, and Q_{AB} are matrix elements which reflect bond orders and charge densities for the LCAO molecular orbitals.

Although an approach focused on the relative importances of the various terms in the paramagnetic expression for screening constants may be theoretically useful to explain large differences in chemical shifts, empirical chemical-shift correlations within series of structurally related molecules are potentially more valuable for structure determinations. One empirical approach, which is especially simple, is correlation of ^{15}N and ^{13}C shifts, because the factors which influence ^{13}C shifts have been extensively investigated, and existence of a correlation implies that the same factors affect both.[3] To this end, the nitrogen shifts in Table I were plotted against the ^{13}C shifts reported for the corresponding carbons of *trans*-2-alkenes[23] (Figure 1). It would have been more appropriate to use the ^{13}C shifts of 1-phenyl-1-alkenes, but too few examples were available. Nonetheless, and despite the rather small number of points, an excellent correlation was observed having a slope of 1.96, an intercept of 300.8, and r = 0.998. This correlation implies that chemical-shift changes induced by the alkyl substituents result from perturbations which act in the same way for each nucleus and, as before,[3] the sensitivity of ^{15}N to these perturbations is about twice that of ^{13}C.

The ^{15}N chemical shifts of *N*-(phenylmethylidene)alkanamines fall between 20.6 and 55.9 ppm. Thus, there is approximately a 250-ppm shift to lower field associated with the structural change, $C_6H_5CH_2{}^*NHR$ to $C_6H_5CH{=}{}^*NR$,[5] and the corresponding change for analogous carbon compounds produces a ^{13}C shift change only about half as large. The very substantially greater downfield shift of ^{15}N over ^{13}C for this kind of structural change is best understood as arising from the ΔE_{av} term in eq 1. Mixing into the ground-state wave function in a magnetic field of an electronic configuration corresponding to a n → π^* transition of one of the nitrogen electrons is expected to lead to a paramagnetic circulation of electrons around the nitrogen and thus decrease the shielding of the nitrogen nucleus. Because there is no unshared pair on the β carbon of ethenylbenzenes, the ΔE_{av} term corresponding to this effect will not be important. In fact, when *N*-(arylmethylidene)alkanamines are protonated[24] and become isoelectronic with phenylethenes as the result of bond formation to the nitrogen unshared electron pair, there is a very large diamagnetic shift (~150 ppm) of the nitrogen resonances.

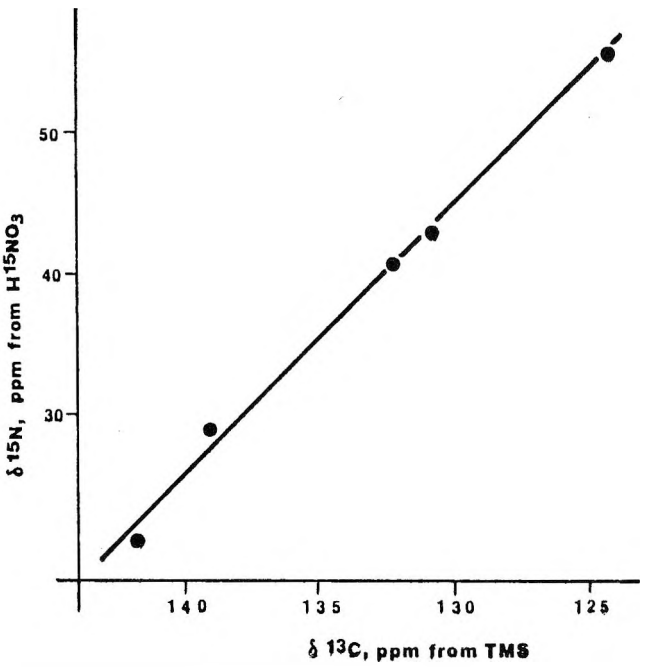


Figure 1. Correlation of the C-2 chemical shifts of *trans*-2-alkenes with the ^{15}N chemical shifts of *N*-(phenylmethylidene)alkanamines.

The α, β, and γ shifts found for *N*-(phenylmethylidene)-alkanamines closely parallel those previously found for primary amines. The α shift derived from the reported ^{14}N resonance position for *N*-(phenylmethylidene)amine[2d] is approximately −8 ppm, which can be compared with the reported α shifts for primary amines of −8.7[3a] and −7.8 ppm.[25] The α effects all produce downfield shifts which seem to increase with increasing substituent electronegativity: α_{CH_3} = −8.1, α_{NHPh} = −16.1, and α_{OH} = −43.9 ppm. These parallel in a remarkable way α effects in the ^{13}C spectroscopy of alkanes, where an α-methyl group generally causes a 9-ppm downfield shift, and a hydroxyl −40 to −50 ppm shifts.[9]

The β_N shift for the imines in Table I is similar to those found for other nitrogen-containing systems, although somewhat smaller than for primary amines. Thus, a single β-methyl group causes a 15.3-ppm downfield shift for the imino nitrogen resonance, with smaller β shifts of −12.1 and −7.9 ppm, respectively, for a second and a third β-methyl substituent. Introduction of methyl groups α to the unsaturated nitrogen atom may be accompanied by increases in steric interactions that could lead to upfield shifts which would oppose the fundamental downfield shift. As the steric bulk at the α carbon increases with additional methyl substituents, the β effect of that substituent decreases in absolute value.

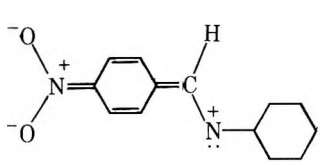
Although the directions of the β shifts parallel those observed in ^{13}C spectroscopy, the magnitude of β_N is more than

twice β_C (−6.0 ppm).[26] It has been suggested for ^{13}C that the β-alkyl substituent parameter arises partly by way of an inductive mechanism and partly through substituent-induced distortion of the α–β bond.[27] For the nitrogen atoms, a substituent-induced polarization of the lone-pair electrons might play an additional role.[3]

As for primary amines, the γ shift was found to be shielding for the imines studied. However, the size of the γ-shift influences is smaller than for amines and, in fact, introduction of a second and a third γ-methyl group has almost no effect. By analogy with alkenes and alkanes,[28] imines could well have rotational conformer populations different from those expected for saturated systems. Thus, interactions between a γ substituent and an imine nitrogen may be quite different from a γ-gauche interaction in a primary amine. Furthermore, the pattern of steric perturbations affects the shifts of unsaturated nitrogens in the same way as saturated nitrogens. Indeed, there are indications that steric interactions of methyl substituents with the nitrogen unshared pair of oximes lead to deshielding of the imino nitrogens.[29]

Electronic Substituent Effects. (a) *N*-(Arylmethylidene)cyclohexanamines. The range of chemical shifts for the 4-substituted *N*-(arylmethylidene)cyclohexanamines in chloroform is 23.8 ppm. The nitrogen shifts depend on the polar characteristics of the individual substituents located on the benzene ring; electron-withdrawing substituents cause downfield shifts, whereas electron-donating substituents cause upfield shifts. The range of ^{15}N shifts in the corresponding para-substituted benzenamines is nearly the same (25.5 ppm),[4] although this is best regarded as coincidence because the type of interaction between the aromatic π system and the nitrogen is rather different for the two series. A good linear correlation is obtained of the ^{15}N shifts of 4-substituted *N*-(arylmethylidene)cyclohexanamines in methanol and chloroform (Table II) with Hammett σ constants (Figure 2). A least-squares treatment gave a line of best fit with a slope of −21.3, an intercept of 31.5, and r = 0.989 for the chloroform values, and for methanol, −26.3, 42.0, and 0.993, respectively.

The substituent-induced shift changes are so large as to be due clearly to the paramagnetic term in the expression for the screening constant. Even if this is so, there are several ways that the shifts can be rationalized. For example, the paramagnetic term depends, in part, on total electron density about the nitrogen nucleus, so any conjugative interaction which might influence electronic distributions at the nitrogen should have an important influence on its chemical shift. Indeed, the downfield shift of benzenamine compared to that of ammonia, and the shifts of amides compared to amines, have been attributed to a decrease in shielding arising from lone-pair delocalization over the aromatic system in the former[30a] and into the carbonyl group in the latter.[30b] The observed downfield nitrogen shifts produced by 4-nitro group substituents might arise from an increase in the contribution of forms such as **2** to the ground state because of the conjugative electron-attracting power of the substituent. The imines are somewhat different from benzenamines and amides because their unshared pairs are in n orbitals essentially orthogonal to the π bonds. Nonetheless, contributions to the ground state of the imines of high-energy states corresponding to n → π^* (or other π^*) optical transitions could be expected to lead to a paramagnetic electron circulation around the nitrogen. Because the nitro group should decrease the energy of the higher state, it could, in consequence, also decrease the sheilding at the nitrogen, as is observed.



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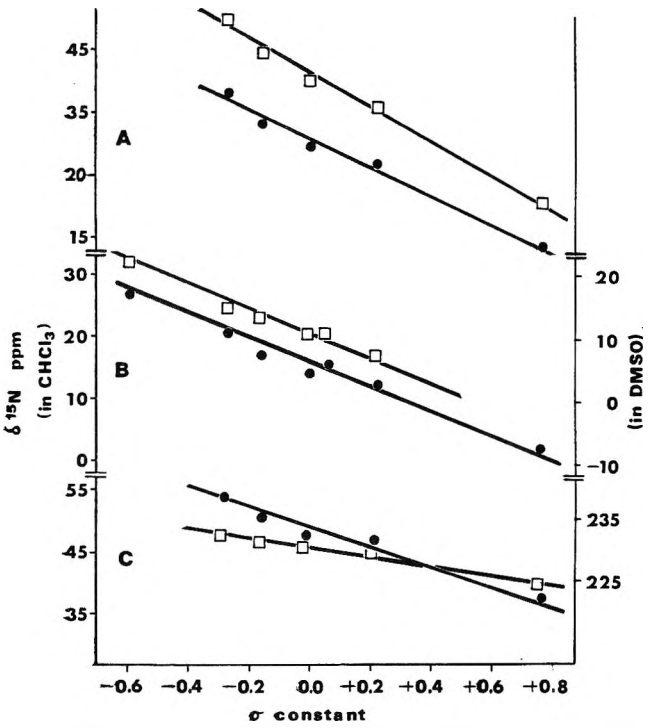


Figure 2. Correlation of ^{15}N chemical shifts with Hammett substituent constants: (A) para-substituted *N*-(arylmethylidene)cycloalkanamines in chloroform (●) and methanol, (□); (B) para-substituted *N*-(arylmethylidene)azanols in chloroform (□) and dimethyl sulfoxide (●); and (C) para-substituted 1-(arylmethylidene)-2-phenyldiazanes, where the scale for the N-1 shifts (●) is shown to the left of the graph, and for the N-2 values (□) to the right.

There is a complication with this interpretation, because we have found the ρ value for the Hammett correlation for *N*-(arylmethylidene)cyclohexanamine hydrotrifluoroacetates[24] to be nearly the same as the one for the unprotonated derivatives reported here. Clearly, if this similarity is as good as it seems to be, there can be no compelling reason to invoke significant shift effects produced by substituents in the 4 position of the phenyl ring as the result of changing the degree of mixing in states corresponding to n → π^* (or other) optical transitions involving π orbitals, because there is no unshared pair on the nitrogen in the protonated imines.

(b) *N*-(Arylmethylidene)azanols. Plots of the ^{15}N chemical shifts of several *N*-(arylmethylidene)azanols in chloroform and in dimethyl sulfoxide against Hammett σ constants are also shown in Figure 2. Least-squares analysis of the data for chloroform gave a slope of −17.7, intercept of 20.8, and r = 0.988. For dimethyl sulfoxide, the respective values were −17.3, 5.8, and 0.989. The analysis of the shifts of the *N*-(arylmethylidene)cyclohexanamines considered above also applies here.

However, additional insight can be gained from a plot of the nitrogen shieldings of the azanols in dimethyl sulfoxide (Table III) against the β-carbon shieldings of 4-substituted ethenylbenzenes.[10] The least-squares fit (Figure 3) has a slope of −2.3, an intercept of 271.0, and r = 0.985. This apparently linear ^{15}N–^{13}C shift correlation indicates that both nuclei respond similarly to polar substituents on the aromatic ring, although, as for the correlation of Figure 1, the ^{15}N shifts appear to be about twice as sensitive as ^{13}C shifts to substituent effects.

(c) 1-(Arylmethylidene)-2-phenyldiazanes. Unfortunately, because of poor solubility, it was not possible to record the spectra of the 1-(arylmethylidene)-2-phenyldiazanes

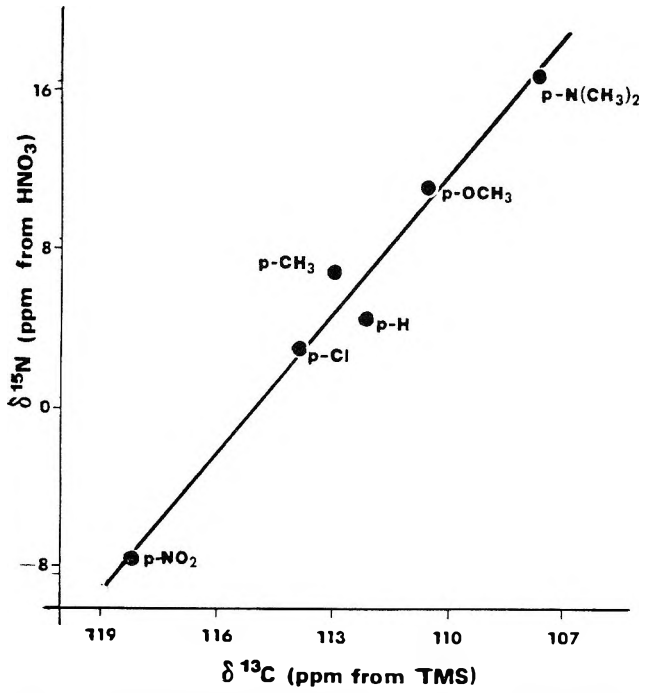
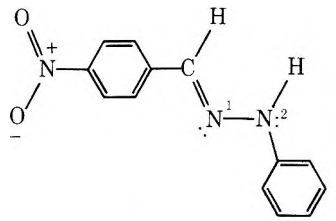
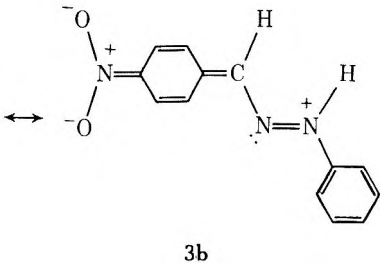


Figure 3. Correlation of β-alkenic carbon shieldings of para-substituted phenylethenes with ^{15}N shieldings of para-substituted *N*-(arylmethylidene)azanols.

(phenylhydrazones) in solvents other than dimethyl sulfoxide. A Hammett-type plot of the imino nitrogen shifts for the series of para-substituted derivatives is nonetheless shown in Figure 2. The line of best fit has a slope of −14.9, an intercept of 48.8, and a correlation coefficient of 0.984. The trends found for the ^{15}N shifts of oximes are evident in the data for the corresponding diazanes, and the imino nitrogen shifts of the diazanes are upfield by 25–30 ppm of the shifts in similarly substituted oximes. Interestingly, the N-2 chemical shifts are quite sensitive to para substituents on the benzene ring. The Hammett correlation of these shifts, also shown in Figure 2, has a slope of −8.0, intercept of 230.8, and r = 0.986. This pattern of sensitivity of N-2 shifts to substituent changes suggests that contributions of resonance structures, such as **3b,** with a 4-nitro group, are important to the N-2 chemical shifts. Contributions of forms such as **3b** also provide a qualitative explanation for the decreased sensitivity of the N-1 shifts of these diazanes to substituent changes compared to the other compounds studied here. This is because in the



3a



3b

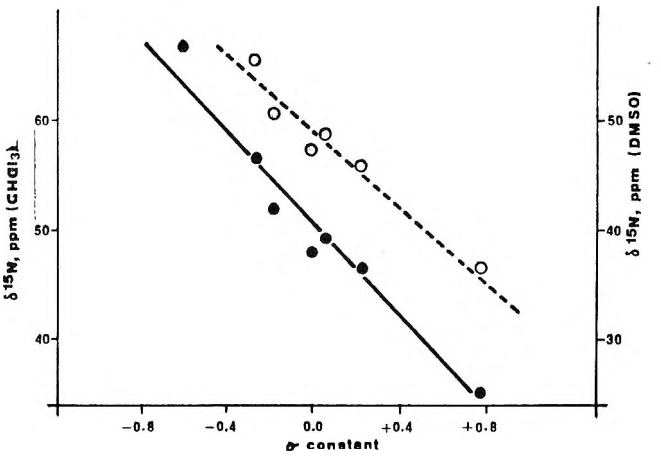
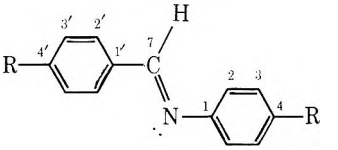


Figure 4. Correlation of ^{15}N chemical shifts of para-substituted *N*-(arylmethylidene)benzenamines with Hammett substituent constants. Separate ^{15}N shift scales are indicated for the two solvents, chloroform (●) and dimethyl sulfoxide (○), to the left and right of the figure, respectively. The methanol line is not shown because of the small number of points.

electron-pairing schemes **3a** and **3b,** N-2 has a greater difference of charge distribution and bonding than N-1.

The N-2 chemical shift of 1-(phenylmethylidene)-2-phenyldiazane is approximately 57 ppm downfield of the phenyl-substituted nitrogen shift of phenylhydrazine.[4] Part of this shift difference can be ascribed to the second-order paramagnetic effect brought about by the interaction of the nitrogen lone pair with the extended π system. Thus, there is a 14-ppm downfield shift in the nitrogen resonances associated with the change $C_6H_{11}\tilde{N}H_2 \rightarrow C_6H_5\tilde{N}H_2$, which can be attributed mainly to the interaction of the aromatic ring with the nitrogen unshared electrons. The other 40 ppm, or more, of the shift difference remains unexplained, especially because the corresponding shift change for a carbon attached to a double bond compared to a saturated carbon is only downfield by a few parts per million. Unlike diazanes whose conformations have been rather well studied,[31] little is known about the conformations about the =N—N< single bond of phenyldiazanes, and it is conceivable that stereoelectronic effects that depend on the disposition of adjacent lone-pair electrons in these systems would account for the additional shielding difference.

(d) *N*-(Arylmethylidene)arenamines. Early NMR studies[14] of various para-substituted *N*-(arylmethylidene)-benzenamines have shown that the H-7 proton chemical shifts correlate with Hammett σ constants for para substituents on the benzenecarbaldehyde moiety, but not for para substituents on the benzenamine, where, in fact, they have only a small



influence. This was reasonably attributed to lack of planarity of the benzenamine aromatic ring and CH=N bond in solution, as is indicated by x-ray data for the crystalline state.[32-34] However, Inamoto and co-workers[35] have demonstrated a Hammett correlation with ρ = −4.4 between the C-7 chemical shifts of the same derivatives and para substituents on the benzenamine ring. These researchers rationalized the apparently anomalous behavior of the H-7 chemical shifts as the result of substituent–field effects.[36]

The ^{15}N chemical shifts of seven para-substituted *N*-(arylmethylidene)benzenamines follow a Hammett relationship, as can be seen from Figure 4. The least-squares lines

have slopes of −16.5, −21.8, and −28.3, intercepts of 49.2, 50.6 and 56.6, and correlation coefficients of 0.976, 0.977, and 0.933 in dimethyl sulfoxide, chloroform, and methanol, respectively. The large negative ρ values have the same sign as the Hammett plots for the ^{13}C shifts of C-1, C-4, and C-7 for the same compounds.[35] The signs of the ρ values (except for that of C-7) accord with the earlier observation[35] that ρ values for each atom in a particular series of compounds appear to alternate in sign and decrease in magnitude as one progresses from the substituted atom along the conjugated framework. It is not possible to compare the absolute magnitudes of ρ for ^{15}N and ^{13}C nuclei because of the generally different sensitivities of the two nuclei to electronic effects.

The ^{15}N shifts of five para-substituted *N*-(phenylmethylidene)arenamines are generally small and do not appear to correlate with Hammett σ constants even though the scatter in the nitrogen shieldings is significantly larger than the experimental error of the measurements (see Table VI).

Similar behavior of the α-carbon shieldings of 4-substituted phenylethenes[10] suggests that the shielding of an α nucleus in an unsaturated group is insensitive to conjugation effects of substituents on the adjoining aryl ring. This could be because little difference in charge distribution and bonding at the α nucleus is expected as the result of electron delocalization in the π system. While the good correlation for the ^{13}C shifts of C-7 with changes in para substituents on the benzenamine ring indicates that there is a reasonable amount of conjugative interaction between the arenamine π system and the orbitals of the C=N bond, the ^{15}N results for these compounds suggest that there is little or no interaction of the aromatic ring with the nitrogen lone-pair electrons.

Solvent Effects. To this point, we largely have confined the discussion to the effects of various substituents within a particular series of structurally related molecules in a particular solvent. Substantial solvent effects have been observed for these compounds, but, unfortunately, limitations on solubility have prevented complete analysis of any of the series in more than two different solvents.

The ^{15}N chemical shifts of the *N*-(arylmethylidene)cyclohexanamines in methanol are 7.0–12.3 ppm upfield of the values for the same derivatives determined in chloroform. The corresponding shift differences for *N*-(arylmethylidene)-benzenamines are from 5.3 to 9.2 ppm. For comparison, the ^{14}N shift of pyridine moved 9-ppm upfield on dilution with methanol[37] and that of quinoline in methanol is 12.3-ppm upfield of its shift in chloroform.[38] The direction of the solvent shifts has general analogy in the ^{15}N shift changes produced on protonation of azine-type nitrogens.[38] This behavior suggests that hydrogen bonding is a major source of the shift changes found for strongly hydrogen-bonding solvents such as methanol. The smaller solvent effects observed for the *N*-phenyl series may be rationalized in terms of the inductive and electron-delocalizing influences of the phenyl group compared to cyclohexyl, thus limiting the extent of solvent interaction with the nitrogen unshared pair of electrons. There are only slight, downfield ^{15}N chemical shifts for these Schiff bases (see Tables V and VI) on changing solvent from chloroform to dimethyl sulfoxide despite the fact that hydrogen-bond association of chloroform with the carbonyl groups of amides is well established, as evidenced by ^{1}H as well as ^{15}N NMR spectroscopy.[38,39] However, chloroform is not really a strong hydrogen-bonding solvent and differences between methanol and dimethyl sulfoxide are not as large as with some other types of $=\ddot{N}-$ compounds.

Solvent effects for the azanol derivatives are at first sight remarkably different from those for Schiff bases. There are large downfield shifts in dimethyl sulfoxide compared to chloroform. The solvent shift $\Delta\delta_{^{15}N}(CHCl_3-Me_2SO)$ ranges from 13.7 to 16.1 ppm. Formation of hydrogen bonds between the oxygen of dimethyl sulfoxide and the oxime group would account for a large portion of the solvent shift. Previous concentration studies[28] on the ^{15}N shift of cyclohexanone oxime in benzene have established intermolecular association of oxime molecules in that solvent. However, in a strong hydrogen-bond acceptor solvent, such as dimethyl sulfoxide, solute–solute interactions should be minimized and hydrogen bonding to the nitrogen unshared pair should become much less important, thus causing the observed downfield shift.

The nitrogen chemical shifts for the compounds studied here are generally linear with the Hammett σ constants which measure the electronic properties of substituents on the aromatic ring. It is interesting that the absolute magnitude of the ρ constants of these correlations becomes larger as the hydrogen-bonding ability of the solvent increases. Thus, ρ for the correlation of the *N*-(arylmethylidene)benzenamines is −16.5 in dimethyl sulfoxide, −21.8 in chloroform, and −28.3 in methanol. This holds true for correlations of the *N*-(arylmethylidene)cyclohexanamine shifts, where ρ is −21.3 and −26.3 in chloroform and methanol, respectively. Clearly, in addition to electron density and π-bond order changes at the nitrogen atom, electronic perturbations brought about by the influence of ring substituents affect hydrogen-bond interactions which can influence nitrogen shifts as well. The Hammett correlations in dimethyl sulfoxide should be useful to estimate shift changes without complications from hyrogen-bonding effects. Although the chloroform–dimethyl sulfoxide chemical-shift differences are relatively small, the Hammett correlations in the two solvents do suggest association of the chloroform with the nitrogen unshared pairs. Indeed, if one supposes a linear relationship of hydrogen-bond energies with the ρ for the ^{15}N chemical-shift changes,[40] then the energy of the chloroform interaction is about 40% of that of methanol.

Although the observed shift differences for oxime derivatives in chloroform and dimethyl sulfoxide are quite large, the ρ values of the Hammett correlations in these solvents are nearly the same. This is not expected from the results with the other compounds, but the oxime shifts in chloroform are clearly complicated by self-association, and, in the absence of data for ρ, where this type of intermolecular hydrogen bonding is not important, it seems unwise to speculate on the reasons for the lack of ρ changes with these solvents.

Registry No.—Methylamine, 74-89-5; ethylamine, 75-04-7; isopropylamine, 75-31-0; *tert*-butylamine, 75-64-9; propylamine, 107-10-8; isobutylamine, 78-81-9; neopentylamine, 5813-64-9; 2-methyl-2-butylamine, 594-39-8; *p*-(dimethylamino)benzaldehyde, 100-10-7; *p*-anisaldehyde, 123-11-5; *p*-tolualdehyde, 104-87-0; benzaldehyde, 100-52-7; *p*-fluorobenzaldehyde, 459-57-4; *p*-chlorobenzaldehyde, 104-88-1; *p*-nitrobenzaldehyde, 555-16-8.

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Stabilities of Trivalent Carbon Species. 4. Electrochemical Reduction of Carbocations in Sulfuric Acid[1]

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The reduction of 11 stable carbocations in aqueous sulfuric acid was studied by rapid-scan triangular-wave cyclic voltammetry. For most cations, two one-electron waves are seen, corresponding to reduction to the radical followed by reduction to the hydrocarbon. The reduction potential of the first wave becomes more negative with increasing sulfuric acid concentration, but the second wave is independent of solvent composition. Differences between reduction potentials for different cations are constant in various solvents, implying similar solvation energies for the cations. The potential of the first reduction is used in an analysis of the ionization of alcohols. The analysis divides the ionization reaction into a bond dissociation and an electron-transfer reaction. The C–O bond dissociation energies increase in the order planar < triarylmethyl < cyclopropenyl alcohols. For planar or triarylmethyl alcohols, the free energy of ionization is independent of dissociation energy within each group and varies directly with the ionization potential of the corresponding free radical. Free energies of ionization of cyclopropenyl alcohols vary with both bond dissociation energies and radical ionization potentials. The second reduction potential measures the radical–anion energy difference and pK_a values of hydrocarbons may be estimated thereby.

The stabilities of very reactive trivalent carbon species, such as aliphatic anions,[4] antiaromatic[5,6] and antihomoaromatic,[7] ions and radicals, have been determined uniquely by electrochemical measurements. Breslow and his co-workers have measured reduction potentials of several carbocations using the techniques of rapid scan triangular wave cyclic voltammetry[5] and second harmonic alternating current voltammetry.[4,8] The reduction potentials for the conversions of cations to radicals ϵ_1 and radicals to anions ϵ_2 were used in a thermodynamic cycle to obtain pK_a values for hydrocarbons (e.g., cyclopropenes) whose corresponding anions are very unstable.

$$ROH \rightleftharpoons R^+ \rightleftharpoons R\cdot \rightleftharpoons R^- \rightleftharpoons RH$$

ΔG related to: pK_{R^+} ϵ_1 ϵ_2 pK_a

Two assumptions are implicit in this calculation: (1) the free energy change for conversion of carbinols to their corresponding hydrocarbons is constant for the series of compounds studied; (2) the medium effect which arises from measuring ionization equilibria and reduction potentials in different solvents is the same for all compounds studied.

We present results of a study of reductions of carbocations in aqueous sulfuric acid, the solvent used for the determination of pK_{R^+} values, which support the validity of the second assumption. Patterns of stabilities of trivalent carbon species of different structural types are also reported.

Aqueous sulfuric acid is a useful solvent for polarography,[9] and studies on the electrochemical behavior of a few carbocations in this medium have been reported previously.[6,7,10,11] In general, the choice of aqueous sulfuric acid as solvent pre-

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Table I. Reduction Peak Potentials,[-] ϵ, of Carbocations in H_2SO_4, 25 °C

Cation	Registry no.	V^a	0.09 M I	0.09 M II	3.0 M I	3.0 M II	6.0 M I	6.0 M II	10.2 M I	10.2 M II	13.8 M I	13.8 M II	17.0 M I	17.0 M II
1	13948-08-8	2							0.58	0.89	0.76	0.91		
		20							0.59	0.89	0.76	0.93		
		40							0.59	0.98	0.76	1.01		
		200							0.58	1.11	0.76	1.09		
2	14039-13-5	20	0.62	1.15	0.72	1.12	0.87	1.10	1.07[b]		1.12[b]			
		40	0.62	1.20	0.71	1.15	0.87	1.15	1.09[b]		1.16[b]			
		200	0.62	1.30	0.74	1.24	0.88	1.26	1.09	1.21	1.23[b]			
3[c]	25187-66-0	20					0.37	1.25	0.53		0.72		0.94	
		40					0.38	1.28	0.55		0.72		0.95	
		200					0.43	1.36	0.56		0.77		0.99	
4	20460-07-5	2			0.40	0.95	0.53		0.78	1.10				
		20			0.45	1.27	0.60		0.80	1.19	0.97			
		40			0.49		0.61	1.15	0.81	1.22	0.99			
		200			0.53		0.64	1.22	0.81	1.28	1.00			
5	25109-40-4	20			0.44	0.94	0.54	1.00	0.78	1.09				
		40			0.45	0.96	0.60	1.04	0.81	1.15	0.89	1.09		
		200			0.48	1.06	0.66	1.14	0.84	1.26	0.93	1.23		
6	26811-28-9	2	0.60		0.69		0.82							
		20	0.63		0.73		0.88		1.05		1.23			
		40	0.64		0.75		0.88		1.06		1.25			
		200	0.69		0.81		0.93		1.12		1.27			
7[c]	33011-97-1	20					0.31	1.18	0.44	1.18	0.62		0.87	
		40					0.32	1.21	0.46	1.22	0.64		0.88	
		200					0.42	1.28	0.50	1.27	0.69		0.92	
8	25109-39-1	20							0.67	1.00				
		40							0.69	1.09	0.84	1.04		
		200							0.71	1.20	0.89	1.14		
9	20685-21-6	2									0.19	0.40		
		20									0.18	0.48	0.37	0.54
		40									0.18	0.50	0.37	0.57
		200									0.19	0.58	0.37	0.64
10	25501-79-5	20			0.51		0.70		1.06					
		40			0.65		0.82		1.11					
		200			0.91		1.05		1.29					
11	12190-17-9	20	1.25		1.31		1.49							
		40	1.26		1.33		1.51							
		200	1.31		1.42		1.60							

[a] Sweep rate, in V/s; concentrations listed for H_2SO_4 in H_2O; I and II correspond to potentials of first and second wave, as described in text; potentials in V referenced to $Hg|Hg_2SO_4$–17 M H_2SO_4. [b] Two-electron wave. [c] Potentials listed for 6.0 M H_2SO_4 were measured in 6.8 M H_2SO_4.

sents three problems in the electrochemical study of carbocation reduction: (1) less stable cations cannot be generated in dilute acid; (2) in concentrated acid, solvent reduction may obscure reduction of the carbocation; and (3) reduction products (radicals, dimers, RH) are poorly solvated in H_2SO_4, adsorb on metal electrodes, and give rise to extraneous nonfaradaic adsorption and desorption peaks.

Fortunately, cations of low stability are reduced at more positive potentials than the solvent, even at high acid concentrations, and it is possible to obtain reduction potentials for cations which have a wide range of stability by adjusting the concentration of sulfuric acid. It is not always possible, therefore, to compare directly reduction potentials for different cations in the same solvent, but, as shown below, the solvent effect on the potential may be taken into account easily.

In general, a carbocation whose stability is sufficient to ensure its complete formation in sulfuric acid may be reduced at the mercury electrode in two steps, first to the radical and then to the hydrocarbon.[6]

$$ROH + H^+ \rightleftharpoons R^+ \overset{e}{\rightleftharpoons} R\cdot \xrightarrow{e,H^+} RH$$

In single-sweep rapid-scan cyclic voltammetry, for most ions two waves may be seen, corresponding to these processes. The first reduction is (almost) reversible with an anodic and cathodic peak; the second reduction is irreversible and shows only a cathodic peak. There is a medium effect on the potential of the first wave, which becomes more negative with increasing concentration of H_2SO_4, but the potential of the second wave is generally insensitive to the solvent composition. In some cases, at high acid concentrations, the first wave merges with the second to show a single two-electron reduction peak. A discussion of these medium effects will be presented separately.

We have examined the behavior of 11 carbocations whose stabilities vary over a range of almost 28 kcal/mol, based on pK_{R^+} values: triphenylmethyl (**1**), tri-*p*-anisylmethyl (**2**), xanthyl (**3**), 9-phenylxanthyl (**4**), 9-phenylthioxanthyl (**5**), tropylium (**6**), dibenzo[*a*,*d*]tropylium (**7**), 5-phenyldibenzo[*a*,*d*]tropylium (**8**), 9-phenylfluorenyl (**9**), sesquixanthydryl (**10**), and triphenylcyclopropenyl (**11**).

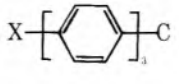
Results

The reduction peak potentials for the carbocations which were measured in 0.09–17.0 M H_2SO_4 are presented in Table I. None of the cations could be observed in the entire range of H_2SO_4 concentrations. The absence of data at low acid concentrations indicates that the cation is not formed; the absence of data at high acid concentrations indicates that the cation reduction is obscured by solvent reduction. The second wave is not seen at all for several cations of interest, such as tropylium **6** and triphenylcyclopropenyl **11**. The approach to elec-

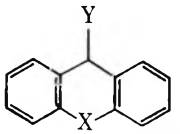
Table II. Solvent Effects on $\Delta\epsilon_1$[a]

Solvent	1	2	11
CH_3CN[b]	0.44, 0.46 (0.44)	−0.03	−0.60 (−0.56)
$(CH_3)_2SO$[b]	0.42	0.16	−0.62
H_2SO_4			
0.9 M		0.03	−0.61
3.0 M		0.07	−0.61
6.0 M		0.05	−0.67
10.2 M	0.54	0.04	
13.8 M	0.51	0.04	
70% ethanol, 2 N $HClO_4$		0.02	

[a] Difference in reduction potential for first wave between indicated cation and tropylium. [b] Taken from ref 5 and 8. Values in brackets from second harmonic AC voltammetry, all others from triangular wave cyclic voltammetry.

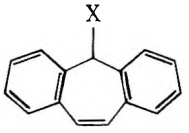


1, X = H
2, X = OCH_3

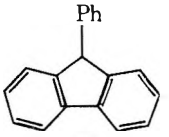


3, X = O; Y = H
4, X = O; Y = Ph
5, X = S; Y = Ph

6



7, X = H
8, X = Ph



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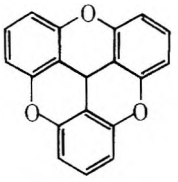

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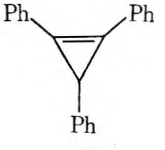

11

trochemical reversibility is denoted by a potential which remains constant as the sweep frequency is changed. The shift of potentials for the first peak to more negative values as the sweep frequency increases, which is displayed by several cations, arises from the rapid dimerization of the radicals near the electrode.[5] Reversible potentials are not obtained for cations which show this behavior. We have taken the peak potentials at the fastest sweep frequency, 200 V/s, to compare cations whose reductions may or may not be reversible. Breslow has shown that results obtained in this manner are in substantial agreement with true reversible potentials obtained by the second harmonic AC technique.[8] Detailed descriptions of the electrochemical behavior of each cation, including voltammograms and i–t curves, are given in ref 3.

Discussion

Solvation Effects. A comparison of the reduction potentials for the first wave in several solvents is presented in Table II. Potentials relative to tropylium as a standard are listed for triphenylmethyl **1**, tri-*p*-anisylmethyl **2**, and triphenylcyclopropenyl **11** cations. Satisfactory agreement is noted in all cases (except for **2** in Me_2SO), which confirms that the solvation energies are similar for the ions in question and the assumption made for the first reduction in Breslow's thermodynamic cycle is valid. The similarity in solvation energies of carbocations of reasonably similar structure has been noted recently in studies of gas phase and solution reactions of these species.[12,13]

The second wave arises from an irreversible reduction to form a hydrocarbon. However, the potential may be taken to measure, approximately, the free-energy difference between the radical and its corresponding anion.

$$R\cdot + e \rightleftharpoons R^-$$

For a related case Streitwieser and Schwager[14] found that reduction potentials of aromatic hydrocarbons in dimethylformamide correlate linearly with reduction potentials in 2-methoxyethanol, with unit slope,

$$R + e \rightleftharpoons R^-\cdot \text{ (DMF)}$$

$$R + e + H^+ \rightarrow RH\cdot \text{ (2-methoxyethanol)}$$

indicating that either potential measured the solution electron affinity of the hydrocarbon.

Of the various radicals which display the second wave, only the potential for 9-phenylfluorenyl **9** is significantly different from the others. We can compare the difference in potential for the second wave between triphenylmethyl **1** and **9** in 13.8 M H_2SO_4, 0.51 V, with the difference in oxidation potential of the corresponding anions in 1,2-dimethoxyethane, 0.45 V, reported by Breslow and Mazur.[15] The difference between the two values is within experimental uncertainty and suggests that the irreversible potentials which we measure may be used as the reversible radical–anion potentials and that the medium effect is negligible for anions as well as cations. Although the concept of solvation of carbanions in concentrated H_2SO_4 is amusing, the results suggest that Breslow's assumption is also valid for the last part of the cycle. The similarity of solvation of hydrocarbon anions was previously discussed by Ritchie and Uschold to explain the constancy of differences in pK_a values for hydrocarbons in different solvents.[16]

Stabilities of Trivalent Carbon Species. We have previously used the reduction potentials of carbocations in sulfuric acid to obtain information about the stabilities of free radicals and carbanions.[6] It is useful to consider heterolysis as the sum of two reactions, bond dissociation and electron transfer:

$$R\text{-}X \xrightarrow{D_{R\text{-}X}} R\cdot + X\cdot \xrightarrow{I_{R\cdot}-A_X} R^+ + X^-$$

$$E_i$$

For gas-phase reactions of several relatively simple R–X compounds, all the energies in the cycle (bond dissociation D, ionization potential I, electron affinity A, and heterolysis energy E_i) have been estimated.[17] However, if X is held constant, relative values of ionization potentials of radicals and bond dissociation energies may be obtained from measurements in solution for complex structures, such as **1**–**11**. Consider the following equilibria:

$$R\text{–}X + R_0^+ \rightleftharpoons R^+ + R_0\text{–}X \qquad \Delta G_i$$

$$R\text{–}X + R_0\cdot \rightleftharpoons R\cdot + R_0\text{–}X \qquad \Delta G_d$$

$$R\cdot + R_0^+ \rightleftharpoons R^+ + R_0\cdot \qquad \Delta G_{et}$$

$$\Delta G_i = \Delta G_d + \Delta G_{et}$$

Free energies of ionization, ΔG_i, may be derived from pK_{R^+} values,[18] where X is OH. Free energies for the electron-transfer reaction, ΔG_{et}, are obtained from reduction potentials, and free energies for the radical-exchange reaction, ΔG_d, are obtained by difference. Differences in reduction potentials between a given cation and **2** in the various solvent systems were calculated from Table I and from the literature,[19] and the mean value was used to obtain ΔG_{et}. We have used tri-*p*-anisylmethyl **2** as our standard R_0 because its reduction

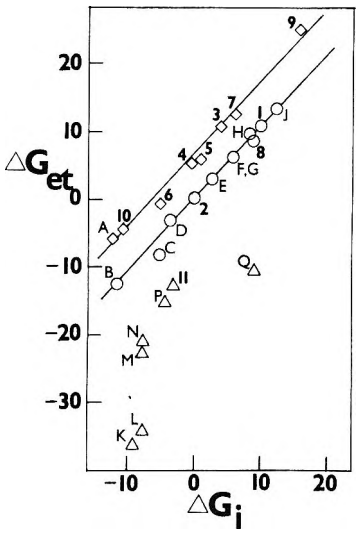

Figure 1. Comparison of ΔG_i and ΔG_{et}, kcal/mol: planar groups, ◇; triarylmethyl groups, ○; cyclopropenyl groups, △. Numbers for points correspond to structures in text. Additional points as follows: A, *N*-methylacridinium. Triphenylmethyl groups substituted in para positions: B, tris(dimethylamino); C, bis(dimethylamino); D, dimethylamino; E, dimethoxy; F, methoxy; G, trimethyl; H, methyl; J, trichloro. Trisubstituted cyclopropenyl groups: K, trimethyl; L, tri-*tert*-butyl; M, dipropylphenyl; N, tri-*p*-anisyl; P, diphenyl-*p*-anisyl; Q, unsubstituted.

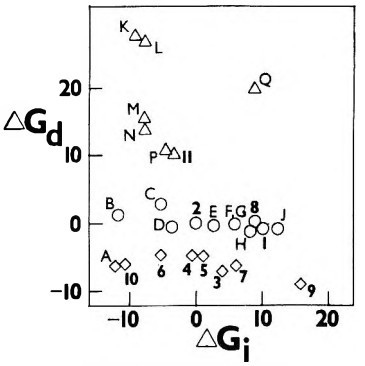

Figure 2. Comparison of ΔG_i and ΔG_d, kcal/mol. Points as listed in Figure 1.

potential has been measured in a wide range of solvents in several laboratories. In an equivalent treatment, Breslow used triphenylmethyl **1**.[8] It is difficult to estimate the probable errors, but a given ΔG_d or ΔG_{et} may be associated with an error of 1–2 kcal/mol or more in some cases.

The results of the calculations are presented graphically in Figure 1, where ΔG_{et} is compared with ΔG_i, and Figure 2, where ΔG_d is compared with ΔG_i. It can be seen that certain patterns emerge from the calculations. Triarylmethyl groups and groups with significant planar portions show linear relationships between ΔG_i and ΔG_{et} (slope 1.1),[20] but ΔG_i is independent of ΔG_d. Dissociation energies of alcohols with planar R groups are about 6 ± 2 kcal/mol less than triarylcarbinols, but within each group, dissociation energies are comparable. The differences in free energies of ionization within the planar or triarylmethyl series are entirely due to differences in ionization potentials of the corresponding radicals.[21]

From Figure 2 one could conclude that all triarylmethyl radicals are formed with equal ease from their corresponding carbinols. This contrasts with the extensive data on triarylmethyl radical stability based on measurements of the dissociation of "hexaarylethanes", which are now known to be erroneous.[22] However, the apparent equality of dissociation energies for triarylcarbinols may be due to the insensitivity of the dissociation energies of alcohols in general to alkyl group structure. For example, the bond dissociation energies of methyl, ethyl, isopropyl, and *tert*-butyl alcohols are 91.1, 90.9, 91.9, and 91.2 kcal/mol, respectively,[17] while the bond dissociation energies for C–H bonds in methane and isobutane differ by 12 kcal/mol. If ΔG_i were measured with other X groups, the conclusion about isoenergetic free radicals could be tested.[23]

The difference in dissociation energies, measured by ΔG_d, between triarylmethyl and planar compounds is noteworthy. The interpretation of the difference is open to discussion. If one assumes that the corresponding alcohols are isoenergetic, then one concludes that planar radicals are more stable than triarylmethyl radicals. On the other extreme, the radicals may be isoenergetic and triarylcarbinols are more stable than planar alcohols. The second argument appears to be refuted by experiments by Freedman and co-workers,[24] who examined equilibria between covalent derivatives of triphenylmethyl **1** and 9-phenylxanthyl **4**.

$$1 - X + 4 - Y \rightleftharpoons 1 - Y + 4 - X$$

Freedman found that the larger X or Y preferred to be bonded to **4** rather than **1** and concluded that relief of steric compression which occurs in ionization was more important for **1** than for **4**. This may be restated as triphenylcarbinol has a higher energy than 9-phenylxanthydrol, which is contrary to the conclusion derived from the isoenergetic radical hypothesis. A *minimum* value for the stabilization of planar radicals, relative to triarylmethyl radicals, is given by ΔG_d, since the corresponding alcohols are not, in fact, isoenergetic.

The dissection of ΔG_i into ΔG_d and ΔG_{et} is particularly instructive when comparing triarylmethyl systems with planar systems. The analysis indicates that both dissociation energies and electron-transfer energies are responsible for differences in free energies of ionization between the two systems. Two cogent examples may be cited. First, tropylium **6** and tri-*p*-anisylmethyl **2** cations differ in pK_{R^+} by 3.9 units, but their reduction potentials are nearly identical. This means that virtually all of the difference in free energy of ionization of these substrates can be accounted for by differences in bond dissociation energies.

The second example compares 9-phenylxanthyl **4** and tri-*p*-anisylmethyl **2**, cations which have about the same pK_{R^+} values. This occurs because of a balance between the two processes: bond dissociation energies ΔG_d favor **4** and electron-transfer energies ΔG_{et} favor **2**. These two examples illustrate the danger in rationalizing differences in pK_{R^+} values for cations of different gross structures. Occasional warnings[25] have been given previously, but the data provided here confirm the necessity for caution in the interpretation of pK_{R^+} values solely in terms of carbocation stability.

The behavior of 5-phenyldibenzo[*a*,d]tropylium (**8**) is, at first consideration, unexpected. The structural resemblance to tropylium **6** and dibenzo[*a*,*d*]tropylium **7** implies that this group should behave like planar systems, rather than triarylmethyl. However, Drieding models suggest that a boat-type seven-membered ring might be easily accommodated and would remove crowding between the phenyl ring and neighboring hydrogens in positions 4 and 6 in a planar seven-membered ring. If ion **8** is a triarylmethyl ion, its stability is easily understood; its pK_{R^+} of −5.7[26] shows that it is slightly more stable than triphenylmethyl cation (pK_{R^+} = −6.6).[18] On the other hand, ad hoc explanations must be offered to accommodate the reduction of stability of cation **8** compared to cation **7**, pK_{R^+} = −3.7,[26] because phenyl substitution stabilizes planar cations, e.g., xanthyl and fluorenyl.[27]

In contrast to the behavior of planar and triarylmethyl

species, cyclopropenyl systems are characterized by ΔG_{et} values which are large and negative and ΔG_d values which are large and positive, both of which may be accounted for by destabilized cyclopropenyl radicals. The limited data suggest different behavior for aryl- and alkyl-substituted cyclopropenyl systems. The apparent high C–O dissociation energies for cyclopropenyl alcohols and the destabilizing effect of alkyl groups on cyclopropenyl radicals has been discussed by Breslow.[8]

Other experiments indicate the difference in behavior of planar and cyclopropenyl systems, with respect to cation and radical stabilities, which parallel our results. Okamoto and co-workers[28] found that when the rate constants for reduction of cations to radicals by chromous ion (as log k) were compared with energies of charge-transfer absorption of complexes of the cations with pyrene, a single correlation fit data both for aryl-substituted tropylium and cyclopropenyl cations. However, a plot of log k vs. pK_{R^+} gives two nearly parallel lines, one for each type of cation. These results may be interpreted in terms of our data, where ΔG_i shows different correlations with ΔG_{et} for the two types of compounds.

The electrochemical behavior of the ions in sulfuric acid precludes using a similar analysis for anions as for radicals. The data may be used qualitatively, however, in a useful way. For example, the reduction of 9-phenylxanthyl 4 radical (a planar radical) to its anion requires about the same energy as the reduction of triphenylmethyl radical to its anion. Because the planar radical is more stable, its anion is consequently more stable than triphenylmethyl anion, or 9-phenylxanthene should be more acidic than triphenylmethane. This is in fact the case.[29] The increased acidity of 9-phenylfluorene relative to triphenylmethane is in part due to the planarity of the fluorenyl anion and in part to the special anion-stabilizing effect (aromaticity) of the cyclopentadienide system. The ionization of 9-phenylfluorene is 16.9 kcal/mol more favorable than triphenylmethane (Me_2SO solvent, ΔpK_a = 12.4 at 25 °C),[16] of which 10–12 kcal may be attributed to charging the radicals and 5–7 kcal to breaking the C–H bonds.

Experimental Section

Cyclic Voltammetry. A three-electrode, single-sweep polarographic system (SSP-2) manufactured by Chemtrix, Inc., of Beaverton, Oregon was used. This apparatus consists of an amplifier unit and a time-base unit built into a Tektronix 564 storage oscilloscope. The potential ranges are 0.5, 1.0, and 2.0 V and scan rates from 0.05 to 200 V/s can be obtained. This apparatus can be used for triangular-wave cyclic voltammetry (TWCV) with triggering to start the potential at a specific time after the beginning of the drop growth. In this study, a drop time of 3 s elapsed before the circuit was triggered. TWCV in the single- and multi-sweep modes were used.

This system can compensate for cell circuit resistance up to 1×10^7 Ω by providing feedback from a third cell electrode (counter). This counter electrode is a piece of platinum wire wrapped around the DME; the DME has a drop time of 7.96 s and a $m^{2/3} t^{1/6}$ value of 1.09 $mg^{2/3}\ s^{-1/2}$ in 3 M acid (open circuit). The reference electrode is a mercurous sulfate electrode containing 17 M sulfuric acid as an electrolyte. The electrode serves as a perfectly nonpolarizable electrode. A potential of 0.256 V vs. SCE was determined previously from the electrocapillary curve and by graphical elimination of the liquid junction potential between diluted and concentrated sulfuric acid.[9] A value of 0.246 V vs. SCE was obtained in this laboratory by determining the reduction potential of Cd^{2+} vs. both SCE and the mercurous sulfate electrode.

A jacketed H cell with the compartments separated by a stopcock and fritted disk was used. Because of IR compensation, the stopcock could be partially closed to prevent contamination of the reference electrode. The 17 M acid in the reference electrode compartment was changed for each compound studied. No appreciable change in the peak potentials of the compounds, remaining in the sample compartment for 40 min, was observed. A Teflon-covered stopper with two holes drilled through it for the electrodes and nitrogen tube covered the sample compartment. Deaeration was continued for 10 min and nitrogen was continuously passed over the solution during the recording of the voltammograms.

Materials. The compounds were dissolved in various concentrations of sulfuric acid to form the respective cations. Stock solutions (5 mM) of the cations were diluted to 0.191, 0.445, and 0.80 mM.

Cations **6** and **11** were used as fluoroborate salts. Tropylium fluoroborate was prepared according to Conrow.[30] Triphenylcyclopropenyl bromide was kindly provided by Professor M. A. Battiste. It was converted to the fluoroborate by reduction to triphenylcyclopropene followed by reaction with trityl fluoroborate. The other cations were generated from their corresponding alcohols, which were commercially available or prepared by standard methods. Sesquixanthydrol, precursor of cation **10**, was kindly provided by Professor J. C. Martin. The mp of all salts and alcohols agreed with literature values.

Registry No.—H_2SO_4, 7664-93-9.

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Reductions of α-Substituted Ketones by Lithium Diisopropylamide

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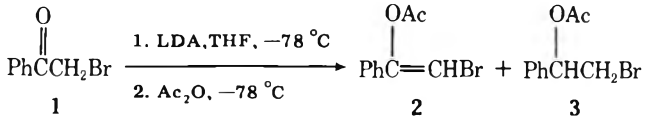
Certain enolizable α-halo- and α-methoxy-substituted ketones undergo rapid reaction with lithium diisopropylamide (LDA) to give reduction products via formal hydride transfer to the carbonyl in competition with enolization. The reducing agent has been verified as LDA by isolation of the oxidized form, the isopropylimine of acetone. This nitrogen analogue of the Meerwein–Ponndorf–Verley reduction gives stereochemistry analogous to that of borohydride or lithium aluminum hydride reductions. From a synthetic standpoint the reduction process can be circumvented in favor of enolization by use of lithium tetramethylpiperidide or lithium hexamethyldisilazide. Reaction of LDA with nonenolizable ketones also leads to reduction, but this process stops short of completion. This has been interpreted in terms of competing nucleophilic addition of LDA to the carbonyl to give an adduct which reverts to starting ketone upon addition of water. Addition of a "ketone scavenger" (methyllithium) to the reaction mixture prior to water quenching does not eliminate the starting ketone. These experiments support the intervention of a 1,2-ketone–LDA adduct.

Lithium diisopropylamide is widely used in synthesis as a hindered, nonnucleophilic base, effecting rapid, kinetically controlled enolization of ketones usually in high yield.[2] During attempts to prepare enolate anions from a variety of enolizable α-halo and α-methoxy ketones by treatment with lithium diisopropylamide (LDA) we have found that, surprisingly, many of these substrates undergo reduction of the carbonyl group in competition with expected enolization. These reactions, over within minutes in ether or tetrahydrofuran (THF) solvent at −78 °C, produce mixtures of reduction and enolization products in which for some ketones the former greatly predominates. Herein we describe the extent of such reduction for several types of ketones with varied α-substituents, the stereochemistry of the reduction, and the interactions of LDA with some nonenolizable ketones as well.

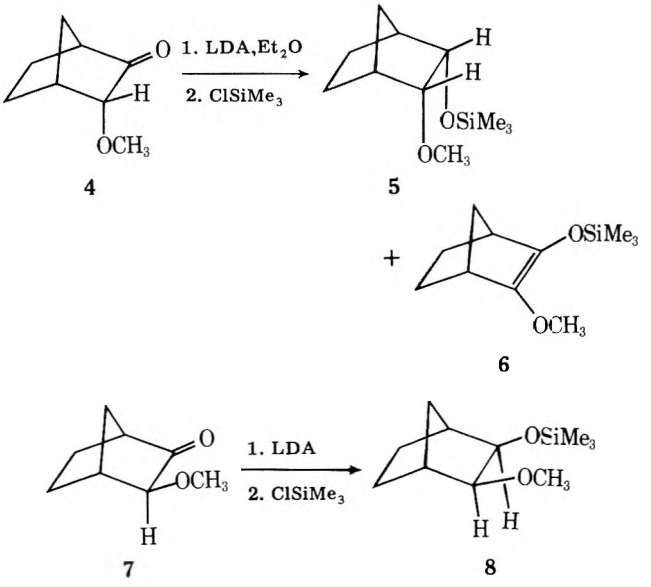
Results and Discussion

Reaction of α-Halo and α-Methoxy Ketones with LDA. We are aware of no reported cases in which LDA has caused reduction of an enolizable ketone;[3] thus we were extremely surprised on examination of the products from the −78 °C reaction of phenacyl bromide **1** with LDA, followed by acetic



anhydride. Obtained in 80% yield was a nearly 2:1 mixture of two products, the minor one of which consisted of the anticipated enol acetate **2** (a single isomer as indicated by the NMR spectrum, but with stereochemistry yet to be determined[4]). The major product proved to be bromo acetate **3**, as shown by spectral comparison with authentic material[5] prepared via acetylation of the sodium borohydride reduction product of **1**. Thus, in the reaction of phenacyl bromide with LDA, reduction of the carbonyl group occurs almost twice as rapidly as ketone enolization.

This type of reaction is not unique to phenacyl bromide. Reaction of LDA with *endo*-3-methoxybicyclo[2.2.1]heptan-2-one, **4**, followed by chlorotrimethylsilane, gave a 71% yield of a 5.6:1 mixture of **5** and **6**. The stereochemistry of **5** was assigned by NMR which showed characteristic coupling (4.3 Hz) of the exo carbinyl protons to the C-1 and C-4 protons. Again carbonyl reduction had occurred at a faster rate than enolization. Reaction of *exo*-3-methoxybicyclo[2.2.1]-heptan-2-one, **7**, under the same conditions gave *none* of the product derived from enolization. The sole product was the silated alcohol **8** in which reduction had occurred completely from the endo side of this norbornyl system.



These startling, unprecedented results prompted us to investigate the reaction of LDA with a number of other enolizable α-halo and α-alkoxy ketones. The results of these studies, summarized in Table I, are deserving of several comments. At least seven of the fourteen compounds studied (i.e., **1**, **4**, **7**, **12**, **16**, **34**, and **39**) produced more reduction[6] than enolization with LDA, while only three ketones (**25**, **32**, and **37**) produced no reduction whatsoever. Unfortunately, these compounds exhibit no clear trend which explains why some undergo reduction while others, along with the majority of ketones not bearing α-halo or α-alkoxy substituents, undergo only enolization. What is clear, however, is that for some types of ketones, reduction by LDA is faster than enolization (that LDA is actually the reducing agent has been shown and is discussed below).

Mechanistic and Stereochemical Aspects. The stereochemistry of the reduction products has been carefully determined for those cyclic ketones studied. In all cases the product hydroxyl group is cis to the α-heteroatom. In the cyclohexanone series this stereochemistry is not surprising, for these same cis products predominate in hydride reductions of the corresponding ketones.[7] Since hydride is delivered from the side opposite the heteroatom substituent, however, this implies that complexation of the reducing agent with this substituent is not a prerequisite for reduction. This mode of reduction is preferred even in the reaction of LDA with *exo*-3-methoxybicyclo[2.2.1]heptan-2-one, **7**, and exo-3-chlorobicyclo[2.2.1]heptan-2-one, **23**. Hydride is delivered to the

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Table I

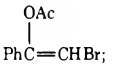
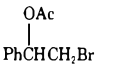
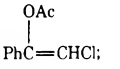
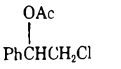
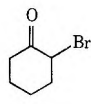
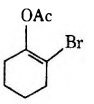
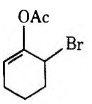
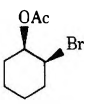
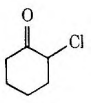
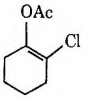
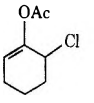
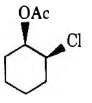
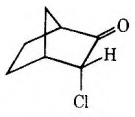
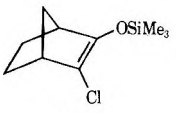
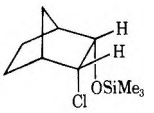
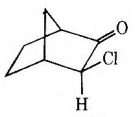
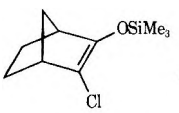
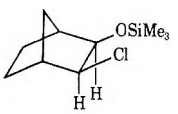
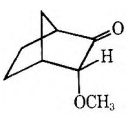
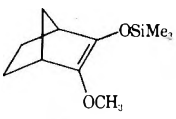
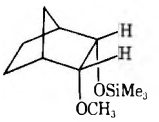
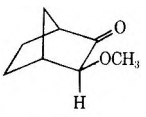
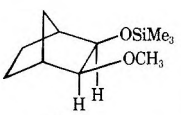
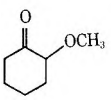
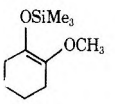
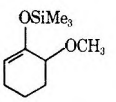
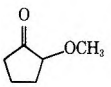
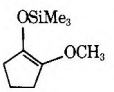
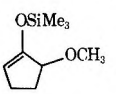
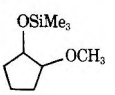
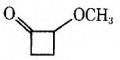
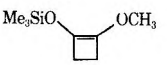
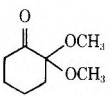
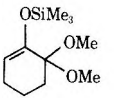
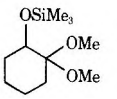
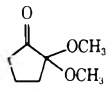
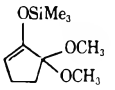
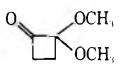
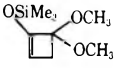
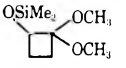
Compound[f]	Base[g]	(No. of equiv)	Solvent	Quenching reagent	Products[h]	Yield[a]	% Reduction[b]	% Enolization[c] toward X
 1	LDA	(1.05)	THF	Ac_2O	 2;  3	80%	63%	
	LHMDS[d]	(1.05)	THF	Ac_2O	2	(none)	81%	0%	
 9	LDA	(1.04)	THF	Ac_2O	 10;  11	72%	43%	
	LHMDS	(1.05)	THF	Ac_2O	10	(none)	83%	0%	
 12	LDA	(1.11)	THF	Ac_2O	 13;  14;  15	50%	53%	75%
	LHMDS	(1.05)	THF	Ac_2O	13	14	(none)	75%	0%	82%
 16	LDA	(1.04)	THF	Ac_2O	 17;  18;  19	58%	42%	73%
	LDA	(1.05)	Ether	Ac_2O	17	18	19	68%	72%	80%
	LHMDS	(1.05)	THF	Ac_2O	17	18	(none)	91%	0%	94%
 20	LDA	(2.2)	Ether	$ClSiMe_3$	 21;  22	90%	17%	
 23	LDA	(2.2)	Ether	$ClSiMe_3$	 21;  24	81%	6%	
	LiTMP[e]		Ether	$ClSiMe_3$	21	(none)	92%	0%	
 4	LDA	(1.3)	Ether	$ClSiMe_3$	 6;  5	77%	85%	
	LTMP	(1.5)	Ether	$ClSiMe_3$	6	(none)	82%	0%	
 7	LDA	(1.5)	Ether	$ClSiMe_3$	 8	79%	100%	
 25	LDA	(1.5)	Ether	$ClSiMe_3$	 26;  27	80%	0%	15%
 28	LDA	(1.5)	Ether	$ClSiMe_3$	 29;  30;  31	74%	~10%	30%
 32	LDA	(1.9)	Ether	$ClSiMe_3$	 33	20%	0%	100%
 34	LDA	(1.5)	Ether	$ClSiMe_3$	 35;  36	82%	80%	

Table I (*continued*)

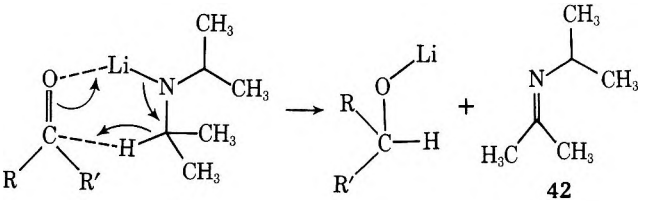
Compound[f]	Base[g]	(No. of equiv)	Solvent	Quenching reagent	Products[h]	Yield[a]	% Reduction[b]	% Enolization[c] toward X
 37	LDA	(2.3)	Ether	$ClSiMe_3$	 38	89%	0%	
 39	LDA	(1.5)	Ether	$ClSiMe_3$	 40  41	40%	72%	

[a] Total yield of purified reduction and enolization products. [b] Percent reduction product in mixture of reduction and enolization products. [c] Percent of enolization product which is enolized toward heteroatom α-substituent. [d] Lithium hexamethyldisilazide. [e] Lithium 2,2,6,6-tetramethylpiperidide. [f] Registry no.: **1**, 70-11-1; **9**, 532-27-4; **12**, 822-85-5; **16**, 822-87-7; **20**, 30860-22-1; **23**, 10464-71-8; **4**, 53329-05-8; **7**, 53329-06-9; **25**, 7429-44-9; **28**, 35394-09-3; **32**, 42083-01-2; **34**, 38461-13-1; **37**, 66057-04-3; **39**, 63703-48-0. [g] Registry no.: LDA, 4111-54-0; LHMDS, 4039-32-1; LiTMP, 38227-87-1. [h] Registry no.: **2**, 66057-05-4; **3**, 5837-69-4; **10**, 66057-06-5; **11**, 829-23-2; **13**, 56974-20-0; **14**, 23029-03-0; **15**, 50421-18-6; **17**, 31151-32-3; **18**, 66057-07-6; **19**, 36375-66-3; **21**, 66057-08-7; **22**, 66057-09-8; **24**, 66057-10-1; **6**, 66057-11-2; **5**, 66057-12-3; **8**, 66057-13-4; **26**, 66057-14-5; **27**, 66057-15-6; **29**, 66057-16-7; **30**, 66057-17-8; **31**, 66057-18-9; **33**, 66057-19-0; **35**, 66057-20-3; **36**, 66057-21-4; **38**, 66057-22-5; **40**, 66057-23-6; **41**, 55057-24-7.

endo side of the bicyclo[2.2.1]heptyl system despite the usually high propensity for exo attack in this system. The same stereochemistry is also seen in the sodium borohydride reduction of **23**.[8]

The LDA reductions also appear to be more stereoselective than mixed hydride reductions. Whereas borohydride reduction of 2-bromocyclohexanone[7a] and lithium aluminum hydride reduction of 2-chlorocyclohexanone[7b] give the cis halo alcohols as major products, appreciable amounts of the trans isomers are also produced. The LDA reactions give exclusively the cis halo alcohols (as acetates). Reaction with *exo*- and *endo*-3-chlorobicyclo[2.2.1]heptan-2-ones, **20** and **23**, also gives exclusively cis alcohols. Additionally we have found that sodium borohydride reduction of *exo*-3-methoxybicyclo[2.2.1]heptan-2-one, **7**, gives a mixture (2.8:1 ratio) of exo and endo alcohols with the exo alcohol predominating. In contrast, the reaction of LDA with **7** gives only the exo silated alcohol **8**. Reasons for the increased stereoselectivity in the reduction of ketones with LDA may lie in the low temperature of the reaction (−78 °C) as well as the steric bulk of the reducing agent.

Considering possible reactions which could account for LDA reductions, one which seems most plausible is a nitrogen analogue of the Meerwein–Ponndorf–Verley reduction, as indicated below. The driving force for such a reaction is the



42

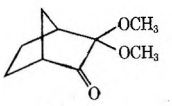
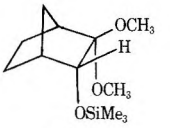
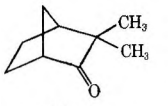
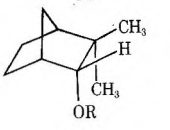
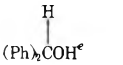
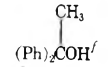
transfer of negative charge from nitrogen to oxygen, and indeed there is precedent for reduction via such a pathway in the reaction of benzophenone with lithium *N*-benzylanilide.[9]

One consequence of this proposed reduction mechanism would be the formation of the oxidized amide reducing agent, that is the isopropylimine of acetone (**42**). In the reaction of phenacyl chloride, **9**, with LDA in THF, a new low boiling compound was indeed formed in large amounts as indicated by gas chromatographic analysis. Separation of a small sample of this material from solvent and residual diisopropylamine by preparative gas chromatography allowed its spectral (NMR) comparison with an authentic sample of **42** prepared via routine methods;[10] the compounds are the same. Diisopropylamine is clearly oxidized in this reaction, strongly suggesting that it serves as the reducing agent for the phenacyl chloride and other ketones.

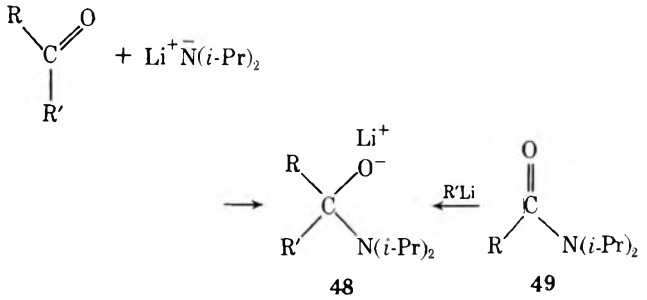
If such a reaction is responsible for the reductions reported in Table I, then amide bases which do not bear hydrogen atoms on the atoms attached to nitrogen should not effect reduction. Indeed, the use of lithium hexamethyldisilazide or lithium 2,2,6,6-tetramethylpiperidide with several compounds which reduce extensively with LDA (**1**, **4**, **9**, **12**, **16**, and **23**) effects no reduction whatsoever. These bases offer a useful alternative to LDA in obtaining enolized product in high yield from "reduction prone" ketones. It is interesting to compare the positions of enolization for several of the ketone structures. Both α-bromo- and α-chlorocyclohexanone enolize largely toward the halogen atom, as expected from the known acidifying effect of these groups.[11] With 2-methoxycyclohexanone, **25**, however, the situation is reversed. Enolization away from the methoxy group heavily predominates (perhaps also to be expected[12]). The trend of increased enolization toward methoxy in **25**, **28**, and **32** is also worth noting. In this case, however, the reasons for the trend are not well understood.

Reaction of LDA with Nonenolizable Ketones. The final phase of this study involved the reaction of LDA with several nonenolizable ketones shown in Table II. Since the enolization pathway is ruled out for all these compounds, it might be expected that reduction would occur as the sole reaction. Indeed, the only products from ketones **43**, **45**, and **47** (runs a, d) are reduction and starting ketone. Oddly enough in no case did reduction reach completion, even with excess LDA. This result can be rationalized in cases when less than 2 equiv of LDA was employed. The by-product imine (**42**) from reductions may well be attacked by LDA itself in a proton abstraction reaction, thus quenching the active amide reducing agent. Such processes have been observed by Wittig in reactions of lithium diethylamide and benzophenone.[9a] With more than 2 equiv of LDA, however, starting material is still recovered, even if the reaction is refluxed for a long period (run **46b**).[9b] This suggests the possibility that perhaps another reaction is competing with reduction, this being 1,2 addition of LDA to the carbonyl. The resulting intermediate **48** is indeed expected to have some stability in aprotic ether or THF solvent, as this is the same intermediate stage at which reaction stops during ketone synthesis from alkyllithium reagents and dialkylamides (e.g. **49** → **48**).[13] Aqueous workup cleaves **48** to produce ketone, which in our case would be starting material.

Table II

Compound[a]	Equiv of LDA	Solvent	Temp, °C	Scavenger	Quenching reagent	Total yield	Products and ratio		
 43	1.5	Ether	−78 to +25	—	$ClSiMe_3$	73%	 44[b] 86	+	St. mat'l. 14
 45							 46		
Run: (a)	1.5	Ether	−78 to +35	—	$ClSiMe_3$	51%	85 (R = $SiMe_3$)[c]		15
(b)	2.2	Ether	−78 to +35	—	H_2O	45%	90 (R = H)[d]		10
Benzophenone (47)							 [e]	St. mat'l.	 [f]
Run: (a)	1.1	THF	−78	—	H_2O	89%	1.2	1	0
(b)	1.1	THF	−78	CH_3Li	H_2O	90%	5	1	4
(c)	0	THF	−78	CH_3Li	H_2O	100%	0	0	100
(d)	4.7	THF	−78	—	H_2O	91%	4.7	1	0
(e)	3.1	THF	−78	CH_3Li	H_2O	61%	5.4	1	0
(f)	3.1	Ether	−78	CH_3Li	H_2O	90%	5.4	1	2.5

[a] Registry no.: **43**, 35611-45-1; **45**, 13211-15-9; benzophenone, 119-61-9. [b] Registry no.: 66057-25-8. [c] Registry no.: 66057-26-9. [d] Registry no.: 640-54-0. [e] Registry no.: 91-01-0. [f] Registry no.: 599-67-7.



48 **49**

To determine whether the recovered starting material from the LDA reductions is present in the reaction mixture as free ketone, or possibly as some nonreactive species such as **48**, a ketone scavenger (methyllithium) was added in excess to the reaction mixture just before workup. Methyllithium certainly reacts rapidly and completely with benzophenone under the reaction conditions (**47c**), and yet ketone was still recovered from all reactions in which methyllithium was added prior to workup (**47b,e,f**). Some species forms in these reactions which is resistant to attack by methyllithium, and yet which regenerates benzophenone on workup. We feel the most reasonable formulation for such a species is adduct **48**.

It can be seen that with 3 equiv of LDA in THF (**47e**), reaction of the ketone was complete (no methyllithium adduct was formed), the ratio of reduction to "regenerated ketone" being about 5:1. When only 1.2 equiv of LDA was used (**47b**), free ketone was indeed present prior to workup and reacted with methyllithium (~40%), but the ratio of reduction to regenerated ketone was still ~5:1. This is the same ratio of reduction to starting material one sees with a large excess of LDA alone (**47d**), and suggests that if adduct **48** is formed, the rate of reduction of benzophenone by LDA is about five times the rate of addition under these conditions.

Conclusions. Our results show that lithium diisopropylamide effects facile reduction of ketones (within minutes at −78 °C), and that this reaction is in many cases competitive with enolization for α-halo and α-alkoxy ketones. It also appears likely that 1,2-addition of LDA to ketones occurs as well, this reaction for benzophenone being only slightly slower than the reduction reaction. In those cases where reduction occurs as an undesired side reaction of ketone enolization by LDA, the problem can be avoided by using lithium tetramethylpiperidide or lithium hexamethyldisilazide as base.

Experimental Section

NMR spectra were recorded on a Varian A-60 A or Varian XL-100 in the Fourier transform mode and are reported in δ (parts per million) relative to tetramethylsilane. Mass spectra were recorded on an AEI Scientific Apparatus MS 902 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. Dry tetrahydrofuran was distilled from lithium aluminum hydride just before use.

Reactions of α-Halo Ketones with Lithium Hexamethyldisilazide. General Procedure. Lithium hexamethyldisilazide was prepared by adding 1.05 equiv of 2.5 M *n*-butyllithium in hexane to a stirred −78 °C solution of 1.1 equiv of hexamethyldisilazane in 4 mL of dry tetrahydrofuran. To this stirred −78 °C solution was added over a 3-min period a solution of 1.0 equiv (usually 2.0 mmol) of the α-halo ketone in 3 mL of dry tetrahydrofuran. After 11 min, 3 equiv of acetic anhydride was added all at once, and after 30 min longer the cold solution was diluted with 80 mL of ether. This mixture was washed with 25 mL of water, three 25-mL portions of 10% hydrochloric acid, and 25 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the crude material was further treated as described below to obtain the following products.

2-Bromo-1-phenylethenyl Acetate (2). The product from 1 mmol of phenacyl bromide was chromatographed on a 20 × 20 cm silica gel thick layer plate, developed with a 2:1 mixture (by volume) of hexane and methylene chloride. Elution of that UV active band having R_f 0.27 afforded 196 mg (81%) of **2** as a pale yellow liquid: IR (film) 1775, 1630 cm^{-1}; NMR ($CDCl_3$) δ 7.42 (5 H, s), 6.57 (1 H, s), 2.31 (3 H, s); mass spectroscopic molecular weight 241.9790 (calcd for $C_{10}H_9O_2Br$, 241.9767).

2-Chloro-1-phenylethenyl Acetate (10). The product from 1.7 mmol of phenacyl chloride was chromatographed on a 15-g silica gel column. Elution with 5% ethyl acetate in hexane afforded 272 mg (84%) of **10** as a colorless oil: IR (film) 1775, 1630 cm^{-1}; NMR ($CDCl_3$)

δ 7.44 (5 H, s), 6.50 (1 H, s), 2.32 (3 H, s); mass spectroscopic molecular weight 196.0322 (calcd for $C_{10}H_9O_2Cl$, 196.0281).

2-Bromocyclohex-1-enyl Acetate (13) and 6-Bromocyclohex-1-enyl Acetate (14). Gas chromatographic analysis of the crude product obtained from 2.0 mmol of 2-bromocyclohexanone **12** showed peaks for **13** and **14** in a ratio of 82:12 with a small peak (~3% total) corresponding to starting material. Chromatography of this material on a 48-g column of silica gel afforded in order of elution with 5% ethyl acetate in hexane fractions A, B, and C containing a total of 328 mg (75%) of colorless liquid. Fraction A contained 235 mg (54%) of the enol acetate **13**; single peak by gas chromatography: IR (film) 1770, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (m), 2.19 (s) and 1.76 (m); mass spectroscopic molecular weight 217.9981 (calcd for $C_8H_{11}BrO_2$, 217.9942). As indicated by gas chromatography, fraction B contained a 1:1 mixture of **13** and **14**. Fraction C contained 14 mg (3.2%) of **14**: IR ($CHCl_3$) 1760, 1680 cm^{-1}; NMR ($CDCl_3$) δ 5.66 (1 H, br t, J = 4 Hz), 4.87 (1 H, m), 2.20 (s); mass spectroscopic molecular weight 217.9959 (calcd for $C_8H_{11}BrO_2$, 217.9942).

2-Chlorocyclohex-1-enyl Acetate (17) and 6-Chlorocyclohex-1-enyl Acetate (18). Gas chromatographic analysis of the crude product from 2.0 mmol of 2-chlorocyclohexane **16** showed peaks for **17** and **18** in a ratio of 94:6. Chromatography of this material on a 50-g column of silica gel afforded in order of elution with 1 to 5% ether in hexane fractions A, B, and C containing a total of 282 mg (81%) of colorless liquid. Fraction A contained 193 mg (55%) of the previously reported[14] enol acetate **17**; single peak by gas chromatography: IR (film) 1760, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.6–2.0 (m), 2.18 (s) and 1.75 (m); mass spectroscopic molecular weight 174.0433 (calcd for $C_8H_{11}ClO_2$, 174.0448). Fraction B contained 83 mg of an 8:1 mixture of **17** and **18** as indicated by gas chromatography. Fraction C contained 6 mg (1.7%) of **18** as an oil; single peak by gas chromatography: IR ($CHCl_3$) 1750 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 5.59 (1 H, t, J = 4 Hz), 4.65 (1 H, m), 2.20 (s); mass spectroscopic molecular weight 174.0466 (calcd for $C_8H_{11}ClO_2$, 174.0448).

Reactions of α-Halo Ketones with Lithium Diisopropylamide in Tetrahydrofuran. General Procedure. Lithium diisopropylamide was prepared by adding 1.04–1.11 equiv of 2.5 M *n*-butyllithium in hexane to a stirred solution of 1.15 equiv of diisopropylamine in 3 mL of dry tetrahydrofuran at −78 °C. To this stirred −78 °C solution was added over a 4–5-min period a solution of the halo ketone (usually about 2.4 mmol) in 5 mL of dry tetrahydrofuran. After 3 min, 3.1 equiv of acetic anhydride was added, and 1 h later the cold mixture was poured into 80 mL of ether. The mixture was washed with three 25-mL portions of water, one 25-mL portion of ice-cold 10% hydrochloric acid, two 25-mL portions of ice-cold 2% aqueous sodium hydroxide, and one 25-mL portion of saturated aqueous sodium chloride, and then dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the crude material obtained was further treated as described below.

Reaction of Phenacyl Bromide (1) with LDA. Analysis by gas chromatography and NMR integration of the product obtained from 338 mg of phenacyl bromide (**1**) indicated a 37:63 ratio of 2-bromo-1-phenylethenyl acetate (**2**) to 2-bromo-1-phenylethyl acetate (**3**). Chromatography of this material on an 8-g silica gel column afforded on elution with 20% methylene chloride in hexane an 80% yield of product in three fractions. The first fraction contained 45 mg (11%) of enol acetate **2**; IR and NMR spectra were identical with those of **2** already described above. The second fraction contained a mixture of **2** and **3** as determined by gas chromatography. The final fraction contained 56 mg (14%) of the previously reported[15] acetate **3** as a colorless oil: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.43 (5 H, s), 6.02 (1 H, t, J = 6 Hz), 3.63 (2 H, d, J = 6 Hz), 2.13 (3 H, s). This material was spectrally identical with a sample of **3** prepared via sodium borohydride reduction in ethanol of **1**, followed by acetylation with acetic anhydride in pyridine.

Reaction of Phenacyl Chloride (9) with LDA. Gas chromatographic and NMR analysis of the product from 369 mg (2.4 mmol) of phenacyl chloride **9** indicated a 57:43 ratio of 2-chloro-1-phenylethenyl acetate (**10**) to 2-chloro-1-phenylethyl acetate (**11**). Chromatography of this material on a silica gel column afforded a 72% total yield of product in three fractions. Eluted first was enol acetate **10**; IR and NMR spectra were identical with those of **10** already described above. The middle fraction contained both **10** and **11**. Finally eluted was the previously reported[16] reduction product **11** as a colorless liquid: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.47 (5 H, s), 6.03 (1 H, t, J = 6 Hz), 3.80 (2 H, d, J = 6 Hz) and 2.18 (3 H, s). This material was spectrally identical with a sample of **11** prepared via sodium borohydride reduction in ethanol of **9**, followed by acetylation with acetic anhydride in pyridine.

Reaction of 2-Bromocyclohexanone (12) with LDA. Gas chromatographic and NMR analysis of the product from 667 mg of 2-bromocyclohexanone (**2**) indicated a 35:12:53 ratio of 2-bromocyclohex-1-enyl acetate (**13**) to 6-bromocyclohex-1-enyl acetate (**14**) to *cis*-2-bromocyclohexyl acetate (**15**).

Chromatography of this material on a silica gel column afforded a 50% total yield of product in three fractions. The first and last fractions contained small amounts of pure **13** and **14**, respectively; IR and NMR spectra were identical with those of **13** and **14** already described in a separate procedure above. Upon preparative gas chromatographic separation, the center fraction afforded a pure sample of the previously reported[17] acetate **15**: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 4.88 (1 H, m), 4.53 (1 H, m). 2.11 (~3 H, s), and 1.2–2.2 (~8 H, m). This material was spectrally identical with a sample of **15** prepared via acetylation of *cis*-2-bromocyclohexanol[7a] by acetic anhydride in pyridine.

Reaction of 2-Chlorocyclohexanone (16) with LDA. Gas chromatographic and NMR analysis of the product from 332 mg (2.5 mmol) of 2-chlorocyclohexanone (**16**) indicated a 45:12:42 ratio of 2-chlorocyclohex-1-enyl acetate (**17**) to 6-chlorocyclohex-1-enyl acetate (**18**) to *cis*-2-chlorocyclohexyl acetate (**19**). Chromatography on a silica gel column afforded a 58% total yield of product in three fractions. The first and last fractions contained small amounts of pure **17** and **18**, respectively, spectrally identical with **17** and **18** prepared in a separate procedure above. Preparative gas chromatographic separation of a small amount of the center fraction afforded the previously reported[7b,17] acetate **19**: IR (film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 5.0 (1 H, m), 4.38 (1 H, m), 2.13, (s). These spectra were identical with those of a sample of **19** prepared via acetylation of *cis*-2-chlorocyclohexanol[7b] by acetic anhydride in pyridine.

Reaction of 2-Chlorocyclohexanone (16) with LDA in Ether. To a stirred solution of 0.31 mL (2.2 mmol) of diisopropylamine in 4 mL of dry ether was added 1.03 mL (2.1 mmol) of 2.05 M methyllithium in ether. After 4 min this solution was cooled with a −78 °C bath and 3 min later a solution of 0.23 mL (2 mmol) of 2-chlorocyclohexanone (**16**) in 3 mL of dry ether was added over a 2-min period. After 14 min, 0.57 mL (6 mmol) of acetic anhydride was added all at once, and 30 min later the mixture was diluted with 80 mL of ether. This mixture was washed with 25 mL of water, two 20-mL portions of 10% hydrochloric acid, and 25 mL of saturated sodium chloride solution, and then dried over magnesium sulfate. The product obtained after removal of solvent under reduced pressure was a 22:6:72 mixture of **17**, **18**, and **19**, respectively, as determined by gas chromatographic and NMR analysis. Chromatography of this material on a 15-g silica gel column afforded in pure form 238 mg (68%) of the same mixture. Characterization of these products has been described above.

Reaction of *exo*-3-Chlorobicyclo[2.2.1]heptan-2-one (23) with LDA. A solution of LDA in ether was prepared from 2.33 g of diisopropylamine and 12.4 mL of 1.84 M methyllithium. After cooling to −78 °C, a solution of 1.50 g of *exo*-3-chlorobicyclo[2.2.1]heptan-2-one **23**[18] in 4 mL of ether was added dropwise over a 10-min period. The mixture was warmed to −50 °C and then recooled to −78 °C. Chlorotrimethylsilane (2.70 g) was added dropwise and the mixture was allowed to warm to room temperature. After 1 h at room temperature an aqueous workup was employed. After drying the organic phase over sodium sulfate, the solvent was removed by distillation through a Vigreux column. The residue was distilled at 14 mm to give 1.81 g (81%) of a mixture of **21** and **24** in a ratio of 94:6 as determined by gas chromatography. Samples of each product were isolated by preparative gas chromatography and identified by NMR spectral comparison with authentic samples prepared as described below. Silyl ether **24** showed the following: NMR ($CDCl_3$) δ (2 H, quartet of doublets, J = 2 Hz, J = 6 Hz), 2.36 (1 H, m), 2.12 (1 H, m), 1.9–1.0 (6 H, m) 0.14 (9 H, s). Silyl ether **24** was identical with a sample prepared by silation of *exo*-3-chlorobicyclo[2.2.1]heptan-*exo*-2-ol with triethylamine and chlorotrimethylsilane.

Reaction of *exo*-2-Chlorobicyclo[2.2.1]heptan-2-one (23) with LiTMP. A solution of LiTMP from 2.08 g of tetramethylpiperidine and 8.0 mL of 1.84 M methyllithium was cooled to −78 °C and a solution of 1.52 g of *exo*-2-chlorobicyclo[2.2.1]heptan-2-one (**23**) in 4 mL of ether was added over a 5-min period. After warming to −50 °C and recooling to −78 °C, 2.0 g of chlorotrimethylsilane was added and the mixture was brought to room temperature. After 1 h at room temperature an aqueous workup followed. The amine was removed by washing the organic phase with a solution of 2.12 g of potassium bisulfate in 20 mL of cold water. After drying over sodium sulfate, the solvent was removed by distillation through a Vigreux column. The residue was distilled to give 2.12 g (92%) of silyl ether **21**, bp 95–97 °C (14 mm); silyl ether **21** showed the following: NMR (CCl_4) δ 2.75 (1 H, m), 2.62 (1 H, m), 1.9–0.9 (6 H, m), 0.22 (9 H, s); mass spectroscopic

molecular weight 216.0736 (calcd for $C_{10}H_{17}ClOSi$, 216.0737).

Methanolysis of 21. A mixture of 1.78 g of **21** and 30 mL of methanol was refluxed for 2.5 h. The solvent was removed by distillation through a Vigreux column and the residue was distilled to give 1.19 (100%) of *endo*-3-chlorobicyclo[2.2.1]heptan-2-one **20**, mp 52–55 °C (lit.[18] mp 55.5–60.5 °C, lit.[19] mp 53–56 °C). Previously reported **20** had the following: NMR (CCl_4) δ 4.07 (1 H, d, J = 4.7 Hz), 3.0–2.5 (2 H, m), 2.2–1.3 (6 H, m).

Reaction of *endo*-3-Chlorobicyclo[2.2.1]heptan-2-one (20) with LDA. The procedure was analogous to that of the exo isomer **23**. LDA from 1.62 g of diisopropylamine and 8.6 mL of 1.84 M methyllithium with 1.04 g of **20** gave 1.41 g (90%) of a 83:17 mixture of **21** and **22**. Samples of each product were isolated by preparative gas chromatography. The major product was identical with the product produced in reaction of **23** with LiTMP. The minor product, silyl ether **22**, showed the following: NMR ($CDCl_3$) δ 4.06 (2 H, AB quartet of doublets, J = 4.0 Hz, J = 8.8 Hz), 2.43 (1 H, m), 2.25 (1 H, m) 2.1–1.0 (6 H, m), 0.12 (9 H, s). The stereochemistry of **22** was assigned based on the magnitude (4.0 Hz) of the coupling in the AB pattern.

Reactions of Methoxy Ketones with Lithium Diisopropylamide. General Procedure. Methyllithium (1.3–2.3 equiv) was added dropwise under nitrogen to a 5 to 10% excess of diisopropylamine dissolved in an equal volume of anhydrous ether. The solution was then cooled to −78 °C. One equivalent of the ketone was dissolved in anhydrous ether and was added slowly dropwise to the −78 °C solution. After the addition was completed, the reaction was warmed slowly to −20–0 °C and recooled immediately to −78 °C. Chlorotrimethylsilane (molar equivalent of the diisopropylamine used) was added all at once and the cold bath was removed. After stirring at room temperature for 30 to 45 min, water was added. The phases were separated and the organic layer was extracted with cold water and saturated sodium chloride solution, and dried (sodium sulfate). The solvents were removed by distillation through a Vigreux column on a steam bath or by rotary evaporator and the residue was distilled.

Reaction of 2-Methoxycyclohexanone (25) with LDA. Diisopropylamine (0.75 g), 3.82 mL of 1.84 M methyllithium, and 0.60 g of **25**[20] gave 0.75 g of products: bp 56–65 °C (1.7 mm). The major product (~85% of the mixture) was 1-trimethylsiloxy-6-methoxycyclohexene (**27**): IR (neat) $\nu_{C=C}$ 5.98 μm; NMR (CCl_4) δ 4.7–4.9 (1 H, m), 3.2–3.5 (4 H, m with sharp s at 3.30), 0.9–2.2 (6 H, m), 0.13 (9 H, s); mass spectroscopic molecular weight 200.1234 (calcd for $C_{10}H_{20}O_2Si$, 200.1233). A signal at δ 3.42 was tentatively assigned as the methoxy signal in **26**.

Reaction of 2-Methoxycyclopentanone (28) with LDA. Diisopropylamine (0.93 g), 4.8 mL of 1.84 M methyllithium, and 0.70 g of **28**[20] gave 0.84 g (74%) of a mixture of three products: bp 76–84 °C (12 mm). The major product (65% of mixture) was 1-trimethylsiloxy-5-methoxycyclopentene (**30**): IR (neat) $\nu_{C=C}$ 6.05 μm; NMR (CCl_4) δ 4.6–4.8 (1 H, m), 3.8–4.1 (1 H, m), 3.22 (3 H, s), 1.4–2.5 (4 H, m), 0.13 (9 H, s). 1-Methoxy-2-trimethylsiloxycyclopentene (**29**) (27% of the mixture) showed: IR (neat) $\nu_{C=C}$ 5.86 μm; NMR (CCl_4) δ 3.50 (3 H, s), 1.4–2.4 (6 H, m), 0.08 (9 H, m). Presence of the reduction product 1-methoxy-2-trimethylsiloxycyclopentane (~10%) **31** was inferred from methanolysis of the product mixture as described below.

Reaction of 2-Methoxycyclobutanone (32) with LDA. Diisopropylamine (1.1 g), 5.64 mL of 1.84 M methyllithium, and 0.54 g of **32**[20] gave 0.19 g (20%) of 1-methoxy-2-trimethylsiloxycyclobutene **33** containing two minor impurities: bp 45–60 °C (25–30 mm); IR (neat) $\nu_{C=C}$ 5.80 μm; NMR (CCl_4) δ 3.59 (3 H, s), 2.07 (4 H, s), 0.14 (9 H, s).

Reaction of *endo*-3-Methoxybicyclo[2.2.1]heptan-2-one (4) with LDA. Diisopropylamine (0.58 g), 3.0 mL of 1.84 M methyllithium, and 0.60 g of **4**[20] gave 0.70 g (77%) of a mixture of **5** and **6**: bp 65–68 °C (1.5 mm). The product ratio was 5.7:1 as determined by NMR. The enol ether **6** was identical with that prepared below. The silyl ether **5** showed: NMR (CCl_4) δ 3.87 (1 H, d of d, J = 9 Hz and 4.3 Hz), 3.1–3.4 (4 H, m with sharp s at 3.21), 0.9–2.4 (8 H, m), 0.05 (9 H, s).

Reaction of 2,2-Dimethoxycyclohexanone (34) with LDA. Diisopropylamine (0.80 g), 4.1 mL of 1.84 M methyllithium, and 0.80 g of **34** (prepared as described below) gave 0.96 g (82%) of a 4:1 mixture of 1,1-dimethoxy-2-trimethylsiloxycyclohexane **36** and 6,6-dimethoxy-1-trimethylsiloxycyclohex-1-ene **35**. Enol ether **35** showed the following: NMR (CCl_4) δ 4.7–5.0 (1 H, m), 3.18 (6 H, s), 0.9–2.2 (6 H, m), 0.09 (9 H, s). Ether **36** showed the following: NMR (CCl_4) δ 3.7–3.9 (1 H, m), 3.09 (6 H, s), 0.9–2.2 (6 H, m), 0.05 (9 H, s).

Reaction of 2,2-Dimethoxycyclopentanone (37) with LDA. Diisopropylamine (0.35 g), 1.8 mL of 1.84 M methyllithium, and 0.21 g of **37** (prepared as described below) gave 0.28 g (89%) of 1-trimethylsiloxy-5,5-dimethoxycyclopent-1-ene **38**: bp 76–84 °C (6–8 mm); IR (neat) $\nu_{C=C}$ 6.03 μm; NMR (CCl_4) δ 4.65–4.85 (1 H, m), 3.20 (6 H, s), 1.5–2.4 (4 H, m), 0.15 (9 H, s). Enol ether **38** lost methanol upon preparative gas chromatography to give 1-trimethylsiloxy-4-methoxycyclopentadiene: IR (neat) $\nu_{C=C}$ 6.13 and 6.34 μm; NMR (CCl_4) δ 5.14 (1 H, q, J = 2.3 Hz, further coupled with J less than 1 Hz) 4.93 (1 H, q, J = 2.3 Hz, further coupled with J less than 1 Hz), 3.64 (3 H, s), 2.62 (1 H, t, J = 2.3 Hz, further coupled with J less than 1 Hz), 0.17 (9 H, s); mass spectroscopic molecular weight 184.0924 (calcd for $C_9H_{16}O_2Si$, 184.0920).

Reaction of 2,2-Dimethoxycyclobutanone (39) with LDA. Diisopropylamine (0.40 g), 1.88 mL of 1.84 M methyllithium, and 0.26 g of **39**[20] gave 0.23 g of a product mixture containing **40** and **41** and unidentified products. Approximately 70% of the product mixture consisted of **40** and **41** which were separated from other products by preparative gas chromatography. Enol ether **40** had the following properties: IR (neat) $\nu_{C=C}$ 6.13 μm; NMR (CCl_4) δ 4.75–4.85 (1 H, m), 3.27 (6 H, s), 2.0–2.2 (2 H, m), 0.20 (9 H, s). Ether **41** had the following properties: NMR (CCl_4) δ 3.9–4.3 (1 H, m), 3.24 (3 H, s), 3.10 (3 H, s), 1.3–2.2 (4 H, m), 0.08 (9 H, s). The products **40** and **41** were present in a 1 to 2.5 ratio.

Reaction of *exo*-3-Methoxybicyclo[2.2.1]heptan-2-one (7) with LDA. Diisopropylamine (0.46 g), 2.3 mL of 1.84 M methyllithium, and 0.40 g of **7**[20] gave 0.48 g (79%) of **8**: bp 65–75 °C (2.0 mm); NMR (CCl_4) δ 3.65 (1 H, d of d, J = 6 Hz and 1.5 Hz), 3.25 (3 H, s), 2.99 (1 H, d of d, J = 6 Hz and 1.5 Hz), 0.7–2.3 (8 H, m), 0.05 (9 H, s); mass spectroscopic molecular weight 214.1407 (calcd for $C_{11}H_{22}O_2Si$, 214.1389).

Reaction of 3,3-Dimethoxybicyclo[2.2.1]heptan-2-one (43) with LDA. Diisopropylamine (0.30 g), 1.45 mL of 1.84 M methyllithium, and 0.30 g of **43**[21] gave 0.37 g of a mixture of unreacted **43**, **44**, and hydrolyzed **44**. Material balance was 73% with the reduction product to starting material ratio of 86:14. Ether **44** had the following properties: NMR (CCl_4) δ 3.68 (1 H, d, J = 4.5 Hz), 3.15 (3 H, s), 3.07 (3 H, s), 2.0–2.4 (2 H, m), 0.9–2.0 (6 H, m), 0.08 (9 H, s); mass spectroscopic molecular weight 244.1491 (calcd for $C_{12}H_{24}O_2Si$, 244.1495).

Methanolysis of Silyl Ethers. General Procedure. The products from reaction of the methoxy ketones with LDA and chlorotrimethylsilane were dissolved in methanol (100 mg of product/mL of methanol) containing a trace of sodium methoxide. The methanolysis was monitored by gas chromatography. When the reactions were completed, the solvent was removed and the products were distilled or collected by preparative gas chromatography and spectra were compared to those of authentic samples.

Methanolysis of 27. Methanolysis of **1a** gave **25** contaminated with trace amounts of another unidentified compound.

Methanolysis of 29, 30, and 31. Methanolysis of the products of reaction of **28** with LDA gave two compounds in a ratio of 9:1. The major product was **28**. The minor product was identified as *cis*-2-methoxycyclopentanol which was independently synthesized as described below.

Methanolysis of 33. Methanolysis of **33** gave 1,1,2-trimethoxycyclobutane. Apparently **32** was ketalized under the reaction conditions.

Methanolysis of 5 and 6. Products from the reaction of **4** with LDA, upon methanolysis, gave a 1:5 mixture of **4** and *endo,cis*-2-methoxy-3-hydroxybicyclo[2.2.1]heptane. The major product was identical with that obtained by borohydride reduction of **4** as described below.

Methanolysis of 35 and 36. Methanolysis of the products of reaction of **34** with LDA gave 2,2-dimethoxycyclohexanol and **34** in a 4:1 ratio.

Methanolysis of 38. Enol ether **38** was methanolyzed to give **37** as the only product.

Methanolysis of 40 and 41. The products from reaction of **39** with LDA, upon methanolysis, gave a 2.1:1 ratio of 2,2-dimethoxycyclobutanol and **39**.

Reduction of Methoxy Ketones with Sodium Borohydride. General Procedure. The ketone was added to a suspension of sodium borohydride in methanol in a cold water bath. Stirring at room temperature was continued for 1 to 2 h and dilute acetic acid was added. The aqueous phase was extracted with ether. The ether phase was extracted with water, dilute sodium carbonate, and saturated sodium chloride, and dried (sodium sulfate). The solvent was removed by distillation through a Vigreux column and the products were distilled.

Reduction of 4. Ketone **4** (0.20 g), 0.05 g of sodium borohydride gave 0.14 g (69%) of endo alcohol: bp 56–58 °C (1.7 mm); IR (neat) ν_{OH}

2.76 μm; NMR (CCl_4) δ 3.79 (1 H, d of d, J = 4 Hz and 9 Hz), 3.1–3.5 (4 H, m with sharp s at 3.34), 2.83 (1 H, s, exchanges with D_2O), 2.1–2.5 (2 H, m), 1.0–2.0 (6 H, m); mass spectroscopic molecular weight 142.1007 (calcd for $C_8H_{14}O_2$, 142.0994). The product was identical with the product of methanolysis of **5**.

Reduction of 7. Ketone **7** (0.24 g) and 0.05 g of sodium borohydride gave 0.17 g (71%) of a 2.8:1 mixture of exo and endo alcohols: bp 60–65 °C (2.0 mm). The exo alcohol had the following characteristics: IR (neat) ν_{O-H} 2.72 μm; NMR ($CDCl_3$) δ 3.68 (1 H, d of d, J = 7 Hz and 2 Hz), 3.42 (3 H, s), 3.1–3.3 (2 H, m, one H exchanged with D_2O and revealed a d of d at 3.23 with J = 7 Hz and 2 Hz), 2.1–2.4 (2 H, m), 0.9–1.9 (6 H, m); mass spectroscopic molecular weight 142.1014 (calcd for $C_8H_{14}O_2$, 142.0994). The alcohol was identical with the product of methanolysis of **8**. The endo alcohol had the following characteristics: IR (in CCl_4) ν_{O-H} 2.79 μm; NMR ($CDCl_3$) δ 3.8–4.0 (1 H, m), 3.33 (3 H, s), 2.85–2.95 (1 H, m), 2.2–2.4 (2 H, m), 0.9–1.9 (6 H, m); mass spectroscopic molecular weight 142.0977 (calcd for $C_8H_{14}O_2$, 142.0994).

Preparation of *cis*-2-Methoxycyclopentanol. *cis*-1,2-Cyclopentanediol[23] (0.68 g) was added to a suspension of 0.18 g of sodium hydride in 3 mL of THF. The mixture was heated to reflux and cooled. Methyl iodide (0.95 g) was added and refluxing was continued for 45 min. Water and ether were added and the phases were separated. The ether layer was extracted with water and saturated sodium chloride, and dried (sodium sulfate). Solvents were removed and the residue was distilled to give 0.31 g of a mixture of mono- and dimethylated diol in about a 1:1 ratio: bp 57–68 °C (15 mm). For the *cis*-methoxy alcohol, the following properties were observed: NMR (CCl_4) δ 3.8–4.2 (1 H, m), 3.3–3.7 (4 H, m with sharp s at 3.33), 2.0–2.3 (1 H, m, exchanges with D_2O), 1.4–2.0 (6 H, m); mass spectroscopic molecular weight 116.0837 (calcd for $C_6H_{12}O_2$, 116.0836). This product was identical with the minor product of methanolysis of the LDA reaction products of **28**.

Preparation of 2-Methoxy-3-trimethylsiloxybicyclo[2.2.1]-hept-2-ene (6). The procedure was the same as that used for the preparation of **21**. Tetramethylpiperidine (4.54 g), 17 mL of 1.84 M methyllithium, 3 g of **4**, and 3.67 g of chlorotrimethylsilane gave 3.74 g (82%) of **6**: bp 65–75 °C (1.7 mm); IR (neat) $\nu_{C=C}$ 5.95 μm; NMR (CCl_4) δ 3.56 (3 H, s), 2.6–2.8 (1 H, m), 2.4–2.6 (1 H, m), 0.7–1.9 (6 H, m) 0.13 (9 H, s); mass spectroscopic molecular weight 212.1238 (calcd for $C_{11}H_{20}O_2Si$, 212.1233).

Preparation of 37. The Swern[23] oxidation procedure was employed. Dimethyl sulfoxide (2.2 mL) was dissolved in 18 mL of methylene chloride and the solution was cooled to −65 °C in a dry ice–acetone bath. Trifluoroacetic anhydride (3.13 g) was added dropwise slowly and stirring was continued for 10 min. 2,2-Dimethoxycyclopentanol[20] (1.28 g), dissolved in 1.5 mL of dimethyl sulfoxide and 15 mL of methylene chloride, was slowly added dropwise. After stirring for 20 min, 3.62 g of trimethylamine was added and the cold bath was removed. Stirring was continued for 15 min at room temperature. Workup consisted of dilution with ether and extraction with several portions of water and saturated sodium chloride, and drying over sodium sulfate. Solvents were removed through a Vigreux column and the residue was distilled to give 1.06 g (84%) of **6**: bp 78–84 °C (12 mm); IR (neat) $\nu_{C=O}$ 5.68 μm; NMR (CCl_4) δ 3.23 (6 H, s), 1.6–2.4 (6 H, m); mass spectroscopic molecular weight 144.0784 (calcd for $C_7H_{12}O_3$, 144.0786).

Preparation of 34. The procedure was identical with that used in the preparation of **37**. Dimethyl sulfoxide (1.33 mL), 11 mL of methylene chloride, 1.97 g of trifluoroacetic anhydride, 1 g of 2,2-dimethoxycyclohexanol[20] (dissolved in 1 mL OF Me_2SO and 2 mL of methylene chloride), and 2.0 g of triethylamine gave 0.89 g (90%) of **5**: bp 66–69 °C (2.1 mm); IR (neat) $\nu_{C=O}$ 5.77 μm; NMR (CCl_4) δ 3.22 (6 H, s), 2.3–2.6 (2 H, m), 1.5–2.1 (6 H, m); mass spectroscopic molecular weight 158.0876 (calcd for $C_8H_{14}O_3$, 158.0943).

Reaction of 3,3-Dimethylbicyclo[2.2.1]heptan-2-one (45) with LDA. Reaction of 1.00 g of camphenilone **45** with LDA from 1.62 g of diisopropylamine and 8.7 mL of 1.84 M methyllithium gave, after quenching with water and an aqueous workup, 0.45 g (45%) of a mixture of 3,3-dimethylbicyclo[2.2.1]heptan-*endo*-2-ol **46** (R=H) and unreacted camphenilone (**45**) in a ratio of 9:1 as determined by gas chromatography.

Isopropylideneisopropylamine (42). To a stirred, −78°C solution of 0.31 mL (2.21 mmol) of diisopropylamine in 4 mL of dry tetrahydrofuran was added 0.73 mL (2.11 mmol) of 2.9 M butyllithium in hexane. Analysis of aliquots from this mixture by gas chromatography showed a large peak of identical retention time to diisopropylamine and no peak corresponding to imine **42**.[10] To the −78 °C solution was then added a solution of 311 mg (2.01 mmol) of phenacyl chloride (**9**) in 3 mL of dry tetrahydrofuran. After 5 min the pressure in the system was cautiously reduced and the cooling bath was removed. The volatiles distilled into a trap cooled at −78 °C. Essentially all of the liquid distilled below room temperature. The reaction flask was approximately 0 °C when the distillation was stopped. Analysis of the distillate by gas chromatography now indicated about a 1:2 ratio of a new peak, corresponding in retention time to authentic imine **42**, and diisopropylamine. Isolation of a sample of the smaller peak by preparative gas chromatography afforded a sample for NMR analysis. The NMR spectrum corresponds to that of imine **42** prepared from isopropylamine and acetone:[10] NMR ($CDCl_3$) δ 3.63 (1 H, sept, J = 6.5 Hz), 1.94 (3 H, s), 1.84 (3 H, s), and 1.11 (6 H, d, J = 6.5 Hz). The spectrum also shows a trace of THF.

Reactions of Benzophenone (47) with LDA. Run (a). To a stirred −78 °C solution of 0.169 mL (1.2 mmol) of diisopropylamine in 3 mL of dry tetrahydrofuran was added 0.46 mL (1.1 mmol) of 2.4 M *n*-butyllithium in hexane. After 3 min a solution of 182 mg (1 mmol) of benzophenone in 3 mL of dry tetrahydrofuran was added dropwise over a 3-min period, causing a lime green color to appear. After 13 min, the −78 °C solution was poured into 80 mL of ether, washed with 20 mL of water, 20 mL of 10% hydrochloric acid, and 20 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate. After removal of the solvent, the resulting product was chromatographed on a 20 × 20 cm silica gel thick layer plate, developed with 18% ether in hexane. Obtained were 74 mg (40%) of benzophenone (R_f 0.36) and 89 mg (49%) of benzhydrol (R_f 0.17); products were spectrally identical with commercially available materials.

Run (b). The same amounts and reaction conditions were employed as in run (a) except that 9 min after addition of the benzophenone solution, 1.07 mL (2.2 mmol) of 2.05 M methyllithium in ether was added. The solution was then allowed to warm slowly to −50 °C over a 1-h period, before being worked up as above. There was obtained 169 mg (90%) of a 5:1:4 mixture of benzhydrol, benzophenone, and 1,1-diphenylethanol as indicated by IR and NMR analysis.

Run (d). To a stirred −78 °C solution of 0.308 mL (2.2 mmol) of diisopropylamine in 3 mL of dry tetrahydrofuran was added 0.875 mL (2.1 mmol) of 2.4 M *n*-butyllithium in hexane. After 3 min a solution of 82 mg (0.45 mmol) of benzophenone in 3 mL of dry tetrahydrofuran was added dropwise over a 5 min period. After 13 min, the reaction mixture was worked up, chromatographed, and analyzed as in run (a) to afford 13 mg (16%) of benzophenone and 62 mg (75%) of benzhydrol.

Run (e). To a stirred −78 °C solution of 0.45 mL (3.3 mmol) of diisopropylamine in 3 mL of dry tetrahydrofuran was added 1.07 mL (3.1 mmol) of 2.19 M *n*-butyllithium in hexane. After 3 min, a solution of 182 mg (1 mmol) of benzophenone in 3 mL of dry tetrahydrofuran was added over a 3-min period. After 13 min, 2.05 mL (4.2 mmol) of 2.05 M methyllithium in ether was added to the green −78 °C solution, and 2 min later the reaction mixture was worked up, chromatographed, and analyzed as in run (a) to afford 17 mg (9%) of benzophenone and 92 mg (50%) of benzhydrol. No 1,1-diphenylethanol could be detected in the crude product by NMR analysis.

Run (f). To a stirred room temperature solution of 0.45 mL (3.3 mmol) of diisopropylamine in 3 mL of dry ether was added 1.51 mL (3.1 mmol) of 2.05 M methyllithium in ether. The solution was cooled in a −78 °C bath, and a solution of 182 mg (1 mmol) of benzophenone in 3 mL of ether was added over a 3-min period. During the addition a blood red color formed, which gradually faded after 5 min. After another 11 min, 2.05 mL (4.2 mmol) of 2.05 M methyllithium in ether was added, and 2 min later the mixture was worked up as in run (a) to afford 168 mg (90%) of a 5.4:1:2.5 mixture of benzhydrol, benzophenone, and 1,1-diphenylethanol as determined by IR and NMR analysis.

Addition of Methyllithium to Benzophenone. Run (c). To a stirred −78 °C solution of 182 mg (1 mmol) of benzophenone in a mixture of 6 mL of dry tetrahydrofuran and 0.38 mL of hexane was added 1.07 mL (2.2 mool) of 2.05 M methyllithium in ether. After 1 min, the −78 °C solution was poured into a mixture of 80 mL of ether and 20 mL of water, and the ether layer was then washed with 25 mL of 10% hydrochloric acid and 25 mL of saturated aqueous sodium chloride solution. Drying the solution over magnesium sulfate and removal of solvent under reduced pressure afforded 198 mg (100%) of crude 1,1-diphenylethanol. No benzophenone could be detected in this product, either by IR or TLC analysis.

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Registry No.—**42**, 3332-08-9; hexamethyldisilazane, 999-97-3; diisopropylamine, 108-18-9; 1-trimethylsiloxy-4-methoxycyclopentadiene, 66057-27-0; *endo,cis*-2-methoxy-3-hydroxybicyclo[2.2.1]heptane, 53329-03-6; *exo,cis*-2-methoxy-3-hydroxybicyclo[2.2.1]heptane, 53329-04-7; *cis*-1,2-cyclopentanediol, 5057-98-7; *cis*-2-methoxycyclopentanol, 13051-91-7; tetramethylpiperidine, 768-66-1; 2,2-dimethoxycyclopentanol, 63703-33-3; 2,2-dimethoxycyclohexanol, 63703-34-4.

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(24) **Note Added in Proof.** We have found that even cyclohexanone, when treated with LDA as described for **4**, affords 34% reduction. The ratio of reduction to enolization appears sensitive to both solvent (more reduction in ether than in THF) and to the nature of the commercial alkyllithium reagent used to prepare the LDA (more reduction with methyllithium containing lithium bromide than when prepared from *n*-butyllithium).

Hydride Transfer Reduction–Rearrangement of 4-Homobrendylcarbinols. Concomitant Ring Enlargement and Skeletal Isomerization in a Tricyclic 2-Norbornylcarbinyl System

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By the brief contact with 95% sulfuric acid and *n*-pentane, 4-homobrend-3-ylcarbinol (**4**) was transformed predominantly into 4-homoisotwistane (**15**), while 2-methyl-4-homobrendan-2-ol (**11**) gave exclusively a mixture of 1- and 2-methyladamantane. 4-Homobrend-exo- and -*endo*-2-ylcarbinol (**9x** and **9n**) afforded both **15** and methyladamantanes. **9x** gave also the simple reduction product exo-2-methyl-4-homobrendane (**10x**), whereas **9n** did not give the corresponding product (**10n**). The ratio of **15** to combined 1- and 2-methyladamantane, which represented the relative importance of the ring enlargement process vs. the rearrangement of the 4-homobrendane skeleton in **9x** and **9n**, was much larger for **9x** than for **9n**. The result was successfully interpreted with consideration of the relative stabilities of the intermediate bridged cations involved in the ring enlargement.

We had been looking for synthetic routes to 2,4-bishomobrendane (tricyclo[6.2.1.0^{4,9}]undecane, **16**), an unknown compound presumed to intervene in some key steps of the acid-catalyzed skeletal rearrangement of tricycloundecane.[1] Hydride transfer reduction–rearrangement[2] of 4-homobrend-2- and -3-ylcarbinols (tricyclo[5.2.1.0^{3,8}]dec-2- and -3-ylcarbinols, **9x, 9n,** and **4,** Scheme I) was thought promising in view of the well-documented ring enlargement of the 2-norbornylcarbinyl to the bicyclo[3.2.1]octyl cation.[3,4] In actuality, however, the method failed to give the hoped-for 2,4-bishomobrendane,[5] but produced 4-homoisotwistane (tricyclo[5.3.1.0^{3,8}]undecane, **15**), a twice-rearranged ring enlargement product, together with 1- and 2-methyladamantane. Concomitant formation of methyladamantanes indicated, as discussed below, the ring enlargement to be partly inhibited in 4-homobrendylcarbinols. The only example of the inhibition of ring enlargement in the 2-norbornylcarbinyl system has been reported hitherto by Whittaker[6] for the acetolysis of 3,3-dimethylnorborn-*endo*-2-ylcarbinyl tosylate. The extent of the inhibition of the ring enlargement in the present 4-homobrendylcarbinyl system was found at variance with the structures and configurations of the carbinols, and these results were successfully interpreted in terms of the stability of the bridged cationic intermediate involved in the ring enlargement process.

Results

Synthesis. Three tricyclic carbinols, 4-homobrend-3-, -*exo*-2-, and -*endo*-2-ylcarbinol (**4, 9x,** and **9n,** respectively), as well as 2-methyl-4-homobrendan-2-ol (**11**) of undetermined configuration, were prepared according to the routes shown in Scheme I. Bromination[7] of 4-homobrendane (**1**)[2a,8] gave exclusively the 3-bromide **2**.[8,9] Its structure was determined unequivocally by ^{13}C NMR spectrometry and lithium–*tert*-butyl alcohol reduction. Ten signals including the lowest field singlet in the ^{13}C NMR spectrum indicated the bromide to be an asymmetrical bridgehead-substituted derivative. Reduction by lithium in *tert*-butyl alcohol reverted the bromide back to the original hydrocarbon **1** to demonstrate the intactness of the skeleton during the bromination. Koch carboxylation of **2** gave the corresponding acid **3,** and the structure of **3** was established by the formation of the same 3-ol **5**[10]

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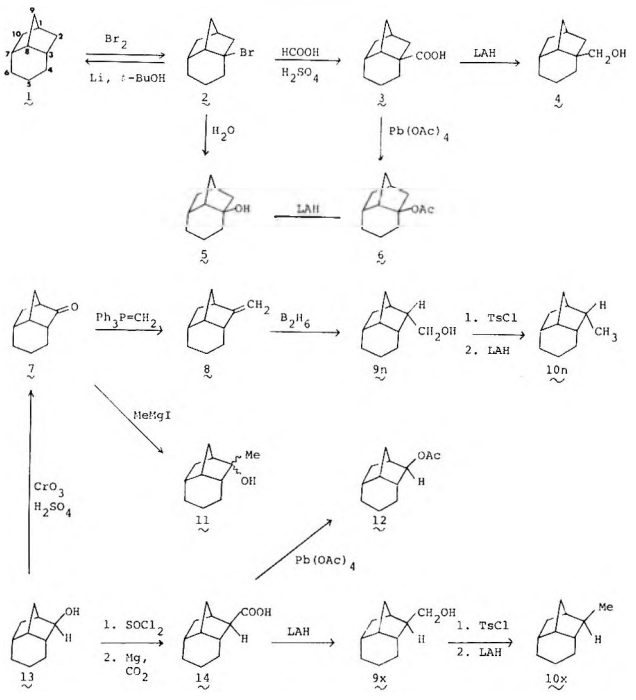
Table I. Product Distribution in the Hydride Transfer Reduction–Rearrangement of 4-Homobrendylcarbinols and Methyl-4-homobrendanol[a]

Run	Reactant	Reaction time, min	Yield, %	Product, %[b] 15[c]	2-Me-Ad	1-Me-Ad	Others
1	4	5	62	93.1	0.8		2.0,[d] 0.4[e]
2		30	63	85.6	3.1	0.4	0.6,[d] 1.8[e]
11	**9x**	5	47	42.5	24.8	2.3	19.7[f]
12		10	[g]	38.8	28.3	2.7	19.5[f]
13		30	[g]	36.0	32.6	3.2	17.9[f]
14		60	50	30.9	40.4	3.8	13.9[f]
21	**9n**	5	36	6.7	79.3	5.9	
22		30	39	6.6	81.8	8.1	
31	**9n + 10n**	5	52	3.4	50.4	3.1	36.1[h]
32	(1:0.3)[i]	10	[g]	2.9	57.0	4.3	26.9[h]
33		30	[g]	2.8	73.4	5.9	8.3[h]
34		60	52	2.4	83.6	6.7	0.2[h]
41	11	5	43		79.9	8.3	
42		30	47		74.3	13.6	

[a] 100 mg of reactant, 1 g of 95% sulfuric acid, and 5 mL of *n*-pentane stirred vigorously at room temperature (~25 °C). [b] Calculated from VPC peak areas. Balance consists of several unidentified compounds. [c] Containing a little *endo*-2,8-trimethylenebicyclo[3.3.0]-octane[1b] as shown by the blip of VPC peak. [d] 2,4-Bishomobrendane (**16**).[2a] [e] Homoadamantane. [f] *exo*-2-Methyl-4-homobrendane (**10x**). [g] Not determined. [h] *endo*-2-Methyl-4-homobrendane (**10n**). [i] A mixture of 4-homobrend-*endo*-2-ylcarbinol (**9n**) and *endo*-2-methyl-4-homobrendane (**10n**) in 1:0.3 molar ratio.

Scheme I



either from the acid via the acetate 6[10] or directly from the bromide **2**. Reduction of the acid **3** gave the desired 3-ylcarbinol **4**.

Hydroboration of 2-methylene-4-homobrendane (**8**), prepared from the corresponding ketone (**7**)[2a,11] by a Wittig reaction, gave almost exclusively a primary alcohol, as indicated by ^1H and ^{13}C NMR. On the basis of predominant exo attack of diborane, as has been mostly the case for polycyclic olefins for steric reasons,[12] an endo configuration **9n** was assigned to the alcohol. The corresponding hydrocarbon, *endo*-2-methyl-4-homobrendane (**10n**), was prepared from **9n** by tosylation and subsequent lithium aluminum hydride reduction.

A 4-homobrendane-2-carboxylic acid (**14**) was obtained from the *exo*-2-ol **13**[2a,11] via treatment with thionyl chloride and Grignard carboxylation. The structure of **14** was proved by lead tetraacetate decarboxylation, leading to the *exo*-2-yl acetate (**12**) of established structure.[2a,11] Lithium aluminum hydride reduction of **14** gave a 2-ylcarbinol (**9x**), which was different from the endo isomer **9n** prepared above. Accordingly, an exo configuration was assigned to **9x**. The acid **14** then should also be the exo isomer. *exo*-2-Methyl-4-homobrendane (**10x**) was prepared from **9x** by the same procedure as that for **10n**.

The above configurational assignments for **9x, 9n, 10x, 10n,** and **14** are consistent with their ^{13}C NMR spectra. All the exo isomers, **9x, 10x,** and **14,** exhibit abnormally high-field (~15 ppm) methylene carbon signals which have been attributed to arise from steric compressions exerted by endo hydrogens (*endo*-2- and -10-H) on the two *β-axial*-methylene substituents.[1,2a] In contrast to this, the highest field triplet (methylene) signals in the spectra of endo isomer **9n** and **10n** are 18.52 and 18.32 ppm, respectively.

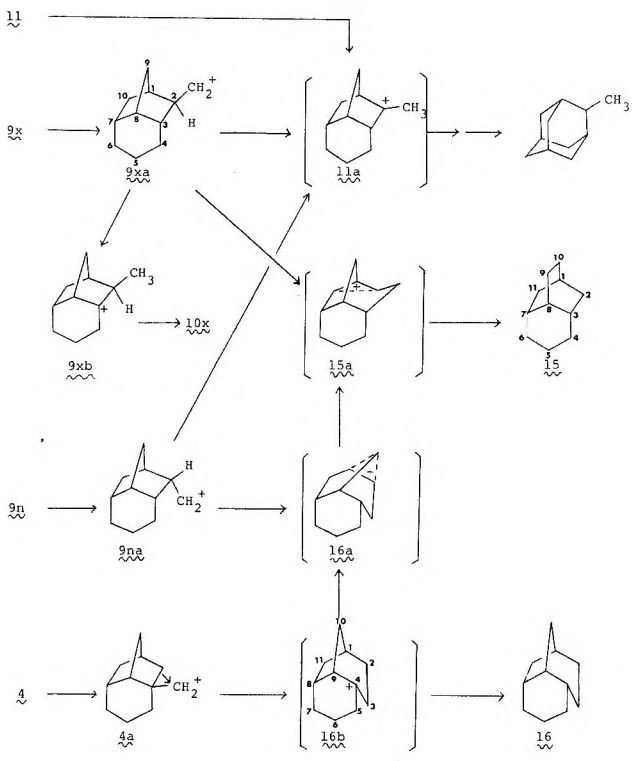
Reaction of methylmagnesium iodide with 4-homobrendan-2-one (**7**) gave a 2-methyl-2-hydroxy-4-homobrendane (**11**). The configuration of the substituents in **11** would most probably be *exo*-methyl-*endo*-hydroxy, for the reasons of predominant exo attack of the Grignard reagent.[13]

Hydride Transfer Reduction–Rearrangement. The alcohols thus obtained were stirred with 95% sulfuric acid and *n*-pentane at room temperature. Analysis and identification of the products were made on Golay GC–MS.[1,2] The reactions were almost complete in 5 min, giving pentane-soluble products in 36–62% yields, and longer reactions caused only secondary conversions of the products accompanied by a few percent increases in yields. For every reaction, several unidentified compounds (*m/e* 150 or 148) were detected which amounted to ~10% of the total products. The number of these unidentified products varied from eight to ten depending upon the precursor alcohols used. The results are summarized in Table I.

The bridgehead carbinol **4** underwent almost exclusively ring enlargement, leading to 4-homoisotwistane (**15**). 2,4-Bishomobrendane (**16**) was detected only in the reaction of this carbinol **4**. In contrast to **4,** the tertiary alcohol **11** gave only methyladamantanes, showing no sign of the ring enlargement.

The 2-ylcarbinol **9x** and **9n** reacted along both directions to afford **15** and methyladamantanes. However, the exo isomer

Scheme II



9x showed a larger tendency to ring enlargement than to the methyladamantane formation (run 11), while the endo isomer **9n** behaved oppositely (run 21). It is also to be noted that the simple hydride-transfer reduction product (**10x**) was formed as a major product only in the reaction of the exo isomer **9x.**

Isomerization of this reduction product **10x** was fairly slow compared to that of the carbinol itself, only 30% of **10x** having disappeared after 60 min of reaction (run 14). The once formed hydrocarbon **10x,** therefore, can not be an intermediate to methyladamantanes in the fast rearrangement of **9x.** The *endo*-methyl isomer **10n,** although it was not detected in the reaction of **9n,** could intervene in the route from **9n** to methyladamantanes, if it reacts very fast. To test this possibility, isomerization of **10n** was also examined. Since 95% sulfuric acid alone did not cause the rearrangement of **10n** appreciably, the corresponding carbinol **9n** was also added as a carbocation source (runs 31–34). Rearrangement of **10n** was much faster than that of the exo isomer **10x,** yet too slow to be considered as an intervening process to methyladamantanes.

Discussion

Ring enlargement leading to 4-homoisotwistane (**15**) was an almost exclusive reaction pathway in the bridgehead carbinol **4.** Detection of a small amount of 2,4-bishomobrendane (**16**), combined with the established high reactivity of **16** and its transformation into **15,**[1b] indicated that the shift of C-2 to give 2,4-bishomobrend-4-yl cation (**16b,** Scheme II) was the predominant process in the reaction of **4a.** Other possible ring enlargements in **4a,** shifts of C-4 and C-8, produce *endo*-2,6-tetramethylenenorbornane (tricyclo[6.2.1.$0^{3,9}$]undecane) and 4-homoprotoadamantane (tricyclo[5.3.1.$0^{3,9}$]undecane), respectively, which are more strained than **16.**[14] These processes, therefore, should be less likely to occur.

1,3-Transfer of 2-H's and 4-H's in **4a** are stereoelectonically[14] allowable to give 3-methyl-4-homobrend-2- and -4-yl cation, respectively, and the latter cation should afford[8,14] methyladamantanes through the shift of C-2 to 7-methylprotoadamantane. However, these hydride transfers were not actually realized. Similar preference to 1,2-alkyl shift over 1,3-hydride transfer was observed for the competitive rearrangement of 2,4-bishomobrend-10-yl (**16**-10-yl) cation which gave predominantly *endo*-2,8-ethano-*cis*-bicyclo[3.3.0]octane (tricyclo[5.3.1.$0^{4,11}$]undecane) over 4-homoisotwistane (**15**) formed via the **16**-2-yl cation.[1b] The shift of C-2 in **4a** would be further favored by the formation of a bridgehead cation **16b,** as compared to hydride transfers which give secondary (bridge) 2- and 4-yl cations.

The tertiary alcohol **11** gave only methyladamantanes. This rearrangement pathway would be explained most reasonably with the intermediacy of a methylprotoadamantane[14] (*exo*-10-methylprotoadamantane) formed from the cation **11a** by the 1,3-transfer of *endo*-4-H to give the **10x**-4-yl cation followed by the shift of methyl-bearing C-2 in the latter cation. Thus the ring enlargement by the incorporation of the methyl group did not occur at all in **11.** This is another example of "no return of methyl group"[14,15] once extruded out the tricycloundecane ring systems.

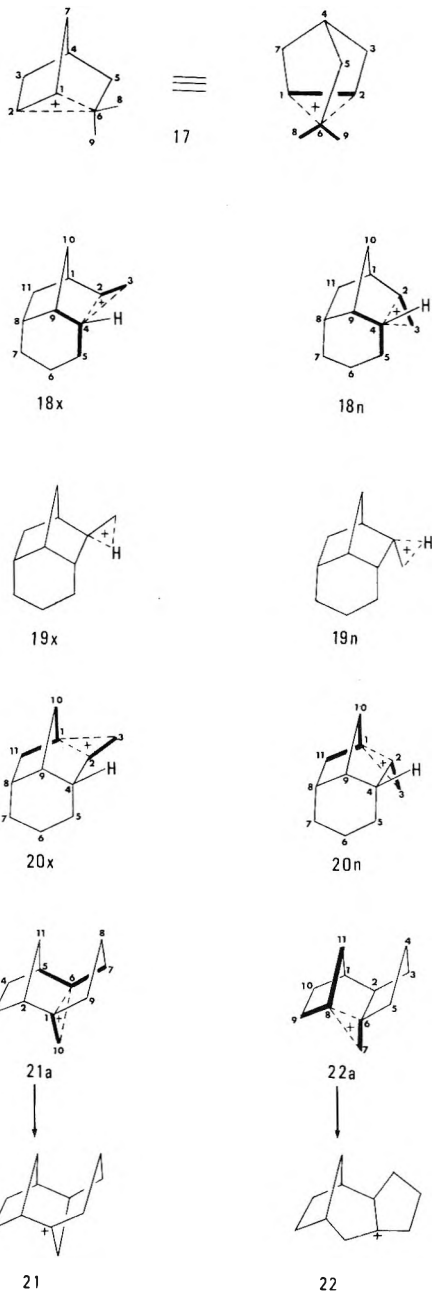
The 2-ylcarbinols, **9x** and **9n,** gave not only 4-homoisotwistane (**15**), but methyladamantanes. These methyladamantanes must be produced mainly by direct isomerization of the 4-homobrendane skeleton in **9x** and **9n,** because the ring enlargement product **15** did not rearrange easily under the present reaction conditions (cf. run 2, Table I). The pathway to methyladamantanes in **9x** and **9n** is presumed to be the same as that in **11,** since a similar ratio (~10:1) of 2- to 1-methyladamatane was found for these precursors (runs 11, 21, and 41). The cation **9xa** and **9na** are connected to **11a** by 1,2-hydride transfers (Scheme II), and these processes should be favorable because of the formation of a stable, tertiary cation.

Ratio of the ring enlargement to the skeletal rearrangement, as measured by the ratio of **15** to combined methyladamantanes, was largely different in the two 2-ylcarbinols, the stronger tendency to ring enlargement than to skeletal rearrangement being noticed in the exo isomer **9x.** The change in the ratios of the two processes with the configuration of the 2-ylcarbinols appears to be interpreted with the relative stabilities of the transition states (or intermediate cationic species), as discussed below.

Schleyer[16] found ~20 times deceleration of solvolysis rates in 6,6-dimethyl-2-norbornyl tosylates as compared to those in the unsubstituted compounds, and attributed the cause to destabilization of the transition state (or bridged intermediate cation) by steric repulsion exerted by the two methyl groups (**17,** Scheme III). Whittaker[6] gave an interpretation in terms of this steric destabilization for the inhibition of the ring enlargement in 3,3-dimethylnorborn-*endo*-2-ylcarbinyl cation. On the other hand, Sauers[17] ascribed the preferable migration of methylene over that of methine in Baeyer–Villiger oxidation of substituted 2-norbornanones to the relief of torsional strain, which was realized only in the methylene migration transition state. McKinney[3d] referred to this explanation in the interpretation of the well-known preference for methylene migration in 2-norbornylcarbinyl ring enlargements. "Tortional strain relief" and "steric destabilization" are two different expressions for the same concept, and we consider that this concept is also applicable to the interpretation of the present variation in the extent of ring enlargement in **9x** and **9n.**

The transition state for the ring enlargement in the exo carbinol **9x** would be represented by **18x** (Scheme III), and that in **9n** by **18n.** In **18n,** the two substituents, C-5 and C-9, on the bridging carbon atom C-4 are situated close to the plane of the bridge and, hence, to C-3 and C-2, respectively. The geometry of these atoms here is quite similar to that in **17,** and we may call this geometry a *parallel* disposition (of C-1–C-2 and C-8–C-9 in **17** and C-2–C-3 and C-5–C-9 in **18n**). In contrast to **18n, 18x** has a *perpendicular* arrangement of C-5–C-9

Scheme III



with respect to C-2–C-3, resulting in C-5 and C-9 apart and away from C-2 and C-3. Then steric repulsions around the cationic center would be larger in **18n** than in **18x**, and the energy difference between **18n** and **18x** may be expected to exceed that between the ground state **9n** and **9x**. On the other hand, the transition state for the first step of the skeletal rearrangement, 1,2-transfer of the 2-hydride to give **11a**, would be **19x** for **9x** and **19n** for **9n**. The activation energy should be similar for these processes, as the transition state retains essentially the same configuration as that in the ground state for each carbinol. Therefore, the ring enlargement in **9x** via **18x** would be more likely to occur than that in **9n** via **18n**.

It might seem that the possibility remains for the ring enlargement in **9x** and **9n** by the shift of C-1 in place of C-3. However, transition states for the shift of C-1, **20x** and **20n**, have parallel geometries something like **18n**, which render these processes less likely to occur.

The same concept appears to explain why ring enlargement in *exo*-2,3-trimethylenenorborn-*endo*-2-ylcarbinol gave exclusively *exo*-2,4-ethanobicyclo[3.3.1]nonane (tricyclo[4.3.1.1^{2,5}]undecane, **21**),[15] although it is less stable[14] than *exo*-2,3-trimethylenebicyclo[3.2.1]octane (tricyclo[6.2.1.0^{2,6}]undecane, **22**).[2b] A perpendicular transition state (**21a**) is involved in the route to the former compound, whereas a parallel one (**22a**) is involved in that to the latter.

Another major difference between the reactions of **9x** and **9n** is formation of the simple reduction product, 2-methyl-4-homobrendane (**10x**), only from the exo compound **9x.** The explanation seems to lie in that only **9x** can give rise by 1,3-hydride transfer to the stable 3-yl cation[10] **9xb** which undergoes skeletal rearrangement with difficulty. Suppression of 1,3-transfer of 3-H in **9n** appears to result from an unfavorable orbital overlap between 3-H and the vacant p orbital on the cationic carbon atom. Stability of the bridgehead cation **9xb,** on the other hand, would be understood from the reasoning stated below.

Any of the shifts of β-carbon atoms of **9xb,** C-1, C-5, C-7, and C-9, to the cationic C-3 center produces skeletal structures more strained than 4-homobrendane.[8–14] In addition, all the hydride transfers stereoelectronically conceivable[14] in **9xb,** 1,2-transfer of *endo*-2-H, 4-H's, and 8-H as well as 1,3-transfer of *syn*-9-H, are definitely unfavorable. 1,2-Transfers to the bridgehead C-3 cationic center should trespass through a highly strained transition state involving ethyleneprotonium bridging to the bridgehead.[18] 1,3-Transfer of *syn*-9-H may be kinetically allowable. However, this process produces less stable, secondary **10x**-9-yl cation and, moreover, all the alkyl shifts in **10x**-9-yl cation lead to more strained, cyclobutane-containing structures. Therefore, the 1,3-transfer of *syn*-9-H should be less likely to occur.[1b] The cation **9xb** is thus considered to have little capability for further skeletal rearrangement. In other words, the cation is situated in a "local minimum" on the rearrangement energy surface.[8,14,15]

Experimental Section

All melting and boiling points are uncorrected. Measurements of IR, ^{1}H and ^{13}C NMR, and mass spectra as well as conventional and preparative VPC and Golay column GC–MS measurements were done on the same instruments as in the previous works.[1,2]

4-Homobrendane (**1**), 4-homobrendan-2-one (**7**), and *exo*-2-hydroxy-4-homobrendane (**13**) were prepared according to our previous methods.[2a]

3-Bromo-4-homobrendane (2). 4-Homobrendane (5 g, 0.037 mol) was stirred with 50 g (0.31 mol) of bromine at room temperature for 25 min. Excess bromine was evaporated off in vacuo, and the residue was taken up in carbon tetrachloride. The solution was washed with a saturated sodium bisulfite solution and water and dried over anhydrous magnesium sulfate. Evaporation of the carbon tetrachloride and sublimation of the residue gave 4.2 g (52% yield) of pure 3-bromo-4-homobrendane (**2**): mp 59–60 °C (sealed tube); ^{13}C NMR ($CDCl_3$) δ_C 19.17 (t), 26.15 (t), 31.88 (t), 35.86 (d), 38.46 (d), 40.69 (t and t), 47.82 (t), 53.20 (d), 75.04 (s); mass spectrum *m/e* (rel intensity) 215 (4, M$^+$), 213 (4, M$^+$), 136 (18), 135 (100), 134 (23), 119 (16), 93 (42), 92 (26), 91 (49), 80 (74), 79 (64), 77 (36), 67 (56).

Anal. Calcd for $C_{10}H_{15}Br$: C, 55.81; H, 6.97; Br, 37.22. Found: C, 56.01; H, 7.11; Br, 36.9.

Hydrolysis of **2** in acetone–water at reflux[7] overnight in the presence of 2 equiv of sodium carbonate followed by purification by sublimation gave 3-hydroxy-4-homobrendane (**5**) in 88% yield: mp 161–162 °C (sealed tube) (lit.[10] mp 161–162 °C); IR (neat) 3350, 1120, 1110, 1090, 980, 890 cm^{-1}; mass spectrum *m/e* (rel intensity) 152 (100, M$^+$), 137 (15), 134 (16), 124 (20), 119 (16), 111 (17), 110 (36), 109 (45), 108 (18), 97 (90).

4-Homobrendane-3-carboxylic Acid (3). A solution of 3.0 g (0.014 mol) of the bromide 2 in 30 mL (0.79 mol) of 99% formic acid was added dropwise with efficient stirring over a period of 30 min to 50 mL of 95% sulfuric acid kept at 0–5 °C. The reaction was stirred for an additional 2 h at the same temperature, and the reaction mixture was poured onto 500 mL of ice–water. Crude 4-homobrendane-3-carboxylic acid (**3,** 1.8 g, 71% yield) was isolated by the same procedure as that for 4-homoisotwistane-3-carboxylic acid.[7] Purification by sublimation in vacuo gave a pure sample: mp 66–67 °C (sealed tube); IR (neat) 2650, 1690, 1450, 1400, 1290, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–2.2 (m, 15 H), 12.1 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ_C 15.26 (t), 26.35 (t), 30.78 (t), 32.97 (t), 33.25 (d), 36.75 (t), 37.23 (d), 40.60 (t), 44.10 (d), 49.29 (s), 186.08 (s); mass spectrum *m/e* (rel intensity) 180 (9, M$^+$), 136 (12), 135 (100), 93 (11), 79 (12), 67 (14).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 9.03.

The acid thus obtained was decarboxylated to 4-homobrend-3-yl acetate (**6**) as follows. A mixture of 1.8 g (0.01 mol) of the acid **3**, 7.2 g (0.016 mol) of lead tetraacetate, 8.4 g (0.086 mol) of anhydrous potassium acetate, and 60 mL of glacial acetic acid was heated for 4 h under reflux with stirring. The mixture was concentrated in vacuo and the residue was extracted with three 20-mL portions of ether. The combined ether extracts were washed with a saturated sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. Evaporation of the ether and purification of the residue by preparative VPC gave 0.87 g (45% yield) of 4-homobrend-3-yl acetate (**6**): IR (neat) 2950, 1730, 1370, 1260, 1250, 1220, 1070 cm^{-1} (lit.[10] 5.73 μm = 1745 cm^{-1}); ^1H NMR ($CDCl_3$) δ 0.9–2.5 (m), including 1.78 (s) (lit.[10] δ 1.0–2.4 (m) with s at 1.79); mass spectrum *m/e* (rel intensity) 194 (1, M^+), 152 (24), 135 (21), 134 (100), 119 (23), 106 (12), 105 (17), 97 (17), 92 (27), 80 (45).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.02; H, 9.48.

Reduction of 0.49 g (0.0025 mol) of the acetate **6** with 0.095 g (0.0025 mol) of lithium aluminum hydride in 10 mL of ether gave 0.35 g (92% yield) of 4-homobrendan-3-ol (**5**), which was identical with the sample obtained from the bromide **2** on comparison of spectra and mixture melting point determination.

4-Homobrend-3-ylcarbinol (4). A solution of 1.8 g (0.01 mol) of the carboxylic acid **3** in 10 mL of dry ether was added dropwise with stirring into a suspension of 0.57 g (0.015 mol) of lithium aluminum hydride in 20 mL of ether. The mixture was heated under reflux for 3 h, cooled, and treated with 1.8 mL of water, 1.8 mL of 3 N sodium hydroxide solution, and then 5.4 mL of water. The ether layer was separated and dried over anhydrous sodium sulfate. Evaporation of the ether and purification of the residue by sublimation in vacuo afforded 1.41 g (85% yield) of pure 4-homobrend-3-ylcarbinol (**4**): mp 90–91 °C (sealed tube); IR (neat) 3600, 1120, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.2 (m, 15 H), 2.80 (s, 1 H), 3.26 (q, 2 H); ^{13}C NMR ($CDCl_3$) δ_C 16.32 (t), 27.00 (t), 30.00 (t), 33.33 (t), 34.23 (d), 36.83 (t), 37.64 (d), 38.98 (t), 42.07 (s), 42.76 (d), 71.10 (t); mass spectrum *m/e* (rel intensity) 166 (1, M^+), 136 (29), 135 (100), 93 (35), 91 (16), 81 (23), 79 (36), 77 (16), 67 (57).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.52; H, 10.83.

2-Methylene-4-homobrendane (8). A solution of 21.4 g (0.060 mol) of methyltriphenylphosphonium bromide and 5.76 g (0.060 mol) of potassium *tert*-butoxide in 100 mL of Me_2SO was stirred at room temperature for 1 h. 4-Homobrendan-2-one (**7**, 6.0 g, 0.040 mol) was added dropwise with stirring to the above solution over a period of 1 h, and then the solution was heated to 150–160 °C for 3 h. The cooled reaction mixture was mixed with 100 mL of cold water and extracted with three 100-mL portions of *n*-pentane. The combined pentane extracts were washed with water and concentrated. The residue was passed through an alumina-packed column (¾ in. × 1 ft) and eluted with *n*-pentane. Evaporation of the pentane gave 4.26 g (72% yield) of pure 2-methylene-4-homobrendane (**8**): IR (neat) 3070, 2940, 2860, 1670, 1450, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–2.8 (m, 14 H), 4.60 (d, 1 H), 4.90 (d, 1 H); mass spectrum *m/e* (rel intensity) 148 (78, M^+), 119 (33), 107 (40), 105 (32), 94 (54), 92 (34), 91 (57), 80 (100), 79 (76), 77 (33).

Anal. Calcd for $C_{11}H_{16}$: C, 89.19; H, 10.81. Found: c, 88.98; H, 10.83.

4-Homobrend-*endo*-2-ylcarbinol (9n). Hydroboration of 3.52 g (0.024 mol) of the methylene-4-homobrendane **8** was carried out in the usual manner in 40 mL of THF with 1.8 g (0.048 mol) of sodium borohydride and 9.1 g (0.064 mol) of boron trifluoride etherate at ambient temperature for 30 min. Oxidation of the reaction mixture with 10 mL of 30% hydrogen peroxide and 10 mL of 3 N sodium hydroxide solution gave crude 4-homobrend-*endo*-2-ylcarbinol (**9n**). Purification by alumina column chromatography with *n*-pentane and ether as eluents afforded 2.8 g (71% yield) of a pure sample: mp 77–78 °C (sealed tube); IR (neat) 3250, 1030, 1000 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.0–2.2 (m, 16 H), 3.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ_C 18.52 (t), 24.24 (t), 25.83 (t), 26.68 (t), 33.22 (d), 34.44 (d), 39.35 (d), 40.93 (t), 43.13 (d), 46.98 (d), 60.55 (t); mass spectrum *m/e* (rel intensity) 166 (2, M^+), 148 (100), 135 (63), 133 (27), 120 (32), 119 (63), 107 (32), 106 (32), 105 (28), 95 (43), 94 (44), 93 (54), 92 (44), 91 (47), 81 (60), 80 (76), 79 (92).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.51; H, 11.00.

***endo*-2-Methyl-4-homobrendane (10n).** 4-Homobrend-*endo*-2-ylcarbinol (**9n**, 0.4 g, 0.0024 mol) was allowed to react with 0.50 g (0.0026 mol) of *p*-toluenesulfonyl chloride in 10 mL of pyridine at room temperature for 5 h to give 0.76 g (99% yield) of the crude tosylate of **9n**: IR (neat) 1360, 1190, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.2 (m, 15 H), 2.40 (s, 3 H), 4.21 (d, J = 7 Hz, 2 H), 7.1–7.6 (q, 4 H).

A sample (0.75 g, 0.0023 mol) of the tosylate obtained above was reduced with 0.18 g (0.0047 mol) of lithium aluminum hydride in 25 mL of ether. The crude product was purified by column chromatography (alumina–*n*-pentane) to give 0.30 g (85% yield) of pure *endo*-2-methyl-4-homobrendane (**10n**): mp 90–91 °C (sealed tube); ^1H NMR ($CDCl_3$) δ 0.9–1.8 (m); ^{13}C NMR ($CDCl_3$) δ_C 11.01 (q), 18.32 (t), 24.46 (t), 25.40 (t), 26.80 (t), 33.68 (d), 34.63 (d), 38.04 (d), 40.99 (t), 43.14 (d), 43.40 (d); mass spectrum *m/e* (rel intensity) 150 (100, M^+), 135 (55), 121 (81), 109 (40), 95 (68), 94 (55), 79 (57), 67 (48).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 88.01; H, 11.98.

2-Methyl-4-homobrendan-2-ol (11). A solution of methylmagnesium iodide was prepared from 8.0 g (0.066 mol) of methyl iodide and 1.6 g (0.066 mol) of magnesium foil in 10 mL of ether. To the solution was added dropwise with stirring a solution of 1.5 g (0.010 mol) of 4-homobrendan-2-one (**7**) in 5 mL of ether, and the reaction was heated under reflux for 2 h. The crude 2-methyl-4-homobrendan-2-ol (**11**) was purified by passage through an alumina column with ether as eluent to give 1.4 g (84% yield) of pure **11**: mp 45–46 °C (sealed tube); IR (neat) 3450, 2930, 1470, 1450, 1290, 1260, 1210, 1160, 1140, 1070, 1050, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.3 (m, with sharp s at 1.12); ^{13}C NMR ($CDCl_3$) δ_C 17.10 (t), 23.55 (t), 25.10 (q), 26.80 (t), 31.75 (d), 33.17 (t), 37.60 (t), 42.39 (d), 42.59 (d), 49.42 (d), 75.00 (s); mass spectrum *m/e* (rel intensity) 166 (22, M^+), 151 (14), 148 (63), 123 (36), 121 (13), 119 (22), 108 (56), 96 (21), 95 (32), 81 (81).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.52; H, 10.85.

4-Homobrendane-*exo*-2-carboxylic Acid (14). A mixture of 6.0 g (0.039 mol) of *exo*-2-hydroxy-4-homobrendane (**13**) and 50 mL of thionyl chloride was heated under reflux for 3 h. Excess thionyl chloride was evaporated off, finally azeotropically with benzene, and the residue was distilled in vacuo to give 3.0 g (45% yield) of 2-chloro-4-homobrendane: bp 57 °C (0.5 mm); ^1H NMR ($CDCl_3$) δ 1.0–2.2 (m, 14 H), 3.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ_C 14.86 (t), 24.89 (t), 26.67 (t), 30.94 (t), 32.12 (d), 38.25 (t), 42.07 (d), 47.22 (d), 48.45 (d), 65.62 (d); mass spectrum *m/e* (rel intensity) 171 (4, M^+), 170 (27), 135 (56), 134 (100), 121 (56), 119 (15), 105 (19), 93 (39), 92 (31), 91 (47), 79 (50), 77 (37), 67 (41).

Anal. Calcd for $C_{10}H_{15}Cl$: C, 70.38; H, 8.80; Cl, 20.82. Found: C, 70.55; H, 8.97; Cl, 20.4.

A sample (2.0 g, 0.012 mol) of the chloride was allowed to react with 0.29 g (0.012 mol) of magnesium in 10 mL of ether, and carbon dioxide was bubbled through the mixture for 2 h at ambient temperature. The crude product was purified by extraction with 5% sodium hydroxide solution, followed by acidification with concentrated hydrochloric acid, and recrystallized from methanol–water to give 0.96 g (46% yield) of pure 4-homobrendane-*exo*-2-carboxylic acid (**14**): mp 63–64 °C (sealed tube); IR (Nujol) 1700, 1310, 1295, 1260, 1230, 940, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.8 (m, 15 H), 11.7 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ_C 14.61 (t), 26.24 (t), 26.83 (t), 33.20 (t and d), 39.17 (d), 39.82 (t), 41.51 (t and t), 49.83 (d), 182.89 (s).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.19; H, 8.91.

Decarboxylation of 0.2 g (0.0011 mol) of the acid **14** with 1.2 g (0.0027 mol) of lead tetraacetate and 1.4 g (0.014 mol) of potassium acetate in 15 mL of acetic acid at reflux for 2 h gave 0.12 g (57% yield) of *exo*-2-acetoxy-4-homobrendane (**12**), which was identical in all respects with an authentic specimen of **12**.[2a]

4-Homobrend-*exo*-2-ylcarbinol (9x). The exo-2-carboxylic acid **14** (0.60 g, 0.0033 mol) was reduced by 0.60 g (0.016 mol) of lithium aluminum hydride in 20 mL of ether. The crude product was purified by column chromatography to give 0.53 g (96% yield) of pure 4-homobrend-*exo*-2-ylcarbinol (**9x**): IR (neat) 3300, 1050, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.2 (m, 15 H), 2.67 (s, 1 H), 3.30 (d, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ_C 15.06 (t), 26.51 (t), 27.16 (t), 33.58 (t and d), 38.33 (t), 38.45 (d), 39.30 (d), 41.70 (d), 48.32 (d), 66.43 (t); mass spectrum *m/e* (rel intensity) 166 (4, M^+), 148 (43), 136 (21), 135 (100), 119 (13), 107 (14), 94 (14), 93 (33), 91 (24), 81 (26), 79 (45), 77 (22), 67 (46).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.58; H, 10.99.

***exo*-2-Methyl-4-homobrendane (10x).** The exo carbinol **9x** (0.35 g, 0.0021 mol) was tosylated with 0.52 g (0.0028 mol) of *p*-toluenesulfonyl chloride in 10 mL of pyridine. The crude tosylate was recrystallized from ether–*n*-hexane to give 0.51 g (76% yield) of a pure sample: mp 59–60 °C; IR (neat) 1350, 1200, 1180 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.0–2.0 (m, 15 H), 2.40 (s, 3 H), 3.76 (d, J = 7 Hz, 2 H), 7.1–7.8 (m, 4 H).

Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.48; H, 7.55; S, 9.99. Found: C, 67.71; H, 7.35; S, 10.3.

The tosylate was reduced with 0.20 g (0.0052 mol) of lithium aluminum hydride in 20 mL of ether. Purification of the crude product by column chromatography gave 0.15 g (63% yield) of pure *exo*-2-methyl-4-homobrendane (**10x**): ^1H NMR ($CDCl_3$) δ 0.9–1.8 (m); ^{13}C NMR ($CDCl_3$) δ_C 15.17 (t), 21.63 (q), 26.11 (t), 27.38 (t), 33.16 (d), 33.81 (t), 38.07 (t), 39.88 (d), 42.46 (d), 44.05 (d), 44.11 (d); mass spectrum m/e (rel intensity) 150 (100, M^+), 135 (58), 121 (51), 109 (27), 108 (33), 107 (18), 95 (56), 94 (48), 93 (31), 81 (33).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.70; H, 12.22.

Registry No.—**1**, 49700-65-4; **2**, 66085-39-0; **3**, 66085-40-3; **4**, 66085-41-4; **5**, 66085-42-5; **6**, 16489-35-3; **7**, 50529-80-1; **8**, 66085-43-6; **9n**, 66085-44-7; **9n** tosylate, 66085-45-8; **9x**, 66140-51-0; **9x** tosylate, 66140-52-1; **10n**, 66085-46-9; **10x**, 66140-53-2; **11**, 66085-47-0; **12**, 61559-34-0; **13**, 50529-94-7; **14**, 66085-48-1; **15**, 43000-53-9; **16**, 51027-87-3; 2-Me-Ad, 700-56-1; 1-Me-Ad, 768-91-2; 2-chloro-4-homobrendane, 66085-49-2; homoadamantane, 281-46-9; *endo*-2,8-trimethylenebicyclo[3.3.0]octane, 28099-09-4.

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Metal Ion Oxidation. 6.[1] Oxidative Acetoxylation of Aromatic Compounds by Silver(II) Complexes in Acetic Acid[2]

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Silver(II) complexes with nitrogen-containing ligands oxidize aromatic compounds (anisole, substituted anisoles, biphenyl, naphthalene, and hexamethylbenzene) in 0.5 M KOAc/HOAc yielding acetoxy derivatives (nuclear or side-chain acetates). Anisole and biphenyl give mainly ortho and para acetates. Results from the competitive oxidation of 4-substituted anisoles gave a Hammett ρ value of −3.4. Nuclear substitution did not show any deuterium isotope effect, whereas side-chain substitution of 4-methoxytoluene gave a k_H/k_D value of 5.9. Oxidation of benzene in trifluoroacetic acid gave phenol after hydrolysis of the reaction product. It is suggested that silver(II) reacts by removing one electron from the aromatic substrate, yielding a radical cation in the initial step. The synthetic utility of the reaction is demonstrated in a catalytic process using either presynthesized bis(2,2′-bipyridine)silver(II) peroxodisulfate or a mixture of silver(I) acetate and 2,2′-bipyridine in the presence of excess potassium peroxodisulfate. Acetates are produced with catalyst efficiencies between 1500 and almost 10 000%.

Although Ag(II) is a very strong oxidant[3] its use as a reagent in organic synthesis has been limited. The oxide, AgO, and the bis(2-pyridine carboxylate), $Ag(pic)_2$, are known to oxidize a variety of organic compounds in aqueous acidic or basic media.[4] More recently it has been shown that AgO dissolved in trifluoroacetic acid (TFA) could affect oxidation of aliphatic hydrocarbons[5] and coupling of phenolic substrates.[6] Kinetic studies have been reported on the oxidation of carboxylic acids by Ag(II)[7–9] or by Ag(I) and peroxodisulfate anion, $S_2O_8^{2-}$.[10] In the latter study it was shown that Ag(II), obtained by the action of $S_2O_8^{2-}$ on Ag(I), was the primary oxidant.

In a preliminary report we described the reaction between some aromatic compounds and bis(2,2′-bipyridine)silver(II) peroxodisulfate, $Ag(bpy)_2S_2O_8$, in acetic acid containing sodium acetate.[11] The major products were arenes acetoxylated in nuclear and/or side-chain (α) positions. Methyl-substituted arenes also gave benzaldehydes. The stoichiometry of the reaction seemed to follow eq 1.

$$3ArH + 2Ag(II) + 2S_2O_8^{2-} + 3OAc^- \rightarrow 3ArOAc + 2Ag(I) + 4SO_4^{2-} + 3H^+ \quad (1)$$

As an example, 4-methoxytoluene was converted into a mixture of 4-methoxybenzyl acetate and 4-methoxybenzaldehyde in a yield of almost 300% based on Ag(II)[12] by $Ag(bpy)_2S_2O_8$. This indicated that Ag(II) as well as $S_2O_8^{2-}$ were involved in the overall reaction. The removal of one electron from the

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Table I. Acetoxylation of 4-X-anisoles by $Ag(bpy)_2S_2O_8$

X	Registry no.	Reaction time, h	Product	Yield (4)[a]	Registry no.
OMe	150-78-7	2	1	190	27257-06-3
F	459-60-9	5	2	105[b]	1200-06-2
t-Bu	5396-38-3	6	1	190	66037-02-3
H	100-66-3	6	1	135[c]	66037-03-4
Cl	623-12-1	12	1	155	66037-04-5
Br	104-92-7	16	1	106	104-93-8

[a] GLC yield. [b] Based on a one-electron reaction. [c] The acetoxyanisoles were formed in a o:m:p ratio of 68:1:31.

Table II. Isomer Distribution in Oxidative Acetoxylation

Substrate	Oxidant	Relative amount of acetates o	m	p
Anisole	$Ag(bpy)_2S_2O_8$	68.0	0.6	31.4
Anisole	$Ag(phen)_2S_2O_8$	68.6	1.4	30.0
Anisole	$Ag(py)_4S_2O_8$	72.9	2.8	24.3
Anisole	$Ag(pic)_2$	65.6	1.9	32.5
Anisole	$Ag(bpy)_2(CF_3SO_3)_2$	69.9	1.7	28.4
Anisole	Anodic[a]	67.4	3.5	29.1
Biphenyl	$Ag(bpy)_2S_2O_8$	21.3	*b*	78.7
Biphenyl	$Ag(phen)_2S_2O_8$	22.8	*b*	77.2
Biphenyl	$Ag(py)_4S_2O_8$	20.5	*b*	79.5
Biphenyl	$Ag(pic)_2$	21.5	*b*	78.5
Biphenyl	$Ag(bpy)_2(CF_3SO_3)_2$	20.9	*b*	79.1
Biphenyl	Anodic[a]	30.7	0.9	68.4

[a] Data taken from ref 17. [b] Less than 0.1% of the meta formed.

arene is probably the primary reaction step and could take place either by the action of Ag(II) as shown in eq 2 or by the sulfate radical anion, $SO_4^{-}\cdot$, as shown in eq 3. The latter species is a strong oxidant and is formed by the decomposition of $S_2O_8^{2-}$ by heat,[13] by a catalyst,[13] by pulse radiolysis,[14] or photochemically.[15] Ag(I) ion is known to be an efficient catalyst[16] (eq 4).

$$ArH + Ag(II) \rightarrow ArH^{+}\cdot + Ag(I) \quad (2)$$

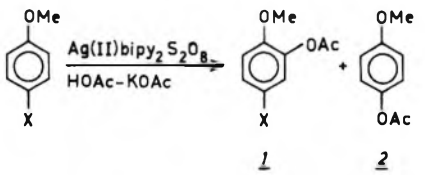
$$ArH + SO_4^{-}\cdot \rightarrow ArH^{+}\cdot + SO_4^{2-} \quad (3)$$

$$S_2O_8^{2-} + Ag(I) \rightarrow SO_4^{-}\cdot + SO_4^{2-} + Ag(II) \quad (4)$$

We now present an extensive study on the acetoxylation of arenes by different Ag(II) complexes. The synthetic use of these reactions is demonstrated by the catalytic action of Ag(II) in the presence of an excess of potassium peroxodisulfate.

Results

Products. In our earlier report[11] we found that oxidation of anisole, biphenyl, naphthalene, 1,4-dimethoxybenzene, and mesitylene by $Ag(bpy)_2S_2O_8$ resulted in the formation of nuclear acetates in yields ranging from 42 to 190%. We now use mainly 4-substituted anisoles as substrates, since they react with Ag(II) at convenient rates making them suitable for mechanistic studies. Oxidation with $Ag(bpy)_2S_2O_8$ in general gave one product (eq 5 and Table I), 4-fluoroanisole



(5)

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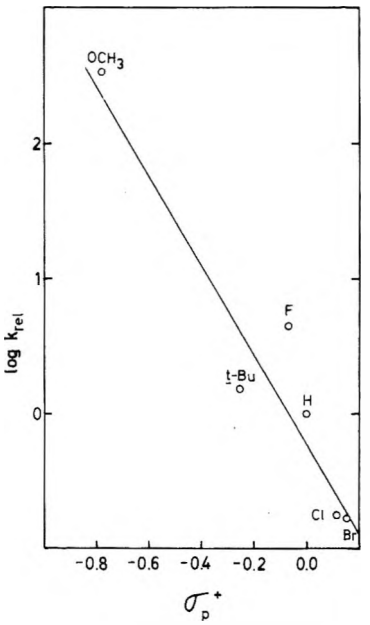


Figure 1. Hammett correlation for competitive acetoxylation of 4-substituted anisoles.

being an exception (see Discussion). The reactions were carried out by adding $Ag(bpy)_2S_2O_8$ to a solution of the substrate in fivefold excess in 0.5 M KOAc/HOAc at room temperature. The reaction was complete when the dark-brown color of the slurry (due to the Ag(II) complex) had changed to colorless.

Isomer Distribution. Anisole and biphenyl were chosen for a detailed study of the isomer distribution in oxidative acetoxylation by different Ag(II) complexes. The results are shown in Table II. Besides the $Ag(bpy)_2S_2O_8$ complex we have studied the corresponding 1,10-phenanthroline (phen) and pyridine (py) complexes. Since it is important from a mechanistic point of view to include Ag(II) complexes containing nonoxidizing counterions we have studied two such Ag(II) complexes, namely $Ag(pic)_2$ and the trifluoromethane sulfonate, $Ag(bpy)_2(CF_3SO_3)_2$. In Table II we have also included data from anodic acetoxylation.[17] No significant difference is observed between different oxidants. We have also compared the oxidation of 4-methoxytoluene by $Ag(bpy)_2S_2O_8$ and $Ag(bpy)_2(CF_3SO_3)_2$, respectively, in KOAc/HOAc. Both oxidants produced a mixture of 4-methoxybenzyl acetate and 4-methoxybenzaldehyde (ratio 3:1) in a quantitative yield based on Ag(II). The same products, although in different ratio and lower yield, are obtained by the action of $Mn(OAc)_3$ in HOAc,[18] $Mn(OAc)_3$ in H_2SO_4/HOAc,[19] $Co(OAc)_3$ in LiCl/HOAc,[20] or by anodic oxidation in HOAc.[17]

Competition Experiments. We initially tried to measure the rate of oxidation of 4-substituted anisoles by $Ag(bpy)_2(CF_3SO_3)_2$ by following the disappearance in Ag(II) spectrophotometrically. However, we had to abandon this technique due to poor reproducibility of the results.[21] Instead we determined the relative rates of oxidation using the same Ag(II) complex, chosen in order to avoid $S_2O_8^{2-}$ as a counterion. The reactions were carried out by adding $Ag(bpy)_2(CF_3SO_3)_2$ to a solution of two substrates, each in a tenfold excess, in 0.5 M KOAc/HOAc. The mixture was stirred at room temperature until colorless and the ratio of the products was determined by GLC. The results are shown in Figure 1 as a Hammett plot of log k_X/k_H vs. the substituent constant σ_p^+,[22] yielding a ρ value of −3.4 (correlation coefficient = 0.95). This may be compared with a ρ value of −2.4 obtained in $Co(OAc)_3$ oxidation of 4-substituted toluenes,[20] or a ρ value of −2.4 from the reaction of $SO_4^{-}\cdot$ with substituted benzenes in aqueous solution.[14] Both these processes are assumed to be electron-transfer oxidations.

Table III. Small-Scale[a] and Preparative-Scale[b] Catalytic Acetoxylation[j]

Substrate	Catalyst	Product	Yield (%) based on Ag(II)[c]	Yield (%) based on Consumed substrate[d]
1,4-Dimethoxybenzene	$Ag(pic)_2$	2-Acetoxy-1,4-dimethoxybenzene	4930	
1,4-Dimethoxybenzene	$Ag(py)_4S_2O_8$	2-Acetoxy-1,4-dimethoxybenzene	1680	
1,4-Dimethoxybenzene	$Ag(phen)_2S_2O_8$	2-Acetoxy-1,4-dimethoxybenzene	8680	
1,4-Dimethoxybenzene	$Ag(bpy)_2S_2O_8$	2-Acetoxy-1,4-dimethoxybenzene	1880[e]	
1,4-Dimethoxybenzene	$Ag(bpy)_2S_2O_8$	2-Acetoxy-1,4-dimethoxybenzene	8720	33
Anisole	$Ag(bpy)_2S_2O_8$	Acetoxyanisoles	5960	39
4-Bromoanisole	$Ag(bpy)_2S_2O_8$	2-Acetoxy-4-bromoanisole	5560	40
4-*tert*-Butylanisole	$Ag(bpy)_2S_2O_8$	2-Acetoxy-4-*tert*-butylanisole	1470[f]	29[f]
4-Methoxytoluene	$Ag(bpy)_2S_2O_8$[i]	4-Methoxybenzyl acetate	7540[g]	35[g]
		4-Methoxybenzaldehyde	2270[g]	12[g]
Hexamethylbenzene	$Ag(bpy)_2S_2O_8$[i]	Pentamethylbenzyl acetate	5370[g]	
		Pentamethylbenzyl alcohol	1660[g]	
Naphthalene	$Ag(bpy)_2S_2O_8$	Acetoxynaphthalenes	6760[h]	

[a] Catalyst (0.1 mmol), $K_2S_2O_8$ (10 mmol), $Ba(OAc)_2 \cdot H_2O$ (4 mmol) and substrate (10 mmol) in 0.5 M NaOAc/HOAc (20 mL) at 40 °C. [b] Carried out on a scale 20 times the small-scale reactions. The catalyst can be replaced by AgOAc and 2,2′-bipyridine. [c] GLC yields in small-scale reactions. [d] Yields of isolated products in preparative reactions. [e] In the absence of Ba(II). [f] At 30 °C. [g] Carried out under argon and with the addition of Ac_2O. [h] The 1- and 2-acetoxynaphthalenes were formed in a ratio of 95:5. [i] Using AgOAc and 2,2′-bipyridine as catalysts the amount of aldehyde formed decreased to a nonsignificant level. [j] Registry No.—4-Methoxytoluene, 104-93-8; hexamethylbenzene, 87-85-4; naphthalene, 91-20-3; $Ag(pic)_2$, 14783-00-7; $Ag(py)_4S_2O_8$, 15810-50-1; $Ag(phen)_2S_2O_8$, 22750-33-0; $Ag(bpy)_2S_2O_8$, 28226-64-4; 4-methoxybenzyl acetate, 104-21-2; 4-methoxybenzaldehyde, 123-11-5; pentamethylbenzyl acetate, 19936-85-7; pentamethylbenzyl alcohol, 484-66-2.

Isotope Effects. It has previously been shown that anodic acetoxylation of anisole, deuteriated in the ring,[17] or trifluoroacetoxylation of deuteriated benzene[23] by Co(III) trifluoroacetate occur with the same rates as with the protiated compounds. We have used $Ag(bpy)_2(CF_3SO_3)_2$ in 0.5 M KOAc/HOAc to study the acetoxylation of mesitylene-*2,4,6-d*$_3$. A comparison between nuclear and α substitution in the deuteriated and the protiated mesitylene showed no isotope effect ($k_H/k_D = 1.1 \pm 0.2$). Using the same oxidant we studied the α acetoxylation of a mixture of equal amounts of 4-methoxytoluene and 4-methoxytoluene-α,α,α-d_3. By determining the deuterium content in 4-methoxybenzyl acetate by MS a k_H/k_D value of 5.9 ± 0.2 was calculated. This value may be compared to those obtained in $Mn(OAc)_3$ oxidation (5.1)[18] and anodic acetoxylation (2.6)[17] of the same compounds.

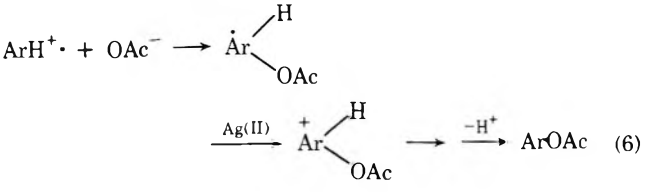
The Effect of Acetate Ion. In our preliminary report[11] we noted that the rate of oxidation with $Ag(bpy)_2S_2O_8$ in HOAc increased significantly when NaOAc was present. We attributed this effect to the buffer capacity of NaOAc, since the reaction produces protons (as H_2SO_4). These might have a deleterious influence on the Ag(II) complex, e.g., by protonation of the bipyridine ligand. Although part of the rate increase might be due to the buffer capacity of acetate ions we now believe that most of the rate increase is caused by the increase in solubility of the Ag(II) complex in HOAc that the acetate ion causes. Thus the solubility of $Ag(bpy)_2S_2O_8$ increased from 0.01 to 0.03 M when the concentration of KOAc in HOAc was increased from 0.5 to 1.0 M.

Reaction in TFA. In several reports it has been shown that the oxidative power of metal ions is greatly increased by carrying out reactions in TFA instead of HOAc, e.g., Co(III),[20,23,24] Mn(III),[24] Pb(IV),[24-26] and Ce(IV).[27] In some cases ESR spectra of radical cations have been observed in TFA.[23,28] Using $Ag(bpy)_2(CF_3SO_3)_2$ in TFA at −10 °C we tried to obtain an ESR spectrum of the radical cation of 1,4-di-*tert*-butylbenzene. Although the information we obtained indicated that the radical cation was formed, the spectrum was poorly resolved, probably due to the instability of the Ag(II) complex in TFA. We also carried out a preparative experiment with the same Ag(II) complex in TFA using benzene as the substrate and obtained (after hydrolysis of the reaction mixture) phenol in a 17% yield, based on Ag(II).

Catalytic Reactions. When the oxidative acetoxylation of aromatic compounds by Ag(II) complexes is carried out with added $K_2S_2O_8$ the formation of acetoxylated arenes is catalytic in Ag(II). Furthermore we have found that the reactions can be carried out starting with AgOAc, 2,2′-bipyridine, and $K_2S_2O_8$. We also noticed a profound effect on the yields when $Ba(OAc)_2$ was present in the reaction mixture, the yields being considerably higher in its presence. Since SO_4^{2-} is formed during the reaction and could inhibit the reaction by precipitation of Ag_2SO_4, it is probable that Ba(II) removes SO_4^{2-} as $BaSO_4$. In view of the high catalytic activity of this system the reaction might be of synthetic value. Results from small-scale experiments and some preparative experiments are shown in Table III.

Discussion

Mechanism. Judging from the results it seems evident that the oxidation with Ag(II) in the absence of $S_2O_8^{2-}$ follows the same mechanism as that proposed for Co(III) and Mn(III) oxidations,[29] i.e., eq 2 is the rate-determining step. The isomer distribution from the acetoxylation of anisole and biphenyl is the same for Ag(II) and the anode reactions. The Hammett correlation gave a ρ value of −3.4 indicating an electron-transfer reaction.[14,20] The oxidation in TFA gave results supporting an electron-transfer reaction, although the evidence was not clear cut. The product from the oxidation of benzene (phenol after hydrolysis of the initially formed phenyl trifluoroacetate) is the same that is obtained by Co(III)[23] and anodic oxidation,[30] respectively, in TFA. The possibility that Ag(II) oxidizes acetate ion to give the acetoxy radical that subsequently reacts with the aromatic substrate is ruled out in the same way as in anodic acetoxylation,[31] although radical substitution may have electrophilic character as shown for isopropoxylation of aromatic substrates ($\rho = -2.3$).[32] The radical cation (eq 2) will be trapped by acetate ion yielding an acetoxycyclohexadienyl radical. This species is rapidly oxi-



dized by Ag(II) to a cation that forms the product after loss of a proton (eq 6). The last step is fast as shown by the absence of a deuterium isotope effect. Oxidative substitution in the side chain, as in 4-methoxytoluene or hexamethylbenzene, takes place according to

$$ArCH_3^{+}\cdot \xrightarrow{-H^+} ArCH_2\cdot \xrightarrow{Ag(II)} ArCH_2^{+} \xrightarrow{OAc^-} ArCH_2OAc \quad (7)$$

The first step in eq 7, loss of a proton from the radical cation, is the slow step as shown by the deuterium isotope effect for substitution in 4-methoxytoluene. The effect is comparable to that obtained in Mn(III) oxidation.[18]

When the oxidation of the aromatic substrates is carried out with Ag(II) and $S_2O_8^{2-}$ present, the mechanism is less clear cut. Some recent studies have convincingly shown that $SO_4^{-}\cdot$, formed by radiolytic[14,33] or metal ion catalytic[34] decomposition of $S_2O_8^{2-}$, is capable of oxidizing aromatic substrates in aqueous solutions. Methoxylated benzene radical cations have been observed.[33] However, the same redical cations have also been generated by Ag(II).[33] Hydroxycyclohexadienyl radicals, intermediates in $SO_4^{-}\cdot$ oxidation of aromatic substrates, have also been observed.[35] Thus, although our reaction conditions are different we cannot rule out the possibility that $SO_4^{-}\cdot$ oxidizes aromatic substrates in KOAc/HOAc. We have also tried to acetoxylate anisole with $K_2S_2O_8$ in KOAc/HOAc. No acetoxyanisoles were formed. The addition of Cu(II) to this system did not change the result. Recent studies have shown that some metal ions promote the formation of phenols in the $SO_4^{-}\cdot$ oxidation[34] and in the radical-induced hydroxylation[36] of benzene derivatives.

Comparison with Anodic Acetoxylation. A comparison of products from oxidation of aromatic substrates by other metal ion oxidants is not useful, since the same substrates have only been used in a few cases. We have already mentioned the similarity between Ag(II), Co(III),[20] and Mn(III)[18] oxidation of 4-methoxytoluene and the Ag(II) and Co(III)[23] oxidation of benzene in TFA. On the other hand Ag(II) and anodic oxidations may be compared. The similarities are striking. The isomer distributions in the acetoxylation of anisole and biphenyl are the same. The product distributions from the acetoxylation of mesitylene,[11,37] naphthalene,[11,37] or 4-methoxytoluene[17] and from the trifluoroacetoxylation of benzene[30] by Ag(II) or by the anode are also the same. Some of the nuclear acetates have been prepared by anodic acetoxylation for reference purposes and the yields are comparable to those obtained by Ag(II) acetoxylation.

The result from the Ag(II) acetoxylation of 4-fluoroanisole is of particular interest, since the anodic acetoxylation[38] yields the same product, 4-acetoxyanisole, i.e., an anomalous substitution product. On the other hand 4-chloroanisole and 4-bromoanisole respectively yield the normal product by both oxidants. In the anodic reaction of 4-fluoroanisole we have shown that the usual reaction mechanism for anodic substitution, analogous to eq 2 and 6, is not valid.[38] Instead we have suggested that fluoride ion is lost at some intermediate stage, e.g., as shown in eq 8 and 9, and we believe it is reasonable to

$$ArF \xrightarrow{-e} ArF^{+}\cdot \xrightarrow{OAc^-} \dot{Ar}\begin{matrix}OAc\\F\end{matrix} \longrightarrow ArOAc^{+}\cdot + F^- \quad (8)$$

$$\dot{Ar}\begin{matrix}OAc\\F\end{matrix} \xrightarrow{-e} Ar^{+}\begin{matrix}OAc\\F\end{matrix} \longrightarrow ArOAc^{2+} + F^- \quad (9)$$

assume that the same is valid for Ag(II) oxidation. However, we have not been able to explain satisfactorily the reduction of the 4-acetoxyanisole radical cation or dication, respectively, to the final product. The possibility exists that these reactive species oxidize either the starting material or the solvent. An analogous substitution reaction has recently been found in nucleophilic photosubstitution of 4-fluoro-, 4-chloro- and 4-bromoanisole, respectively, by cyanide ion or hydroxide ion.[39] There is, however, one major difference between the photosubstitution reaction and the oxidative reactions described above. While the former reaction yields the anomalous substitution products from all three haloanisoles the latter reactions produce the normal substitution product from 4-chloro- and 4-bromoanisole.

Synthetic Utility. The catalytic reactions can be carried out starting with either AgOAc, 2,2′-bipyridine, and $K_2S_2O_8$ or with presynthesized $Ag(bpy)_2S_2O_8$. The yields, based on Ag(II), are high and the reactions might be particularly useful for the preparation of nuclear acetates of activated aromatic derivatives, such as alkoxy- and hydroxy-substituted ones. The difference between the Ag(II) and the anodic acetoxylation reactions is small with regard to product yields. From the experimental point of view, somewhat more sophisticated equipment is needed in the anodic reactions. $S_2O_8^{2-}$ has also been used as cooxidant in Pd(II)-catalyzed acetoxylation of arenes.[40] This reaction, however, is different with respect to mechanism (metalation instead of electron transfer) and product distribution.[41]

Experimental Section

The Ag(II) complexes were prepared according to literature procedures: $Ag(bpy)_2S_2O_8$,[42] $Ag(py)_4S_2O_8$,[42] $Ag(phen)_2S_2O_8$,[43] $Ag(pic)_2$,[44] $Ag(bpy)_2(CF_3SO_3)_2$.[45] 4-Chloroanisole and 4-*tert*-butylanisole were prepared by methylation of the corresponding phenols using dimethyl sulfate.[46] 4-Methoxytoluene-α,α,α-d_3 was prepared according to a literature method.[18] Mesitylene-2,4,6-d_3 was obtained by equilibrating mesitylene three times with a mixture of D_2O and D_2SO_4. Anhydrous acetic acid was frozen out twice before use. Other compounds were of high commercial quality.

Acetoxyanisoles, acetoxybiphenyls, acetoxynaphthalenes, 4-methoxybenzyl acetates, 4-methoxybenzaldehyde, pentamethylbenzyl acetate, and pentamethylbenzyl alcohol were available from earlier work.[17,37] 2-Acetoxy-1,4-dimethoxybenzene was obtained in 68% yield by anodic oxidation of 1,4-dimethoxybenzene.[47] By the same procedure we obtained 2-acetoxy-4-chloroanisole (27% yield) and 2-acetoxy-4-bromoanisole (50% yield) by anodic oxidation of 4-chloroanisole and 4-bromoanisole, respectively. 2-Acetoxy-4-chloroanisole was identified by NMR and MS and by hydrolyzing it into the phenol followed by reaction with 3,5-dinitrobenzoyl chloride yielding the 3,5-dinitro benzoate, mp 171–172 °C (lit mp 171–171.5 °C[48]). 2-Acetoxy-4-bromoanisole, obtained as a solid, mp 64–65 °C (lit. mp 63–64 °C[49]), was identified by NMR and MS.

GLC analysis was done with a Hewlett-Packard Model 6830 A instrument equipped with an electronic integrator on a 2 m × 0.3 cm 5% NPGS on Chromosorb W column. Product yields were calculated from the GLC data after calibration of the authentic samples against a standard. Preparative GLC was carried out with an Aerograph Model A-700 preparative gas chromatograph on a 6 m × 1 cm 20% SE-30 on Chromosorb W column. NMR spectra were recorded on a Varian A 60 spectrometer. MS analysis was done with a LKB Model 9000 mass spectrometer. ESR spectra were recorded on a Varian E-3 spectrometer at −10 °C and at a pressure of 0.01 mmHg.

Small-Scale Reactions with Ag(II) Complexes. The following procedure was used for product studies, isomer distribution studies, and competitive experiments: The Ag(II) complex (2 mmol) was added to a solution of 0.5 M KOAc/HOAc (20 mL) containing the aromatic substrate (10 mmol). The mixture was stirred at room temperature until it became colorless. Dichloromethane was added and the precipitate was filtered off. The filtrate was washed repeatedly with water. The organic phase was then analyzed by GLC. The small-scale catalytic reactions were carried out under the same conditions at 40 °C for 17 h using the Ag(II) complex (0.1 mmol), $K_2S_2O_8$ (10 mmol), $Ba(OAc)_2\cdot H_2O$ (4 mmol), and the aromatic substrate (10 mmol) in 0.5 M NaOAc/HOAc (20 mL).

Preparative-Scale Catalytic Oxidations. To a solution of the aromatic substrate (200 mmol), $Ba(OAc)_2\cdot H_2O$ (80 mmol), in 0.5 M NaOAc/HOAc (400 mL) was added $Ag(bpy)_2S_2O_8$ (2 mmol) and $K_2S_2O_8$ (200 mmol). Instead of the Ag(II) complex AgOAc (2 mmol) and 2,2′-bipyridine (4 mmol) can be used. The slurry was stirred vigorously for 17 h at 40 °C. The oxidations of 4-methoxytoluene and hexamethylbenzene, respectively, were carried out under an argon atmosphere with the addition of Ac_2O (80 mmol). The reaction mixture was then allowed to cool down to room temperature whereupon

water (400 mL) was added. After filtration of the precipitate the solution was washed three times with dichloromethane. The combined organic phases were washed several times with water and dried over anhydrous sodium sulfate. Dichloromethane was then removed by evaporation in vacuo. The isolation of the products is described below.

Oxidation of 1,4-Dimethoxybenzene. The reaction residue was purified by column chromatography on silica gel. Elution with benzene yielded 2-acetoxy-1,4-dimethoxybenzene, recrystallized from ligroin (13.0 g; 66.3 mmol), mp 67–69 °C (lit. mp 68–69 °C[47]).

Oxidation of 4-Bromoanisole. Distillation at reduced pressure gave 4-bromoanisole (20.0 g; 107 mmol). Column chromatography of the residue on silica gel using carbon tetrachloride as an eluent yielded 2-acetoxy-4-bromoanisole, recrystallized from pentane (10.0 g; 40.8 mmol), mp 64–65 °C (lit. mp 63–64 °C[49]).

Oxidation of 4-*tert*-Butylanisole. The starting material (17.0 g; 103.6 mmol) was collected by distillation at reduced pressure. Further distillation had to be interrupted due to decomposition of the product. Instead, 2-acetoxy-4-*tert*-butylanisole (6.4 g; 28.8 mmol) was isolated by preparative GLC and identified by NMR and MS.

Oxidation of 4-Methoxytoluene. Distillation of the reaction residue gave 4-methoxytoluene (3.4 g; 27.8 mmol), 4-methoxybenzaldehyde (3.0 g; 22.1 mmol; bp 125–128 °C (14 mmHg)), and 4-methoxybenzyl acetate (11.1 g; 61.7 mmol; bp 130–14. °C (14 mmHg).

Oxidation of Anisole. The crude reaction mixture was subjected to distillation in a concentric tube column (Fischer Spaltrohr system with 40 theoretical plates) yielding anisole (6.8 g; 63 mmol), 2-acetoxyanisole (5.2 g; 31.3 mmol; bp 104–106 °C (10 mmHg)), and 4-acetoxyanisole (3.6 g; 21.7 mmol; bp 111–112 °C (9 mmHg)).

Registry No.—$Ag(bpy)2(CF_3SO_3)_2$, 34964-02-8; biphenyl, 92-52-4; 2-acetoxyanisole, 613-70-7; 3-acetoxyanisole, 5451-83-2; 1-acetoxynaphthalene, 830-81-9; 1-acetoxynaphthalene, 1523-11-1; 2-acetoxybiphenyl, 3271-80-5; 4-acetoxybiphenyl, 148-86-7.

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Polymeric Reagents. 3. Poly[vinyl(pyridinium chlorochromate)]: A New Recyclable Oxidizing Agent

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Poly[vinyl(pyridinium chlorochromate)] is prepared easily from cross-linked poly(vinylpyridine) resins by reaction with chromic anhydride and hydrochloric acid. The insoluble reagent, which has a capacity of 3.5–3.9 mmol of chlorochromate per gram, is useful in the oxidation of alcohols to carbonyl compounds. The oxidation has a high efficiency, as less than 1 molar equiv of the reagent is consumed in the reaction. Other advantages of the reagent are associated with its insolubility and that of its byproduct which facilitates the workup of reaction mixtures and allows for the quantitative recovery and regeneration of the spent resin. After several regenerations, the reagent is still as reactive as the original material.

Polymeric reagents[1] have recently been developed for use in simple processes such as epoxidation,[2] oxidation,[3] acylation,[4] halogenation,[5] or Wittig[6] reactions. In all of these applications, advantage is taken of the insolubility of the polymeric reagent and of its byproduct which allows for the easy removal of any excess reagent or spent material from the desired product. In addition to being insoluble, polymeric reagents should be easy to prepare, have a capacity sufficient for use on a practical scale, and be designed in such a way that the spent reagent can be regenerated to its initial activity in an easy fashion. In most cases, the ability of the polymer to be regenerated is critical, since few reactions could justify the use of a custom-made polymer which would be discarded once the reaction has been carried out.

We have recently prepared a cross-linked poly(vinylpyridine) resin[5] by a pearl copolymerization technique, and used this resin to produce a fully regenerable brominating agent which could be used over and over again without deteriorating. This paper describes the application of a similar cross-linked poly(vinylpyridine) resin to the synthesis of a poly[vinyl(pyridinium chlorochromate)] and the application of the polymeric oxidizing agent to the oxidation of various alcohols. A somewhat similar reagent[7] was prepared recently by reaction of Amberlyst A-26 with chromic acid. This reagent was claimed to be regenerable, although little experimental data was given and no mention of its capacity after regeneration was made.

Results and Discussion

The poly[vinyl(pyridinium chlorochromate)] reagent (PVPCC) can be prepared very easily by addition of the stoichiometric amount of chromic anhydride and concentrated hydrochloric acid to a suspension of the cross-linked poly(vinylpyridine) (PVP) in water. The resin, which turns to an orange color, can then be washed free of unbound material and be used directly in oxidation reactions or dried for storage. The capacity of the reagent was measured easily by titration with an appropriate reducing agent, and was usually found to be in the range of 3.5–3.9 mmol of oxidizing agent (expressed as chlorochromate) per gram of dry polymer. Our first attempts to use the reagent were made using conditions similar to those described by Corey and Suggs[8] for pyridinium chlorochromate. However, the reaction in dichloromethane was found to be very sluggish, and a large excess of reagent was required to obtain reasonable rates and yields of carbonyl compounds (Table I). More polar oxygenated solvents such as ether or tetrahydrofuran were found to be even less suitable as a marked decrease in the rate of reaction was observed in these solvents. In contrast, nonpolar hydrocarbons such as benzene, or better, heptane or cyclohexane, gave satisfactory results with the rate of reaction increasing with a decrease in solvent polarity. The results of Table II show the effect of solvent and temperature on the rate of oxidation of 1.7 mmol of cinnamyl alcohol with 1.9 g of PVPCC in 10 mL of the solvent indicated. Best results at room temperature were obtained using the solvent of lowest polarity (cyclopentane). As expected, increases in temperature (Table II) and in molar ratio of resin to substrate resulted in increases in rates of oxidation.[9] As can be seen in Table III, the reaction was rapid with 4.5 or 2.2:1 ratios of chlorochromate to alcohol (entries 1 and 2). When the reaction was attempted with a smaller amount of resin (entry 3), the reaction proceeded rapidly to 50% conversion then slowed down considerably, presumably due to a lack of accessibility of the reactive sites.[10] When a similar reaction was attempted with a partially loaded resin (entry 4) in which only approximately 25% of the vinylpyridine units were transformed into the chlorochromate, the reaction proceeded smoothly to completion due to the greater accessibility of the reactive sites. In this experiment the ratio of oxidizing agent to alcohol was of approximately 1.1:1. The reagent was effective in the oxidation of various types of alcohols: allylic, benzylic, secondary, or primary, as shown in Table IV. Preferred reaction conditions included the use of an excess of PVPCC in cyclohexane at 80 °C to increase the rate of reaction and carry the oxidation to completion to facilitate the work-up procedure. The product isolation and purification steps were made easy by the fact that no products of overoxidation, soluble chromium salts, or other impurities were found in the reaction mixture once the oxidation was complete. Thus, the carbonyl compounds could be obtained by a simple filtration followed by washing of the resin to extract all the product, and finally, evaporation of the solvent. Scheme I summarizes the use of the PVPCC reagent. Although the results reported in Table IV were obtained using a 4.5:1 ratio of oxidizing agent to alcohol, titrations of the resins before and after the oxidations showed that <1 molar equiv of the polymeric reagent was actually consumed in the reaction. Table V shows that a polymer used in the oxidation of an alcohol under the conditions reported for Table IV still

Table I. Reaction of Alcohols with a 12-Fold Excess of PVPCC in Methylene Chloride at Room Temperature

Alcohol	Registry no.	Time, days	% conversion
Cinnamyl alcohol	104-54-1	<0.5	100
1-Phenylethanol	60-12-8	2	78
1-Hexanol	111-27-3	3	91
4-Methyl-4-penten-2-ol	2004-67-3	3	61
3-Hexanol	623-37-0	4	86
Cyclopentanol	96-41-3	3.5	100
2-Octanol	123-96-6	4	76

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Table II. Oxidation of Cinnamyl Alcohol with PVPCC:[a] Influence of Solvent and of Temperature on the Extent of Reaction as a Function of Time

Time, min	Dichloromethane, 25 °C	Cyclopentane, 25 °C	Tetrahydrofuran 25 °C	Tetrahydrofuran 80 °C	Benzene 25 °C	Benzene 80 °C	Cyclohexane 25 °C	Cyclohexane 80 °C	Heptane 80 °C
16	15%	56%	9%	15%	38%	80%	52%	97%	96%
36	32%	82%	15%	26%	54%	86%	74%	100%	100%
60	46%	91%	18.5%	31%	65%	92.5%	85%		
110	64%	96%	23.5%	39%	80%	96.5%	98%		
180	79%		26.5%	45%	86%		100%		

[a] Reaction of 1.7 mmol of alcohol with 1.9 g of PVPCC in 10 mL of the solvent indicated.

Table III. Determination of the Reactivity as a Function of the Amount of PVPCC

Entry	Wt of PVP,[a] g	mmol of chlorochromate	mmol of alcohol[b]	% conversion 16 min	36 min	56 min	90 min
1	1	7.7	1.7	96	99+		
2	0.5	3.8	1.7	87	95	97	99+
3	0.25	1.9	1.7	51	53	55	55
4[c]	1	1.9	1.7	38	61	71	81

[a] Amount of PVP used in the preparation of PVPCC. [b] All the reactions were carried out with cinnamyl alcohol in 5 mL of cyclohexane at 75 °C. [c] Reaction with partially loaded (25%) PVP; this reaction reached completion in 20 h.

Table IV. Reaction of PVPCC with Various Alcohols

Alcohol	mmol	PVPCC, g	Solvent, mL	Temp,	Time	% conversion
Cinnamyl alcohol	1.7	1.9	Cyclohexane, 10	80	36 min	100
Cyclohexanol[a]	1.7	2.0	Cyclohexane, 4	75	24 h	94
1-Butanol[b]	1.7	2.0	Cyclohexane, 4	75	4.5 h	90
					24 h	100
Benzyl alcohol[c]	1.7	1.9	Cyclohexane, 4	75	15 min	95
					36 min	100
1-Phenylethanol	1.7	2.0	Cyclohexane, 10	80	3.5 h	96
Cyclopentanol	1.7	1.9	Cyclohexane, 4	77	3.5 h	82
					12 h	99

[a] Registry no.: 108-93-0. [b] Registry no.: 71-36-3. [c] Registry no.: 100-51-6.

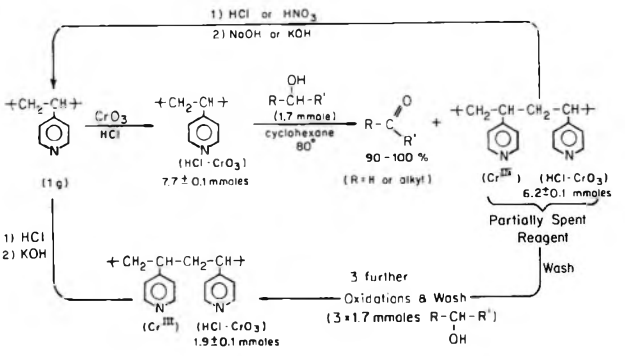
Table V. Determination of the Consumption of Oxidizing Agent and Reactivity of Partially Spent[a] PVPCC

Reaction cycle[b]	mmol of PVPCC	mmol of alcohol	% conversion 16 min	36 min	56 min	120 min	420 min
1	7.7	1.7	96	99+			
2	6.2[c]	1.7	92	99+			
3		1.7	57	83	92	99	
4		1.7	32	47	59	83	99
5	1.9[d]						

[a] Reaction of PVPCC prepared from 1 g of PVP with successive portions of cinnamyl alcohol. [b] Each cycle consists of an oxidation followed by a wash with cyclohexane then water. [c] Data obtained in a parallel experiment. [d] Amount of chlorochromate remaining on the resin after four successive oxidations.

contains enough active reagent to be reused without regeneration in further oxidation reactions. Thus, when the oxidation of 1.7 mmol of cinnamyl alcohol was carried out with 7.7 mmol of PVPCC, the reaction was complete within 36 min, and the partially spent reagent still contained 6.2 mmol of chlorochromate. After washing to remove the cinnamaldehyde, three further oxidations were carried out as shown on Scheme I. After four successive oxidations involving a total of 6.8 mmol of alcohol, the resin still contained 1.9 mmol of chlorochromate for a net consumption of 5.8 mmol. This indicates that the actual consumption of oxidizing agent is of the order of 0.85 molar equiv. It should be noted, however, that the rate of the oxidation reaction decreased in the third and fourth oxidations. The spent polymeric reagent, which turned black during the first oxidation, could be regenerated easily to poly(vinylpyridine) (Scheme I) by complete removal of the chromium salts using consecutive washings with hydrochloric acid and sodium or potassium hydroxide. The recycled poly(vinylpyridine), which was slightly darker than the starting PVP resin, could then be treated with chromic anhydride and hydrochloric acid to produce a PVPCC resin with an activity comparable to that of the original material.[11] The reagent recycled four times was found to be as effective an oxidant as the original material (Table VI). It is expected that the polymeric reagent could withstand many more reaction cycles, since no chemical degradation of the polymer was observed. The limitating factor, as in the case of all macroreticular resins, is the mechanical stability of the polymer beads as repeated handling may result in the slow formation of fine particles which, although reactive, are much harder to handle

Scheme I



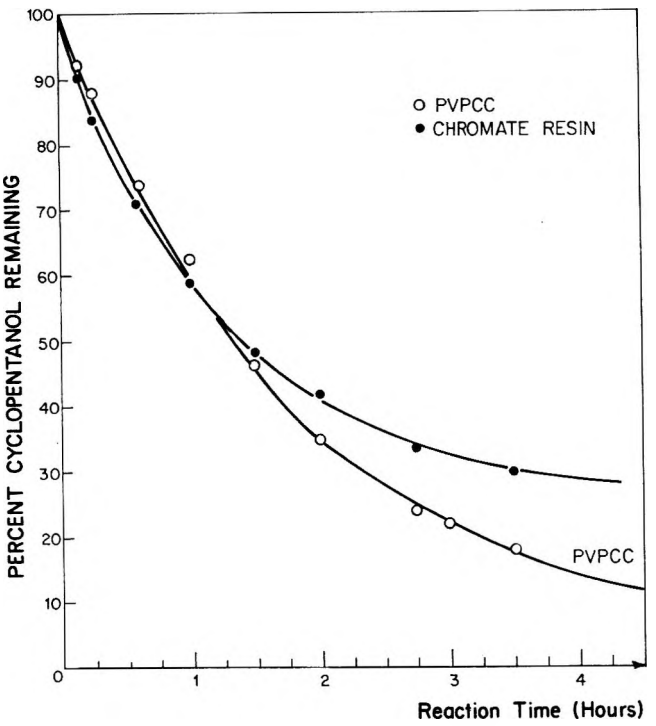


Figure 1. Oxidation of cyclopentanol (1.7 mmol) in 4 mL of cyclohexane at 77 °C using 2 g of resin: comparison of PVPCC with chromate ion exchange resin.

Table VI. Activity of Recycled PVPCC: Oxidation of Cinnamyl Alcohol in Cyclohexane at 80 °C[a]

Resin cycle[b]	Capacity[c]	% conversion 16 min	% conversion 36 min
1	3.58[d]	97	>99
2	3.60	93	98
3	3.86	96	>99
4	3.70	93	>99
5	3.65	95	>99

[a] 1.7 mmol of alcohol with 1.9 g of PVPCC in 10 mL of cyclohexane. [b] Each cycle consists of: preparation of PVPCC, oxidation, and regeneration to PVP. [c] Capacity expressed in millimoles of chlorochromate per gram of resin. [d] In other runs, the initial capacity of PVPCC varied from 3.5 to 3.95 mmol/g.

than spherical beads of well defined sizes. In the case of our PVPCC resin, only a small amount of powdery material was produced in five reaction cycles, and the only losses which were observed were mechanical due to the repeated transfers of the polymer. In most cases, these mechanical losses amounted to less than 2% per cycle.

A comparison of the PVPCC resin with the chromate ion exchange resin described by Cainelli and co-workers[7] was made using 2 g of each resin[12] for the oxidation of 1.7 mmol of cyclopentanol at 77 °C. As can be seen in Figure 1, the two reagents were comparable in their initial reactivity but the reaction with PVPCC required much less time to reach completion than that with the chromate ion exchange resin. Both resins are, however, quite similar in their ease of preparation and their handling. The major difference between the two reagents is probably the better efficiency of the PVPCC, which consumes less CrO_3 and is fully regenerable.

Experimental Section

4-Vinylpyridine was purified by distillation under reduced pressure immediately before use. Divinylbenzene (55–60%) was obtained from Polysciences, Inc., and was used without further purification. The oxidation reactions were monitored by withdrawing small aliquots at regular time intervals for analysis by gas chromatography on a 6-ft column of 15% Carbowax 20M on Chromosorb P.

Preparation of the Cross-Linked Poly(vinylpyridine) Resin (PVP). Poly(vinyl alcohol) (2.4 g) was dissolved in 550 mL of boiling distilled water and the solution was placed in a 2-L resin kettle equipped with Teflon seals, a reflux condenser, a nitrogen inlet, and a mechanical stirrer. The solution was stirred under nitrogen at 80 °C and a solution of 25 g of 4-vinylpyridine and 1.5 g of divinylbenzene in 50 mL of toluene was added rapidly. After addition of 1 g of azobisisobutyronitrile (AIBN) the polymerization was allowed to proceed under constant vigorous stirring. Polymer beads started to appear very rapidly, but the mixture was left at 80 °C overnight. The resin beads were collected by filtration through cloth and were washed extensively with water, acetone, ether, dichloromethane, and finally methanol. After drying under vacuum, 25.1 g of almost white PVP resin beads were obtained. A suitable 2% cross-linked vinylpyridine–divinylbenzene resin is also available commercially from Polysciences, Inc.

Preparation of PVPCC. To 10 g of cross-linked PVP resin (50–100 mesh) suspended in 20 mL of water was added 9 g of chromic anhydride and 10 mL of concentrated hydrochloric acid. The mixture was stirred at room temperature for 1 h and filtered and the resin was washed with distilled water until the filtrate was clear. Freshly prepared PVPCC has a bright orange color which turns to brown upon drying in vacuo (60 °C, 5 h). The resin can be used directly without drying or can be stored in dry form. Titration of the chlorochromate resin was done in two ways: indirectly by titration of the filtrate and wash liquid collected during the preparation of PVPCC, or directly by titration of the chromate displaced from the resin by reaction with aqueous 2 N potassium hydroxide overnight. In a typical titration, a freshly prepared solution of ferrous ammonium sulfate was used to reduce the chromate after acidification with phosphoric acid and using diphenylamine sulfonate as indicator. Both methods gave comparable results; however, the results reported in this text are those which were obtained in the direct titrations. Thus, the PVPCC resin (19.3 g) obtained above from 10 g of PVP contained 3.6 mmol of chlorochromate per gram of dry reagent. The PVPCC resins obtained in similar preparations contained up to 3.95 mmol of chlorochromate per gram. In most cases the PVPCC resins were not dried thoroughly before use, but were simply air dried after washing with water. Typically, a PVPCC resin prepared from 1 g of PVP, 0.92 g of CrO_3, and 1 mL of concentrated HCl contained 7.5–7.9 mmol of chlorochromate after thorough washing with water and air drying.

Oxidation of Alcohols: General Procedure. Best results in the oxidation reactions were obtained using wet PVPCC resins. Thus, in instances where the dry resin was used, it had to be soaked briefly (5–10 min) in water prior to filtration to remove the excess water and before use in oxidation reactions. Alternately, the PVPCC could be prepared immediately before use by reaction of the required amounts of PVP, CrO_3, and HCl, followed by thorough washing with water and filtration. The second procedure was often preferred over the first as it eliminated the lengthy drying step. In a typical oxidation, the PVPCC obtained by reaction of 1 g of PVP with CrO_3 and HCl as described above (or 1.9–2 g of dry reagent soaked in water and filtered) was used in 4–10 mL of cyclohexane at 75–80 °C (Table IV). After addition of 1.7 mmol of the alcohol, the mixture was stirred at 75–80 °C and small aliquots were withdrawn at regular time intervals for chromatographic analysis. The percent conversion was calculated directly from the chromatograms after calibration. Some reactions were also carried out using less PVPCC for the same amount of alcohol (Table III). Reactions were also carried out on a larger scale using, for example, the PVPCC prepared above from 10 g of PVP to oxidize 2.4 g of cinnamyl alcohol in 50 mL of cyclohexane at 60 °C. The reaction was monitored by GLC and had essentially reached completion in 60 min. After 105 min, the reaction mixture was filtered and the resin washed with ether and dichloromethane to extract the cinnamaldehyde. After evaporation of the solvent, 2.0 g of pure cinnamaldehyde (84%) was obtained.

Reactions with Partially Spent PVPCC. PVPCC (7.7 mmol) was prepared from 1.03 g of PVP and the required amounts of CrO_3 and HCl as described above. The resin was used immediately after washing with water for the oxidation of 1.7 mmol of cinnamyl alcohol in 5 mL of cyclohexane at 75 °C. The reaction was followed by GLC and was complete in 36 min. The resin, which had turned almost completely black in this first oxidation, was filtered and washed with cyclohexane to remove all the cinnamaldehyde. After rinsing with water and air drying on filter, the resin was transferred quantitatively to a flask containing 1.7 mmol of cinnamyl alcohol in 5 mL of cyclohexane at

75 °C. This second oxidation proceeded rapidly and was complete in 36 min. After washing and rinsing the resin with cyclohexane and water as above, a third oxidation of another 1.7 mmol of cinnamyl alcohol was carried out. The reaction required 2 h to reach completion. The resin was again filtered and washed as above, then used in a fourth oxidation using another 1.7 mmol of cinnamyl alcohol. This fourth oxidation reached completion in 7 h. After washing with cyclohexane, the resin was soaked in 2 N potassium hydroxide overnight, and the filtrate was titrated with standard ferrous ammonium sulfate in acidic medium. The titration showed that the resin still contained 1.9 mmol of chlorochromate after four successive oxidations of 1.7-mmol portions of cinnamyl alcohol (Table V).

Recycling of the Resin. The spent reagent, which was black after filtration of the desired product, was easily regenerated by washing with 2 N hydrochloric acid (or 2 N nitric acid) followed by 2 N aqueous sodium or potassium hydroxide and rinsing with water. This treatment effectively removed the chromium salts from the polymer and regenerated the PVP resin. The regenerated PVP was usually slightly darker than the original material, but was unaffected in its ability to produce a satisfactory PVPCC reagent (Table VI). After regeneration with CrO_3 and HCl, the recycled PVPCC, which was dark red, had an activity comparable to that of the fresh reagent, and its activity remained essentially constant through repeated oxidation–reduction cycles. The only losses which were observed were mechanical, due to the numerous transfers of wet polymers at the different stages of reaction or recycling. In a typical run these losses amounted to 1–2%.

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Registry No.—Cinnamaldehyde, 104-55-2; 1-phenylethanone, 122-78-1; hexanal, 66-25-1; 4-methyl-4-penten-2-one, 3744-02-3; 3-hexanone, 589-38-8; cyclopentanone, 120-92-3; 2-octanone, 111-13-7; cyclohexanone, 108-94-1; butanol, 123-72-8; benzaldehyde, 100-52-7; PVPCC, 66212-21-3.

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(9) Cainelli et al. (ref 7) claim to observe an increase in rate for higher substrate to resin ratio; this is unlikely.
(10) The data shown on Table V suggest that the active sites may become coated with the oxidized material, thus slowing down the reaction. This is supported by the observation that, after washing with solvent, the partially spent resin can react again at a normal rate.
(11) An alternate regeneration procedure aimed at the selective removal of the spent chromium salt after reaction was not successful, as some CrO_3 leached from the polymer at the same time as the reduced chromium salt.
(12) Reference 7 shows that the recommended ratio of resin to alcohol for most reactions with the chromate ion exchange resin is of 3.5 g of resin per mmol of alcohol. However, such a high ratio is not well-suited for practical applications.

Effects of Structure on the Ease of Electron Removal from *o*-Phenylenediamines

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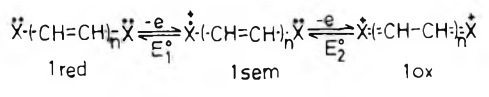
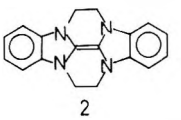
Cyclic voltammetric (CV) data are reported for 23 alkyl-substituted o-phenylenediamine derivatives, including examples with *N,N'*-alkyl bridging and bis bridging. The ^{13}C NMR shift at C_4,C_5 of the aromatic ring appears to be a good criterion for the average amount of lone pair, aromatic ring overlap in the neutral materials. For several examples, both $E°_1$ and $E°_2$ were measured by CV. $E°_1$ varies by over 1.1 V (25 kcal/mol) in the series investigated and is discussed in terms of electronic and steric effects. The dications are argued to be significantly nonplanar from the observed $E°$ values, and the 1,4,5,8-tetramethyl-1,2,3,4-tetrahydroquinoxaline dication was found to have nonequivalent CH_2 hydrogens at −88 °C by ^1H NMR.

Electrochemical studies allow measurement of the standard oxidation potential ($E°$) for electron-transfer reactions, providing that these reactions are electrochemically reversible, which requires both chemical reversibility and that electron transfer is rapid on the time scale of the experiment. $E°$ values are of particular interest because they are a measure (relative to the reference electrode used, or of one compound relative to another[1]) of the free energy difference between oxidized and reduced forms. More than 1 electron can be reversibly added to or removed from some compounds. Hünig[2] has suggested the term "violene" to designate radical cations of systems which have lone pair bearing heteroatoms flanking a π system (symbolized by **1red** below), so that the radical cation has $2n + 3$ electrons shared by $2n + 2$ atoms (**1sem**). For violenes, all three oxidation states are frequently long lived,[2] allowing both $E°_1$ and $E°_2$ to be measured electrochemically and other



physical and chemical methods to be used to characterize these redox-related species. Hünig and co-workers[3] have carried out extensive studies of a variety of violenes. The difference in standard potentials for the two oxidations, $\Delta E° = E°_2 - E°_1$, is a measure of the disproportionation constant for the sem form, because $K_d = (\text{sem})^2/(\text{red})(\text{ox}) = \exp C\Delta E°$, where $C = (23.06 \times 10^3)/(1.987T)$, where $\Delta E°$ is in V, and T is in K. The K_d values observed for violenes vary tremendously with structure. An unusually large K_d was observed for **2**, $K_d = 2.6 \times 10^{14}$ ($\Delta E° = 0.85$ V), while at the other extreme, 3 has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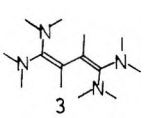
3

a negative $\Delta E°$,[4] the second electron being easier to remove than the first, in spite of the electrostatic problem in going to a dication. Fritsch and co-workers[4] pointed out that only the sem form of **3** has a strong requirement of planarity for the two

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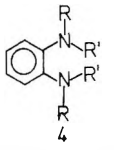
bulky olefins, so that $E°_1$ is increased because of this strain, and $E°_2$ decreased because of strain relief.

Because of our interest in the energy requirements for oxidation of tetraalkylhydrazines,[5] where the sem form is flattened at nitrogen and increases $\mathbf{R}_1\mathrm{N}_1\mathrm{N}_2\mathbf{R}_2$ strain, we have studied a series of their benzologues, 1,2-diaminobenzene derivatives (many of which can be characterized by general formula **4**). Steric interactions between the alkyl groups of the

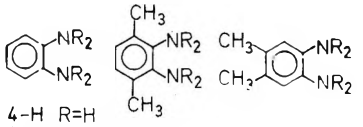


4

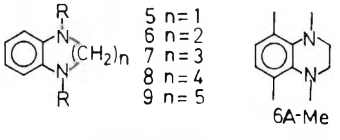
oxidized forms of **4** would be expected to be large and altered considerably when the R′ groups are linked to form a ring. We had originally hoped that by linking the R′ substituents of **4** a conformational dependence upon electron transfer rate such as has proven useful in six-membered ring cyclic hydrazines[6] would be observed electrochemically. This hope was not realized, presumably because of rapid conformational equilibration of conformations in the red forms. Nevertheless, our results show that geometry changes upon electron removal do strongly influence the standard potentials $E°_1$ and $E°_2$ in **4** and reveal that $\mathbf{4}^{2+}$ is decidely nonplanar, in contrast to $\mathbf{4}^{+}\cdot$.

Results

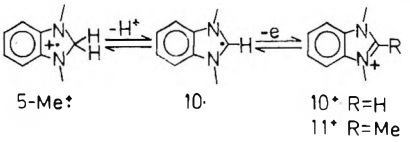
A. Compounds Examined. To compare standard potentials in *o*-phenylenediamines with and without linking of the nitrogen substituents, several compounds were employed. In an attempt to have the formula numbering convey some structural information, we shall use the following system. **4**



will be used for systems where the nitrogen substituents are not linked, followed by abbreviations for these substituents. We also employed 3,6-dimethyl and 4,5-dimethyl ring-substituted compounds in some instances to examine the interplay of the electron-releasing and steric effects of the 3,6-dimethyl compounds. Suffixes A and B are used to designate the aryl ring methyl substitution pattern. The heterocyclic ring size is indicated by the number employed for the polymethylene-bridged compounds **5–9**, with suffix A or B for ring methyls and H or Me for the nitrogen substituents, as in the the example illustrated, **6A-Me.**

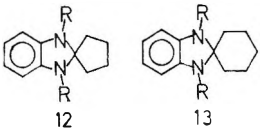


Unfortunately, **5-Me** showed a completely irreversible oxidation peak under all conditions employed (E_p^{ox} = +0.31, 23 °C, 100 mV/s; E_p^{ox} = +0.3, −78 °C, 100 mV/s). We believe that this problem is caused by the aromaticity of the deprotonated 2-electron oxidation product, dimethylbenzimidizolium cation $\mathbf{10}^{+}$. As illustrated in eq 1, formal loss of a proton



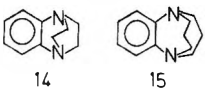
(1)

would give **10**·, which is very unstable relative to **10**$^{+}$. The iodide of the 1,2,3-trimethylbenzimidazolium salt $\mathbf{11}^{+}$ is only reduced irreversibly at −1.76 V (23 °C, 100 mV/s). This indicates that loss of an electron and a proton from $\mathbf{5\text{-}Me}^{+}\cdot$ would give the product $\mathbf{10}^{+}$, which is approximately 2 V (46 kcal/mol) stabler toward oxidation. Although our data do not indicate what pathway is employed, $\mathbf{5\text{-}Me}^{+}\cdot$ decomposes extremely rapidly. In contrast, the four 2,2-dialkyl analogues of **5** studied (**12** and **13**) give cations which are long enough lived

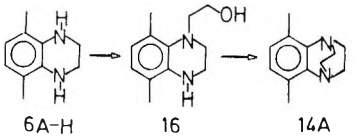


to measure $E°$, although all have noticably shorter lifetimes, especially for the dications, than corresponding derivatives of **6.**

To have examples of **4** in which the nitrogen lone pairs were precluded geometrically from overlap with the aryl ring, bis-bridged systems **14** and **15** were prepared. In an attempt to



improve the yield for ring closure in the preparation of 3,6-dimethylbenzodabco, **14A,** the route shown in eq 2 was em-



(2)

ployed. Attempted isolation of *O*-tosyl-**16** led to apparent O to N rearrangement in concentrated solution, so this intermediate was cyclized directly by addition of *n*-butyllithium to form the *N*-lithio salt without concentration. Unfortunately the yield for **16** → **14A** was low (11%) and we found it more convenient to simply use ethylene bromide and the appropriate tetrahydroquinoxaline to obtain **14** and **14B** and propylene bromide and o-phenylenediamine to obtain **15,** all in very low yield. Because the products are easily sublimed from the tarry reaction products, chromatography did not need to be employed for isolation.

B. Lone Pair, Aryl Interactions. The geometry of the neutral *o*-phenylenediamine derivatives is clearly of interest in considering their oxidation potentials. We had hoped to be able to use low-temperature ^{13}C NMR to get conformational information, but even for **6A-Me,** no conformational broadening could be observed. Because low rotational and nitrogen inversion barriers are expected, perhaps this is not surprising. For *N,N*-dimethylaniline, a rotational barrier of 5.1 kcal/mol has been estimated[7] (although the barrier to nitrogen inversion these authors estimate seems likely to be far too high). *N,N*-Dimethylaniline is thought to have the nitrogen lone pair aligned for maximum overlap with the aryl π system, although the degree of bending at nitrogen seems quite uncertain.[7] One would expect changes in both the NMR and UV spectra upon rotation about the aryl carbon–nitrogen bond to decrease conjugation of the nitrogen lone pairs with the ring. Because deconjugation of the lone pairs should result in less π electron density at C_4,C_5 of the aryl ring, one should expect a downfield shift for $C_{4,5}$ in the ^{13}C NMR. Aromatic ^{13}C-NMR shifts are well known to be sensitive to π electron density.[8] In fact, the C_4,C_5 shifts of the full deconjugated **14** and **15** are rather close to the δ 128.5 of benzene itself, C_4,C_5 of the five-ring compound **12-Me,** which is constrained to have maximum conjugation δ 103.2, and the other compounds are intermediate (see Table I). In UV spectra, decreases in extinction coefficient

Table I. ^{13}C-NMR Chemical Shifts for Some o-Phenylenediamine Derivatives (δ from Internal Me_4Si)

Compd	Solvent	C_{12}	C_{36}	C_{45}	NCH_3	CCH_3	NCH_2	Other
4-Me	$CDCl_3$	144.73	121.20	117.44	41.22			
4A-Me	$CDCl_3$	144.45	135.40	126.70	43.26	18.60		
4B-Me	$(CD_3)_2CO$	143.75	120.04	129.38	41.99	19.11		
12-Me	$(CD_3)_2CO$	141.77	118.13	103.22	32.03		98.36	26.56, 28.66
6-Me	$CDCl_3$	136.25	117.73	110.28	39.08		49.80	
6A-Me	$CDCl_3$	139.69	128.43	123.98	43.90	18.81	45.40	
	$(CD_3)_2CO$	140.89	128.91	124.66	44.00	18.94	46.84	
6B-Me	$(CD_3)_2CO$	135.74	113.51	125.21	39.53	19.10	50.79	
7-Me	$CDCl_3$	143.17	121.29	117.10	42.30		53.60	26.56
8-Me	$(CD_3)_2CO$	142.68	119.73	45.69	38.59		51.26	26.22
9-Me	$(CD_3)_2CO$	145.47	121.39	117.25	37.50		53.90	28.50, 27.17
14	$(CD_3)_2CO$	153.50	123.97	127.39			51.49	
14A	$(CD_3)_2CO$	150.14	130.04	127.45		16.02	50.71	
14B	$(CD_3)_2CO$	150.54	124.82	134.98		19.96	56.67	
15	$(CD_3)_3CO$	152.47	129.05	128.05			51.38	29.06

Table II. Ultraviolet Spectra of Some o-Phenylenediamine Derivatives in Hexane

Compd	λ_{max}, nm (ε)		
5-Me	312 (5200)	264 (5400)	217 (29000)
12-Me	315 (7400)		224 (37000)
6-Me	311 (6100)	263 (3200)	229 (34000)
7-Me	ca. 303 (br) (3900)	266 (9400)	236 (26000)
8-Me	308 (5000)	270 (7500)	234 (29000)
9-Me	301 (4200)	273 (9800)	234 (24000)
6A-Me	ca. 300 (br) (1400)	264 (sh)	234 (24000)
4-Me	294 (2800)	268 (8500)	233 (21000)
4A-Me		269 (3200), 253 (5200)	215 (11000)
14	313 (150)		
14A	320 (21), 307 (24)		
14B	320 (50), 314 (44)	274 (1800), 265 (1500)	

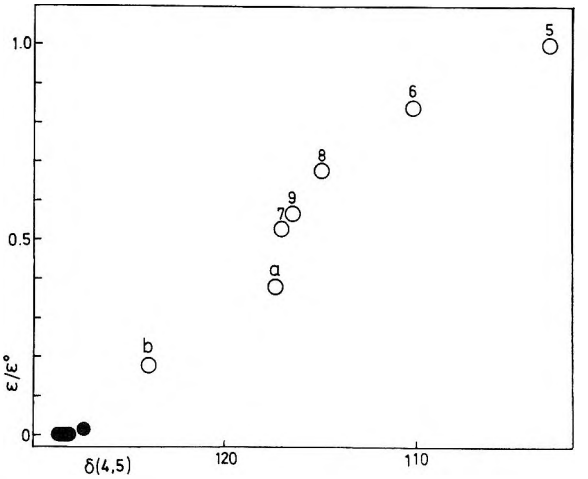


Figure 1. A plot of ϵ/ϵ^0 for the long wavelength UV absorption band vs. the ^{13}C-NMR chemical shift for the C_4,C_5 carbons for some tetraalkyl o-phenylenediamine derivatives. **5** is the five-ring compound **12-Me** (which has the largest extinction coefficient, ϵ^0) and **6–9** are **6-Me** to **9-Me**; (a) the tetramethyl compound **4-Me**; (b) **6A-Me**. The filled figures are for the bicyclic compounds **14** and **15**.

are observed for intramolecular charge-transfer bands when conjugative interaction is decreased, as has been studied for substituted nitroanilines,[9] benzocyclamines,[10] and benzocycloalkylanones.[11] We observe this effect for the longest wavelength band (near 310 nm) for o-phenylenediamines, ε being highest for **12-Me** and dropping substantially for some of the other compounds (see Table II). Because the bands are rather broad for many of the compounds they overlap, making ε (λ_{max}) for the ca. 310 nm band not easily measurable. Especially for the weak bands, the observed ε (λ_{max}) is a composite figure. Both **14** and **15** had observed long wavelength maxima, although conjugative lone pair, aryl ring interaction is geometrically precluded. We presume that the weak maxima observed near 310 nm have a completely different origin than those for ordinary o-phenylenediamines (and can only hope that impurities having intense absorptions in this region are entirely absent). For systems with only one conjugated group attached, analyses to extract twist angle from UV spectra have used a θ = arcos (ϵ/ϵ°) relationship,[9] where ϵ° is for a compound assumed to have zero twist. It is not obvious to us what relationship with θ should actually be followed in o-phenylenediamines, where there are two twist angles (which in principle could be different). Nevertheless, a plot of ε (λ_{max})/ε° vs. δ (C_4,C_5) (see Figure 1) gives a significant correlation (we have no reason to expect a linear correlation), and we suggest that both spectral measurements are reflecting the same thing, the amount of conjugation of the lone pairs with the aryl ring. We note that although **6-Me** has by both techniques larger lone pair, aryl ring conjugation, as expected for the diequatorial *N*-methyl compound, addition of 3,6-methyls in **6A-Me** greatly reduces conjugation, suggesting a change to the diaxial conformation (which, if it were the only conformation occupied, would not give NMR line broadening even if slow nitrogen inversion were achieved). Because of the ease of measurement and the lack of the overlap difficulties encountered in UV spectra of these compounds, we believe that the NMR method is the most reliable indicator of the average amount of conjugation of the long pair nitrogen orbitals with the aromatic ring π system.

C. Electrochemical Studies. Several of the compounds employed do not show reversible cyclic voltammograms at room temperature, and since a principal interest was comparison of E° values, we took our CV data in butyronitrile, a superior low-temperature electrochemical solvent.[12] Other experiences in our laboratories indicate that E° values in butyronitrile are found to be approximately 0.14 V positive of those run in acetonitrile. For conversion of our E° values (all referenced to SCE) to the silver, silver chloride reference electrode employed by Hünig's group, +0.046 V should be added.[13] For most compounds, CV data were determined near 23, 0, −25, and −50 °C. Only −50 °C and room temperature data are quoted in Table III. The values in parentheses are extrapolated from lower temperature results when reversibility was not achieved at room temperature. In a few cases, we could not determine E° at any temperature because of rapid ion decomposition. The results for systems **4–13**, where in at least some example of each system two electrochemically

Table III. Electrochemical Data for some o-Phenylenediamine Derivatives in Butyronitrile (0.1 M Tetrabutylammonium Perchlorate) vs. SCE

		Room temp data				Low temp data			
Compd	Registry no.	Temp, °C	$E°_1$	$E°_2$	$\Delta E°$	Temp, °C	$E°_1$	$E°_2$	$\Delta E°$
4-H	95-54-5	22	Irrev., E_p^{ox} = 0.56 (200 mV/s)			−48	Irrev., E_p^{ox} = 0.50 (200 mV/s)		
4-Me	704-01-8	23	0.60	0.84	0.24	−50	0.55	0.76	0.21
4-Et	57422-67-0	23	(0.61)	(0.85)	(0.24)	−50	0.50	0.78	0.19
4A-Me	66102-30-5	24	(0.68)	(0.72)	(0.04)	−46	0.61	0.65	0.04
4B-Me	54929-05-4	24	0.49	0.71	0.22	−48	0.43	0.61	0.18
6B-H	10579-68-7	24	0.24	Irrev.		−50	0.19	Irrev.	
6-Me	2427-06-7	23	0.36	0.98	0.61	−50	0.33	0.92	0.59
6A-Me	66102-31-6	24	0.53	0.80	0.27	−47	0.53	0.74	0.22
6B-Me	66102-32-7	24	0.22	0.83	0.62	−49	0.17	0.75	0.58
7-H	6516-89-8	23	0.43	Irrev.		−50	0.40	Irrev.	
7-Me	19560-66-8	23	0.39	0.94	0.55	−50	0.35	0.88	0.53
8-H	39161-58-5	24	Irrev.	Irrev.		−56	0.40	Irrev.	
8-Me	39161-60-9	23	0.42	0.88	0.46	−50	0.38	0.81	0.43
9-H	49809-51-0	22	Irrev.	Irrev.		−57	Irrev.	Irrev.	
9-Me	66102-33-8	23	0.59	0.88	0.29	−50	0.56	0.82	0.26
12-Me	66102-34-9	23	0.21	0.91	0.70	−50	0.18	0.85	0.67
12-Et	66102-35-0	23	(0.19)	(0.92)	(9.73)	−50	0.14	0.85	0.70
13-H	3190-03-2	21	0.23	Irrev.		−51	0.24	Irrev.	
13-Me	66102-36-1	23	0.22	0.94	0.72	−50	0.19	0.87	0.69

Table IV. Electrochemical Data for Derivatives of Benzodabco (14) and 9,10-Benzo-1,5-diazabicyclo[3.3.2]dec-9-ene (15)

Compd	Registry No.	Temp °C	Electrochemical behavior
14	7140-45-6	24	Irrev., E_p^{ox} = 1.33 (0.2 V/s)
		−45	Quasirev., $E° \simeq 1.25 \pm 0.03$ (2–10 V/s)
14A	66102-37-2	23	Irrev., E_p^{ox} = 1.27 (0.2 V/s)
		−45	Quasirev., $E° \cong 1.18 \pm 0.04$ (0.5–10 V/s)
14B	66102-38-3	24	Irrev., E_p^{ox} = 1.26 (0.5 V/s)
		−48	Irrev., E_p^{ox} = 1.40 (2 V/s)
15	7140-45-6	21	Irrev., E_p^{ox} = 1.10 (0.2 V/s)

well behaved waves were observed, appear in Table I. We believe the potentials reported to be accurate to +0.01 V.

Only a single, 2-electron oxidation peak was observed experimentally for **4A-Me**. $\Delta E°$ was determined by the procedure of Myers and Shain,[14] using the working curve presented in their paper. They emphasize that the curve is only applicable to reversible systems. We found that the ratio of observed anodic (i_p^a) cathodic peak currents was near one (observed 1.16, 1.02, 1.00, 0.85 at 20, 50, 100, and 200 mV/s scan rates), and that $i_p^a/v^{1/2}$ (v is the voltage scan rate) was nearly constant (3.80, 4.04, 3.75, 3.50 at the same scan rates), both criteria for reversibility. The quoted $\Delta E°$ value of 0.04 V was based on the 20 mV/s scan rate CV curve; we found that the difference in anodic and cathodic peak potentials increased slightly with scan rate, either indicating slight irreversibility or more likely incomplete iR compensation; we believe the $\Delta E°$ figure of 0.04 quoted in Table III is a maximum value, especially since one should begin to see resolution of the two oxidation waves at $\Delta E° > 0.06$.

Several NH-substituted compounds were also examined and some showed reversible behavior for the first electron removal, but none gave long-lived enough dications to detect a reduction wave, so $E°_2$ could not be determined.

Our data for the benzobicyclic systems **14** and **15** are less accurate and are included in Table IV. Reduction waves for both $\mathbf{14}^{+\cdot}$ and $\mathbf{14A}^{+\cdot}$ could be observed at low temperatures, allowing estimation of $E°$, but the decomposition products appear to affect the electrode, because our reproducibility on different days was not as good as with other compounds. Although different workers on different days obtained values for $E°$ of **14** and **14A** varying by ±30–40 mV, data gathered on the same day for these compounds always gave the result that **14A** has about a 50–70 mV lower standard potential than **14**.

Van Duyne and Reilly[12] have discussed the drift to lower potential observed for $E°$ when the temperature is lowered. The observed change was linear and they found $dE°/dT$ values ranging from 0.31 to 0.45 mV/deg for reductions (nitrobenzene, ferrocene, and phenazine) and an oxidation (9,10-diphenylanthracene). Ammar and Saveant[15] studied the two reversible reduction potentials for a series of dinitroaromatic compounds and reported that $\Delta E°$ increases linearly with temperature, although they did not disclose $dE°/dT$ for either step. They separate $\Delta E°$ (and hence K_d) into entropy and enthalpy terms, using $\Delta E° = \Delta E_H - T\Delta\epsilon_s$. Larger $dE°/dT$ values must have been observed for the second electron transfer than the first, because $\Delta\epsilon_s$ is $dE°_1/dT - dE°_2/dT$. This is reasonable considering that a diion should cause more solvent ordering than a monoion. The temperature behavior of some *o*-phenylenediamine $E°$ values is summarized in Table V.

Discussion

A. Steric Interactions in the Radical Cations. The series of compounds studied has the same basic system in which to distribute positive charge, two dialkylamino groups substituted ortho on a benzene ring. The $E°$ values observed will reflect both steric and electronic differences between the various compounds in solution, since $E°$ is a measure of the free-energy difference between reduced and oxidized forms. We shall use the ca. −50° $E°$ values, which have the advantage of not being extrapolated, in the discussion which follows.

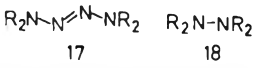
The tetramethyl compound **4-Me** shows a considerably higher $E°_1$ than the N,N′-bridged compounds **5-Me** and **6-Me**, clearly because of increased steric interaction in the electronically preferred completely planar form. As an extreme model, one might consider the possibility that one dimethylamino group of $(\mathbf{4\text{-}Me})^{+\cdot}$ would be completely planar with the ring and the other twisted 90° to minimize steric interaction. If this were the case, $E°_1$ of **4-Me** should be at least as high as that of *N,N*-dimethylaniline, since the twisted dimethylamino group should be electron withdrawing, because

Table V. Temperature Dependence of Oxidation Potentials for Some o-Phenylenediamine Derivatives

Compd	$dE°_1/dT$, mV/deg	$dE°_2/dt$, mV/deg	$-\Delta\epsilon s$, mV/deg	ΔE_H, mV
4-Me	0.61	0.87	0.26	150
4B-Me	0.80	1.29	0.49	70
6-Me	0.46	0.81	0.35	510
6A-Me	0.35	0.86	0.51	120
6B-Me	0.60	1.11	0.51	460
7-Me	0.56	0.80	0.24	480
8-Me	0.56	0.95	0.41	350
9-Me	0.49	0.84	0.35	190
12-Me	0.40	0.85	0.44	570

of the greater electronegativity of nitrogen than carbon, rather than electron releasing. Although *N,N*-dimethylaniline shows an irreversible oxidation wave in acetonitrile,[16] its peak potential is near 0.83 V (converted to our solvent system), indicating a far higher $E°$ value than that observed for **4-Me.** Both dialkylamino groups are clearly contributing to charge delocalization in **(4-Me)**$^{+\cdot}$, as well as for the other compounds considered here.

Studies on hydrazines[5] and 2-tetrazenes[17] have demonstrated that $E°$ is decreased modestly when the alkyl group substituted on nitrogen is lengthened, as would be expected by consideration of Taft σ^* values.[17] Considering the 2-tetrazene systems, **17,** $E°$ is 0.08 V lower for **17-Et** than for



17 18

17-Me. In the corresponding hydrazine system, **18,** $E°$ is only 0.04 V lower for **18-Et** than for **18-Me,** which we have argued[17] occurs principally because of $\mathbf{RN_1N_2R}$ steric strain in the radical cation, which has an olefin-like geometry, with nearly eclipsed $\mathbf{RN_1N_2R}$ groups and larger strain compared to the gauche netural **18.**[5] Electron removal from **17, 18,** and **4** should all cause flattening at nitrogen (or increased barrier for bending from planarity at nitrogen) and alignment of the spin-bearing orbitals at nitrogen with each other (in $18^{+\cdot}$) or with the bridging π system (in $17^{+\cdot}$ and $4^{+\cdot}$). Such a geometrical preference causes little strain in $17^{+\cdot}$, but the strain thus induced is easily detectable in $E°$ values for **18**[17] and would be expected to cause an even greater effect in **4.** We suggest that this is the explanation for the 0.04 V observed *increase* in $E°_1$ for **4-Et** compared to **4-Me,** which is the opposite direction of that expected inductively. When this alkyl, alkyl steric interaction is eliminated (although an increase in alkyl, ring interaction is still present), as in the **12-Et** vs. **12-Me,** the ethyl compound is easier to oxidize than the methyl one (by 0.04 V), as expected.

Another "inductive" effect on $E°_1$ is clearly seen when the benzene ring C_4,C_5 hydrogens are replaced by methyls. See Figure 2 for a graphical presentation of the data. Here there is virtually no steric difference, but the methyls should stabilize the positive charge-bearing carbons on which they are substituted in the cations. The experimental result is an appreciable decrease in $E°$: $\Delta E°_1$**(4B-Me-4-Me)** = −0.21 V (4.8 kcal/mol), $\Delta E°_1$**(6B-Me-6-Me)** = −0.16 V (3.7 kcal/mol). The effects on $E°_2$ are noted to be surprisingly close to those on $E°_1$, −0.15 and −0.17 V, respectively. A rather larger effect upon $E°_2$ than upon $E°_1$ might have been predicted because of greater charge density presumed to be at C_4,C_5 in the dication. The effect of NMe for NH substitution on $E°_1$ was measured for four examples (**6B, 7, 8,** and **13**) and was found to be quite small, an $E°$ decrease of 0.02 to 0.05 V. We presume the small effect reflects a significant steric strain increase in the flatter radical cation when the larger methyl is substituted for hydrogen (for we would expect the true inductive effect to be considerably larger), but solvation differences for replacement of NH by NCH_3 also will affect $E°$ (as always) and we have no way of estimating this effect.

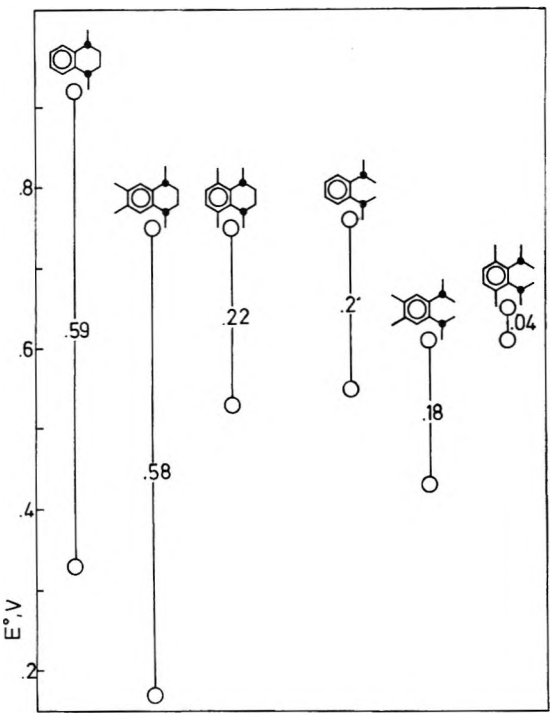
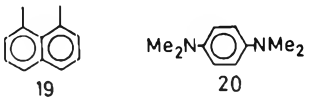


Figure 2. A graphical display of the effect of 3,6 and 4,5 methylation on $E°_1$ and $E°_2$ on **6-Me** and **4-Me.** The numbers given are $\Delta E°$, V.

Increases in steric strain in the radical cation are quite obvious for the substitution of methyl for hydrogen at C_3 and C_6 of **6** and **4** (Figure 2). Despite an inductive effect working in the opposite direction, $\Delta E°$**(4A-Me-4-Me)** is +0.06 V (1.4 kcal/mol) and $\Delta E°_1$**(6A-Me-6-Me)** is +0.20 V (4.6 kcal/mol). The inductive effect of methyl substitution at C_3,C_6 will presumably be substantially smaller than that at C_4,C_5 because charge density should be smaller. The methyl, methyl interaction in 1,8-dimethylnaphthalene (**19**) has been esti-



19 20

mated to be 7.6 kcal/mol,[18] so a significant fraction of the strain expected in a completely planar **(6A-Me)**$^{+\cdot}$ is being observed in $E°_1$ for this compound, making it clear that there is a significantly stronger preference for planarity at the nitrogen atoms in o-phenylenediamine radical cations than there is in the neutral species.

In contrast to the other compounds, the geometry of **12-Me** presumably changes little upon electron removal, because the lone pairs are already well aligned for charge delocalization, and the nitrogens are apparently flatter than in the other

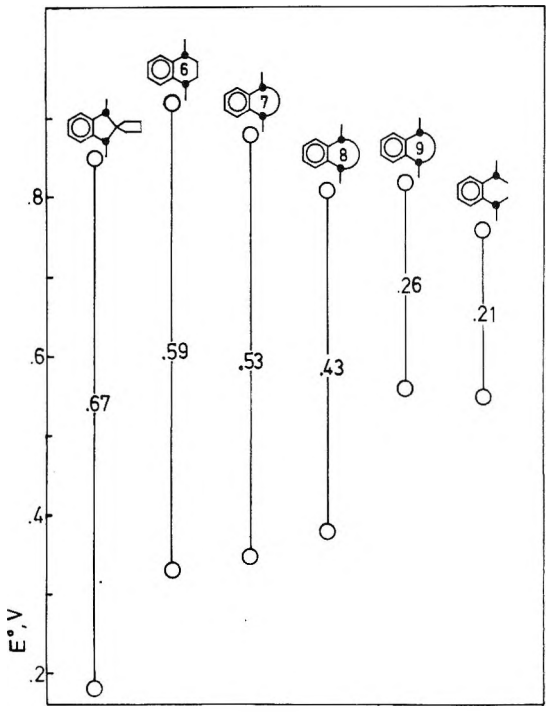
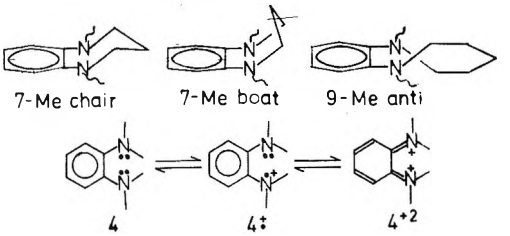


Figure 3. A graphical display of the effect of heterocyclic ring size on $E°_1$ and $E°_2$ for o-phenylenediamine derivatives.

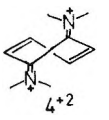
compounds, due to the dialkyl substitution α to the nitrogens. Here the $\Delta E°$ is the largest observed in the o-phenylenediamine series, 0.67 V (−50), 0.70 V (+23 °C), and $E°_1$ is +0.21 V at 23 °C. It is interesting to compare $E°_1$ and ΔE for **12-Me** with those of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine, **20**. $E°_1$ (converted to our solvent) is 0.17 V, $\Delta E°$ = 0.58 V.[19] The 0.05 V difference in $E°_1$ seems surprisingly small, considering that the positively charged nitrogens are closer in $(\mathbf{12\text{-}Me})^{+\cdot}$ and there is a possibility for inductive destabilization through the single connecting carbon in this molecule. Some factors tending to make this difference smaller than it would otherwise be are an increase in strain in planar $(\mathbf{20})^{+\cdot}$ compared to the neutral compound, a probable decrease in strain for $(\mathbf{12\text{-}Me})^{+\cdot}$ compared to the neutral compound (the nitrogens appear to be forced to be one more planar than they would otherwise be by the dialkyl substitution α to the nitrogens), and the inductively greater releasing effect of the dialkyl bridging carbon of **12-Me** replacing two methyls of **20**.

The six- to nine-membered ring heterocyclic compounds have an interesting pattern of $E°_1$ values (Figure 3) in that the first three members of the series, **6-Me, 7-Me,** and **8-Me,** have rather similar $E°_1$ values at 0.33, 0.35, and 0.38 V, respectively. In contrast, $E°_1$ for **9-Me** at 0.56 V is 4.1 kcal/mol higher than for **8-Me** and is close to the value for the acyclic compound, **4-Me.** The interplay of torsional and cross-ring strain in both neutral and radical cationic forms which gives rise to this pattern is presumably quite complex. Unfortunately, we cannot interpret the observed pattern reasonably with the data in hand.

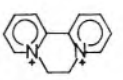
B. Dication Geometry. The most interesting, but initially surprising, aspect of the $E°_2$ values in Table II (see Figures 2 and 3) is the compensating effect of changes in $E°_1$ and $E°_2$. We have discussed $E°_1$ largely in terms of steric destabilizations which occur upon the flattening at nitrogen and aryl,N rotations which must result to enforce the aryl,NR_2 planarity which is energetically preferred for the radical cation. Writing valence bond structures, it is clear than in the dication 4^{2+}, which has each nitrogen sp^2 hybridized, there should be an even stronger requirement for planarity at nitrogen. The tendency for $E°_2$ to decrease when $E°_1$ increases is quite clear in our data. This can hardly be an inductive-dominated result when the similarity of $E°_1$ and $E°_2$ changes in **6B** and **4B** are considered and the seven- to nine-membered ring compounds



are included. Instead, our data seem to require that alkyl,alkyl interaction be smaller in the dication than in the monocation. The only reasonable way this could happen would be if there were significant twisting of 4^{2+} from planarity (see the ex-



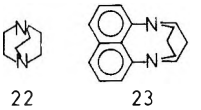
aggerated view below), which models suggest is quite reasonable (4^{2+} is distinctly quinonoid and has greatly reduced aromaticity compared to either $4^{+\cdot}$ or **4**). Twist at the "aryl" NC–CN bonds should be far easier and such a motion would not only decrease steric interactions but increase the N^+,N^+ distance. It is known that diquat dication **21** has a 20.4° aryl,aryl twist angle from an x-ray structure determination.[20]



21

For our systems, we attempted to get evidence for such a twist, which seemed to us to be required by the $E°$ data, by NMR studies. Unfortunately, the dications, although long lived on the CV time scale in many cases, do decompose rather rapidly. Nevertheless, a 0.15 M solution of **6A-Me** at −88 °C gave ^{1}H-NMR singlets at δ 2.28, 2.56, 2.90, and 6.76, which we assign to the CCH_3, NCH_3, NCH_2, and CH protons, respectively. Addition of 2 equiv of $NO^+BF_4^-$ gave a spectrum showing singlets at δ 2.64, 2.56, and 7.53 and a complex multiplet between δ 3.94 and 4.95. We attribute this spectrum to the unstable $(\mathbf{6A\text{-}Me})^{2+}$ species, which could only give a multiplet for the NCH_2 protons if it were nonplanar, and equilibration of the pseudoaxial and pseudoequatorial protons was slow on the NMR time scale. Unfortunately, the species giving this spectrum decomposes in a few minutes at −88 °C.

When lone pair,aryl ring interaction is geometrically precluded, as in **14** and **15**, $E°_1$ is greatly increased and the radical cation lifetime is decreased. We were able to see reduction waves and measure $E°_1$ at low temperature only for **14** and **14A** (Table IV). $E°$ for **14** is considerably higher than for dabco, **22**[21,22] ($E°_1$ = 0.69), which is not surprising because one



22 **23**

through-bond interaction is made far less important (σ_{CC} for an aryl C–C bond should be substantially lower in energy than for a single C–C bond) and the sp^2 carbons are inductively electron withdrawing. There is a distinct, though small, decrease in $E°_1$ for **14A** vs. **14**, which we presume is an inductive effect. Unfortunately, $(\mathbf{14B})^{+\cdot}$ did not have a long enough

lifetime for $E°$ measurements. $(15)^{+\cdot}$ cannot have the through-bond stabilization of $22^{+\cdot}$ and $14^{+\cdot}$. It also quite obviously lacks the dramatic though-space stabilization of $23^{+\cdot}$. ($E° = +0.11$ V in acetonitrile[23]), seeming to indicate that the great strain in **23**, which has essentially planar nitrogens in the neutral form,[23] is very important in lowering $E°_1$ for this compound.

Experimental Section

***N,N,N′,N′*-Tetramethyl-*o*-phenylenediamine (4-Me)** was prepared by methylation of the diamine with trimethyl phosphate[24] and purified by VPC.

***N,N,N′,N′*-Tetraethyl-*o*-phenylenediamine (4-Et)** was prepared by reductive ethylation. *N,N′*-Diethyl compound (0.82 g; 5 mmol), 20 mL of acetonitrile, 2.2 g (50 mmol) of acetaldehyde, and 1.0 g of sodium cyanoborohydride were stirred, while 25 drops of acetic acid were added in 5-drop batches over 7 h. After stirring 12 h, the mixture was basicified (4 mL, 15% NaOH) and extracted with pentane (3 × 25 mL). After drying with sodium sulfate and concentration, the mixture was distilled to give 0.81 g (bp 125 °C (21 min)) of a colorless oil, consisting of **4-Et** with the trimethyl compound as the major impurity; purification was by VPC.

***N,N,N′,N′*-Tetramethyl-3,6-dimethyl-*o*-phenylenediamine (4A-Me)** was prepared by heating the diamine,[25] mp 66–70 °C (lit.[25] mp 75 °C), with a twofold molar amount of trimethyl phosphate[24] in 70% yield; purification was by VPC: NMR ($CDCl_3$) δ 1.2 (s, 6 H), 2.79 (s, 2 H), 6.9 (s, 2 H).[26]

***N,N,N′,N′*-Tetramethyl-4,5-dimethyl-*o*-phenylenediamine (4B-Me)** was prepared by heating the commercial diamine with a twofold molar amount of trimethyl phosphate,[24] giving a 40% yield of crude **4B-Me** after Kügelrohr distillation; purification was by VPC: NMR ($(CD_3)_2CO$) δ 2.11 (s, 6 H), 2.66 (s, 12 H), 6.68 (s, 2 H).[26]

1,4-Dimethyltetrahydroquinoxaline (6-Me) was prepared by $LiAlH_4$ reduction of the bis formate using the method of König and Huisgen,[27] bp 110–120 °C (1 mm) (lit.[27] bp 180–190 (atm)), final purification by VPC.

5,8-Dimethylquinoxaline. To a solution of 9.5 g (7 mmol) of 2,3-diamino-*p*-xylene dissolved in 140 mL of water at 60 °C was added a solution of 10.56 g of 40% aqueous glyoxal (7.3 mmol), 16.6 g of sodium bisulfite, and 68 mL of water which had been heated to 70 °C. After stirring at 60 °C for 45 min, the mixture was cooled to room temperature in an ice bath, neutralized with 38.3 g of sodium carbonate, and extracted with ether (3 × 100 mL). After drying with $MgSO_4$ and removal of ether, sublimation gave 6.0 g (54%) of a light yellow solid: mp 68–70 °C; NMR ($CDCl_3$) δ 2.78 (s, 6 H), 7.50 (s, 2 H), 8.86 (s, 2 H).[26]

5,8-Dimethyl-1,2,3,4-Tetrahydroquinoxaline (6A-H). 5,8-Dimethylquinoxaline (6.0 g; 3.8 mmol) in 200 mL of benzene was stirred over 2.0 g of Alfa pelletized, nonpyrophoric Raney nickel for 15 min and hydrogenated at 40 psi H_2 in a Parr shaker. After filtration, concentration gave 5.1 g (83%): mp 68–69 °C; NMR ($CDCl_3$) σ 2.04 (s, 6 H), 3.44 (m, 6 H), 5.40 (s, 2 H); IR (CCl_4) 3410 cm^{-1} (m).[26]

1,4,5,8-Tetramethyl-1,2,3,4-tetrahydroquinoxaline (6A-Me) was prepared in 87% yield by reductive alkylation (using a procedure similar to that for **4-Et** but using formalin as the aldehyde), bp 105–107 °C (0.1 mm), and solidified after VPC: mp 56–60 °C; NMR ($CDCl_3$) δ 2.30 (s, 6 H), 2.69 (s, 6 H), 3.03 (s, 4 H), 6.72 (s, 2 H).[26]

6,7-Dimethylquinoxaline was prepared from 4,5-dimethyl-*o*-phenylenediamine using the procedure employed for 5,8-dimethylquinoxaline in 71% yield: mp 101–102 °C; NMR ($(CD_3)_2CO$) δ 2.4 (s, 6 H), 7.72 (s, 2 H), 8.66 (s, 2 H).[26]

6,7-Dimethyl-1,2,3,4-tetrahydroquinoxaline (6B-H) was prepared by the same procedure as the 5,8-dimethyl compound (except that the product was less soluble in benzene and the catalyst had to be filtered from a hot solution) in 74% yield: mp 152–153 °C; NMR ($CDCl_3$) δ 2.0 (s, 6 H), 3.24 (s, 4 H), 3.3 (s, 2 H), 6.2 (s, 2 H).[26]

1,4,6,7-Tetramethyl-1,2,3,4-tetrahydroquinoxaline (6B-Me) was prepared by reductive methylation (see **6A-Me**) in 92% yield and purified by Kügelohr distillation: mp 33–36 °C; NMR ($(CO_3)_2CO$) δ 2.0 (s, 6 H), 2.68 (s, 6 H), 3.1 (s, 4 H), 5.14 (s, 2 H).[26]

1,4-Dimethyl-2,3-dibenzo-4,5,6,7-tetrahydro-1,4-diazapine (7-Me) was prepared by reductive methylation (see **6A-Me**) of **7-H**[26] in 24% yield and purified by VPC: NMR ($CDCl_3$) δ 6.87 (s, 4 H), 3.02 (t, 4 H), 2.85 (s, 6 H), 1.76 (pentet, 2 H).[26]

1,4-Dimethyl-2,3-benzo-1,4-diazacyclooct-2-ene (8-Me) was prepared by reductive methylation (see **6A-Me**) of **8-H**[28] in 33% yield and purified by VPC: NMR ($CDCl_3$) δ 6.75 (s, 4 H), 3.21 (m, 4 H), 2.80 (s, 6 H), 1.73 (m, 4 H).[26]

1,4-Dimethyl-2,3-benzo-1,4-diazacyclonon-2-ene (9-Me) was prepared by reductive methylation of **9-H**[28] in 27% crude yield and purified by VPC: NMR ($CDCl_3$) δ 6.71 (s, 4 H), 3.03 (m, 4 H), 2.67 (s, 6 H), 1.65 (m, 6 H).[26]

1,3-Dimethyl-2,2-tetramethylenebenzimidazoline (12-Me) was prepared by refluxing 2.1 g (15.4 mmol) of *N,N′*-dimethyl-o-phenylenediamine and 1.3 g (15.5 mmol) of cyclopentanone in 25 mL of benzene over a water separator for 20 h. Distillation gave 1.55 g (50%) of an oil, bp 120–125 °C (1.5 mm), which solidified (mp 79–81 °C) after sublimation: NMR ($CDCl_3$) δ 6.35 (m, 4 H), 2.76 (s, 6 H), 1.54–2.09 (8 H).[26]

1,3-Diethyl-2,2-spirotetramethylenebenzimidazoline (12-Et) was prepared as **12-Et:** bp 125–123 °C (0.3 mm); 71% yield; NMR ($CDCl_3$) δ 6.36 (m, 4 H), 3.15 (quartet, 4 H), 1.58–2.25 (m, 8 H), 1.27 (t, 6 H).[26]

1,3-Dimethyl-2,2-pentamethylenebenzimidazoline (13-Me) was prepared as **12-Me:** bp 135–140 °C (1.5 mm), 60% yield; mp 55–56 °C (after sublimation); NMR ($CDCl_3$) δ 6.36 (m, 4 H), 2.81 (s, 6 H), 1.28–1.88 (m, 10 H).[26]

5,8-Dimethyl-1-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoxaline (16). A solution of 5.05 g (3.1 mmol) of **6A-H** in 50 mL of methanol was cooled to −78 °C while 1.37 g (3.1 mmol) of ethylene oxide was added. After warming to room temperature, the mixture was stirred for 10 days and concentrated by rotary evaporation. Kügelrohr distillation gave a light yellow oil which solidified upon trituation with ether: 3.32 g (52%); mp 93–95 °C; NMR ($CDCl_3$) δ 2.08 (s, 3 H), 2.29 (s, 3 H), 3.0 (m, 5 H), 3.4 (t, J = 4, 2 H), 3.80 (t, J = 4 Hz, 2 H), 6.74 (d, J = 8 Hz, 1 H).[26]

3′,6′-Dimethyl-2,3-benzo-1,4-diazabicyclo[2.2.2]oct-2-ene (14B). 16 (1.03 g; 5 mmol) in 25 mL of dry tetrahydrofuran was cooled in a dry ice–ethanol slush while 0.12 g (5 mmol) of sodium hydride was added. After stirring at −78 °C for 5 min, 0.95 g (5 mmol) of tosyl chloride was added. After 15 min of stirring, the mixture was warmed slowly to room temperature and 4.5 mL of 1.16 M butyllithium was added dropwise. The THF was distilled off after the solution was stirred for 2 h at room temperature and 25 mL of 1 M sodium bicarbonate was added. Ether extraction gave a dark oil, from which 0.107 g (11%) of **14A** was sublimed during attempted Kügelrohr distillation: mp 85–89 °C; NMR ($(CD_3)_2CO$) δ 2.24 (s, 6 H), 2.4–3.2 (m, 8 H), 6.95 (s, 2 H).[26]

2,3-Benzo-1,4-diazabicyclo[2.2.2]oct-2-ene (15). A mixture of 5.36 g (40 mmol) of **6-H,** 100 mL of dimethylformamide, 6 g of sodium carbonate, and 7.52 g (40 mmol) of ethylene bromide was heated at 120 °C for 2 days and the DMF was distilled off at reduced pressure. Water (80 mL) and sodium hydroxide were added. The strongly basic solution was extracted with ether giving a dark oil from which 160 mg (2.5%) of **14** was sublimed in a Kugelrohr apparatus: mp 140–141 °C (acetone); NMR ($(CD_3)_2CO$) δ 2.51–3.4 (m, 8 H), 7.04–7.86 (m, 4 H).[26]

4′,5′-Dimethyl-2,3-dibenzo-1,4-diazabicyclo[2.2.2]oct-2-ene (14A) was prepared from **6B-H** using the same method as for **14** and giving **14b** in 4.2% yield: mp 119–123 °C (after sublimation); NMR ($CDCl_3$) δ 2.20 (s, 6 H), 2.72 (m, 8 H), 6.82 (s, 2 H).[26]

9,10-Benzo-1,5-diazabicyclo[3.3.2]dec-9-ene (14). A mixture of 5.4 g (50 mmol) of **4-H,** 100 mL of DMF, 5 g of sodium carbonate, and 20.2 g (100 mmol) of 1,3-dibromopropane was treated in the same way as in the preparation of **14,** giving 350 mg (3.7%) of **15:** mp 75–76 °C; NMR ($(CD_3)_2CO$) δ 1.1–1.5 (m, 2 H), 1.9–2.3 (m, 2 H), 2.8–3.4 (m, 8 H), 7.12 (s, 4 H).[26]

Apparatus. The same electrochemical apparatus was used as previously.[6b] All data reported are in butyronitrile[6b] containing 0.1 M tetrabutylammonium perchlorate, are referenced to SCE, and were recorded at planar gold electrode. ^{13}C-NMR spectra were taken on a Varian FX-60 instrument (off-resonance decoupled spectra were used in making assignments) and UV spectra on a Cary 118. An A.E.I. MS.9 was used for high-resolution mass-spectroscopy measurements.

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Registry No.—**4A-H,** 35975-12-3; **4B-H,** 3171-45-7; **5-Me,** 3204-31-7; **6A-H,** 66102-39-4; **16,** 66102-40-7; *N,N′*-diethyl-o-phenylenediamine, 24340-87-2; 5,8-dimethylqiunoxaline, 64931-22-2; 6,7-dimethylquinoxaline, 7153-23-3; *N,N′*-dimethyl-*o*-phenylenediamine, 3213-79-4; cyclopentanone, 120-92-3.

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Stereospecific Vicinal Oxyamination of Olefins by Alkylimidoosmium Compounds

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The reaction of trioxo(*tert*-alkylimido)osmium(VIII) complexes with a variety of olefins (30 different cases) affords, after reduction of the intermediate osmate esters, vicinal amino alcohols in fair to excellent yields. The synthetic utility of this new reaction was evaluated by examining the effects of solvent, temperature, olefin substitution patterns, and functional groups. Where possible the imidoosmium(VIII) reagents were compared to osmium tetroxide. Stereospecific preparations of both (*E*)-1-deuterio-1-decene and (*Z*)-1-deuterio-1-decene are described.

During our studies on oxygen atom transfer chemistry of transition metal oxo compounds (1) with olefins, it occurred to us that similar reactions might take place with the nitrogen (2) and carbon (3) analogues of the oxo species. The transition

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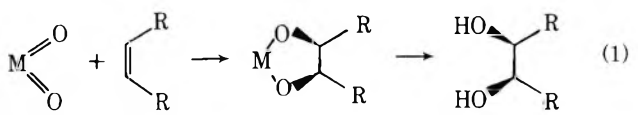
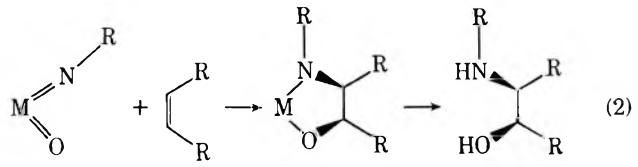
metal oxo compounds which react with olefins are typically d^0 substances having from two to four oxo groups. Cis dihydroxylation of olefins to form vicinal diols is a unique reaction of these oxidants (eq 1). We report here further examples of an aza analogue of this transformation (eq 2).[1]

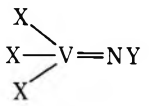


(1)



(2)

The only known d^0 alkylimido transition metal species are compounds of vanadium[2] and osmium.[3] In the case of vanadium the compounds have the general structure **5**, and in the case of osmium only two substances (**6a**[3a,b] and the related monoimido species derived from *tert*-octylamine[3b]) have been described. In addition to the known *tert*-butylimido compound **6a**, we have prepared the new adamantyl derivative **6b** and the *tert*-amyl derivative **6c**. All three were synthesized in about 90% yield by treating the amine with OsO_4 in olefin-free pentane or CH_2Cl_2. We were pleased to find that the imido reagents all reacted with a variety of olefins to afford, after reductive cleavage of the osmate esters, vicinal tertiary alkylamino alcohols in fair to excellent yields. The mode of addition of reagents **6** has been shown to be stereospecific and in most cases highly regioselective.



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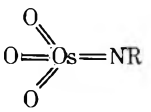


6a, R = *tert*-butyl
b, R = 1-adamantyl
c, R = *tert*-amyl

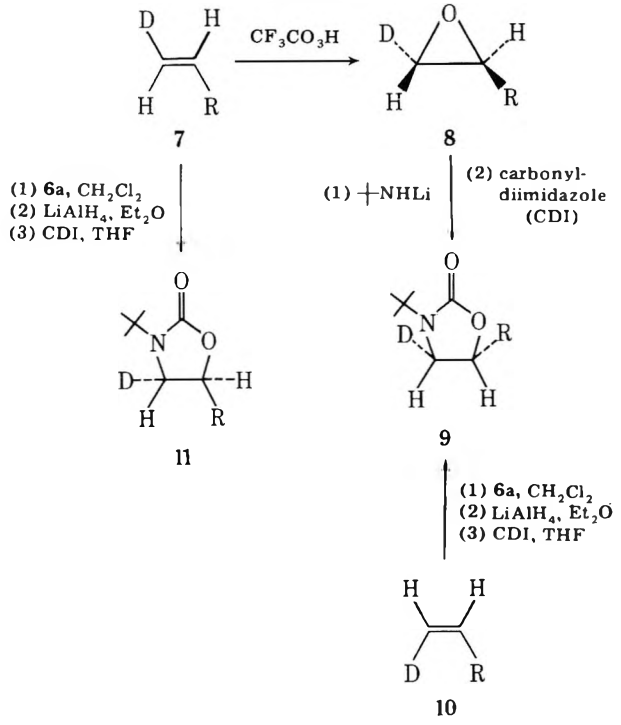
A number of methods are available for synthesis of β-amino alcohols.[4] Each method varies with respect to starting material, overall yield, regiospecificity, and stereochemistry, However, only this new procedure allows direct cis addition of the oxygen and nitrogen moieties to the olefinic bond.

Results and Discussion

Stereochemistry. The mode of the addition of alkylimidoosmium compounds to olefins in CH_2Cl_2 was established

0022-3263/78/1943-2628$01.00/0

Scheme I



7 8 11 9 10

to be cis by reaction of **6a** with the stereospecifically deuterated 1-decenes **7** and **10**, which after hydrolysis and derivitization afforded carbamates **11** and **9**, respectively. The authentic diastereomer **9** was prepared as indicated from olefin **7**; deuterium-decoupled ^1H NMR spectra revealed that **11** contained less than 5% of its diastereomer **9**. Similarly, oxyamination of **10** afforded **9**, which contained less than 5% of its diastereomer **11** (Scheme I).

The stereochemistry of the addition in pyridine was established to be cis by reaction of **6a** with cyclohexene to afford, after hydrolysis of the osmate ester, the amino alcohol **12**. The diastereomer **13**, prepared by opening cyclohexene oxide with

12 13

tert-butylamine, was shown to be different from **12** by GLC, NMR and IR spectroscopy, and melting point. Oxyamination of (*E*)- and (*Z*)-1-phenylpropene with **6a** provided further evidence for a stereospecific addition in pyridine since the two amino alcohol regioisomers obtained from the *E* olefin were nonidentical by GLC and ^1H NMR spectroscopy with the two regioisomers obtained from the *Z* olefin.

Regioselectivity and Solvent Effects. 1-Decene reacts with **6a** in CH_2Cl_2 to afford, after reductive cleavage, a 62% yield of amino alcohol **14** (R = n-C_8H_{17}) and 6% of the 1,2-diol.

14 15

The *complete* regiospecificity of the oxyamination was demonstrated by synthesis of the isomer **15** (R = n-C_8H_{17}); **14** and **15** separate readily on GLC and are distinguishable by TLC. In all cases investigated to date, we have found that reagents **6** always form the new carbon–nitrogen bond at the least substituted carbon.

Solvent plays an important role in the oxyamination process. A poor yield of 2-(*tert*-butylamino)-1-phenylethanol was obtained when **6a** was allowed to react in CH_2Cl_2 with styrene. Benzyl alcohol was another product, presumably produced by oxidative cleavage of the intermediate osmate ester (due to the reductive nature of the workup ($LiAlH_4$), we observed benzyl alcohol rather than benzaldehyde). Henbest[5] found that the reaction of stilbene with OsO_4 in noncoordinating solvents such as cyclopentane afforded considerable benzaldehyde; addition of several equivalents of pyridine completely suppressed the production of benzaldehyde. We have also found that significantly higher yields of amino alcohol were obtained as the coordinating ability of the solvent increased. Yields of amino alcohol from the reaction of styrene with **6a** in CH_2Cl_2, *tert*-butyl alcohol, THF, *tert*-butylamine, and pyridine are shown in Table I. The highest yield of amino alcohol was obtained with pyridine as solvent. *In all of the cases studied where a particular olefin was oxyaminated in CH_2Cl_2 and in pyridine, reactions carried out in pyridine gave consistently higher yields of amino alcohol and less diol.* We have also found that pyridine enhances the rate of addition of the imido compounds to olefins; this parallels a similar observation by Criegee et al.[6] regarding the addition of OsO_4 to olefins.

The reaction of (*E*)-5-decene with **6a** in CH_2Cl_2 afforded only a 20% yield of the amino alcohol and a 50% yield of diol. When oxyaminated in pyridine, the same substrate gave greater than 95% amino alcohol and less than 3% diol. Even more striking are the results from the oxyamination of (*Z*)-5-decene. Only the erythro diol was obtained when the reaction was run in CH_2Cl_2. No amino alcohol was observed by GLC. In pyridine at room temperature the major product was still diol (42%), but 25% amino alcohol was also observed. However, when the reaction of (*Z*)-5-decene was conducted in pyridine at 0 °C (6 days), a 65% yield of amino alcohol and only a 25% yield of diol were observed, demonstrating that the amino alcohol to diol ratio is also temperature sensitive. Despite the cis nature of the double bond in norbornene, cyclohexene, and (*Z*)-1-phenyl-1-propene, good to excellent yields of amino alcohol were achieved at room temperature in pyridine.

In the case of 1-phenyl-2-alkyl-disubstituted double bonds, carbon–nitrogen bond formation usually occurred with some preference for the olefinic carbon adjacent to the aromatic system. Reactions of (*Z*)-1-phenyl-1-propene, (*E*)-1-phenyl-1-propene, and 1,2-dihydronaphthalene with **6a** all afforded mixtures of the 1- and 2-amino alcohol regioisomers in which benzylic amination predominated.

The reaction of trisubstituted olefins with **6** afforded β-amino alcohols in fair to good yield. Citronellol methyl ether gave primarily diol when the reaction was carried out in CH_2Cl_2 and diol and amino alcohol in nearly a 1:1 ratio when the reaction was carried out in pyridine. However, 1-phenylcyclohexene, 1-methylcyclopentene, and 1-phenyl-2-methylpropene all gave the β-amino alcohol as the major product (see Table I). The tetrasubstituted double bond of tetramethylethylene afforded only diol in 82% yield when reacted with **6a** in pyridine; no β-amino alcohol could be detected by NMR spectroscopy.

Dependence of Rate on Olefin Substitution. Table II presents the relative rate data for the consumption of olefins in the reaction of **6a** in CH_2Cl_2 with a series of mono-, di-, and trisubstituted olefins. Interestingly, the di- and trisubstituted olefins reacted slower with the imido reagent than the monosubstituted olefins. (The relative rate data for the oxidation of olefins with OsO_4, unlike the imido reagent, demonstrate that OsO_4 reacts faster with the more highly substituted olefins.[7]) The only other known olefin oxidations which show this rare type of selectivity are $KMnO_4$ in acetic anhydride[7] and aminopalladation.[8] For a given type of substitution pattern, reaction with the imido compound occurs faster when the

Table I

Olefin	Registry no.	Amino alcohol[a]	Registry no.	Yield of amino alcohol,[b] %	Yield of diol, %	Solvent
(*E*)-Cyclododecene	1486-75-5	2-(*tert*-Butylamino)cyclododecanol[c]		3[d]	40[e]	CH_2Cl_2
1-Decene	872-05-9	n-C_8H_{17}(OH)CHCH$_2$NH(*t*-Bu)	55915-71-4	63	6[f]	CH_2Cl_2
				89	<1	Pyridine
				78[g]	<1	Pyridine
Styrene	100-42-5	PhCH(OH)CH$_2$NH(*t*-Bu)	18366-40-0	37[h]	Trace	CH_2Cl_2
				52	<1	*t*-BuOH
				64	<1	THF
				77	<1	*tert*-Butylamine
				92	<1	Pyridine
				74[i,j]		Pyridine
2-Methyl-1-tridecene	18094-01-4	n-$C_{11}H_{23}$(Me)C(OH)CH$_2$NH(*t*-Bu)	55915-72-5	82	<1[k]	CH_2Cl_2
α-Methylstyrene	98-83-9	Ph(Me)C(OH)CH$_2$NH(*t*-Bu)	55915-75-8	93	<1[l]	CH_2Cl_2
α-Methylstyrene		Ph(Me)C(OH)CH$_2$NH(1-admantyl)[m]	55912-76-9	62	<1	CH_2Cl_2
(*E*)-5-Decene	7433-56-9	*threo*-6-(*tert*-Butylamino)-5-decanol[c]	55915-73-6	20	50 (threo)	CH_2Cl_2
				>95	<3	Pyridine
(*Z*)-5-Decene	7433-78-5	*erythro*-6-(*tert*-Butylamino)-5-decanol[c]	55912-74-7	0	53	CH_2Cl_2
				0	54 (erythro)[i]	CH_2Cl_2
				25	42	Pyridine
				65	25	Pyridine (0 °C)
Cyclohexene	110-83-8	*cis*-2-(*tert*-Butylamino)cyclohexanol	55915-78-1	85[i]		Pyridine
Cyclohexene		*cis*-2-(1-Adamantylamino)cyclohexanol[c,m]	65760-97-6	79[i]		Pyridine
Norbornene	498-66-8	*cis-exo*-3-(*tert*-Butylamino)bicyclo[2.2.1]-heptan-2-ol	65760-98-7	94[i]		Pyridine
1,2-Dihydronaphthalene	447-53-0	*cis*-2-(*tert*-Butylamino)-1-hydroxytetralin (69)[o,c]	65760-99-8	38[i,n]	*q*	Pyridine
		cis-1-(*tert*-Butylamino)-2-hydroxytetralin (31)[o,c]	65761-00-4			
p-Cyano-α-methylstyrene	19956-03-7	(*p*-Cyanophenyl)(Me)C(OH)CH$_2$NH(*t*-Bu)	65761-01-5	40[i,g,p]		Pyridine
p-Chloro-α-methylstyrene	1712-70-5	(*p*-Chlorophenyl)(Me)C(OH)CH$_2$NH(*t*-Bu)	65761-02-6	97[i]		Pyridine
p-Methyl-α-methylstyrene	1195-32-0	(*p*-Methylphenyl)(Me)C(OH)CH$_2$NH(*t*-Bu)	65761-03-7	95[i]		Pyridine
p-Methoxy-α-methylstyrene	1712-60-2	(*p*-Methoxyphenyl)(Me)C(OH)CH$_2$NH(*t*-Bu)	65761-04-8	70[i]		Pyridine
p-*N*,*N*-Dimethylamino-α-methylstyrene	25108-56-9	(*p*-*N*,*N*-Dimethylaminophenyl)(Me)C(OH)-CH$_2$NH(*t*-Bu)	65761-05-9	88[i]	10[i]	Pyridine
(*Z*)-1-Phenylpropene	766-90-5	*erythro*-PhCH[NH(*t*-Bu)]CH-(OH)Me (97)[r,c]	65761-06-0	92[i]		Pyridine
		erythro-PhCH(OH)CH[NH(*t*-Bu)]Me (3)[r,c]	65761-07-1			
(*E*)-1-Phenylpropene	873-66-5	*threo*-PhCH[NH(*t*-Bu)]CH(OH)Me (76)[s,c]	65761-08-2	91[i]		Pyridine
		threo-PhCH(OH)CH[NH(*t*-Bu)]Me (24)[s,c]	65760-82-9			
Citronellol methyl ether	55915-70-3	MeO(CH$_2$)$_2$CH(Me)CH$_2$CH$_2$CH[NH(*t*-Bu)]-C(OH)Me$_2$	55915-77-0	0	78[i]	CH_2Cl_2
				38	45	Pyridine
1-Phenyl-2-methylpropene	768-49-0	PhCH[NH(*t*-Bu)]C(OH)Me$_2$	65760-83-0	88[i]	0[t]	Pyridine
1-Phenylcyclohexene	771-98-2	2-(*tert*-Butylamino)-1-phenylcyclohexanol[c]	65760-84-1	65[i]	8	Pyridine
1-Methylcyclopentene	693-89-0	2-(*tert*-Butylamino)-1-methylcyclopentanol[c]	65760-85-2	66[i]		Pyridine
Tetramethylethylene	563-79-1				81[i]	Pyridine

[a] All new compounds have been characterized by spectral and analytical data. [b] GLC yield unless otherwise noted. [c] The stereochemistry was not proven in these cases. However, we feel that there is little doubt that they are the products resulting from stereospecific cis addition of the amino and hydroxyl moieties to the olefin. [d] As amino acetate. [e] As diacetate. [f] A known diol (ref 22). [g] Bisulfite workup. [h] The low yield of product is believed to be caused by oxidative cleavage of the osmate ester intermediate. [i] Isolated yield. [j] Mp 87–88 °C (lit.[21] mp 86–87 °C). [k] A known diol (ref 9). [l] A known diol (ref 23). [m] Oxidized with reagent **6b**. [n] The low yield is believed to be caused by ~25% impurity in the starting material. [o] The numbers in parentheses refer to the ratio of regioisomers. [p] The low yield is believed to be due to the bisulfite workup and impurities in the starting olefin. [q] A known diol (ref 27). [r] Assumed to be the erythro regioisomers (see c above). [s] Assumed to be the threo regioisomers (see c above); all four of the amino alcohol isomers derived from the 1-phenylpropenes are separable by GLC. [t] A known diol (ref 26).

olefin is conjugated to an aromatic ring, e.g., styrene vs. 1-decene and 2-methyl-1-tridecene vs. α-methylstyrene.

Inductive electron-withdrawing groups in the vicinity of an olefin have little effect upon the rate of oxidation as evidenced by the fact that phenyl allyl ether reacted 0.95 times as fast as 4-phenyl-1-butene in pyridine. In contrast, the geometry of the olefin is important. Reagent **6a** reacts 4.2 times faster in methylene chloride with (*E*)-5-decene than with (*Z*)-5-decene; however, the product analysis shows that (*Z*)-5-decene gives exclusively diol while (*E*)-5-decene gives both amino alcohol and diol. The oxyamination of (*Z*)- and (*E*)-1-phenylpropene in pyridine affords only β-amino alcohols and no diol. A competition experiment between these two olefins in pyridine showed that the *E* isomer reacted 4.9 times faster than the *Z* isomer.

Since it has been shown[7,9] for OsO_4 that as the coordinating ability of the solvent is increased the rate differences for olefin oxidation are compressed (not reordered), it is reasonable to anticipate an even larger rate difference for the oxyamination of the 1-phenylpropenes in CH_2Cl_2. However, as the rates become slower, diol formation also begins. From a synthetic standpoint the differences in rate demonstrated by the imido compound are not in general great enough to anticipate selective oxidation of polyenes.

Functional Group Compatibility. The synthetic utility of a reagent is dependent on the selectivity it demonstrates for reaction with a specific functional group. The results of the oxyamination of a series of monosubstituted olefins containing functional groups sensitive to oxidation are shown in Table III. Only 1-phenylbut-3-en-1-ol and *N*-allylaniline afforded,

Table II. Relative Rate Data for Oxidation of Olefins with 6a in CH_2Cl_2

Olefin	Relative rate[a]
(*Z*)-5-Decene	1.0
Citronellol methyl ether	2.9
2,3-Dimethyl-2-octene	3.2
2-Methyl-1-tridecene	3.2
(*E*)-5-Decene	4.2
α-Methylstyrene	6.2
1-Undecene	8.1
Styrene	17.0

[a] Based on the disappearance of olefin.

in addition to the desired amino alcohol, other uncharacterized products. The results of the oxidation of a series of para-substituted α-methylstyrenes by **6a** are displayed in Table I. In general, we have found that imido reagents **6** are milder oxidants than OsO_4. This fact is well illustrated by the oxidation of *N*-allylaniline with OsO_4 which gave only a 10% yield of diol and numerous other products,[10] whereas reagent **6a** gave a 50% yield of amino alcohol. Although we have not screened an extensive series of oxidatively sensitive compounds, we feel that any functional group that is compatible with OsO_4 will be compatible with the imido compounds.

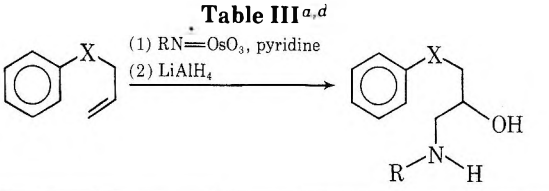
Attempts at Forming Imido Compounds with Other Amines. The usefulness of the oxyamination is limited by the fact that only a select number of primary amines bound to a tertiary carbon center form stable crystalline imido compounds. Attempts to form stable trioxo(alkylimido)osmium(VIII) compounds by methods similar to that used to prepare reagents **6** with the following amines failed: ethyl 2-amino-2-methylpropionate, 2-amino-2-cyanopropane, 1-phenyl-2-amino-2-methylpropane, 1-chloro-3-amino-3-methylbutane, 1-hydroxy-2-amino-2-methylpropane, tritylamine, 1,4-diamino-1,1,4,4-tetramethylbutane, methoxyamine, *p*-toluenesulfonamide, triphenylsilylamine, 1-amino-1-phenylcyclohexane, cyanamide, aniline tosylhydrazine, and 1-amino-1,2,2,3-tetramethylcyclopentane.

In many cases the amine complexed with the OsO_4 to form an unstable red-orange crystalline intermediate which decomposed, occasionally violently, upon warming. Similar complexes were observed during the preparation of reagents **6**, but these intermediates afforded only diols upon reaction with olefins. Thus, the addition of 1 equiv of 1-decene to a solution containing 1 equiv of OsO_4 and 1 equiv of *tert*-butylamine in pentane afforded 1,2-decanediol as the sole product after $LiAlH_4$ workup. The only method we have found to successfully convert the intermediate to the imido compounds **6** was to store it in the dark at room temperature free of solvent in the solid state for 6–12 h. Unfortunately only three of the tertiary amines that were tested survived the solid-state reaction.

The orange solutions of the osmium tetroxide–amine complexes are very stable in the usual organic solvents, revealing no tendency for dehydration to give imido species **6**. More recently,[36] however, we have found that imido complexes **6a** and **6c** are very readily formed by reaction of OsO_4 with the corresponding amines in water (ref 36 contains the experimental details for these preparations). The aqueous procedure fails for amines (e.g., adamantylamine) which are not soluble in water. Even in such cases it should be possible to avoid the sublimation of the imido reagent (e.g., **6b**) by allowing the solid amine–OsO_4 complex to stand overnight (solid-state dehydration step) and then using this crude reagent directly by simply dissolving it in pyridine and adding the olefin substrate.

Reactions of the Imido Reagents with 4-(*tert*-Butyl)-methylenecyclohexane. Henbest[11] used 4-(*tert*-butyl)-methylenecyclohexane as a stereochemical probe for epoxidation by perlauric acid to determine the preference of the reagent for axial vs. equatorial attack. An analogous study with imido compounds **6** was undertaken (Table IV). In both methylene chloride and pyridine imido reagents **6** all showed substantial preference for the sterically less hindered equatorial mode of attack. The preference for equatorial attack is not surprising considering the substantial bulk of these imidoosmium compounds (the oxo bond lengths in OsO_4 are 1.74 Å[12]); notice also that the variation of the alkyl group bound to nitrogen does not effect the ratio of axial to equatorial attack. What is surprising is that a similar selectivity was observed with OsO_4 itself. In fact, OsO_4 even showed a slightly greater preference for equatorial attack than the imido species. An explanation of these apparent anomalies must await better understanding of the mechanisms of these reactions.

Table III[a,d]



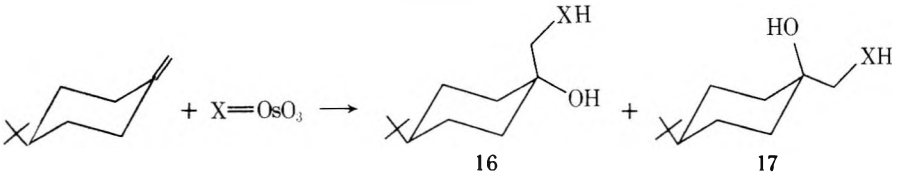
R	X, % CHOH	O	S	NH
tert-Butyl	50[b]	70[c]	66[b]	55[c]
1-Adamantyl		66[c]		
tert-Amyl		88[b]		

[a] Isolated yields. [b] Chromatographed on Florisil. [c] Chromatographed on silica gel. [d] Consistently higher yields have been obtained when chromatographic isolation was accomplished with Florisil instead of silica gel.

Behrman et al.[13] and Criegee et al.[6] have reported the isolation of the OsO_4 pyridine complex. Osmium tetroxide has a very strong oxo stretch (CCl_4) at 960 cm^{-1}. We found that addition of 1 equiv of pyridine showed a new, very strong absorption band at 925 cm^{-1}. Additional equivalents of pyridine diminished the intensity of the 960-cm^{-1} band further with concommitant increase in the intensity of the 925-cm^{-1} band. Yet, even after 3 equiv of pyridine was added the 960-cm^{-1} band did not disappear completely. Imido compound **6a** has two strong oxo stretches (CCl_4) at 925 and 912 cm^{-1}. Addition of 4 equiv of pyridine did not effect the intensity of the oxo bands or produce any new bands in the IR spectrum attributable to oxo stretches. The imido compound is clearly reluctant to add pyridine to its coordination sphere. Pyridine obviously plays an important role during the oxyamination of olefins with imido reagents because of the dramatic changes in diol to amino alcohol ratios observed when it is present. It is, however, unclear at what point along the reaction pathway pyridine coordinates with the metal center.

Optimum Conditions for Osmate Ester Cleavage. During our initial investigations on the oxidation of olefins with **6**, problems were encountered with the cleavage of the intermediate osmate esters. We found that the majority of methods in the literature were only moderately satisfactory. A study was undertaken to determine the best method for ester cleavage. In five separate reactions the osmate ester obtained by reacting 1-decene with **6a** was cleaved by one of the methods shown in Table V. Of the methods tested, only the $LiAlH_4$ and bisulfite cases afforded good yields of the amino alcohol. We have found that $LiAlH_4$ is the best cleavage reagent for osmate esters of oxyaminated olefins which contain no $LiAlH_4$-labile functional groups. In cases where $LiAlH_4$ could not be used the bisulfite workup has proven satisfactory. More recently in a related system we have found that bisulfite reductions of osmate esters are improved by heating to 60–80

Table IV



16 17

X	Solvent	16, %	Registry no.	17, %	Registry no.	Yield (16 + 17), %
 N (6a)	Pyridine	81	65760-86-3	19	65760-87-4	93
 N (6a)	CH_2Cl_2	85		15		
 N (6c)	Pyridine	81	65760-88-5	19	65760-89-6	81
(1-Adamantyl)–N (**6b**)	Pyridine	81	65760-90-9	19	65760-91-0	91
O	Pyridine	86	60380-83-8	14	60380-79-2	
O	CH_2Cl_2	82		18		

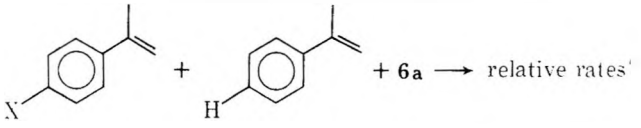
Table V. Osmate Ester Cleavage

1-decene + O_3Os = N + → osmate ester → amino alcohol

Reaction solvent	Ester cleavage solvent	Cleavage reagents	Yield of amino alcohol,[a] %
Pyridine	Et_2O	$LiAlH_4$[b]	89
Pyridine	Pyridine	Bisulfite[c]	78
Dioxane[d]	Dioxane	H_2S[e]	20
THF[f]	THF	H_2S	21
Pyridine	H_2O	HCl, H_2S[g]	No amino alcohol
Pyridine	CH_2Cl_2/H_2O	KOH, mannitol[h]	Bad emulsion

[a] Determined by GLC. [b] Reference 14. [c] Reference 15. [d] Pyridine (10 equiv) was added. [e] Reference 16. [f] Pyridine (5 equiv) was added. [g] Reference 17. [h] Reference 6.

Table VI. Competitive Oxidations of Para-Substituted α-Methylstyrenes with 6a



X	$\frac{k_X}{k_H}$ (CH_2Cl_2)	$\frac{k_X}{k_H}$ (pyridine)
$N(Me)_2$	4.26	1.63
OMe	1.49	1.04
Me	1.14	1.01
H	1.00	1.00
Cl	0.95	1.23
CN	1.93	1.53

[a] Based on disappearance of olefin.

°C for several hours.[24] We would also recommend heating in these bisulfite workups as a likely means of increasing the yields of amino alcohols.

Electronic Effects. Hammett Study. In order to become better acquainted with the electronic factors associated with the reactions of imidoosmium compounds with olefins, a Hammett study was undertaken. Relative rates for the addition of **6a** to a series of para-substituted α-methylstyrenes in pyridine and methylene chloride were determined via competition studies (see Table VI). Authentic β-(*tert*-butylamino) alcohols were prepared and characterized in separate experiments by the addition of **6a** to the appropriate α-methylstyrene (see Table I).[18] A plot of the data shown in Table VI gave U-shaped curves for reactions conducted in both methylene chloride and pyridine. Dondoni observed a similar phenomenon for the 1,3-dipolar addition of nitrile oxides to para-substituted styrenes.[31] Firestone[19,20] rationalized the U-shaped Hammett plot obtained by Dondoni by suggesting that the 1,3-dipolar addition proceeded with diradical character in the transition state, and as such, X groups conjugated to an unsaturated radical center will stabilize the radical intermediate relative to X = H. It is interesting to note that Henbest has found that the addition of OsO_4 to a series of para- and meta-substituted stilbenes gave a normal Hammett plot with $\rho = -0.55$.[5]

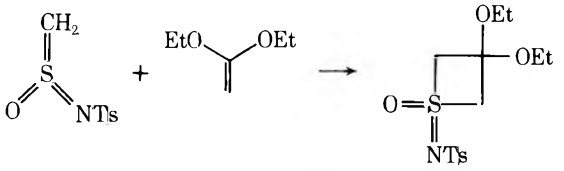
Conclusions

We wish to point out a number of features which make this new synthetic method of considerable interest. (a) The stereochemistry of the addition was shown to be exclusively cis. (b) The reaction of monosubstituted olefins with **6** gave good to excellent yields of the amino alcohol, and the new nitrogen–carbon bond formed exclusively at the terminal olefinic carbon. (c) The reaction of trans disubstituted olefins with **6** at room temperature in pyridine gave excellent yields of amino alcohol, but the ratio of regioisomers was dependent upon the substrate. (d) The yields of amino alcohol from the reaction of **6** with cis disubstituted olefins in pyridine were strongly dependent upon the substrate. The ratio of β-amino alcohol to diol from (*Z*)-5-decene exhibited a marked dependence upon solvent and temperature. (e) The reaction of geminal disubstituted olefins with **6** gave good to excellent yields of β-amino alcohols in pyridine or CH_2Cl_2, and the new carbon–nitrogen bond formed exclusively at the least substituted olefinic carbon. (f) The reaction of trisubstituted double bonds with **6** in pyridine gave moderate to excellent yields of amino alcohol depending on the substrate; the new carbon–nitrogen bond formed exclusively at the least substituted olefinic carbon. (g) The only tetrasubstituted olefin tested, tetramethylethylene, gave only diol upon reaction with **6a** in pyridine at room temperature. (h) Pyridine was the best solvent for the

oxyamination of olefins with reagents **6**. (i) $LiAlH_4$ was the best reagent for cleavage of the intermediate osmate esters. (j) The imido reagents **6** were milder oxidants than OsO_4.

This new synthetic transformation suffers from two important limitations. It requires a stoichiometric amount of osmium reagent **6**, and it is difficult to remove the *tert*-alkyl group from the products. However, a new catalytic procedure for oxyamination of olefins solves both of these problems.[24,37] More recently, it has been found that polyimidoosmium complexes effect cis diamination of olefins.[36]

Although in the present work some data were collected which are also relevant to the mechanism of reaction of these imidoosmium reagents **6** with olefins, we prefer to postpone mechanistic considerations for a later publication. That publication will deal with the general problem of the mechanisms of reactions of olefins with oxo (M=O), imido (M=NR), and ylide ($M=CR_2$) species of both transition metal and main group elements.[25] However, it is worth pointing out at this time that it is remarkable that the trioxoalkylimido reagents **6** exhibit such a strong preference for delivery of the nitrogen to one of the olefinic carbons. This reaction path would appear to be disfavored by the steric bulk in the vicinity of the nitrogen produced by the tertiary alkyl substituents. One finds precedent for this preference of nitrogen over oxygen in the reactions of related sulfur species with olefins. The most elegant example is that of Johnson in



which the iminosulfene reacts with an enol ether to give the [2 + 2] adduct.[29] In this instance the olefin has a smorgasbord of the first row atoms (C, N, and O) to choose from, and it selects carbon, the element furthest to the left. This rule of selection (C > N > O) appears to hold for all known [2 + 2] and [2 + 4] additions of other similar sulfur compounds with olefins and dienes. Whatever the origin of this important effect, it seems that it may have validity for elements other than sulfur.

Experimental Section

Analytical GLC was done on one of the following columns: A, glass, 6 ft × 2 mm, 10% UCW-98 on 80–100 Gas Chrom Q; B, glass, 6 ft × 2 mm, 3% OV-17 on 80–100 Gas Chrom Q; C, glass, 6 ft × 2 mm, 3% FFAP on 80–100 Gas Chrom Q. Preparative GLC was done on one of the following columns: D, copper, 6 ft × 0.25 in, 10% UCW-98 on 80–100 Gas Chrom Q; E, copper, 8 ft × 0.25 in, 20% SE-30 on 45–65 Chromosorb W. All GLC yields were determined by using hydrocarbon internal standards.

Starting Materials. Methylene chloride was purified by stirring it over portions of concentrated sulfuric acid until the acid layer remained colorless. The methylene chloride layer was washed with 10% sodium bicarbonate, water, and brine and dried ($MgSO_4$). Distillation from calcium hydride afforded dry, olefin-free methylene chloride. Pentanes were stirred over portions of concentrated sulfuric acid until the acid layer remained clear. The pentanes were further purified by stirring them over 10% aqueous potassium permanganate overnight. The pentane layer was washed with water and brine and dried ($MgSO_4$). Distillation from sodium metal afforded dry, olefin-free pentanes. Reagent grade pyridine was distilled from calcium hydride and stored over 4A molecular sieves. Ethyl ether was distilled from lithium aluminum hydride before use. Tetrahydrofuran was distilled from sodium–benzophenone, and dioxane was distilled from sodium metal.

Note on Abbreviated Format: Due to the large number of olefins reacted and to the similar nature of the initial stages of each oxyamination, only purification and spectral details are generally given for each case. Thus, the experimental details usually begin following the workup (either $LiAlH_4$ or bisulfite as indicated in parentheses). The general procedures for starting the oxyamination reactions and the $LiAlH_4$ and bisulfite workups are described below.

Oxyamination of Olefins. General Procedure. To an ca. 0.1 M solution of 1 equiv of the trioxo(alkylimido)osmium(VIII) species in olefin-free methylene chloride or pyridine was added 1.0 equiv of olefin with stirring. The reaction mixture darkened at various rates depending on the olefin. The reaction was kept in the dark for 12 h to 2 days depending on the olefin. The resulting osmate ester was cleaved by one of the following methods.

A. Bisulfite Workup. The procedure of Baran[15] was followed. If the initial reaction was conducted in methylene chloride, it was removed at reduced pressure. The brown residue was then subjected to a solution of the following description: for each millimole of osmate ester, 10 mL of pyridine and a solution of 0.5 g of sodium bisulfite in 8 mL of water were added. If the initial reaction solvent was pyridine, one only added the sodium bisulfite solution (0.5 g in 8 mL of H_2O/mmol of osmium reagent). The reaction mixture was stirred for at least 12 h at room temperature (more recent results[24] indicate that heating at 60–80 °C for several hours might be superior, especially in difficult cases) and then extracted once with 40 mL of chloroform (per mmol of osmate ester) and twice with 12 mL of chloroform. The combined chloroform layers were evaporated to dryness at reduced pressure. Further purification was accomplished by standard methods.

B. Lithium Aluminum Hydride Workup. If the reaction was conducted on a 5-mmol scale, we found that a 200-mL flask was the best size for the oxyamination. Due to the heterogeneous nature of the reductive cleavage, considerable volumes of anhydrous ether were necessary to maintain stirring.

Whether the initial solvent was methylene chloride or pyridine, solvent removal at reduced pressure was necessary. Pyridine was removed under high vacuum while methylene chloride was easily removed at aspirator pressure. The brownish-black osmate ester was "dissolved" in anhydrous ether. Generally, 25 mL/mmol of osmate ester was optimum. The reaction vessel was cooled in an ice bath and maintained under nitrogen. To the stirred reaction vessel was added 10 equiv of $LiAlH_4$ (relative to starting osmium reagent). The reaction mixture was stirred for 12 h at room temperature before quenching according to the procedure of Mićović and Mihailovic,[30] a description of which follows. The reaction mixture was cooled in an ice bath and maintained under nitrogen. For every x g of $LiAlH_4$ used in the reductive cleavage, x mL of water was cautiously and slowly added to the reaction mixture. (Rapid stirring was maintained throughout the quench, and more anhydrous ether was added when necessary.) After the addition of water, x mL of 15% aqueous sodium hydroxide was added slowly, followed by $3x$ mL of water. Best results were obtained when the hydrolyzed mixture was stirred for at least 12 h. After 12 h the mixture was filtered and the pad of osmium and aluminum salts was washed once with anhydrous ether. The ether filtrate was concentrated at reduced pressure. Further purification was effected by standard techniques.

Trioxo(*tert*-butylimido)osmium(VIII) (6a). To a 200-mL recovery flask was added 10.0 g (39.4 mmol) of osmium tetroxide and 50 mL of olefin-free pentane. After 5 min of stirring most of the tetroxide had dissolved, and 4.2 g (39.5 mmol) of *tert*-butylamine was added. A rapid exothermic reaction followed causing boiling of the pentane, and a large mass of red-orange crystals settled to the bottom of the flask. The reaction was stirred for 30 min before the solvent was removed at reduced pressure. Care must be taken not to maintain the vacuum longer than necessary because the solid is volatile. The contents of the flask were stored in the dark overnight (16 h) at room temperature before being sublimed (55 °C, 0.005 mm) to afford 11.10 g (91%) of a yellow solid, mp 112 °C dec (see ref 36 for a more convenient preparation of **6a** and **6c**).

Trioxo(1-adamantylimido)osmium(VIII) (6b). To a 200-mL recovery flask was added 6.0 g (23.6 mmol) of osmium tetroxide and 15 mL of olefin-free methylene chloride. To the resulting osmium solution was added 3.57 g (23.6 mmol) of 1-adamantylamine in 75 mL of methylene chloride. A golden-yellow solution resulted, and the addition of 30 mL of pentane did not force precipitation of a solid. The solvent was removed at reduced pressure, leaving behind a red-orange solid. After 6 h of storage in the dark, the residue was a dark yellow-brown color. Sublimation (0.005 mm, 130–135 °C) afforded 8.32 g (91%) of a yellow solid: mp 176–177 °C (sealed capillary); IR (CCl_4) 1215 (N=Os), 925, 915 (Os=O) cm^{-1}; NMR ($CDCl_3$) δ 2.38 (m, 3, NCCCH), 2.18 (d, 6, J = 2 Hz, $NCCH_2$), 1.75 (t, 6, J = 2 Hz, $NCCCCH_2$).

Anal. Calcd for $C_{10}H_{15}NO_3Os$: C, 30.97; H, 3.90; N, 3.61. Found: C, 30.92; H, 3.80; N, 3.61.

Trioxo(2-methyl-2-butylimido)osmium(VIII) (6c). To a 200-mL recovery flask was added 5.0 g (19.6 mmol) of osmium tetroxide and 20 mL of olefin-free pentane. To the stirred solution was

added 2.30 mL (19.6 mmol) of *tert*-amylamine. After stirring for 5 min, the solvent was removed at reduced pressure to leave an orange-red mass which melted upon warming to room temperature. The product was stored in the dark, and 4 h later the liquid had resolidified to a yellow-brown mass. After standing overnight (18 h), it was sublimed (50–60 °C, 0.005 mm) to afford 5.54 g (87%) of yellow product: mp 60–61 °C (sealed capillary); IR (CCl_4) 1210 (Os=N), 930, 915 (Os=O) cm^{-1}; NMR ($CDCl_3$) δ 2.06 (q, 2, J = 6.5 Hz, CH_2), 1.66 (s, 6, $NCCH_3$), 1.10 (t, 3, J = 6.5 Hz, $NCCCH_3$).

Anal. Calcd for $C_5H_{11}NO_3Os$: C, 18.57; H, 3.43; N, 4.33. Found: C, 18.71; H, 3.70; N, 4.29.

Reaction of (*E*)-Cyclododecene with 6a (Bisulfite Workup). To a 50-mL round-bottom flask containing 10 mL of olefin-free methylene chloride, 0.122 g (0.395 mmol) of **6a**, and 0.019 g (0.09 mmol) of pentadecane was added 0.062 g (0.395 mmol) of (*E*)-cyclododecene. The reaction mixture was allowed to stir for 3 days before the methylene chloride was removed at reduced pressure. The residue was dissolved in 4.5 mL of pyridine, and a solution of 0.18 g of $NaHSO_3$ in 3 mL of H_2O was added. Stirring was continued for 24 h. The reaction mixture was then extracted with chloroform. The chloroform layers were combined and concentrated at reduced pressure, affording a brown oil which was acetylated with acetic anhydride/pyridine. The acetylated reaction mixture was analyzed by GLC on column B. The major peak was *threo*-1,2-diacetoxycyclododecane (40% yield). Because of the presence of an unidentified peak before the major one, a GLC–mass spectrum was obtained.[34] The substance was assigned the structure of 1-acetoxy-2-(*tert*-butylamino)cyclododecane based on its mass spectrum: *m/e* 297 [parent (P)], 282 (P − CH_3), 254 (P − Ac), 241, 199, 182.

Oxidation of 1-Decene with 6a in Methylene Chloride ($LiAlH_4$ Workup). After workup an aliquot was analyzed by GLC on column C. The results showed 62% of 1-(*tert*-butylamino)-2-decanol. A small sample of the reaction mixture was acetylated (acetic anhydride/pyridine) and analyzed by GLC on column A, which revealed the presence of 6% of 1,2-diacetoxydecane.

Oxidation of 1-Decene with 6a in Pyridine ($LiAlH_4$ Workup). After workup an aliquot was analyzed by GLC on column A and showed 89% of 1-(*tert*-butylamino)-2-decanol. Less than 1% of diol was observed.

Oxidation of 1-Decene with 6a in Pyridine (Bisulfite Workup). After workup the residue was dissolved in ethyl acetate and analyzed on GLC column A to show 78% of 1-(*tert*-butylamino)-2-decanol. When the same experiment was repeated a 75% yield of amino alcohol was obtained.

1-(*tert*-Butylamino)-2-decanol: Epoxide Opening. In a three-neck 500-mL flask fitted with an addition funnel, magnetic stirring bar, and reflux condenser and maintained under nitrogen was added 300 mL of anhydrous THF and 15.17 g (207 mmol) of *tert*-butylamine (distilled from CaH_2). The reaction flask was cooled in an ice bath, and 21.8 mL of 2.2 M methyllithium was added over a period of 5 min, resulting in vigorous evolution of methane. The mixture was stirred for 1 h before 5.0 g (32.1 mmol) of 1-decene oxide was added. The reaction mixture was refluxed for 24 h. TLC revealed complete consumption of epoxide. The reaction mixture was quenched with water and extracted twice with ether. The combined ether layers were washed with water and brine and then dried ($MgSO_4$). Removal of the solvent at reduced pressure gave 7.2 g of crude yellow oil. Distillation gave 4.1 g (75%) of clear oil (0.060 mm, 73.1–74 °C): IR (neat) 3200–3600 (broad assoc. OH), 1390, 1360 (*tert*-butyl), 1210 (C–N), 1180 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.5 (m, 1, –C**H**(OH)–), 2.5 (m, 4, OH, NH, $-CH_2N-$), 1.4–0.9 (m, 17, aliphatic $-CH_2-$, CH_3), 1.15 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{14}H_{31}NO$: C, 73.29; H, 13.62; N, 6.10. Found: C, 73.16; H, 13.53; N, 6.32.

The cyclic carbamate was prepared in a manner analogous to that described for the preparation of the carbamate of *erythro*-1-deuterio-1-(*tert*-butylamino)-2-decanol (see below): NMR ($CDCl_3$) δ 3.7 (t, 1, J = 7.5 Hz, NCH_2), 3.2 (t, 1, J = 7.5 Hz, NCH_2).

Preparation of 2-(*tert*-Butylamino)-1-decanol. A dry 500-mL three-neck round-bottom flask with vertical joints equipped with a mechanical stirrer, an addition funnel, a condenser capped with a drying tube, and a nitrogen inlet was charged with 23 mL (219 mmol) of *tert*-butylamine in 40 mL of dry ether. The reaction mixture was cooled in a dry ice–2-propanol bath maintained between −10 and −20 °C while a slight flow of nitrogen was maintained through the system. An 8 g (37 mmol) amount of 1-acetoxy-2-decanone[32] in 100 mL of dry ether was added quickly from the addition funnel. After rinsing the addition funnel with a small portion of ether, the nitrogen flow was increased and the addition funnel was charged with 2 mL (21 mmol) of titanium tetrachloride solution (1 M in hexane). The titanium tetrachloride solution was added over 40 min, and the addition funnel was rinsed with a small portion of ether. The brick red reaction mixture was gradually allowed to warm to room temperature while stirring for 1.5 h before it was quickly filtered through a fritted funnel. The solid was collected and washed with dry ether, the filtrate was dried (Na_2SO_4), and the solvents were removed at reduced pressure to afford a thick brown oil, presumably the *tert*-butylimine of 1-acetoxy-2-decanone.

In a dry, nitrogen-purged, 1-L three-neck round-bottom flask equipped with a mechanical stirrer, an addition funnel, and a reflux condenser was placed 2.8 g (74 mmol) of $LiAlH_4$ in 200 mL of dry ether. The system was maintained under a positive pressure of nitrogen, and the crude imine in 160 mL of dry ether was added from the addition funnel so as to maintain a gentle reflux. An additional 2.0 g (53 mmol) of $LiAlH_4$ was added, the reaction mixture was allowed to stir at ambient temperature overnight before it was cooled in an ice bath, quenched,[30] filtered, and dried (Na_2SO_4), and the ether was removed at reduced pressure to afford 5.98 g of a crude yellow oil. The product was purified by molecular distillation, and an analytical sample was obtained by preparative GLC on column D: IR ($CHCl_3$) 3405 (OH, NH, hydrogen bonded), 1395, 1368 (*tert*-butyl) cm^{-1}; NMR ($CDCl_3$) δ 1.12 (s, 9, *tert*-butyl).

1-Deuterio-1-decyne. To a 500-mL round-bottom flask was added 25 mL (0.138 mol) of 1-decyne and 200 mL of ether. The solution was maintained at −40 °C while 78 mL (2 M, 0.155 mol) of butyllithium in hexane was added over a 30-min period. The resulting white mixture was stirred at room temperature for 1 h before 20 mL of deuterium oxide was cautiously added. The ether became nearly colorless, and a white semisolid collected at the bottom of the flask. The ether was decanted, rinsed with 15 mL of dilute hydrochloric acid, 15 mL of saturated sodium bicarbonate, and 15 mL of brine, and dried (Na_2SO_4). The ether solution was concentrated and then distilled to afford 12.3 g (89%) of product: bp 170–176 °C; IR (neat) 2600 (CD) cm^{-1}; deuterium-decoupled NMR ($CDCl_3$) δ 2.20 (t, 2, J = 5 Hz, $C{\equiv}CCH_2$).

(*Z*)-1-Deuterio-1-decene. To a 250-mL round-bottom flask was added 12.3 g (0.088 mol) of 1-deuterio-1-decyne and 10 mL of hexane. An addition funnel was charged with 54 g (0.095 mol) of a 25% solution of diisobutylaluminum hydride in heptane, and the contents were slowly added to the flask over a 2-h period. The reaction mixture was then warmed to 45 °C, and the temperature was maintained for 3 h before the mixture was cannulated into an addition funnel fitted on a 1-L three-neck round-bottom flask equipped with a reflux condenser and a mechanical stirrer. To the flask was added 200 mL of pentane and 50 mL of distilled water. The contents of the addition funnel were slowly added to the rapidly stirred pentane/water emulsion over a 2-h period. The resulting mixture was allowed to stir overnight (10 h) before it was filtered, and most of the solvent was removed at reduced pressure. Distillation afforded 9.00 g (73%) of product: bp 165–169 °C; deuterium-decoupled NMR ($CDCl_3$) δ 5.78 (m, 1, CHD=C**H**), 4.88 (d, 1, J = 10 Hz, C**H**D).

(*E*)-1-Deuterio-1-decene was prepared analogously to the *Z* isomer from 1-decyne, but the vinylalkane was quenched with deuterium oxide: deuterium-decoupled NMR ($CDCl_3$) δ 5.83 (dt, 1, J = 6, 17 Hz, CHD=C**H**), 4.94 (dt, 1, J = 5, 17 Hz, C**H**D).

Oxyamination of (*E*)-1-Deuterio-1-decene with 6a in Methylene Chloride ($LiAlH_4$ Workup). To a 50-mL round-bottom flask was added 0.610 g (1.97 mmol) of trioxo(*tert*-butylimido)osmium-(VIII) (**6a**), 25 mL of methylene chloride, and 0.37 mL (1.9 mmol) of (*E*)-1-deuterio-1-decene. The solution turned black within seconds and was stirred in the dark under nitrogen for 2 days before the methylene chloride was removed at reduced pressure. To the black residue was added 25 mL of ether and 0.70 g of lithium aluminum hydride. The reduction mixture was stirred overnight (14 h) before it was quenched. Removal of the solvent at reduced pressure afforded the crude amino alcohol: NMR ($CDCl_3$) δ 1.10 (s, 9, *tert*-butyl).

The amino alcohol was dissolved in 30 mL of tetrahydrofuran, and 1.5 g (9.3 mmol) of carbonyldiimidazole was added. The solution was refluxed for 36 h before it was quenched with 25 mL of water and 300 mL of ether. The ethereal layer was washed with water (2 × 50 mL) and brine (50 mL) and dried (Na_2SO_4) before the solvent was removed at reduced pressure. The crude carbamate was purified by preparative TLC on silica gel eluting with 65% ethyl acetate in hexane. A second preparve TLC purification using 20% ethyl acetate in hexane then afforded pure product: deuterium-decoupled NMR ($CDCl_3$) δ 3.17 (d, 1, J = 7.5 Hz, C**H**D), 1.40 (s, 9, *tert*-butyl). The NMR spectrum also showed some of the all protio system and a small amount of the other deuterium isomer believed to be derived from nonspecific labeling of the 1-deuterio-1-decene.

Oxyamination of (*Z*)-1-Deuterio-1-decene in Methylene

Chloride with 6a ($LiAlH_4$ Workup). The procedure followed for the (*E*)-deuteriodecene was followed using 0.478 g (3.38 mmol) of (*Z*)-1-deuterio-1-decene. The crude amino alcohol was refluxed in 30 mL of tetrahydrofuran containing 3.5 g (22 mmol) of carbonyldiimidazole for 22 h. The product after workup was purified by preparative TLC on silica gel eluting with 20% ethyl acetate in hexane. Deuterium-decoupled NMR spectroscopy showed >95% of one deuterium labeled isomer as well as a small amount of the all proton compound: deuterium-decoupled NMR ($CDCl_3$) δ 3.65 (d, 1, J = 7.5 Hz, CHD). This isomer was identical with the one obtained by epoxidation of (*E*)-1-deuterio-1-decene with trifluoroperacetic acid[35] followed by epoxide opening with lithium *tert*-butylamide and carbamate formation with carbonyldiimidazole.

2-(*tert*-Butylamino)-1-phenylethanol by the Oxyamination of Styrene with 6a in Pyridine ($LiAlH_4$ Workup). After workup the product was bulb-to-bulb distilled (55 °C, 0.015 mm), affording a clear oil which crystallized from hexane to give 772 mg (74%) of white crystals: mp 87–88 °C (lit.[21] mp 86–87 °C); IR (CCl_4) 3400 (OH), 1390, 1365 (*tert*-butyl), 1220 (C–O), 1190, 1160, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (m, 5, aryl H), 4.6 (dd, 1, J = 4, 8 Hz, H–C–O), 2.75 (m 4, OH, NH, CH_2N), 1.1 (s, 9, *tert*-butyl).

1-(*tert*-Butylamino)-2-methyl-2-tridecanol by the Oxyamination of 2-Methyl-1-tridecene with 6a in Methylene Chloride ($LiAlH_4$ Workup). After workup an aliquot was analyzed by GLC on column A and showed 82% of 1-(*tert*-butylamino)-2-methyl-2-tridecanol and less than 1% of diol. 1-(*tert*-Butylamino)-2-methyl-2-tridecanol: IR (CCl_4) 3450 (OH), 1465 (–CH_2–), 1390, 1360 (*tert*-butyl), 1230 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 2.45 (s, 2, NCH_2), 3.0–2.0 (m, 2, NH, OH), 1.1 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{18}H_{39}ON$: C, 75.72; H, 13.77; N, 4.90. Found: C, 75.73; H, 13.48; N, 4.91.

1-(*tert*-Butylamino)-2-phenyl-2-propanol by the Oxyamination Oxidation of α-Methylstyrene with 6a in Methylene Chloride ($LiAlH_4$ Workup). After workup an aliquot was analyzed by GLC on column A and showed 93% of 1-(*tert*-butylamino)-2-phenyl-2-propanol: IR (CCl_4) 3410 (OH), 1600 (phenyl), 1390, 1360 (*tert*-butyl), 770, 700 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.4 (m, 5, aromatic H), 3.8 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 19.6 Hz, NCH_2), 1.45 (s, 3, HO–C–CH_3), 1.05 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}N_{21}NO$: C, 75.31; H, 10.21; N, 6.75. Found: C, 75.09; H, 10.00; N, 6.55.

1-(1-Adamantylamino)-2-phenyl-2-propanol by the Oxyamination of α-Methylstyrene with 6b in Methylene Chloride ($LiAlH_4$ Workup). After workup the crude product (1.2 g, brown oil) was converted to the amine hydrochloride by reaction with HCl in dry Et_2O and chromatographed on 90 g of silica gel eluting with a mixture of 58% ethyl acetate/40% hexane/2% triethylamine. The combined amino alcohol fractions were bulb-to-bulb distilled (79 °C, 0.1 mm), yielding 0.718 g (62%) of the white crystalline free amine: mp 65.5–67 °C; IR 3460 (OH), 1600 (NH), 1150 (C–O), 1100 (C–N), 700 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (m, 5, aryl H), 2.8 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 14.7 Hz, –NCH_2–C–OH), 2.6–1.2 (m, 20, NH, OH, CH_3–C–OH, adamantyl-N).

1-(*tert*-Butylamino)-2-(4-cyanophenyl)-2-propanol by the Oxyamination of *p*-Cyano-α-methylstyrene with 6a in Pyridine (Bisulfite Workup). After workup the crude brownish black oil was chromatographed on 25 g of Florisil to afford 0.121 g (40%) of a clear oil which upon standing crystallized as a white solid: mp 48–49.5 °C; IR (CCl_4) 3400 (OH), 2875 (CH), 2240 (C≡N), 1390, 1365 (*tert*-butyl) cm^{-1}; NMR ($CDCl_3$) δ 7.55 (s, 4, aromatic H), 2.8 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 12 Hz, CCH_2N), 1.5 (s, 3, HO–C–CH_3), 1.1 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.37; H, 8.67; N, 12.06. Found: C, 71.90; H, 9.00; N, 11.95.

1-(*tert*-Butylamino)-2-(4-chlorophenyl)-2-propanol by the Oxyamination of *p*-Chloro-α-methylstyrene in Pyridine with 6a ($LiAlH_4$ Workup). After workup the crude product was bulb-to-bulb distilled (85 °C, 0.5 mm), affording 0.251 g (96%) of a clear oil: IR (neat) 3420 (OH), 1590 (phenyl), 1390, 1360 (*tert*-butyl), 1210 (C–N), 1090 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 7.35 (s, 4, aromatic H), 2.8 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 16 Hz, CCH_2N), 1.4 (s, 3, HO–C–CH_3), 1.05 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}H_{20}ClON$: C, 64.58; H, 8.34; N, 5.79. Found: C, 64.65; H, 8.46; N, 5.92.

1-(*tert*-Butylamino)-2-(4-methylphenyl)-2-propanol by the Oxyamination of *p*-Methyl-α-methylstyrene in Pyridine with 6a ($LiAlH_4$ Workup). After workup the crude product was chromatographed on 20 g of Florisil to afford 0.233 g (95%) a light yellow oil. The hydrochloride was prepared in ether as a white, powdery solid: mp 215.5–216 °C; NMR of the free amine ($CDCl_3$) δ 1.03 (s, 9, *tert*-butyl), 1.43 (s, 3, $OCCH_3$), 2.32 (s, 3, $CHCCH_3$), 2.75 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 18 Hz, NCH_2), 7.18 (A_2B_2 pattern, 4, J = 9 Hz, aryl H).

Anal. Calcd for $C_{14}H_{24}ClNO$: C, 65.21; H, 9.32; N, 5.43. Found: C, 64.91; H, 9.18; N, 5.31.

1-(*tert*-Butylamino)-2-(4-methoxyphenyl)-2-propanol by the Oxyamination of *p*-Methoxy-α-methylstyrene in Pyridine ($LiAlH_4$ Workup). After workup the crude product was chromatographed on 20 g of Florisil to afford 0.166 g (70%) of an oil. The hydrochloride was prepared as a white powder: mp 182–182.5 °C; NMR of the free amine ($CDCl_3$) δ 1.03 (s, 9, *tert*-butyl), 1.43 (s, 3, $OCCH_3$), 2.75 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 18 Hz, NCH_2), 3.76 (s, 3, OCH_3), 6.75 (A_2B_2 pattern, 4, J = 9 Hz, aryl H).

Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.41; H, 8.77; N, 5.12. Found: C, 61.12; H, 8.70; N, 5.28.

1-(*tert*-Butylamino)-2-(4-*N,N*-dimethylaminophenyl)-2-propanol by the Oxyamination of *p*-*N,N*-Dimethylamino-α-methylstyrene with 6a in Pyridine ($LiAlH_4$ Workup). Workup afforded 329 mg of straw-colored oil. Bulb-to-bulb distillation (85 °C, 0.02 mm) gave 279 mg of a clear oil. Spectral data (NMR) indicated that the yield of amino alcohol was 88% after correcting for the presence of 10% diol impurity: IR (CCl_4) 3440 (CH), 1610 and 1510 (aromatic C–H), 1390 and 1360 (*tert*-butyl) cm^{-1}; NMR ($CDCl_3$) δ 1.05 (s, 9, *tert*-butyl), 1.45 (s, 3, $OCCH_3$), 2.7 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 18 Hz, NCH_2), 2.9 (s, 6, NCH_3), 7.0 (A_2B_2 pattern, 4, J = 9 Hz, aryl H).

Oxidation of (*E*)-5-Decene with 6a in Methylene Chloride ($LiAlH_4$ Workup). After workup an aliquot was analyzed by GLC on column A and showed 20% of *threo*-6-(*tert*-butylamino)-5-decanol and 50% of *threo*-5,6-decanediol.

Oxidation of (*E*)-5-Decene with 6a in Pyridine ($LiAlH_4$ Workup). Analysis of the crude product after workup by GLC on column B showed 95% of *threo*-6-(*tert*-butylamino)-5-decanol and less than 3% of *threo*-5,6-decanediol.

***threo*-6-(*tert*-Butylamino)-5-decanol:** IR (CCl_4) 3350 (OH), 1470 (–CH_2–), 1390, 1365 (*tert*-butyl), 1230 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.1 (bs, 1, H–C–OH), 3.0–2.0 (m, 3, OH, NH, NCH), 1.15 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{14}H_{31}NO$: C, 73.29; H, 13.62; N, 6.10. Found: C, 73.42; H, 13.80; N, 5.93.

Oxidation of (*Z*)-5-Decene with 6a in Methylene Chloride: Isolated Yield ($LiAlH_4$ Workup). After workup, removal of the ether at reduced pressure afforded 0.94 g of a white crystalline solid whose spectral properties and R_f on boric acid treated TLC (35% ethyl acetate/hexane; R_f 0.56; authentic *threo*-5,6-decanediol has R_f 0.63) were identical with *erythro*-5,6-decanediol, 54% yield. The same reaction mixture was analyzed by GLC on column A and showed 53% of 5,6-decanediol. No amino alcohol was present.

Oxidation of (*Z*)-5-Decene with 6a in Pyridine at Room Temperature. The reaction mixture was stirred for 1 day followed by standard workup. Analysis of the reaction mixture by GLC on column A showed 42% of *erythro*-5,6-decanediol and 25% of *erythro*-6-(*tert*-butylamino)-5-decanol.

Oxidation of (*Z*)-5-Decene with 6a in Pyridine at 0 °C. The oxyamination was conducted at 0 °C, and the mixture was stirred for 6 days before the pyridine was removed under high vacuum. Octadecane was added as an internal standard, and the standard $LiAlH_4$ workup was used. Analysis of the reaction mixture by GLC on column A showed 65% of *erythro*-6-(*tert*-butylamino)-5-decanol and 22% of *erythro*-5,6-decanediol. Only 50% of the olefin had reacted after 3 days. The full 6 days were necessary for a high conversion to the products.

***trans*-2-(*tert*-Butylamino)-1-cyclohexanol.** To a 50-mL round-bottom flask fitted with a condenser and maintained under nitrogen was added 1.0 g of cyclohexene oxide (10.2 mmol), 6 mL of water, and 2.15 mL of *tert*-butylamine (20.5 mmol). The reaction mixture was refluxed for 24 h. A yellow-brown layer formed on top of the aqueous layer. The reaction mixture was partitioned between ether and water, and the water layer was extracted twice with ether. The combined ether layers were washed with brine, dried (Na_2SO_4), and evaporated to dryness, yielding 1.0 g of an off-white solid (57%), mp 47–48.5 °C. The amine hydrochloride was prepared in anhydrous Et_2O, mp 217.5–218.5 °C. The free amine analyzed on column C did not coinject with *cis*-2-(*tert*-butylamino)-1-cyclohexanol. The trans amino alcohol: IR (CCl_4) 3490 (OH), 1460 (–CH_2–), 1390, 1360 (*tert*-butyl), 1180 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.0 (m, 1, H–C–O), 2.0 (m, 3, OH, NH, HCN), 1.15 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.35; N, 8.18. Found: C, 69.99; H, 12.34; N, 8.00.

***cis*-2-(*tert*-Butylamino)-1-cyclohexanol by the Oxyamination of Cyclohexene with 6a in Pyridine ($LiAlH_4$ Workup).** After

workup solvent removal yielded, without need of further purification, 127 mg of white crystals (88%), mp 79.1–81.4 °C. The amine hydrochloride was prepared in anhydrous ether, mp 213–214 °C. The amino alcohol: IR (CCl_4) 3450 (OH), 1400, 1360 (*tert*-butyl) cm^{-1}; NMR ($CDCl_3$) δ 3.6 (m, 1, –C**H**(OH)), 3.0–2.0 (m, 3, –CH(NR), OH, NH), 1.5 (s, 8, CH_2), 1.1 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{10}H_{22}ClNO$: C, 57.81; H, 10.67; N, 6.74. Found: C, 57.58; H, 10.8; N, 6.72.

***cis*-2-(1-Adamantylamino)-1-cyclohexanol by the Oxyamination of Cyclohexene with 6b in Pyridine ($LiAlH_4$ Workup).** After workup the solvent was removed at reduced pressure to afford 216 mg of a white crystalline solid (79%), mp 131–132 °C. The amine hydrochloride was prepared in anhydrous ether, mp 312 °C dec. The free amino alcohol: IR (KBr) 3450 (OH), 3100 (NH), 1100 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.5 (m, 1, H–C–O), 2.8 (m, 2, HCN, NH).

Anal. Calcd for $C_{16}H_{28}ClNO$: C, 67.22; H, 9.52; N, 4.90. Found: C, 67.06; H, 9.76; N, 4.80.

***cis*-*exo*-3-(*tert*-Butylamino)bicyclo[2.2.1]heptan-2-ol by the Oxyamination of Norbornene with 6a in Pyridine ($LiAlH_4$ Workup).** Chromatography of the crude product on silica gel afforded 224 mg (94%) of product. The hydrochloride was prepared in anhydrous ether: mp 203 °C; NMR of free amine ($CDCl_3$) δ 3.33 (d, 1, J = 6 Hz, OCH), 2.67 (d, 1, J = 6 Hz, NCH).

Anal. Calcd for $C_{11}H_{22}ClNO$: C, 60.12; H, 10.09; N, 6.37. Found: C, 59.74; H, 9.93; N, 6.40.

Oxyamination of 1,2-Dihydronaphthalene with 6a in Pyridine ($LiAlH_4$ Workup). The crude green oil was chromatographed on Florisil, and the combined amino alcohol fractions afforded a white solid (38%). The hydrochlorides were prepared in anhydrous ether. The amino alcohol fractions contained a mixture of the 1 and 2 cis regioisomers. The mixture of amine hydrochlorides: IR (KBr) 3300 (NH, OH), 2480 (NH_2^+), 1580 (aromatic, H, $N\overset{+}{N}H_2$), 1390, 1380 (*tert*-butyl), 1200 (C–O) cm^{-1}. *cis*-1-Hydroxy-2-(*tert*-butylamino)-tetralin: NMR ($CDCl_3$) δ 4.45 (d, 1, J = 5 Hz, ArC(**H**)OH), 1.25 (s, 9, *tert*-butyl). *cis*-1-(*tert*-Butylamino)-2-hydroxytetralin: NMR ($CDCl_3$) δ 3.95 (s, 1, ArCC(**H**)OH), 1.15 (s, 9, *tert*-butyl). The ratio of the 2-hydroxy isomer to the 1-hydroxy isomer is 69:31 as determined by GLC on column B.

Anal. Calcd for $C_{14}H_{22}ClNO$ (mixture of 1 and 2 regioisomers): C, 65.74; H, 8.67; N, 5.47. Found: C, 65.67; H, 8.74; N, 5.28.

Oxyamination of (*E*)-1-Phenylpropene with 6a in Pyridine ($LiAlH_4$ Workup). GLC analysis on column C showed that the crude product contained two compounds in a ratio of 76:24. The crude reaction mixture was chromatographed on Florisil, and the fractions were analyzed on column C. Fractions were obtained that contained the pure major isomer. This proved to be *threo*-1-(*tert*-butylamino)-1-phenyl-2-propanol by NMR analysis. The hydrochloride was prepared in ether as a white solid: mp 209–210 °C; NMR of free amine ($CDCl_3$) δ 1.02 (m, 12, *tert*-butyl and $OCCH_3$), 2.65–3.7 (m, 4, NH, OH, NCH, OCH), 7.23 (m, 5, aryl H).

NMR analysis of an additional fraction revealed an enrichment in the minor component (67%) which proved to be *threo*-1-phenyl-2-(*tert*-butylamino)-1-propanol, the regioisomer of the major product. The chemical shifts assignable to the minor component in the NMR spectrum of this mixture are δ 1.17 (*tert*-butyl) and 3.90 (d, J = 9 Hz, OCH).

The yield of the combined amino alcohol containing fractions was 91%. An analytical sample of the hydrochloride of a fraction which was an 80:20 mixture of the major and minor isomers was prepared in ether as a white solid.

Anal. Calcd for $C_{13}H_{22}ClNO$: C, 64.08; H, 9.04; N, 5.75. Found: C, 63.98; H, 8.82; N, 5.67.

Oxyamination of (*Z*)-1-Phenylpropene with 6a in Pyridine ($LiAlH_4$ Workup). GLC analysis on column C showed that the crude product contained two compounds in a ratio of 97:3. The crude reaction mixture was chromatographed on Florisil, and the fractions were analyzed by GLC on column C. Fractions were obtained that contained the pure major isomer, which proved to *erythro*-1-(*tert*-butylamino)-1-phenyl-2-propanol by NMR analysis. The hydrochloride was prepared as a white solid in ether: mp 198.5–200 °C; NMR of free amine ($CDCl_3$) δ 0.89 (d, 3, J = 6 Hz, $OCCH_3$), 1.07 (s, 9, *tert*-butyl), 7.28 (m, 5, aryl H).

Anal. Calcd for $C_{13}H_{22}ClNO$: C, 64.08; H, 9.04; N, 5.75. Found: C, 63.76; H, 9.10; N, 5.59.

NMR analysis of a fraction which was a 72:28 (minor isomer/major isomer) mixture of the two isomers revealed that the minor isomer was *erythro*-2-(*tert*-butylamino)-1-phenyl-1-propanol. Chemical shifts assignable to it in the NMR spectrum of the mixture are δ 1.17 (*tert*-butyl) and 4.58 (d, J = 4 Hz, OCH).

The combined weight of the fractions containing the pure amino alcohols was 0.29 g (92%).

Oxyamination of Citronellol Methyl Ether with 6a in CH_2Cl_2 ($LiAlH_4$ Workup). An NMR spectrum of the crude product showed diol as the sole product. The crude oil was chromatographed on 11.0 g of silica gel, yielding 171 mg (78%) of 2,6-dimethyl-8-methoxy-2,3-octanediol.

Oxyamination of Citronellol Methyl Ether with 6a in Pyridine. After workup an aliquot was analyzed on column A and showed a 38% yield of 3-(*tert*-butylamino)-2,6-dimethyl-8-methoxy-2-octanol and a 45% yield of 2,6-dimethyl-8-methoxy-2,3-octanediol.

3-(*tert*-Butylamino)-2,6-dimethyl-8-methoxy-2-octanol: IR (CCl_4) 3400, 1460 (–CH_2–), 1390, 1360 (*tert*-butyl), 1120 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.35 (m and s, 5, CH_3–O–CH_2), 3.0–2.0 (m, 3, OH, NH, NCH–), 1.15 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{15}H_{33}NO_2$: C, 69.44; H, 12.82; N, 5.40. Found: C, 69.25; H, 12.77; N, 5.18.

1-(*tert*-Butylamino)-1-phenyl-2-methyl-2-propanol by the Oxyamination of 2-Methyl-1-phenylpropene with 6a in Pyridine. After workup the crude brownish oil was chromatographed on Florisil. The combined amino alcohol containing fractions were dissolved in dry ether. Hydrogen chloride was bubbled in, and 358 mg (88%) of white powder was collected: mp 214–215 °C; free amine, mp 62–63 °C. The amino alcohol hydrochloride: IR (KBr) 3300 (OH), 1560 (NH), 1390, 1380 (*tert*-butyl), 1190, 1160 cm^{-1}. The free amino alcohol: NMR ($CDCl_3$) δ 7.25 (s, 5, aryl H), 3.6 (s, 1, –CHN), 1.6–3.0 (m, 2, OH, NH), 1.15 (s, 3, CH_3), 1.0 (s, 12, *tert*-butyl, CH_3).

Anal. Calcd for $C_{14}H_{23}ON$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.81; H, 10.81; N, 6.19.

2-(*tert*-Butylamino)-1-phenylcyclohexanol by the Oxyamination of 1-Phenylcyclohexene with 6a in Pyridine ($LiAlH_4$ Workup). After workup the crude product was chromatographed on Florisil to afford a mixture of diol and amino alcohol. The products were dissolved in ether and washed with 2 × 20 mL of 1 N hydrochloric acid. The ether layer was dried (Na_2SO_4) and the solvent removed to afford 19 mg (8%) of diol. The aqueous extract was made basic by the addition of 10% sodium hydroxide and extracted with ether. The ethereal extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure to afford 202 mg (65%) of 2-(*tert*-butylamino)-1-phenylcyclohexanol. Although it has not been proved in this case, the vicinal amino and hydroxyl substituents are almost certainly cis to each other. The hydrochloride was prepared in anhydrous ether: NMR of the free amine ($CDCl_3$) δ 2.97 (m, 1, NCH), 0.78 (s, 9, $NCCH_3$).

2-(*tert*-Butylamino)-1-methylcyclopentanol by the Oxyamination of 1-Methylcyclopentene with 6a in Pyridine ($LiAlH_4$ Workup). The crude product was chromatographed on 20 g of Florisil to afford 140 mg (66%) of an oil which was determined to be one compound by GLC analysis; in this case too, the product is assumed to result from cis oxyamination. The hydrochloride was prepared as a white solid in ether: mp 220–220.5 °C (sealed capillary); NMR of the free amine ($CDCl_3$) δ 1.10 (s, 9, *tert*-butyl), 1.20 (s, 3, $OCCH_3$).

Anal. Calcd for $C_{10}H_{22}ClNO$: C, 57.85; H, 10.60; N, 6.75. Found: C, 57.86; H, 10.50; N, 6.68.

Reaction of Tetramethylethylene with 6a in Pyridine ($LiAlH_4$ Workup). The crude product was chromatographed on 25 g of silica gel and gave 239 mg (82%) of pinacol as a clear glass which crystallized upon standing. All spectral data were identical with that for authentic pinacol.

4-(*tert*-Butylamino)-1-phenyl-1,3-butanediol by the Oxyamination of 1-Phenylbut-3-en-1-ol with 6a in Pyridine ($LiAlH_4$ Workup). The product, a straw-colored oil, was chromatographed on Florisil to afford 177 mg (50%) of solid amino alcohol. The product was twice crystallized from hexane to afford an analytical sample: mp 105–106 °C; NMR ($CDCl_3$) δ 7.34 (m, 5, aryl H), 4.94 (t, 1, J = 6 Hz, aryl C**H**OH), 1.80 (t, 2, J = 6 Hz, $HOCCH_2$–COH), 1.10 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.41; H, 8.84; N, 5.12. Found: C, 61.55; H, 9.05; N, 5.02.

1-(*tert*-Butylamino)-3-phenoxy-2-propanol by the Oxyamination of Allyl Phenyl Ether in Pyridine ($LiAlH_4$ Workup). The product, a dark solid, was chromatographed on silica gel to afford 235 mg (70%) of a beige crystalline product. Crystallization from hexane/methylene chloride afforded an analytical sample: mp 95.5–97 °C; NMR ($CDCl_3$) δ 3.98 (m, 1, OCH), 3.00 (s, 1, OH), 2.78 (m, 2, NCH), 1.15 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.63; H, 9.65; N, 6.31.

1-(1-Adamantylamino)-3-phenoxy-2-propanol by the Oxyamination of Allyl Phenyl Ether with 6b ($LiAlH_4$ Workup). The product, a black oil, was chromatographed on silica gel to afford 236

mg (66%) of a glass which crystallized upon standing overnight. The product was dissolved in anhydrous ether, and hydrogen chloride was introduced to precipitate 221 mg (55%) of the amine hydrochloride as an eggshell-colored solid: mp 223–235 °C; NMR of free amine ($CDCl_3$) δ 3.95 (m, 1, OCH), 1.67 (s, 12, CCH_2C).

1-(2-Methyl-2-butylamino)-3-phenoxy-2-propanol by the Oxyamination of Allyl Phenyl Ether with 6c in Pyridine ($LiAlH_4$ Workup). The crude product was chromatographed on Florisil to afford 244 mg (88%) of a white crystalline solid. Crystallization from hexane afforded an analytical sample: mp 62.5–63.5 °C; NMR ($CDCl_3$) δ 3.95 (m, 1, OCH), 1.05 (s, 6, $NCCH_3$).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.52; H, 10.07; N, 5.79.

1-(*tert*-Butylamino)-3-thiophenoxy-2-propanol by the Oxyamination of Allyl Phenyl Sulfide in Pyridine with 6a ($LiAlH_4$ Workup). The crude product was chromatographed on Florisil eluting with chloroform and 1% triethylamine in chloroform to afford 173 mg (66%) of a pale tan oil. The hydrochloride was prepared in ether/methanol as a white powder: mp 104–105 °C; NMR of the free amine ($CDCl_3$) δ 3.68 (m, 1, OCH), 3.05 (d, 2, J = 6 Hz, SCH_2), 1.07 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}H_{22}ClNOS$: C, 56.60; H, 8.04; N, 5.08. Found: C, 56.50; H, 8.30; N, 5.36.

1-(*tert*-Butylamino)-3-phenylamino-2-propanol by the Oxyamination of *N*-Allylaniline with 6a in Pyridine ($LiAlH_4$) Workup). The crude product, a black oil, was chromatographed on silica gel to afford off-white crystals (52%). Crystallization from hexane afforded an analytical sample: mp 90.5–92 °C; NMR ($CDCl_3$) δ 1.12 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}N_{22}N_2O$: C, 70.22; H, 9.98; N, 12.60. Found: C, 70.18; H, 9.66; N, 12.61.

1-(*tert*-Butylaminomethyl)-4-(*tert*-butyl)cyclohexanol: A. By the Oxyamination of 4-(*tert*-Butyl)methylenecyclohexane with 6a in Pyridine ($LiAlH_4$ Workup). Analysis of the crude reduction product by GLC on column A showed it to consist of an 81:19 mixture of the equatorial and axial alcohols by comparison with the authentic amino alcohols. The crude product was chromatographed on Florisil to afford 228 mg (93%) of a white product: NMR ($CDCl_3$) δ 2.53 (s, 2, NCH_2, axial), 2.35 (s, 2, NCH_2, equatorial), 1.08 (s, 9, *N-tert*-butyl), 0.87 (s, 9, C-4 *tert*-butyl).

Anal. Calcd for $C_{15}H_{32}ClNO$: C, 64.83; H, 11.61; N, 5.42. Found: C, 64.94; H, 11.37; N, 4.93.

B. By Epoxide Opening. To a 25-mL round-bottom flask was added 4.0 mL of *tert*-butylamine, 4.0 mL of distilled water, and 0.20 g (1.26 mmol) of an axial epoxide enriched mixture of the axial and equatorial epoxides of 4-(*tert*-butyl)methylenecyclohexane. The reaction was stirred at reflux for 36 h before the excess *tert*-butylamine was removed at reduced pressure. The resulting aqueous slurry was extracted with methylene chloride, the organic layer was dried (Na_2SO_4), and the solvent was removed, leaving a crude product which was chromatographed on Florisil to afford 206 mg (76%) of a mixture of amino alcohols. The major product from the epoxide opening corresponded to the minor product from the oxyamination and vice versa.

1-(1-Adamantylaminomethyl)-4-(*tert*-butyl)cyclohexanol by the Oxyamination of 4-(*tert*-Butyl)methylenecyclohexane with 6b in Pyridine ($LiAlH_4$ Workup). After workup, analysis of the crude white solid by GLC on column A showed an 81:19 ratio of isomers assigned as the equatorial and axial alcohols, respectively, by analogy to the *tert*-butylamino alcohol analogue. Chromatography on Florisil afforded 320 mg (91%) of product: NMR ($CDCl_3$) δ 2.58 (s, 2, NCH_2, axial), 2.40 (s, 2, NCH_2, equatorial), 0.87 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{21}H_{37}NO$: C, 78.93; H, 11.67; N, 4.38. Found: C, 79.12; H, 11.47; N, 4.42.

1-(2-Methyl-2-butylaminomethyl)-4-(*tert*-butyl)cyclohexanol by the Oxyamination of 4-(*tert*-Butyl)methylenecyclohexane with 6c in Pyridine ($LiAlH_4$ Workup). The crude product proved to be an 81:19 mixture of isomers by GLC analysis on column A. Chromatography on Florisil afforded 227 mg (81%) of an oil which slowly crystallized upon standing. The product was converted to the hydrochloride in anhydrous ether: NMR of free amine (CCl_4) δ 2.42 (s, 2, NCH_2, axial), 2.27 (s, 2, NCH_2, equatorial), 1.00 (s, 6, $NCCH_3$), 0.85 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{16}H_{34}ClNO$: C, 65.83; H, 11.74; N, 4.80. Found: C, 65.66; H, 11.84; N, 4.68.

Reaction of OsO_4 with 4-(*tert*-Butyl)methylenecyclohexane: A. In Pyridine. To a 50-mL round-bottom flask was added 105 mg (0.689 mmol) of 4-(*tert*-butyl)methylenecyclohexane and 175 mg (0.689 mmol) of osmium tetroxide in 4.4 mL of pyridine. The reaction mixture was stirred for 36 h before the solvent was removed at reduced pressure, and 30 mL of ether was added followed by 388 mg of $LiAlH_4$. The reduction mixture was stirred overnight (17 h) before it was quenched to afford a mixture of diols (inseparable under all of the GLC conditions tried) as a white crystalline solid (mp 99–113 °C). The crude product was dissolved in methylene chloride, and part of the solution was transferred to a 50-mL round-bottom flask. Removal of the methylene chloride left 70 mg of crude product. To the 50-mL flask was added 75 mg (0.39 mmol) of *p*-toluenesulfonyl chloride and 1 mL of pyridine. The reaction mixture was stirred for 44 h before ice was added, after which it was stirred for an additional 30 min. The reaction mixture was taken up in 200 mL of ether and rinsed with water. The ether was dried ($MgSO_4$) and the solvent removed to afford a white crystalline solid. The crude monotosylate was dissolved in 15 mL of ether and reduced with 280 mg of $LiAlH_4$ at reflux for 1 h. Workup afforded a white crystalline solid which was 86% equatorial alcohol by GLC analysis on column A.

The assignment of the stereochemistry was confirmed by preparing a mixture of the two alcohols enriched in the axial alcohol from 4-(*tert*-butyl)cyclohexanone and methylmagnesium bromide.[33] A mixture of the two alcohols enriched in the equatorial alcohol was prepared by the lead tetraacetate oxidation of 4-(*tert*-butyl)methylenecyclohexane followed by a sequence of reactions identical with that used for the osmium tetroxide oxidations.[28] All GLC data were consistent with the assigned stereochemistries.

B. In Methylene Chloride. To a 50-mL round-bottom flask was added 203 mg (0.799 mmol) of osmium tetroxide, 4 mL of methylene chloride, and 122 mg (0.799 mmol) of 4-(*tert*-butyl)methylenecyclohexane. The reaction mixture was stirred for 36 h before the solvent was removed and ether added. The ethereal slurry was reduced with 525 mg of $LiAlH_4$ for 17 h. Workup afforded a white crystalline solid (mp 121–123 °C). The two diols were inseparable under all of the GLC conditions tested. The crude product was dissolved in methylene chloride, and part of the solution was transferred to a 50-mL round-bottom flask. Removal of the solvent left 80 mg of white solid. To the crude diol was added 85 mg (0.45 mmol) of *p*-toluenesulfonyl chloride and 1 mL of pyridine. The reaction mixture was stirred for 44 h before ice was added, and stirring was continued for 30 min. The reaction mixture was taken up in ether and rinsed with water. The ether was dried ($MgSO_4$) and the solvent removed at reduced pressure to afford a crystalline solid. The solid was dissolved in ether and reduced with 210 mg (5.5 mmol) of $LiAlH_4$ at reflux for 1 h. Workup afforded a white solid which was shown to be 82% equatorial alcohol by GLC analysis on column A.

Olefin Competition for Relative Rate Determinations. Relative rates for the various substituted olefins and para-substituted α-methylstyrenes were determined by competing one olefin against another in the presence of a deficiency of the oxidant and monitoring the *disappearance of the starting materials* by GLC. The GLC response factors for the two olefins were determined relative to a suitably chosen internal standard. The reactions were analyzed by GLC after being taken to roughly 50% total olefin conversion. The number of millimoles of each remaining olefin was calculated, and the relative rates were determined by using eq 3, in which A_f and B_f are the number of millimoles remaining of olefins A and B, respectively. A_0 and B_0 are the initial number of millimoles of olefins A and B, respectively. In all competitions that were conducted, a solution of the imidoosmium compound was added to a stirred solution of both olefins. The volume of both solutions was adjusted such that the combined solution was approximately 0.1 M with respect to the osmium reagent.

$$\frac{k_A}{k_B} = \frac{\log (A_f/A_0)}{\log (B_f/B_0)} \tag{3}$$

A description of the experimental conditions for the competition of (*E*)-5-decene and (*Z*)-4-octene follows. All of the other reactions were run in an analogous manner. For the sake of brevity, only the olefins that competed and the solvent employed for the oxyamination will be given for the remaining competitions.

Competition of (*E*)-5-Decene and (*Z*)-4-Octene. In a 10-mL round-bottom flask 36.0 mg (0.256 mmol) of (*E*)-5-decene and 28.0 mg (0.249 mmol) of (*Z*)-4-octene were dissolved in 1 mL of olefin-free methylene chloride. The solution was stirred, and 76 mg (0.245 mmol) of trioxo(*tert*-butylimido)osmium(VIII), **6a**, dissolved in 2 mL of olefin-free methylene chloride was added to the olefin solution. Undecane (38 mg, 0.243 mmol) was added to the reaction mixture as the internal standard. The reaction mixture was stirred for 24 h and subsequently analyzed by GLC on column A to show 0.19 mmol of (*Z*)-4-octene and 0.089 mmol of (*E*)-5-decene remaining. By applying

the equation given, $k((E)$-5-decene$)/k((Z)$-4-octene) was computed to be 4.22.

Remaining Competitions: k(styrene)/k(1-decene) = 2.1, CH_2Cl_2; k(1-undecene)/k(2-methyl-1-tridecene) = 2.6, CH_2Cl_2; k(1-dodecene)/k(α-methylstyrene) = 1.31, CH_2Cl_2; k(citronellol methyl ether)/$k((z)$-5-decene) = 2.9, CH_2Cl_2; k(2-methyl-1-tridecene)/k(2,3-dimethyl-2-octene) = 1.01, CH_2Cl_2; $k((E)$-1-phenyl-1-propene)/$k((Z)$-1-phenyl-1-propene) = 4.89, pyridine; k(phenyl allyl ether)/k(4-phenyl-1-butene) = 0.95, pyridine; k(*p*-*N*,*N*-dimethylamino-α-methylstyrene)/k(α-methylstyrene) = 1.63 (pyridine), 4.26 (CH_2Cl_2); k(*p*-methoxy-α-methylstyrene)/k(α-methylstyrene) = 1.49 (CH_2Cl_2), 1.04 (pyridine); k(*p*-methyl-α-methylstyrene)/k(α-methylstyrene) = 1.01 (pyridine), 1.14 (CH_2Cl_2); k(*p*-chloro-α-methylstyrene)/k(α-methylstyrene) = 1.23 (pyridine), 0.95 (CH_2Cl_2); k(*p*-cyano-α-methylstyrene/k(α-methylstyrene) = 1.53 (pyridine), 1.93 (CH_2Cl_2).

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Registry No.—**6a,** 50381-48-1; **6b,** 55946-71-9; **6c,** 63174-17-4; **9** (R = octyl), 55915-80-5; **11** (R = octyl), 55915-79-2; OsO_4, 20816-12-0; *tert*-butylamine, 75-64-9; 1-adamantylamine, 768-94-5; *tert*-amylamine, 594-39-8; *threo*-1,2-cyclododecanediyl diacetate, 65794-87-8; 1-acetoxy-2-(*tert*-butylamino)cyclododecane, 65760-92-1; 1,2-decanediyl diacetate, 60671-14-9; 1-decene oxide, 2404-44-6; 5-octyl-3-(*tert*-butyl)oxazolidin-2-one, 65760-93-2; 2-(*tert*-butylamino)-1-decanol, 65760-94-3; 1-acetoxy-2-decanone, 65760-95-4; 1-acetoxy-2-decanone *tert*-butylimine, 65760-96-5; 1-deuterio-1-decyne, 39650-97-0; 1-decyne, 764-93-2; (*Z*)-1-deuterio-1-decene, 39106-48-4; (*E*)-1-deuterio-1-decene, 39106-47-3; 1-deuterio-1-(*tert*-butylamino)-2-decanol, 65760-69-2; 1-(*tert*-butylamino)-2-(4-methylphenyl)-2-propanol HCl, 65760-70-5; 1-(*tert*-butylamino)-2-(4-methoxyphenyl)-2-propanol HCl, 65760-71-6; *threo*-5,6-decanediol, 58581-16-1; *erythro*-5,6-decanediol, 3266-25-9; *trans*-2-(*tert*-butylamino)-1-cyclohexanol, 65760-72-7; *trans*-2-(*tert*-butylamino)-1-cyclohexanol HCl, 65770-73-8; cyclohexene oxide, 286-20-4; *cis*-2-(*tert*-butylamino)-1-cyclohexanol HCl, 65760-74-9; *cis*-2-(1-adamantylamino)-1-cyclohexanol HCl, 65760-75-0; *cis-exo*-3-(*tert*-butylamino)bicyclo[2.2.1]heptan-2-ol HCl, 65760-76-1; *cis*-1-hydroxy-2-(*tert*-butylamino)tetralin HCl, 65760-77-2; *cis*-1-(*tert*-butylamino)-2-hydroxytetralin HCl, 65760-78-3; *threo*-1-(*tert*-butylamino)-1-phenyl-2-propanol HCl, 65760-79-4; *threo*-1-phenyl-2-(*tert*-butylamino)-1-propanol HCl, 65760-80-7; *erythro*-1-(*tert*-butylamino)-1-phenyl-2-propanol HCl, 65760-81-8; 2,6-dimethyl-8-methoxy-2,3-octanediol, 65760-61-4; 1-(*tert*-butylamino)-1-phenyl-2-methyl-2-propanol HCl, 65760-62-5; 2-(*tert*-butylamino)-1-methylcyclopentanol HCl, 65760-63-6; pinacol, 76-09-5; 4-(*tert*-butylamino)-1-phenyl-1,3-butanediol, 65760-64-7; 4-(*tert*-butylamino)-1-phenyl-1,3-butanediol HCl, 65760-65-8; 1-phenylbut-3-en-1-ol, 936-58-3; 1-(*tert*-butylamino)-3-phenoxy-2-propanol, 64980-40-1; allyl phenyl ether, 1746-13-0; 1-(1-adamantylamino)-3-phenoxy-2-propanol, 36144-08-8; 1-(1-adamantylamino)-3-phenoxy-2-propanol HCl, 40536-65-0; 1-(2-methyl-2-butylamino)-3-phenoxy-2-propanol, 65760-66-9; 1-(*tert*-butylamino)-3-thiophenoxy-2-propanol, 65760-67-0; 1-(*tert*-butylamino)-3-thiophenoxy-2-propanol HCl, 15148-93-3; allyl phenyl sulfide, 5296-64-0; 1-(*tert*-butylamino)-3-phenylamino-2-propanol, 65760-68-1; *N*-allylaniline, 589-09-3; 4-(*tert*-butyl)methylenecyclohexane, 13294-73-0; 4-(*tert*-butyl)methylenecyclohexane axial epoxide, 7787-78-2; 4-(*tert*-butyl)methylenecyclohexane equatorial epoxide, 18881-26-0; 4-(*tert*-butyl)-1-hydroxymethyl-1-cyclohexanol monotosylate (equatorial), 65760-60-3; 1-undecene, 821-95-4.

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(37) **Note Added in Proof.** Two major improvements have recently been made in the osmium-catalyzed oxyamination process: (a) E. Herranz, S. A. Biller and K. B. Sharpless, *J. Am. Chem. Soc.*, in press; (b) E. Herranz and K. B. Sharpless, *J. Org. Chem.*, in press.

Studies of the Mechanism of Chlorination of Indoles. Detection of *N*-Chloroindole and 3-Chloro-3*H*-indole as Intermediates[1]

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N-Chloroindole was stable at low concentration and temperature in nonprotic solvents. It rearranged in alkaline alcoholic media to give 3-chloroindole. Iodometry was used to follow the rearrangement of *N*-chloroindole to 3-chloroindole. An induction period was observed prior to a pseudo-first-order process. The length of the induction period depended on the alcohol used and its proportion relative to *n*-hexane, the presence or absence of base, and traces of water. Addition of water during the rearrangement caused an increase in the apparent concentration of *N*-chloroindole. This indicated the formation of another intermediate capable of reacting with water to either regenerate *N*-chloroindole or form another species which can oxidize iodide ion. The anion of 3-chloroindole is proposed as the intermediate. In the absence of base the formation of a new intermediate which absorbed at 252 nm was observed. During its formation no change in the apparent concentration of *N*-chloroindole could be detected by iodometry. 3-Chloro-3*H*-indole is proposed as this new intermediate. Addition of base caused the rapid disappearance of this band. A mechanism is proposed in which the induction period is seen as the establishment of an equilibrium between *N*-chloroindole, 3-chloro-3*H*-indole, and the conjugate base of 3-chloroindole.

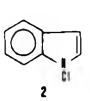
The chlorination of indole and its derivatives has been extensively studied.[3] Early workers used sulfuryl chloride to obtain 3-chloroindole and 2,3-dichloroindole.[4] Since then, besides this reagent,[5-7] others such as chlorine,[5,8-10] *N,N*-dichlorocarbamates,[11-14] *N*-chloroamines,[15] *N*-chlorobenzotriazole,[16] *N*-chlorosuccinimide,[5] phosphorus pentachloride,[5-7,17] *tert*-butyl hypochlorite,[16,18] and aqueous sodium hypochlorite[19,20] have been used to chlorinate indole and its derivatives. These procedures have yielded not only monochloroindoles,[5,7,9,10,15,17,20] but also polychloroindoles,[6,7,17] polychlorinated oxidized products,[5,8,11,15] and 3-chloroindolenines.[16,18,19] The chemistry of the latter group of compounds has been extensively studied.[16,18,19,21] Mono and polychlorinated indoles have also been prepared by indirect routes.[3a,6]

In 1972 the intermediacy of an *N*-chloroindole was suggested as a possibility in the chlorination of 2,3-dimethylindole with aqueous sodium hypochlorite.[19] This suggestion was analogous to the known intermediacy of *N*-chloroanilines in the chlorination of aniline derivatives.[22-24] Recently in a preliminary communication we presented the first evidence for the existence of an *N*-chloroindole as an intermediate in the chlorination of indole with aqueous sodium hypochlorite.[20] In this work the experimental details on the formation and stability of *N*-chloroindole are presented. A mechanism is proposed, based on kinetic and spectral data for the rearrangement of *N*-chloroindole to 3-chloroindole and also that under certain experimental conditions it is possible to detect the formation of 3-chloro-3*H*-indole. This appears to be the first instance in which this type of intermediate has been detected. The mechanism proposed is similar to the mechanisms previously proposed by others for the base-catalyzed hydrogen exchange of indoles and diazo coupling to indoles.[25,26]

Formation and Stability of *N*-Chloroindole

Stirring a solution of indole (**1**) in *n*-hexane, chloroform, or carbon tetrachloride with a freshly prepared solution of aqueous sodium hypochloride resulted in the formation of a light yellow solution containing an intermediate which oxidized iodide ion to iodine. The structure of the titrimetrically observed species could be that of either *N*-chloroindole (**2**) or 3-chloro-3*H*-indole (**3**).

N-Chloroamines[22] and 3-chloroindolenines[19] analogous to



2

3

the above structures are known to oxidize iodide ion. Spectroscopic evidence previously presented conclusively demonstrated that the initially formed intermediate was **2**.[20] In another section of this work evidence will be presented for the subsequent formation of **3** from **2**.

The yields of **2** obtained varied between <80 and 92%. The highest yields were obtained using concentrations of starting indole (**1**) of 0.01 M and with the aqueous sodium hypochlorite prepared from fresh calcium hypochlorite. It was found that as the calcium hypochlorite aged, the yields of **2** progressively diminished. Solutions of **2** can be prepared in the range of 0.01 to ca. 0.06 M. Solutions of *N*-chloroindole (**2**) 0.01 M in *n*-hexane can be stored for more than 14 days at 0 °C with only a slight change in the amount of tritratable chlorine. This can be contrasted with solutions of **2** ca. 0.06 M in *n*-hexane in which no titratable chlorine was observed after 3 days.[27] Unidentified colored material and HCl vapors were produced when **2** decomposed. Concentrated solutions of this species were found to be light sensitive and solid material began to form on exposure to direct sunlight. In general dilute solutions of **2** were stable in aprotic solvents, but upon mixing with alkaline alcohol solutions rearrangement took place.

N-Chloroindole (**2**) rearranged in refluxing alkaline *n*-butyl alcohol to give a 75% yield of 3-chloroindole (**5**). It was more convenient to carry out the kinetic and spectral studies described below in methanol and *n*-propyl alcohol.

Kinetics

Iodometric titrations were used to follow the disappearance of **2** with time. The results of treating the reaction as a pseudo-first-order process are illustrated in Figure 1. As can be seen in this figure, regular kinetics were not observed throughout the whole course of the reaction. An induction period was observed prior to a pseudo-first-order process. During the induction period the apparent concentration of **2** was observed to increase ca. 5% after an initial rapid decrease.

The expression ln (*N*-chloroindole) is used to indicate the total concentration of all species containing titratable chlorine, since the titrimetic method employed in this study cannot differentiate between the *N*-chloroindole (**2**) originally present and any other intermediate formed during the reaction which can also oxidize iodide ion. The induction period was sensitive to the following factors: alcohol used and its proportion relative to that of *n*-hexane, presence or absence of an added base (potassium carbonate in this study), and traces of water. The

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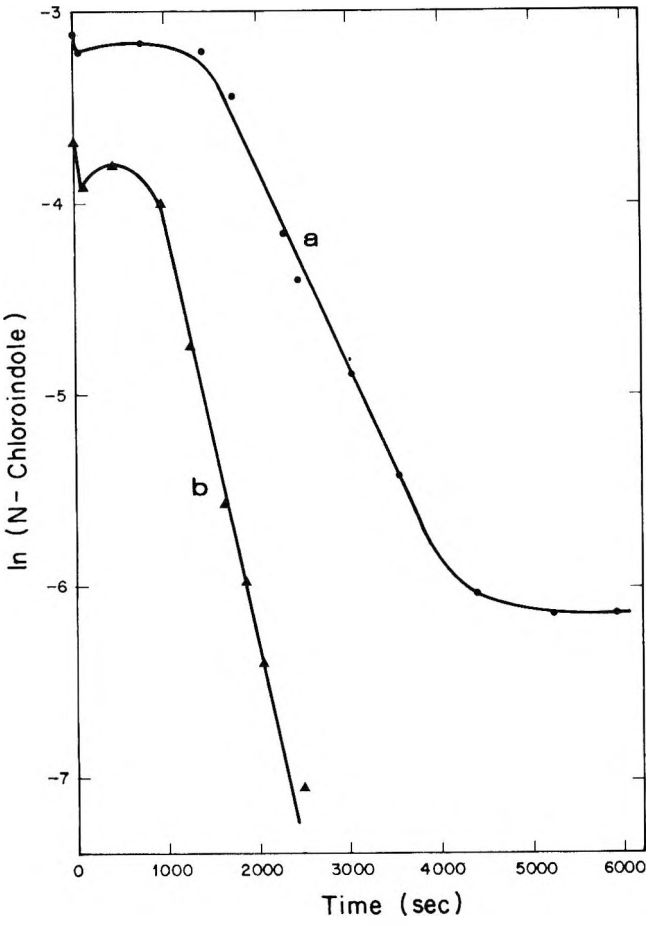


Figure 1. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (6:1 v/v): (a) without base; (b) with 2 g of anhydrous potassium carbonate.

Table I. Effect on Solvent, Base, and Water on the Induction Period

Solvent mixture (v/v)	Base (K_2CO_3)	Water, mL	Induction period, s
n-Hexane–*n*-propyl alcohol (6:1)			1500
n-Hexane–*n*-propyl alcohol (6:1)	2 g		900
n-Hexane–*n*-propyl alcohol (6:1)		0.2[a,b]	8000
n-Hexane–methanol (1:6)			*c*
n-Hexane–methanol (1:6)	Sat.[d]		*e*
n-Hexane–methanol (50:1)			6000
n-Hexane–methanol (50:1)	Sat.[d]		*e*

[a] Water added to alcohol prior to start of the reaction. [b] This volume of water was soluble in the solvent mixture used. [c] Reaction took 104 h for the rate to level off. [d] Methanol saturated with anhydrous potassium carbonate prior to use. [e] Reaction too fast to measure (50 s).

changes in the induction period associated with variations in these factors are summarized in Table I.

The effect of adding water to a rearrangement run in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base, after the pseudo-first-order process began, can be seen in Figure 2. The added water led to an apparent increase in the concentration of *N*-chloroindole.[29] This implied that another intermediate was formed during the reaction which can react with water to give either **2** or another species which also oxidized iodide ion. This was followed by a decrease in the rate of disappearance of **2**.

Another effect of added base can be noted in Figure 1. Only in the presence of added base does the reaction go to completion. Without added base the reaction went only to the

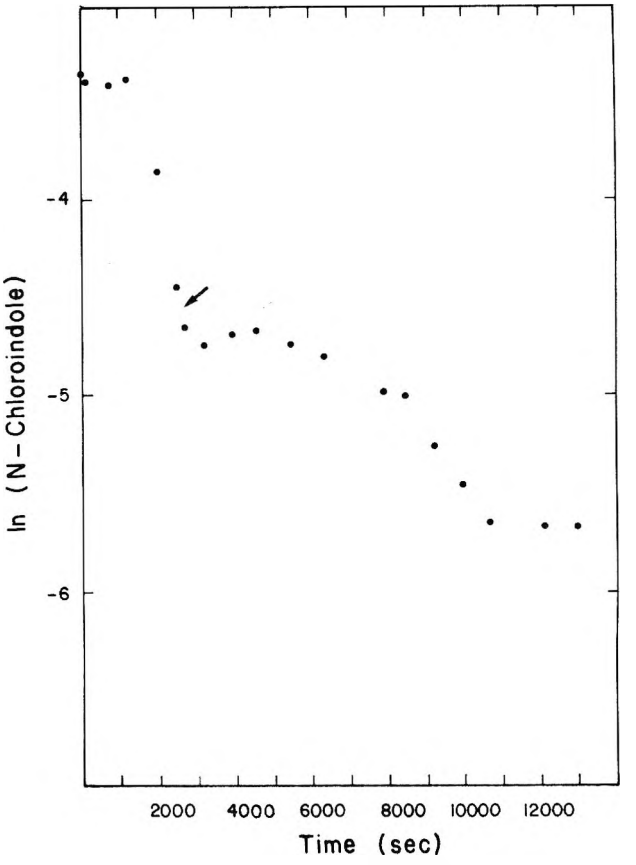


Figure 2. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (saturated with potassium carbonate) (6:1 v/v), addition of 0.2 mL of water →.

extent of 4 half-lives and titratable chlorine was detected with little or no change for at least an additional 4 half-lives.

It is clear from the kinetic data that the rearrangement of *N*-chloroindole was not a simple pseudo-first-order process. The data in Table I indicated that the induction period changes with both the nature and the proportion of alcohol used. Comparison of these results with those noted in Figure 2 for water indicated that the alcohol was also a reactant. The nature of the species which can react with water or alcohols will be discussed in a later section.

Spectral Studies

The conversion of *N*-chloroindole with a λ_{max} of 265 nm to 3-chloroindole which had a characteristic λ_{max} of 283 nm was observed in the UV when the reaction was run in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base (Figure 3). For reactions run in other solvent mixtures and particularly in the absence of base this transformation was not as clearly defined. In these instances there appeared to be formed another species which could be detected as an unresolved broadening in the UV absorbance at lower wavelengths. When the rearrangement was run in *n*-hexane–*n*-propyl alcohol (1:6 v/v) in the absence of base, it was possible to detect the formation of a shoulder at 252 nm. This is illustrated in Figure 4. The shoulder was not detectable when base was present. Ultraviolet spectrum, Figure 4b, was obtained 300 min after the initiation of the reaction and did not change appreciably for at least an additional 60 min. Addition of potassium carbonate 360 min after the initiation of the reaction caused the complete disappearance of this shoulder and a shift in the observed λ_{max} to that of product. This can be seen in Figure 4.

The ultraviolet spectra indicated a pre-equilibrium prior to the formation of product. This was clearly demonstrated by the absence of a change in the spectra for an appreciable

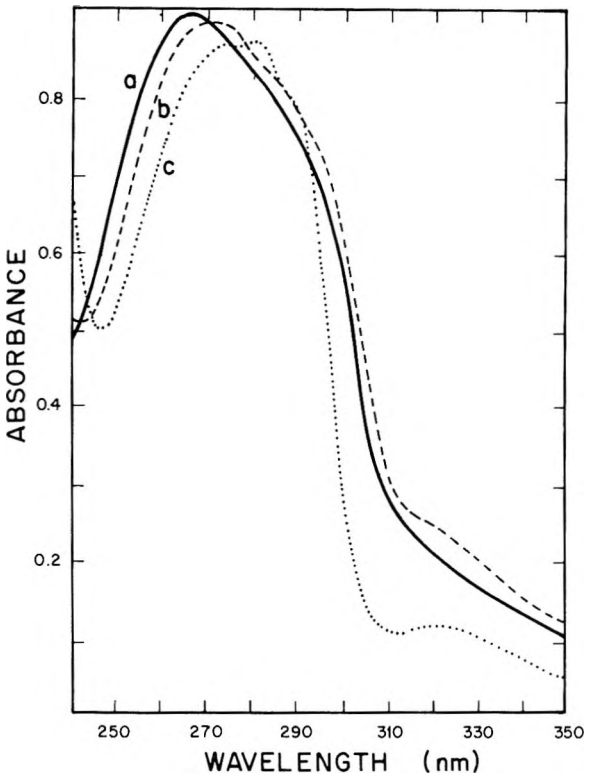


Figure 3. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base: (a) 3 min; (b) 5 min; (c) 60 min.

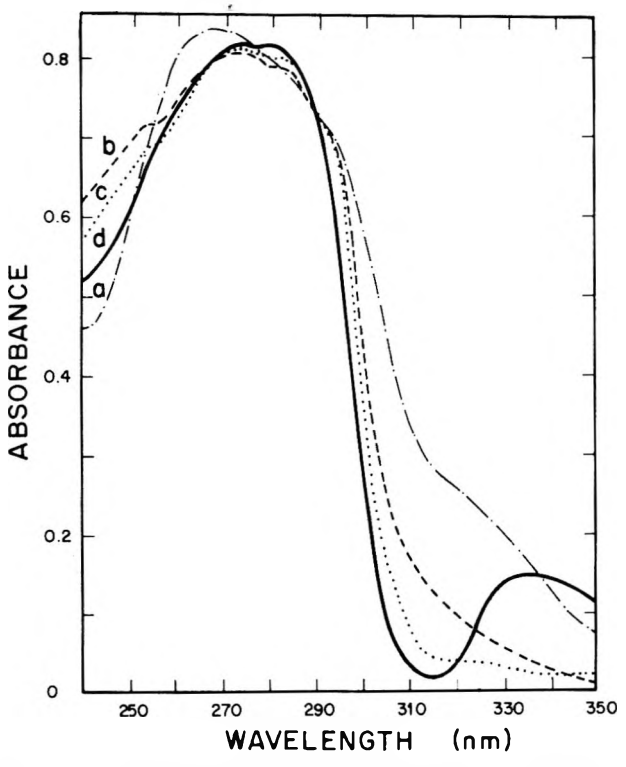


Figure 4. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (1:6 v/v): (a) 15 min; (b) 300–360 min (potassium carbonate added at 360 min); (c) 370 min; (d) 390 min.

period of time. It can be seen by comparing the spectra in Figure 4 with the kinetic data in Figure 5 that the induction period, where little change was observed in the apparent concentration of *N*-chloroindole, corresponded spectrally to the formation of the shoulder at 252 nm and the equilibrium previously noted. The new species formed must also be capable of oxidizing iodide ion since during its formation, as observed by ultraviolet spectroscopy, no change was noted titrimetrically in the apparent concentration of **2**. The disappearance of the shoulder, observed by UV spectroscopy, corresponded to a drop in the apparent concentration of **2**. The spectral data indicated that **2** and the species absorbing at 252 nm must be interconvertible since no continuous conversion of **2** to this new species was noted.

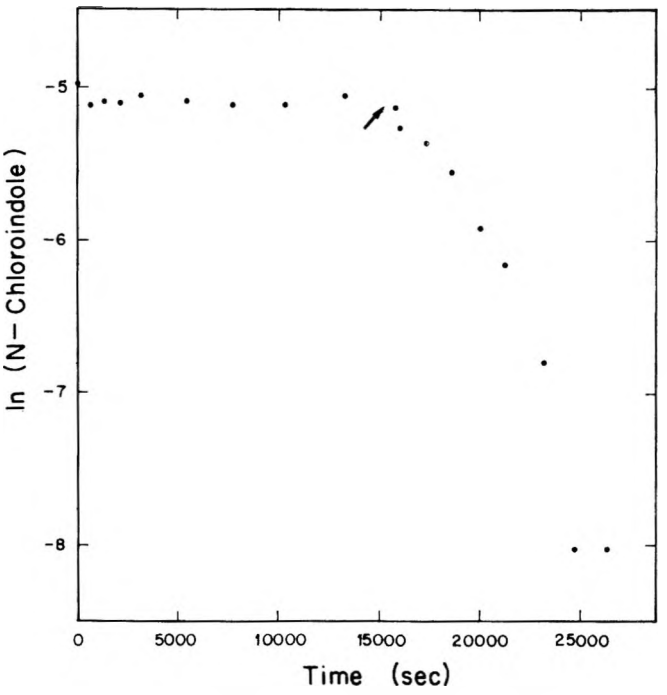


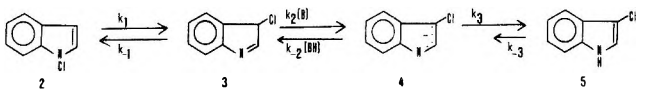
Figure 5. The rearrangement of *N*-chloroindole in *n*-hexane–*n*-propyl alcohol (1:6 v/v); addition of potassium carbonate →.

Formation of yet another species can be observed by UV spectroscopy as a weak absorbance at 320–335 nm. This band can be observed in Figure 4a. In Figure 4b it can be noted that this absorbance has disappeared and the shoulder at 252 nm has formed. The conjugate bases of indoles have been reported to have weak absorbance in the region of 300–350 nm in the UV.[30] Indole (**1**) and 3-chloroindole (**5**) in *n*-hexane–*n*-propyl alcohol (1:6 v/v) in the presence of potassium carbonate formed detectable amounts of their conjugate bases and small peaks were observed at 332 and 327 nm, respectively. It is likely that the band detected at 320–335 nm was due at least in part to the anion of 3-chloroindole. The formation and disappearance of this band during the rearrangement would indicate that the anion of 3-chloroindole is an intermediate in the reaction.

Discussion

The kinetic and spectral data indicated the establishment of a pre-equilibrium which could involve at least three different species: N-chloroindole, the species absorbing at 252 nm, and an intermediate able to react with alcohol or water. It has been reported that in the chlorination of 2,3-dimethylindole with aqueous sodium hypochlorite 3-chloro-2,3-dimethylindolenine was formed.[19] This 3-chloroindolenine derivative was reported to oxidize iodide ion and had a λ_{max} of 266 nm (CH_2Cl_2) as opposed to a λ_{max} of 280 nm for 2,3-dimethylindole. Recently it was reported that the bromination of 2-ethanosulfonyl-3-methylindole with *N*-bromosuccinimide gave the *N*-bromo derivative which absorbed in the UV (EtOH) at 238 and 312 nm.[31] This compound can be converted to the corresponding 3-bromoindolenine which absorbed at 230 and 290 nm in the same solvent. Both compounds were reported to oxidize iodide ion. In general indolenines have

Scheme I



been reported to absorb lower than the comparably substituted indole.[32] The spectral data previously presented strongly indicated that the intermediate absorbing in the UV at 252 nm was 3-chloro-3*H*-indole. This intermediate, by analogy to the other haloindolenines previously noted, would be expected to oxidize iodide ion and its λ_{max} of 252 nm can be contrasted with a λ_{max} of 282 nm for 3-chloroindole (**5**) in the same solvent mixture and of 265 nm for *N*-chloroindole (**2**) in hexane. This is the first instance in which a 3-chloro-3*H*-indole, without further substitution at C-3, has been observed. Kinetic evidence previously presented indicated that a species was formed during the rearrangement reaction that can react with either the alcohol present or water. This species was most likely the conjugate base of 3-chloroindole (**5**). The conjugate base of **5** could react with an alcohol or water to give either 3-chloro-3*H*-indole (**3**) or 3-chloroindole (**5**). A proposed mechanism for the rearrangement of *N*-chloroindole (**2**) to 3-chloroindole (**5**) is summarized in Scheme I.

The induction period may be seen as involving an equilibrium between *N*-chloroindole, 3-chloro-3*H*-indole, and the conjugate base of 3-chloroindole.

This mechanism can be used to explain the observed changes in the induction period as summarized in Table I. The rise noted in the value of ln (*N*-chloroindole) during the induction period can be attributed to the reaction of **4** with the alcohol used to give **3** which was in equilibrium with **2**. Formation of 3-chloro-3*H*-indole (**3**) instead of the more stable **5** would then seem to be the kinetically favored process. The presence of base appeared to shift the equilibrium toward product due to the reduction in the hydrogen ion activity of the medium or because of base involvement in the rate-determining step; however, a combination of both effects is also probable. To obtain a rate expression, for the reaction in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base, the steady state approximation was applied to **3**. This was reasonable based on the observation that the formation of this species was not observed by UV spectroscopy when the reaction was run under these conditions (Figure 3). When 3-chloroindole was dissolved in *n*-hexane–*n*-propyl alcohol (6:1 v/v) with added base, **4** could be detected by UV spectroscopy, but the formation of **3** could not be detected by either UV or iodometric analysis. This indicated that k_{-2} could be disregarded. The following rate expression was then obtained:

$$v = k_r[N\text{-chloroindole}]$$

$$k_r = \frac{k_1}{1 + \{(k_{-1})/k_2[B]\}}$$

Least-squares treatment of the linear portion of Figure 1b gave a value of k_r of $1.8 \times 10^{-3}\ s^{-1} \pm 0.2 \times 10^{-3}\ s^{-1}$. The rate-determining step could be either the cleavage of the N–Cl bond, resulting in the formation of **3**, or the reaction of **3** with base to give **4**. The effect of added base on the reaction would seem to indicate that the latter was the rate-determining step. However, the effect of base on the hydrogen ion activity could also be a factor in the rate change observed. The heterolytic cleavage of the N–Cl bond, leading to the formation of **3**, could occur by two different processes: formation of an indoyl anion and chloro cation or formation of a nitrenium ion and chloride ion. Recent work indicated that 3-bromoindolenines could dissociate to give either a bromo cation or a bromide anion.[31] At present there is not enough evidence to determine which was the preferred mode of cleavage. Kinetic studies on the base-catalyzed hydrogen exchange reactions of [3-$^2H_1$]- and [3-$^3H_1$]indoles[25] and the base-catalyzed diazo coupling to indoles[26] have appeared. An A-S_E2 mechanism has been proposed in these reactions. The reaction scheme proposed in this work is similar to those put forward in the above instances both with respect to the intermediates proposed and the kinectic expression for k_r.

Further studies are in progress on the influence of base on the rearrangement and the direction of heterolysis of the N–Cl bond.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 567 spectrophotometer and ultraviolet spectra with a Cary 15 spectrophotometer or with a Beckman DB-G with an external recorder. A Varian T-60 instrument was used for recording ^1H NMR spectra. Kinetic studies were conducted in a Masterline 2160 constant temperature bath at 30 ± 0.1 °C. Melting points were taken on a Fisher-Johns hot stage and are uncorrected. Indole (Aldrich Gold Label 99%) was used as is. The methanol and *n*-propyl alcohol used in the kinetic and spectral studies were dried prior to use by distilling from magnesium turnings under a static blanket of dry nitrogen.

Aqueous Sodium Hypochlorite Solutions. In a 250-mL flask there was combined 100 mL of water and 1.5 g of calcium hypochlorite (70%, HTH) with stirring until all the solid was dissolved or suspended; to this there was added 4 g of anhydrous sodium carbonate, with stirring for 10 min, and the solution was filtered under suction to remove the calcium carbonate precipitate. This solution was prepared fresh prior to use and gave maximum yields of **2** when 0.01 M of **1** was used. A solution of sodium hypochlorite prepared as above but utilizing 10 g of calcium hypochlorite and 20 g of sodium carbonate in 100 mL of water was used to prepare more concentrated solutions of **2**.

***N*-Chloroindole (2).** To a vigorously stirred solution containing 0.117 g (1.0 mmol) of indole in 100 mL of *n*-hexane there was added 25 mL of freshly prepared sodium hypochlorite solution and 25 mL of water. This mixture was stirred for 3 h at 0 °C and then the organic layer was separated, dried over anhydrous potassium carbonate, and analyzed iodometrically. Solutions were thus obtained which contained 90–92% of *N*-chloroindole (**2**): IR (*n*-hexane) no NH or C=N, 1210, 945, and 730 cm^{-1} (broad); NMR (*n*-pentane) δ 6.49 (1 H, d, C(3)H, J = 3 Hz), and 6.81–7.68 (m, 5 H, C(2)H and aromatic H); λ_{max} (*n*-hexane) 265 nm (log ε 3.72). This procedure gave the optimum yields of **2**. *N*-Chloroindole can be prepared in concentrations of ca. 0.06 M using 100 mL of a more concentrated sodium hypochlorite solution but the yields were lower (<80–83%).

3-Chloroindole (5). To a flask containing 250 mL of *n*-butyl alcohol and 5 g of anhydrous potassium carbonate there was added 4.7 mmol of *N*-chloroindole in 250 mL of *n*-pentane. The solution was heated to distill off the *n*-pentane and then refluxed for 60 min. At the end of this time no active chlorine was detectable. The alcohol was removed under reduced pressure and water and chloroform were added to the residue. The layers were separated and the aqueous phase was extracted with chloroform. The combined fractions were dried with potassium carbonate, filtered, and reduced in volume; the residue was deposited on 2 g of silica gel 60 (70–230 mesh). This was placed on top of a previously prepared column containing 100 g of silica gel 60 and eluted with chloroform; the first 200 mL of eluent contained the product. The residue was recrystalized from petroleum ether (40–60 °C) to give a 75% yield of 3-chloroindole: mp 90–92 °C dec (lit.[4] mp 91.5 °C); IR (KBr) 3415, 1460, 750, 745 cm^{-1}; NMR ($CDCl_3$) δ 7.03–7.73 (m, 5 H, C(2)H and aromatic H).

Kinetics. The kinetics of the rearrangement were followed under anhydrous conditions. Dry nitrogen was obtained by passing nitrogen gas through two columns in series: the first contained silica gel (with an indicator) and the second molecular sieve (Linde 4 Å). Solutions of **2** in *n*-hexane were dried by passing them through a column of anhydrous potassium carbonate (dried for 24 h at 120 °C) into a two-necked flask fitted with a rubber septum. This was carried out in a glove bag in an atmosphere of dry nitrogen. Solutions of **2** in *n*-hexane and the alcohol to be used were thermostated to a temperature of 30 ± 0.1 °C and introduced into a flame-dried three-necked flask, through which nitrogen was passing, with oven dried syringes. Aliquots were removed with calibrated 5.0-mL (±2%) syringes and added to 20 mL of ethanol–acetic acid (1:1 v/v) containing 2 g of potassium iodide. The liberated iodine was titrated with a standardized solution of sodium thiosulfate and the end point was determined visually.

Spectral Studies. The solution of **2** in *n*-hexane was mixed with the appropriate alcohol under dry conditions and then quickly diluted with the same solvent mixture. Spectra were run at room temperature.

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Registry No.—**1**, 120-72-9; **2**, 2959-02-6; **3**, 66037-05-6; **5**, 16863-96-0.

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Generation and Reactions of Halodifluoromethide Ions[1]

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Methyl chlorodifluoroacetate undergoes facile thermal decarbomethoxylation induced by the 1:1 lithium chloride/hexamethylphosphoric triamide complex (LiCl/HMPA). This ester decomposition generates either the chlorodifluoromethide ion or the chlorodifluoromethyllithium/hexamethylphosphoric triamide complex. The nucleophilic intermediate from this ester decomposition may be trapped upon decomposition of the ester in the presence of appropriate electrophilic reagents.

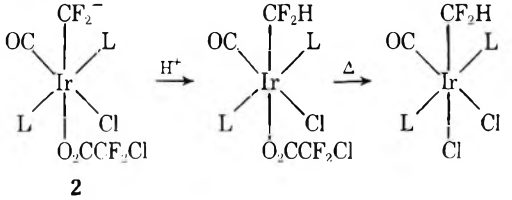
The increasing interest in organofluorine chemistry has resulted in the rapid development of methods for the introduction of fluorinated groups into organic molecules. One area which has received considerable attention in recent years is the generation and reactions of polyfluorinated carbanions.[2,3] Although a wide variety of fluorinated carbanions are known, halodifluoromethide ions have been considered to have no finite existence. The major contributors to this hypothesis are the investigations by Hine and co-workers[4–6] which indicate that the formation of difluorocarbene by either the action of a base upon halodifluoromethanes or the thermally induced decarboxylation of halodifluoroacetate ions is a concerted process not involving the intermediacy of halodifluoromethide ions. In addition, none of the numerous reports in the literature involving difluorocarbene generation via decarboxylation of alkali metal chlorodifluoroacetates present any concrete evidence to indicate the existence of halodifluoromethide ions as reaction intermediates.

In spite of the lack of evidence for the existence of halodifluoromethide ions in the literature, substituted difluoromethide ions which possess substituents that are good carbanion stabilizing groups have been demonstrated to exist as reaction intermediates. Treatment of difluoromethyl phenyl sulfone with sodium methoxide in methanol in the presence of thiophenoxide results in the formation of difluoromethyl phenyl sulfide via trapping of difluorocarbene by the thiophenoxide.[7] In this case, however, the formation of difluorocarbene is a two-step process involving an intermediate difluoromethide ion **1**. The intermediacy of **1** in the

$$PhSO_2CF_2H \xrightarrow[MeOH]{NaOMe} PhSO_2CF_2^- \rightarrow PhSO_2^- + :CF_2$$

1

formation of carbene is indicated by the observation that the sulfone undergoes deuterium exchange much more rapidly than it consumes thiophenoxide. Evidence for a metal-stabilized difluoromethide ion has been reported in the literature recently.[8] Refluxing sodium chlorodifluoroacetate and $IrCl(CO)(PPh_3)_2$ in diglyme resulted in the isolation of either of two difluoromethyl complexes. The formation of these complexes was taken as evidence for the intermediacy of the metallocarbanion **2**.



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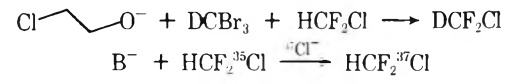
Kesling and Burton[9] have recently reported that treatment of halodifluoromethylphosphonium halides with fluoride ion in the presence of appropriate electrophilic reagents results in the transfer of halodifluoromethyl groups. While the intermediacy of halodifluoromethide ions was not definitely established, the reactions which were reported may best be interpreted as involving such carbanions.

More recently Kimpenhaus and Buddrus[10] have reported that the generation of difluorocarbene by the reaction of halide ions with epoxides in the presence of chlorodifluoromethane in aprotic solvents proceeds via the chlorodifluoromethide ion. The intermediacy of the methide ion was established by H–D exchange studies. Isotopic chlorine exchange also indicated that an equilibrium exists between chlorodifluoromethide ion, carbene, and chloride ion in this system.



In a preliminary report[11] we outlined evidence for the generation and capture of the chlorodifluoromethide ion upon treatment of methyl chlorodifluoroacetate (**3**) with lithium chloride in hexamethylphosphoric triamide (HMPA) in the presence of polyfluoromethyl ketones. We now wish to report in greater detail on the generation of halodifluoromethide ions by the decomposition of methyl halodifluoroacetates induced by halide ions. This report discusses the mechanism of the halide-induced ester decomposition as well as the scope and utility of this method of halodifluoromethide ion generation.

Results and Discussion

The facilitation of decarboalkoxylation reactions by alkali metal halides has been reported.[12-14] However, the use of hexamethylphosphoric triamide (HMPA) as either a solvent or a cosolvent has been reported to effect decarboalkoxylation by alkali halides under much milder conditions than are normally required in the absence of HMPA.[12,15]

In addition to the previously reported[11] facile decomposition of **3** by lithium chloride in HMPA, treatment of **3** with a 1:1 lithium chloride/HMPA complex (LiCl/HMPA)[16] in a variety of aprotic solvents effects the facile decarbomethoxylation of the ester to yield methyl chloride and carbon dioxide. Addition of **3** to a refluxing solution of LiCl/HMPA in THF results in an essentially quantitative yield of carbon dioxide after 4 h. Decarbomethoxylation of **3** by LiCl/HMPA occurs slowly even in refluxing methylene chloride (92% of CO_2 after 12 h), but in general much faster rates of decomposition are obtained utilizing ethereal solvents such as THF or glymes.

Mechanism. The selective cleavage of methyl esters of carboxylic acids in the presence of higher alkyl esters by either lithium chloride[12] or sodium cyanide[17] in HMPA suggested that the decomposition of **3** by LiCl/HMPA proceeds via initial nucleophilic attack by chloride ion upon the methoxyl carbon with subsequent displacement of the chlorodifluoroacetate group. Treatment of **3** with LiCl/HMPA, formed in situ, at 40 °C in THF for 2 h resulted in the isolation of a hygroscopic white solid upon evaporation of the solvent in vacuo. This white solid was characterized as the lithium chlorodifluoroacetate/HMPA complex (**4**) by ^{19}F and ^{1}H

$$3 + \text{LiCl/HMPA} \xrightarrow[\text{THF}]{40\ ^\circ\text{C}} CH_3Cl + ClCF_2CO_2Li/\text{HMPA}$$

4

NMR spectroscopy as well as by its infrared spectrum. Due to the hygroscopic nature of **4**, however, a satisfactory elemental analysis could not be obtained. Quantitative ^{19}F NMR analysis indicated that **4** was formed in essentially quantitative yield after 2 h in the above reaction. Subsequent refluxing of a solution of **4** in THF resulted in an 88% yield of carbon dioxide and complete disappearance of the ^{19}F NMR signal of **4** after 4 h. Based on the above observations, the mechanism of the decomposition of **3** upon treatment with LiCl/HMPA in THF is concluded to involve an initial S_N2 displacement of the chlorodifluoroacetate ion from the methyl group by chloride ion. The resultant complex **4** then decarboxylates under rather mild conditions.

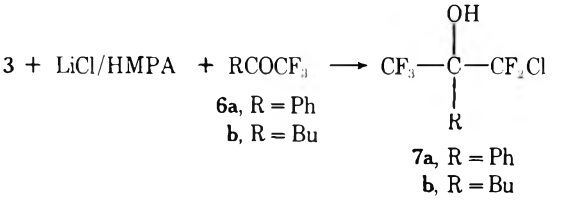
The decomposition of **3** by LiCl/HMPA in THF in the presence of 2,2,2-trifluoroethanol gave an essentially quantitative yield of chlorodifluoromethane (**5**) as determined by

$$3 + \text{LiCl/HMPA} + CF_3CH_2OH \rightarrow HCF_2Cl$$

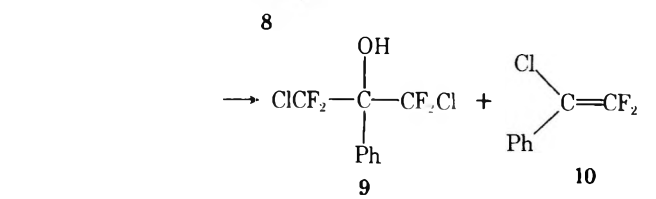
5

^{19}F NMR analysis. No difluoromethyl ether derived from insertion of difluorocarbene into the O–H bond of the alcohol was observed by ^{19}F NMR spectroscopy. The formation of **5** and the absence of any carbene insertion product suggest that decarbomethoxylation of **3** by LiCl/HMPA in THF results in the formation of either a chlorodifluoromethide ion or a chlorodifluoromethyllithium/HMPA complex.

Like the previously reported decomposition of **3** by LiCl in HMPA in the presence of polyfluoromethyl ketones,[11] treatment of **3** with LiCl/HMPA in refluxing THF in the presence of polyfluoromethyl ketones resulted in the formation of tertiary alcohols. Addition of **3** to a refluxing solution of LiCl/HMPA and trifluoromethyl ketones **6** in THF resulted



in the formation of alcohols **7a** and **7b** in yields of 63 and 39%, respectively, upon steam distillation. Authentic samples of **7a** and **7b** were prepared for comparison purposes in 28 and 46% yields, respectively, via the addition of phenyllithium and *n*-butyllithium to chloropentafluoroacetone, similar to related organolithium additions to this ketone reported by Dyatkin and co-workers.[18] The alcohols were the only fluorinated products observed. Similar decomposition of **3** in the presence of α-chloro-α,α-difluoroacetophenone (**8**) resulted in only an

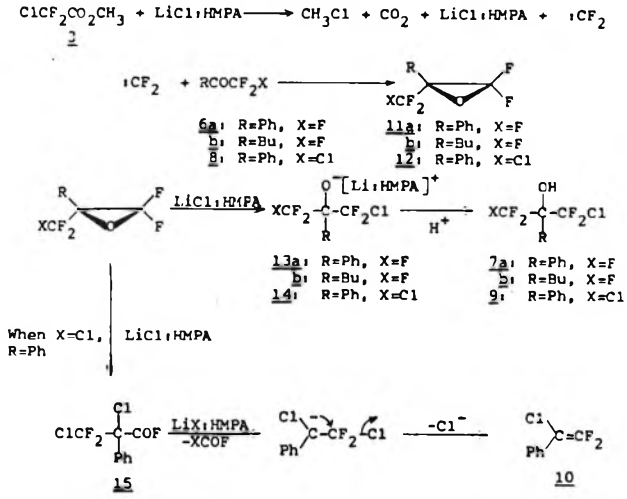


8 **9** **10**

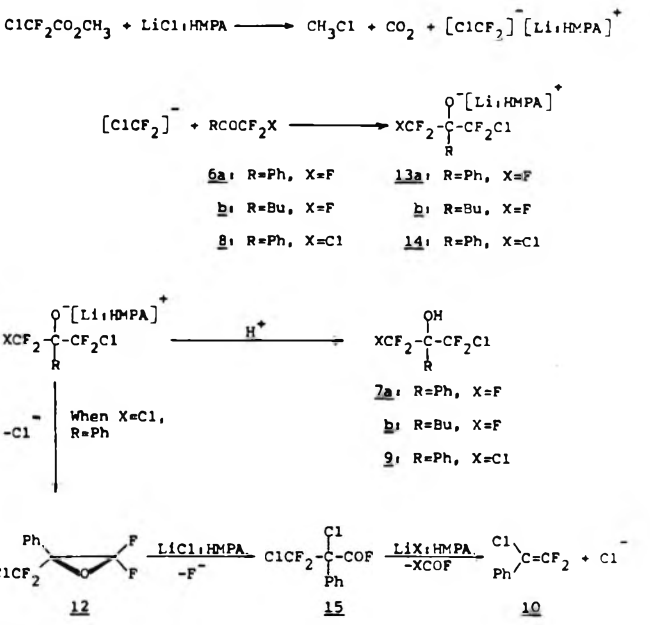
18% yield of the expected alcohol **9**. The major product of this reaction was the olefin **10** which was obtained in a 50% yield. These results are identical with those previously reported.[11]

Two mechanistic interpretations were considered most plausible to account for the observed results of the decomposition of **3** in the presence of the polyfluoromethyl ketones. One mechanism involves concerted formation of difluorocarbene upon decarbomethoxylation of **3**. The carbene thus formed would add across the carbon–oxygen double bond of the ketone[19] **6** to yield intermediate 1,2-epoxides **11** and **12**, as depicted in Scheme I. The epoxides would then be ring opened by chloride ion to yield the observed products. The

Scheme I



Scheme II



formation of the alcohols **7** as the only products of the reaction involving ketones **6** requires that epoxides **11a** and **11b** be ring opened exclusively by chloride ion attack at the 1 position to give lithium alkoxides **13a** and **13b.** On the other hand, ring opening of epoxide **12** would have to occur primarily by chloride attack at the 2 position, resulting in formation of acid fluoride **15,** which would then react further with halide to yield ultimately the observed olefin **10.** Attack by chloride at the 1 position of **12** to give alkoxide **14** would have to occur to only a minor extent to account for the observed low yield of alcohol **9.**

Exclusive attack by chloride at the 1 position of epoxides **11a** and **11b** is considered highly unlikely in view of the fact that nucleophilic ring opening of analogous fluorinated 1,2-epoxides occurs at the 2 position to form acid fluorides rather than at the 1 position in all cases but those involving extremely bulky nucleophiles.[20] Coordination of the epoxide oxygen by the lithium ion might result in chloride attack at the terminal carbon as observed in the electrophilic ring opening of fluorinated 1,2-epoxides by Lewis acid catalysts or by strong protonic acids.[20] Such participation in ring opening by the lithium ion is most likely not operative in this system, however, since the use of the complex LiCl/2HMPA in the decomposition of **3** in the presence of ketones **6** and **8** gave results identical with those observed utilizing LiCl/HMPA. The doubly complexed lithium ion has been demonstrated to be incapable of such coordination to oxiranes.[16b] Therefore, ring opening of the oxiranes **11** and **12** would most likely occur solely by nucleophilic attack by chloride at the 2 position to yield acid fluorides.

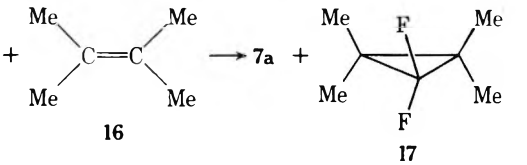
The second mechanism considered, outlined in Scheme II, involves the formation of either chlorodifluoromethide ion or chlorodifluoromethyllithium/HMPA complex upon decarbomethoxylation of **3.** The methide ion or the HMPA-complexed organolithium compound ($ClCF_2Li$/HMPA) would then add to the carbonyl carbon of the ketones to generate the lithium alkoxides **13** and **14** directly. The alkoxides would yield the observed alcohols upon hydrolysis. This mechanism, however, requires that alkoxide **14** undergo an intramolecular S_N2 displacement of chloride by the alkoxy oxygen to form the 1,2-epoxide **12** while alkoxides **13,** which contain the trifluoromethyl substituent, would have to be inert to this intramolecular displacement of chloride. Epoxide **12** would then be ring opened by chloride to ultimately yield olefin **10** as described previously.

The attempted synthesis of the suspected intermediate epoxides **11** and **12** in order to investigate their ring opening behavior was successful only in the case of **12.** Treatment of the alcohols **7a** and **7b** with aqueous potassium hydroxide as by the method of Knunyants et al.[21] resulted in no epoxide formation. Acidification of the reaction mixture, in both cases, resulted in essentially quantitative recovery of the unchanged alcohols. However, treatment of **9** with aqueous potassium hydroxide followed by heating gave a 65% yield of epoxide **12.**

Addition of **12** to a solution of excess LiCl/HMPA in THF at 0 °C resulted in a 96% yield of acid fluoride **15** by ^{19}F NMR analysis. Subsequent refluxing of this solution gave the olefin **10** in 95% yield by NMR spectroscopy. Significantly, no alcohol **9** was observed upon hydrolysis by either ^{19}F NMR or GLC analyses. Thus, ring opening of epoxide **12** occurs exclusively via chloride ion attack at the 2 position. No attack at the 1 position with subsequent alkoxide formation occurs. Therefore, alcohol **9** obtained from the decomposition of **3** in the presence of **8** must be the result of addition of $ClCF_2^-$ or $ClCF_2Li$/HMPA to the ketone as depicted in Scheme II. While the failure of alkoxides **13a** and **13b** to yield epoxides, under the same conditions which yield **12** from **14,** makes comparative predictions of the ring opening behavior of epoxides **11a, 11b,** and **12** somewhat tenuous, it is unlikely that such structurally similar epoxides would exhibit markedly different ring opening behavior. In addition, the failure of alkoxides **13a** and **13b** to ring close is consistent with the requirements of the mechanism outlined in Scheme II. The ring opening of analogous epoxides[20] supports the conclusion that alcohols **7a** and **7b** were also formed by nucleophilic addition of $ClCF_2^-$ or $ClCF_2Li$/HMPA to the ketones (as was **9**) and that they did not result from the ring opening of the epoxides **11a** or **11b.**

That the formation of the alcohols upon decarbomethoxylation of **3** in the presence of ketones **6** and **8** was the result of interception of either $ClCF_2^-$ or $ClCF_2Li$/HMPA and not the result of initial carbene formation, as depicted in Scheme I, was further substantiated by the following two experiments. Addition of **3** to a refluxing solution of LiCl/HMPA, excess **6a,** and excess 2,3-dimethyl-2-butene (**16**) in THF resulted in the formation of a 66% yield of **7a** and a 27% yield of cyclopropane **17.** If difluorocarbene were initially formed upon

3 + LiCl/HMPA + **6a**



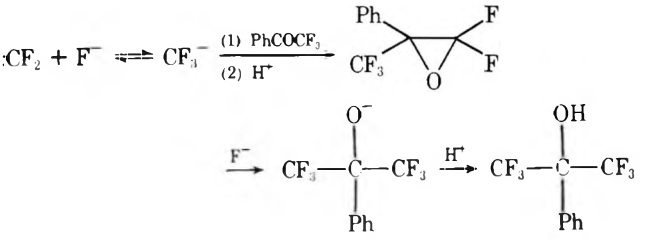
16 **17**

decomposition of **3**, the olefin **16** would compete very effectively with either chloride ion or ketone **6a** for the carbene.[22] Thus, decomposition of **3** to give difluorocarbene directly would have resulted in the formation of cyclopropane **17** as the predominant product. However, the alcohol **7a** was observed to be the predominant product. In fact, the yield of **7a** obtained in the presence of the olefin is essentially the same as that obtained when no olefin was present. These results are interpreted as indicating that either $ClCF_2^-$ or $ClCF_2Li$/HMPA was formed initially upon decarbomethoxylation of **3**. Either of these nucleophilic species then added to the carbonyl carbon of the ketone to yield **7a** upon hydrolysis. The cyclopropane which was formed was the result of difluorocarbene formed by the decomposition of either the methide ion or $ClCF_2Li$/HMPA before reaction with the ketone.

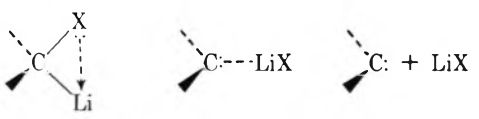
Treatment of **3** with potassium fluoride/18-crown-6 complex[23] in refluxing THF in the presence of **6a** resulted in the consumption of only 35% of the ester **3** after 4 h. However, a 21% yield of the alcohol **7a** was obtained upon hydrolysis.

$$3 + KF/18\text{-crown-}6 + \mathbf{6a} \rightarrow 7a + PhC(CF_3)_2OH$$
$$\mathbf{18}$$

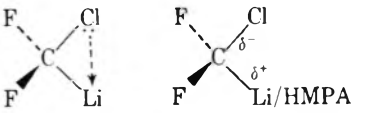
More significantly, however, no 2-phenylhexafluoro-2-propanol (**18**) was detected in the reaction mixture. The failure to obtain alcohol **18** from this reaction is significant in two respects. The lack of formation of **18** in this system indicates that methide ion formation is not the result of capture of initially formed difluorocarbene by halide ion. Also, the absence of **18** indicates once again that the alcohols which are formed by decomposition of **3** in the presence of the polyfluoromethyl ketones do not arise by halide ion ring opening of intermediate epoxides.



While the exact nature of the reactive species formed upon decarboxylation of complex **4** is open to much speculation, little doubt remains that it is indeed a nucleophilic species such as chlorodifluoromethide ion ($ClCF_2^-$) or the complexed carbenoid $ClCF_2Li$/HMPA. The stability of a free carbanion such as $ClCF_2^-$ should be enhanced by the slight degree of coordination or solvation expected in this system, as well as its reactivity increased. A methide ion would be only slightly solvated and only loosely associated with a very highly solvated lithium ion in this reaction medium. Such enhancement of carbanion stability has been observed for the trichloromethide ion formed by the reaction of tris(dimethylamino)-phosphine with carbon tetrachloride.[24] The stability of an organometallic species such as $ClCF_2Li$/HMPA would definitely be enhanced by the complexation of the lithium atom by HMPA. The most generally accepted mechanism for the decomposition of carbenoids such as $ClCF_2Li$ involves the initial loss of an α halogen.[25] Such a mode of decomposition is facilitated by the interaction of the nonbonding electrons on the halogen with the metal. This metal–halogen interaction



would be decreased by either complexation or solvation of the metal atom.[25a] Complexation of the lithium atom in $ClCF_2Li$/HMPA by the strongly electron-donating HMPA[25b] and solvation by THF would result in stabilization of this carbenoid by greatly decreasing the strength of the interaction between the lithium and chlorine atoms.[25b] In addition to



hindering the interaction between the lithium and chlorine atoms, complexation of the lithium atom of $ClCF_2Li$ by HMPA and solvation by THF would also increase the polarity of the carbon–lithium bond,[25b] enhancing the carbanionic character of the carbon atom. This would result in the subsequent acceleration of those reactions in which the nucleophilicity of the carbon atom is important; that is, with electrophilic substrates such as the polyfluoromethyl ketones.

Scope and Limitations. While treatment of **3** with LiCl/HMPA in the presence of polyfluoromethyl ketones in refluxing THF resulted in good yields of tertiary polyfluoro alcohols, presumably via the trapping of a carbanionic intermediate by the ketones, attempts to extend this reaction to less reactive nonfluorinated carbonyl compounds met with little success. Treatment of **3** with LiCl/HMPA in refluxing THF in the presence of benzaldehyde or acetophenone yielded none of the expected chlorodifluoromethyl alcohols. In both cases, steam distillation resulted only in the isolation of tarry residues. In neither case was consumption of the carbonyl compound significant. Analysis of the reaction mixtures by ^{19}F NMR spectroscopy showed that a 15% yield of **5** was formed in the reaction employing acetophenone. The failure of benzaldehyde and acetophenone to yield the expected alcohols suggests that while the carbanionic intermediate in the ester decomposition exhibits sufficient stability to react with carbonyl compounds which are very susceptible to nucleophilic attack, such as the polyfluoromethyl ketones, the rate of reaction with less reactive carbonyl compounds such as benzaldehyde and acetophenone is slower than the rate of decomposition of the intermediate.

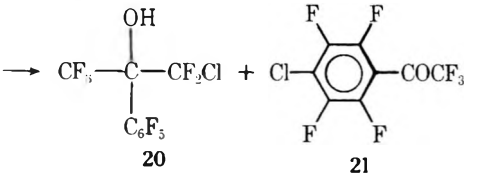
Decarbomethoxylation of **3** in the presence of benzoyl chloride, however, yielded the expected products. Ester decomposition in the presence of the acid chloride, which is very susceptible to nucleophilic displacement of the chloride by an addition/elimination mechanism,[26] resulted in a 40% yield of ketone **8** and small amounts of **10** (15%) and **9** (5%), which

$$3 + LiCl/HMPA + PhCOCl \rightarrow PhCOF + \mathbf{8}\text{–}\mathbf{10}$$

resulted from addition of $ClCF_2^-$ or $ClCF_2Li$/HMPA to **8** as described previously. In addition, a 20% yield of benzoyl fluoride was produced. That **8** was not the result of insertion of difluorocarbene into the carbon–chlorine bond is indicated by the observation that no trifluoroacetophenone (**6a**) was formed in the reaction via carbene insertion into the carbon–fluorine bond of the benzoyl fluoride which was produced in the reaction. The benzoyl fluoride was apparently the result of chloride displacement on benzoyl chloride by fluoride ion generated during ester decomposition.

Decarbomethoxylation of **3** in THF in the presence of octafluoroacetophenone (**19**) resulted in the isolation of two products. Alcohol **20** was obtained in 38% yield and the 4-

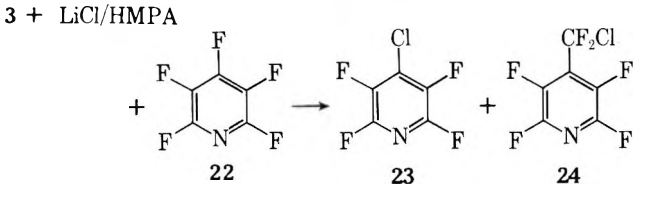
$$3 + LiCl/HMPA + C_6F_5COCF_3$$
$$\mathbf{19}$$



20 **21**

chloro ketone **21** in 52% yield from this reaction. The ketone **21** was also formed in an essentially quantitative yield when **19** was treated with LiCl/HMPA alone in refluxing THF. These results indicate that either substitution of the para fluorine by chloride decreases the reactivity of the carbonyl group of **21** toward nucleophilic attack relative to the carbonyl in **19**, or the ortho fluorines of **19** and **21** deactivate the carbonyl carbon toward nucleophilic attack relative to **6a** or both. Similar inhibition by ortho fluorines in nucleophilic attack at the α position has been reported previously.[18] Other fluorinated products were detected in trace amounts in this reaction mixture by ^{19}F NMR spectroscopy. None of these products were identified, but they are believed to have resulted from formation of small amounts of the perfluoro analogue of epoxide **12** and subsequent ring opening of this oxirane by halide ion or from displacement of ring fluorines of **19** by methide ion or $ClCF_2Li$/HMPA. The relatively low yield of **20** and the large amount of **21** formed in this reaction indicate that attack at the carbonyl carbon by either $ClCF_2^-$ or $ClCF_2Li$/HMPA does not compete very favorably with attack by chloride ion at the para position of the aromatic ring.

Similar results were observed when **3** was treated with LiCl/HMPA in refluxing THF in the presence of pentafluoropyridine (**22**). Pentafluoropyridine is known to be very



susceptible to nucleophilic attack,[27] and indeed **22** was totally consumed in this reaction. Again, the predominant product of the reaction was the result of displacement of the para fluorine by chloride ion. Thus, 4-chlorotetrafluoropyridine (**23**) was obtained in 66% yield. The only other product which was formed was 4-chlorodifluoromethyltetrafluoropyridine (**24**) obtained in 34% yield. No other fluorinated products were observed by ^{19}F NMR spectroscopy in contrast to the transfer of a bromodifluoromethyl group to **22** upon decomposition of bromodifluoromethyltriphenylphosphonium bromide by fluoride ion in the presence of **22**.[28] In this latter case, polysubstitution products as well as those resulting from the transfer of a trifluoromethyl group were observed in addition to bromodifluoromethyl group transfer. A similar attempt at displacement of fluorine from hexafluorobenzene by either the chlorodifluoromethyl group or the chloride ion failed.

The attempted preparation of chlorodifluoroiodomethane (**25**) by decarbomethoxylation of **3** in the presence of positive

$$3 + \text{LiCl/HMPA} + I_2 \rightarrow \underset{\mathbf{25}}{ClCF_2I} + \underset{\mathbf{26}}{CF_2I_2}$$

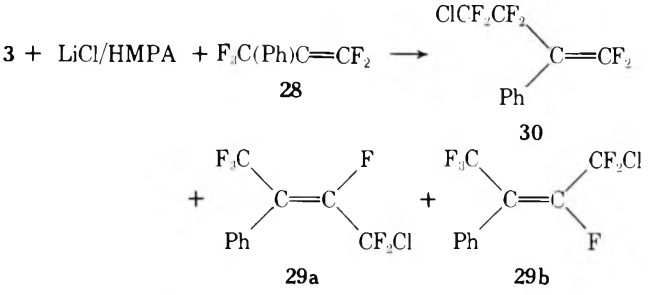
iodine sources met with little success. Treatment of **3** with LiCl/HMPA in refluxing THF in the presence of iodine resulted in no ester decomposition. However, decomposition of **3** did occur in the presence of iodine when triethylene glycol dimethyl ether (triglyme) was used as the solvent. The temperature required for decomposition was somewhat higher than normal, however. Thus, treatment of **3** with LiCl/HMPA in triglyme at 90–95 °C in the presence of iodine resulted in a 15% yield of **25** as well as a 5% yield of difluorodiiodomethane (**26**). The formation of **25** was most likely the result of abstraction of positive iodine from I_2 by either $ClCF_2^-$ or $ClCF_2Li$/HMPA, but it may also have been the result of insertion of difluorocarbene into iodine monochloride (ICl), which may have been formed in the reaction mixture. The formation of **26** most likely occurred by insertion of carbene into I_2, as reported by Mitsch.[29]

The use of iodine monobromide (IBr) as the positive iodine source resulted in a slightly improved yield of **25**. When **3** was

$$3 + \text{LiCl/HMPA} + IBr \rightarrow \mathbf{25} + \underset{\mathbf{27}}{BrCF_2I}$$

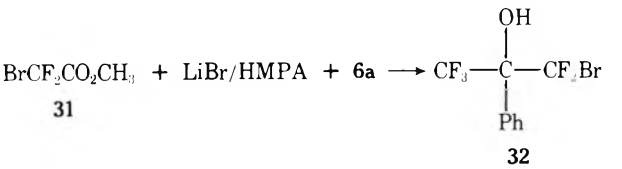
treated with LiCl/HMPA in triglyme at 90–95 °C in the presence of IBr, a 30% yield of **25** resulted as well as a 10% yield of the carbene insertion product **27**. The reason for the higher yield of **25** obtained utilizing IBr as the positive iodine source is not understood at present, although similar results have been observed by others in this laboratory.

Highly fluorinated electrophilic carbon–carbon double bonds are very susceptible to attack by nucleophiles while being rather inert to attack by electrophilic reagents.[30] Especially susceptible to nucleophilic attack are terminal difluoromethylene olefins which have substituents on the β carbon which stabilize an adjacent negative charge. When **3** was treated with LiCl/HMPA in refluxing THF in the presence of 2-phenylpentafluoropropene (**28**), three isomeric



butenes were isolated in a total yield of 53% after 48 h. The predominant product of the reaction was (*Z*)-1-chloro-3-phenylhexafluoro-2-butene (**29a**), which comprised 64% of the product mixture. The minor products were the *E* isomers of the 2-butene **29b** and the 1-butene **30**, which comprised 17 and 19% of the product mixture, respectively. All three products were the result of addition of the $ClCF_2$ group to the 1 carbon followed by elimination of fluoride ion. The isomeric 2-butenes were characterized on the basis of the magnitude of the vicinal $F\text{–}CF_3$ ^{19}F NMR coupling constants, which were 24.1 and 10.9 Hz for the *Z* and *E* isomers, respectively.[31] Essentially identical results were obtained from decomposition of **3** by LiCl/HMPA in the presence of 2-(3-bromophenyl)-pentafluoropropene. The two isomers of the corresponding 2-butene and the 1-butene were formed in an overall yield of 25% with the isomer ratios being the same as those for the reaction involving **28**.

The extension of the decarbomethoxylation reaction to the generation of bromodifluoromethide ion or its alkyllithium analogue has met with limited success. Treatment of methyl bromodifluoroacetate (**31**) with either LiCl/HMPA or LiBr/



HMPA in refluxing THF resulted in essentially quantitative decarbomethoxylation over a period of 12 h. Treatment of **31** with LiBr/HMPA in THF in the presence of ketone **6a** resulted in a 40% yield of a single product upon steam distillation which has tentatively been assigned the structure 1-bromo-2-phenylpentafluoro-2-propanol (**32**) solely on the basis of its ^{19}F NMR spectrum. All attempts at isolating **32** resulted in its decomposition; thus, a vigorous characterization of **32** was not possible. However, the similarity of the ^{19}F NMR chemical shifts and coupling constants of **32** to **7a** and to

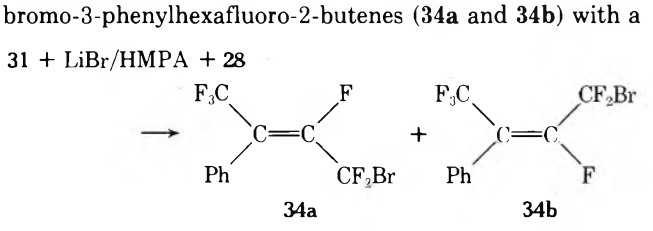
compounds with very similar structures containing the bromodifluoromethyl group gives us confidence in this structural assignment.

Similar treatment of **31** with LiCl/HMPA in the presence of **6a** resulted in the formation of a 12% yield of **7a** as well as a 33% yield of **32**. The ratio of alcohols **32** and **7a** remained constant over a 48-h period in the presence of excess LiCl/HMPA, indicating that **7a** was not the result of displacement of bromide from **32** by chloride ion.

The formation of **7a** suggested the possibility of the formation of either $ClCF_2^-$ or $ClCF_2Li$/HMPA during the course of the decomposition of **31**, possibly via capture of difluorocarbene by chloride ion. However, when **31** was treated with LiCl/HMPA in the presence of both ketone **6a** and olefin **16**, the yields of **32** (35%) and **7a** (13%) were essentially identical with the yields obtained in the absence of the olefin. A 40% yield of cyclopropane **17** was also obtained, indicating that difluorocarbene was indeed formed in the reaction. While carbene was intercepted by **16**, the formation of **7a** in the same yield as observed in the absence of the olefin indicates that formation of this alcohol was not the result of capture of difluorocarbene by chloride ion to generate $ClCF_2^-$, which then added to the ketone. Chloride ion would not be expected to compete with **16** as a scavenger of difluorocarbene; thus, if carbene was an intermediate in the formation of **7a**, the presence of the olefin would have caused a drastic reduction in the amount of alcohol formed due to selective scavenging of the carbene by the olefin.

Treatment of ester **31** with LiCl/HMPA in THF at 40 °C resulted in the formation of **4** (38%) as detected by ^{19}F NMR spectroscopy. A similar experiment at room temperature resulted in the formation of $BrCF_2CO_2Li$/HMPA (**33**) and **4** as detected by ^{19}F NMR spectroscopy. At no time during the course of the reaction was ester **3** observed by NMR spectroscopy. These results indicate that **4** was not formed by displacement of bromide from ester **31** by chloride with subsequent cleavage of ester **3** so formed by chloride ion. Thus, the alcohol **7a** formed during decarbomethoxylation of **31** in the presence of ketone **6a** employing LiCl/HMPA was the result of decarboxylation of **4**, as described previously, which was formed by chloride–bromide exchange occurring, most likely, in the HMPA-complexed lithium bromodifluoroacetate (**33**).

That decarbomethoxylation of **31** results in the generation of either $BrCF_2^-$ or $BrCF_2Li$/HMPA was also demonstrated by treatment of **31** with LiBr/HMPA in the presence of fluoro olefin **28**. This reaction yielded 25% of the isomeric 1-bromo-3-phenylhexafluoro-2-butenes (**34a** and **34b**) with a



Z/E isomer ratio of 4:1. Thus, $BrCF_2^-$ or its complexed alkyllithium analogue may also be generated and utilized as a reactive intermediate in both nucleophilic addition and nucleophilic substitution reactions.

Conclusions

The ability to generate halodifluoromethide ions (XCF_2^-; X = Cl or Br) or their HMPA-complexed alkyllithium analogues (XCF_2Li/HMPA) has been demonstrated. These nucleophilic intermediates may be utilized in a variety of nucleophilic addition or substitution reactions. The products observed in these reactions may best be accounted for in terms of carbanion intermediates $ClCF_2^-$ and $BrCF_2^-$. Competition reactions indicate that the formation of these carbanionic intermediates is not the result of concerted difluorocarbene formation with subsequent halide ion–carbene recombination but that the carbanions are the direct result of decarboxylation of HMPA-complexed lithium halodifluoroacetates **4** and **33** formed by displacement of the halodifluoroacetate ions from the corresponding methyl esters **3** and **31** by halide ions.

In contrast to the generation and transfer of halodifluoromethyl groups by the decomposition of halodifluoromethylphosphonium salts with fluoride ion,[9] the generation of these carbanions by the ester decarbomethoxylation method[21] results in relatively clean reactions without the accompanying formation of myriad side products.[28] In addition, transfer of halodifluoromethide groups to ketones with subsequent alcohol formation may not be accomplished by the phosphonium salt decomposition route.[28] Thus, the halide ion induced decomposition of methyl halodifluoroacetates serves as a very promising, convenient, and useful method for the generation of halodifluoromethide ions.

Experimental Section

Melting points were obtained in capillary tubes using a Thomas-Hoover unimelt apparatus and are corrected. The boiling points were obtained during fractional distillation by means of a partial immersion thermometer and are uncorrected. The infrared spectra were recorded on a Beckman IR-20A spectrophotometer. ^1H NMR spectra were recorded using ca. 10% (w/v) solutions in either $DCCl_3$ or CCl_4 on a Varian A-60 spectrometer with tetramethylsilane (Me_4Si) as an internal standard. ^{19}F NMR spectra were recorded using either aliquots of reaction mixtures or ca. 10% (w/v) solutions operating at 94.075 MHz. All chemical shifts are reported in ϕ^* values upfield from the external (ext) (capillary) $CFCl_3$ standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-66 mass spectrometer operating at 70 eV. Mass spectral samples were isolated from reaction or product mixtures by the analytical GLC capillary technique of Burson and Kenner.[32] Analytical and preparative GLC were performed on a Hewlett-Packard F & M Model 720 dual column gas chromatograph. Product yields were determined by comparison of the relative areas under peaks vs. an appropriate internal standard, corrected for differences in detector responses. Column A was a 10 ft × 0.25 in copper column packed with 15% (w/w) SE-30 on 80–100 mesh Chromosorb P. Column B was a 10 ft × 0.25 in copper column packed with 20% (w/w) SE-30 on 80–100 mesh Chromosorb P. Column C was a 10 ft × 0.25 in copper column packed with 15% (w/w) 20M Carbowax on 80–100 mesh Chromosorb P. Column D was a 10 ft × 0.5 in copper column packed with 20% (w/w) 20M Carbowax on 80–100 mesh Chromosorb P. Quantitative determination of carbon dioxide was performed by sweeping the CO_2 through a saturated solution of barium hydroxide.

Tetrahydrofuran and triglyme were distilled from sodium benzophenone ketyl and stored over 4A molecular sieves under nitrogen. Benzene was distilled from sodium and stored over sodium wire. Hexamethylphosphoric triamide (HMPA) was distilled from sodium at reduced pressure and stored over 4A molecular sieves under nitrogen. The alkali metal halides were dried at 120 °C in a vacuum oven (ca. 1 mmHg) for 24 h and then stored in a desiccator over phosphorus pentoxide. Lithium chlorodifluoroacetate was prepared by neutralization of chlorodifluoroacetic acid with lithium carbonate and was dried at 40 °C in vacuo (ca. 0.2 mmHg) for 24 h. The salt was stored in a desiccator over phosphorus pentoxide. All solids were handled in a glovebag under dry nitrogen and transferred in solid addition tubes sealed by rubber serum stoppers. The polyfluoromethyl ketones were prepared by the method of Dishart and Levine[33] as modified by Herkes and Burton.[34] The 2-arylpentafluoropropenes were prepared by the method of Naae and Burton.[35] The macrocyclic polyether 18-crown-6 was prepared by the literature method.[36]

Methyl Chlorodifluoroacetate (3). Methyl chlorodifluoroacetate was prepared by refluxing a solution of chlorodifluoroacetic acid (Halocarbon Chemical) (130.5 g, 1.00 mol) and excess anhydrous methanol (48.0 g, 1.50 mol) in the presence of concentrated sulfuric acid (40 mL) for 18 h. The reaction mixture was poured into ice water (600 mL), and the lower organic phase was separated, washed with 5% $NaHCO_3$ (2 × 250 mL) and water (2 × 200 mL), dried over 4A molecular sieves, and distilled under nitrogen through a 15 cm Vigreux

column to give a 69% (99.8 g, 0.69 mol) yield of **3**, bp 77.5–78.5 °C (lit.[37] bp 79–81 °C).

Methyl Bromodifluoroacetate (31). Methyl bromodifluoroacetate was prepared in 58% yield by the method of Paleta, Liska, and Posta.[38]

Preparation of LiX/HMPA In Situ. The lithium halide/HMPA complexes (LiX/HMPA) were prepared in situ for each reaction by adding anhydrous lithium halide via a solid addition tube to an equimolar amount of HMPA in the appropriate solvent with vigorous stirring. Formation of the complex was accompanied by a slight exotherm in each case. Complex formation was deemed complete when all of the lithium halide had gone into solution and the exotherm had subsided.

Reaction of 3 with LiCl/HMPA: Isolation of 4. To a solution of LiCl/HMPA (20 mmol) in THF (20 mL) was added **3** (4.35 g, 3.18 mmol) under nitrogen. The solution was heated to 40 °C and analyzed by ^{19}F NMR spectroscopy after 2 h. Using $C_6H_5CF_3$ as an internal standard indicated that an essentially quantitative yield of lithium chlorodifluoroacetate/HMPA complex (**4**) had been formed. The solvent was evaporated under vacuum to yield a viscous orange oil which was crystallized from benzene (10 mL) by freezing the solution and then allowing the benzene to slowly melt. The white solid which precipitated was collected by filtration under dry nitrogen through a Schlenk funnel.[39] The solid was dried in vacuo to give a 42% (2.65 g, 8.4 mmol) isolated yield of **4**: mp 178–180 °C with decomposition; IR (KBr) 2918 (m), 1690 (bs), 1413 (m), 1308 (m), 1190 (s), 1142 (bs), 1070 (w), 990 (s), 870 (w), 845 (w), 814 (m), 738 (s) cm^{-1}; ^1H NMR (10% $DCCl_3$, Me_4Si) δ 2.62 (d), J(PNCH) = 9.2 Hz; ^{19}F NMR (10% $DCCl_3$, $CFCl_3$ ext) ϕ^* +60.9 ppm (s). Anal. Calcd for $C_8H_{18}N_3O_3ClF_2PLi$: C, 30.44; H, 5.75; N, 13.31. Found: C, 28.65; H, 6.36; N, 10.59.

Reaction of 3 with LiCl/HMPA and 2,2,2-Trifluoroethanol. To a solution of LiCl/HMPA (40 mmol) in THF (20 mL) was added 2,2,2-trifluoroethanol (4.05 g, 40.5 mmol) and **3** (2.90 g, 2.12 mL, 20 mmol). The reaction system was connected in series to a cold trap (dry ice–2-propyl alcohol), a large bubbler containing 100 mL of a saturated solution of barium hydroxide, and a mineral oil bubbler, and then the solution was refluxed for 12 h. Analysis of the contents of the cold trap by both ^{19}F and ^1H NMR spectroscopy using $C_6H_5CF_3$ as an internal standard for both indicated that an essentially quantitative yield of chlorodifluoromethane (**5**) was obtained as well as a 92% yield of methyl chloride. The precipitate in the barium hydroxide bubbler was collected by suction filtration in a tared sintered glass crucible to give 3.47 g (17.6 mmol, 88%) of barium carbonate.

Reaction of 3 with LiCl/HMPA and 6a: Preparation of 7a. Ester **3** (4.35 g, 3.18 mL, 30 mmol) was added to a solution of LiCl/HMPA (60 mmol) and **6a** (5.22 g, 3.78 mL, 30 mmol) in THF (30 mL). The reaction mixture was refluxed for 24 h and then steam distilled. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 20 mL). The ether extracts and the organic layer were combined, washed with water (2 × 100 mL), and dried over anhydrous magnesium sulfate, and the ether was evaporated. The residue was then fractionally distilled through a 15 cm Vigreux column to give a 63% (4.91 g, 18.9 mmol) isolated yield of pure **7a**: bp 68–70 °C (8 mmHg); mass spectrum, *m/e* (relative intensity) 260 (9), 175 (88), 127 (19), 105 (100), 77 (44), 69 (15), 51 (20) (calcd for **7a**, 260.6 g/mol); IR (neat) 3588 (s), 3070 (w), 1502 (w), 1453 (w), 1356 (m), 1258 (m), 1218 (bs), 1128 (w), 1103 (w), 1076 (m), 1038 (m), 1021 (m), 948 (w), 918 (s), 845 (s), 756 (m), 728 (w), 716 (s), 692 (m), 669 (w) cm^{-1}; ^1H NMR (10% CCl_4, Me_4Si) δ 8.24–7.28 (m, 5 H, C_6H_5), 3.89 (broad s, 1 H, OH); ^{19}F NMR (10% CCl_4, $CFCl_3$ ext) ϕ^* +61.9 ppm (q, 2 F, CF_2Cl), +73.5 ppm (t, 3 F, CF_3), $J(CF_3, CF_2Cl)$ = 9.5 Hz.

Preparation of 7b. Refluxing a solution of **3** (7.23 g, 5.3 mL, 50 mmol), LiCl/HMPA (100 mmol), and **6b** (15.4 g, 11.5 mL, 100 mmol) in THF (50 mL) for 24 h followed by steam distillation resulted in the isolation of a yellow oil. Fractional distillation through a 15 cm Vigreux column gave a 39% (4.69 g, 19.5 mmol) isolated yield of 98% pure **7b**: bp 52–53 °C (18 mmHg); IR (neat) 3490 (bm), 2970 (m), 2882 (w), 1465 (w), 1283 (w), 1265 (w), 1200 (s), 1132 (w), 1109 (w), 1019 (w), 997 (w), 928 (m), 833 (m) cm^{-1}; ^1H NMR (10% $DCCl_3$, Me_4Si) δ 2.98 (broad s, 1 H, OH), 2.25–0.69 (unresolved m, 9 H, C_4H_9); ^{19}F NMR (10% $DCCl_3$, $CFCl_3$ ext) ϕ^* +62.0 ppm (q, 2 F, CF_2Cl), +74.4 ppm (t, 3 F, CF_3), $J(CF_3, CF_2Cl)$ = 11.4 Hz.

Preparation of 9 and 10. A solution of **3** (2.90 g, 2.12 mL, 20 mmol), LiCl/HMPA (40 mmol), and **8** (3.81 g, 20 mmol) in THF (40 mL) was refluxed for 48 h and then steam distilled to yield a mixture of **8**, **9**, and **10**. Preparative GLC on column B resulted in the isolation of a 50% yield of **10** (1.73 g, 10 mmol); mass spectrum, *m/e* (relative intensity) 176 (32), 174 (100), 139 (59), 119 (40), 89 (18) (calcd for **10**, 174.5 g/mol); IR (neat) 3195 (w), 1734 (s), 1500 (w), 1458 (w), 1305 (m), 1289 (w), 1263 (m), 1200 (w), 1013 (s), 948 (m), 922 (w), 764 (m), 698 (w) cm^{-1}; ^{19}F NMR (10% $DCCl_3$, $CFCl_3$ ext) ϕ^* +83.5 ppm (d, 1 F, vinyl F cis to Cl), +89.1 ppm (d of t, 1 F, vinyl F trans to Cl), J(F, ortho H's) = 1.2 Hz, J(FCF) = 33.2 Hz.

Compound **10** was identical in all respects with an authentic sample previously prepared in these laboratories via the reaction of $C_6H_5CHClCF_2Cl$ and $LiCO_3$.[40] An 18% (1.00 g, 3.6 mmol) isolated yield of **9** was also obtained which was identical in all respects with an authentic sample prepared via the addition of phenylmagnesium bromide to difluorotetrachloroacetone.[18]

Attempted Preparation of 11a. A solution of potassium hydroxide (2.0 g, 35 mmol) in water (15 mL) was added dropwise to **7a** (5.21 g, 20 mmol) with vigorous stirring. The solution was heated to 85–90 °C for 10 min. The reaction mixture was then cooled to 0 °C, but no organic layer separated. The solution was acidified with 6 N HCl, and the organic layer which separated was analyzed by ^{19}F NMR spectroscopy, which showed it to be the unchanged alcohol **7a** which was recovered in 96% yield (5.00 g, 19.2 mmol).

Attempted Preparation of 11b. Treatment of **7b** (12.0 g, 50 mmol) with potassium hydroxide (5.60 g, 100 mmol) in water (70 mL) resulted only in the recovery of 98% (11.8 g, 49.0 mmol) of unchanged **7b** as described above.

Preparation of 12. To **9** (27.7 g, 100 mmol) was added with vigorous stirring potassium hydroxide (11.2 g, 200 mmol) in water (35 mL). The resulting solution was then heated to 70–80 °C for 20 min, and the lower organic layer which formed upon heating was separated, washed with water, taken up in ether, and dried over anhydrous magnesium sulfate. Fractional distillation through a 15 cm Vigreux column gave 65% (15.6 g, 65 mmol) of pure **12**: bp 74–75 °C (27 mmHg) [lit.[20] bp 93 °C (68 mmHg)]; ^{19}F NMR (10% CCl_4, $CFCl_3$ ext) ϕ^* +59.4 ppm (d of d, 2 F, CF_2Cl), +101.8 ppm (d of t, 1 F, F trans to CF_2Cl), +109.5 ppm (d of t, 1 F, F cis to CF_2Cl), $J(ClCF_2$, trans F) = 2.1 Hz, $J(ClCF_2$, cis F) = 19.4 Hz, J(trans F, cis F) = 41.2 Hz.

Reactions of 12 with LiCl/HMPA. To a solution of LiCl/HMPA (50 mmol) in THF (20 mL) cooled to 0 °C in an ice–water bath was added **12** (9.63 g, 40 mmol) at such a rate that the temperature of the reaction did not exceed 5 °C. After stirring at 0 °C for 1 h, ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard indicated the formation of acid fluoride **15** in a 96% yield. The reaction mixture was flash distilled and then fractionally distilled through a 15 cm Vigreux column to give a 30% (3.20 g, 12 mmol) isolated yield of 97% pure **15**: bp 78–80 °C (5 mmHg); IR (neat) 1860 (s), 1203 (bs), 1159 (bs), 1050 (m), 1036 (m), 962 (m), 846 (m), 829 (w), 756 (m), 720 (m), 648 (w) cm^{-1}; ^{19}F NMR (10% $CFCl_3$) ϕ^* −32.9 ppm (t, 1 F, COF), +59.8 ppm (d of d, 1 F, CF^1Cl), +60.0 ppm (d of d, 1 F, CF^2Cl), $J(ClCF_2$, COF) = 9.1 Hz, $J(F^1, F^2)$ = 169.7 Hz. Additional confirmation of **15** was obtained by conversion to the known methyl ester via treatment of **15** with methanol.[41] In addition, a 69% (4.80 g, 27.6 mmol) yield of **10** [bp 50–52 °C (7 mmHg)] was isolated, which was identical with an authentic sample.

When **12** (7.22 g, 30 mmol) was added to a refluxing solution of LiCl/HMPA (70 mmol) in THF (20 mL) and stirred for 16 h, ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard indicated the formation of **10** in a 95% yield. The reaction mixture was flash distilled, the distillate was washed with water (2 × 100 mL), the organic layer was separated, and the aqueous layer was extracted with ether (2 × 10 mL). The ether extracts and the organic layer were combined, dried over anhydrous calcium sulfate, and fractionally distilled through a 15 cm glass helices column to give a 46% (2.40 g, 13.8 mmol) isolated yield of pure **10** which was identical with an authentic sample.

Decomposition of 3 in the Presence of 6a and 16. To a solution of LiCl/HMPA (20 mmol), **6a** (9.25 g, 53 mmol), and **16** (4.32 g, 51 mmol) in refluxing THF (40 mL) was added **3** (2.90 g, 20 mmol). After refluxing for 48 h, GLC analysis using toluene as an internal standard indicated a 67% consumption of **6a** and the formation of a 27% yield of **17**. Compound **17** was identified via comparison of its GC retention time and ^{19}F NMR absorption with an authentic sample.[22]

The reaction mixture was cooled to room temperature, acidified with 6 N HCl (3 mL), and poured into water (100 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. GLC analysis of the organic layer indicated that a 27% yield of **17** and a 66% yield of **7a** were obtained.

Reaction of 3 with KF/18-Crown-6 and 6a. To a solution of 18-crown-6 (6.60 g, 25 mmol), potassium fluoride (5.81 g, 100 mmol), and **6a** (8.71 g, 50 mmol) in THF (50 mL) was added **3** (7.24 g, 5.3 mL, 50 mmol) under nitrogen. The system was connected to a bubbler containing a saturated solution of barium hydroxide. The reaction mixture was refluxed for 4 h to give, upon hydrolysis with 6 N HCl, a 21% yield of **7a** as determined by ^{19}F NMR analysis using $C_6H_5CF_3$

as an internal standard. The precipitated barium carbonate indicated that only 35% decarboxylation had occurred. The absence of **18** was confirmed by comparison (^{19}F, singlet 75.5 ppm) with an authentic sample prepared via addition of phenyllithium to hexafluoroacetone.[18]

Reaction of 3 with LiCl/HMPA and Benzaldehyde. To a solution of LiCl/HMPA (80 mmol) and benzaldehyde (4.24 g, 4.1 mL, 40 mmol) in THF (60 mL) was added **3** (5.78 g, 4.2 mL, 40 mmol). The reaction mixture was refluxed for 48 h. GLC analysis using toluene as an internal standard showed consumption of 2.2 mmol of benzaldehyde. Upon hydrolysis with 6 N HCl no discernible products were detected by ^{19}F NMR analysis.

Reaction of 3 with LiCl/HMPA and Acetophenone. To a solution of LiCl/HMPA (40 mmol) and acetophenone (2.40 g, 20 mmol) in THF (25 mL) was added **3** (2.90 g, 2.12 mL, 20 mmol). The reaction mixture was refluxed for 20 h. GLC analysis using toluene as an internal standard showed consumption of 2.0 mmol of acetophenone. ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard showed, after hydrolysis of the reaction mixture with 6 N HCl, the formation of a 15% yield of **5**: ϕ^* +72.6 ppm (d), J(HCF) = 62.6 Hz.

Reaction of 3 with LiCl/HMPA and Benzoyl Chloride. Ester **3** (2.90 g, 2.12 mL, 20 mmol) was added to a solution of LiCl/HMPA (40 mmol) and benzoyl chloride (2.81 g, 20 mmol) in THF (25 mL), and the solution was refluxed for 48 h. The reaction mixture was then poured into 3 N HCl. GLC analysis of the organic layer using toluene as an internal standard showed the formation of a 20% yield of benzoyl fluoride, 40% of **8**, 15% of **10**, and 5% of **9**, as identified by a comparison of their GLC retention times with those of authentic samples.

Reaction of 3 with LiCl/HMPA and Octafluoroacetophenone (19). Ester **3** (7.23 g, 5.3 mL, 50 mmol) was added to a solution of LiCl/HMPA (100 mmol) and **19** (12.8 g, 49 mmol) in THF (100 mL), and the reaction mixture was refluxed for 20 h. GLC analysis indicated that total consumption of **19** had occurred. The reaction mixture was poured into water (500 mL) containing 6 N HCl (10 mL). The lower organic layer was separated, washed with water (3 × 100 mL), and dried over anhydrous magnesium sulfate. The product mixture was then distilled through a 15 cm Vigreux column to give a 52% (7.46 g, 26 mmol) isolated yield of **21**: bp 78–80 °C (43 mmHg); mass spectrum, *m/e* (relative intensity) 280 (7), 213 (29), 211 (100), 185 (15), 183 (47), 148 (16), 133 (28), 98 (10), 79 (15), 69 (16) (calcd for **21**, 280.5 g/mol); IR (neat) 2899 (w), 1758 (s), 1650 (s), 1499 (s), 1473 (w), 1420 (m), 1326 (m), 1272 (m), 1225 (s), 1181 (s), 1076 (s), 991 (s), 918 (m), 818 (m), 798 (w), 752 (m), 718 (m), 701 (w) cm^{-1}; ^{19}F NMR (10% THF, $CFCl_3$ ext) ϕ^* +78.1 ppm (t, 3 F, CF_3), +139.1 ppm (m, 2 F, ortho F's), +140.5 ppm (m, 2 F, meta F's), J(CF_3, ortho F's) = 11.1 Hz, all other coupling remains unresolved.

A second fraction was collected to give a 38% (6.53 g, 18.6 mmol) isolated yield of **20** (bp 85–87 °C (21 mmHg), which was identical with an authentic sample prepared by the method of Dyatkin.[18]

Reaction of LiCl/HMPA with 19. Ketone **19** (5.28 g, 20 mmol) was added to a solution of LiCl/HMPA (40 mmol) in refluxing THF (20 mL). After refluxing for 3 h, the reaction mixture was poured into a brine solution (200 mL), and the lower organic layer was separated, washed with water (3 × 50 mL), and dried over anhydrous magnesium sulfate. Preparative GLC on column B gave a 95% (5.33 g, 19.0 mmol) yield of 99% pure (GLC) **21**.

Reaction of 3 with LiCl/HMPA and *F*-Pyridine (22). Ester **3** (4.35 g, 3.2 mL, 30 mmol) was added to a solution of LiCl/HMPA (60 mmol) and **22** (5.16 g, 30 mmol) in THF (30 mL). The mixture was refluxed for 48 h, and then ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard showed the formation of a 34% yield of **24** and a 66% yield of **23**. The reaction mixture was flash distilled (60 °C, 4 mmHg), and the flash distillate was concentrated by distillation of the THF through a 30 cm gold-plated monel spinning band column. The residue was separated by preparative GLC on column D to give a 30% (2.12 g, 9 mmol) isolated yield of **24**: mass spectrum, *m/e* (relative intensity) 237 (12), 235 (35), 216 (12), 200 (100), 150 (13), 105 (10), 100 (31), 93 (11), 69 (38) (calcd for **24**, 235.5 g/mol); IR (neat) 1649 (w), 1480 (s), 1423 (m), 1304 (s), 1255 (w), 1218 (w), 1143 (s), 1028 (w), 991 (s), 969 (s), 828 (s), 762 (m), 747 (m), 697 (w), 649 (w) cm^{-1}; ^{19}F NMR (10% CCl_4, $CFCl_3$ ext) ϕ^* +48.7 ppm (t of m, 1 F, CF_2Cl), +86.4 ppm (m, 1 F, 2-F's), +140.2 ppm (m, 1 F, 3-F's), J($ClCF_2$, 3-F's) = 26.8 Hz, J(2-F's, 3-F's) = 12.4 Hz, all other coupling remains unresolved.

23 was isolated in a 60% yield (3.33 g, 18 mmol): mass spectrum, *m/e* (relative intensity) 187 (34), 185 (100), 166 (4), 150 (11), 140 (15), 116 (12), 100 (20) (calcd for **23**, 185.5 g/mol); IR (neat) 1638 (s), 1578 (w), 1480 (s), 1415 (m), 1313 (w), 1271 (w), 1242 (s), 1018 (w), 955 (s), 915 (s), 732 (w), 698 (w) cm^{-1}; ^{19}F NMR (10% CCl_4, $CFCl_3$ ext) ϕ^* +87.5 ppm (m, 1 F, 2-F's), +141.5 ppm (m, 1 F, 3-F's), no coupling could be resolved.

Reaction of 3 with LiCl/HMPA and Hexafluorobenzene. Ester **3** (2.90 g, 2.12 mL, 20 mmol) was added to a solution of LiCl/HMPA (40 mmol) and hexafluorobenzene (3.72 g, 2.3 mL, 20 mmol) in THF (20 mL). The reaction mixture was refluxed for 24 h. ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard indicated that no consumption of hexafluorobenzene occurred.

Reaction of 3 with LiCl/HMPA and Iodine. Ester **3** (1.45 g, 1.06 mL, 10 mmol) was added to a solution of LiCl/HMPA (20 mmol) and I_2 (2.54 g, 10 mmol) in triglyme (25 mL). The reaction mixture was heated at 90–95 °C for 48 h, and then ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard indicated the formation of **25** in a 15% yield and **26** in a 5% yield. The products **25** and **26** were identified by enhancement of their ^{19}F NMR signals with authentic samples.[42]

Reaction of 3 with LiCl/HMPA and Iodine Monobromide. Ester **3** (1.45 g, 1.06 mL, 10 mmol) was added to a solution of LiCl/HMPA (20 mmol) and IBr (2.07 g, 10 mmol) in triglyme (25 mL). The reaction mixture was heated at 90–95 °C for 48 h, and then ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard indicated that a 30% yield of **25** and a 10% yield of **27** had been formed. The products **25** and **27** were identified by enhancement of their ^{19}F NMR signals with authentic samples.[42]

Reaction of 3 with LiCl/HMPA and 2-Phenyl-*F*-propene (28). Ester **3** (21.7 g, 15.9 mL, 150 mmol) was added to a solution of LiCl/HMPA (300 mmol) and **28** (110.4 g, 8.0 mL, 50 mmol) in THF (150 mL). The reaction mixture was refluxed for 72 h. The reaction mixture was then steam distilled, the organic layer was separated, and the aqueous layer was extracted with pentane (3 × 20 mL). The pentane extracts and the organic layer were combined and dried over anhydrous magnesium sulfate. The pentane was then evaporated. Preparative GLC of the residue on column B gave a 46% (4.78 g, 23 mmol) recovery of **28**, a 34% (4.63 g, 17 mmol) yield of **29a**, and a mixture of **29b** (1.24 g, 4.5 mmol, 9%) and **30** (1.37 g, 5 mmol, 10%), as determined by ^{19}F NMR analysis of the mixture. **29a** was characterized as follows: mass spectrum, *m/e* (relative intensity) 276 (27), 274 (81), 239 (100), 219 (93), 189 (26), 169 (55), 151 (14) (calcd for **29a**, 274.5 g/mol); IR (neat) 3070 (w), 1695 (m), 1495 (w), 1449 (w), 1356 (s), 1234 (s), 1190 (s), 1146 (s), 1110 (w), 1076 (w), 976 (s), 948 (m), 914 (w), 812 (s), 762 (m), 723 (w), 698 (s), 658 (w), 634 (w) cm^{-1}; ^{19}F NMR (10% $DCCl_3$, $CFCl_3$ ext) ϕ^* +55.1 ppm (d of q, 2 F, CF_2Cl), +60.7 ppm (d of t, 3 F, CF_3), +111.4 ppm (q of t, 1 F, vinyl F), J($ClCF_2$, CF_3) = 1.2 Hz, J($ClCF_2$, F) = 11.2 Hz, J(CF_3, F) = 24.1 Hz.

29b was characterized by its ^{19}F NMR spectrum (10% $DCCl_3$, $CFCl_3$ ext): ϕ^* +55.7 ppm (t of d, 3 F, CF_3), +56.9 ppm (q of d, 2 F, CF_2Cl), +107.8 ppm (t of q, 1 F, vinyl F), J($ClCF_2$, CF_3) = 15.3 Hz, J($ClCF_2$, F) = 11.1 Hz, J(CF_3, F) = 10.9 Hz.

30 was characterized by its ^{19}F NMR spectrum (10% $DCCl_3$, $CFCl_3$ ext): ϕ^* +69.4 ppm (d of t, 2 F, CF_2Cl), +72.4 ppm (t of d, 1 F, vinyl F cis to C_6H_5), +73.8 ppm (t of t of d, 1 F, vinyl F trans to C_6H_5), +106.7 ppm (d of d of t, 2 F, CF_2), J($ClCF_2$, vinyl F trans to C_6H_5) = 9.4 Hz, J($ClCF_2$, CF_2) = 4.6 Hz, J(vinyl F, vinyl F) = 8.3 Hz, J(CF_2, vinyl F cis to C_6H_5) = 8.6 Hz, J(CF_2, vinyl F trans to C_6H_5) = 27.4 Hz.

Reaction of 3 with LiCl/HMPA and 2-(3-Bromophenyl)-*F*-propene. Ester **3** (2.90 g, 2.12 mL, 20 mmol) was added to a solution of LiCl/HMPA (40 mmol) and 2-(3-bromophenyl)-*F*-propene (5.74 g, 20 mmol) in THF (20 mL). The reaction mixture was refluxed for 48 h. The reaction mixture was then poured into water (150 mL). The organic layer was separated, and the aqueous layer was extracted with Skellysolve B (2 × 15 mL). The organic layer and the Skellysolve extracts were combined and dried over anhydrous magnesium sulfate. The Skellysolve was evaporated, and the residue was separated by preparative GLC on column B to give a 15% (1.06 g, 3.0 mmol) yield of (*Z*)-1-chloro-3-(3-bromophenyl)hexafluoro-2-butene, which was characterized as follows: mass spectrum, *m/e* (relative intensity) 356 (18), 354 (61), 352 (47), 273 (11), 254 (11), 238 (99), 219 (12), 188 (22), 169 (100), 98 (12), 73 (11), 69 (15), 51 (11) (calcd for $C_{10}H_4BrClF_6$, 353.6 g/mol); ^{19}F NMR (10% $DCCl_3$, $CFCl_3$ ext) ϕ^* +55.3 ppm (d of q, 2 F, CF_2Cl), +60.6 ppm (d of t, 3 F, CF_3), +109.8 ppm (q of t, 1 F, vinyl F), J($ClCF_2$, CF_3) = 1.3 Hz, J($ClCF_2$, vinyl F) = 11.4 Hz, J(CF_3, vinyl F) = 24.1 Hz.

Also isolated was a mixture of (*E*)-1-chloro-3-(3-bromophenyl)-hexafluoro-2-butene and 4-chloro-2-(3-bromophenyl)hexafluoro-1-butene (0.35 g, 1.0 mmol, 5%, and 0.35 g, 1.0 mmol, 5%, respectively) as determined by ^{19}F NMR analysis of the mixture. The *E* 2-butene was characterized by its ^{19}F NMR spectrum (10% $DCCl_3$, $CFCl_3$ ext): ϕ^* +55.6 ppm (d of t, 3 F, CF_3), +57.0 ppm (d of q, 2 F, CF_2Cl), +106.0 ppm (t of q, 1 F, vinyl F), J($ClCF_2$, CF_3) = 15.3 Hz, J($ClCF_2$, vinyl F) = 11.3 Hz, J(CF_3, vinyl F) = 11.3 Hz.

The 1-butene was also characterized by its ^{19}F NMR spectrum (10%

$DCCl_3$, $CFCl_3$ ext): ϕ^* +69.4 ppm (d of t, 2 F, CF_2Cl), +71.0 ppm (t of d, 1 F, vinyl F cis to Ar), +72.4 ppm (t of t of d, 1 F, vinyl F trans to Ar), +106.7 ppm (d of d of t, 2 F, CF_2), $J(ClCF_2$, vinyl F trans to Ar) = 10.0 Hz, $J(ClCF_2, CF_2)$ = 4.7 Hz, J(vinyl F, vinyl F) = 5.1 Hz, $J(CF_2$, vinyl F cis to Ar) = 9.3 Hz, $J(CF_2$, vinyl F trans to Ar) = 28.0 Hz.

Reaction of 31 with LiBr/HMPA and 6a. Methyl bromodifluoroacetate (**31**; 3.74 g, 20 mmol) was added to a solution of LiBr/HMPA (40 mmol) and **6a** (3.48 g, 2.76 mL, 20 mmol) in THF (20 mL). The reaction mixture was refluxed for 48 h and then steam distilled to give a 40% yield of **32** as determined by ^{19}F NMR spectroscopy using $C_6H_5CF_3$ as an internal standard. Attempted isolation by preparative GLC on column B resulted in decomposition on the column. The structure of **32** was assigned solely on the basis of its ^{19}F NMR spectrum (Et_2O, $CFCl_3$ ext): ϕ^* +56.6 ppm (q, 2 F, CF_2Br), +73.0 ppm (t, 3 F, CF_3), $J(BrCF_2, CF_3)$ = 11.2 Hz, which is consistent with the assigned structure.

Reaction of 31 with LiCl/HMPA and 6a. Ester **31** (5.80 g, 31 mmol) was added to a solution of LiCl/HMPA (60 mmol) and **6a** (5.22 g, 4.14 mL, 30 mmol) in THF (50 mL). The reaction mixture was refluxed for 48 h, and then GLC analysis using toluene as an internal standard indicated that 16.3 mmol (54%) of **6a** had been consumed. The reaction mixture was steam distilled, and the organic layer was analyzed by ^{19}F NMR using $C_6H_5CF_3$ as an internal standard. This analysis showed that a 33% yield of **32** and a 12% yield of **7a** had been obtained. Attempted isolation by fractional distillation resulted in the formation of a black tarry residue. Alcohol **7a** was identified by enhancement of its ^{19}F NMR signals with an authentic sample.

Reaction of 31 with LiCl/HMPA, 6a, and 16. Ester **31** (3.74 g, 20 mmol) was added to a solution of LiCl/HMPA (40 mmol), **6a** (6.96 g, 5.52 mL, 40 mmol), and **16** (3.36 g, 4.8 mL, 40 mmol) in THF (40 mL). The reaction mixture was refluxed for 48 h and then steam distilled. ^{19}F NMR analysis of the organic layer using $C_6H_5CF_3$ as an internal standard showed a 35% yield of **32**, a 13% yield of **7a**, and a 40% yield of **17**.

Reaction of 31 with LiCl/HMPA. Ester **31** (1.87 g, 10 mmol) was added to a solution of LiCl/HMPA (20 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 1 h, and then ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard indicated the presence of **31** (4.0 mmol, 40%), **33** (3.5 mmol, 35%), and **4** (2.5 mmol, 25%) in the reaction mixture. No ester **3** was observed. The reaction mixture was then heated to 45 °C and maintained at this temperature for 3 h. ^{19}F NMR analysis indicated the total consumption of **31** and the presence of dibromodifluoromethane (1.5 mmol, 15%) and **4** (3.8 mmol, 38%) in the reaction mixture. Both dibromodifluoromethane and **4** were identified by enhancement of their ^{19}F NMR signals with authentic samples.

Reaction of 31 with LiBr/HMPA and 28. Ester **31** (1.87 g, 10 mmol) was added to a solution of LiBr/HMPA (20 mmol) and **28** (2.08 g, 1.60 mL, 10 mmol) in THF (20 mL), and the reaction mixture was refluxed under nitrogen for 48 h. ^{19}F NMR analysis using $C_6H_5CF_3$ as an internal standard indicated the formation of **34a** (2.0 mmol, 20%) and **34b** (0.5 mmol, 5%) as identified by enhancement of their ^{19}F NMR signals with authentic samples.[43] Unreacted **28** was present also (7.4 mmol, 74%). In addition to these signals, traces of other products were observed, but these products were not identified.

Registry No.—**3**, 1514-87-0; **4**, 66070-45-9; **5**, 75-45-6; **6a**, 434-45-7; **6b**, 360-34-9; **7a**, 13006-19-4; **7b**, 53959-78-7; **8**, 384-67-8; **9**, 1892-88-2; **10**, 394-98-9; **12**, 36853-08-4; **15**, 53959-79-8; **16**, 27416-06-4; **17**, 823-25-6; **19**, 652-22-2; **20**, 13006-20-7; **21**, 66070-46-0; **22**, 700-16-3; **23**, 52026-98-9; **24**, 66070-47-1; **25**, 420-49-5; **26**, 1184-76-5; **27**, 753-66-2; **28**, 1979-51-7; **29a**, 66070-48-2; **29b**, 66070-49-3; **31**, 683-98-7; **32**, 66070-50-6; **34a**, 58201-69-7; **34b**, 58201-68-6; chlorodifluoroacetic acid, 76-04-0; LiCl/HMPA, 54215-87-1; LiBr/HMPA, 36239-89-1; 2,2,2-trifluoroethanol, 75-89-8; benzaldehyde, 100-52-7; acetophenone, 98-86-2; benzoyl chloride, 98-88-4; hexafluorobenzene, 392-56-3; iodine, 7553-56-2; iodine monobromide, 7789-33-5; 2-(3-bromophenyl)-*F*-propene, 61587-34-6; (*Z*)-1-chloro-3-(3-bromophenyl)-hexafluoro-2-butene, 66070-51-7; (*E*)-1-chloro-3-(3-bromophenyl)hexafluoro-2-butene, 66070-52-8; 4-chloro-2-(3-bromophenyl)-hexafluoro-1-butene, 66070-53-9.

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(42) Authentic samples of **25–27** were generously supplied by H. S. Kesling.
(43) Authentic samples of **34a** and **34b** were obtained from H. S. Kesling.

Addition to 2,4-Dienes. Ionic and Radical Additions to Ethyl Sorbate

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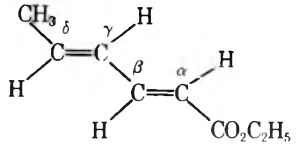
The electrophiles chlorine (Cl_2), methyl hypochlorite (CH_3OCl), bromine (Br_2), methyl hypobromite (CH_3OBr), and *N*-bromosuccinimide (NBS) were added to ethyl sorbate (**1**) under ionic conditions in methanol as solvent. Addition of CH_3OCl and CH_3OBr to neat **1** under ultraviolet illumination resulted in molecule-induced homolysis reactions. Under ionic conditions, addition of electrophiles to the γ,δ bond of **1** represents the major pathway, presumably because addition to the α,β bond of **1** disrupts conjugation of the π system with the carbonyl. Radical reagents attack only the β and δ carbons of **1**, which gives intermediates with delocalization of radicals into the carbonyl. Attack by radical reagents at the δ carbon rather than the β carbon of **1** is preferred because the electron can delocalize over five atoms.

Recently, we reported on the addition of halogens to a diene in which the double bonds are in conjugation with the carbonyl group.[2] We found that in nonpolar solvents chlorine reacts with ethyl sorbate (**1**) by an ionic or radical pathway,



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while bromine prefers to react with **1** by a radical process unless an efficient radical inhibitor is used.

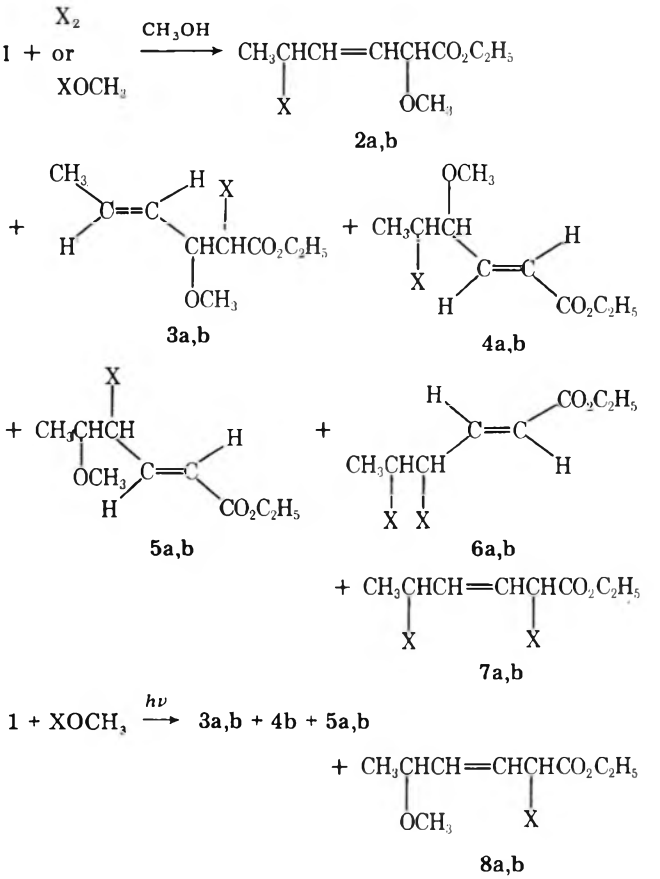
In our previous study[2] only symmetrical electrophiles were used, and therefore the regiospecificity of additions could not be examined. Our goal in this investigation was to determine the regiospecificity and the relative reactivities at the α,β and γ,δ bonds of **1** with ionic and radical reagents. The following unsymmetrical electrophiles were employed under ionic conditions:[3] chlorine (Cl_2) in methanol, methyl hypochlorite (CH_3OCl) in methanol,[3] bromine (Br_2) in methanol, methyl hypobromite (CH_3OBr) in methanol,[3] and *N*-bromosuccinimide (NBS) in methanol. Unsymmetrical radical reagents were comprised of methyl hypochlorite and methyl hypobromite in neat **1** under ultraviolet illumination.[3]

Results and Discussion

Products obtained with these reagents in methanol under ionic conditions and with CH_3OCl and CH_3OBr under radical conditions are listed in Table I. Structural assignments for all of the products except **3b** and **8b** are based on spectral data.[4]

Compounds **3b** and **8b** were labile and could not be isolated by preparative VPC. Support for their structures is based on conversion to **3a** and **8a**, respectively, when a mixture of **3b**, **5b**, and **8b** was treated with excess lithium chloride in dimethyl sulfoxide. Product **8b** was converted quantitatively to **8a** in less than 5 min, and **3b** was converted in high yield to **3a** in 25 min. The reaction of **5b** to **5a** was only ca. 20% complete after 24 h under these conditions. The relative reactivities of **3b**, **5b**, and **8b** with lithium chloride under S_N2 conditions lend additional support to their structure assignments. Compound **8b** is most reactive because the bromine is both allylic and adjacent to a carbonyl.[5] Apparently, **5b** is less reactive than **3b** because an allylic bromine is not as rapidly displaced as a bromine adjacent to a carbonyl.

Under ionic conditions, the data in Table I suggest that **10a** is an intermediate when bromine as an electrophile adds to



a, X = Cl; b, X = Br

the α,β bond of **1** (Scheme I). Products derived from **10a** will serve as a test for the relative rate of nucleophilic ring opening of a halonium ion at a carbon α to a carbonyl[5] vs. a carbon which is allylic. The data in Table I show that with bromine electrophiles only the 1,2-product **3b** is formed by attack at the α,β bond, whereas chlorine electrophiles give the 1,4-product **8a** (compare entries 3–5 with 2 in Table I).[6] The lack of any 1,4-product **8b** with bromine electrophiles indicates that an unsymmetrically bridged bromonium ion is involved at the α,β bond of **10a** since a symmetrically bridged ion should undergo some opening at the α carbon[5] and an open ion should give some **8b**. Possibly the carbon–halogen bond at the α carbon is stronger than the carbon–halogen bond at the β carbon in this bromonium ion because formation of a positive charge adjacent to a carbonyl would be unfavorable.

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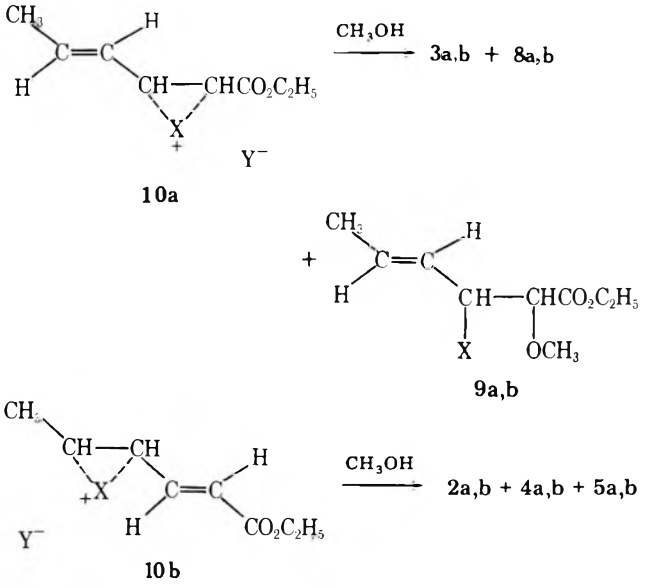
Table I. Addition of Unsymmetrical Halogenating Reagents to Ethyl Sorbate

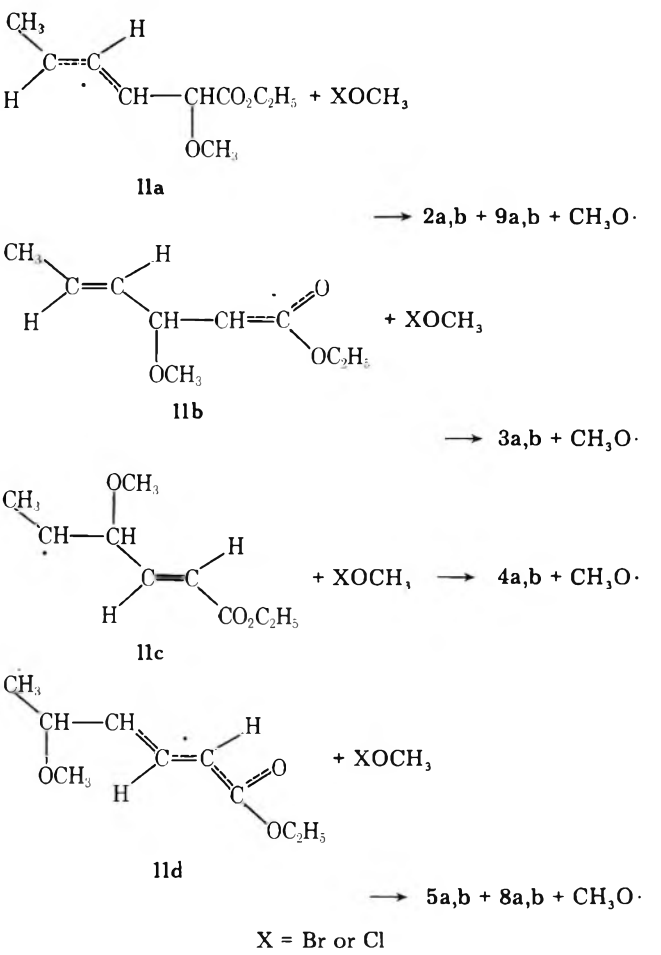
Entry	Reagents[a]	Products, % 1,4-δ-Halo 2a,b	1,4-α-Halo 8a,b	1,2-α-Halo 3a,b	1,2-δ-Halo 4a,b	1,2-γ-Halo 5a,b	Yield,[b] %	% addition α,β bond	% addition γ,δ bond
1	Cl_2/CH_3OH[c]	c	c		83	10	56[d]	0	100
2	CH_3OCl/CH_3OH	6	5		80	9	99	5	95
3	Br_2/CH_3OH	22		24	49	5	73[e]	24	76
4	NBS/CH_3OH	36		12	41	11	61	12	88
5	CH_3OBr/CH_3OH	13		4	78	5	83	4	96
6	CH_3OCl		21	17		62[f]	72	38	62
7	CH_3OBr		6	3	4	87[f]	89	9	91

[a] Reaction was carried out at 0 °C with stirring. Ionic conditions were 0.02 mol fraction of 1 in anhydrous methanol. Radical conditions were neat 1 under nitrogen and illumination with UV light. [b] Determined by VPC to ca. ±3%. [c] Products **2a** and **8a** have the same VPC retention times, and these products can only be determined by NMR analysis. We were unable to collect this peak because it was a minor component (7%), and a substitution product identified in our previous paper[2] had a retention time close to **2a** and **8a**. [d] Yield includes 10% of a γ,δ-dichloro product (**6a**) identified previously.[2] [e] Yield includes 35% of α,β- and γ,δ-dibromo products **6b** and **7b**, which were identified previously.[2] [f] NMR and VPC analysis show a 60:40 ratio of erythro–threo isomers, respectively.

Scheme I



Scheme II



Addition of the electrophile under ionic conditions to the γ,δ bond of **1** (see Scheme I) represents the major pathway of these reactions, presumably because addition to the α,β bond disrupts conjugation of the π system with the carbonyl. Solvent opens the γ,δ-halonium ions of **10b** preferably at the allylic carbon to give products **4a,b** (entries 1–5). The halonium ions at the γ,δ bond must be symmetrically bridged since nucleophilic ring opening at the δ carbon to give *erythro*-**5a,b** is noted (entries 3–5). Formation of these products by a radical pathway seems unlikely since the reactions are in methanol, and a radical reaction would lead to some *threo*-**5a,b**. Products **2a,b** are the result of an S_N2'-like reaction by the solvent when the halonium ion intermediate is formed at the γ,δ bond of **1**.

Ionic reactivity of the α,β and γ,δ bonds in **1** will be governed by the relative energies of the transition states leading to intermediates **10a** and **10b**. Addition of an electrophile might be preferred at the γ,δ bond of **1** because the γ,δ bond is more basic than the α,β bond and conjugation with the ester carbonyl would not be disrupted. On the other hand, a later transition state should favor attack at the α,β bond because a more stable (delocalized) intermediate can be formed. The data in Table I show that the lower-energy (earlier) transition state leading to addition at the γ,δ bond is favored with these electrophiles. Chlorine electrophiles show a greater tendency than bromine electrophiles to attack the γ,δ bond of **1**, which suggests that the chlorine systems have an earlier transition state than bromine in these reactions.

A radical may attack at the α, β, γ, or δ carbon atoms of **1** (Scheme II). Attack by a radical addend at the α carbon of **1** will form a secondary allylic radical intermediate (**11a**), while addition to the β carbon of **1** will give a secondary radical adjacent to a carbonyl, as indicated in **11b**. Similarly, intermediates **11c** and **11d** will contain a secondary radical and a secondary resonance-stabilized radical, respectively. We carried out a control experiment and found that return to the starting diene from radical intermediates **11a–d** is not a significant part of the reaction pathway (see Experimental Section). Thus, the product percentages in Table I (entries 6 and 7) very nearly represent the amount of initial attack by the radical on the α, β, γ, and δ carbons of **1**.

Under radical conditions (molecule-induced homolysis or photolysis) the major products are **5a,b**, which were shown to

be a 60:40 mixture of erythro–threo isomers (entries 6 and 7). Generally, addition of radical reagents to dienes gives primarily 1,4 products.[7] In the radical reactions of CH_3OCl and CH_3OBr with **1** only small amounts of 1,4 products (**8a,b**) are formed because conjugation of the α,β bond with the ester carbonyl would be destroyed by 1,4 addition.

It is curious that there is essentially no radical attack on the α and γ carbons to give intermediates **11a** and **11c**, respectively (Scheme II).[8] Formation of **11a** disrupts resonance conjugation with the ester carbonyl, and intermediate **11c** is not stabilized by resonance. Perhaps attack at the δ carbon is the preferred pathway since the radical can be delocalized over five atoms. Apparently, delocalization of radicals into a carbonyl is energetically favorable because intermediate **11b** is produced rather than **11a** and **11c**.

Experimental Section

Materials and chemicals were obtained commercially except for methyl hypochlorite[9] and methyl hypobromite,[10] which were prepared as described in the literature. Ethyl sorbate was distilled prior to use. IR and NMR spectra were obtained on a Beckman IR-10 spectrophotometer and a Varian T-60 A or XL-100 spectrometer, respectively. Vapor phase chromatographic analysis was accomplished with a Hewlett Packard 5796A flame ionization chromatograph. Preparative vapor phase chromatography was accomplished with a Varian A-9]-P chromatograph. The following columns were used: column A (glass), 4 ft × 4 mm (i.d.), 2.5% SE-30 on 80–100 mesh Chromosorb W; column B (stainless steel), 6 ft × 0.25 in, 3% SE-30 on 80–100 mesh Chromosorb W; column C (stainless steel), 6 ft × 1/8 in, 3% SE-30 on 80–100 mesh Chromosorb W; column D, same as column C but 10 ft; column E (glass), 8 ft × 8 mm (i.d.), 5% Silicone DC-550 on 80–100 mesh Chromosorb W. The pure isolated compounds were reinjected into the VPC instrument and found to be stable under our analysis conditions. The product percentages in Table I and the yields were obtained using area/weight response factors with *p*-chloronitrobenzene as an internal standard. A 275-W sunlamp was used for ultraviolet illumination.

Reaction of Bromine with Ethyl Sorbate (1) in Methanol. To 407 mg (2.9 mmol) of **1** in 4.6 g of anhydrous methanol at 0 °C was added 158 mg (1.0 mmol) of bromine dissolved in 1.0 mL of carbon tetrachloride with stirring. The mixture was stirred for 45 min and then poured into water, extracted with methylene chloride, and dried over anhydrous $MgSO_4$. Analysis by VPC on column A at 70 °C showed products (73%) **2b, 3b, 4b, 5b, 6b,** and **7b** with retention times of 5.6, 7.7, 11, 13, 15, and 19 min, respectively. These compounds, except **3b,** were isolated by preparative VPC on column B. We were unable to isolate the labile product **3b** but assigned it the α,β structure based on its conversion to **3a,** as described below. Spectral data for the γ,δ- and α,δ-dibromo products **6b** and **7b** have been reported previously.[2] The remaining products gave the following spectral properties. **2b:** IR(CCl_4) 2990 (CH), 1750 (C=O), 1445, 1370, and 1300 (CH), 1250 and 1175 (C–O), 1140, 1085, 960 (C=CH), 850 cm^{-1}; NMR (CCl_4) δ 1.30 (t, J = 7.2 Hz, 3 H), 1.81 (d, J = 6.2 Hz, 3 H), 3.23 (s, 3 H), 3.83 (d, J = 3.2 Hz, 1 H), 3.9–4.4 (m, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.2–5.9 (m, 2 H).

4b: IR (CCl_4) 2990 (CH), 1720 (C=O), 1655 (C=C), 1440 and 1365 (CH), 1260 and 1160 (C–O), 1030, 970 (C=CH), 850 cm^{-1}; NMR (CCl_4) δ 1.33 (t, J = 7.5 Hz, 3 H), 1.70 (d, J = 6.4 Hz, 3 H), 3.39 (s, 3 H), 3.4–3.9 (m, 1 H), 3.95–4.4 (m, 1 H), 4.22 (q, J = 7.5 Hz, 2 H), 6.05 (d, J = 16.0 Hz, 1 H), 6.44 (dd, J = 16.0 and 6.4 Hz, 1 H).

5b: IR (CCl_4) 2990 (CH), 1725 (C=O), 1655 (C=C), 1445, 1370, and 1310 (CH), 1260 and 1150 (C–O), 1090, 1030, 970, 800 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.27 (d, J = 6.2 Hz, 3 H), 1.31 (t, J = 7.1 Hz, 3 H), 3.40 (s, 3 H), 3.4–3.8 (m, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 4.4–4.7 (five peak multiplet, 1 H), 6.01 (d, J = 15.5 Hz, 1 H), 6.97 (dd, J = 15.5 and 9.2 Hz, 1 H).

Reaction of *N*-Bromosuccinimide with 1 in Methanol. To 500 mg (3.57 mmol) of **1** in 5.6 of anhydrous methanol at 0 °C was added 130 mg (0.73 mmol) of NBS. The reaction mixture was stirred for 60 min, poured into water, extracted with methylene chloride, and dried over anhydrous $MgSO_4$. Analysis by VPC on column C at 120 °C gave products (61%) **2b, 3b, 4b,** and **5b** with retention times of 8.5, 11, 15, and 16 min, respectively.

Reaction of Methyl Hypobromite with 1. Ionic Conditions. To 700 mg (5.0 mmol) of **1** in 10 mL of anhydrous methanol at 0 °C was added 1.3 mL of a 0.76 M methyl hypobromite solution in carbon tetrachloride with stirring. The reaction mixture was stirred for 20 min. Analysis by VPC of this mixture on column C at 120 °C gave products **2b, 3b, 4b,** and **5b** with retention times of 7, 9, 12, and 13 min, respectively. The spectral properties of these products are given above.

Reaction of Methyl Hypobromite with 1. Radical Conditions. To 700 mg (5.0 mmol) of neat **1** at 0 °C, irradiated with UV light, was added 1.3 mL of a 0.76 M methyl hypobromite solution in carbon tetrachloride. The reaction was complete in 5 min. Analysis by VPC on column D at 120 °C gave products **8b, 3b, 4b,** and **5b** with retention times of 8, 9, 12, and 13 min, respectively. Compound **8b** was not isolated, but its structure is based on its reactivity and conversion to **8a,** as described below. Product **5b** was shown to be a 60:40 mixture of erythro–threo isomers by VPC and NMR analysis. The erythro and threo isomers of **5b** were not completely resolved but had retention times of 24 and 25 min on column D at 105 °C. The 100-MHz NMR ($CDCl_3$) spectra showed a difference in the β-vinyl hydrogens as follows: *erythro*-**5b,** δ 6.97 (dd, J = 15.5 and 9.2 Hz); *threo*-**5b,** δ 7.00 (dd, J = 15.5 and 9.2 Hz).

Reaction of the Product Mixture from Methyl Hypobromite with Lithium Chloride. To 358 mg (1.43 mmol) of **8b, 3b,** and **5b** in a ratio of 1.6:1.0:6.4, respectively, with *p*-chloronitrobenzene as an internal standard in 5 mL of dimethyl sulfoxide at 25 °C was added 304 mg (7.15 mmol) of lithium chloride. Aliquots were withdrawn, added to water, extracted with methylene chloride, and dried over anhydrous magnesium sulfate. Analysis by VPC on column D showed that **8b** was converted quantitatively to **8a** in less than 5 min, while **3b** was converted in ca. 90% yield to **3a** after 25 min. The reaction of **5b** to **5a** with lithium chloride was less than 20% complete after 24 h under these conditions.

Reaction of Chlorine with 1 in Methanol. To 560 mg (4.0 mmol) of **1** in 6.5 g of anhydrous methanol was added 1.0 mL of a 0.80 M chlorine solution in carbon tetrachloride. The reaction mixture was stirred for 45 min at 0 °C and then worked up as described above for bromine in methanol. Analysis by VPC on column D at 110 °C gave products (56%) **2a, 4a,** and **5a** with retention times of 11, 14, and 17 min, respectively. The products had the following spectra. **4a:** IR (CCl_4) 2985 (CH), 1725 (C=O), 1655 (C=C), 1445 and 1365 (CH), 1260 and 1170 (C–O), 1085, 1030, 970 (C=CH), 850 cm^{-1}; NMR (CCl_4) δ 1.30 (t, J = 7.2 Hz, 3 H), 1.47 (d, J = 6.4 Hz, 3 H), 3.36 (s, 3 H), 3.6–4.2 (m, 3 H), 4.20 (q, J = 7.2 Hz, 2 H), 6.00 (dd, J = 0.6 Hz), 6.80 (dd, J = 15.2 and 6.0 Hz, 1 H).

5a: IR (CCl_4) 2990 (CH), 1725 (C=O), 1665 (C=C), 1450, 1370, and 1310 (CH), 1260 and 1170 (C–O), 1090, 1035, 975 cm^{-1}; NMR (CCl_4) δ 1.26 (d, J = 6.2 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 3.41 (s, 3 H), 3.4–3.8 (m, 1 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.3–4.7 (m, 1 H), 6.08 (dd, J = 15.2 and 0.6 Hz, 1 H), 6.90 (dd, J = 15.2 and 7.2 Hz, 1 H).

Reaction of Methyl Hypochlorite with 1. Ionic Conditions. To 1.14 g (8.13 mmol) of **1** in 13 g of anhydrous methanol at 0 °C was added 1.0 mL of a 1.62 M methyl hypochlorite solution in methylene chloride. The reaction mixture was stirred for 45 min and analyzed by VPC on column D at 100 °C (99%): **2a, 8a, 4a,** and **5a** were obtained, and the percent yields are given in Table I. The 1,4-products **2a** and **8a** have the same retention times on columns A–D, and **2a** was therefore collected as a mixture. This mixture gave an IR spectrum similar to **8a.** The NMR (CCl_4) spectrum differed from **8a** in that a doublet (J = 7.0 Hz) for the methyl substitutent on the δ carbon was observed at δ 1.40 for **2a.**

Reaction of Methyl Hypochlorite with 1. Radical Conditions. To 1.14 g (8.13 mmol) of neat **1** at 0 °C, irradiated with UV light, was added 1.0 mL of a 1.62 M methyl hypochlorite solution in methylene chloride. The reaction was stirred for 45 min at 0 °C. Analysis by VPC on column D at 110 °C gave products (72% yield) **8a, 3a,** and **5a** in a ratio of 1.2:1.0:3.7, respectively. Product **5a** was shown to be a 60:40 mixture of erythro–threo **5a** isomers, respectively, by VPC and NMR analysis. Retention times were 16 and 17 min for *threo*- and *erythro*-**5a.** The NMR (CCl_4) spectrum of the erythro–threo **5a** mixture was similar to that reported for *erythro*-**5a** above except for the vinyl hydrogen of *threo*-**5a** [δ 6.95 (dd, J = 15.2 and 6.8 Hz)].

Products **3a** and **8a** were isolated pure by preparative VPC on column E and gave the following spectral data. **3a:** IR (CCl_4) 2990 (CH), 1760 (C=O), 1450 and 1370 (CH), 1265 and 1180 (C–O), 1130, 1020, 955, 850 cm^{-1}; NMR (CCl_4) δ 1.28 (t, J = 7.0 Hz, 3 H), 1.58 (d, J = 6.6 Hz, 3 H), 3.37 (s, 3 H), 4.15 (q, J = 7.0 Hz, 2 H), 4.0–4.7 (m, 2 H), 5.6–6.2 (m, 2 H).

8a: IR (CCl_4) 2980 (CH), 1750 (C=O), 1450 and 1375 (CH), 1255 (C–O), 1180, 1155, 1095, 1025, 965, 850 cm^{-1}; NMR δ 1.20 (d, J = 6.0 Hz, 3 H), 1.30 (t, J = 6.8 Hz, 3 H), 3.23 (s, 3 H), 3.3–3.8 (m, 1 H), 4.20 (q, J = 6.8 Hz, 2 H), 4.5–4.8 (m, 1 H), 5.6–6.0 (m, 2 H).

Reaction of the Product Mixture from Methyl Hypochlorite with Sodium Bromide. To 87 mg (0.42 mmol) of **8a, 3a,** and **5a** in a

ratio of 1.1:1.0:3.5, respectively, with *p*-chloronitrobenzene as a standard in 10 mL of acetone was added 2.5 g of sodium bromide. The mixture was refluxed, and after 40 h **8a** was converted to **8b** in 74% yield. Products **3a** and **5a** did not react under these conditions.

Reaction of Methyl Hypochlorite with *cis,trans*-Ethyl Sorbate Under Molecule-Induced Homolysis Conditions. To 215 mg (1.53 mmol) of *cis,trans*-ethyl sorbate[11] at 0 °C in the dark was added 0.7 mL of 0.495 M methyl hypochlorite solution in carbon tetrachloride.[12] After 3 h at 0 °C, VPC analysis on column C at 50 °C showed that only 1.8% of **1** was formed from *cis,trans*-ethyl sorbate during this reaction. This experiment shows that return to the starting diene from intermediates **11b** and **11d** is a very minor component in this reaction pathway. Therefore, the product percentages in Table I very nearly represent the kinetic product ratio for these radical reactions. Analysis on column C at 105 °C gave products (38% yield) **8a**, **3a**, and *cis*-**5a** in a ratio of 4.5:1.0:1.6, respectively.[13] Products **8a** and *cis*-**5a** were a 60:40 ratio of erythro–threo isomers. Compound **3a** was a broad peak in the VPC analysis, but the erythro–threo isomers were not resolved under these conditions.

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Registry No.—**1**, 5941-48-0; *cis,trans*-**1**, 53282-25-0; **2a**, 66017-96-7; **2b**, 65996-25-0; **3a**, 65996-26-1; **3b**, 65996-27-2; **4a**, 65996-28-3; **4b**, 65996-29-4; *erythro*-**5a**, 65996-30-7; *threo*-**5a**, 65996-31-8; (*Z*)-*erythro*-**5a**, 65996-32-9; (*Z*)-*threo*-**5a**, 65996-33-0; *erythro*-**5b**, 65996-34-1; *threo*-**5b**, 65996-35-2; **6b**, 65996-36-3; **7b**, 62006-45-5; *erythro*-**8a**, 65996-37-4; *threo*-**8a**, 65996-38-5; **8b**, 65996-39-6.

References and Notes

(1) (a) Point Loma College; (b) Bethany Nazarene College.
(2) D. F. Shellhamer, V. L. Heasley, J. E. Foster, J. K. Luttrull, and G. E. Heasley, *J. Org. Chem.*, **42**, 2141 (1977).
(3) Alkyl hypochlorites and hypobromites react by an ionic process in a protic solvent or in a nonpolar aprotic solvent when an acid catalyst is used. In aprotic solvents without an acid catalyst, or in neat olefin or diene, a rapid radical reaction (molecule-induced homolysis) is observed. See (a) G. E. Heasley, V. L. Heasley, D. F. Shellhamer, W. E. Emery III, R. Hinton, and S. L. Rodgers, *J. Org. Chem.*, in press; (b) G. E. Heasley, V. M. McCully, R. T. Wiegman, V. L. Heasley, and R. A. Skidgel, *ibid.*, **41**, 644 (1976); (c) C. Walling and R. T. Clark, *ibid.*, **39**, 1962 (1974); (d) D. F. Shellhamer, D. B. McKee, and C. T. Leach, *ibid.*, **41**, 1972 (1976).
(4) (a) The IR stretching frequency of a double bond in conjugation with a carbonyl is very strong; see R. T. Conley, "Infrared Spectroscopy", Allyn and Bacon, Boston, Mass., 1966, p 99. The nonconjugated double-bond frequency was too weak to be observed at normal concentration of the products. (b) NMR spectral shifts of the β-vinyl hydrogen on the α,β-unsaturated products **4a,b**, **5a,b**, and **6a,b** appear at 0.4–0.9 ppm downfield relative to the α-vinyl protons in these products. Our data show that the protons of a methyl group on the δ carbon in the NMR spectrum resonate at 1.2–1.3 ppm when a methoxy substituent is on the δ carbon, while a halogen on that carbon lowers the chemical shift to 1.4–1.8 ppm. A vinyl methyl appears at 1.28 ppm.
(5) Bimolecular substitution is greatly accelerated when a carbonyl is α to the leaving group; see E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1959, p 284.
(6) The absence of any 1,2 product (**3a**) from addition of chlorine electrophiles to **1** is curious. Addition of chlorine to butadiene in methanol gives only ca. 30% of 1,4 products, while addition to the 1,2 bond in *cis*- and *trans*-1,3-pentadienes gives predominately 1,4 products. See ref 3b.
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(8) The 4% of **4b** formed with methyl hypobromite may be due to a minor ionic component in this reaction.
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(11) *cis,trans*-Sorbic acid was donated by Keith H. Hollenback, University of Oklahoma. The acid was treated with ethanol and boron trifluoride as catalyst to give *cis,trans*-ethyl sorbate.
(12) The *cis,trans*-ethyl sorbate was chosen since the intermediate **11b** destroys a cis α,β bond and would therefore be a sensitive test for a reversible intermediate. Return to the starting diene from **11b** gives back the resonance stabilization energy of a diene to a carbonyl. This molecule-induced homolysis reaction was done in the dark because UV illumination isomerized *cis,trans*-ethyl sorbate to **1**. Reaction of neat **1** with or without UV illumination did not change the product ratio.
(13) Compound **8a** rather than **5a** is the major product when methyl hypochlorite is added to *cis,trans*-ethyl sorbate. Perhaps the cis α,β bond is more reactive than the trans α,β bond of **1**.

Solid–Liquid Phase-Transfer Catalysis by a Quaternary Ammonium Salt. A Comparison with Crown Ethers and Polyalkylamines

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Aliquat 336, a quaternary ammonium salt, has been used as a phase-transfer catalyst for the solid–liquid interface. A comparison of its catalytic ability with that of 18-crown-6 ether and tetramethylethylenediamine has been made. The quaternary ammonium salt is equivalent to and in many cases markedly superior to both crown ether and tetramethylethylenediamine for catalyzing acetate, fluoride, and adeninyl anion displacement reactions. However, the cyanide anion reacts at least 100 times faster when catalyzed by crown ether relative to the quaternary salt.

Crown ethers,[1] polyamines,[2] and ammonium and phosphonium salts[3] have been established as unique and effective catalysts for anionic reactions during the last 10 years. All three of these types of catalysts derive synthetic utility from their ability to solubilize inorganic reagents (and salts) in aprotic nonpolar organic solvents. The anions of these solubilized salts possess tremendous nucleophilicity as a result of a high degree of ionic dissociation[4] and at the same time they lack any significant solute–solvent interaction. The result of this phenomenon is the ability to use inorganic reagents in organic solvents to perform a variety of synthetic reactions[1-3] which would otherwise require more drastic, less desirable conditions.

Although the principles for the catalytic ability of these classes of compounds are similar, the application of each class has until now been different. The crown ethers and polyamines function by complexing with an insoluble reagent rendering the entire entity soluble. The quaternary ammonium salts have traditionally only been used to extract the anions of salts from an aqueous solution into an organic phase for subsequent reaction with a dissolved electrophile. Herein we report our results on the ability of a quaternary ammonium salt (Aliquat 336, Q^+)[5] to function as a phase-transfer catalyst

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Table I. A Comparison of the Ability of Q^+, 18-Crown-6, and TMEDA to Catalyze the Reaction

$$PhCH_2Cl\ (1\ M) + KN \xrightarrow[\text{acetonitrile}]{\text{catalyst}} PhCH_2N + KCl$$

N^- (2.0 equiv)	Registry no.	Catalyst (0.1 equiv)	Registry no.	Half-life, h
CH_3CO_2 (rt)	71-50-1	Q^+	5137-55-3	0.75
		CE	17455-13-9	1.15
		TMEDA	110-18-9	1.30
CN (83 °C)[b]	57-12-5	Q^+		2.2
		CE		0.03
		TMEDA		1.1
F (83 °C)[b]	16984-48-8	Q^+		42
		CE		147
		TMEDA		107
Ad[a] (rt)	50339-88-3	Q^+		1.18
		CE		6.63
		TMEDA		3.23
		NONE		41

[a] Ad^- is the adeninyl anion prepared from adenine and potassium hydroxide. The products obtained from the alkylation of the adeninyl anion under such conditions will be discussed in a forthcoming publication. [b] These reactions also proceed well at room temperature and the trends do not change.

between a *solid–liquid* interface. In this regard it is performing "crown ether type" chemistry.

We have also compared the catalytic efficiency of Q^+ with that of 18-crown-6 (CE) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)[2a] for transporting the acetate,[2a,6] fluoride,[7] cyanide,[2a,8] and adeninyl anions from the crystalline state into an organic solvent. *The data indicate that Q^+ is equivalent to, and in most cases markedly superior to, both CE and TMEDA* (see Tables I and II). However, this trend is dramatically reversed in the case of the cyanide anion.[9,10]

The function of Q^+ in these reactions is to exchange the alkali metal cation for a soluble quaternary ammonium ion. The new quaternary ammonium salt is much more dissociated in the organic phase than the alkali metal salt and therefore much more reactive for displacement reactions. After the chemical reaction occurs, a new Q^+X^- is formed and available for another catalytic performance. The reason for the faster reactions with Q^+ vs. CE and TMEDA is either an enhanced nucleophilicity of the dissolved anion or a greater efficiency in transporting the anion into the organic phase (or both) and must be established experimentally.

Q^+ offers the flexibility of catalyzing reactions in both liquid–liquid and solid–liquid systems at least as well as crown ethers. Furthermore, it overcomes all of the disadvantages accompanying crown ether catalysis. For example, the catalytic ability of *Q^+ is applicable to all cationic species* whereas a specific crown should be chosen for each cation[11] (15-crown-5 for Li^+, 16-crown-5 for Na^+, 18-crown-6 for K^+, etc.) for optimum performance. For those reactions which are particularly slow, greater amounts of Q^+ may be employed since it is soluble in all proportions in all organic solvents; most crown ethers have solubility limits in several solvents. Finally, Q^+ is cheap[5] (3¢/10 g vs. $15/10 g of 18-crown-6) and perhaps most important it is nontoxic.[12] For these reasons we consider Q^+ the phase-transfer catalyst of choice and hope to see many new applications of this versatile catalyst.

Experimental Section

All reactions within a series were done under identical conditions.

Table II. A Comparison of the Ability of Q^+, 18-Crown-6, and TMEDA to Catalyze the Reaction

$$CH_3(CH_2)_4CH_2Br\ (1.0\ M) + KN \xrightarrow[\text{acetonitrile}]{\text{catalyst}} CH_3(CH_2)_4CH_2N + KBr$$

N^- (2.0 equiv)	Catalyst (0.1 equiv)	Half-life, h
CH_3CO_2 (83 °C)[b]	Q^+	0.11
	CE	0.13
	TMEDA	0.15
CN (83 °C)[b]	Q^+	0.98
	CE	0.57
	TMEDA	1.26
Ad[a] (83 °C)	Q^+	0.33
	CE	0.42
	TMEDA	0.54

[a,b] See footnotes *a* and *b* for Table I.

All products were shown to be stable to the reaction conditions. The certainty of anhydrous conditions, and thus a truly solid–liquid system, was assured by slurrying the potassium salt (predried), catalyst, and solvent (sieve dried) with powdered 4A molecular sieves for 24 h prior to adding the alkylating agent. This procedure also ensured that the particle size of the salts was uniformly fine. The values for the half-lives were obtained by removing a small aliquot from the reaction mixture, centrifuging the sample, and analyzing the centrifugate for both starting material and product[13] by GC.[14] A few samples around the 50% conversion point were taken and the half-life was determined by assuming that pseudo-first-order kinetics was operative. Values obtained in this fashion were quite consistent with each other and varied by less than 10%. Conversions greater than 95% and yields above 90% were obtained for those reactions which were continued to completion. Only substitution reactions were observed for hexyl bromide with all three catalysts; elimination did not compete to any significant degree.

A typical procedure follows: A 25-mL flask was charged with 10 mL of acetonitrile containing 1.0 mmol of phase-transfer catalyst (from a 0.1 M stock solution stored over 4A molecular sieves), 20 mmol of potassium OAc^-, CN^-, F^-, or Ad^- (oven dried, vacuum desiccator stored), and 0.5 g of powdered 4A molecular sieves (<3% loss on drying). The vessel was sealed and the mixture was magnetically stirred for 24 h and then the alkylating agent was charged. GC analysis, as described, was used to determine the half-life for conversion of the starting material to product. Replicate experiments were always within ±10%; half-life data are found in Tables I and II.

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(9) The difference in the catalytic ability is even more pronounced at 25 °C: Q^+, $t_{1/2}$ = 34 h; TMEDA, $t_{1/2}$ = 27 h; CE, $t_{1/2}$ = 0.33 h! A possible explanation for the slower rates with cyanide and Q^+ is the low efficiency of the quaternary ammonium salt to solubilize cyanide relative to other nucleophiles. The K_{eq} for Q^+Cl^- and KOAc is 1.76×10^{-2} and K_{eq} for Q^+Cl and KCN is 0.25×10^{-2}. These values were determined by slurrying the reaction mixture (minus alkyl halide) for 1 h, filtering, and titrating the filtrate for chloride.

(10) Other workers have reported that tetrabutylammonium halides are about as reactive as crown ether complexed halides. See D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.*, **96**, 2252 (1974).

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(13) Except for the adenine alkylations where the product was not volatile. In those examples mesitylene was used as an internal standard and the rate of alkylation was determined only by monitoring the disappearance of alkylating agent.
(14) Analyses were performed on a Hewlett-Packard Gas Chromatograph Model 5830A using a 6-ft column packed with 3% SE-30.

Ozonation of Nucleophiles. 8. Secondary Amines[1]

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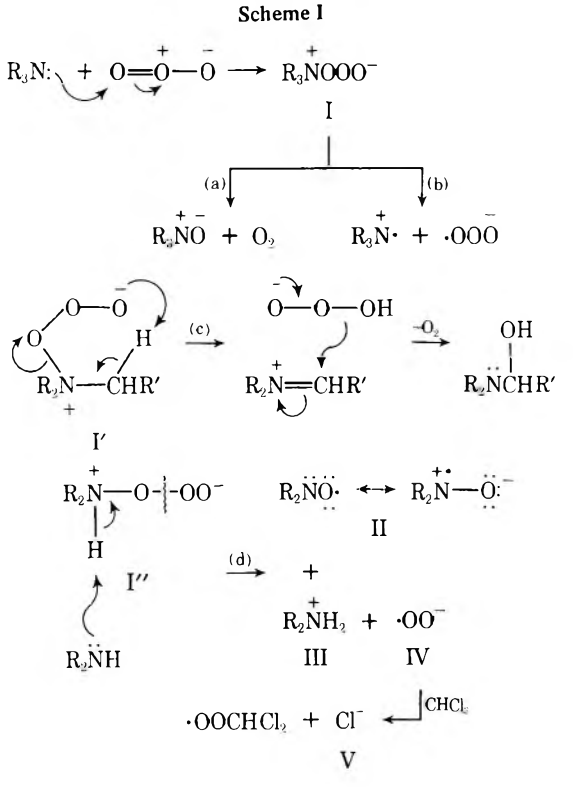
Secondary amines react with ozone via two major routes, one involving nitroxide and ammonium salt formation and the other involving side-chain oxidation. The first appears to be the only reaction type with di-*tert*-butylamine and the major route with diisopropylamine. Side-chain oxidation is the major route with di-*n*-butylamine. Detailed mechanisms are proposed based on present findings and theories developed in earlier studies with primary, secondary, and tertiary amines bearing primary, secondary, and/or tertiary alkyl groups.

Previous papers in this series have been concerned with ozonations of various primary, secondary, and tertiary amines,[2-7] as well as with a similar study regarding certain dialkyl sulfides.[1] Studies with primary amines having primary, secondary, and tertiary alkyl substituents have been published,[2,4,7] but the only secondary and tertiary amines so far included are di-*tert*-butylamine,[5] tri-*n*-butylamine,[2,3] and 1-di-*n*-butylamino-2-butanone.[3] These investigations have led to the proposal of four competing fates (Scheme I) for the initially formed ozone–amine adduct (I). The equations representing these fates (a–d, Scheme I) depict only the initial steps; additional reactions generally follow.

The present paper describes ozonations of diisopropylamine and di-*n*-butylamine and completes and summarizes our studies concerning secondary amines possessing primary, secondary, and tertiary alkyl substituents, as did our earlier paper[7] with primary amines.

The ozonations of diisopropylamine were performed with

Scheme I



1 mol of amine in chloroform (at −65 °C), methylene chloride (−78 °C) and carbon tetrachloride (−20 °C). Ozone reacted quantitatively and the molar ratio of ozone to amine reacting was approximately 2 in the chloroform and methylene chloride reactions and 1 in the carbon tetrachloride reaction. The molecular oxygen yield was 0.7–0.9 mol/mol of ozone reacting. These and other results are shown in Table I, along with results from ozonation of diisopropylhydroxylamine.

The results in chloroform solvent (experiment 1, Table I) were similar to those obtained with di-*tert*-butylamine in the same solvent,[5] with the exception that the nitroalkane yield was only about half as high as with di-*tert*-butylamine and that obvious side-chain oxidation products were obtained. A major product was diisopropylammonium chloride, analogous to findings with di-*tert*-butylamine[5] (as well as with primary amines[7]). However, the ratio of salt to nitro compound was greater than 1 with diisopropylamine but less than 1 with di-*tert*-butylamine.[5] The origin of the salt was shown to be fate d (Scheme I, R = *i*-Pr), as found also for di-*tert*-butylamine,[5] rather than the cation radical–ozonate anion radical route (fate b, Scheme I) characteristic of primary amines.[7] EPR studies, in pentane at −100 °C, Freon 11 at −120 °C, or the neat amine at −70 °C, gave no indication of the ozonate anion radical but showed a strong nine-line signal characteristic of diisopropyl nitroxide (II, Scheme I, R = *i*-Pr)[8] (cf. ref 5). Other workers also have shown that dialkyl or diaryl nitroxides are produced in the first stage of ozonation of secondary amines.[9]

The ozonations of di-*tert*-butylamine in chloroform, to give di-*tert*-butyl nitroxide (II, R = *t*-Bu) and di-*tert*-butylammonium chloride (III + V, Scheme I, R = *t*-Bu), and of di-*tert*-butyl nitroxide to give 2-methyl-2-nitropropane and other products, were described in previous papers.[5,6] Equation 1 describes the overall results.[5]

$$8t\text{-Bu}_2\text{NH} + 14\text{O}_3 + 6\text{CHCl}_3 \rightarrow 4t\text{-BuNO}_2 + 4t\text{-Bu}_2\text{NH}_2^+\text{Cl}^- + 2t\text{-BuOH} + 2\text{Me}_2\text{C=O} + 6\text{Cl}_2\text{C=O} + \text{Cl}_2 + \text{CH}_3\text{OH} + \text{H}_2\text{C=O} + 2\text{H}_2\text{O} + 10\text{O}_2 \quad (1)$$

Reactions analogous to most of those leading to eq 1 (eq 7–10, ref 5 and 6–8, ref 6) would also be expected to occur during ozonations of diisopropylamine and diisopropyl nitroxide, with, however, different weightings and certain additions, the principal one of which has to do with the difference in stabilities of the dialkyl nitroxides involved. Dialkyl nitroxides

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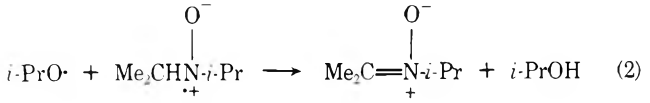
Table I. Ozonation of Diisopropylamine

Expt	Solvent[a]	Temp, °C	O_3/amine reacting[b]	O_2/O_3 evolved[c]	*i*-$Pr_2NH_2^+Cl^-$[d]	$Me_2C{=}N$-*i*-Pr[d]	$CH_3C(=O)N(-H)$-*i*-Pr[d]	$Me_2C{=}O$[d]	*i*-$PrNO_2$[d]	*i*-PrN(O)N(O)-*i*-Pr[d,e]	$Me_2C{=}NOH$[d]	*i*-$PrNH_2$[d]	Other[d]	% accounting[d] for fragments: N[f]	% accounting[d] for fragments: *i*-Pr[g]
1	$CHCl_3$[h]	−65	2.1	0.7	36	3	2	50	27	5	9	6	3[i]	93	94
2	CH_2Cl_2[h]	−78	2.1	0.9	17	4	3	59	23	7	18	17	*j*	96	90
3	CCl_4	−20	1.1	0.8	24	10	4	33	12	0	0	0	3[i] 4[k,l]	54	67
4	$CHCl_3$[m]	−65	1.0[m]	0.5	31[m]	0	0	38	14	*n*	0	0	*o*	45	57

[a] In the first two experiments 20 mmol of amine in 20 mL of solvent was employed. In the other experiments, 3–10 mmol of amine in 5–15 mL of solvent was used. [b] In each case 1 mmol of ozone (in a nitrogen stream) per mmol of starting amine was used and reacted completely. Unreacted amine was determined and the ratio is that of O_3 to amine reacting. [c] Moles of molecular oxygen evolved per mole of ozone reacting. These values were obtained in separate, smaller experiments. [d] Percentage yields based on amine used up, rounded off to the nearest whole number. [e] 2-Nitrosopropane dimer. [f] The N fragment accounting includes amine salt, imine, amide, 2-nitropropane, 2-nitrosopropane dimer, acetone oxime, and isopropylamine. [g] The isopropyl group accounting is based on two isopropyl groups in the starting amine and includes all products shown. [h] The values in these experiments are averages of two experiments. [i] 2-Propanol. [j] Not determined. [k] Active oxygen containing material, possibly 2-isopropyl-3,3-dimethyloxazirane. [l] A small amount of triisopropylurea was isolated. [m] In this experiment the starting amine was diisopropylhydroxylamine and the corresponding hydrochloride was a product. Here, yields are based on starting amine because no method was found for determining unreacted hydroxylamine. This is one reason why the accounting is low. [n] Present. [o] 2-Propanol was identified by GLC.

possessing primary or secondary alkyl groups are much less stable than those with tertiary alkyl groups and are susceptible to attack by radicals to give the corresponding nitrones (VI).[10,11] Thus, the isopropoxide radical would be expected to react as shown in eq 2, rather than to attack the solvent or



i-PrO· + $Me_2CHN^{\cdot+}$-*i*-Pr → $Me_2C{=}N^{+}$-*i*-Pr + *i*-PrOH (2)

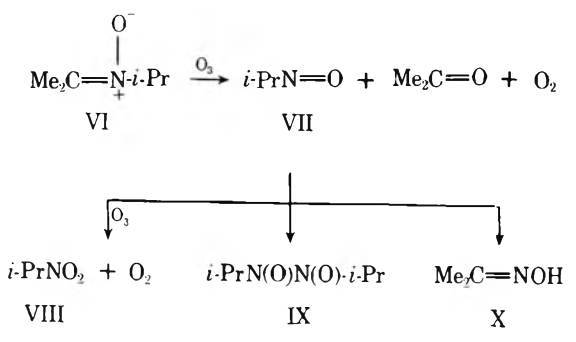
VI

to decompose, as suggested for the *tert*-butoxy radical during the ozonation of di-*tert*-butyl nitroxide.[6] Similar reactions would also be expected for radicals such as ·OOH (to give VI + HOOH) and ·$OOCHCl_2$ (to give VI + $HOOCHCl_2$, followed by $HOOCHCl_2 \rightarrow HOH + O{=}CCl_2$).

Ozonation of nitrone VI should lead to acetone and 2-nitrosopropane (VII), as illustrated in Scheme II.[12] A pale blue color, characteristic of the nitroso compound, was observed throughout the ozonation of diisopropylamine. Various fates of the nitrosopropane (VII) include oxidation by ozone to 2-nitropropane (VIII), dimerization to IX, and isomerization to acetone oxime (X).

In addition to these reactions, reactions such as expressed by eq 3, not previously considered,[5] would be expected to occur during ozonations of both diisopropylamine and di-*tert*-butylamine, since the superoxide anion radical (IV) should behave not only as a nucleophile,[13–16] as previously considered in its attack on the solvent[5] (Scheme I), but also as a base.

Scheme II



$$\cdot OO^- + i\text{-}Pr_2NH_2^+ \rightarrow i\text{-}Pr_2\overset{\cdot\cdot}{N}H + \cdot OOH \quad (3)$$

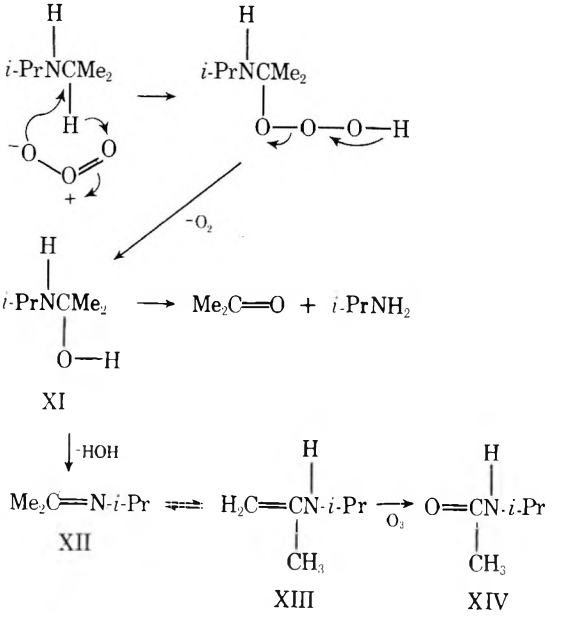
IV

Judicious weightings of these various indicated reactions, along with the likelihood of some oxidation by ozone of isopropyl alcohol to acetone, leads to summation eq 4, which furnishes a reasonably accurate accounting for the products obtained by the nitroxide pathway (fate d, Scheme I, R = *i*-Pr) during ozonation of diisopropylamine.

$$\begin{aligned} 14i\text{-}Pr_2NH + 25O_3 + 6CHCl_3 \rightarrow\ & 6i\text{-}Pr_2NH_2^+Cl^- \\ & + 4i\text{-}PrNO_2 + 7Me_2C{=}O + i\text{-}PrOH \\ & + 2Me_2C{=}NOH + i\text{-}PrN(O)N(O)\text{-}i\text{-}Pr \\ & + 6Cl_2C{=}O + 7H_2O + 21O_2 \end{aligned} \quad (4)$$

Along with the products shown in eq 4 were obtained side-chain oxidation products (Table I, experiment 1). These are rationalized in Scheme III. 1,3-Dipolar insertion[17] is chosen over fate c (Scheme I) for the initiating reaction because of recent results with diisopropylethylamine[18] which showed

Scheme III



that when secondary alkyl groups are present, the less acidic tertiary hydrogen atoms are attacked in preference to secondary hydrogens. Just the opposite should occur if fate c (Scheme I) were in operation. These reactions are summed up in eq 5, which, however, neglects the secondary reactions (XII → XIII → XIV, Scheme III).

$$2i\text{-Pr}_2\text{NH} + 2O_3 \rightarrow \text{Me}_2\text{C=O} + i\text{-PrNH}_2 + \text{Me}_2\text{C=N-}i\text{-Pr} + \text{H}_2\text{O} + 2O_2 \quad (5)$$

Combination of eq 4 and 5 results in eq 6 which fits quite well the experimental results shown in Table I for the ozonation of diisopropylamine in chloroform [cf. yields predicted by the equation, below each product, and the actual yields in Table I, keeping in mind that the yield of the imine (XII) predicted by eq 6 should also include the secondary product, amide XIV, of Scheme III]. The ratio of ozone to amine predicted by the equation is slightly low, but this is understandable since the ozonation of XIII is not included and since the slightly high predicted yields of 2-propanol and acetone oxime indicate that additional oxidation of these substances occurred.

$$\underset{(37.5)}{16i\text{-Pr}_2\text{NH}} + 27O_3 + 6\text{CHCl}_3 \rightarrow 6i\text{-Pr}_2\text{NH}_2^+\text{Cl}^- + \underset{(25)}{4i\text{-PrNO}_2} + \underset{(50)}{8\text{Me}_2\text{C=O}} + \underset{(6)}{i\text{-PrNH}_2} + \underset{(6)}{i\text{-PrOH}} + \underset{(12)}{2\text{Me}_2\text{C=NOH}} + \underset{(6)}{i\text{-PrN(O)N(O)-}i\text{-Pr}} + \underset{(6)}{\text{Me}_2\text{C=N-}i\text{-Pr}} + 6\text{Cl}_2\text{C=O} + 8\text{H}_2\text{O} + 23O_2 \quad (6)$$

XII

The results from ozonation of diisopropylamine in methylene chloride solution (experiment 2, Table I) differed from those in chloroform in two major respects: (1) the yield of diisopropylammonium chloride was cut in half; and (2) the yields of isopropylamine, acetone, and acetone oxime increased considerably in changing from chloroform to methylene chloride (Table I). This is understandable on the basis of the reasonable assumption that methylene chloride is less susceptible to nucleophilic attack than is chloroform, thereby increasing the importance of eq 3 at the expense of attack of IV on methylene chloride (cf. Scheme I). This was also found to be true during the di-*tert*-butylamine ozonations.[5] Further, the results indicate an increased importance of side-chain attack in methylene chloride.

The isolated yields of products from ozonation of diisopropylamine in carbon tetrachloride (experiment 3, Table I) were much lower than those in chloroform or methylene chloride. Some observations, however, can be made. The ozonation, in contrast to those in other solvents, appears to proceed without the formation of a 2-nitrosopropane intermediate, as evidenced by the absence of a blue coloration during the ozonation and of any nitrosopropane dimer or acetone oxime as products. This would appear to exclude reactions involving nitrone VI (Scheme II).

The amine oxide pathway (fate a, Scheme I) was not included as a possibility in any of the above discussions. By this route a secondary amine should produce the corresponding hydroxylamine (by rearrangement of the amine oxide).[5] Table I (experiment 4) shows data from the ozonation of diisopropylhydroxylamine. Although some of the same products resulted from the ozonations of both diisopropylamine and diisopropylhydroxylamine, the material balance from the latter was quite low. Since this was not true with the ozonation of diisopropylamine in chloroform or methylene chloride, it seems unlikely that the amine oxide route made more than a very minor contribution in these reactions. The amine oxide route is also eliminated in the ozonation of diisopropylamine in carbon tetrachloride since no blue color was observed. A blue coloration was evident throughout the ozonation of diisopropylhydroxylamine.

These considerations also cast doubt on the previous conclusion that the amine oxide route played a minor role (ca. 10%) in the ozonation of di-*tert*-butylamine.[5] Actually, the results of ozonation of di-*tert*-butylamine in chloroform at −60 °C[5] can be accounted for just as well by the nitroxide route (path d, Scheme I, R = *t*-Bu) alone if one includes, with proper weightings, the analogue of eq 3 and 7 with those which led to the development of eq 1.[5] Thereby, eq 8 can be developed (cf. yields predicted by the equation, below each product, with the actual yields of ref 5).

$$2(\cdot\text{OOH}) \rightarrow O_2 + 2(\cdot\text{OH}) \quad (7)$$

$$\underset{(43)}{14t\text{-Bu}_2\text{NH}} + 28O_3 + 10\text{CHCl}_3 \rightarrow 6t\text{-Bu}_2\text{NH}_2^+\text{Cl}^- + \underset{(57)}{8t\text{-BuNO}_2} + \underset{(29)}{4t\text{-BuOH}} + \underset{(29)}{4\text{Me}_2\text{C=O}} + 10\text{Cl}_2\text{C=O} + 2\text{CH}_3\text{OH} + 2\text{H}_2\text{C=O} + 2\text{Cl}_2 + 21O_2 + 4\text{HOH} \quad (8)$$

Ozonations of di-*n*-butylamine were performed in chloroform at −60 and 0 °C, methylene chloride at −60 °C, carbon tetrachloride at −25 °C, and pentane at −60 °C. As with diisopropylamine, 1 mol of ozone/mol of starting amine was employed (except in experiment 2 of Table II) and 0.7–0.9 mol of molecular oxygen was evolved/mol of ozone. The ozone, but not the amine, reacted quantitatively. The following ratios of ozone reacting to amine reacting were obtained: $CHCl_3$ and CH_2Cl_2, 1.4–1.5; pentane, 1.3; CCl_4, 1.1. These and other data are exhibited in Table II.

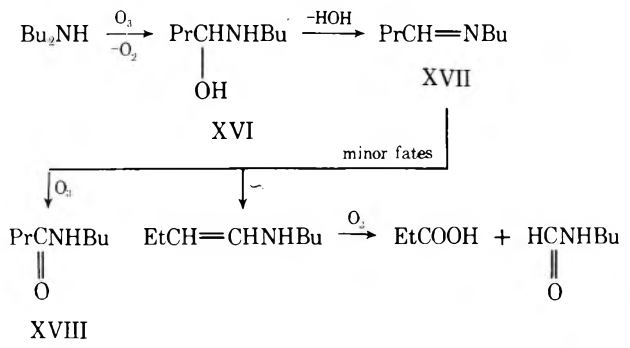
It is noteworthy that in comparison to the diisopropylamine and di-*tert*-butylamine[5] ozonation results, very low yields of nitroalkane and ammonium salt were obtained (except in experiment 2). The major products were *N*-*n*-butylidene-*n*-butylamine (XVII) and the corresponding nitrone (XV). The high butylideneamine yield is indicative of a greatly increased side-chain oxidation. We considered the possibility that the low ammonium salt and the high nitrone yields indicated that amine–ozone adduct fates a and b had replaced fate d (Scheme I) in the ozonation of di-*n*-butylamine. Fate a should result in di-*n*-butylhydroxylamine, which was shown to yield nitrone as a major product of ozonation. In deciding between fates b and d (Scheme I) we monitored the ozonation of di-*n*-butylamine by means of EPR. At −100 °C or below (in Freon 12), the principal radical produced was the ozonate anion radical (fate b, Scheme I). At −60 °C or higher, however, only the di-*n*-butyl nitroxide radical (II, R = *n*-Bu) was observed. Thus, we believe that fate d (rather than a and b) along with fate c (Scheme I) are the major ozonation routes with di-*n*-butylamine under our conditions (cf. other secondary amines).[5,9] The high nitrone yield is readily understandable on the basis that di-*n*-butyl nitroxide (II, R = *n*-Bu), having twice as many α hydrogens, should be more susceptible to attack by radicals (analogous to eq 2) than should diisopropyl nitroxide (II, R = *i*-Pr). In addition, nitrone XV apparently does not react appreciably with ozone under the conditions employed, whereas nitrone VI (from diisopropylamine) is consumed. This must be due to the greater electron density of the sp^2 carbon of VI in comparison to that of XV. Erickson et al.[12c] have shown that ozone attacks nitrones electrophilically. Thus, increased nitrone production also results in a decreased nitroalkane yield, due to the increased importance of (or total replacement by) radical attack on the nitroxide (analogous to eq 2) at the expense of ozonation of the nitroxide

Table II. Ozonation of Di-*n*-butylamine

Expt	Solvent, temp (°C)[a]	Ozone/amine reacting[b]	O_2/O_3-evolved, %[c]	PrCH=N-Bu, %[d]	PrCH-=N$^+$(—O$^-$)Bu, %[d]	Bu-NO_2, %[d]	Pr-CHO, %[d]	PrC-(=O)OH, %[d]	Bu_2N^+-H_2Cl^-, %[d]	PrC-(=O)-NH-Bu, %[d]	Other products, %[d]	% accounting[d] for fragments N[e]	Bu[f]
1	$CHCl_3$, −60	1.5	0.9	43	22	2	10	1	8	2	*g*	79	84
2	$CHCl_3$, −60	2.7[h]	~	3	0	28	36	4	14	4	*i*	49	55
3	$CHCl_3$, 0	1.4	0.7	65	15	6	13	*j*	6	*j*	*j*	92	96
4	CH_2Cl_2, −60	1.4	0.8	39	33	3	9	*j*	5	*j*	*j*	80	83
5	CCl_4, −25	1.1	0.8	55	0	*k*	9	*k*	8	*k*	*l*	63	67
6	Pentane, −60	1.3	0.8	74	*k*	*k*	6	4	0	4	*g*	78	83

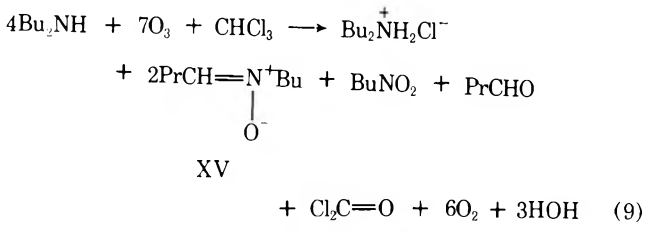
[a] The usual runs employed 5–20 mmol of amine and 2–3 mL of solvent/mmol of amine. [b] One mole of ozone per mole of amine was employed in all except experiment 2. The ozone reacted quantitatively, but not the amine in experiments 1, 3, 4, 5, and 6. The values are moles of ozone reacting per mole of amine reacting. [c] Moles of molecular oxygen evolved per mole of ozone reacting. [d] Percent yields based on amine reacting. [e] The N fragment accounting includes columns 5, 6, 7, 10, 11, and 12. [f] The butyl fragment accounting includes columns 5, 6, 10, and 11 at full value and columns 7, 8, 9, and 12 at half-value. [g] *N*-Butylformamide, 2%, and propionic acid in traces. [h] In this experiment excess ozone was employed and all of the amine reacted. [i] *N*-Butylformamide was present. [j] Not determined. [k] Present in traces. [l] *N*-Butylformamide present in traces.

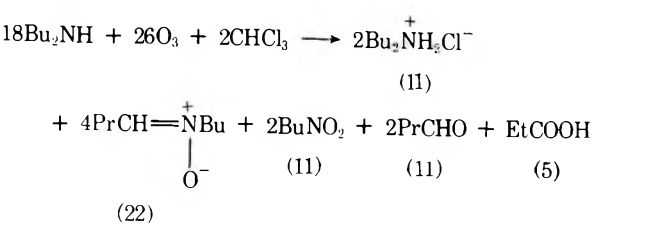
Scheme IV

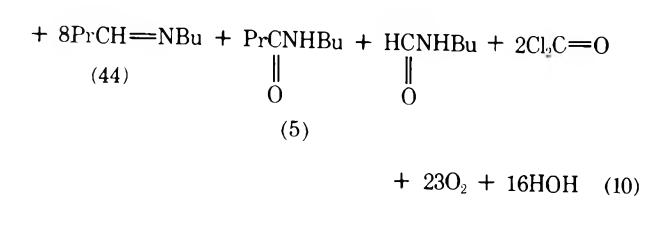


(reactions analogous to those leading to eq 1; see ref 5 and 6). The low ammonium salt yield reflects the increased importance of a reaction analogous to eq 3 in comparison to attack of the superoxide anion radical (IV) on the solvent (see fate d, Scheme I).

Applying these concepts to reactions analogous to those leading to eq 4, eq 9 can be developed as a satisfactory summary of the nitroxide route (fate d, Scheme I) in the ozonation of di-*n*-butylamine in chloroform with 1 molar equiv of ozone



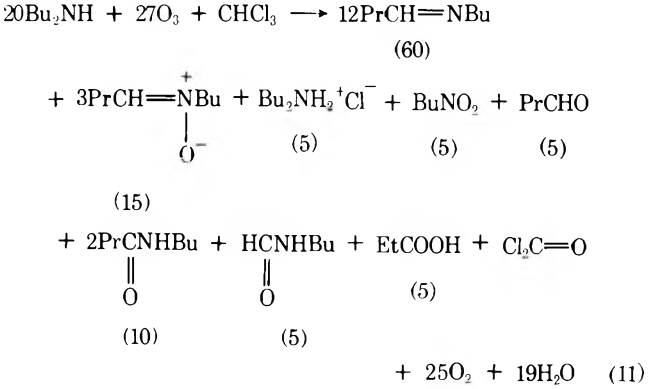




at −60 °C. Scheme IV outlines the side-chain oxidation processes competing with the nitroxide route. Oxidation of XVII to XVIII by ozone bears analogy to results from previous imine ozonations.[12] By combining eq 9 with the reactions of Scheme IV one can arrive at eq 10 as a summation of both routes competing in the ozonation of di-*n*-butylamine under the above conditions. The yields predicted by the equation (to be compared with experiment 1, Table II) are shown below each product in eq 10.

Experiment 2 of Table II portrays the results of ozonation of di-*n*-butylamine in chloroform at −60 °C with excess ozone. Here the nitrone (XV) reacted completely and the major product was 1-nitrobutane.

It is obvious from the results of experiment 3 of Table II that ozonation of di-*n*-butylamine in chloroform at 0 °C resulted in a greatly increased degree of side-chain attack. This is the expected result for side-chain attack via fate c of Scheme I.[3,7] By readjusting the weightings given the reactions utilized in developing eq 10, eq 11 can be obtained for the overall re-



sults in the 0 °C ozonation (experiment 3, Table II). A comparison of the predicted yields and actual yields (Table II) is satisfactory in most cases.

The results from ozonation of di-*n*-butylamine in methylene chloride at −60 °C (experiment 4, Table II) are puzzling. It is obvious that whereas in all other ozonations of di-*n*-butylamine (Table II) side-chain attack was predominant, in this experiment side-chain attack and the nitroxide route made approximately equal contributions. By analogy to ozonation results with tri-*n*-butylamine,[3] more side-chain attack should occur in methylene chloride than in chloroform.

The results with pentane (experiment 6, Table II) and carbon tetrachloride (experiment 5, Table II) solvents, how-

ever, are consistent with the tri-*n*-butylamine ozonation results and the mechanism of fate c (Scheme I) for side-chain attack.[3] In pentane, it appears that only side-chain attack occurred and, in carbon tetrachloride, it was, by far, the major reaction. Since no nitrone was isolated in the carbon tetrachloride experiment, the source of the ammonium salt is uncertain. Either reactions analogous to eq 3 failed to occur or else fate b (Scheme I) was the source of the ammonium salt (see ref 4).

Table III shows the approximate contributions of the various ozonation routes occurring during the ozonations of di-*tert*-butylamine, diisopropylamine, and di-*n*-butylamine under various conditions. In summary, it is evident that, judging from the examples studied, the nitroxide pathway (fate d, Scheme I) is by far the major ozonation route utilized by secondary amines having tertiary and secondary alkyl groups. With those bearing primary alkyl groups, however, side-chain oxidation is predominant in most solvents.

It is surprising that, with di-*n*-butylamine, side-chain oxidation was the major reaction even with chloroform solvent. With tri-*n*-butylamine,[3] amine oxide formation was by far the major reaction in chloroform at −60 °C, while side-chain oxidation was predominant in hydrocarbon solvents. This was also true, though to a lesser degree, with *n*-butylamine.[7] The fact, however, that with di-*n*-butylamine side-chain oxidation increased to 100% in pentane (compared to 56% in chloroform) indicates that side-chain oxidation occurred by the mechanism of fate c (Scheme I) with both di-*n*-butylamine and tri-*n*-butylamine (see discussions in ref 3 and 7). The result with di-*n*-butylamine in methylene chloride (Table III), however, is anomalous. As stated earlier, we suggest that the side-chain oxidation with diisopropylamine occurs by 1,3-dipolar insertion (Scheme III, see ref 18).

Finally, it is noteworthy that the major side-chain oxidation product from ozonation of di-*n*-butylamine was the imine (XVII), whereas acetone and isopropylamine were the principal side-chain oxidation products from diisopropylamine. This reflects the difference in stabilities of the initial oxidation products, amino alcohols XI and XVI. The former, being structurally a product of addition between a primary amine and a ketone, would most easily revert back to these substances, whereas with the latter, derived from an aldehyde and a primary amine, the equilibrium tends to favor the imine.

Experimental Section

Materials. The di-*n*-butylamine and diisopropylamine were J. T. Baker reagent grade; they were dried over potassium hydroxide pellets and distilled. Diisopropylhydroxylamine was synthesized by the procedure of Dustan and Goulding:[19] bp 47–49 (8 mm);[20] mol wt 117 (mass spectroscopy); NMR δ 1.08 (12 H, doublet), 3.08 (2 H, heptet), 6.81 (1 H singlet, diffuse). *N*-Isopropylacetamide was prepared by the method of Lock and Sagar,[21] and isopropylideneisopropylamine was prepared by the method of Norton et al.[22] 2-Nitrosopropane dimer (mp 50–51 °C)[23] and 1-nitrosobutane dimer (UV_{max} 287)[23] were prepared by the procedure of Emmons.[24] *N*-*n*-Butylformamide was prepared by formylation of *n*-butylamine using chloral,[25] $n^{25}D$ 1.4387.[26] *N*-*n*-Butylidene-*n*-butylamine was prepared by the method of Campbell et al.[27] Di-*n*-butylhydroxylamine was obtained by the amine oxide pyrolysis procedure of Cope and Ciganek,[28] mp 51–52 °C.[28b] *C*-*n*-Propyl-*N*-*n*-butylnitrone was prepared by hydrogen peroxide oxidation of di-*n*-butylhydroxylamine as described by Utzinger:[29] UV_{max}, 232 nm; NMR, δ 6.73 (t, J = 6 Hz, **CH**=N), 3.79 (t, J = 7 Hz, $\mathbf{CH_2}$N), 2.57 (m, $\mathbf{CH_2}$CH=N), 1.63 (m, $\mathbf{CH_2CH_2}$CH=NCH$_2$$\mathbf{CH_2CH_2}$), 0.99 (t, 3), 0.96 (t, 3). The other materials used were either obtained commercially or were prepared by standard procedures.

General Procedures. The ozonation setup and procedures, including the use of ozone–nitrogen and the determination of molecular oxygen yields,[30] EPR,[5,7] NMR,[7] and GLC[7] procedures, were as described in earlier papers. The GLC columns employed were: (1) 20% Carbowax 20M on Chromosorb P, ¼ in. by 15 ft; (2) 10% Carbowax 20M-10% NaOH on Chromosorb P, ¼ in. by 20 ft; (3) 5% Celanese ester No. 9 on Haloport F, ¼ in. by 10 ft; (4) 30% silicone gum rubber SE-30 on Chromosorb P, ¼ in. by 10 ft; (5) 20% Dowfax 9N9, 2.5% NaOH on Chromosorb W, ¼ in. by 10 ft; (6) 15% Carbowax 20M on Chromosorb W (AW), ¼ in. by 10 ft; (7) 5% DEGS, 2% H_3PO_4 on Chromosorb P, ¼ in. by 10 ft; (8) 5% Versamid 900 on Chromosorb G (AW), ¼ in. by 5 ft.

Table III. Competitions in Ozonations of Secondary Amines Having Tertiary, Secondary, and Primary Alkyl Groups

Amine	Solvent	Temp, °C	Nitroxide pathway, %	Side-chain oxidation, %
t-Bu$_2$NH	$CHCl_3$	−65	100	
i-Pr$_2$NH	$CHCl_3$	−65	87.5	12.5
i-Pr$_2$NH	CH_2Cl_2	−78	75	25
n-Bu$_2$NH	$CHCl_3$	−60	44	56
n-Bu$_2$NH	$CHCl_3$	0	25	75
n-Bu$_2$NH	CH_2Cl_2	−60	50	50
n-Bu$_2$NH	Pentane	−60	0	100

Ozonation of Diisopropylamine and Diisopropylhydroxylamine. In these experiments 3–20 mmol of amine in 5–20 mL of solvent was ozonized with 1 molar equiv of ozone at the indicated temperature (Table I). The solution was then divided into three equal portions for analysis. With one portion gas chromatographic analyses were performed for 2-nitropropane (column 1, 125 °C); acetone, isopropyl alcohol, isopropylamine, and isopropylideneisopropylamine (column 2, 75 °C); and *N*-isopropylacetamide (column 3, 125 °C). Yields were determined by comparison with standard solutions. Another portion was used for quantitative NMR analyses for diisopropylamine, 2-nitrosopropane dimer, and acetone oxime, using relative peak height ratios and 2-nitropropane as an internal standard. The peaks measured were the high field spikes of the 2-nitropropane and 2-nitrosopropane methyl doublets, the center line of the diisopropylamine methyne heptet, and the acetone oxime methyl singlet. The third reaction mixture portion was used for a Volhard chloride titration in determining the yield of diisopropylammonium chloride.

From the carbon tetrachloride ozonations, there was found, in addition to the above, small amounts of triisopropylurea (water insoluble precipitate; mp 77–78 °C, identified by IR and mass spectra comparison with an authentic sample) and, presumably, 2-isopropyl-3,3-dimethyloxazirane (tentatively identified by NMR methyl peaks δ 1.47 and 1.57, in comparison with a pure sample, and by the fact it gave positive active oxygen, but negative hydroperoxide, tests).

Ozonation of Di-*n*-butylamine. In these experiments 5–20 mmol of amine in 2–3 mL of solvent/mmol of amine was ozonized with 1 molar equiv of ozone at the indicated temperature (Table II). Usually a precipitate formed which, however, melted or decomposed as the temperature of the reaction mixture rose to room temperature. Aliquots were taken for analysis. Unreacted di-*n*-butylamine and *N*-*n*-butylidene-*n*-butylamine were determined on column 5 (75 °C, 4 min, then increased to 175 °C at 6 °C/min), using propylbenzene as an internal standard. These determinations were also checked by quantitative NMR, using 1,1-diphenylethylene as an internal standard. The bands employed were: $Ph_2C{=}C\mathbf{H_2}$ (δ 5.45 s), Pr$\mathbf{CH}$=N$\mathbf{CH_2}$Pr (δ 3.35, t), and (Pr$\mathbf{CH_2}$)$_2$NH (δ 2.62, t). The nitrone also was determined by quantitative NMR, employing the following band: Pr$\mathbf{CH}$=N(O)Bu (δ 6.63, t). 1-Nitrobutane was determined on column 4 (90 °C) using toluene as an internal standard; butyraldehyde was determined on column 6 (90 °C), ethylbenzene internal standard; *N*-*n*-butyl-*n*-butyramide and *N*-*n*-butylformamide were determined on column 8 (170 °C), phenyl propyl ketone internal standard; and butyric acid was determined on column 7 (120 °C), phenyl propyl ketone internal standard (after extraction of the reaction mixture with potassium hydroxide, acidification, and ether extraction). The di-*n*-butylammonium chloride was determined as described for the corresponding salt from diisopropylamine.

Acknowledgment. This work was supported by the Robert A. Welch Foundation (Grant No. F-042) for which the authors are grateful.

Registry No.—Diisopropylamine, 108-18-9; dibutylamine, 111-92-2; di-*tert*-butylamine, 21981-37-3; diisopropylhydroxylamine, 5765-61-7.

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Ozonation of Nucleophiles. 9. Tertiary Amines[1]

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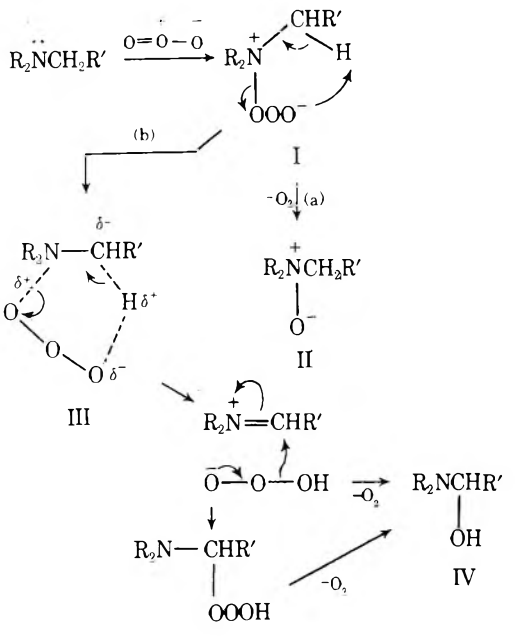
The study of the reactions of amines with ozone has been extended to triisopropylamine and ethyldiisopropylamine. Tertiary amines having primary or secondary alkyl groups react with ozone to give largely side-chain (alkyl group) oxidation products plus an amine oxide. The latter is a minor reaction except for ozonations, in a protic solvent, of tertiary amines bearing primary alkyl groups. With primary alkyl groups the major side-chain oxidation route appears to involve an internal oxidation of the amine–ozone adduct, whereas with secondary alkyl groups side-chain oxidation is best explained by 1,3-dipolar insertion.

Two previous papers[1,2] in this series have summarized our studies concerning the ozonation of primary[2-4] and secondary[1,5] amines bearing primary, secondary, and tertiary alkyl groups. The only tertiary amines previously included in our studies were tri-*n*-butylamine[3,6] and 1-di-*n*-butylamino-2-butanone.[6] The results of these investigations can be rationalized by an electrophilic ozone attack on the amine followed by four competing fates of the amine–ozone adduct (I). The reactions pertinent to the ozonation of tertiary amines are outlined in Scheme I. These include (a) amine oxide (II) formation and (b) intramolecular side-chain oxidation, via III, to amino alcohol IV, followed by further reactions thereof.

Scheme I



Reaction (b), as a route to side-chain oxidation products, involves a transition state (III) with carbanion character.[3,6] The evidence is strong that this is the mechanistic type utilized in primary alkyl side-chain oxidations.[2,3,6] However, the situation is not so clear for secondary alkyl substituents[2] and it is quite possible that 1,3-dipolar insertion[7] (Scheme II) is

Scheme II

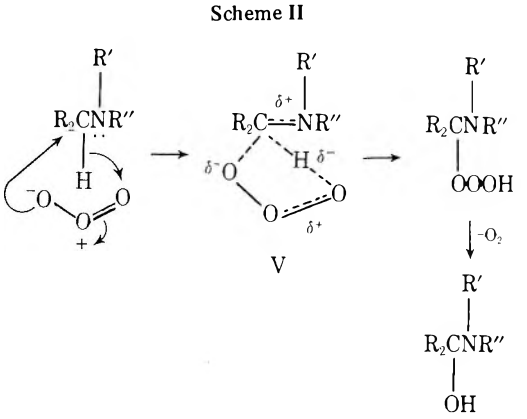


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Table I. Ozonations of Triisopropylamine and Ethyldiisopropylamine

Expt	R and R′ in R_2NR'	Solvent	Temp, °C	O_3/R_3N reacting[a]	Amine oxide[b]	$Me_2C{=}O$[b]	EtN-*i*-Pr[b] (II) H	MeCHO[b]	*i*-Pr_2NH[b] (III)	Salt of II[b]	Salt of III[b]	AcN(*i*-Pr)$_2$[b]	HCN(*i*-Pr)$_2$[b] O	AcN-*i*-Pr[b] Et	Ratio *i*-Pr/Et attack[b]	Ratio side chain: amine oxide reactions[b,c]
1	R = R′ = *i*-Pr	$CHCl_3$	−65	1.6	23	40			17		17	10				50:23[c,d]
2	R = R′ = *i*-Pr	$CHCl_3$	−25	1.5	5	40			15		10	10				50:5[d]
3	R = R′ = *i*-Pr	Pentane	−65	2.1	7	36			14			14				50:7[d]
4	R = *i*-Pr, R′ = Et	Pentane	0	1.9	6	41	20	9	29			5	8	8	49:42 = 1.2[e]	92:6[f]
5	R = *i*-Pr, R′ = Et	Pentane	−30	2.4	7	48	15	8	18			3	6	9	57:27 = 2.1[e]	84:7[f]
6	R = *i*-Pr, R′ = Et	Pentane	−78	2.0	9	55	14	5	14			1	4	12	67:19 = 3.5[e]	86:9[f]
7	R = *i*-Pr, R′ = Et	$CFCl_3$	0	1.8	5	47	17	12	24	7	5	5	7	7	55:41 = 1.3[e]	95:5[f]
8	R = *i*-Pr, R′ = Et	$CFCl_3$	−30	2.0	7	53	15	10	17	7	6	5	5	7	60:33 = 1.8[e]	93:7[f]
9	R = *i*-Pr, R′ = Et	$CFCl_3$	−78	1.8	8	54	15	7	12	5	7	4	3	9	63:26 = 2.4[e]	89:8[f]

[a] In these experiments 3–10 mmol of amine in 6–25 mL of solvent was ozonized with an equivalent number of mmol of ozone. All of the ozone reacted but some of the amine was recovered. The ratio shown is ozone reacting to amine reacting. In several experiments 0.7–0.9 mmol of molecular oxygen was evolved per millimole of ozone reacting. Per millimole of amine reacting, the ratio was 1.07. [b] Percent yield based on millimoles of amine reacting. [c] This accounting assumes that the amine salt(s) arise(s) solely from a secondary reaction of ozone on the secondary amine. It is also possible that it arises via a reaction of the type shown by pathway (a), Scheme IV,[4] followed by displacement of the tertiary amine from its salt by the stronger secondary amine. If so, columns 11 and 12 represent the extent of this reaction, all other yields would decrease slightly (since the starting amine reacted to a greater extent than indicated) and the ratio of side-chain oxidation:oxide formation:salt formation in experiment 1 would be 43:20:14. Similar changes would occur in experiments 2, 7, 8, and 9 also. [d] Side-chain attack total = columns 7 + 13; amine oxide = column 6. [e] Isopropyl attack = columns 7 + 15; ethyl attack = columns 10 + 12 + 13 + 14. [f] Side-chain attack = columns 7, 10, 12, 13, 14, 15; oxide = column 6.

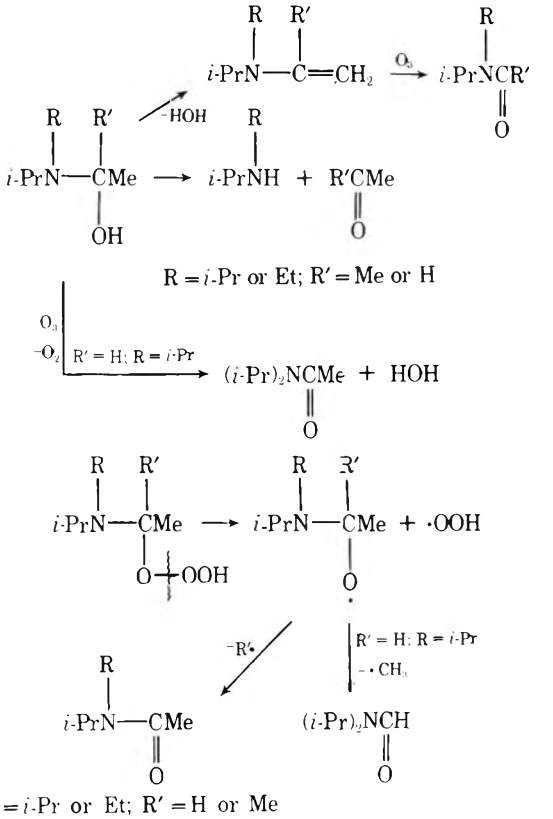
the major route. Here, the transition state (V) has carbonium ion character which is stabilized by the adjacent nitrogen atom.

The amines reported upon in the present study are triisopropylamine and ethyldiisopropylamine, two amines with secondary alkyl substituents. One purpose was to complete the study with tertiary amines that has been carried out with primary[2] and secondary[1] amines. Unfortunately, however, no tertiary amine with only tertiary alkyl substituents is known. The other purpose was to attempt to distinguish between the side-chain oxidation mechanisms outlined in Schemes I and II. The Scheme I attack, involving III, should occur preferentially at the ethyl group of ethyldiisopropylamine, whereas Scheme II should involve the less acidic tertiary hydrogens of the isopropyl groups. Table I displays the results obtained with the two amines ozonized.

The amines were quite reactive toward ozone. No ozone passed through unreacted, and the ratio of ozone reacting per mole of amine reacting generally was 1.5–2. The overall accounting in terms of product yields was very good in the case of ethyldiisopropylamine but only fair for triisopropylamine. It is obvious that, at least, amine oxide formation (fate a, Scheme I) and side chain oxidation (either fate b, Scheme I or Scheme II) occurred. Products of side-chain oxidation were acetone, acetaldehyde, the secondary amines diisopropylamine and ethylisopropylamine, *N,N*-diisopropylacetamide, *N*-ethyl-*N*-isopropylacetamide, and *N,N*-diisopropylformamide. The probable routes to these products are shown in Scheme III.

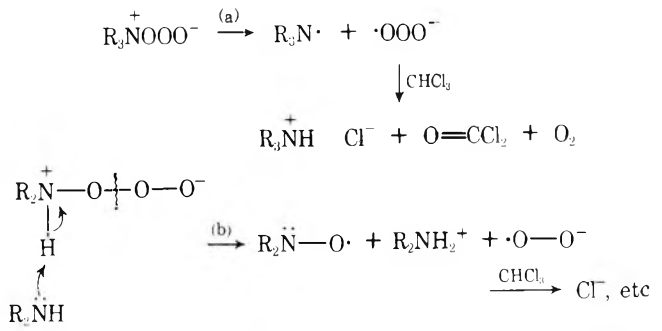
The source of the amine salts (Table I) is uncertain. It could involve either or both of two additional fates found earlier for amine–ozone adducts,[4–6] as illustrated in Scheme IV. Reaction (a) involves the tertiary amine itself. The secondary amine salts, then, would come from displacement of the tertiary amine from its salt by the secondary amine. Reaction (b) is a typical reaction of secondary amines,[1,5] which are by-products

Scheme III



in the ozonation of tertiary amines (Table I). Reaction (b) appears to be the more likely source of the salts. A microozonation of triisopropylamine was monitored by EPR at −65 °C; a signal for diisopropyl nitroxide[1,8] was immediately observed,

Scheme IV



but not for the ozonate anion radical[2,5] (reaction (a), Scheme IV).

It can be seen from Table I that side-chain ozone attack on ethyldiisopropylamine occurred preferentially at the least acidic (tertiary) hydrogens rather than those of the ethyl groups. Since the number of α hydrogens is the same either way, the ratios shown in Table I are meaningful. The selectivity was greater the lower the temperature, as would be expected. This preference for the least acidic hydrogen is to be expected for 1,3-dipolar insertion (Scheme II) but not for reaction b of Scheme I. In contrast, ozone side-chain attack with 1-di-*n*-butylamino-2-butanone occurred preferentially at the more acidic hydrogens α to the nitrogen; these are the ones also α to the carbonyl group.[6] This and observed solvent effects indicated that both 1-di-*n*-butylamino-2-butanone and tri-*n*-butylamine undergo side-chain oxidation via reaction (b) of Scheme I.[6] The solvent effect was that the more protic the solvent, the greater the proportion of amine oxide to side-chain oxidation products with tri-*n*-butylamine.[6] For example at −65 °C, tri-*n*-butylamine afforded 65 and 6% amine oxide in chloroform and pentane, respectively.[6] In contrast, under the same conditions the amine oxide yields from triisopropylamine were 23 and 7% in chloroform and pentane, respectively (Table I). Protic solvents should strongly inhibit the proton abstraction in reaction (b) of Scheme I but not affect appreciably 1,3-dipolar insertion.[6] Thus, the clue obtained in the earlier studies with primary amines,[2] that side-chain ozone attack upon secondary and primary alkyl groups occurs predominantly by the routes shown in Schemes II and I, respectively, is strongly supported by the present work. It is quite possible, however, that in each case the other side-chain oxidation mechanism is competing to a minor extent.

The amine oxide values obtained from triisopropylamine are thought to be accurate. The low accounting of products must be due to loss of side-chain oxidation products. The fact that similar ozone/amine and O_2/O_3 ratios (Table I) were obtained with both tertiary amines is indicative that the two reacted similarly.

The greater than unity ozone/amine reacting ratios, obtained from both amines even though equal molar ratios of ozone and amine were employed initially, are likely due to the extra ozone requirements in Scheme III and to further ozonations of the dialkyl nitroxide of Scheme IV and of the secondary amines and acetaldehyde of Scheme III. The fact that less acetaldehyde than diisopropylamine was obtained (experiments 4–9) indicates that further ozonation of acetaldehyde occurred. Likewise, the greater acetone than ethyliso-propylamine yields indicate further ozonation of the latter. The data also indicate that ethylisopropylamine reacted with ozone more readily than did diisopropylamine, as would be expected for steric reasons.

The ratio of molecular oxygen evolved to ozone reacting (0.8 ± 0.1) also is to be expected from the reaction course under discussion, since oxygen is not a product from several reactions of Scheme III.

In summary, the most important reactions found to occur during ozonation of tertiary amines having primary or secondary alkyl groups are side-chain attack and amine oxide formation. Side-chain attack appears to occur predominantly by 1,3-dipolar insertion (Scheme II) with secondary alkyl groups and by intramolecular proton abstraction (Scheme Ib) with primary alkyl groups. Amine oxide formation is a minor reaction except for ozonations of tertiary amines with primary alkyl groups in a protic solvent.

Experimental Section

Materials. Ethyldiisopropylamine came from Aldrich Chemical Co., Puriss. grade. Triisopropylamine was synthesized by the method of Kuffner and Koechlin:[9] bp 135–139 °C; n^{20}_D 1.4151; mol wt 143.3 (parent ion, mass spectroscopy); NMR δ 0.99 (18 H, doublet) and 3.12 (3 H, heptet). Ethylisopropylamine was prepared from ethylidineisopropylamine[10] by the method of Sommers and Aaland:[11] bp 70–73 °C.[12] *N,N*-Ethylisopropylacetamide was prepared by the method of Lock and Sagar,[13] *N,N*-diisopropylacetamide was prepared by the method of Adelman,[14] and *N,N*-diisopropylformamide was prepared by the method of Kuffner and Koechlin.[9] All other materials were obtained from commercial sources and were purified as required.

General ozonation procedures were as described earlier[2,6] and as shown in Table I. **Amine oxide** and **dialkylammonium chloride** analyses were performed as described previously.[6] All other products were analyzed by previously described GLC procedures[2] using a 10 ft ($\frac{1}{8}$ in. o.d.), 30% Silicone Gum Rubber SE-30 on Chromosorb P column for secondary amines at 30 °C and the amides and triisopropylamine at 76–85 °C. The ethyldiisopropylamine, acetaldehyde, and acetone were analyzed with a 20 ft (1.4 in. o.d.), 10% Carbowax 20M–10% NaOH on Chromosorb P column at 50 °C.

EPR and NMR procedures were as described previously.[2,5]

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Registry No.—Triisopropylamine, 3424-21-3; ethyldiisopropylamine, 7087-68-5.

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Synthesis of the *N*-Alkyl Isomers of 4-Ethoxycarbonyl- or -acetyl-3(5)-alkyl- or -aryl-5(3)-acylpyrazoles from 3(2*H*)-Furanones. Structure Determination. 3[1,2]

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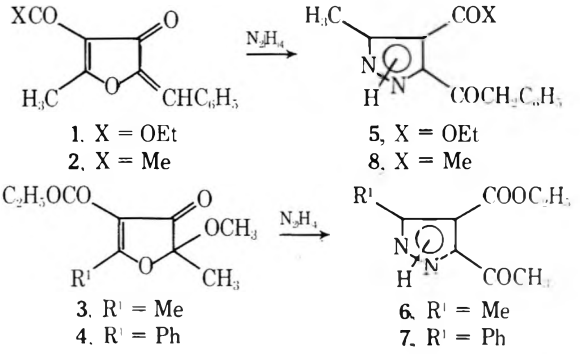
Synthesis of isomeric *N*-alkyl-3,4,5-trisubstituted pyrazoles are described from reaction of 3(2*H*)-furanones with alkylhydrazines or alternatively by alkylation of corresponding N-unsubstituted pyrazoles. Their structures are unambiguously established by ^1H and ^{13}C NMR studies. By comparison of the data of the *N*-alkylpyrazoles with those of the N-unsubstituted pyrazoles, the 5-methyl and 5-phenyl structures were found as the predominant form for these pyrazoles.

Recently, we have reported that the 3(2*H*)-furanones are interesting substrates which undergo ring opening by nucleophilic reagents, leading to new cyclic compounds.[1-3] Our studies concerning the reaction of hydrazine hydrate with 3(2*H*)-furanones **1–4** have led to a useful procedure to obtain 3(5)-acyl-4-ethoxycarbonyl- or -acetyl-5(3)-substituted pyrazoles **5–8**.[1,2]



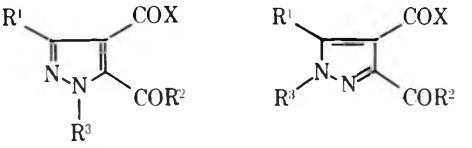
1. X = OEt
2. X = Me

5. X = OEt
8. X = Me

3. R¹ = Me
4. R¹ = Ph

6. R¹ = Me
7. R¹ = Ph

The preparation and structure determination of corresponding N-substituted isomeric pyrazoles **9–16a,b** are described in this paper. Two routes have been investigated: first, the reaction of **1–4** with alkylhydrazines; second, the alkylation of the pyrazoles **5–8**.



9–16a **9–16b**

	R¹	R²	R³	X
9	Me	CH_2Ph	Me	OEt
10	Me	CH_2Ph	CH_2Ph	OEt
11	Me	Me	Me	OEt
12	Me	Me	CH_2Ph	OEt
13	Ph	Me	Me	OEt
14	Ph	Me	CH_2Ph	OEt
15	Me	CH_2Ph	Me	Me
16	Me	CH_2Ph	CH_2Ph	Me

Table I. Spectral Data of Pyrazoles

Compd	Registry no.	UV, nm ($\epsilon \times 10^{-3}$)	^1H NMR chemical shifts ($CDCl_3$) δ, ppm
9a	65969-58-6	212 (9.3) 235 (6.4)	1.37 (3 H, t, J = 7 Hz), 2.47 (3 H, s), 3.47 (3 H, s), 4.37 (2 H, s), 4.40 (2 H, q, J = 7 Hz), 7.31 (5 H, s)
9b	65942-77-0	212 (13.7) 243 (6.8)	1.30 (3 H, t, J = 7 Hz), 2.40 (3 H, s), 3.78 (3 H, s), 4.30 (2 H, s), 4.37 (2 H, q, J = 7 Hz), 7.35 (5 H, s)
10a	65942-78-1	211 (14.1) 241 (6.6)	1.37 (3 H, t, J = 7 Hz), 2.49 (3 H, s), 4.07 (2 H, s), 4.42 (2 H, q, J = 7 Hz), 5.16 (2 H, s), 7.0–7.5 (10 H, m)
10b	65942-79-2	217 (14.2) 236 (7.4)	1.28 (3 H, t, J = 7 Hz), 2.32 (3 H, s), 4.33 (2 H, q, J = 7 Hz), 4.37 (2 H, s), 5.35 (2 H, s), 7.3–7.5 (10 H, m)
11a	65942-80-5	254 (5.4)	1.38 (3 H, t, J = 7 Hz), 2.43 (3 H, s), 2.61 (3 H, s), 3.86 (3 H, s), 4.41 (2 H, q, J = 7 Hz)
11b	65942-81-6	213 (6.3) 245 (5.3)	1.35 (3 H, t, J = 7 Hz), 2.46 (3 H, s), 2.56 (3 H, s), 3.87 (3 H, s), 4.36 (2 H, q, J = 7 Hz)
12a	65942-82-7	214 (9.0) 250 (6.7)	1.35 (3 H, t, J = 7 Hz), 2.35 (3 H, s), 2.50 (3 H, s), 4.31 (2 H, q, J = 7 Hz), 5.41 (2 H, s), 7.13–7.56 (5 H, m)
12b	65942-83-8	216 (13.0) 243 (7.0)	1.31 (3 H, t, J = 7 Hz), 2.38 (3 H, s), 2.61 (3 H, s), 4.36 (2 H, q), 5.40 (2 H, q), 7.11–7.56 (5 H)
13a	65942-84-9	239 (17.5)	1.20 (3 H, t, J = 7 Hz), 2.60 (3 H, s), 4.03 (3 H, s), 7.4–7.63 (3 H, m), 7.63–8.0 (2 H, m)
13b	65942-85-0	239 (14.3)	1.11 (3 H, t, J = 7 Hz), 2.63 (3 H, s), 3.81 (3 H, s), 4.25 (2 H, q, J = 7 Hz), 7.55 (5 H, s)
14a	65942-86-1	213 (12.8) 240 (17.2)	1.18 (3 H, t, J = 7 Hz), 2.35 (3 H, s), 4.30 (2 H, q, J = 7 Hz), 5.58 (2 H, s), 7.33 (5 H, s), 7.45 (3 H, m), 7.85 (2 H, m)
14b	65942-87-2	230 (14.7)	1.11 (3 H, t, J = 7 Hz), 2.68 (3 H, s), 4.25 (2 H, q, J = 7 Hz), 5.33 (2 H, s), 7.00–7.70 (10 H)
15a	65942-88-3	217 (7.4) 259 (6.3)	2.50 (3 H, s), 2.52 (3 H, s), 3.43 (3 H, s), 4.18 (2 H, s), 7.35 (5 H, s)
15b	65942-89-4	218 (9.2) 258 (6.4)	2.34 (3 H, s), 2.45 (3 H, s), 3.81 (3 H, s), 4.40 (2 H, s), 7.37 (5 H, s)
16a	65942-90-7	214 (13.2) 260 (8.3)	2.40 (3 H, s), 2.50 (3 H, s), 3.87 (2 H, s), 5.12 (2 H, s), 7.0–7.5 (10 H, m)
16b	65942-91-8	222 (15.1) 258 (8.5)	2.35 (3 H, s), 2.48 (3 H, s), 4.45 (2 H, s), 5.45 (2 H, s), 7.2–7.5 (10 H, m)

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Table II. Eu(fod)$_3$ Induced Chemical Shifts

Compd	CH_3 (C-3)	NCH_3	CH_2 in CO_2Et at C-4	CH_3 or CH_2 at C-5
9a	2.41	1.49	3.40	2.08
9b	1.82	2.15	3.22	4.09
11a	2.58	2.39	3.59	5.09[20]
11b	2.13	2.65	3.33	4.54[20]

Results and Discussion

The reaction of methylhydrazine with the 3(2*H*)-furanones **1–4** gave mixtures in which the a isomers were the major products (about 3:1 **a/b**) with **9, 11, 13,** and **15.** Benzylhydrazine gave only the **a** isomers **10a,**[4] **12a, 14a, 16a.**

On the other hand, the alkylation of the anions from pyrazoles **5–8** with methyl iodide and benzyl chloride produced, in the most cases, a material wherein the main products of the reaction (70–80%) were the isomeric pyrazoles **9,11–15b** or only **10b** and **16b.** The treatment of **6** and **7** with ethereal diazomethane yielded a 4:1 mixture of **11** and **13 a/b,** respectively. In the same conditions, **5** generated **9a** accompanied by another unidentified product.

The presence of two isomers is clearly revealed in the ^1H NMR spectra, which generally consist of two sets of signals. Simply by comparing the relative signal intensities, the isomeric composition of the crude reaction mixture was determined. The pure isomeric pyrazoles **a** or **b** were obtained by distillation, crystallization, or column chromatography. The pyrazole structure of these compounds was evident from the alkylation reaction and by their ready conversion into pyrazolo[3,4-*d*]pyridazine derivatives with hydrazine hydrate.[5] Proton NMR data for all compounds are collected in Table I and are completely consistent with the assigned structures. The problem remains of deciding which belong to series **a** and which to series **b.**

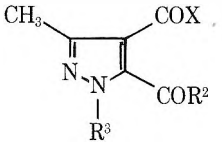
A great deal of work has been done on the structural assignment to *N*-alkyl derivatives of unsymmetrical pyrazoles.[6–17] However, no general solution is available. ^1H NMR studies have dealt with this problem. The 1-alkyl-3- or -5-methylpyrazole pairs show a diamagnetic shift of the methyl peak in going from the 3-methyl to the 5-methyl isomer.[12] However, the methyl peak undergoes a paramagnetic instead of a diamagnetic displacement in pairs of 3- or 5-methylpyrazole carboxylates.[14] Tensmeyer and Ainsworth[15] state that the phenylpyrazoles fall into two groups: those with essentially singlet phenyl peaks and those with multiplet phenyl resonances. A phenyl group attached to a nitrogen or a carbon atom of the pyrazole ring has a multiplet resonance, except in the presence of a substituent α to it; in this case, the phenyl resonance is a singlet, because of the impossibility of the coplanarity of the two rings. When multiplet resonances occur, the *o*-phenyl protons reside preferentially near the plane of the pyrazole ring and are shifted by the magnetic field of the pyrazole ring current.

The position of the phenyl group in the pyrazoles assigned structures **13–14a,b** is indicated by the splitting pattern of the aryl protons. The two ortho protons are seen at δ 7.82 and 7.85 in **13a** and **14a** (see Table I). In UV spectra, the hypochromic effect on going from **13a** to **13b** and hypochromic and hypsochromic effects from **14a** to **14b** were characteristic of ortho-substituted diphenyls and analogous heterocyclic compounds.[18,19]

In 3- or 5-methyl series **9–12, 15,** and **16,** the structural assignment could not be made on the basis of their ^1H NMR spectra. In order to find further support for the alternative structures **a** or **b,** we have measured the lanthanide shift data of the two pairs of the pyrazoles **9** and **11.** The LIS extrapolated for a 1:1 complex with Eu(fod)$_3$ in $CDCl_3$, given in parts per million, are presented in Table II.

It is well established that the 4 position in the pyrazole nucleus has a greater electron density than the 3 and 5 positions.[18,19] A considerable contribution of a dipolar structure with a negative charge on the carbonyl of the ethoxycarbonyl group and a positive charge on the N-1 atom explains the large LIS of the methylene of this group. The most significant differences are observed between the two isomers **a** and **b** on the methylene and the methyl of the acyl groups **9** and **11,** respectively. It seems reasonable to presume that the acyl groups more affected by the complexation must be the less hindered,

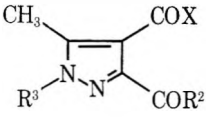
Table III. Carbon-13 Chemical Shifts for Derivatives of the 3-Methyl Series of Pyrazoles ($CDCl_3$)



					COX		COR^2		
Compd	C-3	C-4	C-5	CH_3	CO	X	CO	R^2	NR^3
11a	149.3	110.6	143.0	13.56	162.9	OCH_2: 60.5; CH_3: 14.2	194.3	CH_3: 31.12	CH_3: 38.2
9a	149.3	111.2	143.4	13.5	162.8	OCH_2: 60.5; CH_3: 14.2	194.8	CH_2: 50.6; Ph: C′-1, 132.3; C′-2,6, 129.4;[a] C′-3,5, 128.6;[a] C′4, 127.2	CH_3: 37.3
10a	149.6	112.4	143.6	13.8	163.0	OCH_2: 60.6; CH_3: 14.3	195.3	CH_2: 50.1; Ph: C′-1, 132.5; C′-2,6, 129.6;[a] C′-3,5, 128.6;[a] C′-4, 127.1[b]	CH_2: 54.1; Ph: C′-1, 135.6; C′-2,6, 127.6;[a] C′-3,5, 128.5;[a] C′-4, 127.9[b]
15a	147.0	121.9	144.0	14.6	192.9	CH_3: 29.8	195.4	CH_2: 50.2; Ph: C′-1, 132.5; C′-2,6, 129.6;[a] C′-3,5, 128.6;[a] C′-4, 127.2	CH_3: 36.94
16a	147.1	122.5	143.6	14.7	193.1	CH_3: 29.8	195.5	CH_2: 49.6; Ph: C′-1, 132.6; C′-2,6, 129.7;[a] C′-3,5, 128.5;[a] C′-4, 127.0[b]	CH_2: 54.0; Ph: C′-1, 135.4; C′-2,6, 127.8;[a] C′-3,5, 128.3;[a] C′-4, 128.0[b]

[a,b] These values might be interchanged.

Table IV. Carbon-13 Chemical Shifts for Derivatives of the 5-Methyl Series of Pyrazoles ($CDCl_3$)



Compd	C-3	C-4	C-5	CH_3	COX		COR^2		NR^3
					CO	X	CO	R^2	
11b	149.1	111	143.4	10.4	163.0	OCH_2: 60.3; CH_3: 14.1	193.5	CH_3: 28.2	CH_3: 36.7
6	150.3	110.6	145.5	11.3	163.7	OCH_2: 60.7; CH_3: 14.1	195.2	CH_3: 28.7	H
9b	148.9	112	143.4	10.5	163.2	OCH_2: 60.5; CH_3: 14.0	193.4	CH_2: 47.2; Ph: C′-1, 134.3; C′-2,6, 129.6;[a] C′-3,5, 128.2;[a] C′-4, 126.5	CH_3: 36.7
10b	149.1	112.5	143.5	10.6	163.3	OCH_2: 60.5; CH_3: 14	193.7	CH_2: 47.5; Ph: C′-1, 134.3; C′-2,6, 129.7;[a] C′-3,5, 128.2;[a] C′-4, 126.5[b]	CH_2: 53.7; Ph: C′-1, 135; C′-2,6, 126.7;[a] C′-3,5, 128.7;[a] C′-4, 127.9[b]
5	149.9	111.2	145.6	11.3	163.4	OCH_2: 60.7; CH_3: 14.1	192.2	CH_2: 47.7; Ph: C′-1, 134.0; C′-2,6, 129.6;[a] C′-3,5, 128.3;[a] C′-4, 126.6[a]	H
15b	147.0	121.6	143.1	10.5	196.9	CH_3: 31.1	193.7	CH_2: 46.2; Ph: C′-1, 134.4; C′-2,6, 129.6;[a] C′-3,5, 128.2;[a] C′-4, 126.5	CH_3: 36.7
16b	147.6	122.2	143.2	10.7	197.0	CH_3: 31.2	193.8	CH_2: 46.4; Ph: C′-1, 134.4; C′-2,6, 129.7;[a] C′-3,5, 128.3;[a] C′-4, 126.6	CH_2: 53.7; Ph: C′-1, 134.8; C′-2,6, 126.9;[a] C′-3,5, 128.8;[a] C′-4, 128.1
8	149.3	120.4	144.4	11.2	197.6	CH_3: 31.2	194.8	CH_2: 49.6; Ph: C′-1, 134.0; C′-2,6, 129.6;[a] C′-3,5, 128.4;[a] C′-4, 126.7	H

[a,b] These values might be interchanged.

in best agreement with the 3 position in β of the *N*-methyl group.

The 3- or 5-methyl isomeric structures were also inferred by ^{13}C NMR spectroscopy. All compounds studied gave well-resolved lines which could be assigned by application of the usual shift parameters,[21] from the obtained signal multiplicities in the off resonance spectrum and consultation of the pyrazole literature.[22-25] The assigned structures are first based on the carbon chemical shifts of the observed δ values of the methyl groups in the pairs of the isomeric pyrazoles with those of the model systems: 1,3- or 1,5-dimethylpyrazoles, 1,3,5-trimethylpyrazole.[23] The C-3 methyl signals are shifted on about 2–3 ppm to lower field than the C-5 methyl signals. Moreover, it has been shown[22-24] that the carbon-13 chemical shift for a pyridinic environment N=C< occurs at lower field than for a pyrrolic environment N–C=. Consequently, the signals of the C-3 or C-5 carbons bonded with a methyl group can be attributed, the C-4 signals are easily assigned by their larger shieldings. The remaining signal is assigned to the C-3 or C-5 carbons bonded to an acyl group. The chemical shifts are presented in Tables III and IV. In summary, the comparison of the chemical shifts from two N-alkylated isomeric pyrazoles shows that the C-3 and C-5 shifts change in opposite directions (Table V). The carbons 3, 4, and 5 in series **a** must correspond to carbons 5, 4, and 3, respectively, in series **b**. For all compounds examined, methyl or acyl substitution causes a similar effect at the carbon adjacent to the site of the substitution. The replacement of a *N*-methyl group (**9** and **15**) by a benzyl group (**10** and **16**) gives very weak deshieldings ($\Delta\delta^{max} < 1.2$ ppm). The effect caused by replacing an ethoxycarbonyl group by an acetyl group at the C-4 position is higher at C-3 than at C-5 and appears dominated by inductive effects (Table VI).

The structures of **13a** and **13b** are consistent with ^{13}C NMR spectral comparisons of these materials with previous findings concerning the 1,3- or 1,5-dimethyl-5- or -3-phenylpyrazoles.[23] The C′-1 atom of a phenyl group in the 3 position is more deshielded than in the 5 position. The assignments of the chemical shift values to specific carbon atoms C-3, C-4, and C-5 are determined as above (see Table VII).

We have already shown that the formation of pyrazoles from 3(2*H*)-furanones involves a Michael addition of the

Scheme I

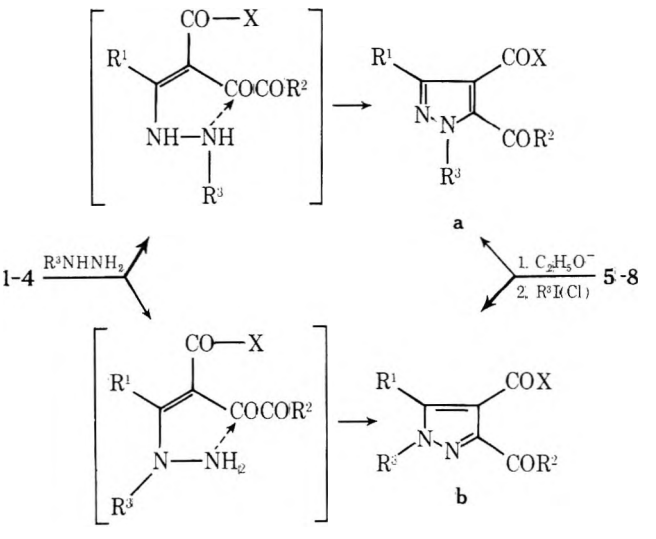
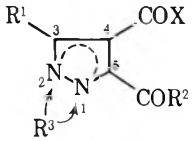


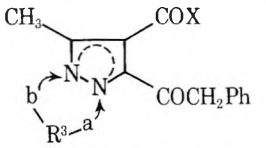
Table V. Change in the Carbon-13 Chemical Shifts ($\Delta\delta$)[a] for Derivatives of N(1)- or N(2)-Alkylated Pyrazoles



Compds compared	C-3	C-4	C-5	R^1	COX		COR^2		NR^3
					CO	X	CO	R^2	
11a, 11b	5.9	−0.4	−6.1	CH_3: 3.2	−0.1	OCH_2: 0.2; CH_3: 0.1	0.8	CH_3: 2.92	CH_3: 1.5
9a, 9b	5.9	−0.9	−5.6	CH_3: 3	−0.4	OCH_2: 0; CH_3: 0.1	1.4	CH_2: 3.4; Ph[b]	CH_3: 0.6
10a, 10b	6.1	−0.4	−5.5	CH_3: 3.2	−0.3	OCH_2: 0.1; CH_3: 0.3	1.6	CH_2: 2.6; Ph[b]	CH_2: 0.5; Ph[b]
15a, 15b	3.9	0.3	−3	CH_3: 4.2	−1.5	CH_3: −1.3	0.8	CH_2: 4; Ph[b]	CH_3: 0.2
16a, 16b	3.9	0.3	−3.9	CH_3: 4	−1.5	CH_3: −1.36	−0.7	CH_2: 3.2; Ph[b]	CH_2: 0.2; Ph[b]
13a, 13b	4.8	−0.4	−6.7	Ph[b]	0.3	OCH_2: 0.5; CH_3: 0	−1	CH_3: 2.8	CH_3: 1.5

[a] $\Delta\delta = \delta C_a - \delta C_b$. Negative numbers represent shift changes to lower field as compared to the chemical shifts observed for the corresponding position in the reference compound. [b] The aromatic carbon absorptions are omitted.

Table VI. Substitution Effects on Replacement of Ethoxycarbonyl by Acetyl Group at the C-4 Position ($\Delta\delta$)[a]



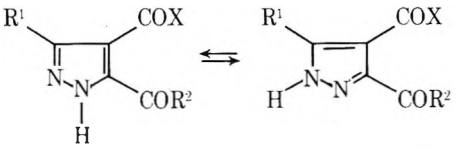
Compds compared	R^3	C-3	C-4	C-5	CH_3	CO	CH_2
9a, 15a	CH_3	2.3	−10.7	−0.6	−1.1	−0.6	0.4
9b, 15b	CH_3	1.9	− 9.6	0.3	0	−0.3	1
10a, 16a	CH_2Ph	2.5	−10.1	0	−0.9	−0.2	0.5
10b, 16b	CH_2Ph	1.5	− 9.7	0.3	−0.1	−0.1	0.9

[a] $\Delta\delta = \delta C(X = OEt) - \delta C(X = CH_3)$.

hydrazine to the C-5 position of the furanone ring.[1,2,26] The composition of the isomeric mixtures obtained with unsymmetrical hydrazines reflects approximatively the relative reactivities of the two nitrogen atoms. Our results imply that the conjugate addition occurs preferentially or exclusively at the unsubstituted nitrogen atom (Scheme I). Although the secondary nitrogen atom is the more nucleophilic,[27-29] the reaction is principally controlled by steric effects. Analogous orientations in conjugate additions were already reported.[30-32]

The factors that influence the site of alkylation of ambident anions from pyrazole derivatives are complex. In most cases studied, both *N*-alkyl isomers were produced.[12,17,30,33-35] The prevailing formation of the isomers **b**, in all cases studied in this paper, suggests that this orientation may be attributed to electronic rather than steric effects. With diazomethane, methylation proceeds on the nitrogen atom nearer to the acyl-withdrawing group as expected from previous findings.[36,37]

The predominance of one tautomeric form for several unsymmetrical pyrazoles has been shown.[12,15-17,38,39] The carbon chemical shifts of the N(1)H and N(2)H tautomers of pyrazole derivatives have been recently reported.[24] Chemical shift comparisons of 3,5-dimethylpyrazole in a reduced tautomeric exchange rate with our 3- or 5-methylpyrazoles **9a,b, 11a,b,** and **15a,b** (Tables III and IV) indicate that the chemical shift alterations induced by the *N*-methyl substitution have a limited effect on the C-3 or C-5 methyl signals: δ CH_3 (C-3) 13.8, CH_3(C-5) 10.6. The methyl carbon chemical shifts in **5, 6,** and **8** are closer in magnitude to the corresponding chemical shifts in **9b, 11b,** and **15b** than to those in **9a, 11a,** and **15a.** The phenyl resonance in **7** is very similar to the values shown for the corresponding *N*-methylpyrazole **13b** (Table VII).



tautomer a, N(1)H tautomer b, N(2)H

Furthermore, these tables show the obvious similarity of the acyl methylene in **5** and **8** and methyl in **6** and **7** as compared with those of **9** and **15** and **11b** and **13b,** respectively. These findings would strongly suggest that the unalkylated pyrazoles **5–8** exist predominantly, at least in deuteriochloroform, in the tautomeric form N(2)H (**b**).

Experimental Section

Melting points were determined on a Kofler hot plate and boiling points are uncorrected. Infrared and ultraviolet spectra were obtained with a Beckmann Model Acculab 2 and DB spectrophotometers. NMR spectra were recorded on Varian A-60 (^{1}H NMR) and Varian X-100-12 FT (^{13}C NMR) spectrometers at 35 °C, using deuteriochloroform solution 0.2 M in pyrazoles and tetramethylsilane as internal reference. The lanthanide induced shift study was done by adding small portions of $Eu(fod)_3$ (25 mg) to a $CDCl_3$ solution containing the pyrazole (0.125 mM in 1 mL). Plots of the chemical shifts vs. ratio $Eu(fod)_3$/pyrazole (0.385, 0.578, 0.771, 0.963) are nearly linear. Elemental analyses were performed by Microanalytical Laboratory, Centre National de la recherche Scientifique, Villeurbanne, France.

3(2*H*)-Furanones **1**[3] and **2**[40] and pyrazoles **5–8**[1,2] were prepared as described in the literature.

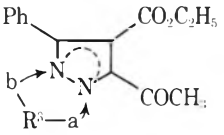
3(2*H*)-Furanones 3 and 4. A solution of 2-acetoxy-2,5-dimethyl-4-ethoxycarbonyl-3(2*H*)-furanone or 2-acetoxy-2-methyl-4-ethoxycarbonyl-5-phenyl-3(2*H*)-furanone (0.05 mol), prepared as described[41,42] in 100 mL of dry methanol acidified with acetyl chloride (0.2 mL), was heated at reflux temperature for 5 h. After evaporation of the methanol, the residue was distilled in vacuo to afford **3** or **4.**

4-Ethoxycarbonyl-2-methoxy-2,5-dimethyl-3-(2*H*)-furanone (3) (9.1 g, 85%): bp 110 °C (0.1 mm); mp 43 °C (hexane); IR (CCl_4) 1745, 1720, 1700 cm^{-1}; UV max (EtOH) 216 nm (ϵ 11 700), 270 (12 000); ^{1}H NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7 Hz), 1.50 (3 H, s), 2.68 (3 H, s), 3.27 (3 H, s), 4.32 (2 H, q, J = 7 Hz). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.05; H, 6.66.

4-Ethoxycarbonyl-2-methoxy-2-methyl-5-phenyl-3-(2*H*)-furanone (4) (12.4 g, 90%): bp 165 °C (0.5 mm); mp 54 °C (hexane); IR (CCl_4) 1730 cm^{-1}; UV max (EtOH) 212 nm (ϵ 9200), 254 (5500), 306 (15 200); ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, t, J = 7 Hz), 1.61 (3 H, s), 3.34 (3 H, s), 4.34 (2 H, q, J = 7 Hz), 7.45–8.15 (5 H, m). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.19; H, 5.75.

Preparation of 1-Alkyl-3-methyl(or phenyl)pyrazoles. Series a. Reaction of 3(2*H*)-Furanones with Methylhydrazine. General Procedure. To a stirred solution (0.02 mol) of **1–4** in acetonitrile (20 mL for **1, 3,** and **4,** 100 mL for **2**) was added slowly methylhydrazine (0.92 g, 0.02 mol). The reaction mixture was allowed to stir at room temperature for 1 h and acetonitrile was evaporated. The crude products were analyzed by GLC or ^{1}H NMR. After further purification pyrazoles **a** were obtained as described below.

Table VII. Carbon-13 Chemical Shifts for Derivatives of 3- and 5-Phenyl Series of Pyrazoles ($CDCl_3$)



Compd	C-3	C-4	C-5	$COOCH_2CH_3$ CO	OCH_2	CH_3	$COCH_3$ CO	CH_3	Ph	NR^3
13a	150.0	113.2	141.6	163.5	61.1	13.7	191.9	30.3	C′-1, 131.7; C′-2,6, 128.4;[a] C′-3,5, 127.8;[a] C′-4, 128.6[a]	CH_3: 39.2
13b	148.3	113.6	145.2	163.2	60.6	13.7	192.9	27.5	C′-1, 128.8; C′-2,6, 129.4;[a] C′-3,5, 128.3;[a] C′-4, 127.9	CH_3: 37.7
7	148.9	111.8	145.3	164.8	61.6	13.7	193.6	27.4	C′-1, 129.3; C′-2,6, 129.4; C′-3,5, 128.3; C′-4, 129.3	H

[a,b] These values might be interchanged.

Reaction of 3(2*H*)-Furanones with Benzylhydrazine. General Procedure. The resulting solutions of **1**–**4** with benzylhydrazine (2.44 g, 0.02 mol) were run as described above for **1** and **2**; the reaction mixture was heated under reflux for 30 min for **3** and **4**. Evaporation of the solvent afforded the crude pyrazoles **b**. Final purification by recrystallization or fractional distillation at reduced pressure gave the pure pyrazoles **a**.

Their spectra are listed in Tables I, III, and VII.

4-Ethoxycarbonyl-1,3-dimethyl-5-phenylacetylpyrazole (9a). The distillation of crude product mixture **9a/9b,** 65:35, afforded **9a:** 3.37 g (59%); bp 170 °C (1 mm). Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.12; H, 6.42; N, 9.66.

1-Benzyl-4-ethoxycarbonyl-3-methyl-5-phenylacetylpyrazole (10a). The residual solid was extracted with boiling hexane (200 mL). The residue obtained by evaporation of the hexane extract was recrystallized from ethyl acetate–hexane, 70:30, to give 5 g (66%) of **10a.**

5-Acetyl-4-ethoxycarbonyl-1,3-dimethylpyrazole (11a). The distillation of the mixture **11a/11b,** 80:20, gave a first fraction [2.5 g; bp 120–130 °C (0.2 mm)] which crystallized. The raw crystals were recrystallized from water–ethanol, 80:20, to afford **11a:** 1.5 g (35%; mp 65 °C). Anal. Calcd for $C_{10}H_{14}O_3N_2$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.42; H, 6.48; N, 13.61.

5-Acetyl-1-benzyl-4-ethoxycarbonyl-3-methylpyrazole (12a). The residue afforded the pure pyrazole **12a** by distillation 180–182 °C (0.5 mm); 3.4 g (60%). Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.21; H, 6.35; N, 9.96.

5-Acetyl-4-ethoxyearbonyl-1-methyl-3-phenylpyrazole (13a). The crude mixture product **13a/13b,** 92:8, gave by distillation **13a** (2.2 g, 40%): bp 160 °C (1 mm). Anal. Calcd for $C_{15}H_{16}O_3N_2$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.44; H, 5.91; N, 10.34.

5-Acetyl-1-benzyl-4-ethoxycarbonyl-3-phenylpyrazole (14a). The crude product was purified by distillation: 4.4 g(63%); bp 230 °C 0.1 mm). Anal. Calcd for $C_{21}H_{20}O_3N_2$: C, 72.39; H, 5.79; N, 8.04. Found: C, 71.83; H, 5.79; N, 8.04.

4-Acetyl-1,3-dimethyl-5-phenylacetylpyrazole (15a). The residue **15a/16b,** 75:25, was distillated at 180–200 °C (0.5 mm) to give a solid distillate which was recrystallized from ethyl acetate–hexane, 20:80 (3 g, 58%); mp 86°C. Anal. Calcd for $C_{15}H_{16}O_2N_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.05; H, 6.25; N, 11.02.

4-Acetyl-1-benzyl-3-methyl-5-phenylacetylpyrazole (16a). The residual solid was recrystallized from ethyl acetate–hexane, 20:80 (4.8 g, 72%); mp 94 °C. Anal. Calcd for $C_{21}H_{20}O_2N_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 76.00; H, 6.10; N, 8.43.

Preparation of 1-Methyl(or benzyl)-5-methyl(or phenyl)-pyrazoles. Series b. General Procedure. A stirred solution of pyrazoles **5**–**8** (0.02 mol) in ethanol (50 mL) containing sodium ethylate (from 0.46 g of sodium) was treated dropwise with methyl iodide (3.5 g, 0.025 mol) or benzyl chloride (2.8 g, 0.022 mol). The mixture was then heated under reflux for 2 h. Solvent was removed in vacuo. The residue was diluted with 20 mL of water, made alkaline, and extracted with ether. After washing with water the solvent was removed by evaporation and the residues were analyzed by ^1H NMR. The crude products were purified by recrystallization, distillation, or chromatography on basic alumina to give pure pyrazoles **b.**

Their spectra are reported in Tables I, IV, and VII.

4-Ethoxycarbonyl-1,5-dimethyl-3-phenylacetylpyrazole (9b) was obtained by recrystallization of residual solid mixture **9a/9b,** 20:80, from ethyl acetate–hexane, 30:70: 3.7 g (65%); mp 71 °C. Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 66.88; H, 6.28; N, 9.87.

1-Benzyl-4-ethoxycarbonyl-5-methyl-3-phenylacetylpyrazole (10b). The crude pyrazole **10b,** 3.55 g (71%), was purified by chromatography over basic alumina and elution with ethyl acetate. Anal. Calcd for $C_{22}H_{22}O_3N_2$: C, 72.91; H, 6.12; N, 7 33. Found: C, 72.67; H, 6.06; N, 7.55.

3-Acetyl-4-ethoxycarbonyl-1,5-dimethylpyrazole (11b). The residual mixture **11a/11b,** 20:80, 3.4 g, was purified by chromatography; 0.6 g was chromatographed on 50 g of basic alumina (activity III). Elution with 7% ethyl acetate in hexane gave **11a** (0.11 g) and then **11b** (0.42 g, 56%). Anal. Calcd for $C_{10}H_{14}O_3N_2$: C. 57.13; H, 6.71; N, 13.33. Found: C, 56.91; H, 6.64; N, 13.24.

3-Acetyl-1-benzyl-4-ethoxycarbonyl-5-methylpyrazole (12b). The solid crude product **12a/12b,** 25:75, afforded **12b** by recrystallization from hexane: 2.6 g (46%); mp 75 °C. Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.01; H, 6.26; N, 9.81.

3-Acetyl-4-ethoxycarbonyl-1-methyl-5-phenylpyrazole (13b). The solid crude product **13a/13b,** 20:80, afforded **13b** by recrystallization from hexane–ethyl acetate, 90:10; 2.2 g (40%); mp 68 °C. Anal. Calcd for $C_{15}H_{16}O_3N_2$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.22; H, 5.92; N, 10.26.

3-Acetyl-1-benzyl-4-ethoxycarbonyl-5-phenylpyrazole (14b) was obtained by crystallization of crude mixture **14a/14b,** 10:90, from hexane–ethyl acetate, 80:20: 3.75 g (54%); mp 76 °C. Anal. Calcd for $C_{21}H_{20}O_3N_2$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.41; H, 5.79; N, 8.09.

4-Acetyl-1,5-dimethyl-3-phenylacetylpyrazole (15b). Distillation of mixture **15a/15b,** 20:80, gave **15a** [0.8 g; bp 180–185 °C(0.5 mm)] and **15b** [3.1 g; 60%; bp 210–215 °C (0.5 mm)]. Anal. Calcd for $C_{15}H_{16}O_2N_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.35; H, 6.45; N, 10.15.

4-Acetyl-1-benzyl-5-methyl-3-phenylacetylpyrazole (16b) was obtained by recrystallization from ethyl acetate–hexane, 20:80; 4.3 g (65%); mp 95 °C. Anal. Calcd for $C_{21}H_{20}O_2N_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.60; H, 6.04; N, 8.46.

Registry No.—**1,** 53252-49-6; **2,** 62723-14-2; **3,** 62538-46-9; **4,** 62538-48-1; **5,** 65942-92-9; **6,** 62538-27-6; **7,** 62538-29-8; **8,** 63195-08-4; 2-acetoxy-2,5-dimethyl-4-ethoxycarbonyl-3(2*H*)-furanone, 53252-54-3; 2-acetoxy-2-methyl-4-ethoxycarbonyl-5-phenyl-3(2*H*)-furanone, 53252-56-5; methylhydrazine, 60-34-5; benzylhydrazine, 555-96-4.

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A New and Facile Synthesis of Trialkylketenimines

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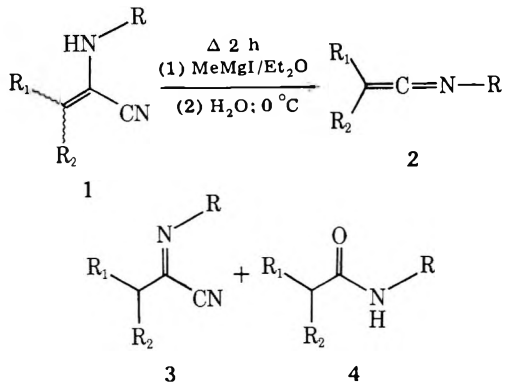
Trialkylketenimines were prepared by reaction of α-cyano enamines with methylmagnesium iodide in ethereal solution. Condensation of trialkylketenimines with primary amines afforded the corresponding amidines.

Ketenimines are an important class of organic compounds, which are apt to undergo a variety of photochemical and thermal cycloadditions.[2a] Several entries into this cumulenic system have been described,[2a] but the overwhelming number of ketenimines described hitherto are substituted with one or more aromatic substituents. A few trialkylketenimines have been prepared from aliphatic imidoyl chlorides and triethylamine[2b,3] or by dehydration of amides.[4] These trialkylketenimines have been used as catalysts for the low-temperature polymerization of ϵ-caprolactam.[5] It was claimed[2a] that the lower trialkylketenimines are not readily accessible due to the easy formation of resinous material. For instance dimethyl-*N*-*n*-butylketenimine was reported to decompose rapidly at −20 °C.[3]

We now report a new and facile synthesis of trialkylketenimines starting from α-cyano enamines **1**, which are easily accessible from disubstituted acetaldehydes via α-chloroaldimines.[6,7] Treatment of α-cyanoenamines **1** with methylmagnesium iodide in diethyl ether afforded, after usual workup with an aqueous ammonium chloride solution, a reaction mixture in which trialkylketenimines **2** were the predominant compounds (Scheme I). When the reaction mixture was subjected to a GC–MS coupling, using on-column injection in order to minimize polymerization of the title compounds, small amounts of imidoylcyanides **3** and *N*-alkylamides **4** were also detected.

Scheme I



Careful distillation in vacuo over a 10-cm Vigreux column allowed separation of ketenimines **2** from compounds **3** and **4**. Trialkylketenimines **2** were obtained in 27–61% yield as colorless liquids and were fully characterized by NMR, IR, and MS. Compounds **2a–e** are stable for several weeks when kept in the refrigerator.

Table I gives a survey of the synthesis of ketenimines **2**, while Table II compiles the spectral properties of compounds **2**. Up to now, NMR data from only one trialkylketenimine, i.e., dimethyl-*N*-cyclohexylketenimine, have been reported.[4]

From the mechanistic point of view, the synthesis of ketenimines **2** can be visualized by methane production and formation of a magnesium salt **5**, from which cyanide is expelled (Scheme II). In this respect the expulsion of cyanide from enamine anion **6** parallels the mechanistic behavior of α-halo enamines, which react as ketenimmonium halides.[8] The production of side products such as imidoylcyanides **3** and amides **4** is interpreted as derived from protonation of salt **5** (workup with water)[9] and addition of water to the ketenimine system, respectively. Surprisingly, reaction of 2-*tert*-butylamino-3-methyl-2-butenenitrile (**1a**) with methylmagnesium iodide in tetrahydrofuran resulted in a complete recovery of

Table I. Synthesis of Trialkylketenimines 2[a]

	Registry no.	R_1	R_2	R	Yield,[b] %	bp, °C (mmHg)
2a	63742-29-0	Me	Me	*t*-Bu	32	34 (13)
2b	66102-41-8	Et	Me	*i*-Pr	27	43–46 (17)
2c	66102-42-9	Et	Me	*t*-Bu	57	43–46 (12)
2d	66102-43-0	Et	Et	*i*-Pr	61	65 (21)
2e	66102-44-1	Et	Et	*t*-Bu	53	72 (19)

[a] All ketenimines **2a–e** gave satisfactory analytical data. [b] Isolated yields by distillation.

Table II. Spectral Properties of Trialkylketenimines 2

	IR (NaCl)[a] $\nu_{C=C=N}$, cm^{-1}	NMR (CCl_4; δ)[b] C alkyl	NMR (CCl_4; δ)[b] N alkyl	MS (70 eV)[c] *m/e* (rel abundance)
2a	2020	1.59 (6 H, s, Me_2)	1.14 (9 H, s, *t*-Bu)	125 (M^+, 56), 110 (20), 69 (88), 68 (29), 57 (100), 56 (16), 55 (14), 54 (25), 42 (35), 41 (76), 40 (18), 39 (23)
2b	2020	1.60 (3 H, s, CH_3C=), 1.00 (3 H, t, 6.5 Hz, MeCC=), 1.91 (2 H, q, 6.5 Hz, CH_2)	1.15 (6 H, d, 6.5 Hz, Me_2), 3.47 (1 H, septet, 6.5 Hz, CH)	125 (M^+, 26), 84 (8), 83 (38), 68 (100), 56 (8), 55 (10), 43 (20), 42 (24), 41 (24), 40 (8), 39 (9)
2c	2020	1.60 (3 H, s, MeC=), 1.00 (3 H, t, 6.5 Hz, MeCC=), 1.92 (2 H, q, 6.5 Hz, CH_2)	1.16 (9 H, s, *t*-Bu)	139 (M^+, 27), 124 (8), 83 (57), 68 (78), 57 (100), 56 (10), 55 (21), 54 (7), 41 (51), 39 (14)
2d	2020	1.02 (6 H, t, 7 Hz, CH_3), 1.96 (4 H, q, 7 Hz, CH_2)	1.16 (6 H, d, 6.5 Hz, Me_2), 3.51 (1 H, septet, 6.5 Hz, CH)	139 (M^+, 36), 124 (3), 97 (65), 96 (9), 82 (100), 70 (10), 69 (6), 68 (6), 55 (32), 54 (7), 43 (30), 42 (12), 41 (38), 39 (14)
2e	2020	1.00 (6 H, t, 7 Hz, CH_3), 1.91 (4 H, q, 7 Hz, CH_2)	1.16 (9 H, s, *t*-Bu)	153 (M^+, 28), 138 (8), 97 (78), 82 (100), 69 (8), 57 (99), 56 (8), 55 (20), 54 (14), 41 (52), 39 (13)

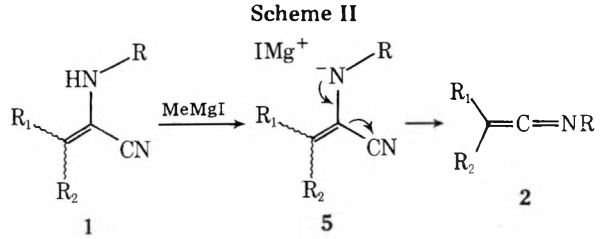
[a] Perkin-Elmer Model 257 spectrophotometer. [b] Varian T-60 NMR spectrometer. [c] AEI MS 20 mass spectrometer coupled with a Pye Unicam gas chromatograph (SE 30 column, He carrier gas).

Table III. Synthesis of Amidines 6

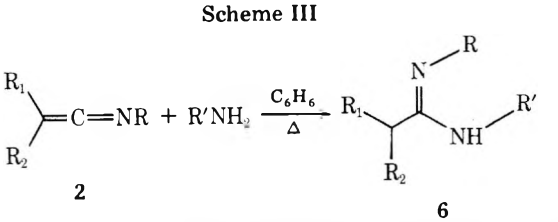
Compd[a]	Registry no.	R_1	R_2	R	R′	Reaction conditions (reflux C_6H_6)	Yield,[b] %
6aa	66102-45-2	Me	Me	*t*-Bu	C_6H_5	2 h; 1 equiv	84
6ab	66102-46-3	Me	Me	*t*-Bu	*p*-$CH_3C_6H_4$	2 h; 1 equiv	78
6ac	66102-47-4	Me	Me	*t*-Bu	*i*-Pr	15 h; 4 equiv	63
6ca	66102-48-5	Me	Et	*t*-Bu	C_6H_5	1 h; 1 equiv	74
6ca		Me	Et	*t*-Bu	C_6H_5	4 h; 1 equiv	60[c]
6db	66102-49-6	Et	Et	*i*-Pr	*p*-$CH_3C_6H_4$	4 h; 1 equiv	68
6dd	66102-50-9	Et	Et	*i*-Pr	*p*-$OCH_3C_6H_4$	2 h; 1 equiv	81
6ea	66102-51-0	Et	Et	*t*-Bu	C_6H_5	4 h; 1 equiv	61
6ec	66102-52-1	Et	Et	*t*-Bu	*i*-Pr	14 h; 4 equiv	77

[a] The first letter refers to the ketenimine substituents (see Table I), while the second letter points to the amine used. [b] Yields were determined by VPC using internal calibration, except otherwise stated. [c] Isolated yield based on α-cyano enamine **1**, without isolating ketenimine **2**.

Scheme II



Scheme III



starting material. On the other hand, phenylmagnesium bromide did not react with **1a** in diethyl ether.

Trialkylketenimines **2**, obtained according to Scheme I, were further characterized by addition of aliphatic and aromatic amines at the cumulenic π system, producing amidines **6**.[10] It is stressed that aliphatic N^1,N^2-disubstituted amidines are not accessible in general. The addition of aliphatic amines (R′ = alkyl) to ketenimines **2** provides a useful synthesis of these compounds (**6**: R, R′, R_1, R_2 = alkyl).

In order to evaluate the synthetic utility of the ketenimine synthesis described here, we tried to "trap" ketenimines **2** in their original ethereal solution (after treatment with aqueous ammonium chloride). As benzene was found to give better results for the amidine synthesis, the amine was added to the initial ethereal solution then ether was evaporated and replaced by benzene.[11] Refluxing this benzene solution of ketenimines **2** and an appropriate amine gave the desired amidines. According to this procedure, starting from 2-*tert*-butylamino-3-methyl-2-pentenenitrile (**1c**) and methyl-

magnesium iodide in diethyl ether, there was obtained a 60% yield of N^2-*tert*-butyl-N^1-phenyl-2-methylbutanamidine (**6ca**). The results of the amidine synthesis are given in Table III. Characterization data are recorded in microfilm supplement pages. The synthesis of amidines 6 from ketenimines, produced in situ as described above, demonstrates the usefulness of this facile and rapid method. Trialkylketenimines **2** can now be synthesized on a large scale without the necessity of distillation, since the ethereal solution can be used directly for further reactions.

Experimental Section

α-Cyano enamines **1** were prepared as previously described.[6,7] The following preparation serves as an example for the transformation of an α-cyano enamine into the corresponding ketenimine.

Synthesis of Trialkylketenimines 2. In a typical experiment, a solution of 18.0 g (0.1 mol) of 2-*tert*-butylamino-3-ethyl-2-pentenenitrile (**1e**) ($R_1 = R_2 =$ Et; R = *t*-Bu) in 20 mL of dry diethyl ether was added dropwise to a freshly prepared solution of methylmagnesium iodide in 130 mL of dry diethyl ether (prepared from 4.2 g (0.175 mol) of magnesium curlings and 24.8 g (0.175 mol) of methyl iodide). After a few minutes an amorphous precipitate (or resinous material) was formed and the mixture was refluxed for 2 h. After cooling to ice-bath temperature the reaction mixture was cautiously triturated with about 75 mL of ice–water and 75 mL of ice-cold saturated aqueous ammonium chloride solution. When the precipitate was decomposed completely, i.e., when homogenous layers were obtained, the ethereal layer was separated, ice was added, and the aqueous layer was twice extracted with ether. Drying of the combined extracts (1 h; $MgSO_4$/K_2CO_3) at ice-bath temperature and evaporation in vacuo at low temperature afforded an oil which was distilled in vacuo using a 10-cm Vigreux column to give 8.1 g of *N*-*tert*-butyldiethylketenimine (**2e**) as a colorless liquid, bp 72 °C (19 mmHg) (yield 53%). In some batches a small amount (1–3%) of *N*-*tert*-butyl-2-ethylbutanamide (**4e**) was present in the distilled product, probably due to capture of moisture during the distillation procedure.

Reaction of Trialkylketenimines 2 with Primary Amines. Typical Procedure. An equimolecular amount of ketenimine **2** and aromatic amine in dry benzene (10% solution) was refluxed for a time indicated in Table III. Evaporation of the solvent in vacuo left an oil which was distilled or analyzed by VPC. In the case of aliphatic amines, a fourfold molar excess was used.

Preparation of Amidines 6 without Isolating Ketenimines 2. The preparation of N^2-*tert*-butyl-N^1-phenyl-2-methylbutanamidine (**6ca**) serves as a typical procedure. The reaction mixture starting from 8.3 g (0.05 mol) of 2-*tert*-butylamino-3-methyl-2-pentenenitrile (**1c**) and 0.0875 mol of methylmagnesium iodide in diethyl ether was triturated with aqueous ammonium chloride as described above. The combined ethereal extracts were dried (1 h; $MgSO_4$/K_2CO_3). After filtration, 4.65 g (0.05 mol) of aniline was added and ether was evaporated in vacuo at low temperature, after which 80 mL of dry benzene was added. This benzene solution was refluxed for 4 h and evaporated to leave an oil, which was distilled in vacuo. The forerun contained mainly aniline and the fraction (6.9 g; yield 60%) boiling at 93–98 °C (0.02 mmHg) was identified as N^2-*tert*-butyl-N^1-phenyl-2-methylbutanamidine (**6ca**). Compound **6ca** solidified on standing, mp 59–61 °C.

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Registry No.—**1a**, 63364-14-7; **1b**, 66102-53-2; **1c**, 66102-54-3; **1d**, 66102-55-4; **1e**, 63364-26-1; benzenamine, 62-53-3; 4-methylbenzenamine, 106-49-0; 4-methoxybenzenamine, 104-94-9.

Supplementary Material Available: Full IR, NMR, and MS data of N^1,N^2-disubstituted alkanamidines **6**, Table IV (3 pages). Ordering information is given on any current masthead page.

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(9) α-Cyano enamines **1** isomerized partially into imidoylcyanides **3** on gas chromatographic analysis.[7] Since both isomers **1** and **3** could be isolated in pure form by preparative GLC it is more appropriate to refer to them as desmotropic forms. Strong bases can also partly convert α-cyano enamines **1** into imidoylcyanides **3**. The latter conversion was encountered when compounds **1** were allowed to react with KO-*t*-Bu–$CHCl_3$–pentane in order to obtain cyclopropanation (unpublished results).
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Synthesis of Symmetrical Diselenides from Aliphatic and Aromatic Aldehydes

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An efficient synthetic procedure that gives high yields of symmetric diselenides from aldehydes has been developed. The reaction of H_2Se with aromatic and aliphatic aldehydes in the presence of amines and $NaBH_4$ yields benzylic and aliphatic diselenides. A variant of this synthesis avoids the handling of toxic H_2Se and involves the reaction of NaHSe with amine hydrochloride and aldehyde, followed by a $NaBH_4$ reduction. Specifically deuterium-labeled benzyl diselenide was prepared and a reaction mechanism is proposed.

Many laboratory methods for the preparation of organic diselenides are based on the displacement of halides or tosylates by nucleophilic selenium species.[1] However, there are essentially no direct or efficient methods to convert other common organic functional groups into diselenides. Among potentially attractive new starting materials for such syntheses are carbonyl compounds, and their reactions with hydrogen selenide and its salts have been explored under a variety of conditions in several isolated examples.

Margolis and Pittman[2] obtained low yields of diselenides

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Table I. Reactions of Aromatic Aldehydes with Hydrogen Selenide

Expt no.	Reactant, mmol	Piperidine, mmol	Reaction time, min	$NaBH_4$, mmol	Diselenide yield, %
1	Benzaldehyde (47)	50	10	12	84
2	Benzaldehyde (47)	0	10	12	41
3	Benzaldehyde (47)	5	10	12	42
4	Benzaldehyde (47)	5	3 days	12	88
5	Benzylidenedipiperidine (23.2)	—	10	12	78
6	*p*-Methylbenzaldehyde (50)	50	10	13	85

when the corresponding ketones were treated with excess hydrogen selenide in the presence of strong hydrochloric acid.

3-Formylindole, when reacted with ammonium selenide, also gave a low (38%) yield of di(3-indolylmethyl) diselenide[3] under relatively basic conditions, in analogy to the conversion of aromatic ketones and aldehydes to disulfides[4-7] by alcoholic ammonium sulfides.

The conversion of benzaldehyde to dibenzyl diselenide has also been observed in its reaction with bis(methoxymagnesium) diselenide[8] in the presence of morpholine. It is interesting to note that no diselenide was isolated in the absence of amine.

The synthesis of various diselenides by a similar amine-catalyzed reaction of carbonyl compounds with hydrogen selenide has recently been described.[9]

These reactions appeared quite reasonable, and yet their combined processes did not constitute an efficient and generally applicable synthetic method. In all these examples rather inefficient use is made of the hydrogen selenide or its salts, much of it serving as a reducing agent. Further, long reaction times are required and the products tend to be heavily contaminated with elemental selenium and with oligoselenides. The latter are difficult to remove from the desired diselenides and suffer from slow decomposition with liberation of selenium upon storage and handling.

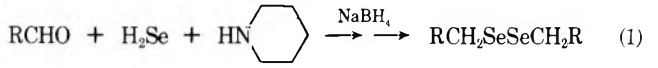
In a preliminary communication[10] we reported a novel synthetic procedure for preparing diselenides from aldehydes where short reaction times produce excellent diselenide yields with high product purity. We found that aromatic and aliphatic aldehydes are readily converted to diselenides by using a two-step, one-pot synthesis involving (a) the interaction of aldehyde, an amine, and hydrogen selenide and (b) treatment of the reaction mixture with sodium borohydride. A convenient variant of the procedure employs sodium hydrogen selenide and an amine hydrochloride to avoid the handling of toxic hydrogen selenide gas.

In this report we document the experimental findings, extend the reaction to the synthesis of a specifically deuterium-labeled diselenide, and propose a reaction mechanism.

Results and Discussion

The conversion of organic aldehydes by reaction with hydrogen selenide and sodium hydrogen selenide in ethanol solution to the corresponding organic diselenides was studied utilizing benzaldehyde as the model compound. Determination of product yields then allowed assessment of the efficiency of the reaction.

Reactions with Hydrogen Selenide. When a slight excess of hydrogen selenide was passed into a solution of benzaldehyde in the presence of 1 molar equiv of piperidine or morpholine in absolute ethanol (expt 1) the solution rapidly turned brown in an exothermic reaction. After 10 min this mixture was treated with sufficient sodium borohydride to give a clear, orange-yellow solution. Addition of water and crystallization of the precipitate gave yellow benzyl diselenide in yields exceeding 80% (eq 1). In the absence of amine, di-



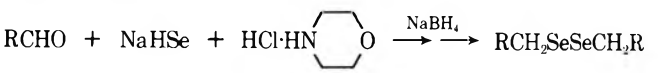
$$\mathrm{RCHO} + \mathrm{H_2Se} + \mathrm{HN}\bigcirc \xrightarrow{\mathrm{NaBH_4}} \mathrm{RCH_2SeSeCH_2R} \quad (1)$$

selenide yields were drastically reduced (expt 2), suggesting that amines must play a major role in the conversion of aldehydes to organic diselenides. The generality of this observation was demonstrated by varying amine concentrations and reaction conditions. Results summarized in Table I show that with only 0.1 molar equiv of piperidine the reaction required 3 days to give yields of diselenide in the 80% range (expt 4). With a 0.1 molar equiv of piperidine we could not exceed a 42% yield after 10 min (expt 3), comparable to what was obtained in the absence of amine. In a similar manner, *N,N'*-benzylidenedipiperidine, an aminal prepared from benzaldehyde and 2 equiv of piperidine,[11] reacted to give 80% benzyl diselenide (expt 5). These results confirm that the amine catalyzes the reactions, probably through the intermediacy of an aminal.

When the sodium borohydride reduction was omitted, diselenide quality and yields were considerably reduced. Since sodium borohydride also reduces diselenides,[12,13] the optimum quantity of this reagent was determined empirically. It was found that 0.25 molar equiv as compared to the aldehyde starting material gave maximum yields of diselenide with little contamination by selenols.

Although an effective reagent, hydrogen selenide gas suffers from the disadvantage of being extremely toxic[14] and its handling must be carefully controlled. Therefore, another approach was developed such that the use of hydrogen selenide gas was avoided.

Reactions with Sodium Hydrogen Selenide. Sodium hydrogen selenide (1.27 equiv), prepared by sodium borohydride reduction of elemental selenium in absolute ethanol,[15] was combined under an atmosphere of nitrogen with 1 equiv each of benzaldehyde and either piperidine hydrochloride or morpholine hydrochloride. Upon heating to reflux a reddish brown solution, similar in appearance to that in the hydrogen selenide reaction, was obtained. Treatment with 0.25 molar equiv of sodium borohydride gave benzyl diselenide in 86% yield, comparable to those in the hydrogen selenide case. Use of this general procedure has led to the synthesis of bis(4,4'-*N,N'*-diethylaminobenzyl) diselenide·2HCl (67%), bis(1-naphthylmethyl) diselenide (92%), bis(2-naphthylmethyl) diselenide (91%), bis(9-anthrylmethyl) diselenide (90%), and bis(1-dodecyl) diselenide (73%) from the corresponding aldehydes (eq 2).



$$\mathrm{RCHO} + \mathrm{NaHSe} + \mathrm{HCl{\cdot}HN}\bigcirc\mathrm{O} \xrightarrow{\mathrm{NaBH_4}} \mathrm{RCH_2SeSeCH_2R} \quad (2)$$

When piperidine (Table II, expt 7) was substituted for the piperidine hydrochloride (Table II, expt 8), the yields were drastically reduced to the 10–15% range. This suggests that the addition of an acid to the sodium hydrogen selenide reaction is essential.

Product yields were optimized following successive modi-

Table II. Reactions of Benzaldehyde with Sodium Hydrogen Selenide

Expt no.	Reactant, mmol	NaHSe, mmol	Amine, mmol	Reaction Time, min	Temp, °C	$NaBH_4$, mmol	Benzyl diselenide yield, %
7	Benzaldehyde (47)	50	Piperidine (50)	20	78	12	13
8	Benzaldehyde (47)	60	Piperidine·HCl (50)	20	78	12	68
9	Benzaldehyde (47)	75	Piperidine·HCl (50)	20	78	12	76
10	Benzaldehyde (47)	75	Piperidine·HCl (50)	45	55–60	12	81
11	Benzaldehyde (47)	75	Piperidine·HCl (50)	60	78	12	83
12	Benzaldehyde (47)	60	Piperidine·HCl (50)	60	78	12	80
13	Benzaldehyde (47)	60	Morpholine·HCl (50)	60	78	12	86
14	Benzaldehyde (12.3)	15	Morpholine·HCl (13)	60	25	3.6	67
15	Benzaldehyde (12.3)	15	Morpholine·HCl (13)	120	25	3.6	74
16	Benzaldehyde (47)	50	Morpholine·HCl (50)	60	78	—	54
17	*N,N'*-Benzylidenedimorpholine (50)	50[a]	—	60	78	—	56
18	*N,N'*-Benzylidenedimorpholine (50)	70[a]	—	60	78	—	82

[a] Hydrochloric acid (100 mmol) was added to the reaction after heating.

Table III. Reactions of Benzaldehyde with Sodium Hydrogen Selenide Using Various Amine Salts

Reactant	Amine salt	Benzyl diselenide yield, %
PhCHO	Ammonium chloride	20
PhCHO	Ammonium chloride	20
PhCHO	Cyclohexylamine·HCl	73
PhCHO	Piperidine·HCl	80
PhCHO	Morpholine·HCl	86
PhCHO	Triethylamine·HCl	64

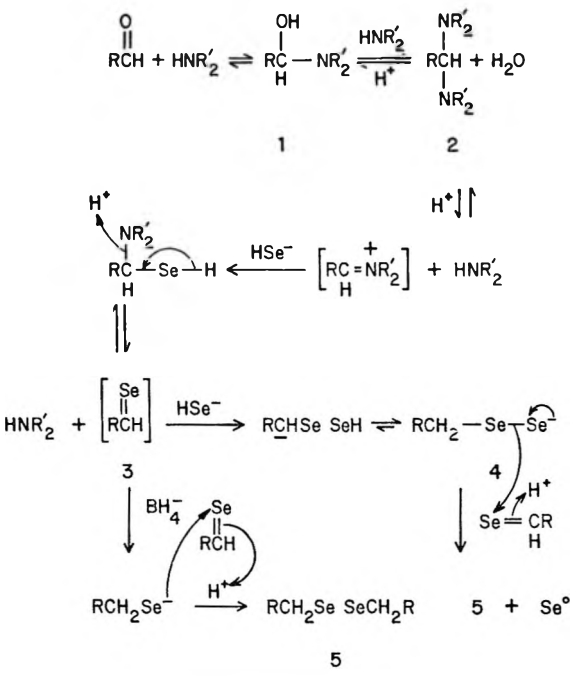
fications in reaction temperatures and reagent concentrations as described in Table II. When the reaction time was increased from 20 min to 1 h at 78 °C (expt 9–12), diselenide yields increased from 68% to more than 80% of theory. An overall yield of 74% was also obtained when sodium hydrogen selenide reacted with benzaldehyde and morpholine hydrochloride at room temperature (expt 14 and 15) for 2 h. These results indicated that, given an appropriate reaction period, satisfactory yields of diselenide may be obtained employing a wide range of reaction temperatures.

The effect of various amines on yields of benzyl diselenide was next investigated (Table III). It was found that secondary amines, i.e., piperidine and morpholine (expt 12 and 13), gave maximum yields of diselenide while decreased yields were obtained with both primary and tertiary amines. Secondary amines and aromatic aldehydes react readily to form hemiaminals and aminals[16] while primary amines yield imines and tertiary amines do not form stable adducts.[17] Thus, the primary step in amine catalysis is assumed to involve formation of secondary amine–aldehyde adducts. Further, our experiments also suggest that favorable reaction conditions are determined by a broad but definite pH range, where either high or low pH extremes decrease reaction rates.

When benzaldehyde was reacted with 1 molar equiv of sodium hydrogen selenide and morpholine hydrochloride with omission of the final sodium borohydride reduction, a 54% yield of benzyl diselenide was obtained (expt 16). This experiment shows that some degree of reduction must occur even in the absence of the final borohydride treatment, possibly by the hydrogen selenide anion. That such a process may be occurring is not surprising in view of reports substantiating the reducing potentials of hydrogen selenide anions.[18]

In order to determine the effectiveness of sodium hydrogen selenide as a reducing species, *N,N'*-benzylidenedimorpholine[19] was reacted with 1.0 and 1.4 molar equiv of sodium hydrogen selenide, respectively, in the presence of 2.0 equiv of

Scheme I



hydrogen chloride (expt 17 and 18). As summarized in Table II, the 1 molar equiv of sodium hydrogen selenide gave a 56% yield whereas the 1.5 molar equiv gave 82% yield, comparable to that obtained with borohydride reduction. The inefficiency of this reaction with 1 molar equiv of sodium hydrogen selenide in the absence of sodium borohydride is the direct result of its dual role as reactant and reducing agent. With sufficient additional reducing agents, such as sodium borohydride, a single molar quantity of sodium hydrogen selenide adequately functions in the conversion of aldehydes to diselenides.

Based upon these experimental results, we propose a mechanistic pathway for this reaction as outlined in Scheme I. In this sequence, the initial reaction involves the formation of an amine–aldehyde adduct such as a hemiaminal or aminal **1** or **2**. Nucleophilic displacement by the hydrogen selenide anion on **1** or **2** followed by an intramolecular elimination leads to a short-lived selenoaldehyde intermediate **3**. In this reaction sequence, we are suggesting two displacement steps, each of which is separately well documented: oxygen is displaced by nitrogen, and nitrogen, in turn, by selenium. The latter reaction is exemplified by formation of 2-selenophthalide from the corresponding imino ester.[20]

The proposed selenoaldehyde intermediate **3**, although never isolated, has previously been postulated as a transient

species in several reactions.[3,21,22] In light of the recent report on a selenoketone,[23] which gave the corresponding diselenide upon reduction with sodium borohydride, the intermediacy of a selenoaldehyde appears reasonable. The absence of selenoaldehyde polymers[24] also indicates that reduction of the postulated intermediate must occur at an exceedingly rapid rate.

Furthermore, we propose that this reduction of the selenoaldehyde **3** involves initial selenophilic attack by the hydrogen selenide anion, forming the diselenol anion **4.** The intermediate **4** could then interact with **3** in a four-centered process analogous to that proposed for the reaction of organic thiosulfates with sodium hydrogen selenide.[18] Upon protonation of the carbanion, the diselenide **5** and elemental selenium are obtained. As elemental selenium is produced, it may interact with unreacted NaHSe to produce the di- or polyselenide anion. That such a process occurs is indicated by the development of an intense red-brown color (characteristic of polyselenide anions) shortly after the reaction starts. This interaction would render the sodium hydrogen selenide less active in the addition and reduction process. However, the hydrogen selenide thus bound may be regenerated by acidification which then reduces the competing loss of sodium hydrogen selenide.[18]

The function of sodium borohydride in the final step involves an alternate reduction mechanism occurring via a hydride addition to the carbon atom of **3,** giving the diselenide **5.** In addition, the final sodium borohydride reduction step also serves as a means of eliminating any trace amounts of selenium by reduction to sodium hydrogen selenide which allows isolation of the precipitated diselenide in clean form.

An alternative and less efficient process which gives small yields of diselenide even in the absence of amines would involve direct nucleophilic attack by the selenide ion on the aldehyde carbonyl. Although the selenide ion is known to be an excellent nucleophile,[4,25] it also behaves as a generally good leaving group.[26,27] Therefore, the direct displacement of oxygen by the selenide anion seems to be difficult and this alternative route appears less attractive than that shown in Scheme I.

This reaction of organic aldehydes with a hydrogen selenide anion in the presence of an amine catalyst introduces an attractive and direct method for obtaining diselenides. The application of this reaction to form deuterium-labeled organic diselenides has also been demonstrated. Using sodium borodeuteride, DCl, ethanol-1-*d*, and benzaldehyde the deuterium-labeled dibenzyl-α-α'-d_2 diselenide was isolated in 54% yields. The potential use of labeled organic diselenides for mechanistic and biochemical studies appears attractive. Application of this synthesis to other similar starting materials is presently being investigated.

Experimental Section

Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained on a JEOL C-60H using Me_4Si as an internal standard. A Perkin-Elmer 267 grating spectrophotometer was used to determine infrared spectra. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. 37921.

Benzyl Diselenide Method I. a. Hydrogen selenide from a lecture bottle was slowly passed into a magnetically stirred solution of benzaldehyde (5.0 g, 47 mmol) and piperidine (4.3 g, 50.4 mmol) in absolute ethanol (70 mL). After 10 min a hot, reddish-brown solution had resulted. To this was added sodium borohydride (0.45 g, 12 mmol) in small quantities. The vigorous reaction resulted in a turbid orange-yellow solution. Addition of water precipitated a yellow solid which was collected, washed rapidly with large amounts of water, and dried. Recrystallization from ethanol gave yellow benzyl diselenide (6.7 g, 84%, mp 91–93 °C; lit.[15] mp 92–94 °C): NMR ($CDCl_3$) δ 3.76 (s, 2, $-CH_2-$), 7.18 (s, 5, C_6H_5). The results of varying reaction times and amine concentrations on benzyl diselenide yields using this procedure are summarized in Table I.

b. Hydrogen selenide was gently bubbled into a stirred solution of *N,N'*-benzylidenedipiperidine[11] (6.0 g, 32.2 mmol) in absolute ethanol (60 mL) contained in a 250-mL Erlenmeyer flask. After 10 min, sodium borohydride (0.25 g, 7 mmol) was added to the dark brown solution resulting in a color change to yellow. The product was precipitated by addition of water, collected, and dried. Recrystallization from ethanol gave benzyl diselenide (3.1 g, 80%, mp 91–92 °C).

Method II. Gray powdered selenium (4.74 g, 60 mmol) and sodium borohydride (2.67 g, 70.6 mmol) were placed into a 500 mL, three-necked flask fitted with a nitrogen inlet, addition funnel, and reflux condenser. The flask was flushed with nitrogen, immersed in an ice bath, and absolute ethanol (100 mL) was added slowly with stirring. Stirring was continued until all selenium had dissolved and a colorless solution resulted. To this solution was added morpholine hydrochloride (6.2 g, 50 mmol) followed by benzaldehyde (5.0 g, 47 mmol). The reaction mixture was heated under reflux for 1 h and cooled to room temperature giving a brown solution. Addition of sodium borohydride (0.45 g, 12 mmol) in small doses resulted in a vigorous reaction and change of the solution color from brown to yellow-orange. Addition of water precipitated a yellow product, which was collected by filtration, washed rapidly with a large volume of water (to prevent formation of contaminants from air oxidation of the mother liquor), and dried yielding 6.9 g (86%) of benzyl diselenide. Recrystallized from ethanol the product had mp 92–93 °C, identical with that of an authentic sample. Table II summarizes benzyl diselenide yields obtained by this method with cited variations in reaction conditions. Results with different amines using the above procedure are listed in Table III.

Method III. d. Sodium hydrogen selenide solution was prepared using sodium borohydride (1.89 g, 50 mmol) and gray selenium (4.26 g, 54 mmol) in 100 mL of absolute ethanol as outlined in method II. To this was added morpholine hydrochloride (6.23 g, 50.4 mmol) and benzaldehyde (5.0 g, 47 mmol). This mixture was heated under reflux for 1 h and cooled to room temperature. Addition of water gave a yellow-green precipitate which was collected, washed with water, and dried. This product was extracted with hot methylene chloride, filtered, and solvent was removed in vacuo leaving a yellow solid. Recrystallization from ethanol gave 4.35 g (54%) of benzyl diselenide.

e. To an ethanolic sodium hydrogen selenide solution, made as described above, was added morpholine (4.34 g, 50 mmol) followed by benzaldehyde (5.0 g, 47 mmol) and reaction was continued as described. After cooling, hydrogen chloride (4.2 mL, 50 mmol) was added and the solution was stirred for 60 min at room temperature. Addition of water gave a yellow-green precipitate, which after workup gave benzyl diselenide (4.40 g, 55%).

f. Sodium hydrogen selenide was prepared using gray selenium (3.95 g, 50 mmol) and sodium borohydride (2.08 g, 55 mmol) to which was added 4,4'-benzylideneoimorpholine[19] (12 33 g, 47 mmol). The reaction was continued as described above. Upon cooling, hydrogen chloride was added (8.5 mL, 100 mmol) which after the usual workup gave 4.45 g (56%) of benzyl diselenide.

g. To an ethanolic sodium hydrogen selenide solution containing selenium (5.57 g, 70.5 mmol) and sodium borohydride (2.94 g, 77.6 mmol) was added 12.33 g (47 mmol) of 4,4'-benzylidenedimorpholine. Following the procedure described previously the reaction gave benzyl diselenide (6.5 g, 82%).

Dibenzyl-α,α'-d_2 Diselenide. To NaDSe solution, prepared with Se (2.0 g, 25.5 mmol), $NaBD_4$ (1.07 g 25.5 mmol), and 50 mL of anhydrous ethanol-d_1 was added 1.74 g (20 mmol) of morpholine, 1.68 mL of 38% DCl/D_2O (20 mmol) and 2.12 g (20 mmol) of benzaldehyde. The reaction mixture was heated to reflux for 1 h. After cooling to room temperature, 0.42 g (10 mmol) of $NaBD_4$ was slowly added to the brown mixture resulting in an orange-yellow solution after 15 min. Addition of water precipitated a yellow solid which was thoroughly washed with water and dried in a vacuum desiccator to give dibenzyl-α,α'-d_2 diselenide (1.85 g, 54%). Recrystallization from ethanol gave yellow needles, mp 91–92 °C: NMR ($CDCl_3$) δ 3.70 (1 H, s), δ 7.20 (5 H, s); IR C–D (ν) 2211 cm^{-1} (calcd 2178 cm^{-1}).

Bis(1-naphthylmethyl) Diselenide. 1-Naphthaldehyde (7.3 g, 47 mmol) was reacted with ethanolic sodium hydrogen selenide and morpholine hydrochloride as described in method II. The yellow product was isolated and dried to give 9.4 g (91%) of bis(1-naphthylmethyl) diselenide. Recrystallization from ethanol gave yellow crystalline plates, mp 110–111 °C: NMR ($CDCl_3$) δ 4.15 (s, 2, $-CH_2-$), 7–8.1 (m, 7, $C_{10}H_7$). Anal. Calcd for $C_{22}H_{18}Se_2$: C, 60.01; H, 4.12; Se, 35.87. Found: C, 60.02; H, 4.10; Se, 35.86.

Bis(2-naphthylmethyl) Diselenide. 2-Naphthaldehyde (7.34 g, 47 mmol) was reacted with morpholine hydrochloride and sodium

hydrogen selenide to give 9.5 g (92%) of 2-naphthylmethyl diselenide. Recrystallization from ethanol gave yellow needles, mp 134–135.5 °C: NMR ($CDCl_3$) δ 3.9 (s, 2, $-CH_2Se$), 7–7.8 (m, 7, $C_{10}H_7$). Anal. Calcd for $C_{22}H_{18}Se_2$: C, 60.01; H, 4.12; Se, 35.87. Found: C, 59.89; H, 4.16; Se, 35.83.

Bis(9-anthrylmethyl) Diselenide. 9-Anthraldehyde (9.69 g, 47 mmol) was reacted in a similar fashion with morpholine hydrochloride and sodium hydrogen selenide to yield 11.9 g (90%) of 9-anthrylmethyl diselenide as a yellow crystalline solid upon recrystallization from toluene, mp 193–195 °C (dec). Anal. Calcd for $C_{30}H_{22}Se_2$: C, 66.68; H, 4.10; Se, 29.22. Found: C, 66.65; H, 4.08; Se, 29.25.

Bis(1-dodecyl) Diselenide. Dodecylaldehyde (8.66 g, 47 mmol) was reacted with morpholine HCl and NaHSe as described in method II. After reduction, the resulting product was extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was removed in vacuo and the yellow oily residue crystallized from cold ethanol to give 8.5 g (73%) of dodecyl diselenide. Recrystallization from acetone yielded a yellow solid, mp 29.5–30.5 °C (lit.[28] mp 30.5–31 °C): NMR ($CDCl_3$) δ 0.9 (t, 3, CH_3-), 1.3 (s, 20, $-CH_2-$), 3.0 (t, 2, $-CH_2-Se$). IR spectra showed no bands other than those for the alkyl groups in the region 4000–625 cm^{-1}.

Bis(4,4′-*N,N*-diethylaminobenzyl) Diselenide. *p*-Diethylaminobenzaldehyde (9.33 g, 47 mmol) was reacted with morpholine hydrochloride, sodium hydrogen selenide, and additional sodium borohydride in the manner described previously. The reaction mixture was extracted with chloroform, washed with water, and dried over $MgSO_4$. Evaporation of solvent in vacuo gave a yellow oil. Dissolved in acetone, the oil was acidified with 5% HCl/EtOH solution to precipitate the *p*-diethylaminobenzyl diselenide·2HCl (8.67 g, 67%) as a yellow crystalline salt, mp 200–202 °C (dec): NMR ($CDCl_2$) δ 1.2 (t, 6, $-CH_3$), 3.6 (b, 4, $-CH_2-N-$), 3.9 (s, 2, $-CH_2-Se-$), 7.2–7.9 (m, 4, Ar). Anal. Calcd for $C_{22}H_{34}N_2Cl_2Se_2$: C, 47.58; H, 6.17; N, 5.04; Cl, 12.77; Se, 28.44. Found: C, 47.33; H, 6.37; N, 4.89; Cl, 12.74; Se, 28.37.

Bis(*p*-methylbenzyl) Diselenide. *p*-Tolualdehyde (6.0 g, 50 mmol) was combined with 4.3 g (50.4 mmol) of piperidine in 70 mL of absolute ethanol and hydrogen selenide as described by method I. Approximately 0.60 g of $NaBH_4$ (13.2 mmol) was added to this solution giving a orange-yellow reaction mixture. The resulting yellow product was recrystallized from methanol and gave yellow needles, 7.8 g (85%) of *p*-methylbenzyl diselenide, mp 61–62 °C: NMR ($CDCl_3$) δ 2.3 (s, 3, CH_3-), 3.73 (s, 2, $-CH_2Se-$), 7.04 (s, 4, Ar). Anal. Calcd for $C_{16}H_{18}Se_2$: C, 52.19; H, 4.93; Se, 42.88. Found: C, 52.18; H, 5.01; Se, 42.82.

Registry No.—Benzaldehyde, 100-52-7; benzyl diselenide, 1482-82-2; *N,N′*-benzylidenedipiperidine, 2538-76-3; 4,4′-benzylidenedimorpholine, 6425-08-7; dibenzyl-α,α′-d_2 diselenide, 65915-28-8; bis(1-naphthylmethyl) diselenide, 53391-04-1; 1-naphthaldehyde, 66-77-3; bis(2-naphthylmethyl) diselenide, 53391-03-0; 2-naphthaldehyde, 66-99-9; bis(9-anthrylmethyl) diselenide, 61098-92-8; 9-anthraldehyde, 642-31-9; bis(1-dodecyl) diselenide, 10564-87-1; dodecylaldehyde, 112-54-9; bis(4,4′-*N,N*-diethylaminobenzyl) diselenide·2HCl, 65915-29-9; *p*-diethylaminobenzaldehyde, 120-21-8; bis(*p*-methylbenzyl) diselenide, 65915-30-2; *p*-tolualdehyde, 104-87-0; H_2Se, 7783-07-5; NaHSe, 12195-50-5; NaDSe, 12175-25-6.

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Iodonium Ylides. The Action of Thiols on Phenyl Dimedonyl Iodone. Oxidation–Reduction vs. Substitution

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The reactions of phenyl dimedonyl iodone (1) with various thiophenols, methanethiol, and hydrogen sulfide were studied. With thiophenol, the major process is oxidation–reduction to diphenyl disulfide (6) (73%), dimedone (7) (70%), and iodobenzene (99%). A 15% yield of phenyl 2-dimedonyl sulfide (8), a product of "substitution", was also obtained. The oxidation of thiophenol by 1 apparently proceeds by initial protonation of the latter by the former and subsequent electron transfer from the resulting thiophenoxide ion to the conjugate acid of 1. The general reaction does not change with para-substituted thiophenols. However, the *ratio* of substitution/oxidation is dependent on the electron-donating capacity of the substituent. With methanethiol the gross reaction is the same. The action of hydrogen sulfide on 1 was reinvestigated, and the spirosulfide 2 (41%), dimedone (7) (28%), and 2,2′-bis(dimedonyl) sulfide (29) (12%) were obtained.

Introduction

Phenyl dimedonyl iodone (1), a stable iodonium ylide,[1] reacts with either phenyl isothiocyanate or methyl isothiocyanate to give low yields of the spirosulfide 2.[2] Since 5,5-dimethylcyclohexane-1,2-thio,3-trione (3) is a possible precursor to 2, we attempted to prepare authentic 3 by the treatment of 1 with hydrogen sulfide.[2] The thiotrione was not obtained, but the spirosulfide was isolated in 40% yield. We subsequently became interested in the reactions of other sulfhydryl compounds, specifically methanethiol and various thiophenols, with phenyl dimedonyl iodone and now report

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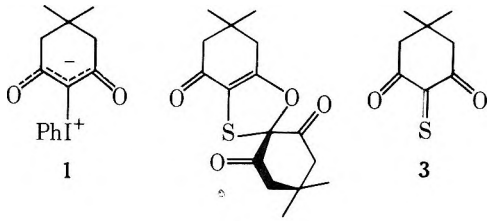
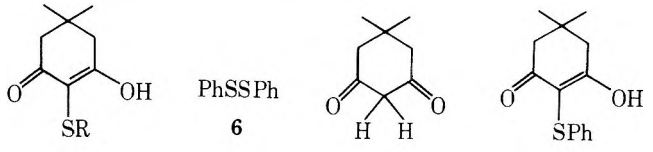


1 2 3

that the oxidation of thiols by **1** is a dominant but not exclusive process.

Results and Discussion

In view of the known ability of diaryliodonium salts to arylate nucleophiles,[3-8] it was anticipated that **1** would react with organic thiols to give primarily sulfides (**4**). In fact, such sulfides were usually minor products. The reaction of **1** with thiophenol (**5**) in dichloromethane at ice bath temperature gave diphenyl disulfide (**6**), dimedone (**7**), and 2-thiophenoxydimedone (**8**) in *isolated* yields of 73, 70, and 15%, respectively, and iodobenzene in 99% yield (determined by GC analysis in a separate experiment).

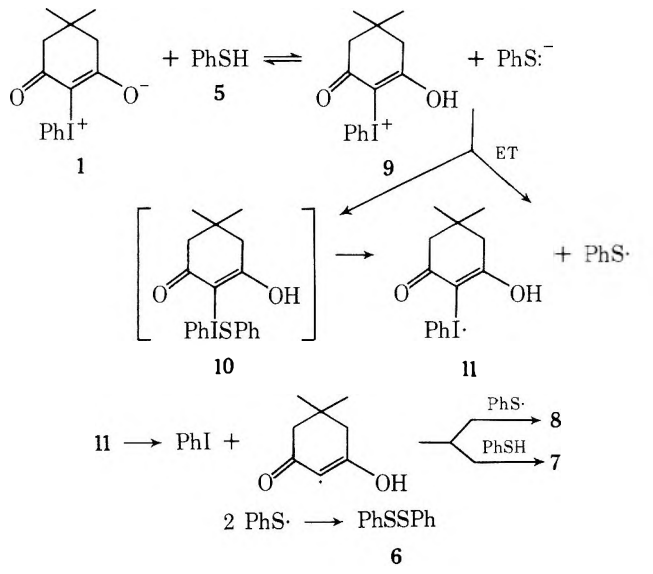


4 6 7 8

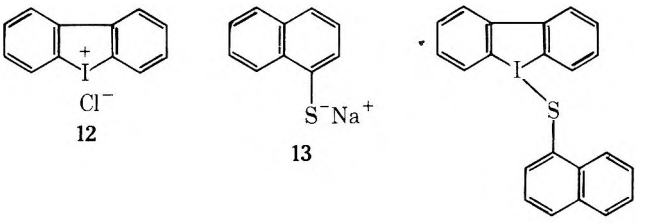
The formation of **6**, **7**, **8**, and iodobenzene from **1** and thiophenol may be rationalized by (a) reversible protonation of **1** by thiophenol to give the phenyl-2-dimedonyliodonium ion (**9**) and thiophenoxide ion; (b) *formal* electron transfer (ET) from the latter species to **9** to give phenyl-2-dimedonyliodine radical (**11**) and thiophenoxyl radical; and (c) homolytic decomposition of **11** followed by various radical abstraction and combination processes (Scheme I). A similar ET mechanism was proposed by Beringer to account for the arylation of indandionate ions by diaryliodonium salts.[9,10]

The reaction between **1** and **5** is complete within minutes and thus the equilibrium constant (K_p) for the protonation of **1** by **5** in dichloromethane has not been determined. However, the pK_a of **9** as the tosylate salt has been measured in aqueous ethanol and is reasonably insensitive to changes in solvent composition (0.72 in pure water, 1.42 in 50% ethanol, and 1.48 in 85% ethanol).[11] The pK_a of thiophenol in 95% ethanol has been reported to be ~9.3.[12] If it is assumed that the pK_a of **9** is ~1.5 in 95% ethanol, a K_p value of 6.33×10^{-9} can be computed for that solvent.

Scheme I

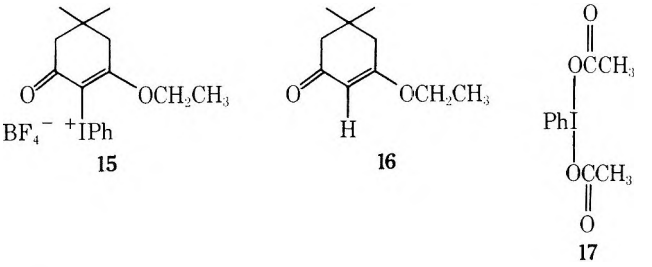


The susceptibility of thiophenoxide ion to electron-transfer oxidation is well known. For example, Meyers and Hsu have recently studied such oxidations by the triphenylmethyl cation.[13] The ET process may actually proceed through the covalent iodine(III) intermediate **10**, which suffers subsequent iodine–sulfur bond homolysis. That covalent iodine(III) compounds can decompose by free-radical pathways is an established fact.[7,14,15] The formation of a sulfur–iodine(III) bond may find precedent in the work of Sandin and his coworkers, who isolated a *stable adduct* when diphenyleneiodonium chloride (**12**) was allowed to react with sodium α-naphthalenethiolate (**13**).[16] A structure for the adduct was not proposed, but the iodine(III) structure **14** seems highly probable.



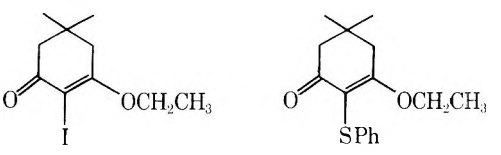
12 13 14

The following experiments indicate that the ET process requires the simultaneous presence of **9** and thiophenoxide ion. Thus, **1** did not react with methyl phenyl sulfide in dichloromethane, and analogy dictates that electron transfer from *un-ionized* thiophenol to **1** must be unlikely. When the known iodonium salt, phenyl-2-(3-ethoxy-5,5-dimethyl-2-cyclohexenonyl)iodonium tetrafluoroborate (**15**), prepared by the condensation of 3-ethoxy-5,5-dimethyl-2-cyclohexenone (**16**) with iodosobenzene diacetate (**17**) in fluoroboric acid[17] and a model for **9**, was treated with thiophenol, there was again no reaction. Even when the electron acceptor **15** is present, thiophenol does not function as an electron donor. Similarly, when **1** was treated with sodium thiophenoxide (the electron donor) in acetonitrile, there was no reaction.



15 16 17

Finally, **15** reacted rapidly with sodium thiophenoxide in acetonitrile at ice bath temperature. After the sodium tetrafluoroborate was removed by filtration (89% yield), the crude product mixture was separated by column chromatography on Florisil to give diphenyl disulfide (**6**; 73%), 2-iodo-3-ethoxy-5,5-dimethyl-2-cyclohexenone (**18**; 38%), 3-ethoxy-5,5-dimethyl-2-cyclohexenone (**16**; 5%), and 2-thiophenoxy-3-ethoxy-5,5-dimethyl-2-cyclohexenone (**19**; 17%). The yield of iodobenzene, determined in a separate experiment, was 57%.



18 19

Formal electron transfer from the thiophenoxide ion to **15**

Table I.[a] Product yields (%) from Reactions of 1 with Various Thiophenols

Thiophenol	Registry no.	% disulfide	Registry no.	% sulfide	Registry no.	% 7[b]	% PhI[c]	σ	Subst/oxid product
p-NO_2	1849-36-1	80.5	100-32-3	0		43	97	+0.778	0
p-Cl	106-54-7	82.5	1142-19-4	10	66102-84-9	86	99	+0.227	0.120
H	108-98-5	73	882-33-7	15	61908-09-6	70	99	0.000	0.205
p-CH_3	106-45-6	72	103-19-5	32	66102-85-0	62	100	−0.170	0.444
p-OCH_3	696-63-9	65	5335-87-5	43	66102-86-1	46	94	−0.268	0.661
O-COOH	147-33-3	95	119-80-2			73			

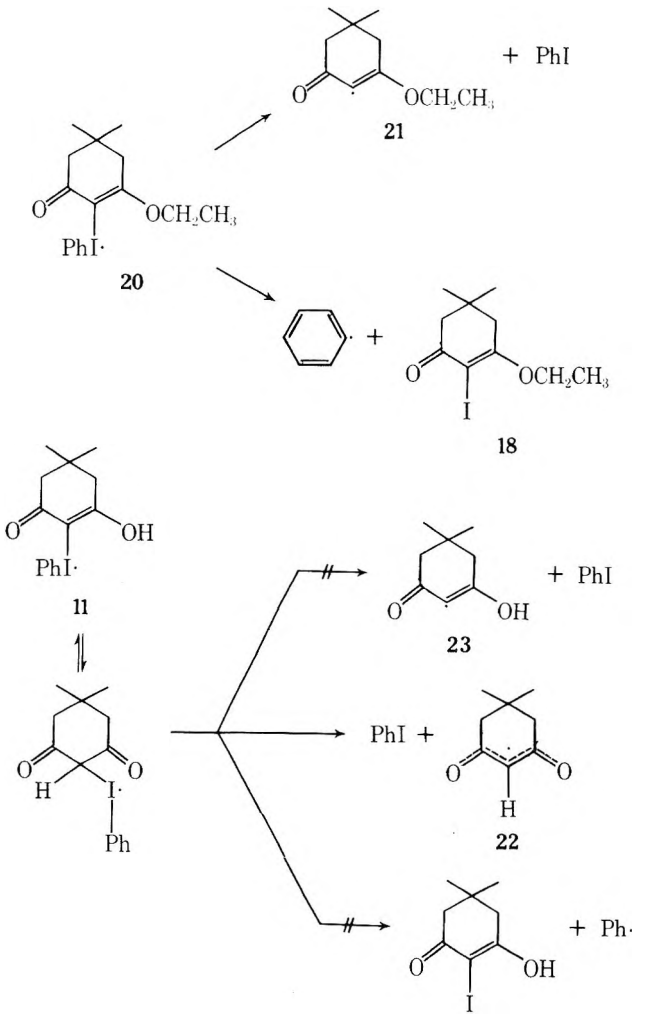
[a] In the Experimental Section, the sulfides are numbered as 8 (X = H), 8a (X = NO_2), 8b (X = Cl), 8c (X = CH_3), and 8d (X = OCH_3); the disulfides are numbered as 6 (X = H), 6a (X = NO_2), 6b (X = Cl), 6c (X = CH_3), and 6d (X = OCH_3). [b] Registry no.: 126-81-8. [c] Registry no.: 591-50-4.

in this reaction to give the iodine radical **20** seems reasonable. However, a significant difference between the decomposition modes of the proposed iodine radicals **11** and **20** is apparent. In **11**, the dimedonyl–iodine bond cleaves to the near exclusion of the phenyl–iodine bond (99% PhI), but in **20** both bonds cleave (57% PhI, 38% **18**). Since *cyclic* vinyl radicals such as **21** are electronically analogous and comparable in energy to the phenyl radical, the formation of both types of radicals from the common precursor **20** is expected and is consistent with the facts. However, the absence of a similar competition in the homolytic collapse of **11** is surprising and points to the involvement of the enolic hydrogen atom. If, for example, that hydrogen is transferred from oxygen to vinyl carbon either before or during decomposition of **11**, the π-radical **22** would be generated instead of the vinyl radical **23**. It is possible that **22** would be sufficiently more stable than either **23** or the phenyl radical to be formed selectively, and this would account for the absence of 2-iododimedone in the product mixture (Scheme II).

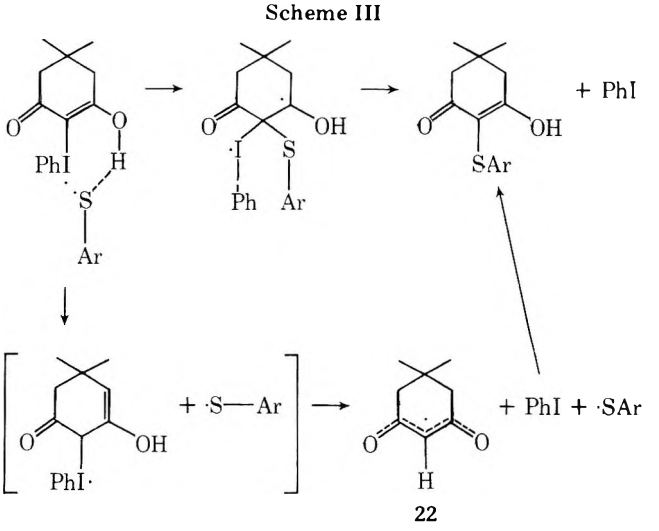
However, an even more complete mechanistic rationale is needed to accommodate the following observations. When **1** was allowed to react with various substituted thiophenols, the yield of substitution product decreased and the yield of oxidation product increased with an increase in electrophilicity of para substituents. The results are summarized in Table I, where the indicated yields are based on isolation except for those of iodobenzene, which were determined by GC analysis. Also in Table I, the ratios (substitution product/oxidation product) are compared to Hammett's σ constants. The correlation between the two is not linear, but a regular dependence is evident; e.g., as the substituent constants increase the indicated ratios decrease.

These results suggest that the substitution products arise primarily from caged radical pairs and that the redox products arise from radicals which have diffused into the bulk solvent (Scheme III). Implicit in this assumption is the suggestion that electrophilic substituents promote diffusion while nucleophilic substituents inhibit it. Perhaps the substitution products, when they are formed in a solvent cage, arise by direct attack of the thiyl radicals on the carbon–carbon double bond of **11** and subsequent elimination of iodobenzene from the intermediate diradical (Scheme III). It seems plausible that the thiophenoxy radicals might be held in proximity to that double bond by hydrogen bonding and, since their basicity decreases with an increase in electrophilicity of X, diffusion would become increasingly more competitive, and the yields of substitution product would diminish. We wish to emphasize, however, that at least a small part of the substitution product probably arises by the coupling of radicals which have diffused into the bulk solvent, and, in that case, radical **22** may be involved.

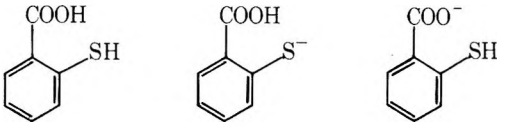
Scheme II



Scheme III



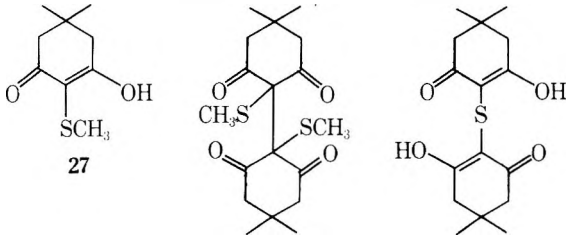
The oxidation of 2-carboxythiophenol (**24**) by **1** deserves comment. It seems clear that while protonation of **1** by the carboxyl function in **24** is a likely process, protonation of **1** by the sulfhydryl group of **24** leads to the observed products.



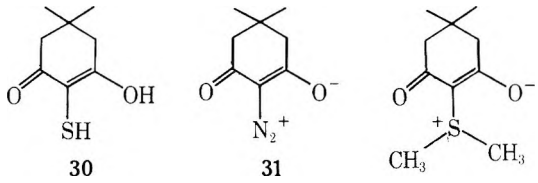
24 **25** **26**

That is, the electron donor is probably the thiophenoxide ion **25** and not the carboxylate ion **26.**

The oxidation–reduction reactions are not restricted to aromatic thiols. When iodonium ylide **I** was allowed to react with methanethiol in dichloromethane at ice bath temperature, the products included **7** (42%) and 2-thiomethoxydimedone (**27**; 33%). No attempt was made to isolate dimethyl disulfide, but its odor in the reaction mixture was unmistakable. At room temperature, the yield of **27** decreased to 17%, and an oxidation product (**28**) was isolated in 18% yield.



27 **28** **29**



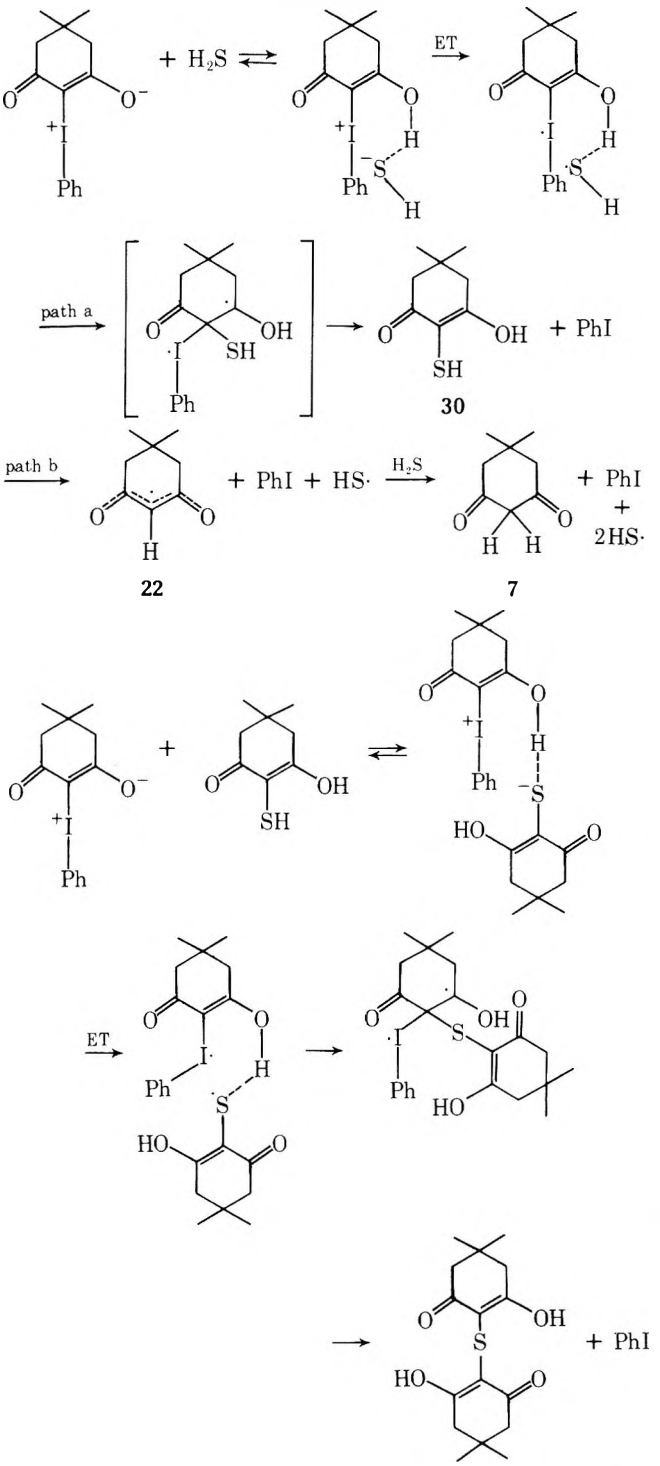
30 **31** **32**

(compound **28** was isolated in 58% yield from **27** and basic potassium ferricyanide). The mechanism for this reaction is probably the same as for **1** and thiophenol. However, in this case, the ratio of reduction (**7**) to substitution (**27**) is significantly lower (1.27 vs. 4.67 for thiophenol).

The reaction between **1** and hydrogen sulfide has been reinvestigated, since only **2** had been previously identified.[2] When a solution of **1** was saturated at room temperature with hydrogen sulfide, a rapid reaction ensued. The crude product mixture was chromatographed on Florisil to give the expected cyclic sulfide **2** (41%), **7** (28%), and 2,2-bisdimedonyl sulfide (**29**; 12%). Inasmuch as **2** and **29** may be viewed as substitution products, the ratio of reduction product to substitution product was 0.53, even lower than with methanethiol. The formation of **7** and **29** from **1** and hydrogen sulfide may proceed as indicated in Scheme IV, where electron transfer is again central. We also suggest that 2-mercaptodimedone (**30**) may be a direct precursor to **29.**

It is instructive to compare the reactivity of **1** toward thiophenol with that of other dimedonyl ylides. When a solution of 2-diazodimedone (**31**)[18] and thiophenol in dichloromethane was allowed to stand at room temperature for 24 h, there was no apparent reaction; compound **31** was recovered (93%). The dimethylsulfonium ylide (**32**)[19,20] was recovered in 95% yield from a similar reaction mixture after 24 h. The failure of compounds **31** and **32** to react with thiophenol may indicate that they are not sufficiently basic to provide threshold concentrations of their conjugate acids. Alternatively, the conjugate acids of **31** and **32** may exhibit reduction potentials sufficiently high that electron transfer from the thiophenoxide ion would be thermodynamically unfavorable. In the case of **32,** the second explanation seems more likely, since **32** is more basic than **1.**[6]

Scheme IV



Experimental Section

General. ^{1}H NMR spectra (60 MHz) were recorded on a Varian Model A-60 NMR spectrometer (with Me_4Si as an internal standard), IR spectra on a Perkin-Elmer Model 337 spectrophotometer, and UV spectra on a Cary-17 UV–vis–IR spectrophotometer. ^{1}H NMR spectra (300 MHz) were recorded on a Varian Model HR-300 NMR spectrometer at The University of Akron's NMR Center. GC analyses were conducted on Hewlett-Packard Model 5750 and F&M Model 700 gas chromatographs. A 10 ft × 1/8 in. stainless steel column packed with 5% silicone rubber (UCC-982-methyl vinyl) on 80–100 mesh Chromsorb G and a 10 ft × 2 mm (i.d.) column of Sp-1000 on 100–120 Chromosorb WAW were utilized. Elemental compositions were de-

termined by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are uncorrected.

Iodobenzene yields for reactions of **1** with various thiophenols and for **15** with sodium thiophenoxide were determined by GC analysis with durene as internal standard in experiments separate from those in which other products were isolated.

The column chromatographic separations discussed herein were conducted on Florisil. The elution fractions were generally about 300 mL in volume, and after solvent removal the fraction residues were subjected to NMR analysis. The specified solvent compositions refer to the solvent added at the top of the column and not that collected from the bottom of the column.

Sodium thiophenoxide,[21] **1**,[1,22] **15** (60%, mp 160–162 °C),[17] **31** (81%, mp 104–106 °C),[18,29] and **32** (79%, mp 169–171 °C)[19,20] were prepared by literature procedures. Compound **16** (83%, mp 57–58 °C)[23] was prepared by TsOH-H_2O catalyzed "esterification" of **7** with ethanol. Compounds **6** and **7** were generally identified by melting point and/or NMR analysis. The NMR spectra of the authentic materials were available for comparison.

Reactions of 1 with Various Thiophenols. The reaction conditions and workup procedure for the reaction of **1** with thiophenol are given below in detail. For other thiophenols, conditions and workups were *similar*, but not identical.

Thiophenol. To a solution of **1** (9.13 g, 26.7 mmol) in CH_2Cl_2 (80 mL), cooled in an ice bath, was added a solution of thiophenol (6.00 g, 54.5 mmol) in CH_2Cl_2 (80 mL) over a period of about 1 min. The reaction mixture was allowed to stir at ice bath temperature for 1 h and subsequently evaporated to dryness. The crude, pale yellow solid (9.1 g) which remained was recrystallized from ethyl acetate (60 mL) and yielded 2.36 g of **7** as long, white needles, mp 145 °C. The filtrate was evaporated to dryness, the residue was taken up in CH_2Cl_2 (10 mL), and the resulting solution was subjected to column chromatography on Florisil (~200 g); 17 fractions were collected: fractions 1–5 (cyclohexane = C_6H_{12}), 6–9 (Et_2O/C_6H_{12}, 2:8), 10–11 (Et_2O/C_6H_{12}, 5:5), 12–13 (Et_2O), 14 (Et_2O/CH_3CO_2Et, 5:5), 15 (CH_3CO_2Et), 16 (CH_2Cl_2), 17 (EtOH). Fractions 1–3 gave **6** (4.32 g), 6–13 gave 8 (0.993 g), and 16 gave **7** (0.145 g). The crude solid from fractions 14 and 15, containing **7** and **8**, was recrystallized from ethyl acetate and gave 0.12 g of **7** (mp 146 °C).

Crude **6** (4.31 g) was recrystallized from methanol as fine, white needles (yield 3.90 g, mp 59–61 °C), crude **7** (2.62 g) was recrystallized from ethyl acetate as long, white needles (yield 2.34, g, mp 149–151 °C), and crude **8** (0.99 g) was recrystallized from cyclohexane as fine, white needles (yield 0.87 g, mp 120–121 °C).

***p*-Nitrothiophenol:** 9.261 g (27 mmol) of **1**, 8.34 g (54 mmol) of *p*-nitrothiophenol, 200 mL of CH_2Cl_2, chromatographic workup. Products were **6a** (6.694 g, 80.5%), mp 178 °C [lit.[24] mp 182 °C], and **7** (1.636 g, 43%).

***p*-Chlorothiophenol:** 9.267 g (27.02 mmol) of **1**, 7.758 g (54.06 mmol) of *p*-chlorothiophenol, 200 mL of CH_2Cl_2, chromatographic workup. Products were: **6b** (6.406 g, 83%), recrystallized from CH_3OH as yellowish scales, mp 68–69 °C [lit.[25] mp 70–71 °C]; **8b**, recrystallized from cyclohexane (0.759 g, 10%), mp 133–134 °C; and **7** (crude yield 3.268 g, 86%).

***p*-Methylthiophenol:** 9.261 g (27 mmol) of **1**, 8.964 g (54 mmol) of *p*-methylthiophenol, 200 mL of CH_2Cl_2, chromatographic workup. Products were: **6c** (4.767 g, 72%), mp 46–48 °C [lit.[26] mp 47–48 °C]; **7** (2.353 g, 62%) and **8c** (2.248 g, 32%).

***p*-Methoxythiophenol:** 9.261 g (27 mmol) of **1**, 7.56 g (54 mmol) of *p*-methoxythiophenol, 200 mL of CH_2Cl_2, chromatographic workup. Products were: **6d** (4.874 g, 65%), green liquid [lit.[26] mp 44 °C]; **7** (1.74 g, 46%); and **8d** (3.24 g, 43%).

2-Carboxythiophenol. A solution of **1** (3.179 g, 9.3 mmol) in CH_2Cl_2 (50 mL) was mixed with a solution of **24** (3.294 g, 21.4 mmol) in CH_3OH (50 mL). Mild heat evolution was observed. The reaction mixture, which became cloudy within 1 min, was allowed to stir at room temperature for 0.5 h. The tan insoluble powder which had formed during that period was then isolated, washed with CH_2Cl_2 (~10 mL), dried, and identified by ^1H NMR analysis as 2,2′-bis(carboxydiphenyl) disulfide: yield, 2.681 g (84%). The filtrate was concentrated and gave 2.739 g of a yellow solid, which was treated with hot ethyl acetate; 0.361 g of the disulfide remained undissolved. The total yield of the disulfide was 95%. When the solution was allowed to cool, dimedone (**7**) crystallized in needles: yield, 0.953 g (73%); mp 146–148 °C.

Characterization of 8: NMR ($CDCl_3$) δ 1.10 [s, 6, $C(CH_3)_2$], 2.47 (s, 3.92, 2 CH_2), 7.18 (s, 5.04, arom), ~8.4 (br s, 1.22, enol OH): IR (KBr) 3.95 (v br band 3.2–5.1 similar to dimedone OH), 6.41 μm (vs); IR ($CHCl_3$) 3.06 (OH), 6.14 μm (conjugated C=O); UV (CH_3OH) λ_{max} 248 (ϵ 19 765), 280 nm (sh tailing to 325 nm, ϵ 7092).

Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49; S, 12.91. Found: C, 68.01; H, 6.50; S, 12.64.

Characterization of 8b: white powder (from cyclohexane): mp 133–134 °C; NMR ($CDCl_3$) δ 1.1 [s, $C(CH_3)_2$], 2.48 (s, 2 CH_2), 7.14 (br "s", arom), 7.8 (br s, enol OH, exchanges with D_2O); IR ($CHCl_3$) 3.06 (OH), 6.35 μm (conj C=O); UV (CH_3OH) λ_{max} 262 nm (ϵ 7375).

Anal. Calcd for $C_{14}H_{15}O_2Cl$ S: C, 59.47; H, 5.31; Found: C, 59.62; H, 5.56.

Characterization of 8c: white powder (from cyclohexane); mp 101–103 °C; NMR ($CDCl_3$) δ 1.08 [s, $C(CH_3)_2$], 2.25 (s, CH_3), 2.45 (s, 2 CH_2), 7.07 (br s, arom), 7.85 (br s, enol OH, exchanges with D_2O); IR ($CHCl_3$) 3.06 (OH), 6.36 μm (conj C=O); UV (CH_3OH) λ_{max} 254 nm (ϵ 10 420).

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.9. Found: C, 68.34; H, 7.04.

Characterization of 8d: mp 109–110 °C (from cyclohexane); NMR ($CDCl_3$) δ 1.07 [s, $C(CH_3)_2$], 2.44 (s, 2 CH_2), 3.73 (s, OCH_3), ~6.67–7.35 (m, arom), 8.00 (br s, enol OH, integrates for 0.5 H, exchanges with D_2O); IR ($CHCl_3$) 3.03 (OH), 6.33 μm (conj C=O); UV (CH_3OH) λ_{max} 254 nm (ϵ 9687).

Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.75; H, 6.47. Found: C, 65.12; H, 6.64.

Reaction of 15 with Sodium Thiophenoxide. To a solution of **15** (8.08 g, 17.6 mmol) in CH_3CN (60 mL), cooled in an ice bath, was added a suspension of sodium thiophenoxide (2.43 g, 18.4 mmol) in CH_3CN (60 mL). The reaction mixture cleared immediately and turned bright yellow, but it became pale yellow, and a white precipitate formed. The reaction mixture was allowed to stir for an additional 1 h at ice bath temperature and, upon subsequent filtration, gave 0.73 g of $NaBF_4$ as a white solid. The pale yellow filtrate was evaporated to dryness and the residue was triturated with CH_2Cl_2 (60 mL), which gave an additional 0.996 g of the insoluble $NaBF_4$. The pale yellow CH_2Cl_2 solution was then concentrated to a wet solid, which was subjected to column chromatography on Florisil (~200 g), 23 fractions being collected: fractions 1–4 (C_6H_{12}), 5–8 (Et_2O/C_6H_{12}, 1:9), 9 (Et_2O/C_6H_{12}, 2.8), 10–11 (Et_2O/C_6H_{12}, 5:5), 12–17 (Et_2O/C_6H_{12}, 8:2), 18–19 (Et_2O), 20–21 (Et_2O/CH_3CO_2Et, 5:5), 22–23 (CH_3CO_2Et). Fractions 1–3 gave **6** (1.466 g), 8–15 gave **18** contaminated with some **16** (wt 2.49 g), and 18–21 gave mostly **19** (1.056 g).

The solids from fractions 8–15 were combined (2.49 g) and washed with two 10-mL portions of ethanol. A white solid (1.01 g), identified as 2-iodo-3-ethoxy-5,5-dimethyl-2-cyclohexenone (**18**), remained undissolved. The ethanol solution, when concentrated to half-volume, yielded an additional 0.55 g of **18**, which was isolated by filtration. The filtrate was then evaporated to dryness, and the residue, upon trituration with ethanol (3 mL), gave 0.28 g of **18**. The resulting ethanol solution was concentrated to a wet, brown solid which was shown by ^1H NMR analysis to be a 1:1 mixture of **16** and **18**. This material was triturated with ether (5 mL) and 0.096 g of **18** was obtained. Thus, the total *isolated* yield of **18** was 1.95 g.

The ether solution from the above trituration was transferred to a molecular still, the solvent was evaporated under a nitrogen stream, and the crude residue was distilled: bp 90–95 °C (~1 mm). In this way, 0.153 g of a thick, light yellow liquid, shown by ^1H NMR analysis to be 3-ethoxy-5,5-dimethyl-2-cyclohexenone (**16**) contaminated with trace impurities, was obtained.

The liquids from fractions 18–21 were combined and, after 2 days under ambient conditions, solidified to a yellow, crystalline material. This crude solid was triturated with two portions (10 mL, 5 mL) of ether and gave 0.801 g of 2-thiophenoxy-3-ethoxy-5,5-dimethyl-2-cyclohexenone (**19**) as a white powder.

Characterization of 18: NMR ($CDCl_3$) δ 1.12 [2, 6, $C(CH_3)_2$], 1.43 (t, J = 7 Hz, $-CH_2\mathbf{CH_3}$), 2.43 (s, 2.3, CH_2), 2.57 (s, 2.1, CH_2), 4.23 (q, J = 7 Hz, 2.1, $-\mathbf{CH_2}CH_3$); IR (KBr) 6.12 (conj C=O), strong bands at 6.45, 7.38, 7.72, and 8.09 μm; UV (CH_3OH) λ_{max} 283 nm (ϵ 9417).

Anal. Calcd for $C_{10}H_{15}O_2I$: C, 40.84; H, 5.15; I, 43.15. Found: C, 40.84; H, 5.30; I, 43.30.

Compound **18** has previously been reported by Neiland and Vanag.[27] It gradually (~2 weeks) decomposes upon storage at room temperature.

Characterization of 19: mp 93–95 °C; NMR ($CDCl_3$) δ 1.12 [s, $C(CH_3)_2$], 1.19 (t, J ~7 Hz, $-OCH_2\mathbf{CH_3}$), 2.37 (s, CH_2), 2.57 (s, CH_2), 4.13 (q, J ~7 Hz, $-\mathbf{OCH_2}CH_3$), 7.14 (*apparent* s, aromatic hydrogens). The resonances at δ 1.12 and 1.19 overlap and were, therefore, integrated together. Also, the combined integration of the ring methylene singlets is reported. NMR integration: theoretical, 9:4:2:5; experimental 9:4.15:1.85:4.77. IR (KBr) 6.10 (C=O of an α,β-unsaturated ketone with a β-OCH_2CH_3 substituent), strong bands at 6.46, 7.37, 7.81, and 8.05 μm; UV (CH_3OH) λ_{max} 252 (ϵ 21 406), plateau at 279 nm (ϵ 2702).

Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.24; S, 11.60. Found: C, 69.80; H, 7.34; S, 11.57.

Reaction of 1 with Methanethiol at ~0 °C. A solution of **1** (8.35 g, 24.4 mmol) in CH_2Cl_2 (200 mL) was cooled in an ice bath and subjected, for 10 min, to a stream of methanethiol. During that time, the yellow color of the ylide solution was discharged. The reaction mixture was then evaporated to a crude solid which was dissolved in hot ethyl acetate (60 ml). Upon cooling, the ethyl acetate solution yielded 1.01 g of **7** as long, colorless needles. The filtrate was concentrated to dryness, and the residue was subjected to column chromatography on Florisil, 18 fractions being collected: fraction 1 (C_6H_{12}), 2–8 (Et_2O/C_6H_{12}, 2:8), 9–12 (Et_2O/C_6H_{12}, 5:5), 13 (Et_2O/C_6H_{12}, 8:2), 14 (Et_2O), 15–16 (CH_3CO_2Et), 17 (CH_2Cl_2), 18 (EtOH). Fractions 1–2 gave a mixture (0.44 g) of **27** and **28**, 3–12 gave **27** (1.131 g), and 13–17 gave a mixture (1.063 g) of **7** and **27**.

The solids (1.064 g) from fractions 13–17 were combined and dissolved in hot ethyl acetate (20 mL). That solution, upon cooling, gave **7** as fine white needles: yield, 0.355 g; mp 149 °C. From the filtrate, a second crop of dimedone (mp 148 °C, 0.072 g) was obtained. Thus, the total *isolated* yield of **7** was 1.441 g (42%).

The filtrate was concentrated to dryness, and the residue was crystallized from cyclohexane (20 mL). There was obtained 0.369 g of crystals, mp 84–86 °C, identified as 2-thiomethoxydimedone (**27**). The total isolated yield of **27**, including the material from fractions 3–12, was 1.500 g (33%). Finally, the combined samples of crude **27** (1.500 g) were recrystallized from cyclohexane as fine white needles: yield, 1.330 g; mp 85–86 °C.

Reaction of 1 with Methanethiol at Room Temperature. A solution of **1** (10.394 g, 30.4 mmol) in CH_2Cl_2 (120 mL) was saturated for 10 min with a stream of methanethiol at room temperature. Once again, the yellow color of the ylide solution was discharged. The reaction mixture was then concentrated to a white solid residue which was taken up in hot ethyl acetate (80 mL). The hot solution, upon cooling to room temperature, gave 1.524 g of fine white needles (mp ~148–149 °C) identified as **7**.

The filtrate was evaporated to dryness, and the residue was subjected to column chromatography on Florisil. The products were **7** (1.897 g, 44.5%), **27** (0.963 g, 17%), and **28** (0.887 g crude, 15.7%, mp 143–145 °C).

Characterization of 27: NMR ($CDCl_3$) δ 1.10 [s, 6, $C(CH_3)_2$], 2.14 (s, 2.9, $-SCH_3$), 2.44 (s, 4, 2 CH_2), 8.08 (br s, 0.8, OH); IR (KBr) 4.2 (enol OH, v br band from 3 to 5 μm similar to spectrum of **7**), 6.46 (very intense), 7.43, 7.68, 7.98 μm (very strong band with three maxima); IR ($CHCl_3$) 3.08 (OH), 6.06 (conj C=O), 6.31 μm (C=C); UV (CH_3OH; 3.95×10^{-5} M) λ_{max} 248 (ϵ 8377), 281 nm (8909); UV (CH_3OH; 4.94×10^{-5} M) λ_{max} 247 (ϵ 8382), 279 nm (7289); UV (CH_3OH; 9.88×10^{-5} M) λ_{max} 248 (ϵ 9081), 286 nm (sh, ϵ 5528).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58; S, 17.21. Found: C, 58.34; H, 7.56; S, 17.07.

Characterization of 28. The crude product was recrystallized from cyclohexane as white crystals (0.761 g, mp 143–145 °C): NMR ($CDCl_3$, 300 MHz, 55 °C) δ 1.18 [s, $C(CH_3)_2$], 2.33 (s, $-SCH_3$), 2.38 (d, $-CH_2-$, J = 14 Hz), 3.35 (d, $-CH_2-$, J = 14 Hz). The doublet at δ 2.38 overlaps with the singlet at δ 2.33. Therefore, the two resonances were integrated together. NMR integration: theoretical, 6:5:2; experimental, 6:5:2. IR ($CHCl_3$) 5.89 (~1690 cm^{-1}, C=O), sh at 5.79 μm.

Anal. Calcd for $2(C_9H_{14}O_2S) - 2H$: C, 58.35; H, 7.07; S, 17.31. Found: C, 58.21; H, 7.47; S, 17.20.

Oxidation of 2-Thiomethoxydimedone (27). To a solution of **27** (0.142 g, 0.764 mmol) in CH_2Cl_2 (5 mL) was added 5 mL of basic potassium ferricyanide solution. The two-phase mixture was allowed to stir under nitrogen for 20 h at room temperature and more CH_2Cl_2 (10 mL) was added. The CH_2Cl_2 layer was then isolated, dried ($MgSO_4$), and concentrated to a white powder, mp ~140 °C, identified by NMR analysis as **28**: yield, 0.083 g; 58%.

Reaction of 1 with Hydrogen Sulfide. A solution of **1** (11.68 g, 34.1 mmol) in CH_2Cl_2 (150 mL) was cooled in an ice bath and saturated with H_2S. The reaction mixture, which had become bright yellow, was allowed to stir at ~0 °C for 30 min and was subsequently evaporated to dryness. The residue, a bright yellow solid, was dissolved in hot ethyl acetate (50 mL). As the solution cooled, it gave long crystalline needles which were isolated, washed with ethyl acetate, and dried; yield, 1.77 g. NMR analysis of the solid revealed the presence of two components, **7** and **29**. Recrystallization of the mixed solids from absolute ethanol gave 0.63 g of 2,2′-thiobisdimedone (**29**) as fine needles; mp 229–231 °C [lit. mp 230–231 °C]. The filtrate was evaporated to dryness, and the white solid which remained was recrystallized from ethyl acetate, two crops of material being isolated; yield 0.72 g, 0.14 g. This product was identified as dimedone (**7**) by its melting point (149–150 °C) and by ^1H NMR analysis.

The original ethyl acetate filtrate was concentrated to dryness, and the material which remained was subjected to column chromatography on Florisil, 24 fractions being collected; fractions 1–2 (C_6H_{12}), 3–5 (Et_2O/C_6H_{12}, 2:8), 6–13 (Et_2O/C_6H_{12}, 3:7), 14–15 (Et_2O/C_6H_{12}, 5:5), 16–17 (Et_2O/C_6H_{12}, 8:2), 18–19 (Et_2O), 20–22 (Et_2O/CH_3CO_2Et, 5:5), 23–24 (CH_3CO_2Et). Fractions 1–8 gave **2** (1.961 g), 9–12 gave *mostly* **2** (0.289 g), 13 gave 0.027 g of mostly **7**, and 14–23 gave 0.840 g of **7** with unknown contaminants.

The solids from fractions 9–12 (0.289 g) were combined and recrystallized from 1:1 (v/v) cyclohexane/CH_2Cl_2, and 0.192 g of **2** was obtained. Thus, the total isolated yield of **2**, including the material from fractions 1–8, was 2.156 g (41%).

The combined solids from fractions 14–23 (0.839 g) were dissolved in hot ethyl acetate. Upon cooling, the solution yielded light yellow needles (0.424 g, mp 148–150 °C) which were isolated and recrystallized from ethyl acetate as long white needles; yield, 0.369 g; mp 149–150 °C. These were identified as **7**. The initial filtrate was concentrated to pale yellow needles which were recrystallized from ethyl acetate as fine, white needles (0.123 g, mp 149–150 °C) also identified as **7**. Thus, the total isolated yield of **7** was 1.36 g (28%).

The final filtrate above was then concentrated to a yellow solid (0.302 g) which was recrystallized from cyclohexane. In this way, 0.173 g of an unknown solid was obtained as a yellow powder; mp 184–185 °C. Although this material has not been identified, its elemental composition has been determined and is the same as that of compound **2**.

Characterization of 2,2′-Thiobisdimedone (29). This material has been reported as a product from the reaction of dimedone with dimethoxy disulfide in the presence of potassium *tert*-butoxide.[28] However, only its melting point has been reported, and, for that reason, we report its characterization here: NMR ($CDCl_3$) δ 1.06 (s, 12 H), 2.40 (s, 8 H), 10.14 (s, 2 H), exchangeable with D_2O; IR ($CHCl_3$) 6.16 (C=CC=O), 3.25 μm (OH).

Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 61.96; H, 7.20; S, 10.55.

Control Experiments: (1) **24** (3.438 g) CH_3OH (50 mL), 3 days, ambient conditions; 3.363 g (98%) of **24** recovered. (2) Thiophenol (5 mL), CH_2Cl_2 (50 mL), 3 days, ambient conditions; only 0.054 g (1%) of **6** obtained. (3) **1** (3.42 g), benzoic acid (2.53 g), CH_2Cl_2 (40 mL), 20 h at room temperature; 2.84 g (83%) of **1** recovered. (4) **15** (2.66 g), thiophenol (1.492 g), CH_3CN (40 mL), 20 h at room temperature; 2.448 g (92%) of **15** recovered. (5) **1** (1.038 g), sodium thiophenoxide (0.544 g), CH_2Cl_2 (40 mL), 20 h at room temperature; 0.509 g (94%) sodium thiophenoxide recovered; 0.988 g (94%) of **1** recovered. (6) **31** (1.826 g), thiophenol (3.012 g), CH_2Cl_2 (35 mL), 24 h at room temperature; 1.699 g (93%) of **31** recovered. (7) **32** (1.613 g), thiophenol (2.018 g), CH_2Cl_2 (30 mL), 24 h at room temperature; 1.539 g (95%) of **32** recovered.

Registry No.—**1**, 35024-12-5; **2**, 56995-07-4; **15**, 2580-24-7; **16**, 6267-39-6; **18**, 66102-87-2; **19**, 66102-88-3; **27**, 64897-93-4; **28**, 66102-89-4; **29**, 66102-90-7; **31**, 1807-68-7; **32**, 7039-33-0; sodium thiophenoxide, 930-69-8; methanethiol, 74-93-1; hydrogen sulfide, 7783-06-4.

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Ring Transformations of Heterocyclic Halogeno Compounds with Nucleophiles. 39.[1] Carbon-13 and Proton Nuclear Magnetic Resonance Investigations on the Mechanism of the Ring Transformation Reaction of Pyrimidines into *s*-Triazines[2]

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Treatment of 4-chloro-2-dimethylaminopyrimidine (**1a**) and its 5-phenyl derivative (**1b**) with potassium amide in liquid ammonia and subsequent workup of the reaction mixtures lead to the formation of 2-dimethylamino-4-methyl-*s*-triazine and 4-benzyl-2-dimethylamino-*s*-triazine, respectively. By extensive ^{13}C NMR investigations of both reaction mixtures in liquid ammonia containing potassium amide, a number of unstable intermediates could be identified: from **1a** the 1:1 anionic σ complex **2a** and the anionic open-chain intermediate aminoethynyldiazabutadiene **3**; from **1b**, the σ complex **2b** and the anionic aminodiazabutadiene **7**, but also a redox product of **7**, i.e., the cyanoaminoazabutadiene **8**. Based upon the results of a deuterium labeling experiment it is assumed that the conversion of **7** into **8** occurs by an intramolecular oxidation–reduction process.

Several papers have been published concerning σ-adduct formation between the nucleophilic amide ion and the parent diazines,[3] as well as some of their derivatives, containing a leaving group (Cl, Br, SCH_3, and SO_2CH_3).[4–8]

The results of these studies show that in the absence of a leaving group the σ complex is stable and does not undergo a subsequent reaction[3,5] but that in the presence of such a leaving group, however, further reactions beyond the stage of the σ adduct can occur.[4–8]

A reaction which has attracted our interest for several years is the ring transformation of 2-substituted 4-chloropyrimidines into 2-substituted 4-methyl-*s*-triazines by potassium amide in liquid ammonia.[9] ^1H- and ^{13}C-NMR spectroscopy indicated that the first step in this ring interconversion is the formation of a 1:1 anionic σ complex **2a** in which the amide ion is thus not attached to C-4, the carbon bearing the halogen substituent, but to C-6.[5,6] More examples of this unexpected addition behavior have been found with other diazines.[4,8]

We have investigated by ^{13}C-NMR spectroscopy two reactions in particular, i.e., the ring transformation of 4-chloro-2-dimethylaminopyrimidine (**1a**) into 2-dimethylamino-4-methyl-*s*-triazine (**5a**) (yield 80% with potassium amide) and the hitherto unknown conversion of 4-chloro-2-dimethylamino-5-phenylpyrimidine (**1b**) into 4-benzyl-2-dimethylamino-*s*-triazine (**5b**) (yield 60% with potassium amide), specially aiming to obtain information about intermediates beyond the stage of the σ adduct.

Results and Discussion

4-Chloro-2-dimethylaminopyrimidine (1a). From the results of our studies we reached the conclusion that the conversion of **1a** into **5a** occurs by the following reaction sequence **1a** → **2a** → **3** → **4** → **5a** (see Scheme I). Evidence for this mechanism is based on the following data. Addition of **1a** to 2 equiv of potassium amide in liquid ammonia gives the σ adduct **2a** (see Table I). Surprisingly we observed that when the excess of potassium amide is raised to 4 equiv and the reaction time is prolonged, the ^{13}C-NMR spectrum of the resulting reaction mixture is completely different from that of the σ complex **2a**. The new spectral data have been assigned to the intermediate aminoethynyldiazabutadiene anion **3** (see Table I). Two sharp signals at δ 113.3 and 118.5 have been attributed to the acetylenic carbons C-4 and C-5 and two signals at δ 168.4 (J_{C-H} = 157 Hz) and 166.0, both being broadened, to C-2 and C-6, respectively.[10] The broadening observed for the resonances of C-2 and C-6 may well find its cause in *E*–*Z* isomerism around the N-1–C-6 double bond.

Also the ^1H-NMR spectrum of a solution, obtained by reaction of **1a** with 4 equiv of KNH_2/NH_3 for 30 min, confirms the formation of intermediate **3**. Besides the sharp singlet at δ 2.62 of the dimethylamino substituent, a very broad adsorption band around δ 8 belonging to H-6 is found.

Intermediate **3** is found to be stable for at least 5 h under the reaction conditions. Under these conditions no indication of the formation of the ultimate reaction product 2-dimethylamino-4-methyl-*s*-triazine (**5a**) could be obtained. However, when the reaction mixture was quenched with ammo-

Scheme I

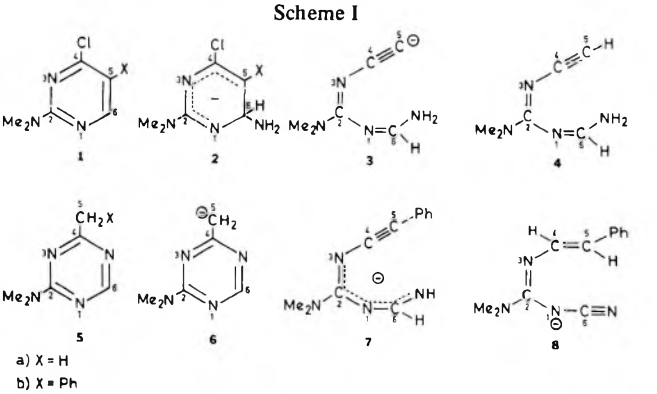

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Table I. Summary of the ^{13}C Chemical Shifts of the Starting Materials 1a and 1b, Intermediates, and Products Obtained in the Reaction of 1a and 1b with KNH_2/NH_3

	Registry no.	C-2	C-4	C-5	C-6	$(CH_3)_2N$	Solvent
1a	23631-02-9	162.3	161.1	108.3	158.7	37.1	$CDCl_3$
1b	65942-50-9	161.1	159.1	121.3	158.9	37.1	$CDCl_3$
2a	57356-50-0	161.2	147.8	86.2	67.3	37.9	KNH_2/NH_3 liq
2b	65942-51-0	160.3	144.4	95.6	70.8	38.3	KNH_2/NH_3 liq
3	65942-52-1	168.4	113.3	118.5	166.0	39.6	KNH_2/NH_3 liq
5a	22404-37-1	163.7	175.8	25.4	166.0	36.1	NH_3 liq
5b	65942-53-2	164.4	176.6	45.5	165.6	36.1	$CDCl_3$
6	65942-54-3	162.4	163.1	66.8	161.7	35.8	KNH_2/NH_3 liq
7	65969-57-5	165.9	105.0	59.7	165.1	37.6	KNH_2/NH_3 liq
		167.6	104.8	59.4	168.0	37.6	KNH_2/NH_3 liq
8	65942-55-4	162.1	141.7	108.8	124.6	38.3	KNH_2/NH_3 liq

nium chloride, the ^{13}C-NMR spectrum of that solution had drastically changed and resonance signals appeared that must be ascribed to the presence of the triazine **5a** (see Table I). Apparently by the addition of ammonium chloride, intermediate **3** is converted to its conjugate acid **4** which easily undergoes the cyclization into **5a**. We have not obtained any evidence for the occurrence of the reverse reaction **5a** → **3**. In fact when **5a** is dissolved in KNH_2/NH_3 anion **6** is formed, as is convincingly shown by the *triplet* splitting found for the side-chain carbon C-5 (J_{C-H} = 153 Hz) and the considerable downfield shift (41.4 ppm) observed on comparison of the chemical shift of this signal with that of the ^{13}C-NMR signal from the methyl group of **5a**, obtained in $CDCl_3$ solution. This downfield shift, together with the value for the J_{C-H} typical for an sp^2 carbon, indicates that in species **6** the negative charge is partly delocalized over the *s*-triazine ring.

4-Chloro-2-dimethylamino-5-phenylpyrimidine (1b). As we have seen the negative charge on C-5 in **3** plays a vital role in the stability of this species, since not **3** but its conjugate acid **4** is found to be able to undergo cyclization. Therefore we became interested in the influence of a substituent in position 5 of the pyrimidine ring. For that purpose we chose the phenyl group. Reaction of 4-chloro-2-dimethylamino-5-phenylpyrimidine (**1b**) with potassium amide in liquid ammonia gave 4-benzyl-2-dimethylamino-*s*-triazine (**5b**) (yield 60%), together with only a small amount of 4-amino-2-dimethylamino-5-phenylpyrimidine. The presence of the phenyl group is found to increase substrate reactivity. Therefore, in order to detect intermediate stages, it was necessary to lower the reaction temperature to −60 °C. Even at this low temperature we could not avoid the fact that two or more intermediate species were simultaneously present in the reaction mixture, making characterization of the reaction intermediates by ^{13}C NMR very troublesome. However, by varying the excess of KNH_2 employed we were able to control the progress of the reaction to some extent. Taking samples at short intervals the rather complex spectra could be analyzed and the rise and fall of three intermediates could be monitored.

It was found that when 1 equiv of KNH_2 is employed first the σ adduct **2b** appears (see Figure 1). The ^{13}C-NMR chemical shifts of this adduct agree well with those recorded for **2a** (see Table I). When **1b** is reacted with 2 equiv of KNH_2 at −60 °C, the ^{13}C-NMR spectrum of a sample of the reaction mixture shows signals that arise from the anionic amino(phenylethynyl)diazabutadiene **7**. Under those conditions only a small number of weak signals of σ adduct **2b** are then observed (see Figure 1).

Of particular interest is the fact that each of the carbon atoms 2, 4, 5, and 6 of intermediate **7** show a pair of singlets in an approximate 1:2 ratio, indicating the existence of two isomers. In these isomers, different values for the C-6–H-6 coupling constants are found, J_{C-6-H} = 169.2 and 162.1 Hz for the major and minor signals, respectively. Based upon the

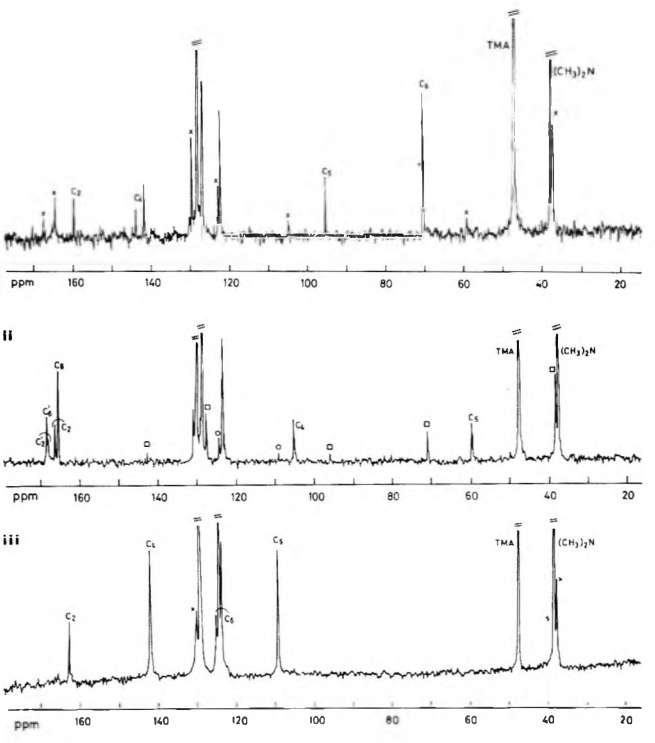


Figure 1. ^{13}C-NMR spectra at 25.2 MHz of reaction intermediates **2b**, **7**, and **8** taken in liquid NH_3: (i) signals mainly from **2b**, × refers to signals from **7**; (ii) signals mainly from **7**, □ and ○ refer to signals from **2b** and **8**, respectively; (iii) signals mainly from **8**, × refers to signals from **7**.

relatively large chemical shift differences found between the resonance pairs from C-2 and C-6 ($\Delta\delta$ = 1.7 and 2.9, respectively) *E*–*Z* isomerism around the N-1–C-6 double bond is proposed, just as has been described for intermediate **3**. Which resonance signals belong to the *E* or *Z* isomer was not determined. C-5 resonates at a somewhat higher field (δ 59.7) compared with the corresponding nucleus in phenylacetylene (δ 84.8). The electron-donating effect, however, exerted by the partly negatively charged N-3 readily accounts for this upfield shift.

In contrast to **1a**, the reaction of **1b** with KNH_2 does not stop at the stage of **7**; in the presence of a fourfold amount of KNH_2 a new intermediate arises, which we assigned structure **8** (see Figure 1 and Table I). From the proton-coupled ^{13}C-NMR spectra the presence of two C-H entities can be easily seen; their absorptions at δ 141.7 and 108.8 are attributed to C-4 and C-5 (J_{C-H} = 152 and 150 Hz, respectively). The signal at δ 124.6 belongs to the nitrile carbon C-6, so the signal at δ 162.1 must originate from C-2.

The ^1H-NMR spectrum showed an AB pattern; chemical shifts were found at δ 8.38 and 5.82, showing a coupling con-

stant of J = 13.3 Hz. Since interproton coupling is known to have its origin in the indirect intramolecular interaction of nuclear moments through bonds,[14] the assumption seems justified that the negative π charge in intermediate **8** does not affect the value of the $J_{H,H}$ to a significant extent, compared with the uncharged conjugate acid of **8**. Comparing the value of the coupling constant of 13.3 Hz with those published for both cis and trans isomers of uncharged 1,2-disubstitute olefines[15,16] (containing methoxy or amino groups, coupling constants for cis isomers range from 6 to 9 Hz and for trans isomers from 12 to 14 Hz) intermediate species **8** is assumed to possess a trans substituted double bond.[17]

The formation of **8** takes place from **7**. This rearrangement involves a redox reaction in which reduction of the triple bond of **7** to a double bond occurs simultaneously with oxidation of the amino substituted C-6. This reaction is similar to the self oxidation–reduction process which aldehydes can take place in the presence of strong bases. The conversion of **7** → **8** can be described to occur by a reversible addition of the amide ion to the C-6–N-1 double bond. The resulting charged tetrahedral complex can act as a hydride donor and transfers the hydride ion in a six-membered cyclic transition state to C-4. After protonation at C-5 and loss of ammonia **8** is formed.

In order to test this hypothesis, we synthesized 4-chloro-6-deuterio-2-dimethylamino-5-phenylpyrimidine. This substrate was reacted with 2 equiv of KNH_2 at first to the level of the open-chain compound **9**. ^{13}C-NMR spectroscopy of a sample of the reaction mixture showed all resonance signals of **7**, except the one originating from C-6. This is because carbon–deuterium multiplets are very weak or lost in the noise of ^{13}C NMR spectra, since they lack nuclear Overhauser effects.[18]

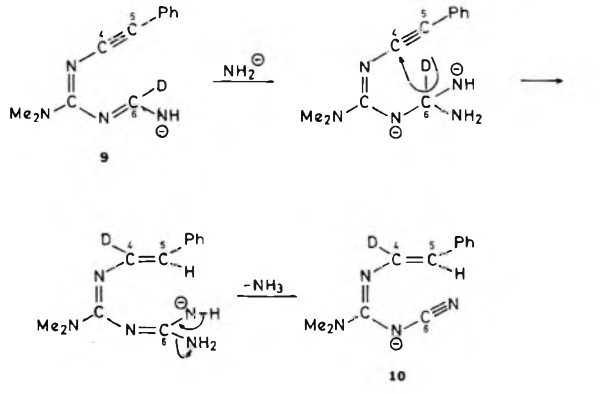
Increasing the excess of potassium amide to fourfold, the signals of **10** appear at the expense of **9**, but now the resonance signal of C-4 is missing, indicating the presence of deuterium at that position (see Scheme II).

Supporting evidence for the presence of deuterium at position 4 is obtained by ^{1}H-NMR spectroscopy showing the absence of the resonance signal from H-4; H-5 now appears as a singlet.

All the data support the proposal of the internal oxidation–reduction mechanism as a reasonable pathway for the formation of **8** from **7**.

^{13}C-NMR spectroscopy of a sample of a reaction mixture containing **8** that has been quenched with ammonium chloride revealed that no cyclization takes place at this level of the reaction (contrary to what has been found for **3** upon quenching). Only if the solvent ammonia has been evaporated will the *s*-triazine **5b** form as is found in the chloroform extract of the resulting residue. The question why **7** undergoes an internal redox reaction into **8** and **3** does *not* may be explained by the fact that, although the first step in this conversion, i.e., addition of the amide ion to C-6, can occur in both species (see Scheme II), the subsequent hydride transfer to C-4 is prevented by the negative charge present in the acetylene group of **3**.

Scheme II



Experimental Section

^{13}C and ^{1}H spectra were obtained with a Varian XL-100-15 spectrometer, equipped with a Varian 620/L16K computer, operating at 25.2 MHz in the FT mode and at 100.1 MHz in the CW mode, respectively.

In $CDCl_3$ solution the deuterium resonance of the solvent was used as an internal field-frequency lock signal. In the case of liquid ammonia as solvent, field-frequency lock was obtained from the ^{19}F-NMR signal of a capillary of hexafluorobenzene positioned along the longitudinal axis of 12 mm (o.d.) sample tubes employed. Spectra were taken at ambient temperature, but when measuring liquid ammonia samples the probe temperature was −50 °C. In $CDCl_3$ solutions ^{13}C and ^{1}H chemical shifts were measured from internal Me_4Si. In NH_3 solutions ^{13}C and ^{1}H chemical shifts were measured from internal trimethylamine and they were converted to the Me_4Si scale adding 47.5 and 2.13 ppm, respectively. Typical ^{13}C spectral parameters were as follows: spectral width 5120 Hz (1.25 Hz/point), acquisition time 0.8 s, pulse delay 1.2 s, pulse width 10 μs. All samples were run as approximately 1 M solutions in NH_3 and they were prepared according to the method described in ref 7. The average accumulation time was 60 min. The IR spectra were recorded with a Hitachi Model EPI-G.3. Mass spectra were obtained with an AEI MS-902 instrument. Melting points are uncorrected.

Preparation of Starting Materials. 4-Chloro-2-dimethylaminopyrimidine (1a) was prepared according to ref 9. **4-Chloro-2-dimethylamino-5-phenylpyrimidine (1b).** 2-Ethylthio-5-phenyl-4-pyrimidone[19] (14.8 g) was heated with dimethylammonium acetate[20] (60 mL) at 160 °C for 2.5 h. The mixture was left overnight and filtered under suction. The white crystals (83 g of crude 2-dimethylamino-5-phenyl-4-pyrimidone) were twice thoroughly washed with water, dried, and subsequently refluxed with freshly distilled phosphorus oxychloride (75 mL) for 2 h. The excess of phosphorus oxychloride was evaporated and the residue was treated with ice water. The resulting mixture was carefully neutralized with aqueous ammonia (0 °C < t < 5 °C) and extracted with ether. After evaporation of the solvent the residue was distilled in vacuo. The fraction boiling between 130 and 135 °C (0.4 mmHg) was collected; yield 11.9 g. Anal. Calcd for $C_{12}H_{12}ClN_3$: C, 61.7; H, 5.2. Found: C, 61.8; H 5.1.

4-Chloro-6-deuterio-2-dimethylamino-5-phenylpyrimidine. 4,6-Dichloro-2-dimethylamino-5-phenylpyrimidine (4.5 g) and hydrazine hydrate (100%) (17 mL) are refluxed in ethanol (40 mL) for 0.5 h. On cooling 3.75 g of 4-chloro-2-dimethylamino-6-hydrazino-5-phenylpyrimidine separate out as white needles (mp 127–128 °C from ethanol). This compound is refluxed in a small volume of CD_3OD, yielding after evaporation of the solvent hydrazino deuterated starting material, 1.6 g of which are dissolved in $CDCl_3$ (30 mL) containing CD_3NO_2 (7 mL) as a D donor and reacted at 40 °C in an inert atmosphere (N_2) with MnO_2/C[21] (30 g) that is added portionwise over 2 h. The reaction mixture is kept at 40 °C for another 0.5 h and then filtered under suction. The residue is washed well with chloroform. The oil obtained after evaporation of the filtrate is purified twice by column chromatography over Silica with $CHCl_3$ and benzene–ethyl acetate (4:1), respectively, as eluent, yield 0.5 g. The deuterium content at position 6 was about 90% as determined by ^{1}H NMR using the signal from the dimethylamino group as an internal standard.

4,6-Dichloro-2-dimethylamino-5-phenylpyrimidine. To a boiling mixture of *N,N*-dimethylguanidine·HCl (24.6 g) in methanol (absolute) (150 mL) containing sodium methoxide (21.6 g) was added with stirring diethyl phenylmalonate (47.2 g). After 4 h of reaction time, the mixture is left overnight at ambient temperature. The white precipitate is filtered off and the filtrate is acidified with acetic acid. The resulting voluminous paste is washed with water and dried at 80 °C over phosphorus pentoxide in vacuo. This crude 4,6-dihydroxy-2-dimethylamino-5-phenylpyrimidine is treated with phosphorus oxychloride (360 mL) as described before. (See the preparation of 4-chloro-2-dimethylamino-5-phenylpyrimidine.)

After evaporation of the excess of phosphorus oxychloride and neutralization, the precipitate is collected and extracted with ether. Evaporation of the solvent afforded a colorless oil that solidified upon standing. Recrystallization from aqueous ethanol yielded 17.7 g, mp 80–81 °C (lit.[22] 81–82 °C) (overall yield 33%). Anal. Calcd for $C_{12}H_{11}Cl_2N_3$: C, 53.7; H, 4.2. Found: C, 53.6; H, 4.4.

Reaction of 1b with Potassium Amide into 4-Benzyl-2-dimethylamino-*s*-triazine (5b). Dry liquid ammonia (20 mL) con-

densed in a 50-mL three-neck round-bottom flask, equipped with a dry ice/acetone condenser. Potassium (390 mg) and a few crystals of $Fe(NO_3)_3 \cdot 9H_2O$ catalyst were added. After stirring for 30 min at reflux temperature 0.58 g of 4-chloro-2-dimethylamino-5-phenylpyrimidine (**1b**) was added at −60 °C. After 4 h the reaction was quenched with ammonium chloride and the ammonia was evaporated. The residue was extracted with ether and the extract was evaporated to dryness. Separation from the by-product 4-amino-2-dimethylamino-5-phenylpyrimidine (yield 0.037 g (7%); mp 119–120 °C. Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.3; H 6.6. Found: C, 67.2; H, 6.8) was performed by column chromatography (silica): yield 0.32 g; oil; picrate mp 143–144 °C. Anal. (picrate) Calcd for $C_{18}H_{17}N_7O_7$: C, 48.8; H, 3.9. Found: C, 48.8; H, 4.0.

Acknowledgment. We are indebted to Dr. C. A. Landheer and Mr. W. P. Combé for mass spectroscopic data, to Mr. W. Ch. Melger for chromatographic advice, and to Mr. H. Jongejan for carrying out the microanalyses.

Registry No.—**5b** picrate, 65942-58-7; 2-dimethylamino-5-phenyl-4-pyrimidone, 65942-56-5; 4,6-dichloro-2-dimethylamino-5-phenylpyrimidine, 61769-99-1; 4-chloro-2-dimethylamino-6-hydrazino-5-phenylpyrimidine, 65942-57-6; *N,N*-dimethylguanidine hydrochloride, 22583-29-5; diethyl phenylmalonate, 83-13-6.

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(10) In order to assign C-4 and C-5 in **3** correctly we acquired ^{13}C-NMR spectral information on the chemical shifts of acetylide anions. It was found by dissolving 3-methoxypropyn ($HC^1{\equiv}C^2C^3H_2OCH_3$) in liquid ammonia containing 2 equiv of potassium amide that in the acetylide anion thus formed the ^{13}C-NMR signals of C-1 and C-2 are shifted downfield 75.7 and 28.2 ppm with respect to the parent compound measured in $CDCl_3$ (74.8 ppm → 150.5 ppm for C-1 and 79.9 ppm → 108.1 ppm for C-2). Distinction between C-1 and C-2 in the acetylide form could be made on the basis of the triplet splitting ($^2J_{C-H}$ = 5.6 Hz) found for C-2 when wide band proton noise decoupling was *not* utilized. A deshielding effect upon anion formation is also found in a number of organolithium compounds, in which the metallated acetylenic carbons are shifted downfield with respect to the parent acetylenes.[11,12] Furthermore we compare the ^{13}C-NMR spectrum of ethoxyethyn (δ_{C-1} 23.2 and δ_{C-2} 89.4)[13] [in this compound the ^{13}C NMR shifts of the acetylenic carbons are strongly subjected to the +M and −I effects due to the neighboring oxygen atom] with that of its anion generated in KNH_2/NH_3. In this medium C-1 and C-2 are found to resonate at δ 72.5 and 116.2, respectively (downfield shifts of 49.3 and 26.8 ppm with respect to the parent compound). These data clearly show that the assignments proposed for C-4 and C-5 in **3** are quite reliable.
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Chemistry of Heterocyclic Compounds. 28. Reactions of Halopyridines with Mercaptide. Synthesis of Multiheteromacrocycles Possessing 2,6-Pyridino Subunits Connected by Carbon–Sulfur Linkages[1]

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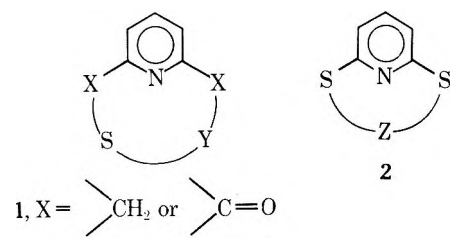
2,6-Dihalopyridines have been successfully incorporated into "crown ethers" (3); however, utilizing similar procedures to prepare the related thio "crown ethers" (e.g., 8) has met with very limited success. The major isolated products from nucleophilic displacement of halide from 7 by mercaptide were derived from numerous competitive reactions of the thiols, such as polymerization, fragmentation, oxidation, and oligomerizations. The desired carbon–sulfur bridged 2,6-pyridino macrocycles were isolated as minor components from these reactions.

Recently, we reported the synthesis of ethereal macrocycles which incorporated the 2,6-pyridino moiety.[2] Although numerous related thioethereal macrocycles have been reported,[3] the vast majority possess a backbone (**1**) in which the sulfur atom is isolated from the pyridine ring by either a methylene[4] or a carbonyl group.[5] Only recently has a second type of macrocyclic system (**2**) been constructed in which the sulfur atoms are directly connected to the 2 and 6 positions of the pyridine nucleus.[6] We herein describe the reactions of 2,6-dihalopyridines with different sulfur nucleophiles as well as the preparation and characterization of carbon–sulfur bridged 2,6-pyridino macrocycles of the latter type (**2**).



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The preparation of macrocyclic polyethers possessing the 2,6-pyridino subunit (e.g., **3**) has been accomplished,[2] and their general catalytic behavior is currently being studied;[7] however, the corresponding thioethers were yet unknown but were desirable for comparison studies. Important differences

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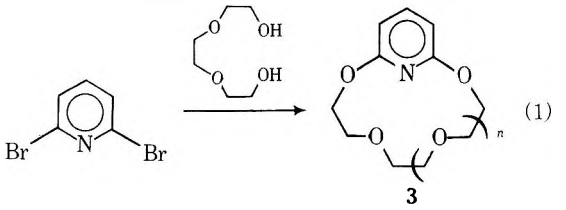
were anticipated in view of the increased nuclear size of sulfur vs. oxygen, a smaller C–S–C vs. C–O–C bond angle, decreased electronegativity of sulfur relative to oxygen, and diminished C–S vs. C–O ionic bond character. General nucleophilic substitution (eq 1) of 2,6-dihalo (pyridine) substituents, as uti-



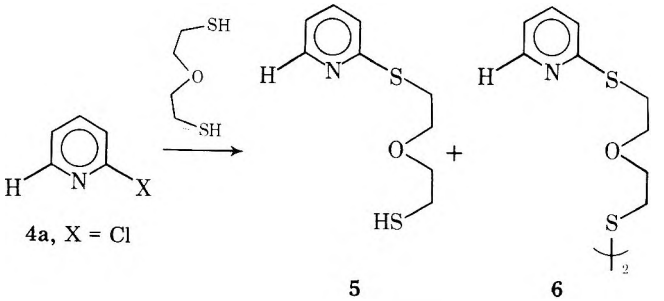
(1)

3

lized in the construction of **3**,[2] should be applicable to the synthesis of the thioether macrocycles.[8] The mercaptides were generated by either treatment of the appropriate bisthiol with diisopropylethylamine, as both base and solvent, or with sodium hydride in anhydrous xylene. As noted previously for glycols,[9] in order to minimize thermal fragmentation or oligomerization of the thioglycols, the reaction temperatures must be maintained below the upper 140 °C limit.

A. Reactions of 2-Halo- and 2,6-Dihalopyridines with Bis(2-mercaptoethyl) Ether. Reaction of 2-chloropyridine (**4a**) with the bismercaptide generated from bis(2-mercaptoethyl) ether upon treatment with 2 equiv of oil-free sodium hydride in anhydrous xylene gave a low yield of the 1:1 thiol **5** accompanied by its oxidation product, disulfide **6**. Isolation of a considerable amount of unreacted **4a** was unexpected in view of the lengthy reaction time. The overall nucleophilic displacement of chloride to give the corresponding pyridyl sulfides was considerably slower than the reaction of **4a** with the dianion of diethylene glycol.[2] Abramovitch and Newman[10] have specifically studied the action of 2-halopyridines with MeO^- and MeS^- and have concluded that MeS^- has a higher reactivity than MeO^- in either MeOH or HMPA. Thus, in hydrocarbon solvents a reversal of the sensitive balance in nucleophilicities of MeS^- and MeO^- occurs, which is attributed to either solvation of the thioalkoxide ion or the polarizability of the nucleophile and/or leaving group.

Thiol **5** undergoes facile air oxidation to the corresponding disulfide **6**. Total exclusion of air during the reaction was at-

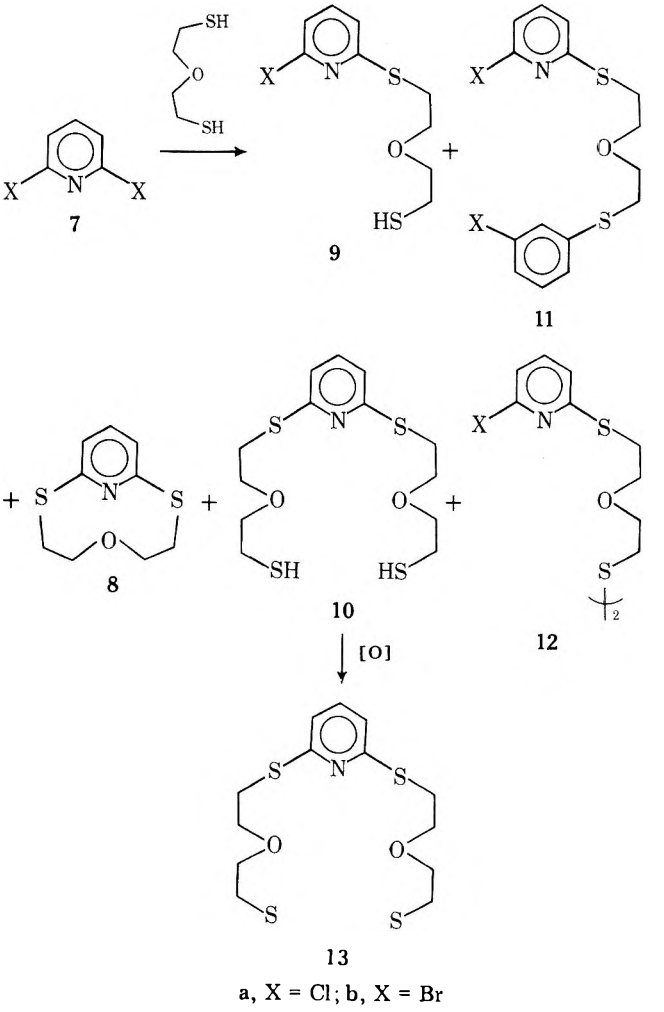


4a, X = Cl

5 6

tempted; however, during the workup procedure air oxidation could not be easily prevented.

The similar reaction of 2,6-dichloropyridine (**7a**) with bis(2-mercaptoethyl) ether dianion afforded the desired 1:1 macrocycle **8** along with numerous noncyclized thiols **9a** and **10**, sulfide **11a**, and disulfide **12a**. Macrocycle **8**, which possesses a ten-membered ring, is the smallest cyclic ring formed via this ring formation procedure. The diminished C–S–C bond angles and increased nuclear size of sulfur in **8** are believed to relieve the strain which is present in the corresponding unknown carbon–oxygen macrocycle (**3**, $n = 0$). The down-field shift ($\Delta\delta$ = ca. 0.2) experienced by the β protons of **8** is indicative of the rigidly held 2,6-hetero bridge. Vögtle and Weber[4a] have previously synthesized **8** by a reverse procedure in which 2,6-dimercaptopyridine was treated with β,β-dihaloethyl ether.[11]



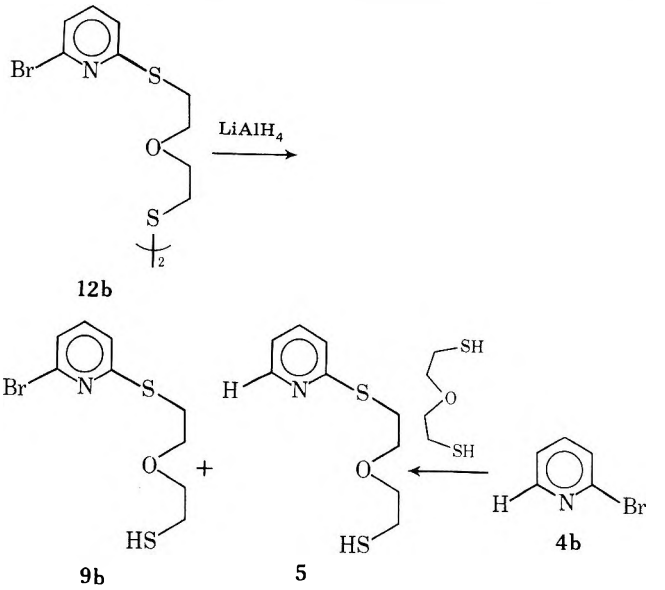
7 9 11

8 10 12

13

a, X = Cl; b, X = Br

In order to evaluate the effect of a leaving group and varied dianion preparations, 2,6-dibromopyridine (**7b**) was refluxed with bis(2-mercaptoethyl) ether in anhydrous diisopropylethylamine under nitrogen for 30 h. Only traces of **8** were detected, whereas **11b** was isolated in 18% yield at the expense of the 1:1 thiol **9b**. Extended reaction times (7 days) did not greatly effect the product distribution; similar percentages of unreacted **7b** were isolated. The dithiols in the reaction appear to be undergoing diverse competitive degeneration, the fate of which has not been determined. The 1:1 thiol **9b** was refluxed in diisopropylethylamine, resulting in cyclization to **8** in low yield and in oxidation to disulfide **12b**. Bisthiol **10**



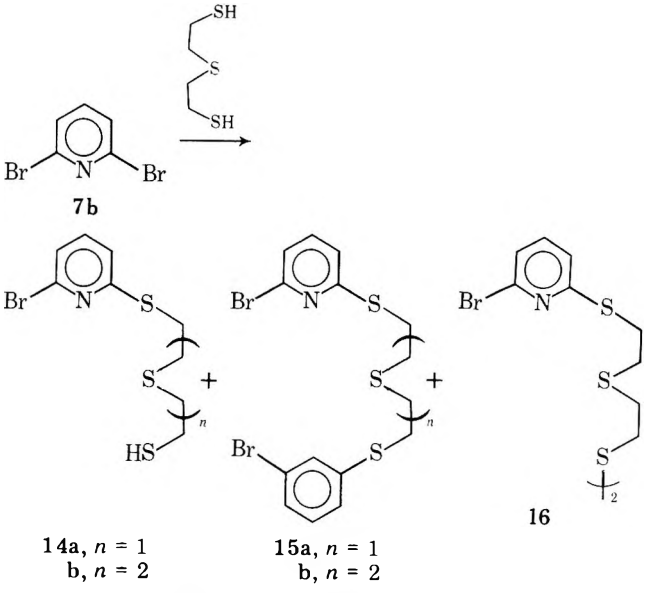
12b

9b 5 4b

was isolated in 2% yield and could be converted into the novel macrocyclic disulfide **13** upon oxidation.

Disulfide **12b** was reduced with lithium aluminum hydride in ether to give **9b** in 20% yield along with the debrominated thiol **5**. Hydrogenolyses of halo substituents from the pyridine nucleus by the action of hydride are known.[12] The other disulfides prepared in this study have similarly been reduced to prove the presence of the S–S bond.

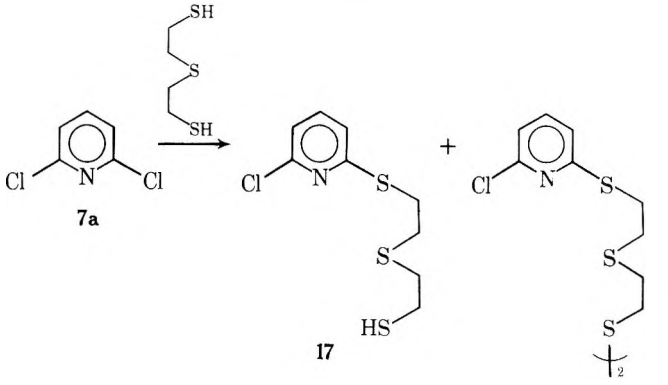
B. Reactions of 2-Halo- and 2,6-Dihalopyridines with Bisthiols. 2,6-Dibromopyridine (**7b**) and bis(2-mercaptoethyl) sulfide in refluxing diisopropylethylamine afforded the expected thiol **14a**, the 2:1 sulfide **15a**, and disulfide **16**, as well as sulfide **15b**, which resulted from initial oligomerization of bis(2-mercaptoethyl) sulfide followed by reaction with 2 equiv of **7b**. Intermediate **14b** was not isolated from the reaction. The percentage of oligomerization products is very similar to that of previous alkoxide studies.[2] Treatment of **7a** with the dianion of bis(2-mercaptoethyl) sulfide (via the sodium hydride procedure) afforded only **17** and **18**. Disulfide **18** was smoothly reduced to **17**, thus confirming its assignment.



14a, n = 1
b, n = 2

15a, n = 1
b, n = 2

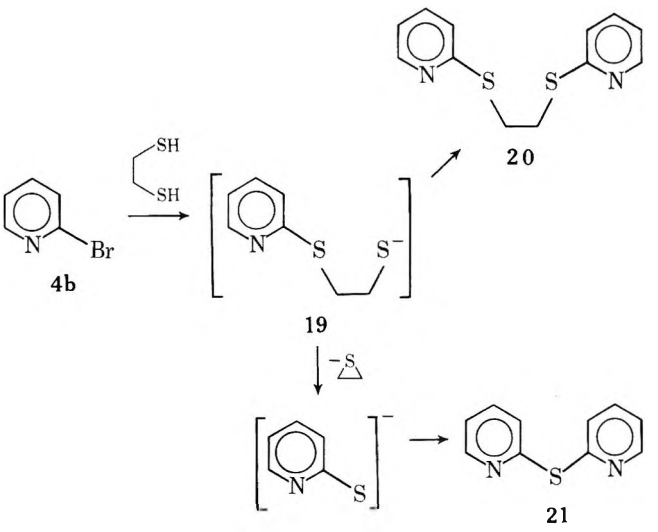
16



17

The NMR spectra of these polysulfides are ill-defined, and only the α methylenes can be assigned unequivocally. Elemental analyses and mass spectral data help to substantiate the structural assignments of oligomerized products.

2-Bromopyridine (**4b**) was treated with 1,2-ethanedithiol in the tertiary amine to generate initially intermediate **19**, which undergoes conversion to 2,2′-ethylenedithiodipyridine (**20**). Competitively, **19** fragmented ethylene sulfide, under the basic conditions, to give 2-pyridyl mercaptide, which reacted with **4b** to yield (23%) bis(2-pyridyl) sulfide (**21**). Sulfide **21** has been previously prepared from 2-pyridinethiol and **4a**,[13] as well as the action of 2-halopyridines with either sodium sulfide or thiourea.[14] Oligomers of **20** were noted in



20

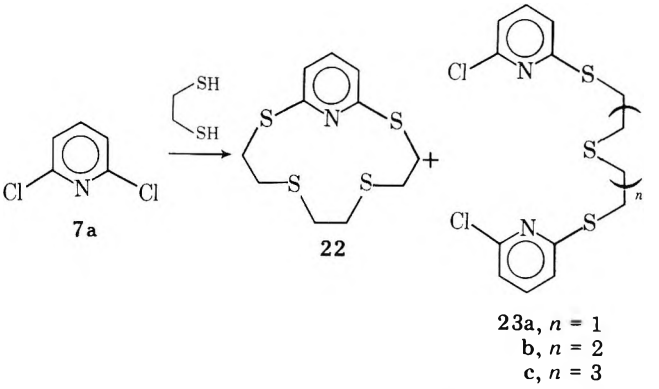
4b

19

21

the reaction mixture; however, no attempt was made to isolate or characterize these side products.

Further evidence of oligomerization was realized when **7a** was treated with the dianion of ethanedithiol generated by method A. The only major macrocycle isolated was **22**, which arose from the dianion of 3,6-dithiaoctane-1,8-dithiol. The oligomerized 2:1 adducts **23** were also isolated, but the desired



7a

22

23a, n = 1
b, n = 2
c, n = 3

product (from ethanedithiol) was not detected. Thus, ethanedithiol, much like ethylene glycol,[2] does not undergo the smooth reactions like the higher members of these glycol series.

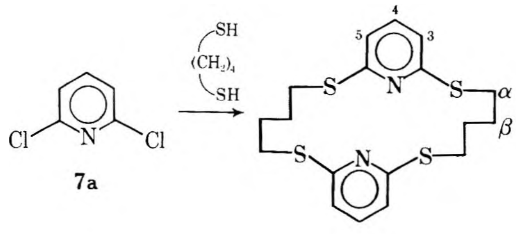
Lastly, in an attempt to evaluate the cyclization of dithiols connected by four methylene groups, **7a** was treated with 1,4-butanedithiol. The desired 2:2 macrocycle **24** was isolated in less than 0.5% yield. The lack of any templating effect was demonstrated in part by this low yield formation of **24** as well as by the isolation of the lower members of the polymeric series [2:1, **25**; 3:2, **26**; 4:3, **27**]. Numerous thiols and bisthiols were detected, but no attempt was made to isolate or characterize these oils. The NMR data for **24**–**27** have been analyzed and are given in the Experimental Section.

Conclusions

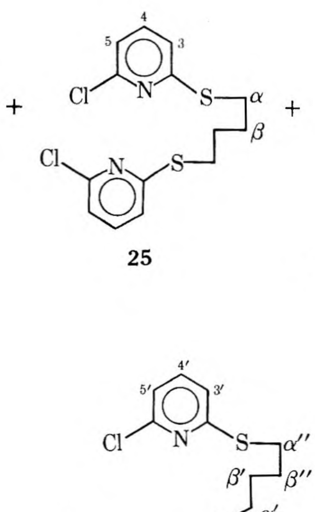
The template effect, which was realized in part during the formation of previous macrocyclic polyoxaethers,[2] was not demonstrated in the studies due to the apparent diminished sulfur to metal ion coordination. This phenomenon has been demonstrated in the synthesis of other simple macrocyclic polythiaethers.[15] The low reactivity of the 2,6 substituents on the pyridine nucleus toward nucleophilic attack as well as the clear decreased nucleophilicity of the mercaptides (vs. alkoxides) under similar reaction conditions further retard the cyclization process in relation to the competitive reactions of the thiols, such as, polymerization, fragmentation, oxidation, and oligomerization.

Table I. Reaction Conditions and Product Distribution

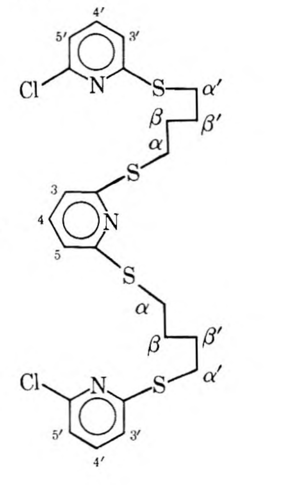
Reagents	Method	Reaction time, h	Products	Starting material
4a + $O(CH_2CH_2SH)_2$	A	72	**5** (9%), **6** (5%)	
7a + $O(CH_2CH_2SH)_2$	A	72	**8** (0.6%), **9a** (24%), **10** (2%), **11a** (6%), **12a** (6%)	**7a** (30%)
7b + $O(CH_2CH_2SH)_2$	B	60	**9b** (17%), **11b** (18%), **12b** (2%)	**7b** (38%)
	B	168	**9b** (13%), **11b** (8%), **12b** (2%)	**7b** (37%)
7b + $S(CH_2CH_2SH)_2$	B	60	**14a** (10%), **15a** (6%), **15b** (1%), **16** (1.2%)	**7b** (66%)
7a + $S(CH_2CH_2SH)_2$	A	72	**17** (6%), **18** (0.5%)	**7a** (85%)
4b + $(CH_2SH)_2$	B	60	**20** (11%), **21** (23%)	**4b** (52%)
7a + $(CH_2SH)_2$	A	72	**22** (1.3%), **23a** (10%), **23b** (4%), **23c** (1%)	**7a** (60%)
7a + $(CH_2CH_2SH)_2$	A	72	**24** (0.1%), **25** (7.5%), **26** (6%), **27** (3%)	**7a** (60%)



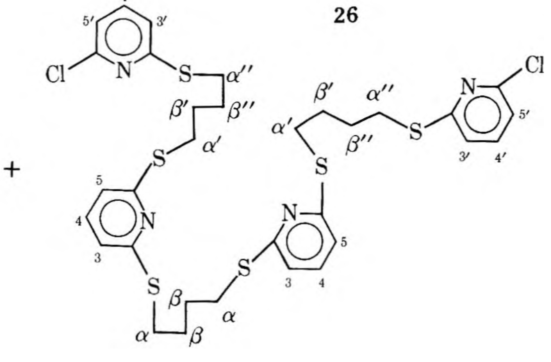
7a **24**



25



26



27

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared and ultraviolet spectra were recorded with Beckman IR-7 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, ^1H NMR spectra were taken in deuteriochloroform solutions with Me_4Si as an internal standard (δ = 0 ppm) on a Varian HA-100 spectrometer by either Mr. J. Martin or Ms. V. Majestic. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMS-4 mass spectrometer by either Ms. P. Moses or Mr. C. Guzman. Molecular weights were obtained with a Hewlett-Packard 302 vapor pressure osmometer using benzene or chloroform as the solvent and benzil as the reference by Dr. J. D. Sauer. Thermogravimetric analyses (TGA) were performed with a DuPont 950 thermogravimetric analyzer. For preparative thick-layer chromatography (ThLC), 2 mm silica gel (Brinkman PF 254-366) plates (activated at 150 °C for 4 h) were used, eluting with the stipulated solvent system.

All reaction solvents were distilled under an inert atmosphere prior to use. Sodium hydride (57% oil dispersion) was first washed with petroleum ether (bp 30–60 °C) and then dried in vacuo prior to use. The thiols were distilled under argon and stored under anhydrous conditions.

Table I gives the method used, reaction times, and product distributions. All analytical data are tabulated in Table II (furnished as supplementary material); the data for all new compounds are within experimental error (±0.4%).

Reaction of 2-Chloropyridine with Bis(2-mercaptoethyl) Ether. Method A. Sodium Hydride. To a suspension of sodium hydride (1.5 g, 63 mmol) in anhydrous xylene (200 mL) were added 2-chloropyridine (3.9 g, 34.4 mmol) and bis(2-mercaptoethyl) ether (2.4 g, 17.4 mmol), and the mixture was refluxed under nitrogen for 3 days. After the mixture was cooled, water was carefully added and the xylene layer separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo (unreacted starting 2-chloropyridine was also removed) to afford a viscous liquid which was chromatographed (ThLC) eluting four times with petroleum ether–acetone (15:1) to give two major fractions.

Fraction A yielded the 1:1 thiol **5**: bp 75–80 °C (0.2 mm, microdistilled); NMR ($CDCl_3$) δ 1.60 (t, SH, J = 8.2 Hz, 1 H), 2.66 (dt, δ-CH_2, J = 8.2, 6.5 Hz, 2 H), 3.40 (t, α-CH_2, J = 6.4 Hz, 2 H), 3.61 (t, γ-CH_2, J = 6.5 Hz, 2 H), 3.72 (t, β-CH_2, J = 6.4 Hz, 2 H), 6.92 (ddd, 5-pyr H, J = 7.3, 5.0, 1.3 Hz, 1 H), 7.14 (ddd, 3-pyr H, J = 8.2, 1.3, 0.9 Hz, 1 H), 7.42 (ddd, 4-pyr H, J = 8.2, 7.3, 2.0 Hz, 1 H), 8.38 (ddd, 6-pyr H, J = 5.0, 2.0, 0.9 Hz, 1 H); IR (neat) 2550 (SH), 1290, 1135 cm^{-1}.

Fraction B afforded disulfide **6**: TGA inflection point, 295 °C; NMR ($CDCl_3$) δ 2.89 (t, δ-CH_2, J = 6.5 Hz, 4 H), 3.39 (t, α-CH_2, J = 6.4 Hz, 4 H), 3.73 (t, γ-CH_2, J = 6.5 Hz, 4 H), 3.75 (t, β-CH_2, J = 6.4 Hz, 4 H), 6.92 (ddd, 5-pyr H, J = 7.3, 5.0, 1.3 Hz, 2 H), 7.15 (ddd, 3-pyr H, J = 8.2, 1.3, 0.9 Hz, 2 H), 7.42 (ddd, 4-pyr H, J = 8.2, 7.3, 2.0 Hz, 2 H), 8.38 (ddd, 6-pyr H, J = 5.0, 2.0, 0.9 Hz, 2 H); IR (neat) 3030, 1590, 1295, 1145 cm^{-1}.

Reaction of 2,6-dichloropyridine with bis(2-mercaptoethyl) ether afforded a residue which was chromatographed (ThLC) eluted four times with hexane–acetone (15:1) to give five major fractions.

Fraction A was recrystallized from hexane to afford the crystalline 1:1 macrocycle **8**: mp 119–121.5 °C (lit. mp 110–112 °C,[10] 92–94 °C[4a]); NMR ($CDCl_3$) δ 3.28 (t, α-CH_2, J = 5.9 Hz, 4 H), 3.95 (t, β-CH_2, J = 5.9 Hz, 4 H), 6.88 (d, 3- or 5-pyr H, J = 8.2 Hz, 1 H), 6.89 (d, 5- or 3-pyr H, J = 7.5 Hz, 1 H), 7.30 (dd, 4-pyr H, J = 8.2, 7.5 Hz, 1 H); MS (70 eV) m/e 213 (M^+, $C_9H_{11}S_2NO$, 49.2%), 168 ($C_7H_6S_2N$, 100%).

Fraction B was microdistilled to give **9a**: bp 110–115 °C (0.7 mm); NMR ($CDCl_3$) δ 1.60 (t, SH, J = 8.1 Hz, 1 H), 2.67 (m, δ-CH_2, J = 8.1, 6.5 Hz, 2 H), 3.37 (t, α-CH_2, J = 6.5 Hz, 2 H), 3.64 (t, γ-CH_2, J = 6.5 Hz, 2 H), 3.73 (t, β-CH_2, J = 6.5 Hz, 2 H), 6.95 (dd, 3- or 5-pyr H, J = 7.9, 0.9 Hz, 1 H), 7.05 (dd, 5- or 3-pyr H, J = 7.9, 0.9 Hz, 1 H), 7.39 (t, 4-pyr H, J = 7.9 Hz, 1 H); IR (neat) 2530 (SH), 1290, 1140 cm^{-1}.

Fraction C afforded **11a**: bp 125–140 °C (0.17 mm, microdistilled); NMR ($CDCl_3$) δ 3.38 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.78 (t, β-CH_2, J = 6.5 Hz, 4 H), 6.92 (dd, 3- or 5-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.04 (dd, 5- or 3-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.36 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (neat) 2910, 1570, 1290, 1150 cm^{-1}; MS (70 eV) m/e 360 (M^+, 0.96%), 172 ($C_7H_7NS^{35}Cl$, 100%).

Fraction D was rechromatographed (ThLC) eluting three times with hexane–acetone (8:1) to afford **10**: bp 100–110 °C (0.09 mm); NMR ($CDCl_3$) δ 1.58 (t, SH, J = 8.1 Hz, 2 H), 2.67 (m, δ-CH_2, J = 8.1, 6.4 Hz, 4 H), 3.39 (t, α-CH_2, J = 6.4 Hz, 4 H), 3.61 (t, γ-CH_2, J = 6.4 Hz, 4 H), 3.71 (t, β-CH_2, J = 6.4 Hz, 4 H), 6.83 (d, 3- or 5-pyr H, J =

8 Hz, 1 H), 6.84 (d, 5- or 3-pyr H, J = 7.5 Hz, 1 H), 7.22 (dd, 4-pyr H, J = 8, 7.5 Hz, 1 H); IR (neat) 2530 (SH), 1620, 1290, 1130 cm^{-1}.

Fraction E was rechromatographed (ThLC) eluting three times with hexane–acetone (8:1) to afford disulfide **12a:** TGA inflection point, 308 °C; NMR ($CDCl_3$) δ 2.9 (t, δ-CH_2, J = 6.5 Hz, 4 H), 3.37 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.67–3.84 (m, CH_2O, 8 H), 6.94 (dd, 3- or 5-pyr H, J = 7.7, 0.8, Hz, 2 H), 7.05 (dd, 5- or 3-pyr H, J = 7.7, 0.8 Hz, 2 H), 7.37 (t, 4-pyr H, J = 7.7 Hz, 2 H); IR (neat) 2900, 1570, 1290, 1140 cm^{-1}.

Reaction of 2,6-Dibromopyridine with Bis(2-mercaptoethyl) Ether. Method B. Diisopropylamine. A mixture of 2,6-dibromopyridine (4.0 g, 16.9 mmol), bis(2-mercaptoethyl) ether (2.35 g, 17.0 mmol), and diisopropylethylamine (25 mL) was refluxed under nitrogen for 60 h. The solvent was removed in vacuo, affording a residue which was dissolved in dichloromethane and extracted with dilute sodium carbonate solution in order to remove unreacted dithiol (20%). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give a residue which was chromatographed (ThLC) eluting eight times with cyclohexane–ethyl acetate (25:1) to afford three major fractions.

Fraction A afforded thiol **9b** as a pale yellow oil: bp 119–128 °C (0.06 mm, microdistilled); NMR (CCl_4) δ 1.50 (t, SH, J = 8.2 Hz, 1 H), 2.62 (dt, δ-CH_2, J = 8.2, 6.5 Hz, 2 H), 3.32 (t, α-CH_2, J = 6.5 Hz, 2 H), 3.58 (t, γ-CH_2, J = 6.5 Hz, 2 H), 3.67 (t, β-CH_2, J = 6.5 Hz, 2 H), 6.99–7.35 (m, pyr H, 3 H); IR (neat) 2560 (SH), 1570, 1290, 1150, 1120 (br), 1050 cm^{-1}.

Fraction B afforded **11b** as a dark yellow oil: bp 185–200 °C (1.0 mm); NMR (CCl_4) δ 3.32 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.72 (t, β-CH_2, J = 6.5 Hz, 4 H), 6.96–7.32 (m, pyr H, 6 H); IR (neat) 2900, 1570, 1290, 1150, 1080 cm^{-1}.

Fraction C yielded disulfide **12b** as a pale yellow oil: TGA inflection point, 298 °C; NMR (CCl_4) δ 2.83 (t, δ-CH_2, J = 6.5 Hz, 4 H), 3.31 (t, α-CH_2, J = 6.5 Hz, 4 H), 3.64 (t, γ-CH_2, J = 6.5 Hz, 4 H), 3.71 (t, β-CH_2, J = 6.5 Hz, 4 H), 6.94–7.33 (m, pyr H, 6 H); IR (neat) 2880, 1540, 1380, 1250, 1150, 980 cm^{-1}.

Reduction of 2,2-[Dithiobis(ethyleneoxyethylenethio)]-bis[6-bromopyridine] (12b). The disulfide **12b** (50 mg, 0.085 mmol) in anhydrous diethyl ether (7 mL) was added dropwise to a suspension of lithium aluminum hydride (ca. 3 mg, 0.079 mmol) in ether (ca. 10 mL) over a 10-min period. The mixture was refluxed under argon for 20 min; two additional aliquots of lithium aluminum hydride (3 mg each) were added. After the last addition, the mixture was refluxed for 10 min and then stirred overnight at room temperature. The reaction was quenched with water, acidified with dilute (1%) hydrochloric acid, and extracted with diethyl ether. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated, affording a residue which was chromatographed (ThLC) eluting four times with hexane–acetone (8:1) to give three major fractions. Fraction A yielded the cleaved 1:1 thiol **9a:** 10 mg (20%); identical with the previously isolated material. Fraction B afforded **5:** 10 mg (27%); NMR data were identical with a previously prepared sample. Fraction C afforded unreacted starting disulfide **12b:** 7 mg (14%).

Cyclization of 9b. Preparation of 8. Thiol **9b** (210 mg, 0.71 mmol) in diisopropylethylamine (20 mL) was refluxed under nitrogen for 6 days. The solvent was removed in vacuo, and the residue was chromatographed (ThLC) eluting three times with hexane–acetone (10:1) to give three fractions.

Fraction A afforded the 1:1 macrocycle **8:** 30 mg (20%); mp 117–119 °C (hexane) (lit.[10] mp 110–112 °C). Fraction B yielded unreacted starting material: 60 mg (29%); bp 119–128 °C (0.6 mm, microdistillation). Fraction C afforded the oxidized disulfide **12b:** 65 mg (30%); identical NMR spectrum with a previously prepared sample.

Reaction of 2,6-dibromopyridine with bis(2-mercaptoethyl) sulfide gave a residue which was chromatographed (ThLC) eluting eight times with hexane–acetone (20:1) to afford four major fractions.

Fraction A yielded the 1:1 thiol **14a** as a pale yellow oil: bp 160 °C (2.4 mm, microdistillation); NMR ($CDCl_3$) δ 1.77 (t, SH, J = 8.0 Hz, 1 H), 2.68–2.98 (m, β-CH_2, 6 H), 3.22–3.39 (m, α-CH_2, 2 H), 7.06 (dd, 3- or 5-pyr H, J = 7.5, 1.3 Hz, 1 H), 7.12 (dd, 5- or 3-pyr H, J = 7.5, 1.3 Hz, 1 H), 7.31 (t, 4-pyr H, J = 7.5 Hz, 1 H); IR (neat) 2525 (SH), 1275, 1260, 1140, 780 (br) cm^{-1}.

Fraction B was rechromatographed (ThLC) eluting with hexane–acetone (10:1) to afford pure 2:1 sulfide **15a:** bp 160–170 °C (0.5 mm); NMR ($CDCl_3$) δ 2.87–3.04 (m, β-CH_2, J = 7.2 Hz, 4 H), 3.35–3.51 (m, α-CH_2, J = 7.2 Hz, 4 H), 7.02–7.35 (m, pyr H, 6 H); IR (neat) 2900, 1545, 1375, 1275, 1155, 1070 cm^{-1}.

Fraction C was recrystallized from diethyl ether–acetone to give sulfide **15b:** mp 68–71 °C; NMR ($CDCl_3$) δ 2.77–2.96 (m, β-CH_2, 4 H), 2.97 (s, γ-CH_2, 4 H), 3.26–3.45 (m, α-CH_2, 4 H), 7.07 (dd, 3- or 5-pyr H, J = 7.5, 1.4 Hz, 2 H), 7.12 (dd, 5- or 3-pyr H, J = 7.5, 1.4 Hz, 2 H), 7.30 (t, 4-pyr H, J = 7.5 Hz, 2 H); IR (KBr) 2885, 1565, 1375, 1160 cm^{-1}; MS (70 eV) m/e 524 (M^+, 0.43%), 338, 336 ($C_{11}H_{15}NS_3NBr$, 25%), 218, 216 (C_7H_7NSBr, 100%), 191, 189 (C_5H_4NSBr, 60%).

Fraction D was recrystallized from diethyl ether–acetone to afford disulfide **16:** mp 59–62 °C; NMR ($CDCl_3$) δ 2.75–2.95 (m, β-CH_2, J = 7.5 Hz, 4 H), 3.0 (br s, γ, δ-CH_2, 8 H), 3.26–3.45 (m, α-CH_2, J = 7.5 Hz, 4 H), 7.07 (dd, 3- or 5-pyr H, J = 7.6, 1.3 Hz, 2 H), 7.12 (dd, 5- or 3-pyr H, J = 7.6, 1.3 Hz, 2 H), 7.31 (t, 4-pyr H, J = 7.6 Hz, 2 H); IR (KBr) 2900, 1550, 1370, 1210, 1135 cm^{-1}; MS (70 eV) m/e 616 (M^+, 0.25%), 218, 216 (C_7H_7NSBr, 100%), 191, 189 (C_5H_4NSBr, 41%).

Reaction of 2,6-dichloropyridine with bis(2-mercaptoethyl) sulfide according to method A afforded a residue which was chromatographed (ThLC) eluting four times with hexane–acetone (15:1) to give two major fractions other than the unreacted starting material.

Fraction A was rechromatographed (ThLC) eluting once with 10:1 hexane–acetone and then once with 8:1 hexane–acetone to yield the 1:1 thiol **17:** bp 90–100 °C (0.1 mm); NMR ($CDCl_3$) δ 1.75 (m, SH, J = 7.9 Hz, 1 H), 2.67–3.0 (m, β-CH_2, 6 H), 3.26–3.42 (m, α-CH_2, 2 H), 6.95 (dd, 3- or 5-pyr H, J = 7.8, 0.9 Hz, 1 H), 7.03 (dd, 5- or 3-pyr H, J = 7.8, 0.9 Hz, 1 H), 7.39 (t, 4-pyr H, J = 7.8 Hz, 1 H); IR (neat) 2875 (SH), 1565, 1380, 1280, 1160 cm^{-1}.

Fraction B gave disulfide **18:** TGA inflection point, 310 °C; NMR ($CDCl_3$) δ 2.78–2.94 (m, β-CH_2, 4 H), 2.99 (br s, γ, δ-CH_2, 8 H), 3.29–3.45 (m, α-CH_2, 4 H), 6.95 (dd, 3- or 5-pyr H, J = 7.7, 0.8 Hz, 2 H), 7.04 (dd, 5- or 3-pyr H, J = 7.7, 0.8 Hz, 2 H), 7.38 (t, 4-pyr H, J = 7.7 Hz, 2 H); IR (neat) 2820, 1570, 1430, 1290, 1160 cm^{-1}.

Reaction of 2-bromopyridine with 1,2-ethanedithiol afforded a viscous residue which was chromatographed (ThLC) eluting three times with cyclohexane–ethanol (4%) to give two major fractions.

Fraction A was recrystallized three times from dichloromethane–hexane to afford **20:** mp 109–111 °C; NMR ($CDCl_3$) δ 3.5 (s, SCH_2, 4 H), 6.93 (ddd, 5-pyr H, J = 7.2, 5.0, 1.3 Hz, 2 H), 7.22 (ddd, 3-pyr H, J = 8.2, 1.3, 0.9 Hz, 2 H), 7.46 (ddd, 4-pyr H, J = 8.2, 7.2, 2.0 Hz, 2 H), 8.40 (ddd, 6-pyr H, J = 5.0, 2.0, 0.9 Hz, 2 H); IR (KBr) 3350, 1640, 1585, 1460, 1280, 1150 cm^{-1}.

Fraction B was distilled to afford di-2-pyridyl sulfide (**21**): bp 160–170 °C (8 mm) [lit.[12] bp 190 °C (6 mm)]; identical with an authentic sample.

Reaction of 2,6-dichloropyridine and 1,2-ethanedithiol gave a residue which was chromatographed (ThLC) eluting four times with hexane–acetone (10:1) to afford four major fractions.

Fraction A was recrystallized from petroleum ether (bp 30–60 °C) and acetone to afford macrocycle **22:** mp 158.5–160.5 °C; NMR ($CDCl_3$) δ 2.71–2.89 (m, β-CH_2, 4 H), 2.84 (s, γ-CH_2, 4 H), 3.43–3.61 (m, α-CH_2, 4 H), 6.84 (d, 3- or 5-pyr H, J = 8.2 Hz, 1 H), 6.85 (d, 5- or 3-pyr H, J = 7.1 Hz, 1 H), 7.25 (dd, 4-pyr H, J = 8.2, 7.1 Hz, 1 H); IR (KBr) 2870, 1550, 1390, 1280, 1155 cm^{-1}; MS (70 eV) m/e 289 (M^+, 55%), 203 ($C_7H_9NS_3^+$, 75%), 168 ($C_7H_6NS_2^+$, 37%), 143 ($C_5H_5NS_2^+$, 100%).

Fraction B yielded **23a:** bp 160 °C (1.1 mm); NMR ($CDCl_3$) δ 2.88–3.04 (m, β-CH_2, 4 H), 3.37–3.52 (m, α-CH_2, 4 H), 6.92 (dd, 3- or 5-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.03 (dd, 5- or 3-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.37 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (neat) 3000, 1535, 1375, 1250, 1140 cm^{-1}; MS (70 eV) m/e 376 (M^+, 9.2%), 232 ($C_9H_{11}NS_2{}^{35}Cl^+$, 100%), 172 ($C_7H_7NS^{35}Cl$, 88%), 145 ($C_5H_4NS^{35}Cl^+$, 81%), 112 ($C_5H_3N^{35}Cl^+$, 44%).

Fraction C was rechromatographed (ThLC) with hexane–acetone (15:1), affording **23b:** TGA point of inflection, 343 °C; NMR ($CDCl_3$) δ 2.79–2.94 (m β-CH_2, 4 H), 2.96 (s, γ-CH_2, 4 H), 3.29–3.45 (m, α-CH_2, 4 H), 6.92 (dd, 3- or 5-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.01 (dd, 5- or 3-pyr H, J = 7.8, 1.0 Hz, 2 H), 7.35 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (neat) 2890, 1550, 1370, 1250, 1150 cm^{-1}; MS (70 eV) m/e 436 (M^+, 1.2%), 292 ($C_{11}H_{15}NS_3{}^{35}Cl^+$, 32%), 172 ($C_7H_7NS^{35}Cl^+$, 100%), 145 ($C_5H_4NS^{35}Cl^+$, 62%).

Fraction D was recrystallized from hexane and acetone to afford **23c:** mp 48–50 °C; NMR ($CDCl_3$) δ 2.77–2.93 (m, β-CH_2S, 4 H), 2.89 (br s, γ, δ-CH_2, 8 H), 3.27–3.44 (m, α-CH_2, 4 H), 6.94 (dd, 3- or 5-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.02 (dd, 5- or 3-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.37 (t, 4-pyr H, J = 7.8 Hz, 2 H); IR (KBr) 2905, 1540, 1380, 1210, 1150 cm^{-1}; MS (70 eV) m/e 496 (M^+, 1%), 352 ($C_{13}H_{19}NS_4{}^{35}Cl^+$, 48%), 204 ($C_7H_7NS_2{}^{35}Cl^+$, 28%), 172 ($C_7H_7NS^{35}Cl^+$, 100%), 145 ($C_5H_4NS^{35}Cl^+$, 85%).

Reaction of 2,6-dichloropyridine and 1,4-butanedithiol afforded a residue which was chromatographed (ThLC) eluting three times with hexane–acetone (10:1) to give three major fractions.

Fraction A was recrystallized from hexane–acetone to give the 2:2 macrocycle **24:** R_f 0.41 [hexane–acetone (10:1)]; MS (70 eV) m/e 394 (M^+, 4%), 198 ($C_9H_{12}NS_2^+$, 100%), 170 ($C_7H_8NS_2^+$, 32%), 168

($C_7H_6NS_2^+$, 41%), 164 ($C_9H_{10}NS^+$, 25%), 143 ($C_5H_5NS_2^+$, 50%), 110 ($C_5H_4NS^+$, 77%). Due to the limited quantity of sample, further spectral studies were not conducted.

The mother liquor from fraction A was concentrated to afford the 2:1 compound **25:** mp 56–58 °C; NMR δ 1.77–1.95 (m, β-CH_2, 4 H), 3.12–3.30 (m, α-CH_2, 4 H), 6.91 (dd, 3- or 5-pyr H, J = 7.9, 1.0 Hz, 2 H), 7.01 (dd, 5- or 3-pyr H, J = 7.9, 1.0 Hz, 2 H), 7.34 (t, 4-pyr H, J = 7.9 Hz, 2 H); IR (KBr) 2990, 1540, 1245, 1130 cm^{-1}.

Fraction B was recrystallized from diethyl ether and hexane to afford the 3:2 open-chain compound **26:** mp 55–56 °C; NMR ($CDCl_3$) δ 1.77–1.96 (m, all β-CH_2, 8 H), 3.10–3.29 (m, all α-CH_2, 8 H), 6.80 (d, 3- or 5-pyr H, J = 8.2 Hz, 2 H), 6.92 (dd, 3′- or 5′-pyr H, J = 7.7, 0.9 Hz, 2 H), 7.01 (dd, 5′- or 3′-pyr H, J = 7.7, 0.9 Hz, 2 H), 7.2 (t, 4-pyr H, J = 8.2 Hz, 1 H), 7.35 (t, 4′-pyr H, J = 7.7 Hz, 2 H); IR (KBr) 2915, 1535, 1395, 1125 cm^{-1}.

Fraction C was recrystallized from hexane and acetone to afford the 4:3 compound **27:** mp 80.5–82 °C; NMR ($CDCl_3$) δ 1.77–1.94 (m, all β-CH_2, 12 H), 3.10–3.27 (m, all α-CH_2, 12 H), 6.79 (d, 3- or 5-pyr H, J = 8.2 Hz, 2 H), 6.80 (d, 5- or 3-pyr H, J = 8.0 Hz, 2 H), 6.92 (dd, 3′- or 5′-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.01 (dd, 3′- or 5′-pyr H, J = 7.8, 0.9 Hz, 2 H), 7.20 (dd, 4-pyr H, J = 8.2, 8.0 Hz, 2 H), 7.34 (t, 4′-pyr H, J = 7.8 Hz, 2 H); IR (KBr) 2920, 1560, 1380, 1130 cm^{-1}.

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Registry No.—**4a,** 109-09-1; **4b,** 109-04-6; **5,** 66119-95-7; **6,** 66119-96-8; **7a,** 2402-78-0; **7b,** 626-05-1; **8,** 54945-37-8; **9a,** 66119-97-9; **9b,** 66119-98-0; **10,** 66119-99-1; **11a,** 66120-00-1; **11b,** 66120-01-2; **12a,** 66120-02-03; **12b,** 66120-03-4; **13,** 66120-04-5; **14a,** 66120-05-6; **15a,** 66120-06-7; **15b,** 66119-82-2; **16,** 66119-83-3; **17,** 66119-84-4; **18,** 66119-85-5; **20,** 66119-86-6; **21,** 4262-06-0; **22,** 66119-87-7; **23a,** 66119-88-8; **23b,** 66119-89-9; **23c,** 66119-90-2; **24,** 66119-91-3; **25,** 66119-92-4; **26,** 66119-93-5; **27,** 66119-94-6; bis(2-mercaptoethyl) ether, 2150-02-9; bis(2-mercaptoethyl) sulfide, 3570-55-6; 1,2-ethanedithiol, 540-63-6; 1,4-butanedithiol, 1191-08-8.

Supplementary Material Available: All analytical data for the new compounds in Table II (2 pages). Ordering information is given on any current masthead page.

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A Convenient Synthesis of Tertiary Alkyl *N*-Phenylcarbamates from Tertiary Alcohols and Phenyl Isocyanate with a Lithium Alkoxide Catalyst[1]

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Although the direct addition of tertiary alcohols to isocyanates usually gives no reaction at low temperatures and produces olefins on being heated, the use of catalysts, such as lithium alkoxides and dibutyltin diacetate, makes possible the synthesis of tertiary alkyl *N*-phenylcarbamates in good yields. Thus the addition of *tert*-amyl alcohol to phenyl isocyanate in the presence of lithium *tert*-amyloxide gave *tert*-amyl *N*-phenylcarbamate in an 81% yield. For comparison the same reaction in the presence of dibutyltin diacetate gave a 60% yield of the carbamate and the uncatalyzed reaction gave a 15% yield. The addition of *tert*-butyl alcohol to phenyl isocyanate in the presence of lithium *tert*-butoxide gave an 82% yield of *tert*-butyl *N*-phenylcarbamate. By the same technique the *N*-phenylcarbamates of 1,1-diphenylethanol, 2-phenyl-2-propanol and 3-ethyl-3-pentanol were prepared in 74, 77, and 39% yields, respectively.

In a program to evaluate various tertiary alkyl oxycarbonyl groups as blocking groups for amines a convenient synthesis of tertiary alkyl *N*-phenylcarbamates was desired. However, a search of the literature indicated that there were no good general methods described for the synthesis of tertiary alkyl derivatives. Since a number of very active catalysts have been

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Table I. Reaction of Tertiary Alcohols with Phenyl Isocyanate[a]

Tertiary alcohol	Registry no.	Catalyst	Time, min	Temp, °C	Yield of carbamate, %
tert-Amyl	75-84-3	LiOR	25	37	81
		$Bu_2Sn(OAc)_2$	145	25–40	60
		None	145	25–27	15
tert-Butyl	75-65-0	LiOR	10	37	82
		$Bu_2Sn(OAc)_2$	14	32–60	42
		None	1440	25	27
2-Phenyl-2-propanol	617-94-7	LiOR	55	25–36	77
1,1-Diphenylethanol	1883-32-5	LiOR	30	37	74
3-Ethyl-3-pentanol	597-49-9	LiOR	30	25–60	39[8]

[a] Registry no. 103-71-9.

reported for use in the synthesis of polyurethanes, it was hoped that one of these catalysts would increase the rate of addition of tertiary alcohols to isocyanates sufficiently to make possible a convenient synthetic procedure.

Davis and Farnum[3] reported that the relative rates of the uncatalyzed reactions of primary, secondary, and tertiary alcohols with phenyl isocyanate had the relative ratios of 100:33:1, respectively. The primary alcohols react fairly rapidly at room temperature with phenyl isocyanate, while the secondary alcohols usually must be warmed before they will react rapidly. On the other hand, most of the tertiary alcohols react slowly, even at 100 °C, and the main product is not the carbamate but the corresponding olefin. For example, Neuberg and Kansky[4] reported the reaction of *tert*-butyl and *tert*-amyl alcohols with 1-naphthyl isocyanate produced the *tert*-butyl *N*-1-naphthylcarbamate in a 35% yield and the *tert*-amyl derivative in a 3.4% yield. There are scattered reports in the literature of attempts to use isocyanates with tertiary alcohols, but in no case were any yields of products given.

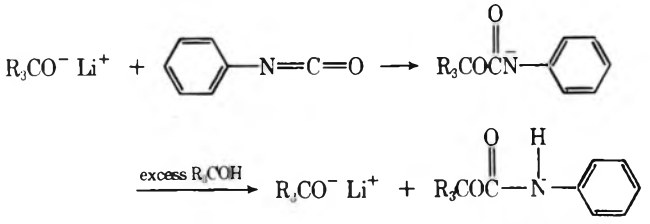
Although there have been many reports concerning the use of basic catalysts for the isocyanate–alcohol reaction, the disclosure by Cox and Hostettler[5] that organo–tin compounds are very effective as catalysts for the primary alcohol–isocyanate reaction led to the speculation that it might also increase the rate of addition with tertiary alcohols. Thus, they had shown that dibutyltin diacetate had a catalytic effect on the phenyl isocyanate–methanol reaction which was 2400 times as great as the activity of triethylamine. Since the organo–tin compounds are amphoteric, they apparently combine the action of the acid catalysts with that of the medium strength base catalyst to produce a synergistic effect.

tert-Butyl alcohol appears to be the exception to the general case of tertiary alcohols, in that its N-aryl carbamates can be formed readily and in fair yields without catalysts.[4] For this reason the effect of dibutyltin diacetate on the reaction of *tert*-butyl alcohol with phenyl isocyanate was determined for the addition reaction in both dibutyl ether and without a solvent. The qualitative effects of the catalyst were determined by treatment of one of two similar portions of *tert*-butyl alcohol and isocyanate with the catalyst and by the use of a spectrophotometer to follow the disappearance of the isocyanate absorption band at 4.5 μm. On a preparative scale the reaction of *tert*-butyl alcohol and phenyl isocyanate in the presence of dibutyltin diacetate gave a 42% yield of the *tert*-butyl *N*-phenylcarbamate after the reaction mixture was allowed to stand for 15 min, while the uncatalyzed reaction gave a 27% yield after being allowed to stand for 18 h.

Unlike *tert*-butyl alcohol, *tert*-amyl alcohol does not react with phenyl isocyanate at a satisfactory rate in the absence of a catalyst. Although the dibutyltin diacetate catalyst did not greatly accelerate the reactions of *tert*-amyl alcohol, the catalyzed reaction is still much more rapid then the uncatalyzed reaction. When the reaction was carried out on a preparative scale with dried *tert*-amyl alcohol in the presence of the organotin catalyst, a 60% yield of the *tert*-amyl *N*-phenylcarbamate was obtained.

Since Tarbell[6] had shown that the catalytic power of the basic catalysts was related to the relative basicities as determined by Hall,[7] we thought it would be of interest to study much stronger bases as catalysts for this reaction. Although the early investigators showed that alkoxides are very effective catalysts for the trimerization, dimerization, and polymerization of phenylisocyanate, these easily prepared polar bases have been apparently neglected as catalysts for other isocyanate reactions. For these reasons we decided to investigate the use of alkoxides as catalysts for the tertiary alcohol addition to phenyl isocyanate.

One could visualize the reaction of the tertiary alkoxide with an isocyanate in the presence of a large excess of tertiary alcohol to be as follows:



The key to the successful addition appeared to be the use of a small amount of lithium alkoxide in the presence of an excess of the tertiary alcohol. It was expected that the tertiary derivatives would be stable under the basic conditions and prevent the elimination reaction which would produce the olefin. In the choice of the particular alkali metal salt, there were several considerations that appeared to favor lithium over sodium and potassium. Generally, the lithium salts are more soluble in organic solvents and therefore greater concentrations of the alkoxides can be achieved by the use of lithium alkoxides of high molecular weight alcohols.

Lithium *tert*-amyl oxide was found to be an extremely active catalyst for the trimerization of phenyl isocyanate. However, if the isocyanate is added dropwise to an excess of *tert*-amyl alcohol in ethyl ether solution, which also contains a small quantity of the alkoxide, then the ether boils vigorously on each dropwise addition. Thus, the carbamate formation is optimized by the use of an excess of tertiary alcohol to avoid the isocyanate trimerization and the use of ethyl ether as a solvent to keep the reaction mixture cool and thus avoid alcohol dehydration. By the use of this technique an 81% yield of *tert*-amyl *N*-phenylcarbamate was obtained. It was found that sodium and potassium alkoxides are almost as effective as lithium alkoxide in the promotion of a rapid reaction of phenyl isocyanate with a tertiary alcohol; however, lithium hydroxide, which can form if water is present, does not interfere with this reaction.

Since only low yields have been reported for the addition of *tert*-butyl alcohol to phenyl isocyanate, this reaction was

reinvestigated with lithium *tert*-butoxide as a catalyst. To ensure a smooth reaction ether was added to the solution of the lithium alkoxide in excess alcohol and a seed crystal was added after one-third of the isocyanate had been added. By this technique an 82% yield of *tert*-butyl *N*-phenylcarbamate was obtained in less than 10 min.

In order to demonstrate the generality of this synthetic method, the *N*-phenylcarbamates of three other tertiary alcohols, several of which were quite sensitive to acid-catalyzed dehydration, were investigated and the results are listed in Table I. Thus, we have demonstrated that lithium alkoxides can be used as effective catalysts for the synthesis on a preparative scale of *tert*-alkyl *N*-phenylcarbamates by the direct reaction of isocyanates with tertiary alcohols. A qualitative procedure for the preparation of solid derivatives from a wide variety of tertiary alcohols with isocyanates has been reported separately.[1]

Experimental Section[9]

***tert*-Amyl *N*-Phenylcarbamate. A. Addition Reaction Catalyzed by Lithium Alkoxide.** After 0.2 g of lithium metal had been reacted with 60.0 g (0.68 mol) of *tert*-amyl alcohol (dried over calcium hydride), 100 mL of ethyl ether (dried over calcium hydride) was added. From the addition funnel 40.0 g (0.34 mol) of phenyl isocyanate was added dropwise with vigorous stirring just rapidly enough to keep the solution boiling gently. Upon completion of the isocyanate addition the resulting solution was extracted with five 100-mL portions of water. After the ether was removed from the dried solution by evaporation, the residue was dissolved in 50 mL of petroleum ether (bp 30–36 °C); no insoluble residue remained. When the solution was stored at −20 °C overnight, the precipitated carbamate was removed by filtration. Two-thirds of the petroleum ether was removed from the filtrate by evaporation and the concentrated solution was stored at −20 °C for an additional 24 h to give a second crop. The combined precipitates were recrystallized from petroleum ether to yield 56.0 g (81%) of pure *tert*-amyl *N*-phenylcarbamate, mp 42 °C (lit.[10] mp 42 °C).

B. Addition Reaction Catalyzed by Dibutyltin Diacetate. To a homogeneous mixture of 2.75 g (0.025 mol) of phenyl isocyanate and 2.0 g (0.0225 mol) of dried *tert*-amyl alcohol was added 0.05 g (0.0002 mol) of dibutyltin diacetate. The temperature of the mixture slowly rose from 25 to 40 °C over a period of 25 min. After the mixture was allowed to stand for 2 h, it had cooled to room temperature to give a viscous liquid. After the mixture had been allowed to stand overnight, no odor of phenyl isocyanate was noted. When 10 mL of petroleum ether (bp 30–60 °C) was added, an insoluble residue of 0.1 g remained undissolved and was removed by filtration. After the filtrate was stored at −20 °C for 24 h and the resulting solid was collected by filtration and washed with 5 mL of cold petroleum ether, 2.8 g (60%) of *tert*-amyl *N*-phenylcarbamate, mp 43–44 °C, was obtained.

C. Uncatalyzed Addition Reaction. When an experiment nearly identical with that described in B above but omitting the dibutyltin diacetate was performed, a temperature rise of only 2 °C was noted and 0.7 g (15%) of the carbamate was obtained.

***tert*-Butyl *N*-Phenylcarbamate. A. Addition Reaction Catalyzed by Lithium *tert*-Butoxide.** A freshly cut 0.06-g piece of lithium metal was reacted with 14.8 g (0.20 mol) of *tert*-butyl alcohol (dried over calcium sulfate and then calcium hydride). After 35 mL of dry ether was added to form a slightly cloudy solution, a solution of 29.8 g (0.25 mol) of phenyl isocyanate in 35 mL of ether was added dropwise at such a rate as to maintain gentle reflux. After about one-third of the isocyanate solution had been added, the addition was interrupted and a seed crystal of *tert*-butyl *N*-phenylcarbamate was introduced to prevent excessive supersaturation and the resulting uncontrollable reaction. After the mixture had been allowed to stand for an additional 5 min, filtration gave 39.9 g of crude product, mp 100–115 °C. Recrystallization from boiling ligroin gave 31.5 g (82%) of pure *tert*-butyl *N*-phenylcarbamate, mp 135–6 °C (lit.[10] mp 136 °C).

B. Addition Reaction Catalyzed by Dibutyltin Diacetate. To a homogeneous mixture of 2.7 g (0.025 mol) of phenyl isocyanate and 2.0 g (0.025 mol) of thoroughly dried *tert*-butyl alcohol was added 0.05 g (0.0002 mol) of dibutyltin diacetate. When the mixture was shaken rapidly, within 12 min its temperature rose quickly from 32 to 60 °C. At 14 min its temperature rose very sharply, and with much vigor the reacting mass suddenly solidified. The reaction mixture was dissolved completely in about 20 mL of boiling petroleum ether (bp 100–120 °C). When the solution was cooled, 3.9 g (42%) of white crystalline needles of the *tert*-butyl *N*-phenylcarbamate, mp 134–136 °C, separated.

2-Phenyl-2-propyl *N*-Phenylcarbamate. To 13.6 g (0.10 mol) of dry 2-phenyl-2-propanol in 50 mL of dry ether was added 0.03 g of freshly cut lithium metal, which partially dissolved over a 30-min heating period on a steam bath. Over a 10-min period 12.0 g (0.10 mol) of phenyl isocyanate in 25 mL of dry ether was added with vigorous stirring. After the addition was complete, the mixture was heated under reflux for an additional 45 min. When the mixture was cooled to room temperature and allowed to stand for 2 h, the mass crystallized. The ether was removed by evaporation on a steam bath and the residue (27.2 g) was recrystallized from 100 mL of boiling ligroin to give 19.7 g (77%) of 2-phenyl-2-propyl *N*-phenylcarbamate, mp 110–111 °C (lit.[11] mp 113 °C).

1,1-Diphenylethyl *N*-Phenylcarbamate. To 0.5 g of 1,1-diphenylethanol melted in a test tube was added about 0.05 g of freshly cut lithium metal. The resulting solution was added to 9.9 g of a 10.4-g sample (0.053 mol) of 1,1-diphenylethanol in 50 mL of dry ether and the mixture was stirred until homogeneous. With stirring a solution of 7.26 g (0.061 mol) of phenyl isocyanate in 40 mL of dry ether was added rapidly to maintain gentle reflux. After the ether had been removed by evaporation, the crude solid was recrystallized from methanol to yield 12.5 g (74%) of 1,1-diphenylethyl *N*-phenylcarbamate, mp 119–120 °C. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03. Found: C, 79.70; H, 6.30.

3-Ethyl-3-pentyl *N*-Phenylcarbamate. After 0.05 g of lithium metal had been dissolved in 5.0 g (0.043 mol) of 3-ethyl-3-pentanol, 5.0 mL (5.5 g, 0.05 mol) of phenyl isocyanate was added dropwise with stirring over a period of 15 min. An oily product began to separate when approximately one-half of the isocyanate had been added. Upon complete addition of the isocyanate, 50 mL of petroleum ether (bp 30–60 °C) was added and the mixture was heated to boiling. After 0.9 g of an insoluble residue was removed by filtration, the filtrate was cooled overnight at −20 °C. Filtration gave 6.4 g of crude carbamate which was recrystallized from 20 mL of petroleum ether by cooling at −20 °C to yield 3.9 g (39%) of pure 3-ethyl-3-pentyl *N*-phenylcarbamate, mp 61–62 °C (lit.[6] mp 61 °C).

Registry No.—*tert*-Amyl *N*-phenylcarbamate, 37534-82-0; *tert*-butyl *N*-phenylcarbamate, 3422-01-3; 2-phenyl-2-propyl *N*-phenylcarbamate, 5037-72-9; 1,1-diphenylethyl *N*-phenylcarbamate, 5037-73-0; 3-ethyl-3-pentyl *N*-phenylcarbamate, 66303-76-2.

References and Notes

(1) Presented in part before the Division of Organic Chemistry at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 1960; a previous paper in this series is *J. Chem. Educ.*, in press.
(2) Taken in part from a thesis submitted to the Graduate School of the University of Maryland in partial fulfillment of the degree of Master of Science.
(3) T. L. Davis and J. M. Farnum, *J. Am. Chem. Soc.*, **56**, 883 (1934).
(4) C. Neuberg and E. Kansky, *Biochem. Z.*, **20**, 446 (1909); *Chem. Abstr.*, **4**, 1483 (1910).
(5) E. F. Cox and F. Hostettler, Abstracts of Papers, 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959, p 112–O.
(6) D. S. Tarbell, R. C. Mallatt, and J. W. Wilson, *J. Am. Chem. Soc.*, **64**, 2229 (1942).
(7) N. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930).
(8) Reference 6 had previously prepared this carbamate in an unreported yield but purified it by distillation. Apparently the alkali metal acetate used as the catalyst did not carry the reaction far enough to permit isolation by crystallization.

(9) The authors are grateful to Dr. Franz Kasler for the microanalysis.

(10) E. Lambling, *Bull. Soc. Chim. Fr.*, **19**, 777 (1898).
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Manganese Dioxide Oxidation of Aryl 1,2-Diaminoimidazoles

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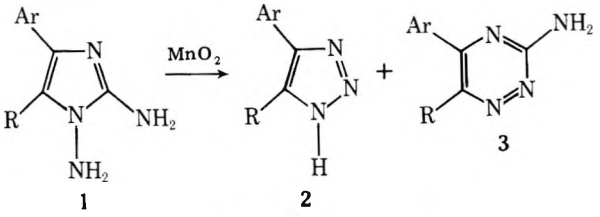
The oxidation of aryl 1,2-diaminoimidazoles (**1**) with manganese dioxide to 1,2,3-triazoles (**2**) and/or 3-amino-1,2,4-triazoles (**3**) is described. Aroyldiazomethanes (**4**), benzonitriles (**5**), and acetophenones (**6**) were minor products of this oxidation. The formation of **2** and **3** from the monoaryl imidazoles (**1a–c**) is viewed as proceeding via the formation of the *C*-nitrenes (or nitrenoids) which open to the α-hydrazono-*N*-cyanoimines (**8**), followed by cyclization to either **2** or **3**. The α-hydrazono-*N*-cyanoimines (**8**) can also account for the formation of **4** and **5**, while fragmentation of the *N*-nitrenes would explain the presence of the acetophenones (**6**). The mechanism of the oxidation of 4,5-diphenyl-1,2-diaminoimidazole (**1d**) and 1,2-diaminobenzimidazole (**1e**) is also discussed.

The manganese dioxide oxidation of 4-phenyl-1,2-diaminoimidazole (**1a**) to 4(5)-phenyl-1,2,3-triazole (**2a**) and 3-amino-5-phenyl-1,2,4-triazine (**3a**) has been recently described in a communication.[2a] The formation of **2a** and **3a** was

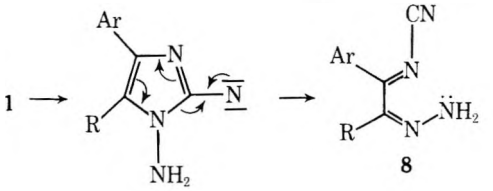


+ $ArCOCHN{=}\overset{+}{N}$ + $ArC{\equiv}N$ + $ArCOCH_3$ (1)

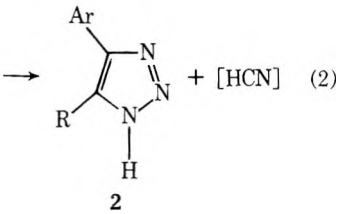
4 **5** **6**

a, R = H; Ar = Ph
b, R = H; Ar = *p*-BrC_6H_4
c, R = H; Ar = *p*-$CH_3OC_6H_4$
d, R = Ar = Ph
e, R, Ar =

rationalized via formation of the *C*-nitrene (or nitrenoid) **7a** which could then undergo ring opening to the α-hydrazono-*N*-cyanoimine (**8**) thence to the observed products **2a** and **3a**.



7 **8**



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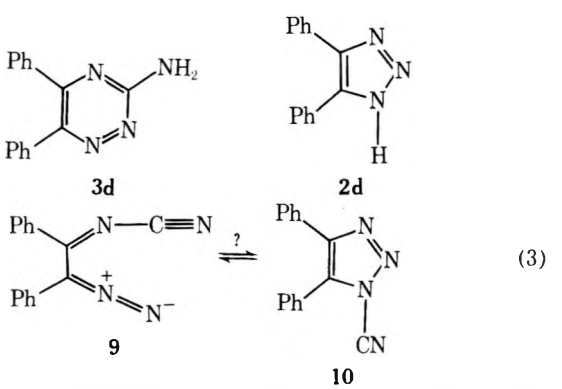
The possible alternate reaction paths of the postulated intermediates, coupled with the need to determine the scope and mechanism of this oxidation, made a more detailed investigation desirable. This paper reports the oxidation of 4-aryl-(**1a–c**), 4,5-diphenyl-1,2-diaminoimidazoles (**1d**), and 1,2-diaminobenzimidazole (**1e**).

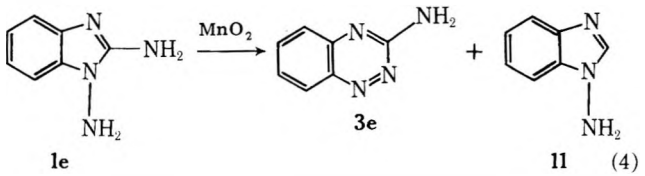
Results

The oxidation of 4-aryl-1,2-diaminoimidazoles (**1**)[2b] with manganese dioxide in benzene at reflux gave 4-aryl-1,2,3-triazoles (**2**) and 3-amino-5-aryl-1,2,4-triazines (**3**) as the major products (Table I). However, careful workup of the reaction mixtures permitted the isolation of minor products **4, 5,** and **6**. Oxidation of 4,5-diphenyl-1,2-diaminoimidazole (**1d**) gave the corresponding 3-amino-5,6-diphenyl-1,2,4-triazine (**3d**) as the major product (62%) while only 10% of 4,5-diphenyl-1,2,3-triazole (**2d**) was isolated; in addition, benzonitrile (**5a**), benzil, and a compound which appears to be compound **9** (or in equilibrium with the isomeric 4,5-diphenyl-1-cyanotriazole **10**) were isolated. No benzotriazole could be detected from the oxidation of 1,2-diaminobenzimidazole (**1e**); the major



3d **2d**

9 **10** (3)

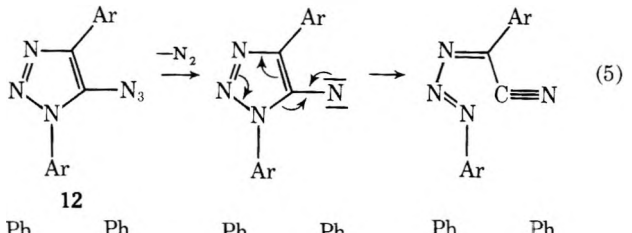


1e **3e** **11** (4)

product (33%) was 3-aminobenzotriazine (**3e**) along with trace amounts of 1-aminobenzimidazole (**11**).

Discussion

The formation of the triazoles **2** can be best rationalized in terms of *C*-nitrene (or nitrenoid) intermediates (**7**) which then undergo fragmentation to α-hydrazono-*N*-cyanoimines (**8**). Cyclization of **8** by displacement of cyanide by the NH_2 group would then yield the 1,2,3-triazoles with elimination of hy-



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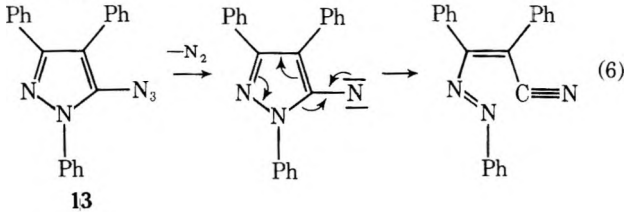

13 (6)

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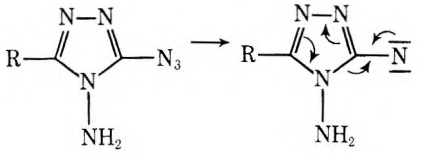
Table I. Oxidation of 4-Aryl-1,2-diaminoimidazoles

Ar	Registry no.	R	Triazole (2), %	Registry no.	Triazine (3), %	Registry no.
p-BrC_6H_4	15970-41-9	H	55	5301-98-4	6	65943-30-8
C_6H_5	15970-40-8	H	46	1680-44-0	11	942-60-9
p-$CH_3OC_6H_4$	15965-79-4	H	35	5301-97-3	25	65943-31-9



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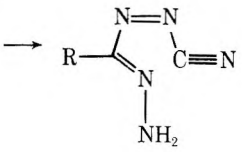
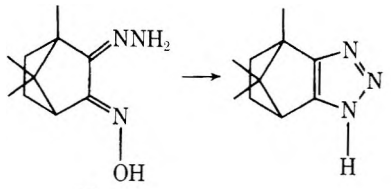


(7)



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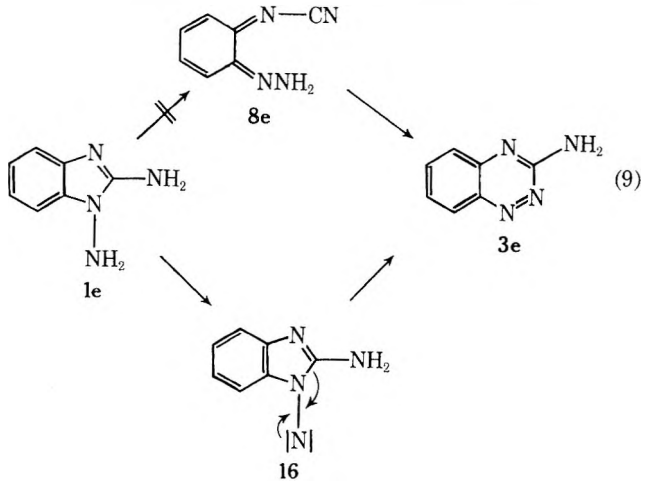
(8)

drogen cyanide. There exists ample precedent in the literature for both of these reactions. Smith and his group[4] had reported the fragmentation of 1,4-diaryl-5-azidotriazoles (**12**) and of 5-azidopyrazoles (**13**). Takimoto and Denault described the formation of 3-amino-*s*-tetrazines from the thermal decomposition of 1-amino-3-azido-*s*-triazoles (**14**).[5] The cyclization of α-hydrazono oximes (**15**) to 1,2,3-triazoles (eq 8)[6] provides an analogy for the cyclization of **8** to **2**.

The absence of benzotriazole from the oxidation of **1e** is consistent with the formation of the α-hydrazono-*N*-cyanoimine intermediate (**8**) in the case of the other imidazoles **1**. Indeed the participation of an intermediate of type **8** (**8e**)



8e

1e

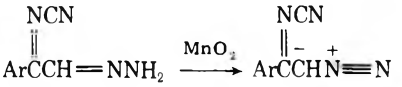
3e

16

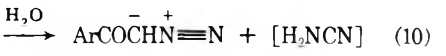
(9)

in this case would result in disruption of the aromatic ring.[7] The formation of **3e** must then be understood via oxidation to the *N*-nitrene (**16**) followed by a diazene–hydrazone rearrangement.[8]

Although the diazene–hydrazone rearrangement could account economically for the formation of the 3-amino-5-aryl-1,2,4-triazines (**3**) from the *N*-nitrenes which might be derived from **1**, the presence of aroyldiazomethanes (**4**) and benzonitriles (**5**) strongly favors the α-hydrazono-*N*-cyanoimines **8** as intermediates which explain not only the formation of **3**[2a] but also that of the nitriles and of the diazo ketones. Further oxidation of the hydrazone **8** would lead to the α-diazocyanoimines **17** which could then be hydrolyzed to **4** (eq 10). The possible formation of related compound **9** was



8 17



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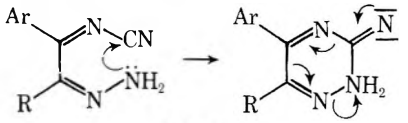
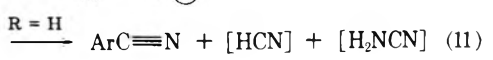
(10)

mentioned earlier. The generation of the benzonitriles may also be understood in terms of yet another novel path of **8** as shown below. It is interesting to note that **2d** (R = Ph) gave a sufficient amount of benzonitrile (in this case a second

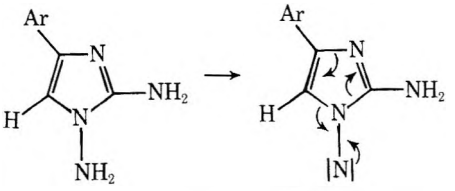


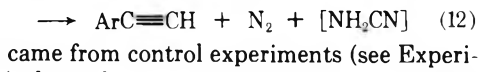


(11)

molecule of benzonitrile would be generated instead of hydrogen cyanide) to be characterized in subsequent chromatography of the reaction mixture.

On the other hand, the presence of the acetophenone **6** (and of benzil in the case of **2d**) must be ascribed to the anticipated *N*-nitrene (**18**) fragmentation path[9] to the acetylenes followed by hydration to the ketones. Support for the validity of the

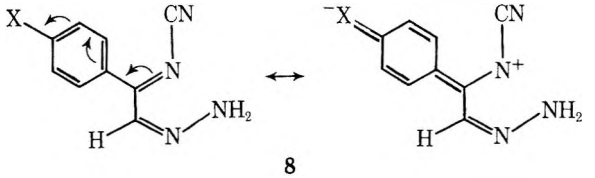




(12)

hydration step came from control experiments (see Experimental Section); desoxybenzoin is known to be oxidized to benzil under these conditions.[10]

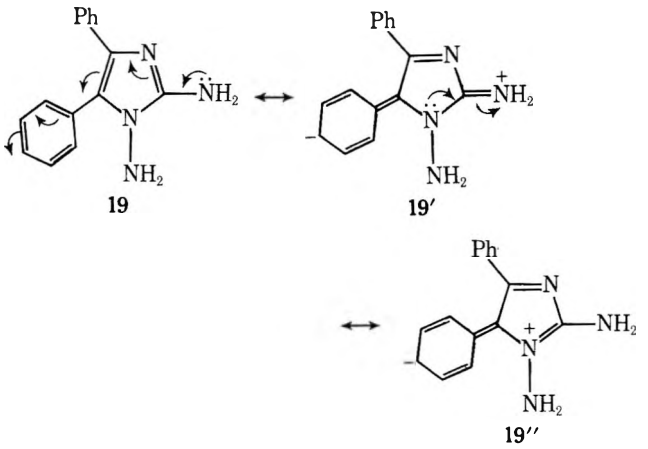
The variation in the yields of triazoles **2** and triazines **3** further militates against the diazene–hydrazone rearrangement as a rationalization for the formation of the 1,2,4-triazines in the case of **1a–c**, as both the generation and rearrangement of the *N*-nitrene would not be expected to be substantially affected by the para substituent of the 4-aryl group. On the other hand if α-hydrazono-*N*-cyanoimines (**8**)



8

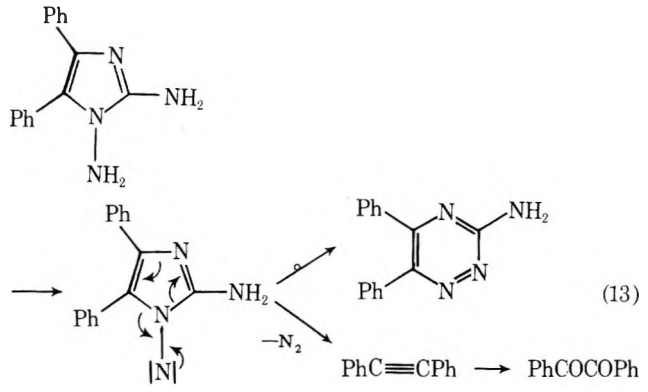
are intermediates, an electron-withdrawing substituent in the para position would favor formation of the triazole while an electron-donating substituent would not, as was observed (Table I).

The unexpectedly high yield of **3d** (and the correspondingly low yield of triazole **2d**) in the oxidation of **1d** would suggest that the triazines **3d** arose via the diazene–hydrazone rear-



19 19′ 19″

rangement of the *N*-nitrene since the susceptibility of the 2-amino group to oxidation would be reduced by the 5-phenyl substituent (structure **19′**) while the *N*-amino group should remain unaffected (the contribution of structure **19″** should be negligibly small). This view would be further supported by the measurable amount (8%) of benzil isolated in this reaction.



(13)

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus (below 250 °C) or on a Mel-Temp apparatus (above 250 °C) and are uncorrected. Infrared spectra were determined neat or as KBr pellets using a Perkin-Elmer 137. ^{1}H NMR spectra were obtained on a Hitachi Perkin-Elmer R24. Elemental analyses were performed by the Microanalysis Laboratory, University of Massachusetts at Amherst. The notation for solvents used in chromatography, e.g., 9:1–6:4 v/v, means that this particular combination of solvents was used in the range 9:1 to 6:4. Precoated TLC plates (silica gel 60 F-254 supported on a glass plate) were used and the eluent was chloroform–ethanol (1:1 v/v).

4-Aryl- and 4,5-diphenyl-1,2-diaminoimidazoles were prepared by the procedure of Beyer et al.[2b] **1,2-Diaminobenzimidazole**[11] was obtained from 2-(*o*-aminophenyl)-1-acetylhydrazine[12] and cyanogen bromide.

Oxidation of 1,2-Diaminoimidazoles with Manganese Dioxide. General Procedure. A suspension of the 1,2-diaminoimidazole (10 mmol) and activated manganese dioxide (7.0 g)[10] in benzene (40 mL) was heated to reflux for 17 h. The inorganic material was removed by filtration and washed with hot ethanol (20 mL × 3). The combined filtrates were evaporated to near dryness. The residual material was deposited on a preparative chromatographic column (silica gel, mesh 60–200, 35–40 g). Elution was performed with hexane–benzene, benzene, benzene–chloroform, chloroform, chloroform–ethanol, and finally ethanol.

4-Phenyl-1,2-diaminoimidazole. The reaction mixture (from 10 mmol of the imidazole) was worked up as described in the general procedure. Elution with benzene gave acetophenone (17 mg, 1.4%) and benzoyldiazomethane (16 mg, 1.1%). The identity of these compounds was determined by comparison of their IR spectra with those of authentic samples. Elution with chloroform–benzene (1:7 v/v) gave an unknown compound (13 mg) whose IR spectrum indicated the presence of an NH group. Elution with chloroform gave 4(5)-phenyl-1,2,3-triazole (672 mg, 46%), mp 147–147.5 °C (lit.[13] mp 147–148 °C). Its IR spectrum was superimposable upon that of an authentic sample. Elution with chloroform–ethanol (9:1 v/v) gave 3-amino-5-phenyl-1,2,4-triazine (187 mg, 11%), mp 233–234 °C (lit.[14] mp 233–235 °C). Its IR spectrum was superimposable upon that of an authentic sample.

4-(*p*-Bromophenyl)-1,2-diaminoimidazole. The reaction mixture (from 10 mmol of the imidazole) was worked up as described in the general procedure. Elution with benzene gave a mixture (25 mg) of *p*-bromobenzonitrile and *p*-bromoacetophenone whose IR spectrum showed a characteristic nitrile band (2220 cm^{-1}). The presence of *p*-bromoacetophenone was confirmed by derivatization as its 2,4-dinitrophenylhydrazone whose IR spectrum was superimposable upon that of an authentic sample. Further elution with benzene gave a colored compound (10 mg), whose IR spectrum showed a typical diazo band (2110 cm^{-1}) and a carbonyl band (1600 cm^{-}). Continued elution with benzene gave an unknown compound (72 mg), mp 174–180 °C dec, whose IR spectrum indicated the presence of an NH group. Elution with benzene ethanol (95:5 v/v) gave 4(5)-(*p*-bromophenyl)-1,2,3-triazole (1.24 g, 55%), mp 184–185 °C (lit.[15] mp 185–187 °C). Its IR spectrum showed a characteristic NH absorption (3150 cm^{-1}). Elution with benzene–ethanol (6:4 v/v) gave 5-(*p*-bromophenyl)-3-amino-1,2,4-triazine (0.15 g, 5.8%), mp 249–253 °C dec, whose IR spectrum showed typical NH_2 absorption (3270 and 3100 cm^{-1}). Anal. Calcd for $C_9H_7BrN_4$: C, 43.05; H, 2.81; N, 22.31. Found: C, 43.05; H, 2.87; N, 22.20.

4-(*p*-Methoxyphenyl)-1,2-diaminoimidazole. The reaction mixture (from 10 mmol of the imidazole) was worked up as described in the general procedure. Elution with benzene–hexane (1:1 v/v) gave *p*-anisonitrile (3 mg, 0.2%) whose identity was confirmed by its IR spectrum and its NMR spectrum. Elution with benzene gave a mixture (9 mg), consisting mainly of *p*-methoxyacetophenone. Its IR spectrum was superimposable upon that of *p*-methoxyacetophenone, but additional absorptions at 2220 (w) and 2170 cm^{-1} (w) suggested the presence of the *N*-cyanotriazole. Elution with benzene–chloroform (6:1 v/v) gave *p*-methoxyacetophenone (6 mg, 0.4%) whose IR spectrum was superimposable upon that of an authentic sample. Elution with benzene–chloroform (1:1–1:3 v/v) gave a colored compound (4 mg). Its IR spectrum showed a typical diazo ketone, 2120 and 1620 cm^{-1}. Elution with chloroform gave an unknown compound (8 mg). Its IR spectrum indicated the presence of an NH group. Further elution with chloroform gave 4(5)-(*p*-methoxyphenyl)-1,2,3-triazole (610 mg, 34.7%), mp 167–168 °C (lit.[13] mp 171–171.5 °C). Its IR spectrum showed a characteristic triazole type NH absorption (3130 cm^{-1}): ^{1}H NMR (Me_2SO-d_6, Me_4Si as standard) δ 3.82 (s, 3 H), 6.80–7.20 (d, 2 H, J_{ab} = 8.7 Hz), 7.60–8.00 (d, 2 H, J_{ab} = 8.7 Hz), 8.21 (s, 1 H). Elution with chloroform–ethanol (8.2 v/v) gave 3-amino-5-(*p*-methoxyphenyl)-1,2,4-triazine (514 mg, 25.5%), mp 214–216 °C. Its IR spectrum showed NH_2 absorptions (3300 and 3150 cm^{-1}) and was similar to that of 3-amino-5-phenyl-1,2,4-triazine: ^{1}H NMR (Me_2SO, Me_4Si as standard) δ 4.08 (s, 3 H), 6.70–7.30 (d, 2 H, J_{ab} = 9.1 Hz), 7.85–8.35 (d, 2 H, J_{ab} = 9.1 Hz), 9.05 (s, 1 H).

4,5-Diphenyl-1,2-diaminoimidazole. The reaction mixture (from 10 mmol of the imidazole) was worked up as described in the general procedure. Elution with benzene gave a mixture (174 mg) of benzil and benzonitrile whose identities were determined by comparison of their IR spectra with those of authentic samples. Benzil was also identified as its 2,4-dinitrophenylhydrazone whose IR spectrum was superimposable upon that of an authentic sample. Elution with benzene gave an unknown oily product (135 mg) and a compound (284 mg) which seems to be *N*-cyanoimino-1,2-diphenyldiazoethane. The IR spectrum of the latter compound showed a strong absorption at 2180 cm^{-1}, a value which had been reported for *N*-cyanoiminodiazoalkane.[3] Elution with benzene–chloroform (9:1–6:4 v/v) gave 4,5-diphenyl-1,2,3-triazole (148 mg, 9.6%), mp 138–139 °C (lit.[13] mp 140 °C). Its IR spectrum was superimposable upon that of an authentic sample. Elution with chloroform and with chloroform–ethanol (4:1 v/v) gave 3-amino-5,6-diphenyl-1,2,4-triazine (1.53 g, 62%), mp 163–169 °C (lit.[16] mp 175 °C). Its IR spectrum showed characteristic NH_2 absorptions (3420, 3250 cm^{-1}).

Oxidation of 1,2-Diaminobenzimidazole with Manganese Dioxide. A mixture of 1,2-diaminobenzimidazole (1.247 g, 8.4 mmol) and activated manganese dioxide (6.0 g) in benzene (50 mL) was heated to reflux for 17 h. The inorganic material was removed by filtration and washed with benzene (20 mL × 3). Evaporation of benzene gave 3-amino-1,2,4-benzotriazine (333 mg, 27.1%), which was purified by sublimation (120–130 °C (0.5 mmHg)) to yield a yellow solid, mp 205–206 °C (lit.[17] mp 207 °C). The inorganic material was then washed with hot ethanol (30 mL × 3). Evaporation of the ethanol gave a residue (0.526 g) which was deposited on a preparative column chromatography (silica gel mesh 60–200, 40 g). Elution with ethyl acetate (250 mL) gave yellow colored material (0.2374 g) which was

purified further by sublimation (120–130 °C (10.5 mmHg)) to afford a yellow solid (0.2337 g). Recrystallization of the yellow solid from benzene gave yellow crystals, mp 133–135 °C. Further sublimation of these yellow crystals at 70–85 °C (0.5 mmHg) gave 71 mg of 3-amino-1,2,4-benzotriazine, mp 160–180 °C. The residue from this sublimation was white solid, mp 146–147 °C. TLC showed this compound to consist mainly of 1-aminobenzimidazole, mp 150–152 °C.[18] Elution with ethyl acetate–ethanol and ethanol gave a brown colored material (0.1646 g), which was ecrystallized from benzene–chloroform to give an unknown solid, mp 128–132 °C dec.

Preparation of 1-Cyano-4- and 5-phenyltriazoles. Oil-free sodium hydride was prepared from a 50% oil dispersion of sodium hydride (0.69 g) by washing with petroleum ether (30–60 °C). The petroleum ether was decanted and the residue was evacuated under reduced pressure (0.5 mmHg). Dry THF (25 mL) was added to the sodium hydride and the mixture was stirred for 1 h. A solution of 4(5)-phenyltriazole (1.40 g, 10 mmol) in dry THF (20 mL) was added dropwise to the mixture. The resulting thick emulsion was stirred for 1 h. To this mixture was added a solution of cyanogen bromide (1.38 g, 13 mmol) in dry THF (15 mL) at such a rate that the temperature remained below 25 °C. The mixture was stirred for an additional 1.5 h. Sodium bromide was filtered and evaporation of THF gave a yellow solid (1.78 g, ~100%). The IR spectrum of this yellow solid showed a strong nitrile band (2250 cm^{-1}) and a weak diazo band (2180 cm^{-1}), mp 38–39 °C.

Reaction of *N*-Cyanotriazoles with Manganese Dioxide in Benzene. The mixture of triazoles (0.742 g) prepared above and activated manganese dioxide (0.388 g) in benzene (20 mL) was heated to reflux for 17 h. The inorganic material was filtered and the filtrate was evaporated to give a residue (0.759 g) whose IR spectrum showed the isolated products to be the starting *N*-cyanotriazoles.

Oxidation of 4-Phenyl-1,2-diaminoimidazole with Manganese Dioxide in the Presence of Phenylacetylene. A mixture of the imidazole (1.537 g, 8.8 mmol), phenylacetylene (500 mg), and activated manganese dioxide (7.0 g) in benzene (40 mL) was heated to reflux for 17 h. The workup was as described in the general procedure. Elution with benzene–hexane (1:1–9:1 v/v) gave acetophenone (39 mg) whose identity was confirmed by its IR and its NMR spectra. Elution with benzene–hexane (9:1 v/v) and with benzene gave benzoyldiazomethane (12 mg, 0.9%). Elution with benzene–chloroform (1:1 v/v) gave an unknown compound (55 mg). Elution with benzene–chloroform (1:9 v/v) gave 4(5)-phenyl-1,2,3-triazole (240 mg, 19%). Its IR spectrum was superimposable upon that of an authentic sample. Elution with chloroform and chloroform–methanol (9:1 v/v) gave a mixture (398 mg) of the triazole and 3-amino-5-phenyl-1,2,4-triazine. The yields of the triazole and the triazine were estimated to be 20 and 9.6% respectively by integration of the NMR spectrum (the peaks at δ 8.52 and 8.95 were used with CH_3COOH as solvent).

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Registry No.—**1d**, 19933-51-8; **1e**, 29540-87-2; **2d**, 5533-73-3; **3d**, 4511-99-3; **3e**, 20028-80-2; **11**, 6299-92-9; 2-(o-aminophenyl)-1-acetylhydrazine, 6299-91-8; cyanogen bromide, 506-68-3; 5-cyano-4-phenyl-1,2,3-triazole, 65969-54-2; 1-cyano-5-phenyl-1,2,3-triazole, 65943-32-0; manganese dioxide, 131-13-9.

References and Notes

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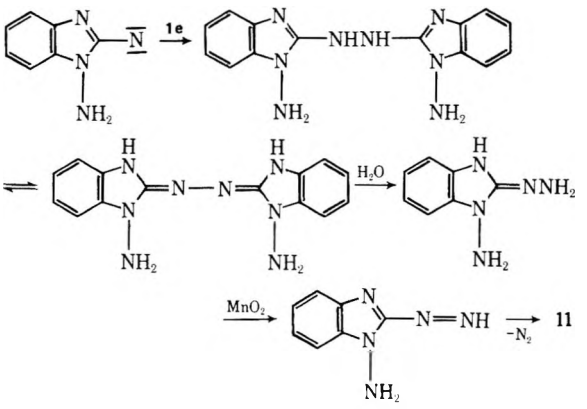
(7) Further support for this view comes from the isolation of 1-aminobenzimidazole (**11**) in trace amounts. Although the path by which **11** is formed is not obvious, one may speculate that it arose from the *C*-nitrene as shown below.



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Mesoionic Compounds. 43. Ring Annelation Utilizing the Isomeric *anhydro*-2- and 3-Hydroxythiazolo[2,3-*b*]benzothiazolium Hydroxide Mesoionic Systems[1]

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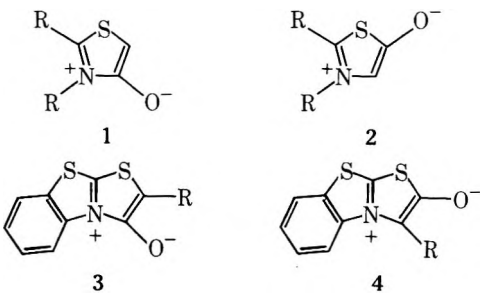
The isomeric *anhydro*-2- and 3-hydroxythiazolo[2,3-*b*]benzothiazolium hydroxides are convenient substrates for annelation of a five- and six-membered ring to benzothiazole, yielding the pyrrolo[2,1-*b*]benzothiazole and the 1*H*-pyrido[2,1-*b*]benzothiazol-1-one ring systems, respectively. The former mesoionic ring system could only be trapped by acetylenic dipolarophiles in situ, whereas the latter was readily available from 2-mercaptobenzothiazole and α-bromophenylacetyl chloride. The latter mesoionic ring system also reacted with *N*-phenyl- and *N*-ethylmaleimide as well as fumaronitrile, affording 1:1 primary cycloadducts.

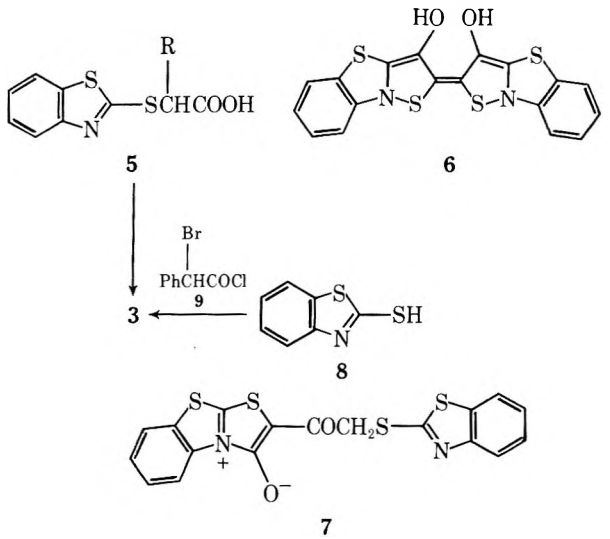
Annelation of one or more rings to many of the well-characterized five-membered mesoionic ring systems would greatly extend their potential in synthetic applications but relatively few of these fused ring systems have been studied in detail to date.[2] Conspicuously absent are reports of their ability to undergo cycloadditions[3] analogous to those well characterized in five-membered systems containing masked "1,3-dipoles". We now report the synthesis and characterization of the *anhydro*-3-hydroxythiazolo[2,3-*b*]benzothiazolium hydroxide system **3** and the in situ generation and trapping of the isomeric *anhydro*-2-hydroxythiazolo[2,3-*b*]benzothiazolium hydroxide system **4**, the ring-fused analogues of the *anhydro*-4- and 5-hydroxythiazolium hydroxide systems **1** and **2**, respectively.[4,5]



1 **2**

3 **4**

Compounds of type **1** are readily available by cyclodehydration of the corresponding thioglycolic acid or by reaction of the appropriate thioamide with an α-haloacyl chloride derivative.[6] An earlier application[7] of the former procedure to 2-benzothiazolylthioglycolic acid (**5**; R = H) using hot acetic anhydride gave a highly insoluble dye formulated as **6**. The difficulty in obtaining definitive spectral data for this product still leaves the question of its structure in doubt and its physical characteristics indicate that it is most likely a polymer. Treatment of **5** with a 1:1 mixture of Ac_2O–Et_3N at room temperature gave a brick-red solid with ν_{CO} 1595, 1660 cm^{-1} and aromatic protons at δ 8.20–7.21 and a singlet at δ 4.80, integrating in the ratio of 4:1. It was not possible to obtain a molecular ion in the mass spectrum of this product but an ion at *m/e* 180 is consistent with the structure for this product being **7**, obtained by reaction of the initially formed mesoionic ring system with the mixed anhydride of the thioglycolic acid **5** and Ac_2O. Variation of these reaction conditions did not appreciably alter the formation of **7**.



5 **6**

7

Reaction of **5** with dicyclohexylcarbodiimide also gave a deep-red product whose infrared spectrum was not quite compatible with the mesoionic-type structure **3** (R = H). Attempted purification of this product resulted in decomposition. Reaction of **8** with bromacetyl chloride gave an unstable, greenish crystalline product with ν_{CO} 1595, 1665 cm^{-1}, thought to be **3** (R = $COCH_2Br$). These experiments indicate that the ring system **3** is too reactive for isolation unless a stabilizing substituent such as a phenyl or an electron-withdrawing acyl group is introduced into the 2 position.

Condensation of 2-mercaptobenzothiazole (**8**) with α-bromophenylacetyl chloride (**9**) in $CHCl_3$/$2Et_3N$ occurred readily, affording **3** (R = Ph) in 62% yield. Although several possibilities exist for the initial site of reaction with these reagents, only two final ring-closed products are possible. The isomeric system **4** (R = Ph) was excluded by the synthesis of **3** (R = Ph) from α-phenyl-2-benzothiazolylthioglycolic acid (**5**, R = Ph) and Ac_2O/Et_3N. Reaction of **8** with α-bromo-α-carboethoxyacetyl chloride would be anticipated to yield **3** (R = COOEt). However, the product isolated was identified as 2-benzothiazolyl disulfide, apparently formed by oxidation of **8** by the α-bromo-α-carboethoxyacetyl chloride, such an oxidation not being without precedent.[6]

The mesoionic system **3** contains a "masked" thiocarbonyl ylide dipole, represented by **3** ↔ **3a** ↔ **3b**, and underwent ready reaction with electron-deficient dipolarophiles. With dimethyl acetylenedicarboxylate in refluxing toluene addition to **3** occurred and the product isolated was methyl 1-oxo-2-phenyl-1*H*-pyrido[2,1-*b*]benzothiazole-3,4-dicarboxylate (**11**, R = $COOCH_3$) (80%). This facile extrusion of sulfur from the postulated intermediate **10** (R = $COOCH_3$) is no doubt associated with the presence of the 5,6-double bond in **10**, similar extrusions of sulfur being well established in analogous cycloadducts from monocyclic systems.[5] Dibenzoylacetylene and hexafluoro-2-butyne underwent similar ready cycloaddition to **3** giving the appropriately substituted derivatives of **11** in good yields. These fused pyridones were characterized by analytical and spectral data (Experimental Section).

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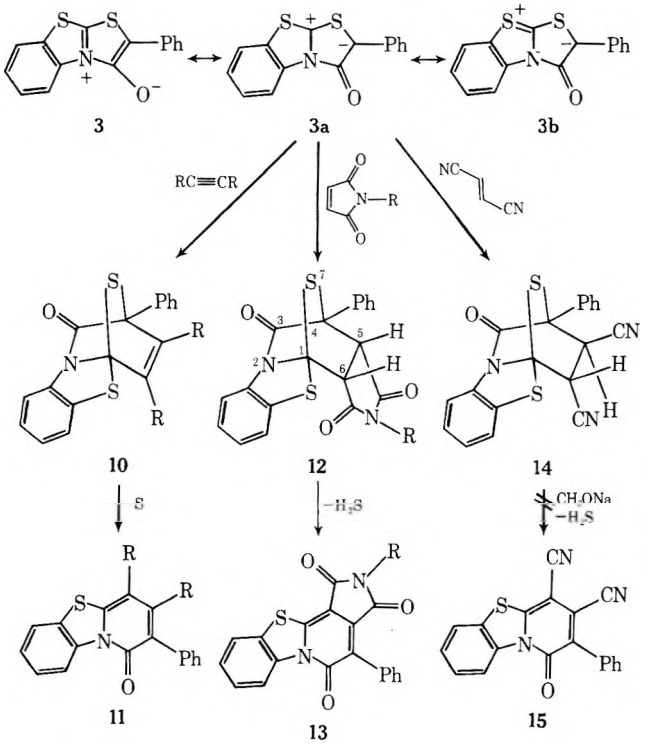
Olefinic dipolarophiles reacted equally as readily with **3**. With *N*-phenylmaleimide in refluxing toluene reaction was complete in 30 min, giving an 84% yield of a product established as the primary cycloadduct **12** (R = Ph). The NMR spectrum, besides aromatic protons, showed two AB doublets at δ 4.33 and 4.10 (J = 7.0 Hz) and the endo configuration for **12** was assigned in analogy with those obtained from the monocyclic *anhydro*-4-hydroxythiazolium hydroxide system and *N*-phenylmaleimide.[4] Efforts to obtain satisfactory analytical data for this compound were unsuccessful. However, both positive and negagive ion CI mass spectra[8] confirmed the assigned molecular weight (456) with ions being observed at $[M + H]^+$ 457, $[M + NH_4]^+$ 474, and $[M - H]^-$ 455. *N*-Ethylmaleimide also reacted readily with **3** giving the cycloadduct **12** (R = Et) (92%) in which the H_5 and H_6 protons of the fused system were again part of an AB doublet at δ 3.99 and 3.86 (J = 6.5 Hz).

These primary cycloadducts were always contaminated by minute amounts of a yellow product, extremely insoluble in most solvents. Complete conversions of the primary 1:1 cycloadducts into this yellow product were readily effected by refluxing **12** (R = Et, Ph) in xylene, H_2S being eliminated. These fused pyridones were readily characterized by their intense molecular ions and analytical data (Experimental Section).

Fumaronitrile also underwent ready cycloaddition with **3** (R = Ph) giving the 1:1 primary cycloadduct **14** in 90% yield. In the NMR spectrum ($CDCl_3$), the protons α to the cyano groups appeared as a singlet at δ 4.11, shifted to δ 5.41 in Me_2SO-d_6, but the exo-endo relationship of these H_5–H_6 protons cannot be determined unambiguously from these data. In contrast to the above adducts, **14** was extremely stable thermally, not losing H_2S on refluxing over 40 h in xylene. Treatment of **14** with sodium methoxide, a process known to cause elimination of H_2S in the cycloadducts obtained from monocyclic systems,[4] only resulted in tar formation, none of the expected pyridone **15** being isolated. In this particular



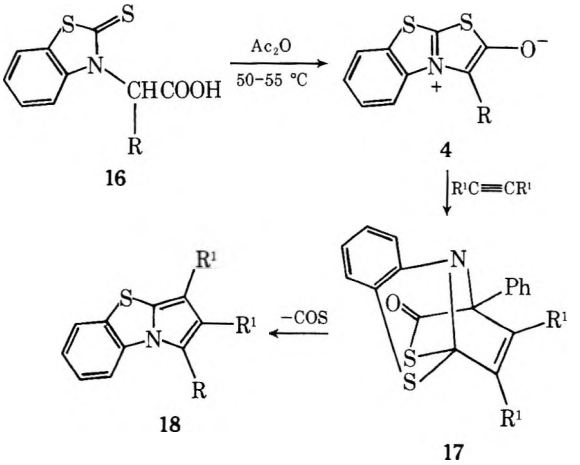
reaction initial removal of a proton from the adduct **14** can result in two C–S bond cleavages: one leads to pyridone formation and with the other a thiophenolate ion would result. This seems to be the most likely cause of tar formation. In the mass spectrum of **14** the most intense ion observed is *m/e* 327, corresponding to the loss of H_2S from the molecular ion *m/e* 361 (13), providing confirmation of structure **14**.

These ready cycloadditions to fused five-membered mesoionic ring systems of this general type are the first observed where addition occurs at a bridgehead carbon atom. No doubt influenced by the sulfur atom at the 9 position, formation of the 1:1 primary cycloadducts **10**, **12**, and **14** does not result in any loss of benzenoid resonance energy, a factor which may be used to explain the nonreactivity of *anhydro*-3-hydroxythiazolo[3,2-*a*]pyridinium hydroxide in related reactions.[9]

In view of the reactivity of **3**, the isomeric *anhydro*-2-hydroxythiazolo[2,3-*b*]benzothiazolium hydroxide system **4** was of interest as elimination of COS from an initial 1:1 cycloadduct from **4** and acetylenic dipolarophiles would provide a convenient means of annelation of a pyrrole ring to benzothiazole. The most direct synthesis of this ring system would be by cyclodehydration of 2-thioxobenzothiazol-3-ylacetic acid (**16**, R = H), prepared from 2-methylthiobenzothiazole and ethyl bromoacetate followed by hydrolysis.[10] Attempts to achieve ring closure of **16** (R = H) with Ac_2O/Et_3N at room temperature or with *N*,*N*-dicyclohexylcarbodiimide were unsuccessful, the products obtained apparently being formed by decomposition of the mesoionic system **4** (R = H). However, generation of **4** (R = H) with Ac_2O in the presence of dimethyl acetylenedicarboxylate at 50–55 °C resulted in trapping of this mesoionic system with the ultimate isolation of methyl pyrrolo[2,1-*b*]benzothiazole-2,3-dicarboxylate (**18**, R = H; R^1 = $COOCH_3$) in good yield. The intermediate **17** was presumably involved in the reaction, readily losing COS to form **18**. Analytical and spectral data were in agreement with structure **18**, especially a singlet proton at δ 7.88 (H_1) comparable to the chemical shift δ 7.58 of the analogous proton in methyl indolizine-2,3-dicarboxylate.[11]

Dibenzoylacetylene and hexafluoro-2-butyne also reacted readily with the unstable ring system **4** (R = H) giving the corresponding derivatives of **18** (R = H; R^1 = COPh and R = H; R^1 = CF_3), respectively.

It was anticipated that introduction of a 3-phenyl substituent into **4** would stabilize the ring system sufficiently to allow its isolation. However, attempts to prepare **16** (R = Ph) by



reaction of 2-mercaptobenzothiazole with ethyl α-bromophenylacetate failed.

Experimental Section[12]

2-Mercaptobenzothiazole was purified[13] as follows: The thiol (50.0 g) was dissolved in aqueous sodium hydroxide solution (150 mL of 10% solution) with thorough stirring. After 15 min, the insoluble material was removed by filtration, the cold mother liquor was treated with charcoal, and this mixture was refluxed overnight when the hot reaction mixture was filtered. After cooling, the mother liquor was treated with 15% HCl solution to ca. pH 4 and the snow-white product was collected and dried.

Attempted Preparation of *anhydro*-3-Hydroxythiazolo[2,3-*b*]benzothiazolium Hydroxide (3; R = H). A. By Cyclodehydration of 2-Benzothiazolylthioglycollic Acid. The acid[7] **5** (R = H) (2.0 g) was treated with a mixture of Ac_2O (2 mL) and Et_3N (2 mL) and, after stirring at room temperature for 10 min, anhydrous Et_2O (10 mL) was added. A brick-red solid separated: mp 177–179 °C; IR (KBr) 1660, 1595 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 8.20–7.21 (m, 4, aromatic), 4.80 (s, 1); mass spectrum, *m/e* (rel intensity) 180 (82), 166 (65). This product is best represented by structure **7**.

B. Ring Closure with *N,N*-Dicyclohexylcarbodiimide. A suspension of the acid **5** (R = H) (1.12 g, 5 mmol) in CH_2Cl_2–CH_3CN was treated with *N,N*-dicyclohexylcarbodiimide (1.03 g, 5 mmol), an exothermic reaction occurring with the development of a red coloration. After 3 h the insoluble material was removed and the filtrate was concentrated in vacuo. Addition of anhydrous ether precipitated a red solid of indefinite melting point: IR (KBr) 3400 (CH), 1750, 1715, 1695 cm^{-1} (CO).

Preparation of *anhydro*-3-Hydroxy-2-phenylthiazolo[2,3-*b*]benzothiazolium Hydroxide (3; R = Ph). Method A. A suspension of 2-mercaptobenzothiazole (0.84 g, 5 mmol) in dry $CHCl_3$ (50 mL) was treated dropwise with α-bromophenylacetyl chloride (1.17 g, 5 mmol) at room temperature with rapid stirring. After 10 min Et_3N (1.01 g, 10 mmol) was added dropwise and stirring was continued for a further 30 min. The reaction mixture was washed with cold water (2 × 15 mL), dried (Na_2SO_4), and then concentrated. Addition of a small amount of anhydrous Et_2O gave an orange solid which crystallized from chloroform–ether as orange plates: 0.9 g (63%); mp 180 °C dec; IR (KBr) 1615, 1590 cm^{-1} (CO); λ_{max} (CH_3OH) 420 (log ϵ 4.04), 282 nm (4.21); NMR ($CDCl_3$) δ 7.90–7.05 (m, aromatic); M^+· 283 (62). Anal. Calcd for $C_{15}H_9NOS_2$: C, 63.59; H, 3.20; N. 4.94. Found: C, 63.22; H, 3.11; N, 5.16.

Method B. A stirred mixture of 2-mercaptobenzothiazole (1.68 g, 10 mmol) and α-bromophenylacetic acid (2.16 g, 10 mmol) in anhydrous benzene (70 mL) was treated dropwise with Et_3N (1.01 g, 10 mmol). After stirring for 4 h at room temperature, the product was washed with water (2 × 15 mL) and dried (Na_2SO_4) and the benzene was then evaporated in vacuo. The oily residue was dissolved in anhydrous benzene (2 mL) and treated with a mixture of Ac_2O (2 mL) and Et_3N (2 mL). After 15 min anhydrous ether was added giving an orange solid which crystallized from $CHCl_3$–Et_2O as orange plates: 1.45 g (51%); mp 180 °C dec; identical[14] with the product prepared by A above.

Reaction of *anhydro*-3-Hydroxy-2-phenylthiazolo[2,3-*b*]-benzothiazolium Hydroxide (3, R = Ph) with Dipolarophiles. The mesoionic compound and the dipolarophile (equimolar amounts) in toluene were heated under reflux until all the mesoionic compound had reacted (TLC). The toluene was evapoarated in vacuo and the residue was recrystallized from an appropriate solvent.

Methyl 1-Oxo-2-phenyl-1*H*-pyrido[2,1-*b*]benzothiazole-3,4-dicarboxylate (11, R = $COOCH_3$), obtained from **3** (R = Ph) and dimethyl acetylenedicarboxylate after 3 h of reflux, crystallized as colorless needles from $CHCl_3$–EtOH: 80%; mp 245 °C; IR (KBr) 1740, 1695, 1655 cm^{-1} (CO); λ_{max} (CH_3OH) 375 (log ϵ 4.25), 360 (4.18), 310 nm (4.24); NMR ($CDCl_3$) δ 7.82–7.2 (m, 9, aromatic), 3.92 (s, 3, CH_3), 3.58 (s, 3, CH_3); M^+· 393 (100). Anal. Calcd for $C_{21}H_{15}NO_5S$: C, 64.10; H, 3.84; N, 3.56. Found: C, 63.97; H, 3.85; N, 3.52.

3,4-Dibenzoyl-2-phenyl-1*H*-pyrido[2,1-*b*]benzothiazol-1-one (11, R = COPh), from **3** (R = Ph) and dibenzoylacetylene after 3 h, separated as yellow prisms from $CHCl_3$–EtOH: 62%; mp 230 °C; IR (KBr) 1670, 1635 cm^{-1} (CO); λ_{max} (CH_3OH) 370 (log ϵ 4.04), 257 nm (4.25); NMR ($CDCl_3$) δ 7.77–7.22 (m, aromatic); M^+· 485 (78). Anal. Calcd for $C_{31}H_{19}NO_3S$: C, 76.68; H, 3.95; N, 2.88. Found: C, 76.45; H. 3.89; N, 2.69.

3,4-Bis(trifluoromethyl)-2-phenyl-1*H*-pyrido[2,1-*b*]benzothiazol-1-one (11, R = CF_3), from **3** (R = Ph) and hexafluoro-2-butyne after 4 h, formed yellow prisms from acetonitrile: 33%, mp 186–187 °C; IR (KBr) 1670 cm^{-1} (CO); λ_{max} (CH_3OH) 390 (log ϵ 4.23), 372 (4.22), 250 (4.19), 224 nm (4.48); NMR ($CDCl_3$) δ 8.03–7.27 (m, aromatic); M^+· 413 (67). Anal. Calcd for $C_{19}H_9F_6NOS$: C, 55.21; H, 2.20; N, 3.39. Found: C, 54.94; H, 2.20; N, 3.62.

Reaction of 3 (R = Ph) with *N*-Phenylmaleimide. *N*-Phenylmaleimide and **3** (R = Ph) in refluxing toluene for 30 min gave the 1:1 primary cycloadduct **12** (R = Ph) as colorless needles from $CHCl_3$–EtOH: 84%; mp 164–165 °C dec; IR (KBr) 1725, 1720 cm^{-1} (CO); λ_{max} (CH_3OH) 267 nm (log ϵ 4.50); NMR ($CDCl_3$) δ 7.37–7.07 (m, 14, aromatic), 4.33 (ABd, 1, J = 7.0 Hz, H_5), 4.10 (ABd, 1, J = 7.0 Hz, H_6); mass spectrum, *m/e* $[M + H]^+$ 457, $[M + NH_4]^+$ 474. $[M - H]^-$ 455.

The above adduct **12** (R = Ph) was heated in xylene for 30 h affording **13** (R = Ph) as small, yellow needles from DMF–$CHCl_3$: 41%; mp 348–349 °C; IR (KBr) 1730, 1715 cm^{-1} (CO); M^+· 422 (100). Anal. Calcd for $C_{25}H_{14}N_2O_3S$: C, 71.09; H, 3.34; N, 6.33. Found: C, 71.09; H, 3.25; N, 6.51.

Reaction of 3 (R = Ph) with *N*-Ethylmaleimide. Under analogous conditions to those above, the 1:1 primary cycloadduct **12** (R = Et) separated as colorless needles from $CHCl_3$–EtOH: 92%; mp 176 °C dec; IR (KBr) 1725, 1700 cm^{-1} (CO); λ_{max} (CH_3OH) 220 nm (log ϵ 4.63); NMR ($CDCl_3$) δ 7.83–7.03 (m, 9, aromatic), 3.99 (ABd, 1, J = 6.5 Hz, H_5), 3.86 (ABd, 1, J = 6.5 Hz, H_6), 3.53 (qt, 2, J = 7.0 Hz, CH_2CH_3), 1.12 (t, 3, J = 7.0 Hz, CH_2CH_3); M^+· 408 (53). Anal. Calcd for $C_{21}H_{16}N_2O_3S_2$: C,61.73; H, 3.95; N, 6.86. Found: C, 61.95; H. 3.88; N, 6.74.

The above adduct **12** (R = Et), on heating in refluxing xylene for 24 h, gave **13** (R = Et) as yellow needles from $CHCl_3$–EtOH: 51%; mp 246–247 °C; IR (KBr) 1705, 1660 cm^{-1} (CO); λ_{max} (CH_3OH) 417 (log ϵ 3.71), 340 (3.95), 232 nm (3.98); NMR ($CDCl_3$) δ 7.90–7.27 (m, 9, aromatic), 3.71 (qt, 2, J = 7.0 Hz, CH_2CH_3), 1.26 (t, 3, J = 7.0 Hz, CH_2CH_3); M^+· 374 (100). Anal. Calcd for $C_{21}H_{14}N_2O_3S$: C, 67.35; H, 3.77; N, 7.48. Found: C, 65.80; H, 3.85; N, 7.23.

Reaction of 3 (R = Ph) with Fumaronitrile. From **3** (R = Ph) and fumaronitrile after 3 h, the 1:1 primary cycloadduct **14** was obtained as yellow needles from CH_3CN: 90%; mp 201–202 °C; IR (KBr) 2250, 2220 (CN), 1750 cm^{-1} (CO); λ_{max} (CH_3OH) 407 nm (log ϵ 3.55); NMR ($CDCl_3$) δ 7.5 (m, 5, aromatic), 7.17 (m, 4, aromatic), 4.11 (s, 2, CHCN); M^+· 361 (13). Anal. Calcd for $C_{19}H_{11}N_3OS_2$: C, 63.14; H, 3.07; N, 11.62. Found: C, 63.08; H, 2.98; N, 11.69.

Trapping of *anhydro*-2-Hydroxythiazolo[2,3-*b*]benzothiazolium Hydroxide (4, R = H) with Acetylenic Dipolarophiles. 2-Thioxobenzothiazol-3-ylacetic acid (**16**, R = H), Ac_2O (4 mL), the dipolarophile, and dry benzene (5 mL) were stirred at 50–55 °C for 3 h. The reaction mixture was washed with K_2CO_3 (2 × 10 mL of 5% aqueous solution) and water (10 mL) and dried (Na_2SO_4). After evaporation of the benzene, the residue was recrystallized from an appropriate solvent.

Methyl Pyrrolo[2,1-*b*]benzothiazole-2,3-dicarboxylate (18, R = H; R¹ = $COOCH_3$) formed small, colorless needles from EtOH: 43%; mp 152 °C; IR (KBr) 1755 cm^{-1} (CO); λ_{max} (CH_3OH) 290 (log ϵ 4.06), 217 nm (5.30); NMR ($CDCl_3$) δ 7.88 (s, 1, H_1), 7.70–7.21 (m, 4, aromatic), 3.87 (s, 6, CH_3); M^+· 289 (20). Anal. Calcd for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.83; N, 4.84. Found: C, 57.95; H. 3.81; N, 4.79.

2,3-Dibenzoylpyrrolo[2,1-*b*]benzothiazole (18, R = H; R¹ = COPh) was obtained as cream prisms from $CHCl_3$–EtOH: 57%; mp 214 °C; IR (KBr) 1650 cm^{-1} (CO); λ_{max} (CH_3OH) 335 (log ϵ 4.19), 285 (4.34), 252 (4.56), 205 nm (4.62); NMR ($CDCl_3$) 7.93 (s, 1, H_1), 7.8–7.17 (m, 14, aromatic); M^+· 381 (80). Anal. Calcd for $C_{24}H_{15}NO_2S$: C, 75.58; H, 3.97; N, 3.67. Found: C, 75.77; H, 3.97; N, 3.60.

2,3-Bis(trifluoromethyl)pyrrolo[2,1-*b*]benzothiazole (18, R = H, R¹ = CF_3) required a bath temperature of 70–75 °C for formation from **16** (R = H) and hexafluoro-2-butyne. After chromatography of the crude residue on silica gel using benzene as eluent, the tricyclic system crystallized from *n*-hexane as small, colorless needles: 29%, mp 122 °C; IR (KBr) 1545 cm^{-1} (CF_3); λ_{max} (CH_3OH) 300 (log ϵ 3.77), 292 (3.70), 220 nm (4.84); NMR ($CDCl_3$) δ 7.80–7.23 (m, H_1 and aromatic); M^+· 309 (100). Anal. Calcd for $C_{12}H_5F_6NS$: C, 46.60; H, 1.63; N, 4.53. Found: C, 46.57; H. 1.50; N, 4.35.

Registry No.—**3** (R = H), 66085-19-6; **3** (R = Ph), 66085-20-9; **4** (R = H), 66085-21-0; **5** (R = H), 6295-57-4; **7**, 66085-22-1; **8**, 149-30-4; **9**, 19078-72-9; **11** (R = $COOCH_3$), 66085-23-2; **11** (R = COPh), 66085-24-3; **11** (R = CF_3), 66085-25-4; **12** (R = Ph), 66085-26-5; **12** (R = Et), 66085-27-6; **13** (R = Ph), 66085-28-7; **13** (R = Et), 66085-29-8; **14**, 66085-30-1; **16** (R = H), 59794-34-2; **18** (R = H; R¹ = $COOCH_3$), 66085-31-2; **18** (R = H; R¹ = COPh, 66085-32-3; **18** (R = H; R¹ = CF_3), 66085-33-4; α-bromophenylacetic acid, 4870-65-9; dimethyl acetylenedicarboxylate, 762-42-5; dibenzoylacetylene, 1087-09-8; hexafluoro-2-butyne, 692-50-2; *N*-phenylmaleimide, 941-69-5; *N*-ethylmaleimide, 128-53-0; fumaronitrile, 764-42-1.

References and Notes

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(12) Spectral characterizations and reaction work-up procedures were as described in previous papers in this series. Microanalyses were by Instranal Laboratories, Inc., Rensselaer, N.Y.
(13) We thank Dr. J. J. D'Amico for this procedure which ensures complete elimination of 2-benzothiazolyl disulfide often present as a contaminant.
(14) Criteria for identity were superimposable IR spectra, no depression in mmp, and identical r_f values.

Notes

Mesoionic Compounds. 44. Synthesis and Cycloaddition Reactions of the *anhydro*-1-Hydroxythiazolo[3,2-*a*]quinolinium Hydroxide System[1]

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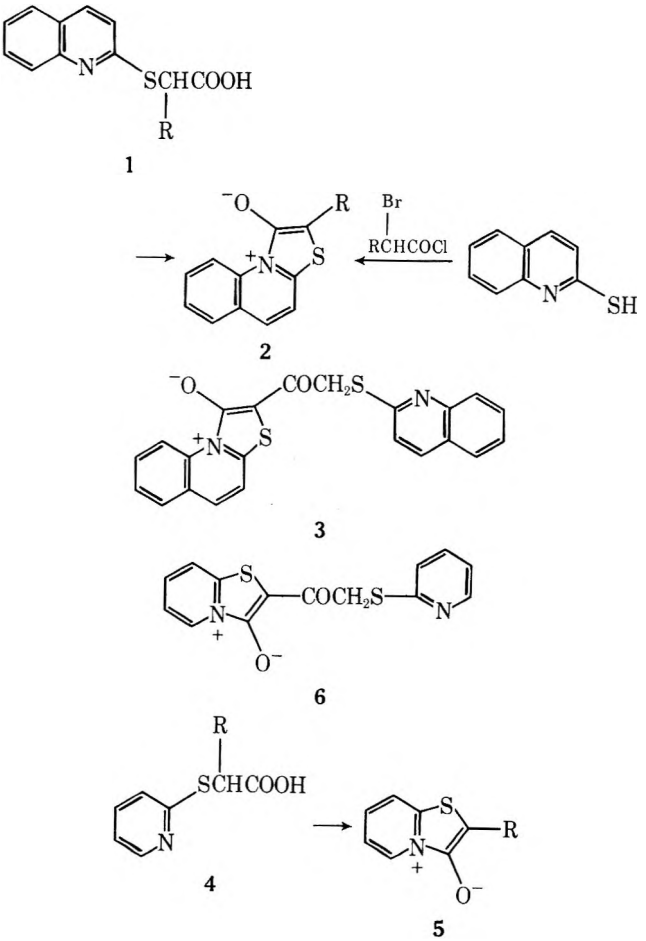
In an accompanying publication,[2] we reported the ready cycloaddition of the isomeric *anhydro*-2- and 3-hydroxythiazolo[2,3-*b*]benzothiazolium hydroxides with acetylenic dipolarophiles to the pyrrolo[2,1-*b*]benzothiazole and the 1*H*-pyrido[2,1-*b*]benzothiazol-1-one ring systems, respectively. As sulfur is isoelectronic with a double bond, we anticipated that the *anhydro*-1-hydroxythiazolo[3,2-*a*]quinolinium hydroxide system **2** should also be of interest as a substrate for cycloaddition reactions. The results obtained with this ring system are described below.

anhydro-1-Hydroxythiazolo[3,2,-*a*]quinolinium hydroxide (**2**, R = H) has been reported earlier,[3] prepared by the cyclodehydration of the 2-quinolinylthioglycolic acid (**1**, R = H) with Ac_2O. On repetition of this procedure, a dark-brown-bronze product was obtained which was difficult to isolate in a pure state despite repeated recrystallizations. However, the observed spectral data were inconsistent with structure **2** (R = H); although infrared carbonyl absorptions at 1610 and 1600 cm^{-1} are compatible with the C_1-carbonyl group, an absorption at 1660 cm^{-1} suggests attachment of a carbonyl group to C_2. The NMR spectrum, in addition to the aromatic multiplet at δ 7.93–7.26, showed a singlet at δ 4.98 which is consistent with structure **3** for this product (vide infra). Similar results were also obtained in the attempted preparation of *anhydro*-3-hydroxythiazolo[3,2-*a*]pyridinium hydroxide (**5**, R = H) from 2-pyridinylthioglycolic acid (**4**, R = H) with Ac_2O under the previously reported conditions.[3] The yellow crystalline product obtained showed ν_{CO} 1680, 1620, and 1600 cm^{-1} and a singlet at δ 4.16 in its NMR spectrum in addition to an aromatic multiplet. Its molecular weight was shown to be 302, and these data require revision of the assigned structure **5** (R = H) to that of **6**, The same product was also obtained from the reaction of bromoacetyl chloride and 2-mercaptopyridine and the formation of **6** is indicative of a high electron density at the 2 position of **5** (R = H). Authentic samples of this ring system have been prepared by the reaction of 2-mercaptopyridine with δ-bromophenylacetyl chloride[4] and 2-bromo-2-ethoxycarbonylacetyl chloride[5] giving **5** (R = Ph) and **5** (R = COOEt), respectively. With a variety of electron-deficient dipolarophiles, no cycloaddition of **5** (R = Ph, COOEt) was observed.

Blocking of the 2 position in **2** with a phenyl substituent proved to be the most effective way of obtaining an authentic example of this ring system and reaction of 2-mercaptoquinoline with α-bromophenylacetyl chloride gave an 82% yield of **2** (R = Ph) as deep-red plates. A carbonyl absorption at 1610 cm^{-1} is consistent with this structure which was confirmed by an alternative synthesis by ring closure of 2-quinolinyl-α-phenylthioglycolic acid (**1**, R = Ph).

Reaction of **2** (R = Ph) with dimethyl acetylenedicarboxylate in refluxing toluene for 6 h gave a yellow crystalline product anticipated to be **8** (R = R^1 = $COOCH_3$). However, the infrared spectrum indicated only ester carbonyl bands at 1725 and 1705 cm^{-1} and no absorption due to the ring carbonyl group was present. The mass spectrum showed M^+· 359



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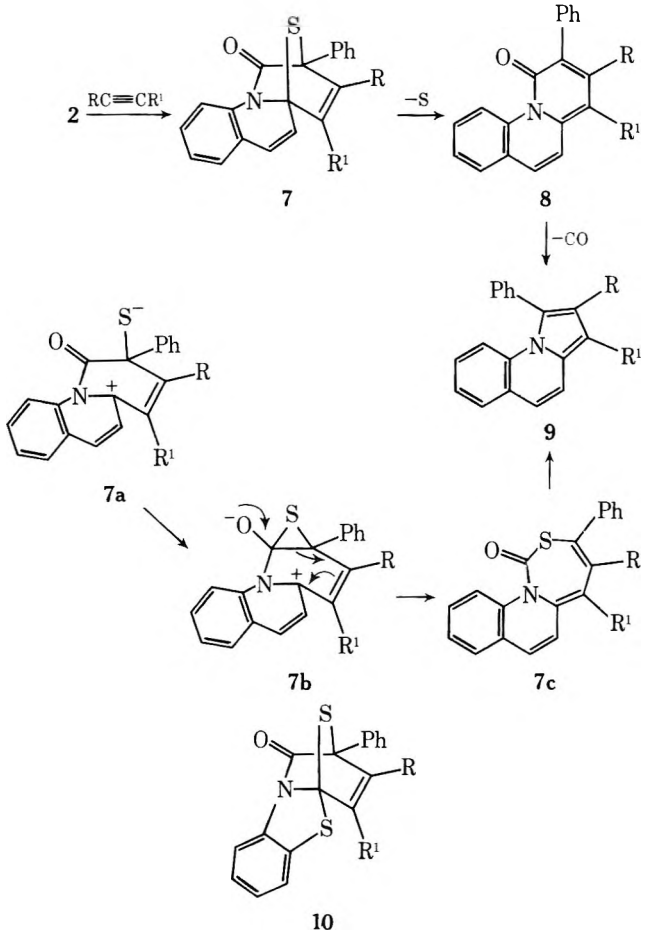
and, in conjunction with analytical data, established the structure of the product as methyl 1-phenylpyrrolo[1,2-*a*]-quinoline-2,3-dicarboxylate (**9**) (R = R^1 = $COOCH_3$). The physical and spectral characteristics of **9** (R = R^1 = $COOCH_3$) were in agreement with reported values.[4]

It would be very unusual for **8** (R = R^1 = $COOCH_3$), formed by thermal extrusion of sulfur from the initial 1:1 adduct **7** (R = R^1 = $COOCH_3$), to lose CO at 110 °C forming the tricyclic system **9** (R = R^1 = $COOCH_3$) and this pathway can be definitely excluded on the basis of the thermal stability of **12** described below as well as by the formation of COS in the reaction. Also it should be noted that in the reaction of *anhydro*-3-hydroxy-2-phenylthiazolo[2,3-*b*]benzothiazolium hydroxide with acetylenic dipolarophiles the anticipated pyridones were obtained.[2]

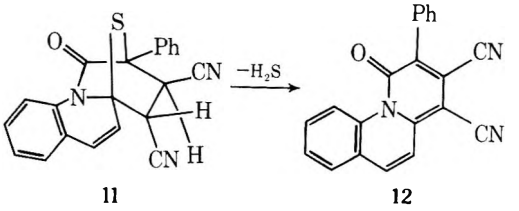
Trapping of COS from the reaction of **2** (R = Ph) with dimethyl acetylenedicarboxylate suggests the formation of **7c** as an intermediate via the sequence **7a** → **7b** → **7c.** A similar intermediate is not formed from **10** presumably due to the difference in stabilities between the intermediate carbonium ions **7a** and the analogous one derived from **10.** It should be noted that **9** would also be obtained if the structure of the initial mesoionic system **2** (R = Ph) were actually that of the 3-hydroxy isomer. This possibility can be excluded by the alternative synthesis of **2** (R = Ph) and the cycloaddition with fumaronitrile described below.

Ethyl propiolate reacted readily with **2** (R = Ph) giving the corresponding derivative of **9** (R = H; R^1 = COOEt). The



chemical shift of H_2 (δ 7.13) is in agreement with that reported[7] for a pyrrole proton in a similar fused ring environment. Dibenzoylacetylene, however, did not give any cycloaddition product even in refluxing xylene, most likely a consequence of severe steric crowding in **7** (R = R^1 = COPh) rather than any lack of reactivity in **2** (R = Ph) with dibenzoylacetylene.

Fumaronitrile also reacted readily with **2** (R = Ph) giving the fused pyridone **12,** presumably formed by loss of H_2S from



the primary cycloadduct **11.** The stability of **12** in boiling xylene excludes any possibility of the loss of CO from **8** (R = R^1 = $COOCH_3$) above to give **9** (R = R^1 = $COOCH_3$).

Experimental Section[8]

2-Mercaptoquinoline was purified as follows. The thiol (10.0 g) was dissolved in NaOH solution (50 mL of 10% solution) and the undissolved material was filtered. The filtrate was refluxed with charcoal for 30 min and filtered hot and the cooled filtrate was acidified with aqueous HCl (20% solution). The precipitated thiol was collected, washed with water, and dried.

Cyclodehydration of 2-Quinolinylthioglycolic Acid (1, R = H). 2-Mercaptoquinoline (3.22 g, 20 mmol) and bromoacetic acid (2.78 g, 20 mmol) in anhydrous benzene (50 mL) were treated with Et_3N (2.8 mL, 20 mmol) and stirred for 15 h. The reaction mixture was washed with water (2 × 20 mL) and dried (Na_2SO_4) and the benzene was evaporated in vacuo.

One-half of the above oil was dissolved in dry benzene (5 mL), cooled to 0 °C, and treated with an ice-cold mixture of Ac_2O (1.5 mL) and Et_3N (1.5 mL). After stirring for 15 min, the reaction mixture was allowed to warm to room temperature and anhydrous ether was added, precipitating an orange solid. This was recrystallized from $CHCl_3$–Et_2O, separating as an unstable orange powder which decomposed on standing: mp 162–163 °C dec; IR (KBr) 1700, 1655, 1605 cm^{-1}.

The remaining portion of the oil was treated with Ac_2O (1.5 mL) and Et_3N (1.5 mL) at room temperature, an exothermic reaction resulting. The brown needles that separated after 15 min and the additional solid precipitated by addition of anhydrous ether were collected: mp 174 °C; IR (KBr) 1700, 1660, 1615 cm^{-1}.

When a sample of the thioglycolic acid was treated with Ac_2O, rapidly heated to boiling and then cooled quickly, the addition of EtOH deposited a dark solid. It crystallized from pyridine–ethanol as dark-brown prisms: mp 178–182 °C dec (lit[3] mp 194 °C); IR (KBr) 1660, 1610, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.93–7.26 (m, 8, aromatic), 4.98 (s, 1, CH_2).

Cyclodehydration of 2-Pyridinylthioglycolic Acid (4; R = H). A mixture of the acid (0.75 g, 4.44 mmol) and Ac_2O (4 mL) was heated quickly to boiling and cooled immediately. The deposited solid was recrystallized from EtOH forming yellow plates of **6:** 75%; mp 187 °C (lit.[3] mp 180 °C); IR (KBr) 1680, 1620, 1600 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.46–6.63 (m, 8, aromatic), 4.16 (s, 2, CH_2); M^+· 302 (31). Anal. Calcd for $C_{14}H_{10}N_2O_2S_2$: C, 55.62; H, 3.33; N, 9.26. Found: C, 56.11; H, 3.57; N, 9.10.

Reaction of 2-Mercaptopyridine with Bromoacetyl Chloride. The thiol (0.55 g, 5 mmol) in dry $CHCl_3$ (30 mL) was treated dropwise with bromoacetyl chloride (0.78 g, 5 mmol). After stirring for 5 min, Et_3N (1.4 mL, 10 mmol) was added and the reaction mixture was stirred for an additional hour. The $CHCl_3$ solution was washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and concentrated. Addition of Et_2O precipitated a greenish-yellow product that crystallized from EtOH as yellow needles, 78%, mp 187 °C, identical[9] with **6** prepared above.

***anhydro*-1-Hydroxy-2-phenylthiazolo[3,2-*a*]quinolinium Hydroxide (2, R = Ph). A.** A solution of 2-mercaptoquinoline (1.61 g, 10 mmol) in dry $CHCl_3$ (50 mL) was treated dropwise with α-bromophenylacetyl chloride (2.34 g; 10 mmol) at room temperature. After stirring for 10 min, Et_3N (2.02 g; 20 mmol) was added dropwise and stirring was continued for a further 30 min. The reaction mixture was washed with cold water (2 × 15 mL), dried (Na_2SO_4), and concentrated. Addition of a small amount of anhydrous Et_2O gave a deep-red solid that crystallized from $CHCl_3$–Et_2O as deep-red plates: 82%; mp 199–200 °C dec; IR (KBr) 1610 cm^{-1}; λ_{max} (CH_3OH) 482 (log ε 4.14), 306 (3.92), 270 nm (3.84); NMR ($CDCl_3$–Me_2SO-d_6) δ 8.13–7.07 (m, aromatic); M^+· 277 (64). Anal. Calcd for $C_{17}H_{11}NOS$: C, 73.62; H, 4.00; N, 5.05. Found: C, 73.74; H, 3.94; N, 4.88.

B. A stirred mixture of 2-mercaptoquinoline (3.22 g, 20 mmol) in

benzene (50 mL) and α-bromophenylacetic acid (4.3 g, 20 mmol) was treated dropwise with Et_3N (2.02 g, 20 mmol) and stirred for 6 h at room temperature. Insoluble material was filtered and the filtrate was diluted with $CHCl_3$, washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated. Addition of benzene gave 2-quinolinyl-2-phenylthioglycolic acid (**1**, R = Ph) as a colorless solid which crystallized from $CHCl_3$–benzene as colorless prisms: mp 140 °C dec; IR (KBr) 1705 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 8.21–7.28 (m, 11, aromatic), 5.85 (s, 1, CH). Anal. Calcd for $C_{17}H_{13}NO_2S$: C, 69.11; H, 4.43; N, 3.74. Found: C, 69.36; H, 4.42; N, 4.73.

The above acid (2.0 g, 7 mmol) in anhydrous benzene (2 mL) was treated with a mixture of Ac_2O (4 mL) and Et_3N (4 mL) and stirred for 1 h at room temperature. Addition of anhydrous Et_2O precipitated a deep-red solid that crystallized from $CHCl_3$–Et_2O as deep-red plates: 88%; mp 198–199 °C dec, identical[9] with that prepared above.

Reaction of *anhydro*-1-Hydroxy-2-phenylthiazolo[3,2-*a*]quinolinium Hydroxide (2, R = Ph) with Dimethyl Acetylenedicarboxylate. The above mesoionic compound (0.81 g; 3 mmol), dimethyl acetylenedicarboxylate (0.5 g; 35.2 mmol), and toluene (30 mL) were refluxed for 6 h. Evaporation of the toluene in vacuo and trituration of the residue with hot EtOH gave a yellow solid that crystallized from $CHCl_3$–EtOH as yellow needles of methyl 1-phenylpyrrolo[1,2-*a*]quinoline-2,3-dicarboxylate (**9**, R = R^1 = $COOCH_3$): 66%; mp 160–161 °C (lit.[6] mp 161–162 °C); IR (KBr) 1725, 1705 cm^{-1}; λ_{max} (CH_3OH) 350 (log ε 4.06), 277 (4.03), 227 nm (sh, 4.39); NMR ($CDCl_3$) δ 8.28–7.16 (m, 11, aromatic), 3.91 (s, 3, $COOCH_3$), 3.71 (s, 3, $COOCH_3$); M^+· 359 (100). Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.68; H, 4.64; N, 3.76.

In one experiment dry N_2 was passed through the reaction mixture and the effluent gases condensed in an alcoholic solution of piperidine. Concentration of this solution resulted in colorless needles of *N,N'*-pentamethylenethiocarbamic acid, recrystallized from acetone, mp 112–113 °C (lit.[10] mp 113–115 °C), identical[9] with an authentic sample.

Ethyl 1-phenylpyrrolo[1,2-*a*]quinoline-3-carboxylate (9, R = H; R^1 = COOEt) was obtained as yellow needles from $CHCl_3$–EtOH from **2** (R = Ph) and ethyl propiolate in refluxing toluene over 7 h: 95%; mp 98 °C; IR (KBr) 1700 (CO), 1660 cm^{-1}; λ_{max} (CH_3OH) 420 (log ε 3.75), 370 (4.0), 285 (4.16), 240 (sh, 4.40), 227 nm (sh, 4.42); NMR ($CDCl_3$) δ 8.28 (d, 1, *J* = 9.0 Hz, aromatic), 7.77–7.26 (m, 10, aromatic), 7.13 (s, 1, H_2), 4.4 (q, 2, *J* = 7.0 Hz, $\mathbf{CH_2}CH_3$), 1.4 (t, 3, *J* = 7.0 Hz, $CH_2\mathbf{CH_3}$); M^+· 315 (100). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 4.53; N, 4.44. Found: C, 79.59; H, 5.25; N, 4.37.

Reaction of 2 (R = Ph) with Fumaronitrile. The mesoionic compound (0.53 g, 2 mmol), fumaronitrile (0.16 g, 2 mmol), and toluene (30 mL) were refluxed for 24 h. Evaporation of the toluene in vacuo and trituration of the residue with hot ethanol gave a solid that crystallized from $CHCl_3$: EtOH as golden yellow needles of 3,4-dicyano-2-phenyl-1*H*-pyrido[1,2-*a*]quinolin-1-one (**12**): 28%; mp 304–305 °C; IR (KBr) 2210 (CN), 1685 cm^{-1} (CO); M^+· 321 (80). Anal. Calcd for $C_{21}H_{11}N_3O$: C, 78.49; H, 3.45; N, 13.08. Found: C, 78.20; H, 3.24; N, 12.93.

Registry No.—1 (R = H), 56919-56-3; 1 (R = Ph), 66102-80-5; **2** (R = Ph), 43091-21-0; **3**, 66102-81-6; 4 (R = H), 10002-29-6; **6**, 66102-82-7; **9** (R = H; R = COOEt), 52249-53-3; **9** (R = R^1 = $COOCH_3$), 20958-83-2; **12**, 66102-83-8; 2-mercaptoquinoline, 2637-37-8; bromoacetic acid, 79-08-3; 2-mercaptopyridine, 2637-34-5; bromoacetyl chloride, 22118-09-8; α-bromophenylacetyl chloride, 19078-72-9; α-bromophenylacetic acid, 4870-65-9; dimethyl acetylenedicarboxylate, 762-42-5; ethyl propiolate, 623-47-2; fumaronitrile, 764-42-1.

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Synthesis of α-Methoxyaliphatic Acids from Chloroform and Aliphatic Aldehydes with Sodium Hydride as Catalyst in Tetrahydrofuran

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The preparations of α-methoxyaliphatic acids, which we report here, have not been reported previously by any other method. A number of earlier articles have reported the condensation of chloroform (or bromoform) with aryl aldehydes to produce either aryl trihalomethyl-substituted methanols[1] or the products of the reaction of such alcohols[2] with base and/or solvent. In the latter cases, α-substituted arylacetic acids are often produced, where the α substituent has been methoxyl[3] (or alkoxyl,[4] in general), hydroxyl,[5] amino,[6] and even chloro.[7]

Past attempts to carry out similar reactions with aliphatic aldehydes replacing the aryl aldehydes have met with little success,[8] resulting usually in the formation of tars (from aldol condensations) rather than the alkyl (trichloromethyl)-methanols (aliphatic ketones[8] do, however, condense with chloroform, usually in 80% yields). Thus, at moderate temperatures (10–15 °C), most aliphatic aldehydes undergo the aldol condensation in the presence of strong base. To avoid this competing reaction, we have devised a procedure described below involving the addition of the aldehyde in chloroform to sodium hydride at 0–5 °C. The resulting alkyl (trichloromethyl)methanol containing solution, on addition of methanolic potassium hydroxide and heat, is converted to the product α-methoxyaliphatic acid, allowing a "one-batch" conversion.

$$RCHO + HCCl_3 + THF \xrightarrow[(2)\ NaOH/CH_3OH]{(1)\ NaH/THF} \underset{\displaystyle OCH_3}{\overset{\displaystyle RCHCO_2H}{|}}$$

There is evidence[9] for a general mechanism for these related haloform condensations, a mechanism involving an epoxide intermediate, which undergoes ring opening with solvent (or base) nucleophile to produce the various α-substituted acids after hydrolysis:

$$RCHO + CHCl_3\ (\text{or } CHBr_3) \xrightarrow[\text{catalyst}]{\text{base}} \underset{\displaystyle OH}{\overset{\displaystyle RCHCCl_3}{|}}$$

$$\xrightarrow{KOH} RCH\underset{O}{\overset{Cl}{\diagup\!\diagdown}}C\overset{Cl}{\diagdown} \xrightarrow{XH} \underset{\displaystyle X}{\overset{\displaystyle RCHC(=O)Cl}{|}} \xrightarrow{H_2O} \underset{\displaystyle X}{\overset{\displaystyle RCHCO_2H}{|}}$$

In our chloroform condensation, the yields of the α-methoxyaliphatic acids have been generally good, varying from 51 to 63%, in most cases (with one 24% exception).

Other variations tried were a mixture of Me_2SO and THF (Me_2SO–THF 1:10) and 1,4-dioxane as solvent systems. The use of bromoform (replacing chloroform), a variety of reactant stoichiometries and orders of addition, potassium hydroxide in methanolysis (replacing sodium hydroxide), and a number of temperature conditions were tried. The reaction did not work if bromoform was substituted for chloroform. Also, we were not able to modify the methodology to produce the α-hydroxy- or α-aminoaliphatic acids. However, alkyl (trichloromethyl)methanols were isolated in good (80%) yields in two trials (using isobutyraldehyde and *n*-pentanal) and thus we feel certain that given the right conditions these other α-substituted aliphatic acids should be achievable.

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Experimental Section

To a 100-mL three-necked flask are added 250 mL of tetrahydrofuran (THF) and slightly more than 1/3 mol of sodium hydride (about 9 g). This mixture is cooled to between 0 and 5 °C in an ice–salt bath and kept under nitrogen gas throughout the reaction (much aldehyde oxidation occurs otherwise).

The aliphatic aldehyde (1/8 mol) and chloroform (1/4 mol = 20.4 mL) is added to the flask dropwise over a period of 1–1.5 h after which the solution is stirred for an additional 3–3.5 h at the ice–salt bath temperature. (The reaction is exothermic and is likely to erupt from the flask if the temperature is allowed to rise above 20 °C.) Then 35 g of sodium hydroxide pellets dissolved in 150 mL of methanol are added to the flask dropwide with continued stirring over a period of 1 h. During the methanol addition the reaction is exothermic but the temperature is maintained below 40 °C with the ice bath. After completion of this addition, the reaction mixture is heated with a Glas-col heater and the temperature is kept in the range of 70–75 °C for a period of 2–3 h during methanolysis. The reaction mixture is allowed to stand overnight while cooling down to room temperature. Usually a yellow or pale-yellow solution containing a thick layer of white precipitate is obtained which is transferred to a beaker along with 200–250 mL of distilled water, warmed if necessary to dissolve all the inorganic products. The solution, which should be highly basic (pH 12), is cooled and extracted several times with ether to remove the neutral and basic materials. The solution is adjusted to pH 1, with hydrochloric acid. An oily layer appears on the solution surface, consisting of the α-methoxyaliphatic acid and trace impurities. This oil is removed by three 50-mL ether extractions. The ether extract is dried with sodium sulfate, refluxed with activated charcoal, and filtered and the ether is evaporated (the last traces under vacuum). The crude oils obtained suggest yields in the range of 69–80% of the theory. Vapor phase chromatograms run of these oils show impurities to average 5–8% of the crude acid giving yields before purification of 62–76% (with one exception, α-methoxyundecanoic acid, whose yield is 45%).

The purification of these oily acids is accomplished using a microdistillation system under reduced pressure. The final analytical product distillates varied in yield from 51 to 63% (24% for α-methoxyundecanoic acid).

Analytical and Spectroscopic Data of the α-Methoxyaliphatic Acids. General. Distillations were carried out using Bantam Ware apparatus. The infrared spectra were obtained on a Beckman IR-8. ^{1}H NMR spectra were obtained using a Joelco Model JNM-C-60HL and are reported in parts per million downfield from internal tetramethylsilane. The indicated yields are amounts obtained after careful distillation, one fraction of which was analytically pure.

2-Methoxyheptanoic acid: bp 246–250 °C; yield 54%; IR_{max} (neat) 3200–2500, 1700, 1420, 1190, 1120, 1095, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, triplet), 1.45 (8 H, complex), 3.44 (3 H, singlet), 3.69 (1 H, triplet), 13 (1 H, singlet). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.06; OCH_3, 19.37. Found: C, 60.00; H, 10.14; OCH_3, 18.93.

2-Methoxyoctanoic acid: bp 49–52 °C (12 mmHg); yield 53%; IR_{max} (neat) 3200–2500, 1700, 1420, 1190, 1120, 1095, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, triplet), 1.40 (10 H, complex), 3.42 (3 H, singlet), 3.75 (1 H, triplet), 13.1 (1 H, singlet). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41; OCH_3, 17.81. Found: C, 61.97; H, 10.24; OCH_3, 18.12.

2-Methoxy-3,4-dimethylhexanoic acid: bp 246–250 °C; yield 56%; IR_{max} (neat) 3200–2500, 1700, 1420, 1360, 1195, 1095, 940 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (9 H, complex), 1.8 (4 H, complex), 3.52 (3 H, singlet), 3.78 (1 H, complex), 13.45 (1 H, singlet). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41; OCH_3, 17.81. Found: C, 62.01; H, 10.34; OCH_3, 17.53.

2-Methoxy- 3-methylbutanoic acid: bp 197–201 °C; yield 59%; IR_{max} (neat) 3200–2500, 1700, 1420, 1375, 1160, 1190, 1095, 980–900 cm^{-1}; NMR ($CDCl_3$) δ 1 (6 H, quartet), 2.1 (1 H, septet), 3.56 (1 H, doublet), 3.48 (3 H, singlet). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.58; H, 9.06.

2-Methoxpentanoic acid: bp 193–197 °C; yield 57%; IR_{max} (neat) 3200–2500, 1700, 1420, 1190, 1120, 1095, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (3 H, triplet), 1.65 (4 H, complex), 3.45 (3 H, singlet), 3.72 (1 H, triplet), 13.9 (1 H, singlet). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15; OCH_3, 23.48. Found: C, 54.38; H, 9.16; OCH_3, 23.53.

2-Methoxyhexanoic acid: bp 47–50 °C (13 mmHg); yield 53%; IR_{max} (neat) 3200–2500, 1700, 1420, 1190, 1120, 1095, 720 cm^{-1}; NMR (CCl_4) δ 0.98 (3 H, triplet), 1.42 (6 H, complex), 3.43 (3 H, singlet), 3.69 (1 H, triplet), 12.8 (1 H, singlet). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65; OCH_3, 21.22. Found: C, 57.37; H, 9.74; OCH_3, 20.69.

2-Methoxynonanoic acid: bp 260–264 °C; yield 54%; IR_{max} (neat) 3200–2500, 1700, 1420, 1195, 1110, 1095, 940, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, triplet), 1.43 (12 H, complex), 3.45 (3 H, singlet), 3.77 (1 H, triplet), 13.2 (1 H, singlet). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71; OCH_3, 16.48. Found: C, 63.83; H, 10.59; OCH_3, 16.62.

2-Methoxydecanoic acid: bp 278–281 °C; yield 51%; IR_{max} (neat) 3200–2500, 1705, 1420, 1095, 720 cm^{-1}; NMR (CCl_4) δ 0.98 (3 H, triplet), 1.42 (14 H, broad complex), 3.45 (3 H, singlet), 3.77 (1 H, triplet), 13.5 (1 H, singlet). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.69. Found: C, 65.37; H, 10.96.

2-Methoxy-2-cyclohexylethanoic acid: bp 241–245 °C; yield 63%; IR_{max} (neat) 3200–2500, 1700, 1410 (doublet), 1110, 950–880 (broad) cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.79; H, 9.36.

Registry No.—2-Methoxyheptanoic acid, 64769-03-5; 2-methoxyoctanoic acid, 66018-23-3; 2-methoxy-3,4-dimethylhexanoic acid, 66018-24-4; 2-methoxy-3-methylbutanoic acid, 66018-25-5; 2-methoxypentanoic acid, 66018-26-6; 2-methoxyhexanoic acid, 66018-27-7; 2-methoxynonanoic acid, 66018-28-8; 2-methoxydecanoic acid, 66018-29-9; 2-methoxy-2-cyclohexylethanoic acid, 15540-18-8; hexanal, 66-25-1; heptanal, 111-71-7; 2,3-dimethylpentanal, 32749-94-3; 2-methylpropanal, 78-84-2; butanal, 123-72-8; pentanal, 110-62-3; octanal, 124-13-0; nonanal, 124-19-6; cyclohexanecarboxaldehyde, 2043-61-0; chloroform, 67-66-3; sodium hydride, 7646-69-7; tetrahydrofuran, 109-99-9.

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Revision of the Stereochemical Assignment of a Cyclobutane Derivative from Chalcone Photodimerization via X-ray Diffraction Analysis

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In a previous report[2] some of us described the stereochemistry of a chalcone photodimer as having β-truxinic structure **1**. This stereochemical assignment was made essentially on the basis of ^{1}H-NMR data and their comparison with data for a number of structurally related compounds. Subsequently, because the two internal rotation angles θ_1 and θ_2 of the benzoyl groups permit different conformational preferences, we wished to compare the conformation in the solid state with that derived from our data in solution. Furthermore, we wanted to determine if the cyclobutane ring was puckered out of the plane because of the four bulky substituents attached to it. In fact, few data exist in the literature[3,4] about the solid-state structure of cyclobutane derivatives in which no bonds of the four-membered ring are inserted in a fused structure or in which each carbon of the ring bears one substituent.

For these reasons, an x-ray structure determination was

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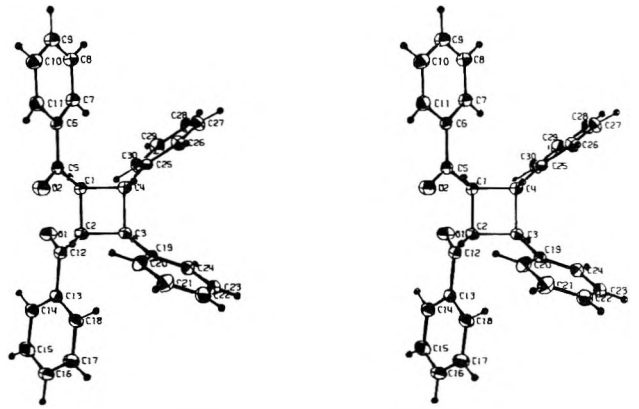


Figure 1. Stereoscopic view of a single molecule of 2.

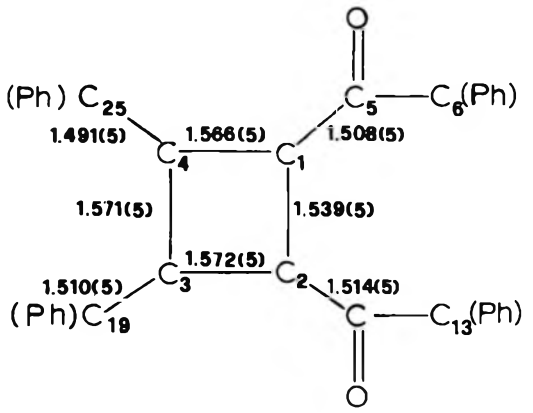
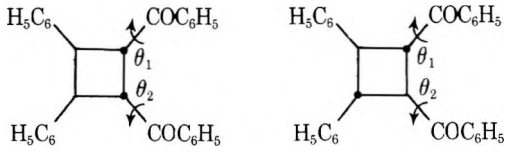


Figure 2. Selected bond distances and partial numbering scheme.

undertaken. The relative stereochemistry found in this study shows a δ-truxinic structure **2**, thus our previous assignment of structure **1** was incorrect.



1 **2**

The three-dimensional structure of this photodimer of chalcone (mp 126 °C) was determined by x-ray structure analysis of crystals obtained from ethyl alcohol solution. A single colorless crystal was used to collect 2056 observed reflections with $2\theta < 130°$ on a Syntex $P2_1$ diffractometer (Cu Kα radiation). The space group is monoclinic, $P2_1/c$, with four molecules per unit cell: a = 10.902 (4) Å; b = 9.671 (4) Å; c = 21.426 (6) Å; and β = 90.69 (3)°; ρ_{obsd} = 1.22 g cm^{-3}; ρ_{calcd} = 1.222 g cm^{-3}. The structure was solved by direct methods[5] and refined by full-matrix least squares (for all nonzero reflections) to an unweighted R factor of 0.059 and a weighted R factor of 0.057.[6] Anisotropic temperature factors were used for all non-hydrogen atoms.

A stereoscopic drawing of one molecule is shown in Figure 1; bond distances in the ring and a partial numbering scheme are given in Figure 2. The bond lengths and bond angles are in general close to accepted values. Remarkably, bond lengths C2–C3, C3–C4, and C1–C4 are longer than normal C–C single bonds but their values are not unusual in substituted cyclobutanes.[3,4] There are no close contacts between molecules in the crystal.

The four-membered ring is slightly nonplanar; the torsion angles are in fact C1–C2–C3–C4 7.23°, C1–C4–C3–C2 −7.10°, C2–C1–C4–C3 7.25°, and C3–C2–C1–C4 −7.25°. Hence no other structures have been reported with an intermediate degree of puckering, i.e., in the range 1–18°.[4]

Torsion angles of the two benzoyl groups are C2–C1–C5–C6 176.58° and C1–C2–C12–C13 −172.83°, while torsion angles of the two phenyl groups are C1–C4–C25–C26 139.12° and C2–C3–C19–C20 −28.82°. Angle ABCD is considered positive if, when looking along the B–C bond, A has to be rotated clockwise to eclipse B, according to a well-known convention.[7]

The intramolecular nonbonded distance O1- - -O2 is 4.31 Å.

The preferred conformation is thus well inside the energetically allowed area generated as a function of the internal rotation angles θ_1 and θ_2 of the benzoyl groups in an energy exclusion map.[8]

Acknowledgments. We thank Professor I. C. Paul, Department of Chemistry, University of Illinois, Urbana, for the use of facilities in his x-ray laboratory.

Registry No.—**2**, 24825-07-8.

Supplementary Material Available: Tables of atomic coordinates in fractions of the unit cell parameters, bond lengths, and bond angles (5 pages). Ordering information is given on any current masthead page.

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Carbon Acidity. 57. Equilibrium Acidities of *o*- and *p*-Benzylbiphenyl. Steric Inhibition of Acidity

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We have previously reported[1] a number of relative ion pair acidities (pK_{CsCHA}) based on competitive equilibria with cesium cyclohexylamide (CsCHA) in cyclohexylamine (CHA).

$$R_1H + R_2^-Cs^+ \rightleftarrows R_1^-Cs^+ + R_2H \quad (1)$$

$$K = [R_2H][R_1^-Cs^+]/[R_1H][R_2^-Cs^+] \quad (2)$$

$$\log K = pK(2) - pK(1) \quad (3)$$

We report in this note the pK_{CsCHA} values obtained for the title hydrocarbons.[2] The results provide an assessment of the *o*-phenyl steric effect on the carbon acidity of diarylmethanes.[3]

Results and Discussion

Spectral data not reported previously are summarized in Table I. Table II gives results for the individual equilibrium runs.

Table I. Absorption Maxima for Cesium Salts in Cyclohexylamine

Hydrocarbon	λ_{max}, nm	$10^{-3}\epsilon$
o-BBP (*o*-benzylbiphenyl)	460	36.0 ± 1.4
p-BBP (*p*-benzylbiphenyl)	525	65.0 ± 2.7

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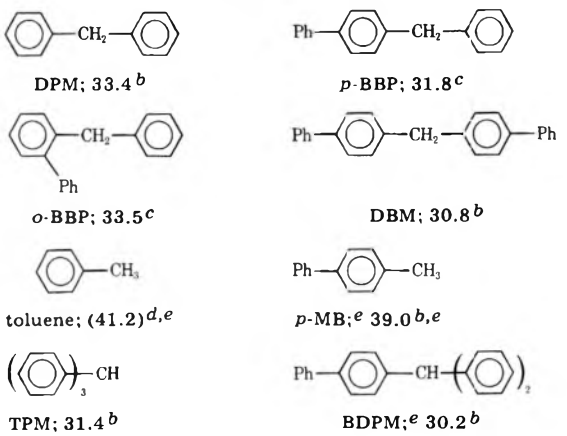
Table II. Summary of Equilibrium Constants

R_1H[a]	R_2H[a]	K	log K	n[b]	pK (per H)[c]
TPM	*p*-BBP	1.47 ± 0.28	0.17 ± 0.07	10	31.92 ± 0.12[d]
DCH	*p*-BBP	3.26 ± 0.37	0.51 ± 0.05	6	31.72 ± 0.14[d]
p-BBP	*o*-BBP	50.30 ± 12.7	1.69 ± 0.11	6	33.51 ± 0.12[e]
T*p*TM	*o*-BBP	1.46 ± 0.45	0.16 ± 0.13	8	33.50 ± 0.14[e]

[a] Abbreviations and pK_{CsCHA} values for indicators used are as follows: TPM, triphenylmethane, 31.45; T*p*TM, tri-*p*-tolylmethane, 33.04; DCH, 5*H*-dibenzo[*a*,*d*]cyclohepta-1,3-diene, 31.21. [b] Number of determinations. [c] pK of R_2H followed by the accumulated probable error, relative to pK_{CsCHA} (9-phenylfluorene) = 18.49. [d] Weighted average pK_{CsCHA} of *p*-BBP is 31.82 ± 0.12. [e] Weighted average pK_{CsCHA} of *o*-BBP is 33.51 ± 0.12.

Table III. Effect of *p*-Phenyl Substituents on pK_{CsCHA} of Arylmethanes[a]



[a] pK_{CsCHA} per hydrogen. Abbreviations used are as follows: *p*-MB, *p*-methylbiphenyl; BDPM, *p*-biphenylyldiphenylmethane. [b] Reference 1b. [c] This work. [d] A. Streitwieser, Jr., M. R. Granger, F. Mares, and R. A. Wolf, *J. Am. Chem. Soc.*, **95**, 4257 (1973). [e] A. Streitwieser, Jr., and F. Guibe, *J. Am. Chem. Soc.*, in press.

The pK value of 31.82 obtained for *p*-benzylbiphenyl (*p*-BBP) appears reasonable in view of the pK's already reported for diphenylmethane (DPM) and di-*p*-biphenylylmethane (DBM)[1b] (Table III). The results show an expected attenuation of substituent effects: substitution of a phenyl group into the para position of toluene gives a pK decrease of 2.2, the first *p*-phenyl substituent in diphenylmethane gives a ΔpK of 1.6, and the second gives a further ΔpK of 1.0. For comparison, a single *p*-phenyl substituent in triphenylmethane (TPM) causes a pK lowering of 1.3 pK units (Table III).

From Dreiding models it seems likely that steric interactions will prevent the biphenylyl group from achieving coplanarity in the anion of *o*-BBP and probably interfere with the conjugation to the central carbon. The experimental result that *o*-BBP has essentially the same acidity as the unsubstituted DPM (ca. 1.7 pK units less acidic than *p*-BBP) suggests that this effect is just balanced by the inductive effect of the *o*-phenyl group.

Experimental Section

Melting points were determined on a Büchi apparatus and are not corrected. Visible spectra were measured on a Cary 118 spectrometer (20 nm/in.; 1 nm/s).

Procedure. The procedure for measuring the spectra of the cesium salts has been described in detail.[4] The equilibrium constants in Table II were determined using the previously reported procedures.[1,5] This table is arranged such that the more acidic hydrocarbon is given as R_1H in equilibrium 1, and K is always >1. Table III summarizes the results as pK values. These values actually relate to the equilibrium of each hydrocarbon in eq 1 with 9-phenylfluorene, with a pK of 18.49 assigned to the latter, and are given on a per hydrogen basis.

***o*- and *p*-Benzylbiphenyl.** A commercial sample of benzylbiphenyl (Eastman Organic Chemicals; a mixture of the ortho and para isomers) was initially purified by subliming out the biphenyl present as a contaminant [32–35 °C (1 mm)]. The residual mixture (150 mg) was cleanly separated by preparative thin-layer chromatography (TLC) on a 20 × 20 cm silica gel F-254 plate (Brinkman Co.) with cyclohexane as eluent to give (after recrystallization from 95% EtOH) 13 mg of biphenyl [R_f 0.95; mp 68–69 °C (lit.[6a] mp 69–70 °C)], 59 mg of *o*-benzylbiphenyl [R_f 0.83; mp 54–55 °C (lit.[6b] mp 54 °C)], and 22 mg of *p*-benzylbiphenyl [R_f 0.70; mp 83–84 °C (lit.[6b] mp 85 °C)].

Acknowledgment. This work was supported by NIH USPH Grant GM-12855.

Registry No.—*p*-BBP, 613-42-3; *o*-BBP, 606-97-3.

References and Notes

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Synthesis of 2,6-Diacetonylpiperidine. X-ray Diffraction Analysis of Its *N*-Benzoyl Derivative[1]

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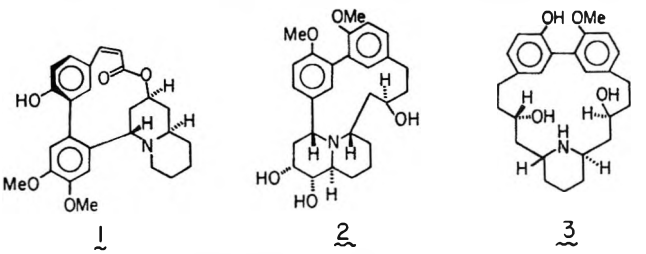
The 39 alkaloids which have been isolated from members of the *Lythraceae* plant family[2] may be classified according to three structural types. The type I alkaloids, quinolizidine lactones, are represented by cryogenine (**1**).[2a] The type II alkaloids, e.g., lythrancine I (**2**),[2b] are also quinolizidine alkaloids, but with a carbocyclic ring. Finally, the type III alkaloids are piperidine alkaloids, e.g., lythranidine (**3**).[2c] Some of the



1 **2** **3**

type I alkaloids have been investigated for use as sedatives, antiinflammatory agents, and as diuretics.[3] There have been no reports of pharmacological studies on the type II or III al-

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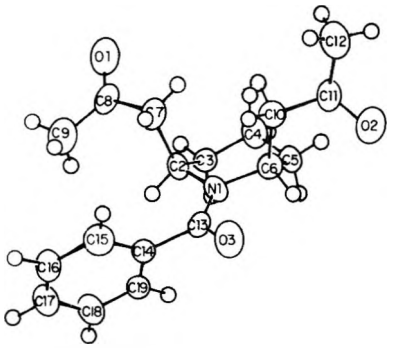
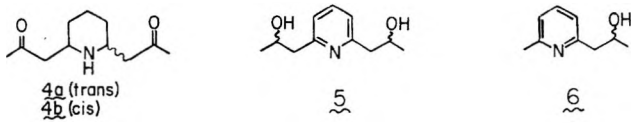


Figure 1. A labeled drawing of *N*-benzoyl-2,6-diacetonylpiperidine showing 50% probability ellipsoids for the nonhydrogen atoms.

kaloids. There has likewise been no report of synthetic studies on these latter two classes of alkaloids.

The type II and III alkaloids have been proposed to arise biogenetically from a common precursor, *trans*-2,6-diacetonylpiperidine (**4a**).[4] This dione is also an attractive starting material for the syntheses of these alkaloids. Elaboration of **4** into the type II or III skeletons may be envisioned to occur via pelletierine[5] and/or Claisen–Schmidt condensations. Thus, we began our synthetic studies on these alkaloids with a study of the preparation of **4**.

Our initial route utilized a bisfunctionalization of 2,6-lutidine. Thus, a THF solution of lutidine was treated with 2 equiv of lithium diisopropylamide at −70 °C to yield a dark-red solution.[6] The solution became light yellow when an excess of acetaldehyde was distilled into it. Normal workup of this solution afforded a crude oil. Separation of the components of this oil by chromatography afforded a 43% yield of the diol, **5**, presumably as a mixture of diastereomers, as well as a 25%

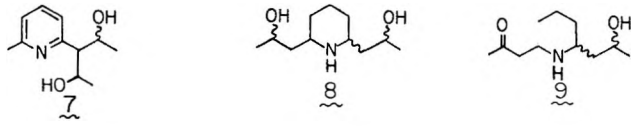


4a (trans)
4b (cis)

5

6

yield of the monofunctionalized lutidine, **6**.[7] There is no evidence for the occurrence of the nonsymmetric diol, **7**. Hydrogenation of **5** resulted in an 86% yield of the piperidine diol, **8**. This latter compound was very difficult to purify and was routinely utilized without further purification.



7

8

9

The final step in this sequence, the oxidation of the diol to the dione, proved to be unexpectedly difficult. The presence of the secondary amine limits the choice of oxidation reagents. All of the methods investigated suffered from either low material recovery (i.e., Jones or Fieser oxidations) or low percent conversions (i.e., pyridinium chlorochromate,[8] polymer-bound CrO_3,[9] Oppenauer, or Moffat oxidations). The former problem was a result of the formation of an emulsion upon basification of the oxidation mixture. The latter series of reagents was studied in an attempt to avoid this problem. The best results in the entire series were obtained with Jones reagent. Thus, a 26% yield of **4**, as well as an 8% yield of **9**, was obtained after chromatography of the crude oil from the Jones oxidation. The overall yield of **4** by this route was 9.6%. The oxidation of the pyridine diol, **5**, to the corresponding dione by these reagents was likewise not very successful. Attempts to selectively block the nitrogen in **8** were unsuccessful. Since there did not appear to be much chance for improvement in the oxidation step we considered other synthetic routes.

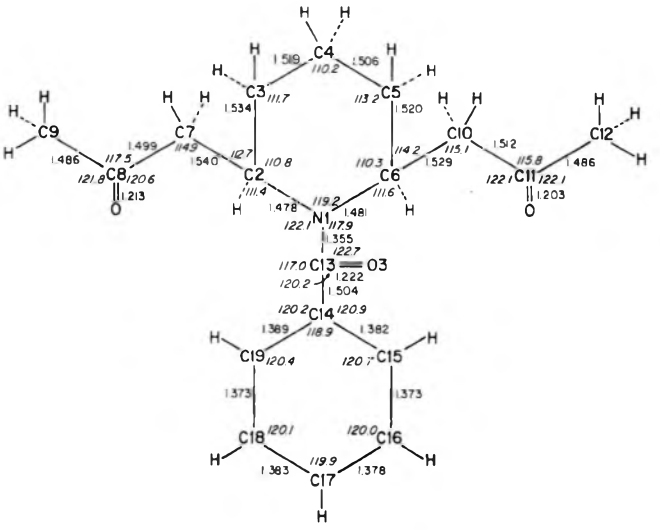
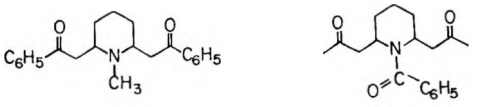


Figure 2. Bond distances and bond angles for *N*-benzoyl-2,6-diacetonylpiperidine. The average standard deviations are 0.006 Å and 0.4°, respectively.

Dione **4** is structurally similar to the *Lobelia* alkaloids, e.g., lobelanine (**10**). Lobelanine had been prepared by Schöpf and Lehmann by the condensation of glutaraldehyde, methylamine, and benzoylacetic acid in a buffered solution.[10] A similar condensation was attempted by stirring a solution of glutaraldehyde, ammonium chloride, and acetoacetic acid in a phosphate buffer (pH 2–3) overnight. Methylene chloride extraction of the basified solution yielded a dark-brown oil



10

11

which could be further purified by Kugelrohr distillation. The yield of **4** by this method was 12%. The condensation has also been attempted at pH's 4, 6, and 10, but the yields were even lower. The simplicity of this method makes the yield acceptable.

The NMR, IR, and mass spectra, as well as the TLC behavior, of **4** prepared from lutidine are identical with those of the material obtained from the glutaraldehyde condensation. Likewise, the hydrochlorides have the same melting–decomposition points. Thus, the two procedures probably yield the same diastereomer of **4**. All of our further studies have utilized material prepared by the condensation route.

The catalytic hydrogenation of 2,6-lutidine has been reported to afford *cis*-2,6-dimethylpiperidine.[11] The synthesis of lobelanine produced the cis isomer.[12] Thus, it could also be assumed that the diastereomer of **4** obtained in this study was the cis isomer. However, we wished to definitely establish the stereochemistry of the product. The NMR spectrum of **4** was not useful for this purpose since a first-order spectrum could not be obtained using lanthanide shift reagents nor could we prepare a characterizable 2,4-dinitrobenzenesulfonamide of **4** in order to apply the method of Raban et al.[13] However, the preparation of the crystalline benzamide, **11**, in 90% yield from **4** suggested the application of X-ray diffraction.

The molecular conformation of **11** as determined by the X-ray diffraction study (see Experimental Section) is shown in Figure 1. The bond lengths and bond angles involving nonhydrogen atoms are given in Figure 2. Several related structural features of the molecule are apparent from these results: the acetonyl groups at C-2 and C-6 are cis to one another; the amide group (N-1, C-13, and O-3) is planar; and the piperidine ring exhibits a flattened chair conformation. The

cis diaxial substitution avoids the contacts involving the planar amide group and the acetonyl groups which would occur if the latter were equatorial ($A^{1,3}$ strain).[14] At the same time flattening of the piperidyl ring, which results from the planarity of the amide, serves to prevent contact between the methylene hydrogens on C-7 and C-10. Even with the acetonyl groups in axial positions, the phenyl ring is unable to assume coplanarity with the amide carbonyl group due to the steric conflict between the hydrogen on C-2 of the piperidyl ring and the hydrogen on either C-19 or C-15 of the phenyl ring.

The cis relationship of the acetonyl groups in **11** indicates that **11** was obtained from *cis*-2,6-diacetonylpiperidine (**4b**). This is the first application of X-ray crystallography to a compound related to the Lobelia alkaloids. It verifies the stereochemical findings previously made on these alkaloids.[12]

Thus, the material which we have prepared by two different routes has the improper stereochemistry for synthesis of the type II and III *Lythraceae* alkaloids. Work is now in progress to find methods for the conversion of **4b** into **4a**.

Experimental Section

General. NMR spectra were recorded with a Varian T-60 spectrometer and are reported in ppm downfield from tetramethylsilane. Infrared spectra were recorded with a Perkin-Elmer 457 spectrophotometer. Mass spectra were recorded on a Nuclide mass spectrometer. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith Laboratories, Inc. An Aldrich Kügelrohr apparatus was utilized for bulb-to-bulb distillation. All commercially available reagents were used without further purification unless otherwise specified.

1. 2,6-Di(2-hydroxypropyl)pyridine (5). To a 0 °C solution of 70 g (0.69 mol) of diisopropylamine in 250 mL of dry tetrahydrofuran (THF), 63 mL of 8 N *n*-butyllithium in hexane (0.50 mol) was slowly added. After stirring for 15 min, 26.75 g (0.25 mol) of 2,6-lutidine in 60 mL of dry THF was added dropwise. Stirring was continued for 45 min after the addition was completed. Acetaldehyde (28 mL) was distilled into the deep red solution and the now yellow reaction mixture was allowed to warm to room temperature (3 h). The mixture was diluted with 100 mL of water, basified with 6 N sodium hydroxide, and extracted with methylene chloride (3 × 250 mL). The extracts were dried (Na_2SO_4) and concentrated in vacuo to yield 34.9 g of a brown oil.

Column chromatography of 10.1 g of this crude oil on 200 g of alumina (activity grade III) gave, upon elution with 25% acetonitrile in ether, 2.70 g (25% yield) of 2-methyl-6-(2-hydroxypropyl)pyridine (**6**)[7] as an oil: IR (film) 3340, 1595, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, J = 6 Hz, 3 H), 2.47 (s, 3 H), 2.83 (d, J = 6 Hz, 2 H), 4.22 (h, J = 6 Hz, 1 H), 5.3 (br s, 1 H), 7.2 (m, 3 H). Signal at δ 5.3 disappears after shaking with D_2O.

Further elution of the above column with acetonitrile gave 6.10 g (43% yield) of 2,6-di(2-hydroxypropyl)pyridine (**5**) as an oil: IR (film) 3325, 1595, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (d, J = 6 Hz, 6 H), 2.87 (d, J = 6 Hz, 4 H), 4.23 (h, J = 6 Hz, 2 H), 4.78 (br s, 2 H), 7.3 (m, 3 H). Hydrochloride (from isopropyl alcohol): mp 139–140 °C dec. Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.84; N, 6.05; Cl, 15.30. Found: C, 57.28; H, 8.01; N, 5.84; Cl, 15.47.

2. 2,6-Di(2-hydroxypropyl)piperidine (8). To a solution of 3.17 g (16 mmol) of **5** in 30 mL of acetic acid was added 1 g of 0.5% rhodium on aluminum oxide. The slurry was exposed to hydrogen in a Parr hydrogenator for 24 h. The catalyst was removed and the solution was concentrated. The resulting solution was diluted with 30 mL of water, basified with 6 N sodium hydroxide, and extracted with methylene chloride. The extracts were dried (Na_2SO_4) and concentrated to yield 2.81 g (86% yield) of **8** as a brown oil: IR (film) 3300 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.0 (m, 16 H), 1.14 (d, J = 6 Hz), 2.8 (m, 2 H), 3.4–4.2 (m, 4 H), 3.7 (br s, 4 H). After shaking with D_2O δ 3.7 changed to 2 H, m.

3. Jones Oxidation of 2,6-Di(2-hydroxypropyl)piperidine (8). To a solution of 5.05 g (25 mmol) of **8** in 20 mL of acetone at 0 °C was added Jones reagent made from 55 mmol of CrO_3. After 2 h, excess sodium thiosulfate solution was added and the solution was basified with sodium hydroxide. The resulting emulsion could not be filtered but was washed several times with ether. The combined organic layers were dried (Na_2SO_4) and concentrated to yield 2.35 g of a brown oil. Chromatography of this oil on 80 g of alumina afforded two characterizable products. The first, **4**, eluted with ether–methylene chloride mixtures and was obtained in 26% yield (1.80 g): IR (film) 3320, 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.9 (m, 6 H), 2.10 (s, 6 H), 2.45 (d, J = 6 Hz, 4 H), 2.7 (br s, 1 H), 2.8–3.3 (m, 2 H). After shaking with D_2O the δ 2.7 signal disappears. Mass spectra m/e 197 (21), 140 (85), 139 (92), 112 (58), 96 (100), 82 (94), 43 (72). Hydrochloride (from isopropyl alcohol): mp 202–202.5 °C dec. Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99; Cl, 15.17. Found: C, 56.37; H, 8.71; N, 5.89; Cl 15.26.

Further elution of the column with methylene chloride gave 0.41 g (8% yield) of **9** as a pink solid. Two successive sublimations (47 °C (0.05)) afforded a white solid: mp 73–4 °C; IR (KBr) 3400, 3260, 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.0 (m. 11 H), 1.15 (d, J = 6 Hz), 2.12 (s, 3 H), 2.47 (d, J = 6 Hz, 2 H), 2.6–3.3 (m, 3 H), 4.0 (m, 1 H); mass spectra m/e 199 (10), 142 (57), 140 (100), 82 (84). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.59; H, 10.90; N, 7.24. Hydrochloride (from isopropyl alcohol): mp 199.5–200 °C dec. Anal. Calcd for $C_{11}H_{22}ClNO_2$: C, 56.52; H, 8.62; N, 5.99; Cl, 15.17. Found: C, 56.42; H, 8.66; N, 5.96; Cl, 15.23.

4. 2,6-Diacetonylpiperidine (4). Condensation Method. To a three-neck flask equipped with a mechanical stirrer was added, in order, 200 mL of 25% glutaraldehyde solution (0.50 mol), 300 mL of deoxygenated water, 39.6 g (0.74 mol) of ammonium chloride in 500 mL of water, sodium acetoacetate solution [prepared by stirring a solution of 156 g (1.2 mol) of ethyl acetoacetate and 58 g of sodium hydroxide in 500 mL of water for 1.5 h], and 88 g (0.25 mol) of disodium hydrogen phosphate in 500 mL of water. The pH of the resulting red solution was initially adjusted to 2.5–3.0 by careful addition of concentrated hydrochloric acid. The mixture was allowed to stir for 24 h at room temperature. Finally, 33 mL of concentrated hydrochloric acid was added and the solution was heated for 1 h on a steam bath. After cooling, the mixture was basified and the resulting precipitate was removed by filtration. The aqueous solution was extracted with methylene chloride (8 × 250 mL) and the combined extracts were dried and concentrated to yield 18.2 g of a brown oil. Kügelrohr distillation of 1.14 g of this crude oil afforded 0.757 g (12% yield) of **4** as a yellowish oil which slowly darkened on standing. IR, NMR, and mass spectra were the same as in procedure 3. Picrate (from ethanol): mp 190.5–191 °C dec. Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.15. Found: C, 48.01; H, 5.17; N, 12.98. Hydrochloride (from isopropyl alcohol): mp 198–198.5 ° dec. Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99; Cl, 15.17. Found: C, 56.70; H, 8.80; N, 6.09; Cl, 15.29.

5. *N*-Benzoyl-2,6-diacetonylpiperidine (11). A solution of 1 g (7.1 mmol) of freshly distilled benzoyl chloride in 10 mL of CH_2Cl_2 was added dropwise with stirring over a 1-h period of 0 °C under nitrogen to a solution of 0.6 g (2.59 mmol) of 2,6-diacetonylpiperidine hydrochloride in 100 mL of CH_2Cl_2 and 15 mL of 10% aqueous NaOH. The reaction mixture was stirred at 0 to 24 °C for 8 h. The CH_2Cl_2 layer was separated from the aqueous phase and the aqueous phase was extracted with three 50-mL portions of CH_2Cl_2. The organic layers were combined and concentrated. A CH_2Cl_2 solution of the crude extract was treated with 10% aqueous NaOH until the excess benzoyl chloride was destroyed. The organic layer was then dried (Na_2SO_4) and the solvent was removed in vacuo to leave 0.705 g (90% yield) of solid material. An analytical sample of **11** was obtained by recrystallization (ethanol): mp 109–110 °C; IR (KBr) 1715, 1695, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.7 (m, 6 H), 2.10 (s, 6 H), 2.76 (d, J = 7 Hz, 4 H), 4.83 (b m, 2 H). 7.26 (s, 5 H). Anal. Calcd for $C_{18}H_{23}O_3N$: C, 71.73, H, 7.69, N, 4.65. Found: C, 71.86, H, 7.79, N, 4.58.

6. Diffraction Experiment on 11. Single crystals of **11**, grown from an ethanolic solution, were found to belong to the monoclinic system with unit cell dimensions: a = 9.688 (3), b = 7.517 (3), c = 11.744 (4) Å, and β = 106.87 (3) °. The systematic absences ($0k0$, k = odd) are consistent with either $P2_{1/M}$ or $P2_1$. The latter space group was assumed on the basis of noncentrosymmetrical intensity statistics. The measured density of 1.17 g/cm^3 agrees well with the calculated density of 1.16 g/cm^3 for Z = 2 molecules per unit cell. Three-dimensional intensity data were collected on a Syntex $P2_1$ automated diffractometer using monochromatized Mo Kα radiation (λ = 0.71069 Å). The θ–2θ scan technique was used to measure 1178 unique reflections within the range $0° < 2\theta < 45°$ of which 1039 reflections were considered observed [$I > 1.25\sigma(I)$]. Lorentz and polarization corrections were applied to the data. The structure was solved using the Multan program package,[15] which employs a multiple solution–tangent refinement method. The 22 nonhydrogen atom parameters were refined with anisotropic temperature factors by a full matrix, least-squares technique. All 23 hydrogen atoms were located in difference Fourier maps and refined isotropically. The final weighted and unweighted R values are 0.048 and 0.039, respectively.

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Registry No.—**4b,** 66120-45-4; **4b,** HCl, 66120-46-5; **4** picrate, 66120-56-7; **5** isomer 1, 66120-47-6; **5** isomer 2, 66120-48-7; **5** isomer 1 HCl, 66120-49-8; **5** isomer 2 HCl, 66120-50-1; **6,** 66120-51-2; **8,** 66120-52-3; **9,** 66120-53-4; **9** HCl, 66120-54-5; **11,** 66120-55-6; 2,6-lutidine, 108-48-5; acetaldehyde, 75-07-0; glutaraldehyde, 111-30-8.

Supplementary Material Available: A table of final positional and thermal parameters (3 pages). Ordering information is given on any current masthead page.

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A Simple Carbon-13 Nuclear Magnetic Resonance Spectroscopic Method for Distinguishing between Open-Chain and Pseudoacid Chlorides

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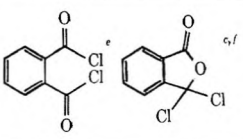
The structures of acid chlorides containing a carbonyl group at the γ position have been the subject of many reports. The possibility of the formation of cyclic forms (called pseudochlorides) of such molecules has been raised and substantiated in some cases. In many more instances, however, these structures have been postulated where evidence is weak or inconclusive. We wish to recommend a simple method that clearly distinguishes between pseudochloride and open-chain forms based on their ^{13}C magnetic resonance spectra.

The γ-diacid dichlorides are the most widely studied potential pseudochlorides. Phthaloyl chloride, for instance, has been isolated in two forms, and the higher melting isomer assigned the pseudochloride structure on the basis of dipole moment,[1] parachor,[2] and chemical reactivity.[3]

The γ-keto acid chlorides have been assigned the cyclic pseudochloride structure by chemical evidence,[4,5] infrared,[6] and ^1H NMR[7] spectroscopy.

The γ-ester acid chlorides are the group for which the evidence for the pseudochloride structure is least convincing.

Table I. ^{13}C Chemical Shifts of Aromatic Acid Chlorides

	Chemical shifts,[b] δ			
Carbon[a]				
C-1′	167.3	169.1	164.5	170.0
C-2′	167.3	104.6		
Acetate C=O			168.9	169.7
Acetate CH_3			20.7	21.0
C-1	134.3	136.0	124.3	122.2
C-2	134.3	150.6	150.5	151.3
C-3	130.1	122.8	124.3	122.3
C-4	133.4	136.3	136.1	134.8
C-5	133.4	125.6	126.4	126.1
C-6	130.1	132.0	134.2	132.5

[a] Carbons are numbered as follows: C-1 is in the aromatic ring σ bonded to a carbonyl carbon (which is C-1′); C-2 is in the aromatic ring and bears the ortho substituent (C-2′); C-3 to C-6 then follow in sequence. [b] Assignments within a column that differ by less than 1 ppm should be regarded as tentative. [c] For preparation see ref 16. [d] For preparation see ref 14. [e] Registry no. 88-95-9. [f] Registry no. 601-70-7. [g] Registry no. 5538-51-2. [h] Registry no. 50-78-2.

o-Acetoxybenzoyl chloride, for instance, has been found to exist in the open form by one set of chemical reactivity criteria[8] and to have a pseudochloride structure by another.[9] Infrared spectroscopy, in general, has given inconclusive results because of overlapping signals.[8] ^1H NMR spectroscopy has been employed to assign the open-chain structure to γ-carbomethoxypropionyl chloride on the basis of its methoxy proton signal at δ 3.66, compared to δ 3.29 for protons of this type in levulinic acid pseudomethyl ester, although the expected chemical shifts in the two pseudochlorides are not strictly comparable.[7]

Since molecules capable of existing as pseudochlorides were involved in synthetic work currently of interest in this laboratory, and because of the conflicting evidence available on the topic, the ^{13}C spectra of representative acid chlorides from each of the three groups were investigated. It was expected that π bonding and the magnetic anisotropy of the carbonyl group in the open-chain form would result in a large downfield chemical shift of this carbon signal in the ^{13}C spectra; such a large shift was not anticipated for the quaternary carbon in the pseudochloride structure.

Inspection of the first two entries of Table I substantiates this prediction. The lower melting phthaloyl chloride (entry 1) has carbonyl carbon absorptions at δ 167.3, reflecting its open-chain structure; the higher melting isomer (entry 2) has absorptions at δ 169.1 and 104.6, due to the carbonyl and quaternary carbons, respectively, in the cyclic pseudochloride structure. Moreover, the symmetry of the open-chain structure is revealed by having only three absorptions for the ring carbons; the nonsymmetrical pseudochloride has six additional peaks.

Clear evidence for the pseudochloride nature of levulinic acid chloride (entry 1, Table II) is seen in the ^{13}C spectrum, where only one carbonyl resonance is seen at δ 174.4. The resonance assigned to the quaternary carbon of the pseudochloride structure is again seen at δ 104.6, further substantiating the prediction made above.

Succinyl chloride (entry 2, Table II) is found to exist in the open-chain form, both on symmetry grounds (since only two resonances are seen in its ^{13}C spectrum) and by the chemical shift argument (the carbonyl resonance appears only at δ

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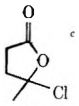
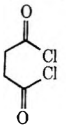
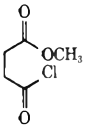
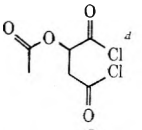
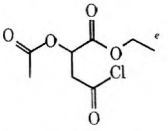
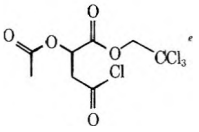
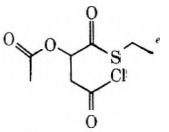
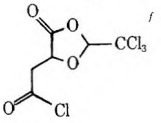
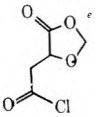
Table II. ^{13}C Chemical Shifts for Aliphatic Acid Chlorides

Structure[a]	Registry no.	Chemical shifts,[b] δ							
		C-1	C-2	C-3	C-4	Acetate		Other	
	40125-55-1	174.4	39.7	28.1	104.6			31.0 (CH_3)	
	543-20-4	172.3	41.6	41.6	172.3				
	1490-25-1	171.2	29.1	41.7	172.8			51.9 (Me ester)	
	65995-77-9	169.5	73.6	46.7	169.3	169.9	20.0		
	65995-82-6	167.5	67.4	47.5	169.5	169.9	20.1	62.2	13.8
	65995-78-0	166.2	66.9	47.1	169.4	169.6	20.1	74.5	105.3
	65995-79-1	106.9	73.3	48.0	169.2	169.6	20.4	23.2	14.2
	65995-80-4	170.8	70.8	47.3	169.0			122.1	105.0
	65995-81-5	171.0	69.1	46.9	169.1			95.2	

[a] Carbons are numbered as follows: C-1 of levulinate is the carbonyl carbon; C-2 of malate derivatives is σ bonded to an oxygen; C-1 of γ-carbomethoxypropionyl chloride is the ester carbonyl. [b] Assignments for a given compound that differ by less than 1 ppm should be regarded as tentative. [c] For preparation see ref 17. [d] For preparation see ref 18. [e] For preparation see ref 19. [f] For preparation see ref 20.

172.3, and there is no resonance between δ 80 and 120). This substantiates previous work,[1,2,4,10,11,12] in which only the open-chain form has been found.[13,14]

According to the ^{13}C spectrum, *o*-acetoxybenzoyl chloride (entry 3, Table I) exists as an open-chain structure, since two carbonyl resonances are seen at δ 164.5 and 168.9, and no signal is observed between δ 80 and 120. The signal at δ 164.5 is assigned to the acid chloride carbonyl carbon by comparison to the parent acid (entry 4, Table I). The chemical shift change of 6 ppm upfield from acid to acid chloride is similar to that found in other cases.[15]

The other entries in Table II are ester acid chlorides, all capable of existing in pseudochloride form. The ^{13}C NMR data show that each has an absorption in the carbonyl region (δ 169–170) for the acid chloride and none in the δ 80–100 region; thus all exist as open-chain structures.

The ^{13}C NMR technique thus provides a method for distinguishing between pseudo- and open-chain chlorides, which is capable of observing the presence of even a small fraction of the tautomeric structure.

Experimental Section

Samples for analysis were prepared in $CDCl_3$ at 5–10% (w/v) concentrations with Me_4Si (0.1%) as internal standard. Sample temperature during irradiation was maintained at 300 K. ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer operating at 22.63 MHz in the pulsed Fourier transform mode with a deuterium lock. Free induction decay data were accumulated using 8192 data points for a sweep width of 5000 Hz and processed with a Nicolet 1089 computer. Data were acquired both with and especially without simultaneous broad band irradiation of protons at 90 MHz in order to intensify the carbonyl and quaternary carbon signals, relative to other signals. Carbon nuclei were pulsed with a 90° tilt angle using a 40-μs pulse; the interval between pulses was often 60 s or more. Accumulations were continued until the signal/noise ratio on the least intense peak was at least 20:1 using spectral smoothing amounting to line broadening of 1 Hz. Thus it would be expected that signals from tautomeric structures comprising 5% or more of the sample would have been observed. Chemical shift assignments were made by single-frequency off-resonance decoupling experiments, single-frequency proton irradiation, and reference to other compounds.[15] These methods allowed unequivocal assignments for all but aromatic or carbonyl carbons. Such resonances were assigned by comparison

within the series, so that uncertainty exists only for those signals differing by less than one part per million.

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Synthesis and Thermal Rearrangements of Methylenecyclobutanes

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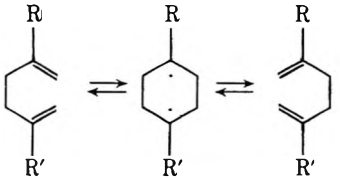
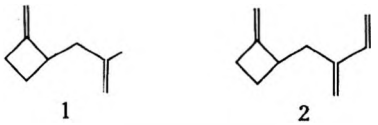
The Cope and Claisen rearrangements play a prominent role in contemporary synthetic organic chemistry; an understanding of the influence of substituents on the rate and mechanism of these reactions is of considerable importance.[1,2] Relatively few quantitative studies of this type, however, are available.[3] The influence of substituents at the 2 and 5 positions of 1,5-hexadiene is particularly important in the long-standing question regarding the possible intervention of 1,4-diradical intermediates in [3,3] sigmatropic rearrangements (eq 1).[4] We report here the synthesis and thermal re-

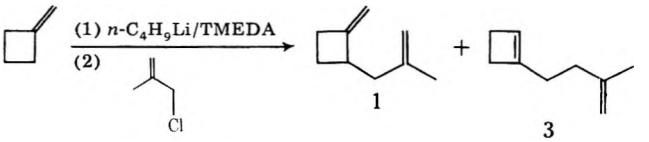


(1)

arrangements of methylenecyclobutanes **1** and **2**; a kinetic analysis of their thermal chemistry permits us to document the influence of a vinyl substituent in the Cope rearrangement.



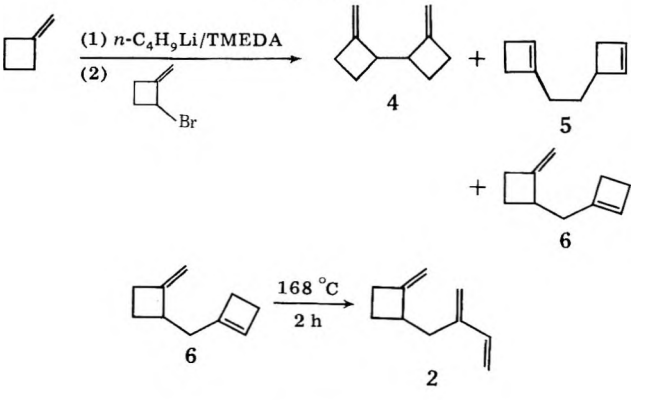
2-(2-Methyl-2-propenyl)methylenecyclobutane (**1**) was prepared by the reaction of 1-cyclobutenylmethyllithium with methallyl chloride.[5] The products (90%) consist of a mixture of isomers (**1**/**3**) in a ratio of 85:15. Pure **1** was isolated by



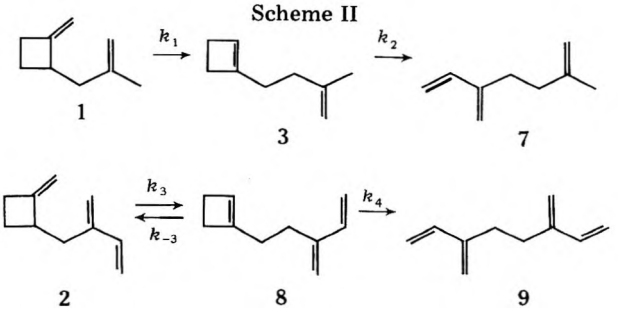
preparative VPC. Compound **2** was obtained by the procedure outlined in Scheme I. Condensation of 2-bromomethylenecyclobutane with 1-cyclobutenylmethyllithium results in the formation of three isomeric $C_{10}H_{14}$ hydrocarbons, **4**–**6**.[6] The unsymmetrical coupling product 2-(1-cyclobutenylmethyl)-methylenecyclobutane (**6**), when heated for 2 h at 168 °C, yields triene **2** and two additional isomeric olefins (vide infra).

Thermolysis of methylenecyclobutanes **1** and **2** initiates the sequence of rearrangements shown in Scheme II. Both Cope rearrangement products (**3** and **8**) react further via electrocyclic ring opening to produce polyenes **7** and **9**. During the course of our investigations it was noted that the rearrangement of **2** occurs under significantly milder conditions than that of **1**. This observation was quantified in the following manner. The rate of Cope rearrangement of **1** (k_1) was determined by monitoring its rate of disappearance over a range of temperatures (gas phase, sealed tubes) and extrapolating, $k_1(170.6\ °C) = 5.47 \times 10^{-7} s^{-1}$. The rate of electrocyclic ring opening (**3** → **7**) was also measured, $k_2(170.6\ °C) = 5.19 \times 10^{-4} s^{-1}$.[7] The rate of Cope rearrangement of **2**, k_3, was calculated as follows. Disappearance of **2** at 170.6 °C was found to be $k_{obsd} = 3.75 \times 10^{-5} s^{-1}$. The ratio of k_4/k_{-3} was obtained from the rate of appearance of **9** and **2** during the initial stages of the reaction of **8**, $k_4/k_{-3} = 2.97$. A steady state approximation was then used to calculate k_3. The validity of this approximation was confirmed by computer simulation of concentration vs. time plots (assuming $k_2 = k_4$) using the MS1M4 program.[8] The best value for the rate of Cope rearrangement of **2** was found, $k_3(170.6\ °C) = 5.01 \times 10^{-5} s^{-1}$. Using this number to calculate the relative rate of Cope rearrangement, **2**/**1** = k_3/k_1 = 91 (170.6 °C).

Scheme I



Scheme II



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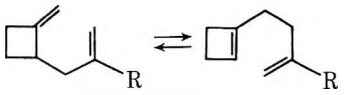
Methylenecyclobutanes 1 and 2 differ only with respect to the substituents at the 2 position of the 1,5-hexadiene chain (eq 2). The >90-fold rate enhancement resulting from sub-



(2)

1, R = CH_3
2, R = CH_2=CH

stitution of a vinyl for a methyl group ($\Delta\Delta G^{\ddagger}_{443.6}$ = 3.9 kcal/mol) implies that the Cope rearrangement of methylenecyclobutanes is quite sensitive to electron-delocalizing groups at the 2(5) position of the 1,5-hexadiene chain. The rate difference, however, is smaller than what one would expect on the basis of the relative radical stabilizing abilities of methyl and vinyl groups.

This finding is in qualitative agreement with the earlier results of Dewar and Wade,[9] who report a 69-fold rate increase at 189.8 °C when phenyl is substituted for hydrogen at the 2 position of 1,5-hexadiene. The similar response to phenyl and vinyl substituents in two disparate [3,3] sigmatropic rearrangements suggests the rate enhancement is a general phenomenon. These results are entirely consistent with, and have been interpreted in terms of,[9,10] a biradicaloid transition state that leads to a 1,4-diradical intermediate (eq 1). Electron-delocalizing groups are expected to stabilize transition states with developing unpaired electron density at the site of substitution. Implicit in this analysis, however, is the expectation that phenyl and vinyl groups will have little influence on the hypothetical pericyclic transition state.[11] This has indeed been proposed by Dewar and Wade[9] although it must be recognized that alternative explanations have been offered.[12]

Experimental Section

Infrared spectra were measured on a Perkin-Elmer 287 spectrophotometer. Only major infrared bands are given. Proton NMR spectra were recorded on either Varian A 56-60 or Bruker WH 90 spectrometers. Preparative VPC analyses were performed on a Varian Aerograph 920 gas chromatograph using a 15 ft, 30% SE-30 on 60/80 Chrom W (AW-DCMS) column at 100 °C. Analytical VPC were obtained on either a Hewlett Packard 700 laboratory chromatograph using a 10 ft, 10% Hi Eff on 60/80 Gas Chrom R column or a Hewlett Packard 5710A chromatograph equipped with a 15 ft, 8% SE-30 on 80/100 Gas Chrom Q column.

2-(2-Methyl-2-propenyl)methylenecyclobutane (1). Methylenecyclobutane[13] (9.8 mL, 100 mmol) was added over 5 min to a stirred solution of TMEDA (33 mmol), hexane (20 mL), and *n*-butyllithium (15 mL, 2.22 M, 33 mmol) at −78 °C under nitrogen. Stirring was continued at −78 °C for 15 min and then the reaction mixture was allowed to warm to room temperature. After stirring for 6 h the reaction mixture consisted of two yellow liquid phases. The mixture was cooled again to −78 °C, and 3-chloro-2-methylpropene (1.49 g, 16.5 mmol) in hexane (5 mL) was added over a 30-min period with stirring. The cold bath was removed, and the reaction mixture was stirred at room temperature for 3.5 h before it was quenched with saturated NH_4Cl (10 mL). The organic layer was washed (5% HCl, 3 × 10 mL), dried (Na_2SO_4), and then concentrated by distillation. Analysis and product isolation was performed by VPC. Two isomers were obtained in 93% yield; in order of elution, 2-(2-methyl-2-propenyl)methylenecyclobutane (1) [IR ($CDCl_3$) 3088, 2985, 2940, 2925, 1673, 1651, 1449, 1429, 1377, 872 cm^{-1}; NMR ($CDCl_3$) δ 1.7 (s, 3 H), 1.8–2.8 (m, 6 H), 3.0 (m, 1 H), 4.67 (br s, 4 H)] and 1-(3-methyl-3-butenyl)cyclobutene (3) [IR ($CDCl_3$) 3075, 3040, 2925, 2845, 1648, 1628, 1445, 1372, 874, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.70 (s, 3 H), 2.12 (s, 4 H), 2.40 (s, 4 H), 4.65 (br s, 2 H), 5.65 (s, 1 H)]. The ratio of products 1/3 was 85:15.

Reaction of 1-Cyclobutenylmethyllithium with 2-Bromomethylenecyclobutane. In a similar manner 2-bromomethylenecyclobutane (0.95 g, 6.5 mmol)[14] was added to 1-cyclobutenylmethyllithium (one-half scale). After workup and distillation, the residue was vacuum transferred. Analysis and isolation were performed as before by preparative VPC. Three isomeric $C_{10}H_4$ hydrocarbons were formed in 85% overall yield; their relative yields, in order of increasing retention time, are 4 (22.5%), 6 (45.5%), and 5 (32%). 2-(2-Methylenecyclobutane)methylenecyclobutane (4): IR ($CDCl_3$) 3072, 2980, 2940, 2920, 2882, 1670, 1450, 1425, 1405, 874 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.5 (m, 8 H), 3.1 (m, 2 H), 4.7 (br s, 4 H). 2-(1-Cyclobutenylmethyl)methylenecyclobutane (6): IR ($CDCl_3$) 3075, 3050, 2925, 2850, 1675, 1630, 1430, 1300, 1075, 874, 855 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.0 (m, 2 H), 2.0–2.9 (m, 8 H), 3.0 (m, 1 H), 4.7 (br s, 2 H), 5.7 (s, 1 H). 1,2-Bis(1-cyclobutenyl)ethane (5): IR ($CDCl_3$) 3040, 2920, 2840, 1630, 1062, 853 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (br s, 4 H), 2.35 (br s, 8 H), 5.65 (br s, 2 H).

2-(2-Methylidene-3-butenyl)methylenecyclobutane (2). 2-(1-Cyclobutenylmethyl)methylenecyclobutane (6) (11.7 mg, 0.087 mmol) was diluted with 0.7 mL of cyclohexane, degassed by several freeze–thaw cycles, and then sealed. After heating at 168 °C for 2 h, the tube was cooled, opened, and analyzed by VPC. Triene product 2 was found (81%) in addition to minor amounts of starting material (6, 3%), 5-(1-cyclobutenyl)-3-methylidene-1-pentene (8, 5%), and 3,6-dimethylidene-1,7-octadiene (9, 11%). Compound 2: IR (CS_2) 3085, 3070, 2970, 2930, 2910, 1672, 1595, 988, 900, 891, 871 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.7 (m, 6 H), 3.18 (m, 1 H), 4.75 (m, 2 H), 4.98–5.32 (m, 4 H), 6.39 (dd, *J* = 17.4 and 10.2 Hz, 1 H). Compound 8 showed the following: IR (CS_2) 3085, 3040, 2940, 2915, 1631, 1595, 988, 901, 891, 851 cm^{-1}; NMR ($CDCL_3$) δ 2.29–2.46 (m, 8 H), 5.01–5.33 (m, 4 H), 5.71 (s, 1 H), 6.39 (dd, *J* = 17.8 and 11.0 Hz, 1 H). Spectral properties of tetraene 9 are consistent with those reported.[15]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—1, 66290-31-1; 2, 66290-32-2; 3, 66290-33-3; 4, 66290-34-4; 5, 66290-35-5; 6, 66290-36-6; 8, 66290-37-7; 9, 3382-59-0; methylenecyclobutane, 1120-56-5; 3-chloro-2-methylpropene, 563-47-3; 2-bromomethylenecyclobutane, 32442-49-2; 1-cyclobutenylmethyllithium, 66290-38-8.

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(7) Compare, for example, the rate of ring opening of 1-(2-propenylcyclobutene, k(170.6 °C) = 5.04 × 10^{-4} s^{-1}: D. Dickens, H. M. Frey, and R. F. Skinner, *J. Chem. Soc., Faraday Trans. 1*, **65**, 453 (1969).
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Synthesis of Biphenyl 2,3-Oxide

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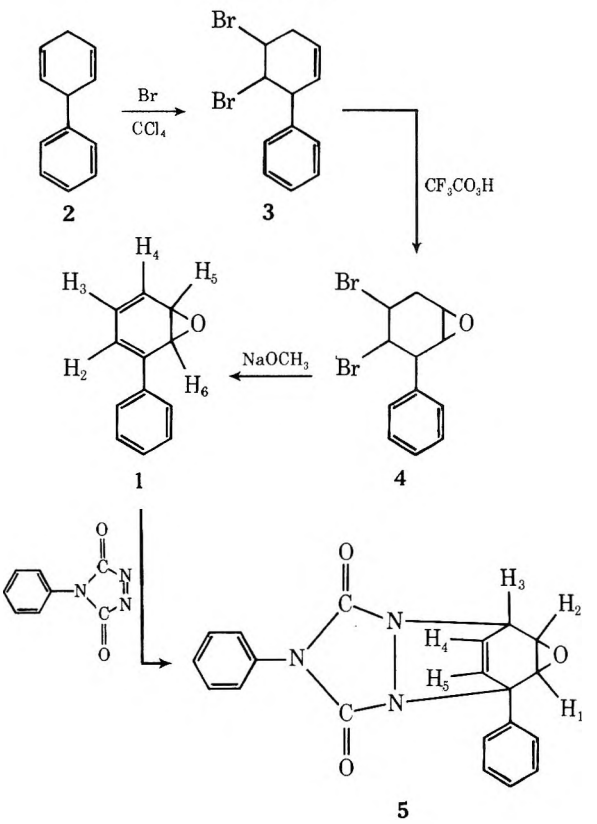
A recent study reported that the polynuclear aromatic hydrocarbons (PAH), including biphenyl, are ubiquitous pollutants which frequently reach concentrations of 0.1 ng/m^3.[1a]

Scheme I



Furthermore, biphenyl is also the parent hydrocarbon from which the polychlorinated biphenyls, widespread and persistent environmental contaminants,[1b] are derived. Since PAHs are metabolized by hepatic monooxygenases via arene oxides, some of which are mutagenic and carcinogenic,[2] we have attempted to prepare biphenyl oxides in order to study their properties. The present report describes the first synthesis of a biphenyl oxide [5,6-epoxy-1-phenyl-1,3-cyclohexadiene (1), hereafter called biphenyl 2,3-oxide].

Scheme I outlines the synthetic procedure utilized for the formation of 1. The addition of bromine to 2 resulted in an oil which analyzed for 3-phenyl-4,5-dibromocyclohexene (3). The NMR of 3 was quite complex indicating a mixture of diastereoisomers. No attempt was made to separate the diastereoisomers since the ratio of aliphatic hydrogens to aromatic hydrogens was as expected. The synthesis of 4 was accomplished using the procedure of Emmons and Pagano.[3] The NMR of 4 again showed the presence of diastereoisomers. The diastereoisomeric mixture of 4 gave the correct elemental analysis. The dehydrohalogenation of the diastereoisomeric mixture of 4 was accomplished using sodium methoxide at 0 °C. Analysis of 1 by TLC indicated the presence of a single product. Since 1 was unstable at room temperature, a Diels–Alder adduct (5) of 1 and the dienophile 4-phenyl-1,2,4-triazoline-3,5-dione was prepared and was found to have the expected elemental analysis. Compound 5 was stable indefinitely at room temperature.

The NMR spectrum of 1 (Scheme I) was obtained in tetrahydrofuran. The signal for the vinyl hydrogen H_2 appeared within the envelope of aromatic hydrogens due to the benzene ring. Multiplets at 4.27 and 4.53 ppm were assigned to the oxirane hydrogens H_5 and H_6, respectively, based on their chemical shifts[4] and on the fact that H_6 appears as a doublet of doublets while H_5 is a complex multiplet at 100 MHz. Coupling constants of 2.4 and 3.4 Hz at H_6 are due to coupling to H_2 and H_5 but are too close in magnitude to be individually assigned. Complex multiplets at 6.42 and 6.63 ppm were assigned as hydrogens H_3 and H_4. If analogy can be drawn to the spectrum of benzene oxide,[5] the signal at lower field is due to hydrogen H_3.

The instability of 1 prompted us to examine the breakdown products of 1 both in the presence and absence of water. Solutions of 1 in dry tetrahydrofuran and water were sealed and stirred for 4 h. GLPC analysis indicated that in both cases only two products were found, 2-phenylphenol and 3-phenylphenol in the ratio of 49:1.

Previously, studies of the isomerization of 3- and 4-chlorobenzene oxides established that neither arene oxide produced much 3-chlorophenol upon isomerization.[7] Since 3-chlorophenol is a metabolite of chlorobenzene in mammals, a non-arene oxide pathway was suggested to account for its formation.[8] Recent studies on the metabolism of biphenyl have shown that the ratio of 2- to 3-phenylphenol formed by liver microsomes varies from 1:1 to 2:1 depending on the species of animal studied.[9] In light of the present results which indicate that 3-phenylphenol is only a trace isomerization product from biphenyl 2,3-oxide under a variety of conditions, Billings and McMahon[9] suggested that a non-arene oxide pathway was responsible for the formation of 3-phenylphenol.

Experimental Section

NMR spectra were recorded on Varian HA-100 and Varian HR 220-MHz instruments. Mass spectra were obtained on a Finnegan 1015-D. 3-Phenyl-1,4-cyclohexadiene was obtained from the Aldrich Chemical Co. Since heating promoted decomposition of the diene, it was used without purification even though 5–10% biphenyl was present.

3-Phenyl-4,5-dibromocyclohexene (3). A solution of 3-phenyl-1,4-cyclohexadiene (3 g of crude material) dissolved in 20 mL of carbon tetrachloride was cooled to 0–5 °C. A solution of 10% bromine in carbon tetrachloride was added dropwise with stirring until the reaction mixture remained red for 30 s. A solution of sodium thiosulfate was added to decompose excess bromine. The carbon tetrachloride solution was dried and concentrated to an oil which was distilled to provide 3-phenyl-4,5-dibromocyclohexene (2.8 g, 0.009 mol) bp 150–2 °C (1.8 mm). The mass spectrum of 3 showed a parent peak at 314 and a parent +2 peak at 316. The NMR spectrum (CCl_4) was complex owing to the presence of stereoisomers. However, the ratio of aliphatic hydrogens to aromatic hydrogens was 7:5 as required. The analysis follows for the mixture of stereoisomers. Anal. Calcd for $C_{12}H_{12}Br_2$; C, 45.60; H, 3.83; Br, 50.57. Found: C, 45.83; H, 3.61; Br, 50.18.

3-Phenyl-4,5-dibromo-1,2-epoxycyclohexane (4). Peroxytrifluoroacetic acid, prepared from 15 mL of trifluoroacetic anhydride and 3 mL of 90% hydrogen peroxide, in 25 mL of methylene chloride was added dropwise with stirring to a slurry of 3 (1 g, 0.003 mol) and sodium carbonate (5 g) in 50 mL of methylene chloride. The diminution of 3 was monitored by GLPC (3% SE-30 on Gas Chrom Q at a flow rate of 80 cm^3/min, programmed from 100 to 200 °C at a rate of change of 10 °C/min). The GLPC chromatogram showed the appearance of four new peaks. The four new products were isolated by centrifuging the methylene chloride solution away from the sodium carbonate. Removal of the solvent under reduced pressure yielded a mixture of the four stereoisomers of 4 (0.63 g, 0.0018 mol, 61%). The NMR spectrum (CCl_4) of the isomer mixture was complex, but integrated for an aliphatic hydrogen to aromatic hydrogen ratio of 7:5. Anal. Calcd for $C_{12}H_{12}Br_2O$: C, 43.40; H, 3.64; Br, 48.13. Found: C, 43.21; H, 3.72; Br, 48.33.

Biphenyl 2,3-Oxide (1). In a 50 mL Erlenmeyer flask equipped with a stirrer and an addition funnel 4 (0.5 g, 0.0015 mol) was dissolved in 25 mL of dry tetrahydrofuran. The solution was cooled to 0 °C and sodium methoxide (2 g) was added slowly with stirring. Stirring was continued for 2 h, after which the reaction mixture was poured onto a column of neutral alumina. Compound 1 was eluted with tetrahydrofuran. Removal of the solvent under reduced pressure yielded 1 (0.08 g, 0.00046 mol, 31%). The 100 MHz NMR spectrum [tetrahydrofuran (D_8) at −20 °C]: 4.27 ppm (m, 1 H, H_5), 4.53 ppm (dd, 1 H, H_6), 6.42 ppm (m, 1 H, H_4), 6.63 ppm (m, 1 H, H_3), 7.40 ppm (m, 6 H, H_2 + aromatic H). The coupling constants of J = 2.4 and 3.4 Hz were observed at H_6.

On thin layer chromatography (silica gel, benzene/chloroform/ethyl acetate (1:1:1) containing 5% triethylamine) the arene oxide gave a single spot at R_f 0.4 provided the spotting area of the plate had been

pretreated with triethylamine while 2-phenylphenol chromatographed at R_f 0.2.

Direct GLPC analysis of **1** under the conditions described in the synthesis of **4** indicated that thermal isomerization occurred to a 49:1 mixture of 2-phenylphenol (2.5 min) and 3-phenylphenol (3.5 min). The same ratio of phenols was observed after **1** had completely isomerized in water (4 h) or tetrahydrofuran (4 days) at room temperature.

A Diels–Alder adduct (**5**) of **1** was prepared by adding 4-phenyl-1,2,4-triazoline-3,5-dione[6] to a solution of **1** in tetrahydrofuran. The adduct **5** was collected and recrystallized from benzene, mp 125–126 °C. The mass spectrum of **5** showed a parent peak at 345. The 220 MHz NMR spectrum ($CDCl_3$) of **5** showed H_1 3.68, H_2 3.84, H_3 5.43. H_4 6.30, H_5 6.80, and ten aromatic hydrogens at 7.3–8.2 ppm with $J_{1,2}$ = 4.2, $J_{1,5}$ = 1.4, $J_{2,3}$ = 4.4, $J_{2,4}$ = 1.1, $J_{3,4}$ = 6.0, $J_{3,5}$ = 1.4, and $J_{4,5}$ = 8.5 Hz. Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.55; H, 4.38; N, 12.17. Found: C, 69.71; H, 4.22; N, 12.21.

Registry No.—**1**, 65916-08-7; **2**, 4794-05-2; **3**, 65916-09-8; **4**, 65916-10-1; **5**, 65916-11-2; 4-phenyl-1,2,4-triazoline-3,5-dione, 4233-33-4.

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Alkylation and Silicon Pummerer Rearrangement of Chloromethyl Phenyl Sulfoxide. A Thiol Ester Acyl Anion Equivalent

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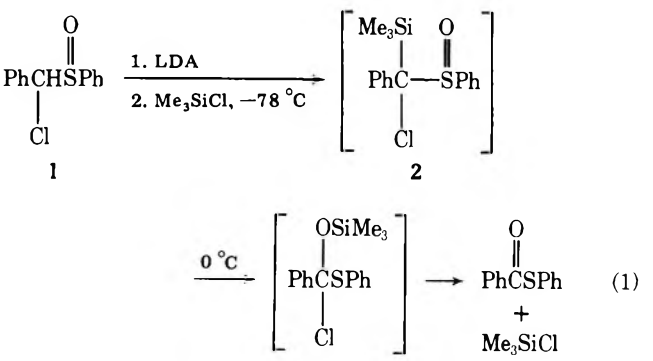
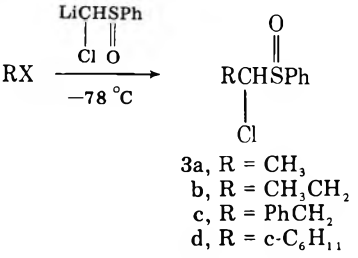
In recent years considerable attention has been given to the development of acyl anion equivalents for aldehydes, ketones, esters, and other carbonyl functions.[1] As part of a program to develop new methods for the synthesis of thiol esters, we have been interested in finding procedures for the nucleophilic introduction of the thiol ester group. We report here the first example of a carbothioate acyl anion equivalent which is capable of homolagation of alkyl halides permitting conversion to thiol ester derivatives.[2] Acyl anion equivalents that permit the introduction of a thiol ester function are of interest in view of the high relative reactivity of the thiol ester group and the potential therein for other synthetic applications.

The key step in this transformation is silicon Pummerer rearrangement[3,4] of an α-chloro sulfoxide, leading to the thiol ester involving facile elimination of chlorotrimethylsilane in the final step. This process is illustrated in eq 1, where α-chlorobenzyl phenyl sulfoxide (**1**) has been silyated with chlorotrimethylsilane at −78 °C to give **2**. Upon warming to 0 °C **2** is converted to *S*-phenyl thiolbenzoate in 74% isolated yield.[5]

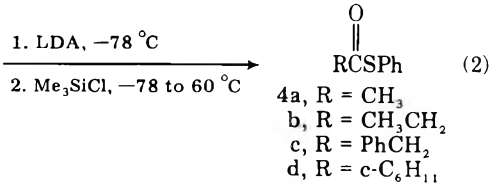


(1)

The overall transformation of alkyl halides to *S*-phenyl thiol ester homologues involves initial alkylation of chloromethyl phenyl sulfoxide followed by silicon Pummerer rearrangement of this derivative to give the thiol ester. Butyllithium induced alkylation of chloromethyl phenyl sulfoxide with chloromethylamines has been reported to occur in 40–45% yield.[6] We have found that high yields may be obtained in the alkylation of chloromethyl phenyl sulfoxide when lithium diisopropylamide (LDA) is employed as the base.[7] Alkylation of the lithiochloromethyl phenyl sulfoxide with 2 equiv of methyl iodide results in a 95% yield of a 6:4 diastereomeric mixture of α-chloroethyl phenyl sulfoxides (**3a**). Less than 4% of the bismethylation byproduct was formed according to NMR analysis of the crude reaction mixture. Primary alkyl bromides as well as secondary alkyl iodides have been employed, including ethyl bromide, benzyl bromide, and cyclohexyl iodide. With the latter two halides 1 equiv of alkyl halide was used and yields in the range of 87–90% of the diastereomeric mixture of alkylated α-chloro sulfoxide products (**3**) were produced.

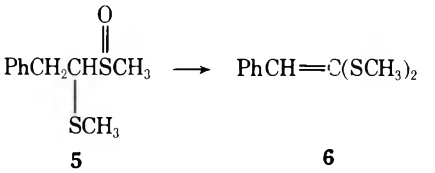


3a, R = CH_3
b, R = CH_3CH_2
c, R = $PhCH_2$
d, R = c-C_6H_{11}



(2)

4a, R = CH_3
b, R = CH_3CH_2
c, R = $PhCH_2$
d, R = c-C_6H_{11}



5 **6**

The presence of an α-halo substituent appears to be necessary in order to obtain silicon Pummerer rearrangement leading to formation of the thiol ester group. For example, it has been reported that α-methylthio sulfoxide **5** undergoes the silicon Pummerer rearrangement to give elimination product **6** in 86% yield. In a parallel reaction carried out under similar conditions on structurally related α-chloro sulfoxide **3c**, thiol ester **4c** was obtained as the major product in 60% yield. Although it is necessary to carefully dry the alkylated α-chloro sulfoxide (**3**) prior to the rearrangement step we found that careful purification of these products by column chromatography was not necessary in order to obtain ac-

0022-3263/78/1943-2713$01.00/0

ceptable yields of the corresponding thiol esters (**4**). The conversion of alkylated chloromethyl phenyl sulfoxide to thiol ester can be carried out in one pot without isolation of the intermediate α-chloro α-trimethylsilyl sulfoxide (e.g., **2**). In the reaction of **1**, following silylation at −78 °C, warming to 0 °C was sufficient to obtain rearrangement (eq 1). However, with the alkylated chloromethyl phenyl sulfoxides (**3**) obtained from methyl iodide, benzyl bromide, ethyl bromide, and cyclohexyl iodide, refluxing at 60 °C for 2 h was required in order to obtain a satisfactory yield of thiol ester (**4**) (eq 2). In these reactions minor amounts of other products were produced, including some that according to NMR retained the trimethylsilyl substituent; however, attempts to isolate these compounds were unsuccessful due to their low relative stability.

Experimental Section[8]

***S*-Phenyl Thiolbenzoate.** α-Chlorobenzyl phenyl sulfoxide (**1**;[9b] 1.25 g, 5.0 mmol) in THF (2 mL) was added dropwise with stirring over a 3-min period to lithium diisopropylamide (5.0 mmol, prepared from 0.50 g of diisopropylamine and 3.2 mL of 1.58 M *n*-BuLi in hexane at 0 °C) in THF (10 mL) under a nitrogen atmosphere at −78 °C. It was stirred at −78 °C for 30 min and then the anion solution was transferred to excess chlorotrimethylsilane (1.62 g, 15 mmol) in THF (10 mL) at −78 °C dropwise with stirring over a 5-min period. The reaction mixture was allowed to warm to 0 °C. After stirring for 1 h at 0 °C, 2% hydrochloric acid (5 mL) was added dropwise and the mixture was extracted with dichloromethane (3 × 40 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the product as a yellow solid. This was crystallized from hexane–ether to give white crystals (0.790 g, 74%): mp 54–55 °C (lit.[10] 55–56 °C); NMR ($CDCl_3$) δ 8.50–7.85 (m, 2 H), 7.60–7.20 (m, 8 H); IR (KBr) 1685 cm^{-1}.

Alkylation of Chloromethyl Phenyl Sulfoxide. A solution of lithium diisopropylamide (15 mmol) in THF was prepared under nitrogen by addition of 6.8 mL of 2.2 M *n*-butyllithium in hexane to a solution of 1.52 g of diisopropylamine in THF (15 mL) at −78 °C followed by stirring at −78° for 15 min. To this was added dropwise (5 min) with stirring a solution of chloromethyl phenyl sulfoxide[9] (2.61 g, 15 mmol) in THF (3 mL). The resulting light yellow solution was then allowed to stir at −78 °C for 30 min. At this point a solution of the alkyl halide (1 equiv of benzyl bromide or cyclohexyl iodide was used while 2 equiv of the more volatile methyl iodide or ethyl bromide were used) in THF (3 mL) was added and stirring was continued for 30 min at −78 °C before the ice bath was removed and the reaction was allowed to warm to room temperature. Stirring was continued for 45 min at room temperature before the reaction was stopped by pouring into a 2% HCl–ice mixture. The product was extracted with methylene chloride (3 × 50 mL) which was dried (Na_2SO_4) and concentrated to give the product as an oil. 1-Chloroethyl phenyl sulfoxide (**3a**; 95% yield) as well as 1-chloropropyl phenyl sulfoxide (**3b**; 95% yield) were further dried by short-path distillation under reduced pressure. 1-Chloro-2-phenylethyl phenyl sulfoxide (**3c**; 87% yield) and α-chlorocyclohexylmethyl phenyl sulfoxide (**3d**; 90% yield) were dried by allowing them to stand overnight under reduced pressure (1 mm) at room temperature. In all cases a mixture of both diastereomers was obtained. After drying, this mixture was used directly without further purification in the silicon Pummerer rearrangement to form the corresponding thiol esters.

The diastereomeric mixture (6:4) of 1-chloroethyl phenyl sulfoxides (**3a**) obtained using methyl iodide as the alkylating agent was separated by column chromatography on silica gel, eluting with benzene–ethyl acetate (9:1). The first isomer obtained from the column gave the following NMR data ($CDCl_3$): δ 7.85–7.30 (m, 5 H), 4.50 (q, 1 H, J = 7 Hz), 1.82 (d, 3 H, J = 7 Hz). The second isomer eluted from the column was the major isomer: NMR ($CDCl_3$) δ 7.80–7.30 (m 5 H), 4.70 (q, 1 H, J = 7 Hz), 1.58 (d, 3 H, J = 7 Hz). This second isomer gives the same NMR data as that isolated in the reaction of ethyl phenyl sulfoxide with sulfuryl chloride.[9b]

Conversion of Alkylated Chloromethyl Phenyl Sulfoxides to Thiol Esters. To a solution of lithium diisopropylamide (5 mmol) in THF (10 mL) under nitrogen at −78 °C was added a solution of the alkylated chloromethyl phenyl sulfoxide (**3**; 5 mmol) in THF (2 mL) dropwise over a period of 2 min. This was allowed to stir at −78 °C for 30 min. The resulting anion solution was then added dropwise (5 min) to chlorotrimethylsilane (2.7 g, 2.5 mmol) in THF (10 mL) at −78 °C. The reaction was allowed to warm to room temperature (30 min) and then warmed slowly (1 h) to reflux (60 °C). Refluxing was continued for 2 h before the reaction was stopped by cooling to room temperature, followed by addition to a mixture of 2% HCl and ice. The product was extracted with ether (3 × 50 mL) and dried (Na_2SO_4) and the ether concentrated to give an oil which was immediately subjected to column chromatography on silica gel eluting with benzene–hexane (1:1). In this manner the following thiol esters (**4**) were prepared.

S-Phenyl thiolacetate (**4a**) was obtained from 1-chloroethyl phenyl sulfoxide (**3a**) in 63% yield following short-path distillation [bp 65 °C (1 mm); lit.[10] bp 95 °C (7 mm)]: NMR ($CDCl_3$) δ 7.33 (s, 5 H), 2.31 (s, 3 H); IR (film) 1700 cm^{-1}.

S-Phenyl thiolpropionate (**4b**) was obtained from 1-chloropropyl phenyl sulfoxide (**3b**) in 62% yield following short-path distillation [bp 90–95 °C (bath temp) (1 mm); lit.[11] bp 170–180 °C (10 mm)]: NMR ($CDCl_3$) δ 7.22 (s, 5 H), 2.62 (q, 2 H, J = 8 Hz), 1.15 (t, 3 H, J = 8 Hz); IR (film) 1705 cm^{-1}.

S-Phenyl phenylthiolacetate (**4c**) was obtained from 1-chloro-2-phenylethyl phenyl sulfoxide (**3c**) as a light yellow solid in 60% yield after column chromatography on silica gel. White crystals were obtained after crystallization from hexane: mp 39 °C (lit.[10] mp 40 °C); NMR ($CDCl_3$) δ 7.31 (s, 5 H), 7.28 (s, 5 H), 3.85 (s, 2 H); IR (KBr) 1700 cm^{-1}.

S-Phenyl cyclohexanecarbothioate (**4d**) was obtained from α-chlorocyclohexylmethyl phenyl sulfoxide (**3d**) in 58% yield following short-path distillation [bp 130–140 °C (bath temperature) (3 mm): NMR ($CDCl_3$) δ 7.12 (s, 5 H), 2.8–2.4 (m, 1 H), 2.1–1.1 (m, 10 H); IR (film) 1705 cm^{-1}].

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Registry No.—**1**, 21128-89-2; **2**, 66102-71-4; **3a** isomer 1, 66102-72-05; **3a** isomer 2, 66102-73-6; **3b** isomer 1, 66102-74-7; **3b** isomer 2, 66102-75-8; **3c** isomer 1, 66102-76-9; **3c** isomer 2, 66102-77-0; **3d** isomer 1, 66102-78-1; **3d** isomer 2, 66102-79-2; **4a**, 934-87-2; **4b**, 18245-72-2; **4c**, 18245-74-4; **4d**, 58587-03-4; *S*-phenyl thiolbenzoate, 884-09-3; chloromethyl phenyl sulfoxide, 7205-94-9; benzyl bromide, 100-39-0; cyclohexyl iodide, 626-62-0; methyl iodide, 74-88-4; ethyl bromide, 74-96-4.

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Reduction of Enol Phosphates to Alkenes with Titanium Metal

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The reduction of selectively generated enol phosphates (and/or enol phosphorodiamidates) by lithium metal in ethylamine (or liquid ammonia) has been demonstrated to be an exceedingly useful synthetic method for the regioselective synthesis of alkenes from ketones.[1-3] Enolate anions of the type 2A, generated under thermodynamically controlled conditions,[4] afford enol phosphates 3A upon treatment with diethyl phosphorochloridate in the presence of tetramethylethylenediamine (TMEDA). Reduction of enol phosphates 3A then produces thermodynamically more stable alkenes 4A. Enolate anions of the type 2B,[5] generated under kinetically controlled conditions, upon the addition of diethyl phosphorochloridate in TMEDA give enol phosphates 3B. Reduction of enol phosphates 3B then affords thermodynamically less stable alkenes 4B. Thus either alkene 4A or 4B can be prepared with a high degree of regioselectivity depending on how the respective enolate anions are generated.[6] We wish to report herein a new method for reducing enol phosphates to alkenes in high yield under aprotic conditions utilizing freshly prepared titanium metal.[7]

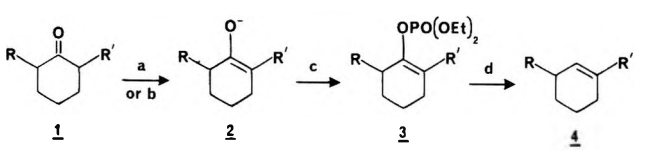
Highly activated titanium metal can be freshly prepared from anhydrous titanium(III) chloride by reduction with either magnesium[8] or potassium[9] metals in anhydrous tetrahydrofuran. The optimum stoichiometry for this reduction (eq 1) utilizes 6 to 6.6 equiv of potassium metal to prereduce 2 equiv of anhydrous titanium(III) chloride in refluxing dry tetrahydrofuran (0.75 to 1 h) followed by the addition of 3 equiv of enol phosphate and further reflux for 1 to 4 h. After cooling to 5 °C (ice bath) the reaction mixture is then quenched with 100% ethanol, filtered through silica gel, concentrated in vacuo, and either distilled or crystallized to afford the respective alkene in high yield.

$$6K + 2TiCl_3 \xrightarrow[THF]{\Delta} 2Ti \xrightarrow[\text{2. EtOH, 5 °C; 3. filter, } SiO_2\text{; 4. } -THF]{\text{1. } 3RC(OPO(OEt)_2)=CH_2,\ \Delta/THF} 3RCH=CH_2 \quad (1)$$

Table I lists the starting ketones, respective methods used to generate specific enolate anions, alkene products, yields of the enol phosphates, times for the reductions, and the respective yields for each reduction. This new reduction method is exceedingly simple and it appears to be quite general for ketones not conjugated with aromatic rings. No over reduction was observed in the case of diene products from ketones **14**, **15**, and **16**; however, the reduction of the enol phosphate derived from isobutyrophenone (**17**) proceeds very rapidly to give isobutylbenzene in 93% yield. Reduction of the enol phosphate derived from camphor (**6**) by this new method followed by quenching with deuterium oxide does not incorporate deuterium.[11]

In conclusion, this new reduction method appears to be quite general for the regioselective conversion of ketones (not conjugated to aromatic rings) to specific alkenes or dienes in excellent yields. The distinct advantages of this new reduction method over that of lithium in ethylamine are higher yields (81–100%) and utility in the regioselective synthesis of dienes. Further investigations and extentions of this reduction method are currently under investigation.

Scheme I[e]



[a] Ac_2O, $HClO_4$ (cat), CH_2Cl_2; 2 × CH_3Li, THF. [b] 1.1 × LDA, THF. [c] $ClPO(OEt)_2$, TMEDA. [d] Reduction. [e] A, R = H; R′ = CH_3. B, R = CH_3; R′ = H.

Experimental Section

Materials and Techniques. Melting points were determined on a Büchi melting-point apparatus. All melting points and boiling points are uncorrected and are reported in °C. Analytical gas-phase chromatography (GC) was performed on a Varian Aerograph Model 1400, equipped with a flame ionization detector with helium as the carrier gas using a 6 ft, stainless steel, ⅛ in. diameter column, packed with 3% SE-30 on Varaport 30, 100/120 mesh with a flow rate of 15 mL/min at ambient temperature. Silica gel PF 254 + 336 (E. Merck No. 7748) and silica gel "Baker Analyzed" reagent (60–200 mesh) were used for thin layer and column chromatography, respectively. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 237B grating infrared spectrophotometer. Spectra were taken as 10% solutions in spectroquality carbon tetrachloride or chloroform using balanced 0.1-mm sodium chloride cells or were taken as thin films between sodium chloride plates. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer in the solvent indicated. Ultraviolet (UV) spectra were recorded on a Beckman Model 26 spectrophotometer. Tetrahydrofuran (THF) and ether were freshly distilled from lithium aluminum hydride immediately before use in all reactions. Tetramethylethylenediamine (TMEDA) was freshly distilled from calcium hydride. Anhydrous titanium(III) chloride (Alfa No. 77116) was transferred under N_2 and utilized directly. All reactions were performed under an atmosphere of dry nitrogen utilizing an apparatus designed by Johnson and Schneider.[13] All equipment was dried in an oven at 120 °C for several hours prior to use then allowed to cool in a desiccator over Drierite. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. 48160.

General Method for Reduction of Enol Phosphate Esters. *cis*-Cyclopentadecene (11A).[14] Anhydrous titanium(III) chloride (0.105 g, 0.681 mmol) was stirred in THF (10 mL) and potassium metal (cut in small pieces, 0.117 g, 2.99 mg-atom) was added. This slurry was then stirred at reflux for 1 h until no trace of potassium metal was visible. The diethyl enol phosphate ester derived from cyclopentadecanone (**11**) (0.360 g, 1.00 mmol) was added and the mixture was stirred at reflux for 4 h. The reaction mixture was then cooled to 5 °C in an ice bath and quenched with absolute ethanol (1.0 mL), filtered through silica gel, and concentrated in vacuo. The pale yellow residual oil (0.223 g) was distilled to give 0.195 g (94%) of *cis*-cyclopentadecene (**11A**): bp 120 °C (0.6 mm) [lit.[14] bp 122–123 °C (1.2 mm)]; IR (thin film) 710 cm^{-1} (*cis*-CH=CH); NMR (CCl_4) δ 1.40 (s, 22 H, CH_2), 2.20 (m, 4 H, CH_2CH=CH), 5.30 (t, 2 H, CH=CH).

Method a. 1-Methylcyclohexene (4A).[10,15] 1-Acetoxy-2-methylcyclohexene (1.50 g, 9.74 mmol) was dissolved in THF (10 mL) and a trace of 2,2′-dipyridyl (0.007 g) was added. The mixture then cooled to −30 °C and methyllithium (12.5 mL, 1.6 M in ether, 20.0 mmol) was added dropwise at a rate maintaining the internal temperature of the reaction mixture below 0 °C. To the resulting red-orange solution was added diethyl phosphorochloridate (1.72 g, 10.0 mmol) and stirring was continued for 1 h. The reaction mixture was then poured into ice cold water (30 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residual oil (2.461 g) was chromatographed on silica gel to give 1.956 g (81%) of the desired enol phosphate ester as an oil: IR (thin film) 1675 (C=C), 1250, 1035, and 970 cm^{-1} (trialkyl phosphate); NMR (CCl_4) δ 1.35 (t, 6 H, J = 7 Hz, CH_3CH_2O), 1.50 (s, 3 H, CH_3), 4.10 (m, 4 H, J = 7 Hz, CH_3CH_2O). This enol phosphate ester was then immediately reduced as in the above procedure for 2 h to afford 0.628 g (83%) of 1-methylcyclohexene (**4A**): bp 109–110 °C (760 mm) [lit.[15] bp 110 °C (760 mm)]; IR (thin film) 1670, 800 cm^{-1} (CH=C); NMR (CCl_4) δ 1.40 (s, 3 H, CH_3), 5.50 (m, 1 H, CH=C).

Method b. *cis*-Cyclooctene (8A).[16] To a cold (−30 °C) solution of lithium diisopropylamide (LDA) [prepared from diisopropylamine (0.505 g, 5.00 mmol) and *n*-butyllithium (4.0 mmol, 2.0 mL, 2.0 M in

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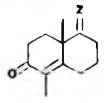
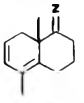
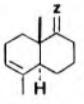
Table I

Ketone	Registry no.	Method	Alkene	Registry no.	% yield enol phosphate	Registry no.	Time (reduction),	% yield alkene	Ref
2-Methylcyclohexanone (1)	583-60-8	a	4A	591-49-1	81	30908-58-8	2	83	10
		b	4B	591-48-0	99	30908-59-5	2	90	10
4-*tert*-Butylcyclohexanone (5)	98-53-3	b	4-*tert*-Butylcyclohexene	2228-98-0	99	62845-83-4	1	100	20
Camphor (6)	76-22-2	b	2-Bornene	464-17-5	95	65898-11-5	1	81	11
Tetrahydroeucarvone (7)	4436-59-3	b	1,4,4-Trimethylcycloheptene	4755-36-6	97	65898-12-6	4	97	21
Cyclooctanone (8)	502-49-8	b	*cis*-Cyclooctene	931-87-3	97	65898-13-7	4	89	16
Cyclononanone (9)	3350-30-9	b	*cis*-Cyclononene	933-21-1	99	65898-14-8	4	92	22
Cyclodecanone (10)	1502-06-3	b	*cis*-Cyclodecene	935-31-9	97	65898-15-9	4	98	23
Cyclopentadecanone (11)	502-72-7	b	*cis*-Cyclopentadecene	34458-54-3	96	65898-16-0	4	94	14
2-Dodecanone (12)	6175-49-1	b	1-Dodecene	112-41-4	98	65898-17-1	4	95	24
2-Tridecanone (13)	593-08-8	b	1-Tridecene	2437-56-1	99	65898-18-2	4	96	24
 z = $OCH_2CH_2CH_2O$ (14)	33760-61-1	b		65898-10-4	98	65898-19-3	4	90	
		d		23931-36-4	56	23931-35-3	4	92	1
4-Cholesten-3-one (15)	601-57-0	b		4771-50-4	55	65898-20-6	1	99	12
		c		747-90-0	52	65898-21-7	1	92	12
		d		28338-69-4	48	65898-22-8	4	84	17
		e		23931-38-6	56	23931-37-5	4	84	1
Testosterone (16)	58-22-0	f		7244-00-0	48	65942-41-8	4	86	19
Isobutyrophenone (17)	611-70-1	b	Isobutylbenzene	538-93-2	100	10409-55-9	1	93	25

[a] Corresponding enol acetate, 2 to 2.2 × CH_3Li, THF, −78 to 0 °C. [b] 1.1 × LDA, THF, TMEDA (4:1), −78 to 0 °C. [c] 0.95 × LDA, THF, TMEDA (4:1), room temperature. [d] Li, NH_3, Et_2O. [e] $Li(CH_3)_2Cu$, Et_2O. [f] 2.0 × LDA, THF, −78 to 0 °C followed by 2 × $ClPO(OEt)_2$. All new compounds gave satisfactory combustion analyses.

hexane) in THF (5.0 mL)] was added cyclooctanone (0.504 g, 4.00 mmol) in TMEDA (1.25 mL) dropwise with vigorous stirring. After completion of the addition the cooling bath was removed and the mixture was allowed to warm to 0 °C. Diethyl phosphorochloridate (0.688 g, 4.00 mmol) was added and the stirring was continued for 1 h. The mixture was then poured into ice water (30 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residual oil (1.295 g) was then chromatographed on silica gel to give 1.016 g (97%) of the enol phosphate ester: IR (thin film) 1675 (CH=C), 1260, 1035, and 975 cm^{-1} (trialkyl phosphate); NMR (CCl_4) δ 1.35 (t, 6 H, J = 7 Hz, $\mathbf{CH_3CH_2O}$), 1.50 (s, 8 H, CH_2), 2.20 (m, 4 H, $\mathbf{CH_2}$C=C), 4.10 (m, 4 H, J = 7 Hz, $CH_3\mathbf{CH_2O}$), 5.45 (m, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.379 g (89%) of *cis*-cyclooctene (**8A**): bp 138–139 °C (760 mm) [lit.[16] bp 140 °C (760 mm)]; IR (thin film) 752 cm^{-1} (CH=CH); NMR (CCl_4) δ 1.50 (m, 8 H, CH_2), 2.20 (m, 4 H, $\mathbf{CH_2}$CH=CH), 5.65 (t, 2 H, CH=CH).

Method c. $\Delta^{3,5}$-Cholestadiene (15C).[12] To a solution of lithium diisopropylamide (0.048 g, 0.45 mmol) in THF (2.0 mL) at 0 °C was added slowly with stirring 4-chlosten-3-one (0.192 g, 0.499 mmol) dissolved in THF (2.0 mL) and TMEDA (1.0 mL). This mixture was then allowed to stir and equilibrate at room temperature for 3.5 h before quenching with diethyl phosphorochloridate (0.172 g, 1.00 mmol). After stirring for an additional hour at room temperature the reaction mixture was then poured into cold water (20 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residual oil (0.296 g) was chromatographed on silica gel to give 0.135 g (52%) of the desired enol phosphate ester: IR ($CHCl_3$) 1670 (CH=C), 1250, 1025, and 960 cm^{-1} (trialkyl phosphate); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, $\mathbf{CH_3CH_2O}$), 4.35 (m, 4 H, J = 7 Hz, $CH_3\mathbf{CH_2O}$), 5.40 (m, 1 H, CH=C), and 5.50 (s, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 1 h to afford 0.088 g (92%) of $\Delta^{3,5}$-cholestadiene (**15C**): mp 78.9–80.4 °C [lit.[12] mp 78.4–80.3 °C]; UV λ_{max} (EtOH) 228 (ϵ 18 300), 235 (ϵ 20 400), 243.5 nm (ϵ 13 200); IR ($CHCl_3$) 1655 (C=C), 840 cm^{-1} (CH=C); NMR ($CDCl_3$) δ 5.40 (m, 1 H, CH=C), 5.60 (m, 2 H, CH=C).

Method d. 5α-Cholest-3-ene (15D).[17] Anhydrous liquid ammonia (5 mL) was distilled through two KOH filled drying towers into a flask containing ether (2 mL). Lithium wire (0.007 g, 1.0 mg-atom) was added to the flask resulting in a dark blue solution. To this solution was added dropwise 4-cholesten-3-one (0.192 g, 0.500 mmol) dissolved in ether (1.0 mL). After the addition was completed, the ammonia was then allowed to evaporate and diethyl phosphorochloridate (0.172 g, 1.00 mmol) was added. The reaction mixture was allowed to stir for 1 h and then poured into cold water (20 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo to afford 0.207 g of a pale yellow oil. Chromatography on silica gel gave 0.125 g (48%) of the desired enol phosphate ester: IR ($CHCl_3$) 1680 (CH=CH), 1250, 1025, and 975 cm^{-1} (tri-

alkylphosphate); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, CH_3CH_2O), 4.10 (m, 4 H, J = 7 Hz, CH_3CH_2O), 5.10 (m, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.077 g (84%) of cholest-3-ene (**15D**): mp 71.5–72.5 °C [lit.[17] mp 72.0–7.25 °C]; IR ($CHCl_3$) 1660 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 5.28 (m, 1 H, CH=CH) and 5.60 (m, 1 H, CH=CH).

Method e. 5-Methyl-5β-cholest-3-ene (15E). To a solution of lithium dimethyl cuprate [prepared from purified CuI (0.190 g, 1.00 mmol) and methyllithium (1.25 mL, 2.00 mmol, 1.6 M in ether)] in ether (10 mL) at −40 °C was added 4-cholesten-3-one (0.192 g, 0.50 mmol) in ether (1.0 mL). This mixture was then allowed to warm to room temperature and diethyl phosphorochloridate (0.344 g, 2.00 mmol) was added. After stirring for 3 h at room temperature the reaction mixture was then poured into an ice-cold mixture of equal volumes of saturated aqueous NH_4Cl solution, saturated aqueous NH_4OH solution, and water. The mixture was then extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo to give 0.185 g of a yellow oil. Chromatography on silica gel gave 0.149 g (56%) of the enol phosphate ester: IR ($CHCl_3$) 1675 (C=CH), 1250, 1025, and 975 cm^{-1} (trialkyl phosphate); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, CH_3CH_2O), 4.10 (m, 4 H, J = 7 Hz, CH_3CH_2O), and 5.10 (m, 1 H, C=CH). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.090 g (84%) of 5-methyl-5β-cholest-3-ene (**15E**): mp 78–80 °C [lit.[1,18] bp 150–180 °C (0.05 mm)]; IR ($CHCl_3$) 1660 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 5.27 (m, 1 H, CH=C) and 5.60 (m, 1 H, C=CH).

Method f. $\Delta^{2,4}$-Androstadiene-17β-ol (16F).[19] To a cold (−30 °C) solution of lithium diisopropylamide prepared from diisopropylamine (0.144 g, 1.42 mmol) and n-butyllithium (0.5 mL, 1.0 mmol, 1.0 M in hexane) in THF (5.0 mL) was added testosterone (0.144 g, 0.500 mmol) in THF (1.0 mL) dropwise with vigorous stirring. After the addition was completed the cooling bath was removed and the mixture was allowed to warm to 0 °C. Diethyl phosphorochloridate (0.344 g, 2.00 mmol) was added and the stirring was continued for an additional 30 min. The mixture was then poured into water (20 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo: The resulting oil, 0.203 g, was chromatographed on silica gel to give 0.102 g (48%) of the desired enol phosphate ester: IR (thin film) 3450 (OH), 1655 (C=C), 1250, 1025, and 960 cm^{-1} (trialkyl phosphate); NMR ($CDCl_3$) δ 1.35 (t, 6 H, J = 7 Hz, CH_3CH_2O), 4.20 (m, 4 H, J = 7 Hz, CH_3CH_2O), 5.10 (s, 1 H, C=CH), and 5.40 ppm (m, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.056 g (86%) of $\Delta^{2,4}$-androstadien-17β-ol (**16F**): mp 170–171 °C [lit.[19] mp 171–173 °C]; UV (EtOH) λ_{max} 266 (ϵ 6030), 273 (ϵ 5720) nm; IR ($CHCl_3$) 3450 (OH), 1640, and 728 cm^{-1} (CH=CHCH=C); NMR ($CDCl_3$) δ 3.80 (m, 1 H, CHOH), and 5.55 (m, 3 H, CH=CHCH=C).

Acknowledgments. We graciously thank the National Institute of General Medical Sciences (Grant No. GM 18759) and the Robert A. Welch Foundation (Grant No. E-518) for the funds to support this research program.

Registry No.—$TiCl_3$, 7705-07-9; 1-acetoxy-2-methylcyclohexene, 1196-73-2; diethyl phosphorochloridate, 814-49-3.

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(4) Generation of the thermodynamic enolate anion can be accomplished either by treatment of the ketone with 0.95 equiv of lithium diisopropylamide in THF followed by an appropriate amount of time at room temperature for equilibration or treatment of the corresponding enol acetate with 2 to 2.2 equiv of methyllithium in THF: see ref 6.
(5) Generation of the kinetic enolate anion can be accomplished by treatment of the ketone with 1.1 equiv of lithium diisopropylamide in THF: see ref 6.
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Oxidation with Supported Oxidants. 2. Preparation of Sulfoxides by Alumina-Supported Sodium Metaperiodate

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Recent interest in utilizing reagents impregnated on inorganic solid supports has been proved to be successful for organic synthesis in a number of aspects, such as selectivity, reactivity, and manipulative convenience.[1-10] We have engaged in the study of selective oxidations of a variety of functional groups based on this concept. In this note we wish to report our results on a facile preparation of sulfoxides from sulfides by using sodium metaperiodate supported on acidic alumina.

The development of efficient reagents for selective oxidation of sulfides to sulfoxides has been a challenge for many years. The most commonly employed reagent for this purpose is sodium metaperiodate,[11,12] for which a careful control of reaction temperature and the quantity of oxidant is in general of necessity. The use of alumina-supported thallium(III) nitrate may circumvent such inconvenience but the reagent is toxic and is reactive toward many other functional groups, and the reaction is sensitive to steric hindrance.[10] None of these disadvantages exists, however, in the newly developed procedure using supported sodium metaperiodate.

The supported oxidant can readily be prepared by soaking the inorganic support with a hot 1.67 M solution of sodium metaperiodate and then evaporating to dryness. The oxidation is carried out simply by vigorous stirring of this solid oxidant with the solution of a sulfide at room temperature. The products were isolated by removal of the solid reagents by filtration and then evaporation of the solvent. Systematic study on some ten inorganic supports, including alumina, celite, charcoal, florisil, montmorillonite clays, and silica gel, indicated that the acidic alumina and the acidic clays, Girdler Catalyst K-10 and KO, are by far the most effective ones. The readily available chromatographic adsorbent, Merck acidic Aluminium oxide 90 for column chromatography, was then employed for the present purpose. Solvent also plays an im-

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Table I. Preparation of Sulfoxides from Sulfides by Oxidation with Alumina-Supported Sodium Metaperiodate[c]

Sulfoxide	Registry no.	Time, h	Isolated yield, %	Bp, °C (Torr) [mp, °C]
1,4-Oxathian 4-oxide	109-03-5	0.5	91	97–101 (1) [41–43]
Tetramethylene sulfoxide	1600-44-8	0.5	85	97–103 (3)
Di-*n*-butyl sulfoxide	2168-93-6	1	85	87–89 (1) [30–31]
Di-*sec*-butyl sulfoxide	13153-06-5	2.5	91	72–74 (1)
Di-*tert*-butyl sulfoxide	2211-92-9	1.5	85	[55–58]
Diallyl sulfoxide	14180-63-3	3	87	98–102 (3)
Benzyl isopropyl sulfoxide	33038-70-9	1.5	85	79–81 (1)
2-(Methylsulfinyl)ethanol	21281-74-3	0.5	67	130–133 (1) [33–35]
Methyl phenyl sulfoxide	1193-82-4	5	88	98–102 (1)
Isopropyl phenyl sulfoxide	4170-69-8	5	89	107–108 (1)
2-*exo*-Norbornyl phenyl sulfoxide[a]	65956-70-9	13	85	(38–40)
3-*endo*-Chloro-2-*exo*-norbornyl phenyl sulfoxide[a]	65956-71-0	34	85	(89–90)
Diphenyl sulfoxide	945-51-7	48	90	(69–71)
Benzo[*b*]thiophene *S*-oxide		48	0[b]	

[a] The structure was confirmed by IR, NMR, mass spectra, and satisfactory elemental analysis. [b] Recovery of starting material. [c] Registry no. 7790-28-5.

portant role in this oxidation. Ethanol (95%) was found to be superior to dichloromethane, dichloromethane saturated with water, benzene, benzene saturated with water, carbon tetrachloride, or tetrahydrofuran. An excess, 2 equiv, of the oxidant is required for complete conversion of sulfides to sulfoxides in a reasonable time. A variety of sulfides have been studied and the results are summarized in Table I. Although the yield is comparable with that which has been obtained from the oxidation with aqueous sodium metaperiodate,[11,12] in the present procedure the reaction is faster and easier to conduct.

The crude product was found to be essentially free from sulfone. Purification by the conventional distillation, recrystallization, or sublimation gave the pure sulfoxide, and the yield was in general no less than 85%. The inertness of benzo[*b*]thiophene is likely the consequence of its aromatic character. The relatively low yield, 67%, of 2-(methylsulfinyl)ethanol[13] might be due to the cleavage of the glycol-like carbon–carbon bond by sodium metaperiodate, similar to the case of thia derivatives of sugars.[15] Unsaturated functions[16] and chloro substituent can be tolerated. Unlike the oxidation of sulfides with iodobenzene dichloride[17] the electronic effect of the chloro and phenyl groups seems to be significant.

Evidently the facile oxidation of sulfides to sulfoxides with sodium metaperiodate supported on acidic alumina has the advantages of manipulative convenience, excellent yield, and wide application. Although the nature of the supported sodium metaperiodate or the principal factor responsible for its remarkable performance is not yet understood, the present method provides an additional example to illustrate the superiority of inorganic solid-supported reagents, which might soon become a new category of the most useful reagents in general organic synthesis.

Experimental Section

Preparation of the Supported Oxidant. Merck acidic Aluminium oxide 90 for column chromatography[18] (33.4 g) was added in one portion to a magnetically stirred solution of 21.4 g (0.1 mol) of sodium metaperiodate in 60 mL of water at 60 °C. The mixture was stirred for 20 min at 60 °C and then dried in a rotatory evaporator. The resulting white powder was heated at 120 °C for 16 h to get a constant weight. The concentration of the oxidant is 3 mmol on 1 g of alumina. This supported oxidant can be stored in a desiccator for months without losing its activity.

General Oxidation Procedure. To a solution of 0.05 mol of the sulfide in 50 mL of 95% ethanol was added 54.8 g (0.1 mol) of the supported oxidant in one portion at room temperature. The mixture was stirred vigorously at the same temperature until the sulfide was completely consumed, as was detected by GC analysis on a Varian Model 1420 instrument with 6 ft × $\frac{1}{8}$ in. 5% Carbowax 20M column. After filtration of the solid and removal of most of the ethanol from the filtrate, 25 mL of dichloromethane was added. The solution was dried over anhydrous sodium sulfate and the solvent was stripped off. The sulfoxide was purified by distillation, recrystallization, or sublimation. For the known sulfoxides IR and NMR spectra and bp and/or mp were found to be identical with literature data unless otherwise mentioned. For new sulfoxides satisfactory elemental analysis was obtained.

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Registry No.—1,4-Oxathiane, 15980-15-1; tetrahydrothiophene, 110-01-0; di-*n*-butyl sulfide, 544-40-1; di-*sec*-butyl sulfide, 626-26-6; di-*tert*-butyl sulfide, 107-47-1; diallyl sulfide, 592-88-1; benzyl isopropyl sulfide, 770-34-3; 2-(methylthio)ethanol, 5271-38-5; methyl phenyl sulfide, 100-68-5; isopropyl phenyl sulfide, 3019-20-3; 2-*exo*-norbornyl phenyl sulfide, 24584-22-3; 3-*endo*-chloro-2-*exo*-norbornyl phenyl sulfide, 13204-36-9; diphenyl sulfide, 139-66-2.

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Regiospecificity of Organometallic Azide Attack on Citraconic Anhydride

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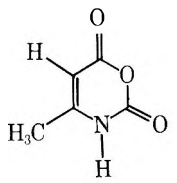
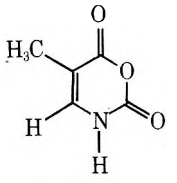
Previous work from this laboratory has shown the generality of the reaction of substituted maleic anhydrides with trimethylsilyl azide to produce the biologically important oxazinedione isostere of pyrimidinediones.[1] Obviously, the synthetic utility of this reaction relative to other routes[2] to substituted oxaziniones depends on which regioisomer, 4-X or 5-X, is obtained. Since both 4-substituted, e.g., oxaorotate,[2a] and 5-substituted, e.g., oxathymine,[2b,c] oxazinediones are of interest, our investigation centered on methods for driving the reaction toward either 4-X or 5-X. Our initial report[1b] reported exclusive production of 4-CH_3 in the reaction of citraconic anhydride with trimethylsilyl azide in chloroform. The subsequent report by Skoda[2b] of a mixture of 4-CH_3 and 5-CH_3 oxazinediones in this reaction caused a reexamination of our procedure.



4-CH_3

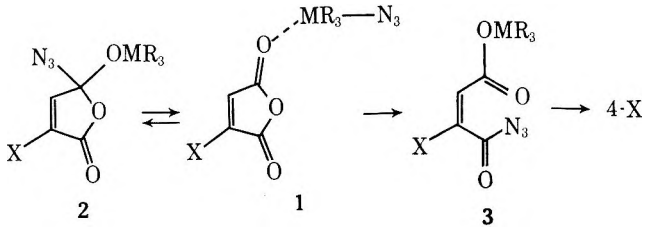


5-CH_3

Since the olefinic ^1H NMR resonances of 4-CH_3 (δ 5.41) and 5-CH_3 (δ 7.35) are well separated, the reaction may be easily monitored by NMR spectroscopy. The crude oxazinedione fraction obtained by ethanolysis of the reaction mixture contains a 7:3 ratio of 4-CH_3 and 5-CH_3 products. In our previously used[1b] recrystallization solvent ethyl acetate, 5-CH_3 remains in the mother liquors. Not surprisingly, a zealously recrystallized analytical sample was pure 4-CH_3. When chloroform is used as recrystallization solvent, 5-CH_3 is less soluble and can be selectively crystallized.

In attempts to selectively produce either regioisomer, we varied solvent and organometallic azide. Rather discouragingly, where there is any measurable yield, a 2:1 mixture of 4- and 5-CH_3 is produced. Me_3SiN_3 in dioxane (80 °C, 2.5 h) or the bulkier triethylsilyl azide (neat, 70 °C, 4.5 h) gave the same isomer distribution, but only 10–17% yield. Triethylsilyl azide in benzene, or triphenylsilyl azide either neat or in chloroform, totally failed to react. Sodium azide in dioxane, HMPT, DMF–benzene, or even dioxane with 10 mol % of trimethylsilyl azide as catalyst also failed to react.

For all substituted maleic anhydrides[1b,c] the 4-X oxazinedione, *the product of attack at the more hindered carbonyl*, is the major regioisomer, regardless of the electronic nature of X (halogen, aryl, or alkyl). This observation is best rationalized by assuming that the reaction is initiated by complexation of azide at the less hindered carbonyl of **1**,[8] followed by preferential attack of N_3 on the other carbonyl, leading irreversibly to oxazinedione. Addition generating **2** is reversible while that leading to acyl azide **3**[1b] is not.



2 **1** **3**

The reaction of simple carbonyls with Me_3SiN_3 is slow.[3] The reduced yield with Et_3SiN_3 and the nonreactivity of Ph_3SiN_3 and NaN_3 are in agreement with their lessened ability, relative to Me_3SiN_3, to complex with carbonyls. Triphenylsilyl azide, for example, is unreactive with acyl halides under conditions where trimethylsilyl azide reacts smoothly.[4]

Tri-*n*-butylstannyl azide, a recently proposed[5] alternative to trimethylsilyl azide, afford somewhat better yields of oxazinedione (up to 47%), but with hardly any regiospecificity. The facility with which tin expands its coordination sphere[6] and the demonstration that 1,8-bis(trimethylstannyl)-naphthalene is less crowded than its silicon analogue[7] imply that an organotin can complex readily with citraconic anhydride.

In conclusion, although none of the organometallic azides studied produces a single regioisomer from citraconic anhydride, for maximum yield and ease of workup tri-*n*-butylstannyl azide is the reagent of choice for conversion of maleic anhydride to oxazinediones. For synthesis of regioisomeric oxazinediones, the β-keto ester route[2a] is preferred.

Experimental Section

General Comments. ^1H NMR spectra were determined on Varian XL-100-15 and Perkin-Elmer R-32 spectrometers using internal Me_4Si as a standard. Silyl azides were purchased from Petrarch Systems, Inc., Levittown, Pa. Column chromatography (silica gel Woelm Activity I) and thin-layer chromatography (silica gel GF) were performed with ethyl acetate as eluent. Solvents were dried over Linde 4A molecular sieves. Ratios of 4- and 5-methyloxazinedione product were determined by careful NMR integration of the olefinic hydrogen resonance.

Citraconic Anhydride with Trimethylsilyl Azide in Chloroform. The previously reported procedure[1b] was modified to maximize the isolated yield of 5-CH_3. By refluxing a mixture of 1 mol each of citraconic anhydride and trimethylsilyl azide in 150 mL of chloroform for 19 h and subsequent ethanolysis, 45 g (35%) of a mixture of methyloxazinediones was obtained, mp 103–120 °C. The ratio of 5-CH_3 (δ 1.80 and 7.35) to 4-CH_3 (δ 2.11 and 5.41) was 30:70. Two fractional crystallizations from $CHCl_3$ afforded pure 5-methyloxazinedione in variable yield, mp 138 °C dec (lit. 130[2b] and 134–135 °C[2d]). Recrystallization of the crude mixture from EtOAc[1b] afforded pure 4-methyloxazinedione.

Citraconic Anhydride with Tri-*n*-butylstannyl Azide. A mixture of 44 mmol of citraconic anhydride and 50 mmol of tri-*n*-butylstannyl azide[5a] in 50 mL of chloroform was heated at reflux for 3.5 h and then hydrolyzed with 0.9 mL of water. Extraction into ethyl acetate and column chromatography gave 2.61 g (47%) of methyloxazinediones; the 4-CH_3/5-CH_3 ratio was 60:40. The yield with benzene solvent was 33%; in a neat reaction the yield was 10%.

Acknowledgment. We thank Professors P. Grieco and D. Dalton for helpful discussions. The NMR spectrometer was obtained with the aid of NSF Grant CHE-76-05757.

Registry No.—4-CH_3 oxazinedione, 51440-82-5; 5-CH_3 oxazinedione, 51255-10-8; citraconic anhydride, 616-02-4; trimethylsilyl azide, 4648-54-8; tributylstannyl azide, 17846-68-3.

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1-Trimethylsilyloxy-1-cyclopropylethylene: A Useful Reagent for the Preparation of β-Cyclopropyl-α,β-unsaturated Ketones

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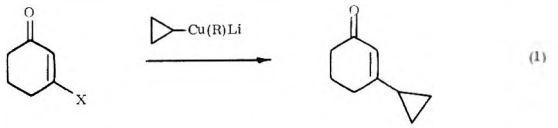
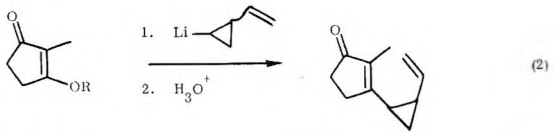
We report below the preparation of 1-trimethylsilyloxy-1-cyclopropylethylene (**1**) and its application to the synthesis of β-cyclopropyl-α,β-unsaturated ketones (vinylcyclopropanes), which are currently of interest from a synthetic viewpoint.[2] The preparation and thermal rearrangement of β-cyclopropyl-α,β-unsaturated ketones have been the subject of several recent accounts in the literature.

β-Cyclopropyl-α,β-unsaturated ketones have previously been prepared by 1,4-conjugate addition of either lithium phenylthio(cyclopropyl)cuprate or lithium dicyclopropylcuprate to β-halo-α,β-unsaturated ketones (eq 1).[2a,3] β-Vinyl-

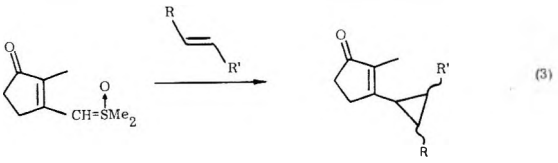


(1)



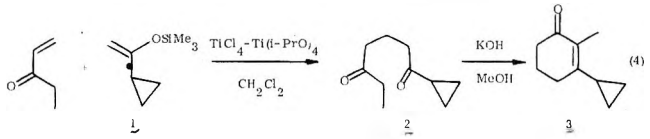
(2)

cyclopropyl enones have been prepared by 1,2 addition of 1-lithio-2-vinylcyclopropane to 3-alkoxy enones as illustrated in eq 2.[4-6] Finally, Marino has reported a route to functionalized β-cyclopropyl enones employing 2-methylcyclopentenone 3-dimethylsulfoxonium methylide (eq 3).[7]



(3)

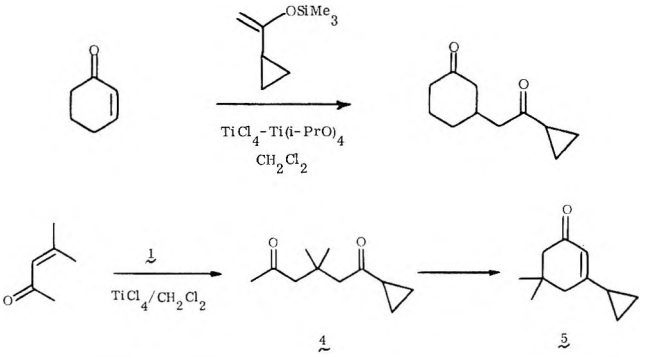
We wish to report an efficient, convenient two-step synthesis of β-cyclopropyl enones which complements existing synthetic methodology. Our method employs the 1,4 addition of 1-trimethylsilyloxy-1-cyclopropylethylene (**1**) to Michael acceptors followed by aldol cyclization. The method as applied to α,β-unsaturated ketones is depicted in eq 4.



(4)

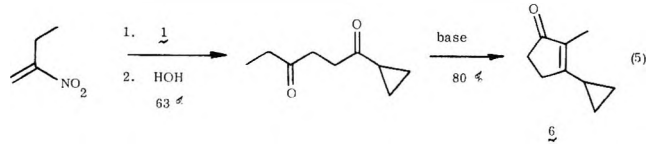
The required 1-trimethylsilyloxy-1-cyclopropylethylene (**1**) can, in principle, be prepared directly by silylating cyclopropyl methyl ketone employing triethylamine–chlorotrimethylsilane or indirectly via silylation of its corresponding enolate employing chlorotrimethylsilane. Using the latter approach, commercially available cyclopropyl methyl ketone upon treatment at −78 °C with lithium diisopropylamide in tetrahydrofuran followed by addition of chlorotrimethylsilane gave a 78% yield after distillation of 1-trimethylsilyloxy-1-cyclopropylethylene as a colorless liquid (see Experimental Section).

In a preliminary experiment we observed the smooth Michael addition (92%) of silyl enol ether **1** to cyclohexenone in methylene chloride using 1.1 equiv of titanium tetrachloride and 0.55 equiv of titanium tetraisopropoxide.[8] Similar treatment of ethyl vinyl ketone with silyl enol ether **1** gave a 66% yield of 1,5-diketone **2**, which upon treatment with methanolic potassium hydroxide gave rise to an 83% yield of β-cyclopropyl enone **3** (eq 4). Mesityl oxide underwent a smooth reaction in 93% yield with **1** in methylene chloride employing only titanium tetrachloride. The resulting diketone **4** upon cyclization (KOH/MeOH) generated the β-cyclopropyl enone **5**.



4 5

The Michael reaction of compound **1** with 2-nitro-1-butene[9] [$TiCl_4$ (1.1 equiv)–Ti(*i*-PrO)$_4$ (0.55 equiv), methylene chloride, −78 °C] followed by aqueous treatment at 60–65 °C and aldol cyclization [KO-*t*-Bu, *t*-BuOH–benzene (2:1), 15 min] demonstrates the potential of this reaction sequence for the synthesis of β-cyclopropylcyclopentenones of type **6** (eq 5).



(5)

6

Experimental Section

All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz (Varian A-60D or T-60 spectrometer). Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (Me_4Si) (δ_{Me_4Si} 0.00 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 instrument. High-resolution spectra were recorded on a Varian MAT CH5-DF instrument.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran was distilled from lithium aluminum hydride. *tert*-Butyl alcohol was freshly distilled from potassium. Methylene chloride was passed through a column of alumina. Titanium tetrachloride was distilled prior to use.

1-Trimethylsilyloxy-1-cyclopropylethylene (1). A solution of 3.6 g (42.9 mmol) of cyclopropyl methyl ketone in 6.0 mL of anhydrous tetrahydrofuran was added dropwise over a period of 20 min to a cooled (−78 °C) solution of lithium diisopropylamide [prepared from diisopropylamine (10 mL, 72 mmol) and *n*-butyllithium (44 mL, 68 mmol)] in 70 mL of dry tetrahydrofuran. After the reaction mixture was stirred an additional 30 min at −78 °C, 12.5 mL (100 mmol) of chlorotrimethylsilane was added. Stirring was continued for 1 h. The reaction was quenched by the addition of water (10 mL) followed by 300 mL of pentane. The separated organic layer was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded a liquid which upon distillation gave 4.35 g (78%) of pure 1-trimethylsilyloxy-1-cyclopropylethylene: bp 38–40 °C (12 mmHg); IR (CCl_4) 1650 cm^{-1}; NMR (CCl_4) δ 4.02 (d, 1 H, J = 1.0 Hz), 3.91 (d, 1 H, J = 1.0 Hz), 1.25 (m, 1 H), 0.50 (m, 4 H), 0.19 (s, 9 H).

Addition of 1-Trimethylsilyloxy-1-cyclopropylethylene to Cyclohexenone. A solution of 418 mg (2.2 mmol) of titanium tetrachloride and 312 mg (1.1 mmol) of titanium tetraisopropoxide in 2.5 mL of methylene chloride was added dropwise (~10 min) to a cooled solution (−78 °C) of 198 mg (2.0 mmol) of cyclohexenone and 342 mg (2.2 mmol) of 1-trimethylsilyloxy-1-cyclopropylethylene in 7.0 mL of methylene chloride. After 45 min at −78 °C the reaction was quenched with 10% aqueous potassium carbonate solution (2.0 mL). The organic layer was diluted with 30 mL of ether, separated, and dried over anhydrous magnesium sulfate. After filtration and removal

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of the solvents in vacuo there was obtained an oil which was directly purified on 50 g of silica gel. Elution with hexane–ether (3:1) gave 333 mg (92%) of pure Michael adduct: bp 105 °C (bath temperature) (15 mmHg); IR (CCl_4) 3080, 1700, 1712 cm^{-1}; NMR (CCl_4) δ 0.64–1.00 (m, 4 H). Anal. Calcd for $C_{11}H_{16}O_2$: M^+ 180.11503. Found: M^+ 180.11523.

2-Methyl-3-cyclopropylcyclohex-2-enone (3). A solution of 418 mg (2.2 mmol) of titanium tetrachloride and 312 mg (1.1 mmol) of titanium tetraisopropoxide in 3.0 mL of methylene chloride was added dropwise over a period of 10 min to a solution of 168 mg (2.0 mmol) of ethyl vinyl ketone and 342 mg (2.2 mmol) of silyl enol ether **1** in 8 mL of methylene chloride cooled to −78 °C. Stirring at −78 °C was continued for 45 min. The reaction was quenched with 10% aqueous potassium carbonate solution and the resulting diketone was extracted with methylene chloride. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The resulting crude diketone was chromatographed on 40 g of silica gel. Elution with hexane–ether (3:1) gave 221 mg (66%) of diketone **2**: bp 75 °C (bath temperature) (16 mm Hg); IR (CCl_4) 3088, 1712, 1698 cm^{-1}; NMR (CCl_4) δ 2.7–2.2 (m, 6 H), 2.1–1.5 (m, 3 H), 1.01 (t, 3 H, J = 7 Hz), 1.0–0.7 (m, 4 H).

The above diketone (160 mg, 0.95 mmol) was treated with potassium hydroxide (84 mg, 1.5 mmol) in 4.0 mL of methanol for 16 h at room temperature. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution and the product was extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. Chromatography of the crude product on 20 g of silica gel afforded 120 mg (84%) of crystalline enone **3**: mp 35 °C (lit.[2a] mp 36–37 °C); IR (CCl_4) 3080, 1665, 1616 cm^{-1}; NMR (CCl_4) δ 1.83 (s, 3 H), 0.6–0.9 (m, 4 H).

3-Cyclopropyl-5,5-dimethylcyclohex-2-enone (5). A solution of 625 mg (3.33 mmol) of titanium tetrachloride in 6.0 mL of methylene chloride was added dropwise over a period of 15 min to a cooled (−78 °C) solution of 300 mg (3.06 mmol) of mesityl oxide and 520 mg (3.33 mmol) of silyl enol ether **1** in 15 mL of methylene chloride. After an additional 30 min at −78 °C, the reaction was quenched by the addition of a 10% aqueous potassium carbonate solution. Extraction with chloroform followed by drying ($MgSO_4$) afforded 700 mg of crude diketone which was chromatographed on silica gel. Elution with ether–hexane (1:1) gave 508 mg (93%) of pure 1,5-diketone **4**: bp 90 °C (bath temperature) (15 mmHg); IR ($CHCl_3$) 1710, 1695 cm^{-1}; NMR (CCl_4) δ 2.71 (s, 2 H), 2.57 (s, 2 H), 2.02 (s, 3 H), 1.60 (m, 1 H), 1.08 (s, 6 H), 0.82 (m, 4 H).

The above diketone (300 mg, 1.6 mmol) was treated with 108 mg (2.0 mmol) of potassium hydroxide in 2.0 mL of methanol at room temperature for 8 h. The reaction was quenched with saturated aqueous ammonium chloride solution and worked up as described above. Purification of the crude enone on silica gel gave 250 mg (93%) of pure **5**: bp 70 °C (bath temperature) (15 mmHg); IR (CCl_4) 3080, 1665, 1621 cm^{-1}; NMR (CCl_4) δ 5.78 (bs, 1 H), 2.2–2.0 (m, 4 H), 1.45 (m, 1 H), 1.08 (s, 6 H), 1.0–0.6 (m, 4 H).

2-Methyl-3-cyclopropylcyclopent-2-enone (6). A solution of 418 mg (2.2 mmol) of titanium tetrachloride and 312 mg (1.1 mmol) of titanium tetraisopropoxide in 3.0 mL of methylene chloride was added slowly (10 min) to a cooled (−78 °C) solution of 202 mg (2.0 mmol) of 2-nitro-1-butene and 342 mg (2.2 mmol) of 1-trimethylsilyloxy-1-cyclopropylethylene in 7.0 mL of methylene chloride. After 1.5 h at −78 °C, 2.0 mL of water was added and the temperature of the reaction was gradually raised to 40 °C. The reaction mixture was refluxed for 5 h. The reaction was diluted with water and the product isolated by extraction with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave crude diketone which was chromatographed on silica gel. Elution with hexane–ether (4:1) gave 194 mg (63%) of pure cyclopropyl 3-oxopentyl ketone: hp 65 °C (bath temperature) (16 mmHg); IR (CCl_4) 3085, 1718, 1700 cm^{-1}; NMR (CCl_4) δ 2.9–2.2 (m, 6 H), 1.91 (m, 1 H), 1.1–0.6 (m, 4 H), 1.03 (t, 3 H, J = 7 Hz). Anal. Calcd for $C_9H_{14}O_2$: M^+ 154.09938. Found: M^+ 154.09912.

A solution of the above diketone (100 mg, 0.71 mmol) in 1.0 mL of dry benzene was added to a solution of potassium *tert*-butoxide in *tert*-butyl alcohol [prepared from 39 mg (1.0 mmol) of potassium in 2.0 mL of *tert*-butyl alcohol]. After 15 min the reaction was quenched by addition of aqueous ammonium chloride. The product was isolated by extraction with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave the crude product, which was directly chromatographed on 15 g of silica gel. Elution with hexane–ether (4:1) afforded 80 mg (82%) of pure cyclopentenone **6**[2a,3] as an oil: bp 60 °C (bath temperature) (16 mmHg); IR (CCl_4) 3095, 1695, 1635 cm^{-1}; NMR (CCl_4) δ 0.75–1.20 (m, 4 H), 1.75 (bs, 3 H), 1.80–2.30 (m, 5 H). Anal. Calcd for $C_9H_{12}O$: M^+ 136.08882. Found: M^+ 136.08866.

Acknowledgment. This investigation was supported by a Public Health Service Grant from the National Cancer Institute (CA 13689-06).

Registry No.—**1**, 42161-96-6; **2**, 66270-49-3; **3**, 61735-56-8; **4**, 66270-50-6; **5**, 66270-51-7; **6**, 59939-09-2; cyclopropyl methyl ketone, 765-43-5; chlorotrimethylsilane, 75-77-4; cyclohexenone, 930-68-7; cyclopropyl (3-oxocyclohexyl)methyl ketone, 66270-52-8; ethyl vinyl ketone, 1629-58-9; mesityl oxide, 141-79-7; 2-nitro-1-butene, 2783-12-2; cyclopropyl 3-oxopentyl ketone, 66270-53-9.

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Reaction of Triarylvinyl Bromides with Lithium Aluminum Hydride[1]

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Theoretical calculations have shown that the direct S_N2 displacement at a vinylic carbon is energetically unfavorable[2] and it has been pointed out in a recent review[3] that such a reaction has so far not been observed. Where an inversion component in solvolytic displacements with vinylic systems has been observed, the intervention of an ion pair with shielding effects rather than a backside S_N2 displacement is suggested as the mechanism.[4] In an early study on $LiAlH_4$ reductions, Trevoy and Brown[5] proposed a general mechanism for the reaction involving a nucleophilic attack on carbon by complex hydride ions. Among the reactions reported by Trevoy and Brown was the conversion of β-bromostyrene to styrene, and if the proposed mechanism applies, this would constitute a direct displacement on a vinylic carbon. In the present work, the reactions of $LiAlH_4$ with a number of triarylvinyl bromides were studied in order to obtain some mechanistic information on this reaction.

The triarylvinyl bromides used in the present study included triphenylvinyl, tri-*p*-tolylvinyl, tri-*p*-anisylvinyl, *cis*-2-phenyl-1,2-di-*p*-tolylvinyl, and *cis*-1,2-di-*p*-anisyl-2-phenylvinyl bromides (**1**, **2**, **3**, *cis*-**4**, and *cis*-**5**, respectively). These were available from earlier studies in this laboratory on degenerate rearrangements in triarylvinyl cations generated from solvolyses with these bromides as substrates.[6] Treatment of **1**,[6a,b] **2**,[6e] and **3**[6c] with an excess of $LiAlH_4$ in ether gave the corresponding triphenylethylene (**6**), tri-*p*-tolylethylene (**7**), and tri-*p*-anisylethylene (**8**), respectively,

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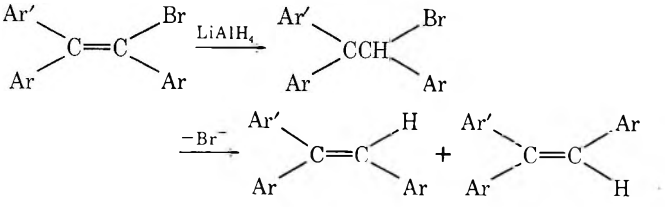
and these results are in agreement with expectations from the reported conversion of β-bromostyrene to styrene.[5] A similar treatment with *cis*-**4** or *cis*-**5** gave an essentially 1:1 mixture of the cis and trans olefins, *cis*- and *trans*-1-phenyl-1,2-di-*p*-tolylethylene (*cis*- and *trans*-**9**) from *cis*-**4** and *cis*- and *trans*-1,2-di-*p*-anisyl-1-phenylethylene (*cis*- and *trans*-**10**) from *cis*-**5**. Identification of the olefinic products in all of these reactions was made by comparison of their ^1H NMR spectra with known spectral data or with those of authentic samples prepared from dehydration of the corresponding 1,1,2-triarylethanols[6] by treatment with H_3PO_4.[7]

The formation of a mixture of *cis*- and *trans*-**9** from *cis*-**4** and *cis*- and *trans*-**10** from *cis*-**5** definitely eliminated a direct backside displacement as the mechanism for the $LiAlH_4$ reduction of triarylvinyl bromides, thus giving further confirmation to earlier conclusions that the S_N2 reaction at vinylic carbon is energetically unfavorable. The observed results, however, may be reasonably explained by an addition–elimination route[8] as shown below.



Experimental Section

Reaction of Triarylvinyl Bromide with $LiAlH_4$. A solution of 200 mg of triarylvinyl bromide **1**, **2**, **3**, *cis*-**4**, or *cis*-**5** in 25 mL of anhydrous ether was placed in a round-bottom flask fitted with a reflux condenser. $LiAlH_4$ (1.0 g) was added in small portions over a period of about 10 min. The mixture was then refluxed for 12 h and cooled in an ice bath and the excess $LiAlH_4$ was destroyed by the slow addition of 50 mL of H_2O. The ether layer was separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined ether solution was dried over $MgSO_4$ and the ether was removed, giving a residual triarylethylene in yields ranging from 50–65%. The mass spectrum of each product showed the expected molecular ion for the triarylethylene and the absence of any unreacted triarylvinyl bromide.

From bromides **1**, **2**, and **3**, the products triphenylethylene (**6**), tri-*p*-tolylethylene (**7**), and tri-*p*-anisylethylene (**8**), respectively, were crystallized from CH_3OH. Olefin **6** melted at 67–68 °C (lit.[9] mp 67–68 °C) and showed an ^1H NMR spectrum identical with that reported previously for an authentic sample of **6**.[9] Olefin **7** melted at 113–114 °C (lit.[10] mp 114 °C): ^1H NMR ($CDCl_3$) δ 2.25, 2.34, 2.37 (CH_3, 3 s), 6.8–7.2 (aromatic + C=CH, m). This spectrum was the same as that of an authentic sample of **7** prepared from the H_3PO_4 dehydration[7] of 1,1,2-tri-*p*-tolylethanol.[6e] Olefin **8** melted at 100–101 °C (lit.[7] mp 100–101 °C): ^1H NMR ($CDCl_3$) δ 3.74, 3.80, 3.83 (CH_3O, 3 s), 6.6–7.3 (aromatic + C=CH, m). These spectral absorptions were essentially the same as those reported for **8** by Rappoport et al.[11] and were identical with the spectrum of **8** prepared from dehydration[7] of 1,1,2-tri-*p*-anisylethanol.[6c]

The product from *cis*-**5** was an oil. It was identified as a mixture of *cis*- and *trans*-1,2-di-*p*-anisyl-1-phenylethylene (*cis*- and *trans*-**10**) since its ^1H NMR spectrum showed four CH_3O singlets at ($CDCl_3$) δ 3.69, 3.77 (for *trans*-**10**), and 3.71 and 3.80 (for *cis*-**10**), with the aromatic and vinyl protons at δ 6.5–7.3. The four CH_3O absorptions observed were essentially the same as those for *cis*-**10** and *trans*-**10** reported by Rappoport and Apeloig.[12] 1-Phenyl-1,2-di-*p*-tolylethylene (**9**) (stereochemistry not specified) has been prepared as an oil, bp 182–183 °C (0.01 Torr).[13] In the present work, the product from *cis*-**4** was also an oil. Its ^1H NMR spectrum showed three singlets in the CH_3 region at ($CDCl_3$) δ 2.22 (6 H), 2.30 (3 H), and 2.34 (3 H) while the aromatic and vinyl protons absorbed at δ 6.8–7.3. These data indicated that the olefinic product from *cis*-**4** was a mixture of *cis*- and *trans*-**9**, with the CH_3 absorptions at δ 2.22 and 2.30 for *trans*-**9** and at δ 2.22 and 2.34 for *cis*-**9**.

Registry No.—**1**, 1607-57-4; **2**, 66184-02-9; **3**, 25354-46-5; *cis*-**4**, 64833-13-2; *cis*-**5**, 26326-64-7; **6**, 58-72-0; **7**, 6629-83-0; **8**, 7109-27-5; *cis*-**9**, 66184-01-8; *trans*-**9**, 66184-00-7; *cis*-**10**, 26326-61-4; *trans*-**10**, 15789-91-0.

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The Triphenylmethyl Radical: Equilibrium Measurements and the Reaction with Thiophenol[1]

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Rate constants for hydrogen atom transfer reactions to organic free radicals are usually determined only by rather complex methods with considerable uncertainties. However, an incidental observation during a study of the isotope effect for the reaction of thiophenol with the triphenylmethyl radical (the trityl radical) led to an order of magnitude estimation of the rate constant. That is, the color of the radical was not instantaneously discharged upon mixing the reagents at 0 °C.[4] It was clear that a careful measurement could yield a more precise value.

At the same time, it was clear that the determination of the rate constant required values for the equilibrium constant. In order to use the earlier isotope effect work, it was necessary to use toluene as the solvent. Previous determinations had been made in benzene and other solvents, but not toluene.[5] Depending upon the method of measurement, there was also an uncertainty of a factor of 2.[5] The availability of an apparatus that would allow us to handle and accurately dispense volumes of air and moisture-sensitive solutions prompted us to remeasure the dissociation constant in toluene by spectrophotometric methods, as originally done by Ziegler.[5] The discrepancy between spectrophotometric and magnetic measurements has now been resolved.[1] It arose primarily from the diamagnetic susceptibility of the dimer. Subsequently, the same apparatus was used to measure the rate of reaction of the trityl radical with thiophenol.

Dissociation of 1-Diphenylmethylene-4-triphenylmethyl-2,5-cyclohexadiene. The measurements were made at the 516-nm maximum absorbance of the trityl radical. At this wavelength the dimer does not significantly absorb, so the absorbance in the 1-cm cell used is

$$A = \epsilon(R\cdot) \qquad (1)$$

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Table I. Equilibrium Constants for the Dissociation of the Trityl Dimer in Toluene

T, °C	$K \times 10^4$,[a] M	ϵ[a]
−5	0.516	635
0	0.808	651
10	1.49	652
20	3.09	661
30	5.86	656

[a] These values differ slightly from those in ref 1 because of the application of a correction for thermal expansion or contraction of the solvent.

where (R·) is the radical concentration. This can be related to the dimer concentration (D) and the total stoichiometric dimer concentration (D_0) as shown:

$$(D) = (D_0) - (R\cdot)/2 \quad (2)$$

The desired equilibrium constant is given by the expression

$$K = (R\cdot)^2[(D_0) - (R\cdot)/2] \quad (3)$$

Rearranging this expression and substituting for (R·) gives

$$(D_0)/A = (A/K\epsilon^2) + (1/2\epsilon) \quad (4)$$

Thus, a plot of $(D_0)/A$ vs. A should be linear with a slope of $1/K\epsilon^2$ and an intercept of $1/2\epsilon$. A plot of this sort is shown in Figure 1, corresponding to measurements made in toluene solution at 20 °C. A least-squares fit to the straight line yields $K = 3.08 \times 10^{-4}$ mol/L and $\epsilon = 661$. Determinations made at −5, 0, 10, and 30 °C were likewise satisfactorily linear. In order to extract equilibrium and extinction coefficient data, it is necessary to allow for thermal expansion or contraction of the toluene[7] since the solutions were made at room temperature and then brought to the measurement temperature. The results are presented in Table I; the extinction coefficient is 655 ± 4 L/mol cm^{-1}, and the equilibrium constants are reasonably well fitted by the equation $K = (5.56 \pm 2.66) \times 10^4 \exp[(-11\,075 \pm 130 \text{ cal/mol})/RT]$. The results differ slightly from the preliminary report[1a] because of the thermal expansion correction. From magnetic susceptibility measurements[8] there is an indication that the equilibrium constant in toluene solution should be approximately 73% as large as the equilibrium constant in benzene.[8] Applying this correction to the results of Ziegler and Ewald in benzene[5] leads to an expected value of 3×10^{-4} mol/L at 20 °C in toluene, in good agreement with the value obtained in the present work. The value of ΔH in benzene from Ziegler, 11.5 kcal/mol, is likewise in reasonable agreement considering the solvent change and the combined experimental errors.

Reaction of the Trityl Radical with Thiophenol. The reaction of the triphenylmethyl radical with thiophenol is as follows:

$$\begin{gathered} D \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2R\cdot \\ R\cdot + PhSH \overset{k_2}{\rightleftharpoons} RH + PhS\cdot \\ PhS\cdot + R\cdot \overset{k_3}{\rightleftharpoons} PhSR \end{gathered} \quad (5)$$

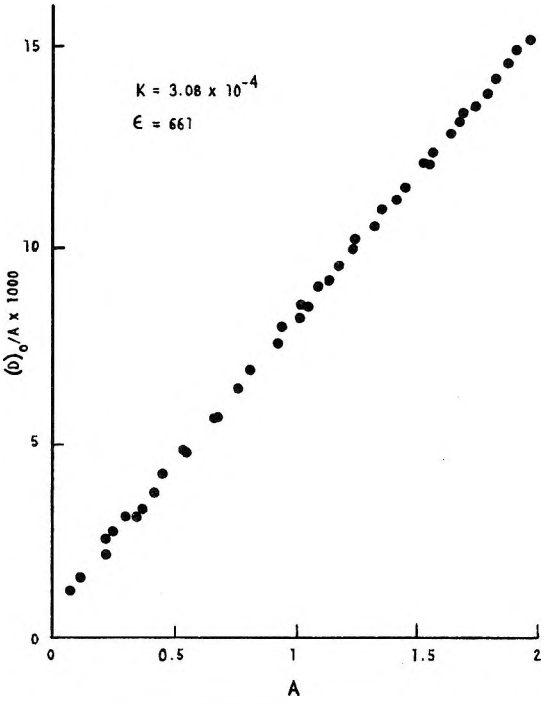

Figure 1. $(D_0)/A$ vs. A plot of dimer at 20 °C in toluene.

The reaction of the phenylthiyl radical with undissociated dimer is possible,[4] but with an insufficient amount of thiol this side reaction and the reversal of the hydrogen transfer are unimportant under the conditions employed. Assuming that a steady state in phenylthiyl radicals is achieved, the following may be derived:

$$-d(R\cdot)/dt = 2k_{-1}(R\cdot)^2 - 2k_1(D) + 2k_2(R\cdot)(PhSH) \quad (6)$$

If the initial equilibrium is fast compared to the reaction of the radical with thiophenol, the first two terms cancel, leaving a second-order expression:

$$-d(R\cdot)/dt = 2k_2(R\cdot)(PhSH) \quad (7)$$

which because of the prior equilibrium cannot be integrated in the usual way. However, it was found upon mixing solutions of the triphenylmethyl radical and thiophenol in toluene that the reaction did not proceed according to this expression. Thus, the complete eq 6 must be used. A computer was used to integrate this equation numerically by the Runge–Kutta method[9] given values for k_1, k_1, k_2, (D_0), and (S_0). From the literature values for k_1[10] and the equilibrium constants measured in this work, values for k_{-1} could be calculated. The experimental and calculated curves of the radical absorbance vs. time were compared for various values of k_2. The results presented in Table II correspond to the values of k_2 which best fit the observed curves. An example of such a determination is shown in Figure 2. The rate constants are adequately fitted by eq 8.

$$k_2 = (2.65 \pm 1.76) \times 10^7 \exp[(-9060 \pm 178 \text{ cal/mol})/RT] \quad (8)$$

Table II. Rate Constants and Isotope Effects for the Reaction of the Trityl Radical with Thiophenol

T, °C	k^H_{obsd}[a]	k^H_{calcd}[b]	k^D_{obsd}[a]	k^D_{calcd}[c]	k^H/k^D	k^H/k^D[d]
0	1.63	1.48	0.245	0.227	4.54	5.60
10	2.36	2.67	0.407	0.452	5.38	6.82
20	4.58	4.63	0.861	0.860	5.91	7.61
40	13.5	12.5	2.87	2.75	6.52	8.56

[a] In M^{-1} s^{-1}; the average of about 10 independent measurements. [b] Calculated from eq 8. [c] Calculated from eq 9. [d] Calculated using the Swain–Schaad equation from the tritium isotope effects of ref 4.

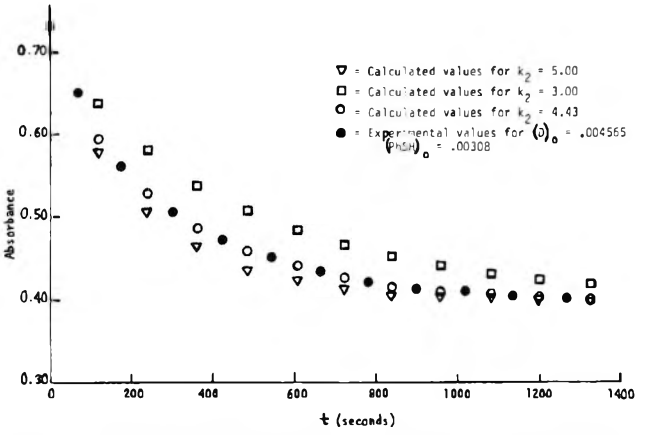

Figure 2. Typical plot of absorbance vs. time for observed and calculated values of triphenylmethyl concentration in its reaction with thiophenol in toluene.

Table II also shows results with deuterated thiophenol and the isotope effects. Since there was only 92% deuteration, the results do not have great quantitative significance; lower values than are predicted from the application of the Swain–Schaad[11] equation to the tritium isotope effects[4] are thus to be expected. The data are reasonably fit by the equations

$$k_2^D = (6.8 \pm 3.8) \times 10^7 \exp[(-10\,600 \pm 151 \text{ cal/mol})/RT] \quad (9)$$

$$k^H/k^D = 0.4 \exp(1540/RT) \quad (10)$$

The temperature dependence of the isotope effect could confirm the suggestion of tunneling[12] made from the tritium data[4] and strengthened by the more extreme result with mesityl mercaptan.[13] The incomplete deuteration makes such arguments far from compelling, but the conclusion that the reaction being followed is indeed the hydrogen atom transfer is incontrovertible.

The precision of the rate constants measured here appears to be good, perhaps within ±10%. The temperature was controlled to within ±0.1 °C except at 0 °C, where the control was ±0.2 °C. Individual runs were fit by the computer program to better than 10%, but the overall range of rate constants is sensitive to the accuracy of the earlier rate constants as well as the equilibrium constant. In work to be published in a related system, we avoid this problem.

Conclusion

The equilibrium constant for the dimerization of the triphenylmethyl radical has been measured over the temperature range of −5 to 30 °C. The values agree well with those measured in a different solvent in the same way by Ziegler but are not in agreement with the magnetic measurements in which the wrong dimer structure was used. The rate constant for the reaction of the trityl radical with thiophenol has been measured. The measurements on incompletely deuterated thiophenol confirm that the rate constants measured are indeed for the hydrogen atom transfer and are in imperfect but adequate agreement with the earlier tritium isotope effect measurements.

Experimental Section

Kinetic Measurements. The solutions for kinetic measurements were prepared using an automatic sampling system constructed by P. S. Glaspie. (The details of this apparatus are presented in ref 1b.) The device consists of two specially constructed syringes driven by reversible motors acting on precision screws. A disc with a number of evenly spaced holes is attached to the back of each screw. This chops the beam of light between a light-emitting diode and a phototransistor. The pulses are counted using transistor–transistor logic circuits. The amount of fluid to be delivered from each syringe is independently preset. The device causes the delivery of a predetermined amount from each syringe and automatically refills the syringes from a reservoir. Each syringe delivers its fluid through a glass capillary tip into a thermostatted cell in a Cary 14 spectrophotometer. The temperature was measured using a Wheatstone bridge and a calibrated thermistor which extended into the solution in the cell. Argon gas was used continually to sweep the cell compartment.

Materials. Commercial triphenylmethyl chloride (Aldrich) was recrystallized from acetyl chloride, mp 113–114 °C (uncor) (lit.[15] mp 112.5–113 °C). Toluene was dried over Linde 4A molecular sieves and bulb-to-bulb distilled immediately before use. Acetone was refluxed with potassium permanganate until the purple color persisted for hours. It was then distilled under nitrogen onto 4A molecular sieves and bulb-to-bulb distilled.

1-Diphenylmethylene-4-triphenylmethyl-2,5-cyclohexadiene. Under a vigorous nitrogen flow, mercury (46 g, 0.228 mol) was added to a solution of 15.9 g (0.057 mol) of triphenylmethyl chloride in 150 mL of purified acetone in a 250-mL flask equipped with a vacuum stopcock. The flask was pumped on for several minutes and the stopcock closed. It was stirred magnetically overnight in the dark. The flask was then placed in a glovebag which was purged with argon at least six times. The flask was opened, and the mixture was filtered to remove excess mercury and mercurous chloride and concentrated to 40 mL. The resulting solid was collected on a sintered glass filter. After recrystallizing in a similar manner five times from purified acetone, the white solid, mp 152–153 °C (uncorr) (lit.[16] mp 150–152 °C), was then placed in an ampule fitted with a vacuum stopcock. The ampule was evacuated, removed from the glovebag, and sealed. Due to the light sensitivity of the triphenylmethyl radical in solution, the above procedure was performed in a darkened room. This procedure is an adaptation of that used by Leftin and Lichtin.[15]

An alternative procedure is the use of an apparatus similar to that of Dorfman.[17] Essentially, it is a large scale Schlenk tube. The apparatus consisted of two 500-mL round-bottom flasks whose necks had been extended. The necks were joined by a short length of 25-mm tubing containing a sintered glass disc. One of the flasks was fitted with a 24/40 male joint so it could be removed. Rather than opening the flask containing the radical solution in a glovebag, it was opened by pressurizing it with argon and filtered directly into the recrystallizer. One neck was stoppered, the other was fitted with a vacuum stopcock, and the system was evacuated and closed off. By tilting the apparatus, the radical solution was filtered through the glass disk into the other flask. The acetone was then bulb-to-bulb distilled back into the other flask until the dimer precipitated out. The slurry was then filtered through the disk. Fresh acetone was distilled back onto the solid, and the procedure was repeated several times. After the dimer was sufficiently pure, it was rinsed off of the disk with fresh acetone. At this point, all of the acetone was distilled into the other flask. The apparatus was placed in a glovebag. It was opened under argon, the flask containing the purified solid was removed, and the dimer was loaded into ampules as before.

Thiophenol. Reagent grade thiophenol was dried over Linde 4A molecular sieves for 10 days. The thiophenol was then decanted into a round-bottom flask and distilled under a nitrogen atmosphere taking only a small middle fraction. This procedure was repeated twice, each time taking only the middle fraction. Final distillation gives material of bp 168.5–169 °C (uncor).

Deuterium-Labeled Thiophenol. Thiophenol was refluxed with 99% D_2O for 3 h, the water was distilled out, and the procedure was repeated three times with fresh 99% D_2O. The thiophenol was then dried over magnesium sulfate for 24 h and distilled as described previously for thiophenol. Comparison of the S–H signal with the C_6H_5 signals using proton NMR spectroscopy was used to assay the protium and hence the deuterium content. The thiophenol contained 8% H on S. The step in which deuterium is lost is believed to be on drying over magnesium sulfate, and the procedure is therefore not recommended. We have since obtained thiophenol-*d* with less than 1% protium content by various distillation procedures.

Acknowledgment. Support of this work by a grant from the Robert A. Welch Foundation is gratefully acknowledged.

Registry No.—1-Diphenylmethylene-4-triphenylmethyl-2,5-cyclohexadiene, 18909-18-7; triphenylmethyl chloride, 76-83-5; triphenylmethyl, 2216-49-1; thiophenol, 108-98-5; trityl dimer, 31713-29-8.

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(b) In part from the Ph.D. Thesis of P. S. Glaspie, Rice University, 1974.
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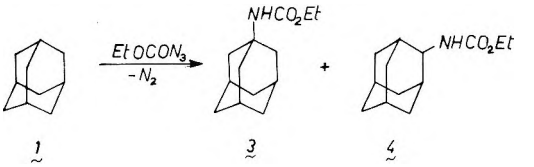
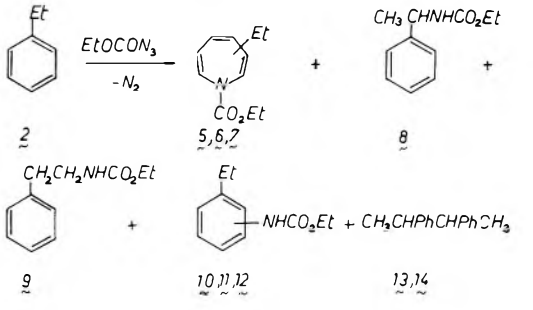
Scheme I



Scheme II



Singlet Ethoxycarbonylnitrene Stabilization by Dichloromethane. Thermolysis of Ethyl Azidoformate in Adamantane and Ethylbenzene

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Some evidence was gained in favor of the formation of a solvent–singlet ethoxycarbonylnitrene complex. It has been reported that dichloromethane,[1,2] hexafluorobenzene,[3,4] and 1,4-dioxan[5] stabilize the singlet state of EtOCON, generated by ethyl azidoformate, during the C–H insertion reaction. Quite recently Takeuchi et al.[6] discussed the situation for EtOCON generated in the THF–CH_2Cl_2–cyclohexane system and their conclusions were against a stabilizing effect during thermolysis.

We now report on some more data supporting our opinion on this matter for the thermal decomposition of $EtOCON_3$ in adamantane (**1**) and in ethylbenzene (**2**). This choice was suggested for the former hydrocarbon by the low steric hindrance for the bridgehead C–H bonds compared to that of the CH_2 groups and for the latter one by the high stability of the radical $Ph\dot{C}HCH_3$, in connection with the possibility of the triplet EtOCON participation in the C–H insertion reaction.[7] The reaction between adamantane and $EtOCON_3$ in CH_2Cl_2 has been reported and a 6.0 tertiary/secondary reactivity ratio was found.[8]

We confirmed this figure and found a 23% yield (based on ethyl azidoformate) of 1-adamantylurethan (**3**) and 2-adamantylurethan (**4**). The reactivity ratio for the thermolysis of $EtOCON_3$ in a cyclohexane solution[9] of adamantane was 4.0. In this case the absolute yield of **3** and **4** was 7% while a 11% yield of cyclohexylurethan was found. The decrease in the reactivity ratio and in the yield is in agreement with the formation of a dichloromethane–singlet nitrene complex with a steric demand larger than that of a free nitrene, and it is consistent with our first results on decalins[1] as well as with Belloli's finding on *trans*-1,2-dimethylcyclohexane.[2] In fact in the case of *cis*- and *trans*-decalin, where the tertiary C–H bonds are the most crowded ones, we observed an increased tertiary/secondary reactivity ratio when the thermolysis was run in the absence of CH_2Cl_2. The above interpretation is corroborated by the results we obtained in the photolysis of $EtOCON_3$ in a cyclohexane solution of adamantane. Under these conditions the value of reactivity ratio was 4.1 which was quite close to that (4.0) of the thermolysis in cyclohexane. Since it is known that about 30% of the photolytically generated EtOCON is formed in the triplet state, this should not be involved in the insertion reaction giving the 1- or 2-adamantylurethan.

The thermolysis of $EtOCON_3$ in ethylbenzene has been previously described by Photis[10] and azepines **5–7** were recognized as the main products. We reinvestigated the above thermolysis and compared the results with those of the thermolysis carried out in the presence of CH_2Cl_2. From careful GC analysis, GC–MS study, and comparison with authentic samples we are able to give a more complete picture of the actual situation. Observed products **5–14** are indicated in Scheme II and their relative amounts and absolute yields are shown in Table I.

N-Ethylphenylurethans **10–12** are the isomerization[11] products of azepines **5–7** in the reaction with CH_2Cl_2, as confirmed by heating the products of the thermolysis of $EtOCON_3$ in ethylbenzene after addition of CH_2Cl_2. Urethan **8** arising from EtOCON insertion into benzylic CH_2 is formed in low yield (5%) in thermolysis with CH_2Cl_2, i.e., under the stabilization conditions of the singlet ethoxycarbonylnitrene. The amount of this urethan rises to 16% in the thermolysis without solvent. It is noteworthy that the parallel increase from 6 to 23% of hydrocarbons **13** and **14** comes from the coupling of $Ph\dot{C}HCH_3$ in the absence of dichloromethane. In our opinion this trend is confirmed by the consideration that the ratio of insertion product **8** to the sum of **5, 6, 7, 10, 11,** and **12** products, derived from the singlet EtOCON addition to the benzene ring,[12] goes from 0.056 to 0.26 and seems to indicate

Table I. Thermolysis of $EtOCON_3$ in Ethylbenzene

Reaction conditions	Products, %[a]				Ratio
	5 + 6 + 7	8	10 + 11 + 12	13 + 14	8/(5 + 6 + 7 + 10 + 11 + 12)
90 °C, 15 h, CH_2Cl_2	9 (4.5)	5 (2.5)	80 (41)	6 (3)	0.056
90 °C, 15 h, neat	61 (21.5)	16 (5.5)		23 (8)	0.26

[a] Relative yields; absolute yields are given in parentheses (see Experimental Section).

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the participation of the triplet EtOCON in the insertion reaction.[13]

In conclusion, the above results indicate in both cases the formation of a dichloromethane–singlet ethoxycarbonylnitrene complex and the probable involvement of triplet EtOCON in the insertion reaction in the benzylic C–H bonds.

Experimental Section

GC analyses were performed on a Perkin-Elmer F 11 gas chromatograph equipped with a column of 2% OV 17 (2 m × 2 mm). Absolute yields have been evaluated by comparison of the peaks of the reaction mixture with those of standard solutions. Infrared spectra (in CCl_4) were obtained on a Perkin-Elmer 257 Infracord instrument. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R32 90 MHz spectrometer, using Me_4Si as an internal standard and CCl_4 as solvent. GC–MS were obtained on an AEI-MS 12 spectrometer at an ionization potential of 70 eV, coupled to a Varian 1400 gas chromatograph using a column of 2% OV 17 (2 m × 2 mm).

Ethyl azidoformate was prepared from ethyl chloroformate and sodium azide.[14] Adamantane was obtained from EGA. **3** and **4** were prepared according to a reported procedure.[8] **3:** IR 3440 (NH) and 1725 cm^{-1} (CO); NMR δ 1.2 (t), 1.6–2.2 (m), 4.0 (q), 4.2 (broad). **4:** IR 3450 (NH) and 1720 cm^{-1} (CO); NMR δ 1.2 (t), 1.6–2.0 (m), 4.0 (q), 4.2 (broad). Ethylbenzene was obtained from Fluka.

Thermolysis of Ethyl Azidoformate in Adamantane. (a) In Cyclohexane. Adamantane (204 mg; 1.5 mmol), 144 mg (1.25 mmol) of ethyl azidoformate, and 504 mg (6 mmol) of cyclohexane were placed in a sealed tube and heated at 90 °C for 15 h. GC analysis of the crude product showed that the ratio of **3** to **4** was 4.0 (corrected for numbers of H). The other reaction product cyclohexylurethan does not interfere in the area calculations, showing a shorter retention time.

(b) In Dichloromethane. Adamantane (204 mg; 1.5 mmol), 29 mg (0.25 mmol) of ethyl azidoformate, and 2.5 mL of dichloromethane were placed in a sealed tube and heated at 90 °C for 15 h. The observed tertiary/secondary reactivity ratio was 6.0.

Photolysis of Ethyl Azidoformate in a Cyclohexane Solution of Adamantane. Adamantane (204 mg; 1.5 mmol), 315 mg (2.75 mmol) of ethyl azidoformate, and 1.625 mL (15 mmol) of cyclohexane were photolyzed[7] in a quartz vessel using a medium pressure Hanovia PCR lamp for 6 h. The observed tertiary/secondary reactivity ratio was 4.1.

Thermolysis of Ethyl Azidoformate in Ethylbenzene. Ethylbenzene (1 mL) and 0.1 mL of ethyl azidoformate were placed in a sealed tube and heated at 90 °C for 15 h. The crude mixture was analyzed by GC–MS. The first three peaks (61) were attributed to the isomeric azepines **5–7;** their mass spectra were very similar and the only prominent peaks were at *m/e* 193 (M), 120 (M − EtOCO), and 91 (tropylium ion). The following peak (16) had the same retention time and coincident MS with **8,** synthesized by EtOCOCl treatment of 1-phenylethylamine, obtained by Na/EtOH reduction of acetophenone oximes: *m/e* 193 (M, 36), 178 (92), 164 (73), 147 (16), 132 (37), 120 (58), 106 (100), 105 (71), 91 (12), 79 (92), 77 (60). For synthesized **8:** IR 3440 (NH) and 1720 cm^{-1} (CO); NMR δ 1.2 (t), 1.5 (d), 4.0 (q), 4.8 (broad), 7.3 (s). The following two peaks (23) had the same retention time and coincident MS with meso and *d,l* mixtures of 2,3-diphenylbutanes (**13** and **14**) reported:[15] *m/e* 210 (M), 105 (base peak). The last peak (<0.5%) had the same retention time and coincident MS with **9,** synthesized by EtOCOCl treatment of commercial 2-phenylethylamine (Fluka): *m/e* 193 (M, 16), 164 (7), 120 (7), 104 (38), 102 (100), 91 (74), 77 (10), 65 (10). For synthesized **9:** IR 3450 (NH) and 1725 cm^{-1} (CO); NMR δ 1.2 (t), 2.8 (t), 3.4 (sextet), 4.0 (q), 4.5 (broad), 7.3 (s).

Thermolysis of Ethyl Azidoformate in Ethylbenzene and Dichloromethane. Ethyl azidoformate (0.1 mL), 1 mL of ethylbenzene, and 10 mL of dichloromethane were placed in a sealed tube and heated at 90 °C for 15 h. The crude mixture was analyzed by GC–MS. The major peaks (80%) were the isomeric *N*-ethylphenylurethans **10–12,** as confirmed by the identity of retention times and MS with those obtained by EtOCOCl treatment of the amines coming from Sn/HCl reduction of the isomeric nitroethylbenzenes:[16] *m/e* 193 (M), 178, 147, 134, 132, 120, 106, 91, 77, 65.

Acknowledgment. The National Research Council (CNR), Rome is acknowledged for financial support.

Registry No.—**1,** 281-23-2; **2,** 100-41-4; **3,** 25192-03-4; **4,** 17778-75-5; **5,** 31536-49-9; **6,** 66085-10-7; **7,** 66085-11-8; **8,** 1623-51-4; **9,** 6970-83-8; **10,** 28352-95-6; **11,** 66085-12-9; **12,** 28238-56-4; **13,** 4613-11-0; **14,** 2726-21-8; ethyl azidoformate, 817-87-8; dichloromethane, 75-09-2.

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2,3-Bis(trimethylsilyloxy)-1,3-butadiene as a Useful Reactive Diene in the Diels–Alder Reaction[1]

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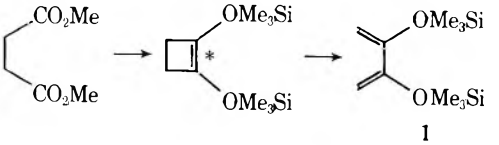
In the course of our present work we have needed to synthesize a number of substituted phthalimides, among them 4,5-dimethoxyphthalimide (**5**) (methahemipinimide). Our synthetic approach to **5** employs a Diels–Alder reaction utilizing the novel diene 2,3-bis(trimethylsilyloxy)-1,3-butadiene (**1**).[2] Further investigation has demonstrated that **1** is indeed a synthetically useful, versatile diene in the Diels–Alder reaction.

2,3-Bis(trimethylsilyloxy)-1,3-butadiene was prepared by the method of Bloomfield and co-workers (Scheme I) although we were able to increase the yield of **1** from 76 to 84% by the addition of 2% by weight hydroquinone to inhibit polymerization during the pyrolysis of the cyclobutene.

The diene **1** was found to readily cycloadd to the dienophiles listed in Table I with the indicated yields. The cisoid conformation of **1** is apparently easily attained since the Diels–Alder cycloadditions occurred under fairly mild conditions. In a typical experiment, 1 equiv each of **1** and the dienophile were either refluxed in dry toluene under a nitrogen atmosphere or heated to 150–200 °C in a sealed combustion tube for 24 h. The products were isolated by fractional vacuum distillation or fractional sublimation.

Our original aim was the synthesis of methahemipinimide (**5**), so the cycloadduct **2** was oxidized and further transformed

Scheme I



1

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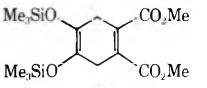
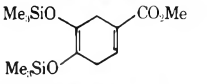
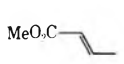
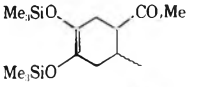
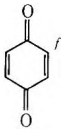
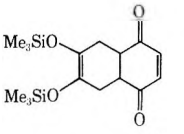
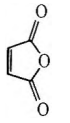
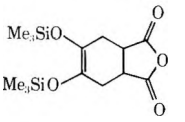
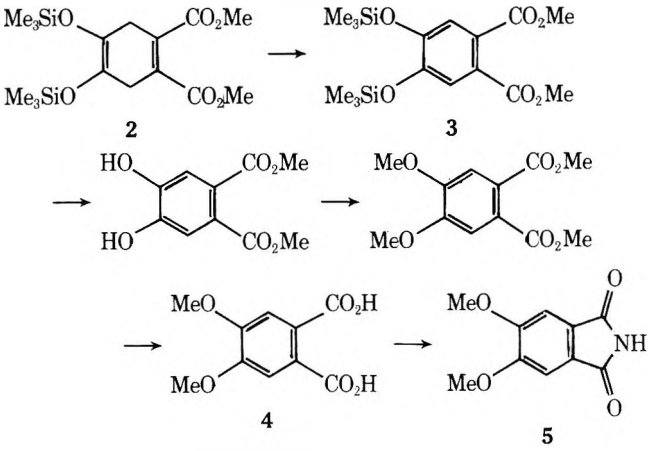
Table I. Diels–Alder Cycloadditions to 2,3-Bis(trimethylsilyloxy)-1,3-butadiene

Dienophile	Registry no.	Reaction conditions	Adduct[a]	Registry no.	Yield,[b] %
$MeO_2CC{\equiv}CCO_2Me$	762-42-5	c	 2	66322-98-3	82
$MeO_2CC{\equiv}CH$	922-67-8	d, 150 °C		66322-99-4	81
	623-43-8	d, 200 °C		66323-00-0	42, 80[e]
	106-51-4	c		66323-01-1	78
	108-31-6	c		65005-70-1	61

[a] Satisfactory analytical data were obtained for all adducts listed, except 2 (see Experimental Section). [b] Isolated yields. [c] Refluxing toluene. [d] Combustion tube. [e] Based on recovered starting material. [f] Three equivalents of quinone were used.

Scheme II



into metahemipinic acid (4) and the imide according to the synthetic sequence outlined in Scheme II.

Heating the cycloadduct 2 with 1 equiv of sulfur to 210 °C for 15 min yielded the aromatic compound 3 in 95% yield. Hydrolysis of the trimethylsilyloxy groups of 3 with water[4] at room temperature gave a quantitative yield of the diphenol. Subsequent methylation of the diphenol with dimethyl sulfate[5] (94% yield) followed by saponification of the methyl esters with 10% aqueous sodium hydroxide (88% yield) and imide formation by heating the diacid with 2.0 equiv of urea[6] to 180 °C in ethylene glycol (95% yield) gave the desired product, metahemipinimide (5).

Thus the diene 1 appears to be synthetically versatile. An extremely electron rich diene, it is apparently reactive despite its bulky 2,3-substituents since it cycloadds to a variety of dienophiles in high yields under mild conditions. In its utility it is comparable to the 1,3-dialkoxy butadiene systems under investigation by Danishefsky[7] and the 2-alkoxy 3-thioalkoxybutadiene system studied by Trost.[8] The easily hydrolyzable trimethylsilyloxy groups afford the possibility of transformation to 1,2-diones or diols, ortho diphenols or quinones, and methoxy, dimethoxy, and methylenedioxy derivatives, to name a few. With oxidation to aromatic derivatives this scheme is immediately attractive as a potential route to the broad class of adrenergic stimulants, the catecholamines, and as a possible entry into the synthesis of a number of CNS agents, among them some derivatives of morphine. It is hoped that this Diels–Alder diene will find wide applicability in the synthesis of a host of biologically important molecules.

Experimental Section

All melting points are uncorrected. IR spectra were determined with a Perkin-Elmer 337 infrared spectrophotometer. NMR spectra were recorded using a Varian Associates EM390 spectrometer and chemical shifts are reported in parts per million on the δ scale from internal Me_4Si. Mass spectral data were obtained at 70 eV using a Varian MAT CH-5 mass spectrometer. Microanalyses were performed by Atlantic Microlab, Inc. Atlanta, Ga.

2,3-Bis(trimethylsilyloxy)-1,3-butadiene (1).[2] 1,2-Bis(trimethylsilyloxy)cyclobutene (83.4 g) and hydroquinone (0.85 g) were placed in a 2.54 cm by 76.2 cm heavy-walled combustion tube and degassed by bubbling argon through the solution for 5 min. The tube was cooled to liquid nitrogen temperature and sealed off under vacuum. Heating to 180 °C for 6 h and vacuum distillation of the product at 10 mm, 77–79 °C, yielded 70.0 g (84%) of 1 which gave the following spectral absorptions: NMR (CCl_4) δ 0.20 (s, 18 H), 4.23 (s, 2 H), and 4.74 ppm (s, 2 H).

Diels–Alder Cycloadditions: Method A. One equivalent each of the diene 1 and the dienophile were refluxed in dry tolune (distilled from sodium) for 10–24 h under a nitrogen atmosphere. Rotary evaporation of the solvent and vacuum distillation as described or sublimation at 110 °C (0.002 mm) yielded the product. **Method B.** One equivalent each of the diene 1 and the dienophile were placed in a 1.3 cm by 20.3 cm heavy-walled combustion tube, degassed by bubbling argon through the mixture, sealed off under vacuum, and heated to 150–200 °C for 24 h. Vacuum distillation as described or sublimation at 110 °C (0.002 mm) yielded the product.

Cycloaddition of 1 to Dimethyl Acetylenedicarboxylate. Method A (10 h) yielded 82% of a clear liquid 1,2-bis-(trimethylsilyloxy)-4,5-bis(carbomethoxy)-1,4-cyclohexadiene (bp 117–120 °C (5 μm)). The adduct gave the following spectral absorptions: IR (neat) 3.4, 5.8, and 6.0 μm; NMR (CCl_4) δ 0.18 (s, 18 H), 3.04 (s 4 H), and 3.73 (s, 6 H); mass spectrum *m/e* (rel intensity) 372 (46), 341 (19), 251 (70), and 73 (100). The product could not be sufficiently purified for elemental analysis.

Cycloaddition of 1 to Methyl Acetylenecarboxylate. Method B (150 °C, 24 h) yielded 81% of a clear liquid, 1,2-bis(trimethylsilyloxy)-4-carbomethoxy-1,4-cyclohexadiene, after Kugelrohr distillation at 115 °C (0.002 mm). The product gave the following spectral absorptions: IR (neat) 3.4, 5.8, and 5.85 μm; NMR (CCl_4) δ 0.14 (s, 9 H), 0.18 (s, 9 H), 2.97 (m, 4 H), 3.73 (s, 3 H), and 6.80 (m, 1 H); mass spectrum m/e (rel intensity) 314 (37), 193 (22), 147 (29), 75 (27), and 73 (100). The product could not be purified satisfactorily for elemental analysis.

Cycloaddition of 1 to Methyl Crotonate. Method B (200 °C; 24 h) yielded 42% (80% relative to unreacted starting material as determined by NMR of the crude reaction mixture) of a clear liquid, 1,2-bis(trimethylsilyloxy)-4-carbomethoxy-5-methyl-1-cyclohexene, after Kugelrohr distillation at 105 °C (0.002 mm). The adduct gave the following spectral data: IR (neat) 3.4, 5.75, and 5.86 μm; NMR (CCl_4) δ 0.12 (s, 9 H), 0.14 (s, 9 H), 0.92–1.03 (m, 3 H), 1.67–2.50 (m, 6 H), and 3.68 (s, 3 H); mass spectrum *m/e* (rel intensity) 330 (100), 230 (18), 182 (20), 165 (16), 147 (48), 73 (99), 58 (14), 43 (48), and 28 (17). Anal. Calcd for $C_{15}H_{30}O_4Si_2$: C, 54.50; H, 9.14. Found: C, 54.25; H, 9.13.

Cycloaddition of 1 to Benzoquinone. Method A (24 h) using 3 equiv of benzoquinone to minimize 2:1 cycloadduct formation yielded 78% of a yellow solid 6,7-bis(trimethylsilyloxy)-5,8,9,10-tetrahydro-1,4-naphthoquinone (mp 81.5–83 °C) which gave the following spectral absorptions: IR (KBr) 3.4 and 6.0 μm; NMR (CCl_4) δ 0.13 (s, 18 H), 2.0–2.75 (m, 4 H), 3.05–3.35 (m, 2 H), and 6.63 (s, 2 H); mass spectrum *m/e* (rel intensity) 338 (50), 147 (23), 73 (100), and 45 (13). Anal. Calcd for $C_{16}H_{26}O_4Si_2$: C, 56.77; H, 7.74. Found: C, 56.54; H, 7.81.

Cycloaddition of 1 to Maleic Anhydride. Method A (24 h) yielded 61% of a white solid, 4,5-bis(trimethylsilyloxy)-1,2,3,6-tetrahydrophthalic anhydride (mp 51–51.5 °C), with the following spectral absorptions: IR (KBr) 3.4, 5.4, and 5.75 μm; NMR ($CDCl_3$) δ 0.16 (s, 18 H), 2.57–2.67 (m, 4 H), and 3.33–3.47 (m, 2 H); mass spectrum *m/e* (rel intensity) 328 (31), 167 (18), 147 (43), 75 (24), 73 (100), and 45 (13). Anal. Calcd for $C_{14}H_{24}O_5Si_2$: C, 51.19; H, 7.36. Found: C, 50.96; H, 7.40.

Oxidation of Cycloadduct 2. The cycloadduct **2** (65.8 g, 0.177 mol) and sulfur (5.66 g, 0.177 equiv) were heated with stirring in a 250-mL round-bottom flask fitted with a condenser. At 210 °C the mixture vigorously evolved hydrogen sulfide gas. The vessel was maintained at 210 °C for 15 min and then cooled. The reaction mixture was diluted with 100 mL of carbon tetrachloride and 35 g of copper power (previously washed with dilute hydrochloric acid, water, acetone, and finally carbon tetrachloride) was added to remove any unreacted sulfur. The solid materials were filtered off, the solvent was rotary evaporated, and the product was distilled under vacuum (0.002 mm, 120–125 °C) to yield 62.44 g (95.3%) of a clear liquid, dimethyl 4,5-bis(trimethylsilyloxy)phthalate (**3**). The phthalate derivative showed the following spectral absorptions: IR (neat) 3.4 and 5.8 μm; NMR (CCl_4) δ 0.27 (s, 18 H), 3.83, (s, 6 H), and 7.17 (s, 2 H); mass spectrum *m/e* (rel intensity) 370 (92), 339 (17), 251 (100), and 73 (92). Anal. Calcd for $C_{16}H_{26}O_6Si_2$: C, 51.86, H, 7.07. Found: C, 51.77; H, 7.08.

Hydrolysis of 3. The phthalate **3** (61.8 g, 0.167 mol) was stirred with 100 mL of water at room temperature overnight. The water and hexamethyldisiloxane were rotary evaporated to yield 37.6 g (99.6%) of a white solid, dimethyl 4,5-dihydroxyphthalate. Recrystallization from Skellysolve B/ethyl acetate gave white needles, mp 141.5–142.5 °C, with the following spectral properties: IR (KBr) 2.9, 3.0, 3.4, 5.8, 5.9, and 6.2 μm; NMR (acetone-d_6) δ 3.80 (s, 6 H), 7.25 (s, 2 H), and 8.83 (br s, 2 H); mass spectrum *m/e* (rel intensity) 226 (42), and 195 (100). Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 53.14; H, 4.49.

Conversion of Dimethyl 4,5-Dihydroxyphthalate to Imide 5. Dimethyl 4,5-dihydroxyphthalate (33.47 g, 0.148 mol) was dissolved in 500 mL of dry acetone. Potassium carbonate (90 g, 0.652 mol) and dimethyl sulfate (41 g, 0.326 mol) were added and the solution was refluxed with stirring under a nitrogen atmosphere for 8 h, at which point the solution gave a negative ferric chloride test. The salts were filtered off and the acetone was removed by rotary evaporation. Water (50 mL) was added and the organic product was extracted with three 300-mL portions of ether. The ether layers were combined, washed with water, and dried over magnesium sulfate and the ether was rotary evaporated to yield 35.4 g (94%) of a white solid, dimethyl 4,5-dimethoxyphthalate, mp 88–89 °C, with the following spectral properties: IR (KBr) 3.33, 3.4, 5.78, 5.84, and 6.27 μm; NMR (CCl_4) δ 3.80 (s, 6 H), 3.87 (s, 6 H), and 7.04 (s, 2 H); mass spectrum *m/e* (rel intensity) 254 (66) and 223 (100).

The dimethoxyphthalate (34.35 g, 0.135 mol) was saponified by refluxing in 125 mL of 10% aqueous sodium hydroxide solution for 3 h. The solution was cooled and acidified to pH 1 with concentrated hydrochloric acid and the precipitate was filtered off and dried under vacuum to yield 26.9 g (88%) of a white solid, 4,5-dimethoxyphthalic acid, mp 198–199.5 °C dec (lit.[9] mp 193–199 °C). The phthalic acid derivative (**4**) gave the following spectral absorptions: IR (KBr) 3.1–3.6 (br), 4.2 (br), 5.85, 6.12, and 6.3 μm; NMR (Me_2SO-d_6) δ 3.83 (s, 6 H) and 7.23 (s, 2 H); mass spectrum *m/e* (rel intensity) 226 (100).

The diacid **4** (26.5 g, 0.117 mol), urea (14 g, 0.234 mol), and 250 mL of ethylene glycol were heated with stirring to 180 °C until no more ammonia evolved as tested by pH paper. The solution was cooled and the product was filtered off, washed with water, and dried under vacuum to yield 23.1 g (95%) of a cream-colored solid, 4,5-dimethoxyphthalimide. Recrystallization from acetic acid gave white needles, mp > 320 °C (lit.[10] mp >300 °C), with the following spectral properties: IR (KBr) 3.02, 5.7, 5.8, and 6.25 μm: NMR (Me_2SO-d_6) δ 3.88 (s, 6 H) and 7.33 (s, 2 H); mass spectrum *m/e* (rel intensity) 207 (12), 206 (100), 192 (19), 164 (12), 136 (20), and 121 (22).

Registry No.—**1**, 31411-71-9; **3**, 66323-02-2; **4**, 577-68-4; **5**, 4764-20-9; 1,2-bis(trimethylsilyloxy)cyclobutene, 17082-61-0; hydroquinone, 123-31-9; dimethyl 4,5-dihydroxyphtholate, 66323-03-3; dimethyl 4,5-dimethoxyphthalate, 17078-61-4; urea, 57-13-6.

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(1) Financial support from the National Institutes of Health under Grant GM 18349 is gratefully acknowledged. D.R.A. thanks the National Science Foundation for a Traineeship.
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Peroxy Acid Oxidation of Alkyl Phenyl Disulfides

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The oxidation of an unsymmetrical disulfide, RS–SR′, with 2 equiv of a suitable oxidizing agent might yield two possible thiolsulfonates, namely, RSO_2–SR′ and RS–SO_2R′, provided no cleavage of the S–S bond occurs in the course of the oxidation. Depending on the nature of the substituent groups, one might expect to observe a preponderance of one isomeric product over the other.[1] In connection with another study, we found it desirable to establish the relative reactivity of phenyl- vs. alkyl-substituted sulfur atoms toward peroxy acid in such unsymmetrical disulfides. Toward this end, the peroxy acid oxidation of ethyl phenyl disulfide (**1**) and benzyl disulfide (**2**) was studied.

$$\underset{\mathbf{1}}{CH_3CH_2SSC_6H_5} \xrightarrow{MCPBA} \underset{\mathbf{1a}}{CH_3CH_2SO_2SC_6H_5}$$

$$\underset{\mathbf{2}}{C_6H_5CH_2SSC_6H_5} \xrightarrow{MCPBA} \underset{\mathbf{2a}}{C_6H_5CH_2SO_2SC_6H_5}$$

Upon oxidation of ethyl phenyl disulfide (**1**) with 2.3 equiv of *m*-chloroperoxybenzoic acid (MCPBA), phenyl ethanethiolsulfonate (**1a**) was formed as the major product in ca. 75 ± 10% yield. Similarly, oxidation of **2** with MCPBA (2.0 equiv) afforded **2a** in ca. 65% yield. In both reactions, considerable amounts of difficultly separable materials were produced; however, none of the possible alternate isomeric products, ethyl benzenethiolsulfonate (**1b**) or benzyl benzenethiolsulfonate (**2b**), respectively, were detectable in the crude oxi-

$$\underset{\mathbf{1b}}{CH_3CH_2SSO_2C_6H_5} \qquad \underset{\mathbf{2b}}{C_6H_5CH_2SSO_2C_6H_5}$$

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dation products as determined by ^1H NMR spectral assays using, for comparison, ^1H NMR spectral characteristics of authentic **1b** and **2b** which had been independently prepared (the latter also is an intermediate in the preparation of **2**; see Experimental Section).

The selectivity observed in the above oxidations becomes explicable if one views the sulfur bound to phenyl in **1** and **2** as being the relatively electron-poor sulfur center in each disulfide, due to delocalization of its electrons into the phenyl ring and/or to a relatively greater electron-donating ability of the ethyl group in **1**, or benzyl group in **2**, to the remaining sulfur atom. Thus, initial reaction of disulfide **1** or **2** with an electrophilic reagent such as MCPBA would be expected to occur at the latter more electron-rich (nucleophilic) sulfur to produce the corresponding thiolsulfinate[2] which, upon further reaction with peroxy acid, presumably undergoes preferential oxidation at the already partially oxidized sulfur atom[3,4] to yield the observed thiolsulfonate.

We have observed that less than 35% of the total final product is unaccounted for in each of the two oxidations studied and that this lesser portion of the total product in each case includes no detectable amounts of **1b** or **2b** (as already mentioned above), or of either of the two predicted products of "scrambling" of the S–S linked portions of **1** or of **2** due to disproportionation via an α-disulfoxide[4] derivable from any intermediate thiolsulfinate(s) formed. Hence, it seems reasonable that the straightforward course of oxidation suggested above for **1** and **2** is the major pathway operative in the peroxy acid oxidation of *alkyl aryl disulfides* and that electronic effects are of primary importance in determining the regiospecificity of the initial oxidation of such disulfides to thiolsulfinates.[5] In this respect our results also accentuate similar conclusions already put forth by Block and O'Connor[2] concerning the importance of electronic effects on the outcome of the peroxy acid oxidations of unsymmetrical dialkyl disulfides to thiolsulfinates.

Experimental Section

Preparation of Ethyl Phenyl Disulfide (1).[6] A solution of 0.16 g (0.002 mol) of pyridine in 7 mL of absolute ethanol was added dropwise during 15 min to a stirred solution of 0.53 g (0.002 mol) of phenyl α-toluenethiolsulfonate (**2a**)[7] and 0.13 g (0.002 mol) of ethanethiol in 20 mL of absolute ethanol at 0–3 °C. The reaction mixture was stirred at 0–3 °C for 15 min and at 20 °C for 5.5 h. The solution was diluted with water and extracted with diethyl ether. The combined organic extracts were washed with dilute $NaHCO_3$ solution and water and dried ($MgSO_4$). The solvent was evaporated in vacuo below 30 °C to yield 0.30 g (88%) of an oily residue which on evaporative distillation afforded 0.20 g (58%) of pure **1** as a pale yellow oil: bp 46 °C (0.1 mm) [lit. bp 126 °C (15 mm),[6a] 89–90 °C (1.2 mm),[6b] 66 °C (0.1 mm)[6c]]; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3), 2.75 (q, J = 7 Hz, 2), and 7.0–7.7 (m, 5).

Formation of Phenyl Ethanethiolsulfonate (1a) by Oxidation of Ethyl Phenyl Disulfide (1) with *m*-Chloroperoxybenzoic Acid (MCPBA). A solution of 475 mg (ca. 2.3 mmol) of MCPBA (85% pure; Aldrich Chemical Co.) in 10 mL of CH_2Cl_2 was added during 45 min to a stirred solution of 180 mg (ca. 1.0 mmol) of **1** in 10 mL of CH_2Cl_2 at −24 °C. Stirring was continued for 2 h below −20 °C followed by an additional 16 h at +20 °C. A ^1H NMR spectrum of a $CDCl_3$ solution of the total crude product in an aliquot removed from the reaction mixture at this point revealed that, in addition to a small amount of dissolved *m*-chlorobenzoic acid, **1a** was the only major product present (ca. 75 ± 10% by ^1H NMR assay); *no detectable amount* (i.e., <3%) *of* **1b** *was evident*. The reaction mixture, after partial concentration in vacuo and removal of the insoluble *m*-chlorobenzoic acid, was evaporated to dryness. The residue was fractionally crystallized several times from CCl_4, yielding 185 mg (84%) of crude **1a** which was ca. 80% pure by ^1H NMR assay. Recrystallization from diethyl ether gave 80 mg (37%) of **1a** as colorless crystals: mp 50–52 °C (lit.[5] mp 52 °C); ^1H NMR ($CDCl_3$) δ 1.4 (t, J = 7 Hz, 3), 3.2 (q, J = Hz, 2), and 7.2–7.8 (m, 5).

Preparation of Ethyl Benzenethiolsulfonate (1b). The following procedure was adapted from a procedure described by Boldyrev et al.[8] A solution of 0.62 g (0.010 mol) of C_2H_5SH in 30 mL of CCl_4 was added dropwise to a stirred solution of 2.1 g (0.013 mol) of Br_2 in 50 mL of CCl_4 during 10 min at −25 to −20 °C. Nitrogen was bubbled through the solution for 0.5 h (to remove HBr). Benzene (50 mL) and a mixture of 2.0 g of benzenesulfinic acid (excess) in 50 mL of water were added to the above solution, and stirring was continued for an additional 10 min. The aqueous layer was discarded. The benzene layer was washed with dilute $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent in vacuo afforded 2.5 g of a pale yellow oil which on vacuum distillation gave 1.80 g (89%) of pure **1b** as a colorless oil: bp 104–106 °C (0.15 mm) [lit.[8] bp 90–91 °C (0.10 mm)]; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 3), 3.03 (q, J = 7.5 Hz, 2), 7.4–7.8 (m, 3), and 7.8–8.1 (m, 2).

Preparation of Benzyl Phenyl Disulfide (2).[9,10] A solution of 0.40 g (0.005 mol) of pyridine in 20 mL of anhydrous diethyl ether was added dropwise during 10 min to a stirred solution of 1.32 g (0.005 mol) of benzyl benzenethiolsulfonate (**2b**) and 0.55 g (0.005 mol) of benzenethiol in 30 mL of anhydrous diethyl ether at 24 °C under nitrogen. The mixture was stirred for 2.5 h and washed with water and dilute $NaHCO_3$ solution. The aqueous phase was back-extracted with diethyl ether, and the combined diethyl ether solutions were dried ($MgSO_4$) and evaporated in vacuo below 30 °C to yield 1.05 g (90%) of **2**, purity ca. 95% (^1H NMR assay). Evaporative distillation[11] at 103–105 °C (bath) (0.1 mm) afforded pure **2** as a pale yellow oil [lit. bp 130–132 °C (2 mm),[9] 112 °C (0.01 mm)[10]]: ^1H NMR ($CDCl_3$) δ 3.91 (s, 2) and 7.1–7.6 (m, 10); ^{13}C NMR ($CDCl_3$) δ_C 43.3 ($^{13}CH_2$) and 126.1–129.3 ($^{13}C_6H_5$).[14]

Formation of Phenyl α-Toluenethiolsulfonate (2a) by Oxidation of Benzyl Phenyl Disulfide (2) with *m*-Chloroperoxybenzoic Acid (MCPBA). A solution of 400 mg (2.0 mmol) of MCPBA (ca. 85% pure) in 10 mL of CH_2Cl_2 was added dropwise during 17 min to a stirred solution of 232 mg (1.0 mmol) of pure **2** in 8 mL of CH_2Cl_2 at −2 °C under N_2. Stirring was continued for 1 h at ca. −6 °C and for 4.5 h at 20 °C. The reaction mixture was filtered to remove insoluble *m*-chlorobenzoic acid. The filtrate was evaporated, and the residue was fractionally crystallized several times from CCl_4–diethyl ether until 250 mg of a pink solid, mp 95–104 °C, containing **2a** and some other intractable products in a ratio of 7:3, respectively, was obtained (^1H NMR assay). Recrystallization from diethyl ether gave 120 mg (45%) of pure **2a** as colorless crystals: mp 108–110 °C (lit.[7] mp 110–111 °C); ^1H NMR ($CDCl_3$) δ 4.43 (s, 2) and 7.3–7.6 (m, 10).[12]

Preparation of Phenyl α-Toluenethiolsulfonate (2a). The procedure of Kice and Engebrecht[7] was modified as follows. A solution of 1.1 g (0.010 mol) of benzenethiol in 50 mL of benzene was added dropwise to a stirred CCl_4 solution (25 mL) containing 1.9 g (0.012 mol) of Br_2 during 10 min at −10 °C. Nitrogen was bubbled through the solution for 40 min to remove the HBr which was formed. Benzene (50 mL) and a mixture of 2.0 g of α-toluenesulfinic acid[7] in H_2O (60 mL) were added to the solution. Stirring was continued for 5 min. The reaction mixture was transferred to a separatory funnel and shaken for 15 min. The aqueous phase was removed, and the benzene layer was washed with dilute $NaHCO_3$ solution and water and dried ($MgSO_4$). Removal of the solvent in vacuo afforded 2.2 g (83%) of crude 2a which on recrystallization from Et_2O–CH_2Cl_2 yielded 1.7 g (64%) of pure **2a**: mp 109–111 °C (lit. mp 110–111,[7] 117.1 °C[13]); ^1H NMR ($CDCl_3$) δ 4.43 (s, 2) and 7.3–7.6 (m, 10); ^{13}C NMR ($CDCl_3$) δ_C 65.9 ($^{13}CH_2$) and 127.4–136.0 ($^{13}C_6H_5$).[14]

Preparation of Benzyl Benzenethiolsulfonate (2b). A solution of 3.72 g (0.030 mol) of α-toluenethiol in 150 mL of benzene was added dropwise to 100 mL of CH_2Cl_2 containing 4.8 g (0.030 mol) of Br_2. The reaction mixture was kept at −17 to −20 °C during the 20 min addition period. The deep red solution was stirred at −20 °C for 30 min longer. Nitrogen was then bubbled through the solution for 15 min. The solution was diluted with 200 mL of benzene, and a mixture of 5.0 g (0.035 mol) of benzenesulfinic acid in 150 mL of water was added to the stirred solution. The red color of the sulfenyl bromide was rapidly and completely discharged. The reaction mixture was quickly transferred into a separatory funnel, shaken for 30 min, and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dilute $NaHCO_3$ solution, and brine and dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow oil (7.6 g) containing **2b** and dibenzyl disulfide in a 3:1 molar ratio (^1H NMR assay). Several recrystallizations from CCl_4–hexane afforded 4.3 g (54%) of pure **2b** as colorless crystals: mp 40–42 °C (lit.[1c] 43 °C); ^1H NMR ($CDCl_3$) δ 4.27 (s, 2), 7.21 (m, 5), and 7.25–7.95 (m, 5); ^{13}C NMR ($CDCl_3$) δ_C 40.2 ($^{13}CH_2$) and 126.6–133.4 ($^{13}C_6H_5$).[14]

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Registry No.—**1**, 4032-81-9; **1a**, 1129-40-4; **1b**, 1127-31-7; **2**, 16601-17-5; **2a**, 37945-60-1; **2b**, 16601-01-7.

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(1) For example, see (a) G. Leandri and A. Tundo, *Ric. Sci.*, **23**, 1646 (1953); *Chem. Abstr.*, **48**, 12699 (1954); *Ann. Chim. (Rome)*, **44**, 74 (1954); (b) W. Walter and P.-M. Hell, *Justus Liebigs Ann. Chem.*, **727**, 50 (1969); (c) S. Hayashi, M. Furukawa, J. Yamamoto, and K. Hamamura, *Chem. Pharm. Bull.*, **15**, 1310 (1967); (d) G. Stájer, E. A. Szabó, J. Pintye, F. Klivényi, and P. Sohár, *Chem. Ber.*, **107**, 299 (1974).

(2) Cf. the results of peroxyacid oxidations of methyl and ethyl 2-methyl-2-propyl disulfides reported by E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96**, 3921 (1974).

(3) That such preferential oxidation may occur at the –SO– of a thiolsulfinate has already been suggested by Walter and Hell, see ref 1b, and by A. Padwa and R. Gruber, *J. Org. Chem.*, **35**, 1781 (1970).

(4) It should be noted, however, that alternate pathways from disulfides to thiolsulfonates have been suggested which include, e.g., intramolecular disproportionation of an unstable α-disulfoxide intermediate (which, incidentally, is not ruled out in the cases cited in ref 3) and/or induced disproportionation of an intermediate thiolsulfinate(s) initiated by sulfinyl radicals (RS(O)·) formed by spontaneous cleavage of a small amount of α-disulfoxide produced by direct oxidation of the intermediate thiolsulfinate(s). The latter pathway should, however, normally lead to additional thiolsulfonate products derived from scrambling of the species produced by cleavage of the S–S bond of the intermediate thiolsulfinate(s) upon attack by RS(O)· radicals. For a timely summary and some recent experimental data pertinent to this aspect of the oxidation of thiolsulfinates, see M. M. Chau and J. L. Kice, *J. Am. Chem. Soc.*, **98**, 7711 (1976). See also S. Oae, Y. H. Kim, T. Takata, and D. Fukushima, *Tetrahedron Lett.*, 1195 (1977).

(5) For those previously reported cases where at least *some* nonscrambled thiolsulfonate products were formed and examined, in two series of unsymmetrical diaryl disulfides[1a,b] oxidation appeared to occur (in the absence of steric effects) at the sulfur atom furthest removed from the relatively more electron-withdrawing substituent, in apparent agreement with our results for **1** and **2**. In another study, Walter and Hell[1b] found that peroxyacid oxidation of a series of three pyridyl alkyl disulfides gave low yields of thiolsulfonates (12, 16, and 34%) in which the alkyl-substituted sulfur had been oxidized to $-SO_2-$, as would also have been predicted by our results (assuming also, as we have, that only the –S(O)– sulfur of an intermediate thiolsulfinate is oxidized further to yield the observed thiolsulfonate). However, in contrast to our observations with **1** and **2**, where the major products (in over 65% yield) are **1a** and **2a**, the above reports also mention that considerable amounts of "scrambling" and/or "decomposition" products are simultaneously formed, especially where the oxidations of *diaryl disulfides* (ref 1a,b,d; see also ref 4) were examined, thereby indicating that at least some, and perhaps even all, of the final thiolsulfonate products observed arose from intermediate α-disulfoxides by the pathway(s) suggested in ref 4 (at least one of which has received support from Chau and Kice's data[4]). Consequently, the predictive value of these reports[1a,b,d] in terms of identifying the site(s) of initial oxidation to yield thiolsulfinate(s), as well as the structure of the major thiolsulfonate that will be finally produced, must be considered dubious.

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(11) Attempted vacuum distillation of a sample of **2**, purity ca. 95% (^{1}H NMR assay), at an oil bath temperature of 140 °C led to formation of an equimolar mixture of diphenyl disulfide and dibenzyl disulfide (^{1}H NMR assay).

(12) In the course of oxidations of **2** in which less than 2 equiv of MCPBA was consumed, the disappearance of the singlet due to the CH_2 of **2** at δ 3.91 gave rise to two new CH_2 singlets, one (due to **2a**) at δ 4.43 and another at δ 4.33; the latter decreased in intensity with corresponding increases in the intensity of the peak at δ 4.43. No characteristic sharp and intense peaks due to **2b** at δ 4.27 or 7.21 were in evidence. The peak at δ 4.33 is most probably due to phenyl α-toluenethiolsulfinate (as opposed to benzyl benzenethiolsulfinate) since no additional peaks were in evidence in the δ 7.7–8.1 region where deshielded protons ortho to an –S(O)– substituent on phenyl normally occur. For similar reasons, the peak at δ 4.33 would not seem to be attributable to an intermediate α-disulfoxide. Further evidence bearing on this latter point comes from an oxidation of **2** in which ca. 1.6 equiv of MCPBA was used, yielding a product mixture having both CH_2 singlets, as before, at δ 4.43 and 4.33; in this case no further disappearance of the singlet at δ 4.33 was observed once the *m*-chloroperoxybenzoic acid was completely consumed (as would be expected for phenyl α-toluenethiolsulfinate, but not for an α-disulfoxide which, as suggested by Chau and Kice's results[4] and those of Oae,[4] would be expected to be highly unstable). [Note that the CH_2 groups of thiolsulfinates and α-disulfoxides would not *normally* be expected to give rise to *singlets* unless accidental degeneracy exists. Thus, the thiolsulfinate from **2** could also show an AB system, and the "α-disulfoxide" could show a pair of AB systems corresponding to *RR/SS* and *RS/SR* configurations at sulfur.]

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(14) We thank Dr. Jacob Schaefer (Central Research Division, Monsanto Co., St. Louis, Mo.) for obtaining the ^{13}C NMR spectra of **2**, **2a**, and **2b**. The ^{13}C NMR chemical shifts are reported in δ (ppm) downfield from Me_4Si, based on $\delta(Me_4Si) = \delta(CDCl_3) - 77.0 = 0.0$ ppm.

The Resorcinol–Maleic Anhydride Condensation Product. An Unequivocal Proof of Structure

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No less than four structures have been proposed for the crystalline product formed on condensation of resorcinol with maleic anhydride in the presence of zinc chloride or concentrated sulfuric acid. Two of these structures, namely bis-(2′,4′-dihydroxyphenyl)but-2-en-1,4-dione[1] and 4,4-bis(2′,4′-dihydroxyphenyl)but-2-en-4-olide[2] are untenable on the basis of the NMR spectrum whereas the isomeric γ-lactone **1**[3] and δ-lactone **2**[4] structures are indistinguishable by this or other spectrometric methods. Unequivocal structural proof by chemical methods was therefore essential.

Methylation of the phenolic condensation product[3] or its triacetate[4] yielded a tetramethyl ether methyl ester **3**, R = Me, or **4**, R = Me, but assignment of either one or the other of these structures to this compound was not possible from the spectroscopic evidence. Although both esters **3**, R = Me, and **4**, R = Me, had been obtained previously[5] by Friedel–Crafts condensation of resorcinol dimethyl ether with 2,4-dimethoxyphenylsuccinic anhydride followed by esterification and structural assignments made on analogical arguments, the formation of both isomers in the same reaction precludes such assignments in the absence of more definitive evidence.

Structure **4**, R = Me, for the tetramethyl ether methyl ester was initially supported by comparison of the NMR spectrum with that of its oxime. Thus, the methine proton exhibited a 43-ppm upfield shift on oximation, whereas one of the methylene protons showed an upfield shift of 28 ppm and the other a downfield shift of 14 ppm. In contrast, oximation of an ester having structure **3**, R = Me, would be expected to show a more pronounced effect upon the methylene protons compared to the methine proton, although such shifts would be sensitive to stereochemistry.

However, hydrolysis of the ester to the free acid and reduction of this compound with sodium borohydride provided unequivocal chemical evidence in favor of structure **3**. The crystalline reduction product, mp 121–2 °C, analyzed for $C_{20}H_{22}O_6$, showed a strong lactone carbonyl band at 1770 cm^{-1} in the infrared spectrum and exhibited a strong peak in the mass spectrum at *m/e* 314 due to expulsion of CO_2 from the molecular ion. The NMR spectrum indicated the presence of two 2,4-dimethoxyphenyl groups and a strongly coupled 4-spin system. The product must therefore be either 2,4-bis(2′,4′-dimethoxyphenyl)-γ-butyrolactone (**5**) or 3,4-bis(2′,4′-dimethoxyphenyl)-α-butyrolactone (**6**) which would result from lactonization of the secondary alcohol initially produced on reduction of the acids **3**, R = H, or **4**, R = H, respectively. Further analysis of the NMR spectrum readily distinguished between the isomeric lactones **5** and **6** since the high-field methylene proton signals occurred as a multiplet at δ 2.30 and a multiplet at δ 2.92, whereas the benzylic methine protons appeared as double doublets at δ 4.05 and 5.74. The reduction product is therefore the 2,4-disubstituted lactone **5**, the magnitude of the coupling constants indicating

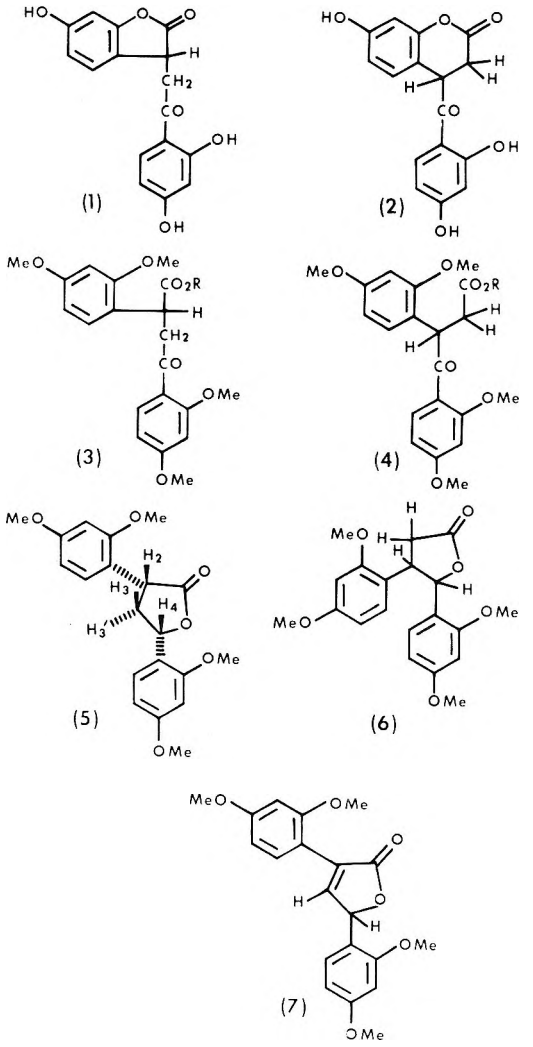

Figure 1.

the cis configuration, as determined for related δ-butyrolactones.[6]

The precursor of the latter is thus the acid **3**, R = H, which on heating under reflux in acetic anhydride gave the dehydro derivative of the lactone **5**, namely 2,4-bis(2′,4′-dimethoxyphenyl)but-2-en-4-olide (**7**). The infrared spectrum of the latter showed the expected α,β-unsaturated lactone carbonyl band at 1750 cm^{-1}, while the NMR spectrum exhibited doublets due to the H_3 and H_4 protons at δ 7.87 and 6.33 (J = 2 Hz),[7] respectively.

The synthesis of the lactones **5** and **7** via the acid **3**, R = H, and its corresponding ester **3**, R = Me, from the resorcinol–maleic anhydride condensation product therefore unequivocally establishes the structure of the latter as 3-(2′,4′-dihydroxybenzoylmethyl)-6-hydroxybenzofuran-2-one (**1**).

Experimental Section[8]

Melting points are uncorrected. The ^1H NMR spectra were obtained with a Varian HA-100 spectrometer in $CDCl_3$ solution. Infrared spectra were recorded with a Perkin-Elmer Model 237B spectrophotometer in $CHCl_3$ solution.

Methyl 2,4-Bis(2′,4′-dimethoxyphenyl)-4-oxobutyrate Oxime. The ester **3**, R = Me (0.5 g), hydroxylamine hydrochloride (1.0 g), and NaOAc (1.0 g) were heated together at 100 °C in 50% aq EtOH (40 mL) for 1 h. The mixture was poured into H_2O and the precipitated solid was filtered off and recrystallized from aqueous MeOH as white prisms: mp 139–141 °C; NMR δ 3.29 (dd, J = 14, 9 Hz, 1 H, CH_2), 3.52 (dd, J = 14, 6 Hz, 1 H, CH_2), 4.16 (dd, J = 9, 6 Hz, 1 H, CH), 3.55 (s, 3 H, OCH_3), 3.62 (s, 3 H, CO_2CH_3), 3.77 (s, 3 H, OCH_3), 3.78 (s, 6 H, 2 × OCH_3), 6.24–6.54 (m, 4 H, ArH), 6.76 (d, J = 8 Hz, 1 H, ArH), 7.05 (d, J = 8 Hz, 1 H, ArH). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.5; H, 6.25; N, 3.47. Found: C, 62.6; H, 6.32; N, 3.44.

2,4-Bis(2′,4′-dimethoxyphenyl)-γ-butyrolactone (5). The acid **3**, R = H (1.5 g), in MeOH (100 mL) was treated with $NaBH_4$ (2.0 g), added in portions, and the solution was stirred at room temperature overnight. The mixture was poured into H_2O and the precipitated solid was filtered off, washed, air dried, and recrystallized from MeOH as white needles (0.6 g), mp 119–121 °C. The aqueous solution was extracted with Et_2O, acidified with dilute hydrochloric acid, and extracted with $CHCl_3$. The extract was washed, dried, and evaporated and the residue was recrystallized from MeOH to give a further quantity of the lactone (0.75 g): mp 119–121 °C; IR 1770 cm^{-1} (lactone C=O); NMR δ 2.30 (m, $J_{2,3\beta}$ = 12.5, $J_{3\beta,4}$ = 10.5, and $J_{3\alpha,3\beta}$ = 13.0 Hz, 1 H, H-3 β), 2.92 (m, $J_{2,3\alpha}$ = 9.0, $J_{3\alpha,4}$ = 6.0 Hz, and $J_{3\alpha,3\beta}$ = 13.0 Hz, 1 H, H-3α), 3.80 (s, 6 H, 2 × OMe), 3.82 (s, 6 H, 2 × OMe), 4.05 (q, $J_{2,3\alpha}$ = 9.0, $J_{2,3\beta}$ = 12.5 Hz, 1 H, H_2), 5.74 (q, $J_{3\alpha,4}$ = 6.0, $J_{3\beta,4}$ = 10.5 Hz, 1 H, H_4), 6.38–6.60 (m, 4 H, ArH), 7.11 (d, J = 9 Hz, 1 H, ArH), 7.42 (d, J = 8 Hz, 1 H, ArH); MS m/e 358 (M^+), 314 (M − CO_2). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.15. Found: C, 67.1; H, 6.19.

2,4-Bis(2′,4′-dimethoxyphenyl)but-2-en-4-olide (7). The acid **3**, R = H (0.75 g), in Ac_2O (10 mL) was heated under reflux for 3 h[6] and the solution was allowed to cool and was poured into ice–water. The precipitate was filtered off, washed with H_2O, air dried, and recrystallized from Me_2CO–MeOH as pale yellow prisms: mp 150–151 °C (0.5 g); IR 1750 cm^{-1} (α,β-unsaturated lactone C=O); NMR δ 3.81 (s, 3 H, OMe), 3.84 (s, 6 H, 2 × OMe), 3.87 (s, 3 H, OMe), 6.32 (d, J = 2 Hz, 1 H, H_4), 6.38–6.63 (m, 4 H, ArH), 7.11 (d, J = 9 Hz, 1 H, ArH), 7.87 (d, J = 2 Hz, 1 H, H_3), 8.26 (d, J = 8 Hz, 1 H, ArH). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found. C, 67.4; H, 5.63.

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Registry No.—**1**, 15833-58-6; **3** (R = Me), 15833-60-0; **3** (R = Me) oxime, 66239-92-7; **3** (R = H), 66239-93-8; **5**, 66239-94-9; **7**, 66239-95-0; resorcinol, 108-46-3; maleic anhydride, 103-31-6.

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Facile Reaction of Alcohols and Phenols with Borane–Methyl Sulfide. A New, General, and Convenient Synthesis of Borate Esters

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In our exploratory studies involving the synthesis and reduction characteristics of alkoxyborohydrides,[1] we required a simple and direct route to alkyl and aryl borates of varying structures, applicable to preparation of fractional molar quantities.

Existing routes of borate esters[2] can be broadly classified into three types: (1) direct esterification of boric acid or anhydride with azeotropic distillation of water; (2) transesterification with a low boiling borate (usually methyl or ethyl borate); and (3) reaction of sodium borohydride with acetic acid in the presence of excess alcohol (eq 1).

$$NaBH_4 + CH_3COOH + ROH \text{ (excess)} \rightarrow CH_3COONa + B(OR)_3 + 4H_2\uparrow \quad (1)$$

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Table I. Synthesis of Borate Esters by the Reaction of Alcohols and Phenols with Borane–Methyl Sulfide

Registry no.	Borate	Procedure	Isolated yield, %	Bp, °C (mm)	Mp, °C	n_D^{20}	^{11}B NMR (ppm)[a,b]
2467-15-4	*n*-Dodecyl	A	99			1.4470	+17.8
22238-17-1	*sec*-Butyl	B	91[c]	85 (14)		1.3951	+17.4
5419-55-6	Isopropyl	B	83[c]	60 (12)		1.3868	
22238-21-7	3-Pentyl	B	90[c]	85–87 (2)		1.4100	
40589-09-1	3-Methyl-2-butyl	B	82[c]	82–83 (2)		1.4068	
2467-16-5	Cyclohexyl	C	86[c]	145–150 (0.4)	58–60		
21105-05-5	*l*-Menthyl	C	81[c]		155–158		+17.9
7397-43-5	*tert*-Butyl	B	83[c]	60 (12)		1.3872	+15.3
22238-22-8	*tert*-Amyl	B	87[c]	85 (6)		1.4110	
1095-03-0	Phenyl	C	84[c]	172 (0.35)	98–100		

[a] For a new sign convention in ^{11}B NMR spectroscopy, see *J. Organomet. Chem.*, **131**, C43 (1977). [b] F. H. Davis, I. J. Terchi, and D. N. Gheeley, *J. Org. Chem.*, **36**, 1300 (1971). [c] Yield after distillation or recrystallization from suitable solvent systems.

Each of these methods possesses certain drawbacks such as the need for careful fractional distillation and/or excess alcohol, contamination of the products with inorganic materials, moderate yields, etc. These problems become especially significant in preparation of borate esters which are solids or high boiling liquids[3] or in which the alcohol component is expensive.

Accordingly, the development of a general procedure for the synthesis of borate esters appeared highly desirable. Recently, borane–methyl sulfide has emerged as an attractive reagent for the hydroboration of olefins and the reduction of organic functional groups.[4,5]

The complex reacts with alcohols and phenols to yield borates (eq 2).

$$3ROH + BH_3 \cdot SMe_2 \rightarrow B(OR)_3 + SMe_2 + 3H_2\uparrow \quad (2)$$

Straight-chain primary alcohols and unhindered phenols react vigorously evolving all of the three hydrogens at room temperature. With secondary and tertiary alcohols, the first two of the three hydrogens are evolved rapidly and instantly, whereas the evolution of the third hydrogen is quite sluggish. However, subsequent heating of the reaction mixture at gentle reflux results in complete hydrogen evolution.

The reactions were carried out by the dropwise addition of an essentially stoichiometric quantity of the alcohol to the BMS complex stirred at 25 °C. With alcohols and phenols which are solids, the BMS was added dropwise to the neat material previously weighed into the reaction flask (the reaction can be carried out with the precise stoichiometric quantities of the reagents as in synthesis of tri-*n*-dodecyl borate). Hydrogen evolution was quantitative and no residual hydride was found upon hydrolysis; the borate esters, produced in quantitative yield after removal of volatile dimethyl sulfide under aspirator vacuum, were >98% pure as determined by refractive index, ^{1}H and ^{11}B NMR, and boron analysis. Variations in substrate structure were readily accommodated (see Table I). These results show that direct stoichiometric reaction of borane–methyl sulfide with hydroxy compounds provides a clean, convenient, general route to analytically pure borate esters of widely varying structures.[6]

Experimental Section

Alcohols and phenols utilized in this study are the commercial products of the highest purity. They were further purified by distillation over calcium hydride or recrystallization when necessary. Neat borane–methyl sulfide, approximately 10 M, was utilized as received from Aldrich Chemical Co., Milwaukee, Wis.

All reactions were carried out under dry nitrogen atmosphere, using oven dried (150 °C) or flamed glassware.

^{11}B NMR spectra were recorded on a Varian XL-100 spectrometer equipped with a Nicolet 1080 data acquisition system. ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer.

Procedure A. A dry 100-mL flask (equipped with an injection port, poly-TFE covered magnetic stirring bar, and a reflux condenser connected to a bubbler) was purged with nitrogen. Then 5.2 mL (52 mmol) of $BH_3 \cdot SMe_2$ was introduced and, with stirring and cooling with a water bath, 35.4 mL (156 mmol) of *n*-dodecyl alcohol was added dropwise over 10 min. After 1 h (hydrogen evolution was quantitative) dimethyl sulfide was removed under reduced pressure to constant weight. Tri-*n*-dodecyl borate, 29.15 g (99%), was obtained as a clear viscous liquid. Hydrolysis of a sample of the ester and titration of liberated boric acid indicated purity to be 99%.

Procedure B. Apparatus and the reaction conditions were as in procedure A except that when hydrogen evolution ceased at room temperature, the mixture was heated gently under reflux to complete the hydrogen evolution.

Procedure C. Apparatus and reaction conditions were as in procedure B except that BH_3·SMe_2 was added to the solid substrate. The results are summarized in Table I.

Registry No.—BH_3·SMe_2, 13292-87-0; dodecanol, 112-53-8; 2-butanol, 78-92-2; 2-propanol, 67-63-0; 3-pentanol, 584-02-1; 3-methylbutan-2-ol, 598-75-4; cyclohexanol, 108-93-0; *l*-menthyl alcohol, 2216-51-5; *tert*-butyl alcohol, 75-65-0; *tert*-amyl alcohol, 75-85-4; phenol, 108-95-2.

References and Notes

(1) (a) C. A. Brown, *J. Am. Chem. Soc.*, **95**, 4100 (1973); (b) C. A. Brown, S. Krishnamurthy, and S. C. Kim, *J. Chem. Soc., Chem. Commun.*, 391 (1973).

(2) (a) H. Steinberg and D. L. Hunter, *Ind. Eng. Chem.*, **49**, 174 (1957), and the references cited therein; (b) H. Schiff, *Ann. Suppl.*, **5**, 154 (1867); (c) P. D. Geroge and J. R. Ladd, *J. Am. Chem. Soc.*, **77**, 1900 (1955); (d) H. C. Brown, E. J. Mead, and C. J. Shoaf, *ibid.*, **78**, 3613 (1956); (e) J.-M. Lalancette and Y. Beauregard, *Can. J. Chem.*, **46**, 659 (1968).

(3) B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970). They reported their inability to distill hindered alkylborates. We have observed that olefin formation or trialkylboroxine formation frequently accompany distillation of higher borates, especially those derived from tertiary alcohols.

(4) (a) C. F. Lane, *J. Org. Chem.*, **39**, 1437 (1974); (b) C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *ibid.*, **39**, 3052 (1974); (c) C. F. Lane, *Aldrichimica Acta*, **8**, 20 (1975).

(5) Borane–methyl sulfide complex (~10.0 M) is commercially available from Aldrich Chemical Co., Milwaukee, Wis.

(6) The crude borate esters may be readily hydrolyzed with D_2O to pure deuterated alcohols. Hydrolysis is accomplished by adding 3.5 equiv of D_2O in which 0.5 equiv of sodium has been dissolved. After warming to ~75 °C for several hours, a borate glass appears from which the alcohols may be decanted under inert atmosphere.

Communications

Borane Complexes in Trifluoroacetic Acid. Reduction of Indoles to Indolines and Generation of Bis(trifluoroacetoxy)borane

Summary: Borane–tetrahydrofuran (THF) in trifluoroacetic acid produces acid-stable $BH[OC(O)CF_3]_2$·THF, and constitutes a convenient, rapid, high-yield method for the selective reduction of indoles to indolines in the presence of other functional groups.

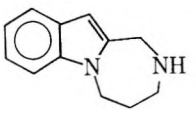
Sir: In the area of selective reductions, we have been exploring the properties of borane complexes in trifluoroacetic acid (TFA). Such mixtures may give rise to mono- and/or bis(trifluoroacetoxy)boranes, potentially useful reducing agents.[1] We have found that bis(trifluoroacetoxy)borane (**1**) is readily formed and that it is *stable to excess TFA*, thus providing one of the few "hydride" reducing agents usable in a strongly acidic medium. Borane–tetrahydrofuran (THF) in TFA has been developed into a convenient, mild, rapid procedure for the conversion of indoles to indolines. This indole reduction study has also served as a vehicle for defining the selectivity of the reagent to various functional groups.

Our choice of borane–THF in TFA was based on the reported inertness of trichloroacetic acid to reduction by borane complexes at 25 °C.[2] Addition of borane–THF to a large excess of anhydrous TFA evolved gas (hydrogen) immediately. Subsequent addition of water to the resultant mixture caused further gas evolution, indicating that the TFA had not consumed all of the available hydride. Hydrogen evolution was measured in two different experiments: (1) treatment of excess TFA with commercial 1 M borane–THF (with 5% $NaBH_4$ present) at 0 °C gave 2.1 molar equiv of hydrogen; (2) commercial 10 M borane–methyl sulfide gave 2.0 molar equiv of hydrogen.[3] Thus, an intermediate adduct such as **1**, or a mixture of species representing its stoichiometric equivalent, was generated.

$$BH_3\text{·THF} + 2CF_3COOH \rightarrow [CF_3C(O)O]_2BH\text{·THF} + 2H_2$$
$$\mathbf{1}$$

Evaporation (in vacuo, 30 °C) of excess THF, in an experiment involving the treatment of 2 molar equiv of TFA with 1 M borane–THF at 0–5 °C, left a colorless liquid. ^1H NMR (neat) showed only complexed THF (no B–H resonance was discernible). However, the IR spectrum (neat) exhibited a single, strong B–H absorption at 2540 cm^{-1} (indicating a monomeric, nonbridged species),[4] a carbonyl absorption at 1780 cm^{-1}, and typical C–H and C–F stretching bands. A ^{11}B NMR study of a fresh solution of borane–THF in excess TFA showed disappearance of the B–H coupling of borane–THF (quartet at δ −1.2), giving rise to a broad singlet at $\delta \sim +2.5$ (both in parts per million downfield from boron trifluoride etherate). These spectral data are consistent with formation of tetracoordinate species **1**.[5] An NOE-suppressed, ^1H-decoupled ^{13}C NMR spectrum of the isolated neat liquid showed no uncomplexed THF (THF resonances occur at δ 25.8, 67.9) and strongly supported the assignment: δ [Me_4Si; external D_2O lock; 14-μs (90°) pulse; 20-s repetition] 25.4 (s), 76.4 (broadened s), 135.2 (q, $^1J_{CF}$ = 284 Hz), 157.8 (q, $^2J_{CF}$ = 40.9 Hz); relative integrated areas 2.0, 1.9, 2.2, 1.8, respectively.

To apply this new reducing agent, we looked initially at the (hydride) reduction of indoles to indolines, which generally requires a strongly acidic medium since reduction presumably proceeds via a 3*H*-indolenium ion. Substrate **2**[6] was chosen for study because a number of published methods were found to be unsatisfactory for transforming it to indoline **3**[7] (see Table I). Although isolated **1** and TFA, and unisolated **1** generated in excess TFA, were successful, we favored a procedure in which the indole was reduced while **1** was being produced. This made use of any viable reducing agents preceding formation of **1** [i.e., BH_3–THF or $CF_3C(O)OBH_2$]. Addition of borane–THF to a solution of **2** in TFA at 0 °C completely reduced **2** to **3** in ~2 min! The yield of **3** was 98% (GLC) (86% isolated). Significantly, production of trifluoroacetyl and 2,2,2-trifluoroethyl byproducts, formed with $NaBH_4$ in TFA[8] (see Table I), was avoided. The minimum reagent ratio required for complete reduction was determined to be 1.5 mol of BH_3–THF per mole of indole.



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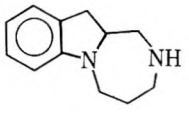

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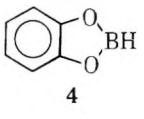

4

From the comparative data (Table I), borane–THF, borane–pyridine,[9] and catecholborane (**4**),[10] all in TFA, are effective reagents for the reduction of **2**. $NaBH_3CN$ in TFA[11] is also effective.[12] Borane–methyl sulfide with added THF is good and borane–trimethylamine[13] is poor. Catecholborane (**4**) is interesting in its structural relationship to **1**; consequently, the similarity of **1** and **4** in the reduction of **2** was not unpredictable. Use of Cl_3CCOOH or $F_2CHCOOH$ with borane–THF was unsatisfactory for converting **2** to **3**.

Table I. Reduction of 2 to 3

reducing agent	isolated yield of 3, %[a]	remarks
isolated **1** in TFA	86	2.5 mol of **1** per mole of indole
BH_3·THF/TFA	86 (98[b])	
BH_3·pyridine/TFA	90	
BH_3·Me_2S/THF/TFA[c]	72	15% unreacted **2**
4/TFA	78	
BH_3·NMe_3/TFA	(~20)	incomplete reduction
$NaBH_3CN$/TFA[11]	81	
$NaBH_3CN$/HOAc[8,12]	(<5)	
$NaBH_4$/TFA[8]	(~35)	*d*
BH_3·THF/CH_3OH/$NaOCH_3$[e]	(~20)	~75% unreacted **2**
BH_3·THF/aqueous HCl[11,f]	(~30)	~70% unreacted **2**
BH_3·NMe_3/aqueous HCl[13]	(~15)	~85% unreacted **2**
Tin/concentrated HCl/Δ	(~5)	48-h reaction time
H_2/5% Pd on $BaSO_4$/acid[7]	(<5)	

[a] GLC yield in parentheses. [b] GLC yield using internal reference and detector response factor. [c] Without added THF this reduction is not satisfactory. [d] CH_2CF_3 indoline (~10%), CH_2CF_3 indole (~15%), and $C(O)CF_3$ indole (~15%) byproducts were formed (identified by GLC/mass spectrometry). [e] S. A. Monti and R. R. Schmidt, III, *Tetrahedron*, **27**, 3331 (1971). [f] H. Plieninger, H. Bauer, W. Bühler, J. Kurze, and U. Lerch, *Justus Liebigs Ann. Chem.*, **680**, 69 (1964).

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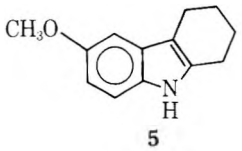
Table II. Reduction of Various Indoles to Indolines[a]

entry	substrate	yield of indoline, %[b]	remarks
1	tetrahydrocarbazole	80 (90)[c]	only cis product[d,e]
2	**5**[f]	90[g]	only cis product
3	tryptamine	86[h]	
4	2-methylindole	88	
5	5-nitroindole	(70)	some "dimeric" product
6	indole	(27)	"dimeric" product formed
7	indole	(84)	inverse addition
8	2,3-dimethylindole	82	trans/cis = ~2[e]
9	1-cyanomethylindole[i]	73[j]	inverse addition
10	1-(2-aminoethyl)indole[k]	~65[j]	inverse addition
11	**6**[l]	80[m]	only cis product
12	**7**[11]	70	only cis product[11]
13	**8**[n]	80[o]	isomer ratio = ~2.5
14	2-phenylindole	0	indole unchanged
15	2-carbethoxyindole	0	indole unchanged
16	*N*-benzoyltryptamine	80[9]	inverse addition

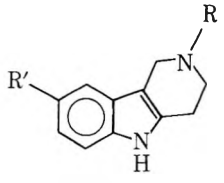
[a] Normal addition procedure unless otherwise noted. All indoles and indolines are known compounds. Indoline products were characterized by ^{1}H NMR and, when appropriate, by IR, UV, and melting point data. (See paragraph on supplementary material at end of paper). [b] Isolated yield; GLC yield, obtained using internal reference and detector response factor, given in parentheses. [c–o] See supplementary material.

The borane–THF procedure, applied to a variety of indoles (see Table II), generally afforded instantaneous reduction at 25 °C. The method is well suited to the reduction of indoles bearing basic nitrogen functionality, substitution which impedes reduction or causes formation of undesirable byproducts with many other methods. Selectivity of the reagent is evident from the unreactiveness of ester (entry 15), nitrile (entry 9), nitro (entry 5), ether (entry 2),[14] and amide (entry 16). The method herein is not effective for the reduction of indoles with phenyl (entry 14) and carbethoxy (entry 15) substituents at the 2 position. Although certain indoles "dimerize" (entries 5 and 6) or suffer other side reactions under the standard reduction conditions, this problem can be improved by employing an inverse addition scheme (entries 7, 9, 10, and 16).

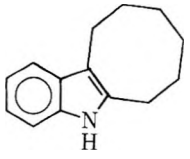
Stereochemical results for reduction of tetrahydrocarbazole, **5**, 2,3-dimethylindole, **6**, **7**, and **8** are shown in Table II (entries 1, 2, 8, and 11–13). A 2,3-fused six-membered ring gave only *cis*-indoline, regardless of whether the fused ring was carbocyclic or heterocyclic. On the other hand, 2,3-dimethyl substitution and 2,3-eight-membered ring fusion gave a mixture of *cis*- and *trans*-indolines.



5



6, R = R′ = CH_3
7, R = $CH_2CH_2C_6H_5$; R′ = H



8

General experimental procedures are as follows (see paragraph on supplementary material at end of paper). **(1) Normal Addition.** The indole (1 mmol) in 3 mL of TFA at 0 °C under nitrogen is treated slowly with 2 mL of BH_3–THF (1 M in THF). After addition, the reaction mixture is diluted with 0.1 mL of H_2O. The TFA and THF are evaporated and the residual mixture is basified with 10% NaOH. Extraction with CH_2Cl_2 and evaporation of the (extract) solvent provides the indoline product.

(2) Inverse Addition. The indole (1 mmol) in 2 mL of BH_3–THF is cooled to 0 °C and treated slowly with 2 mL of TFA. Workup similar to the above furnishes the indoline product.

In summary, borane–THF in TFA offers a rapid, mild, high-yield method for the reduction of indoles to indolines. The method is particularly useful for aminoalkyl-substituted indoles, substrates on which other methods are often deficient. Bis(trifluoroacetoxy)borane,[15] easily synthesized from borane–THF and TFA, is potentially interesting as a selective reducing agent, especially since it is stable in a strongly acidic medium. Catecholborane should also be useful as a reducing agent in TFA.[16] We are currently investigating the reactivity of **1** with other functional groups.

Acknowledgment. The authors thank Mr. Albert J. Molinari for some experimental data, and Mr. Martin S. Mutter and Ms. Roberta R. Acchione for spectral data. We also are grateful to Dr. William Wise (University of Pennsylvania) for use of ^{11}B NMR facilities.

Supplementary Material Available: References (c through o) to compounds in Table II and specific experimental procedures (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Acyloxyborane species have been discussed, see: (a) H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970); (b) C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, **39**, 3052 (1974); (c) A. Pelter, M. G. Hutchings, T. E. Levitt, and K. Smith, *J. Chem. Soc. D*, 347 (1970); (d) C. F. Lane, *Chem. Rev.*, **76**, 773 (1976); (e) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960).
(2) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).
(3) Evolution of the ~2 molar equiv of hydrogen was instantaneous. On standing at 0 °C, the resultant solutions evolved 0.1 molar equiv of additional hydrogen in 30 min, then evolution virtually ceased. Subsequent addition of water released hydrogen, in an amount corresponding to theory (total of 3 molar equiv).
(4) L. J. Bellamy, "Advances in Infrared Groups Frequencies", Chapman and Hall, London, 1968, p 118, and references cited.
(5) Our IR and ^{11}B NMR results are in accord with data recently reported on bis(acyloxy)boranes: H. C. Brown and T. P. Stocky, *J. Am. Chem. Soc.*, **99**, 8218 (1977).
(6) B. E. Reynolds and J. R. Carson, U.S. Patent 3 867 374 (1975); 3 689 503 (1972). Compound **2**, which was assigned the name azepindole by the USAN Council on Drugs, is an antidepressant of clinical interest.

(7) R. Jonas, H. Müller-Calgan, and H.-J. Schliep, U.S. Patent 3 980 797 (1976).
(8) G. W. Gribble, P. Lord, J. Skotnicki, S. Dietz, J. Eaton, and J. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974).
(9) A report on the reduction of indoles using borane–pyridine and aqueous or ethanolic mineral acids appeared during the course of our research, see: Y. Kikugawa, *J. Chem. Res.*, 212 (1977).
(10) For a survey of the reducing properties of **4** see: G. W. Kabalka, J. D. Baker, Jr., and G. W. Neal, *J. Org. Chem.*, **42**, 512 (1977).
(11) J. G. Berger, F. Davidson, and G. Langford, *J. Med. Chem.*, **20**, 600 (1977).
(12) For a report on $NaBH_3CN$ in acetic acid see: G. W. Gribble and J. H. Hoffman, *Synthesis*, 859 (1977).
(13) J. G. Berger, *Synthesis*, 508 (1974).
(14) Ethers, such as THF and anisole, can be cleaved by borane reagents; e.g., see M. Node, H. Hori, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 2237 (1976), and references cited therein.
(15) The isolated THF complex, **1**, was not stable to prolonged storage at room temperature under dry nitrogen. After a few days, no active hydride remained and the liquid became very viscous. Therefore, we suggest the use of freshly prepared material. In the preparation of **1**, too slow addition of BH_3–THF and unnecessary standing of the reaction mixture were avoided, since polymerization of THF was observed. Removal of excess THF to give **1** alleviated the polymerization problem.
(16) Catecholborane and **1** reduced **2** at about the same rate.

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Dimethylaluminum Methylselenolate: A Remarkable Reagent for the Preparation of Active Acyl-Transfer Agents

Summary: The preparation of a new aluminum reagent, dimethylaluminum methylselenolate (**1**), has been achieved. This reagent has been shown to react with a variety of *O*-alkyl esters to provide methylselenol esters, active acyl-transfer agents, in excellent yield.

Sir: We would like to report the preparation and use of a remarkably efficient and versatile reagent for the conversion of *O*-alkyl esters to their corresponding methylselenol esters. This reagent, dimethylaluminum methylselenolate (**1**), is conveniently prepared by heating a toluene solution of trimethylaluminum (Texas Alkyls) with powdered selenium (ROC/RIC) for 2 h at reflux.[1]

$$Me_3Al + Se \xrightarrow[2\ h]{\text{toluene, reflux}} \underset{\mathbf{1}}{Me_2AlSeMe}$$

The yellow-colored solution so generated is then ready for use. Aliquots of the reagent are withdrawn by syringe and transferred to the reaction vessel containing the ester, or other organic substrate, dissolved in argon-degassed methylene chloride. All reactions are carried out under an argon atmosphere in a good fume hood.

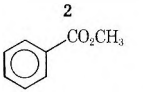
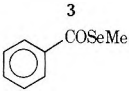
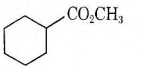
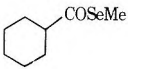
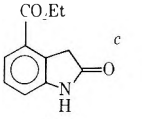
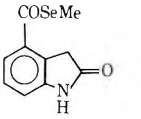
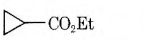
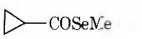
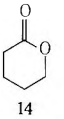
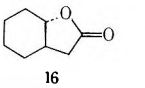
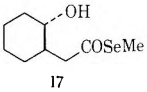
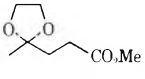
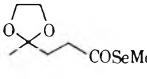
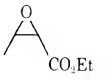
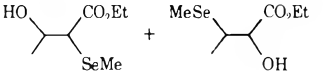
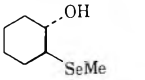
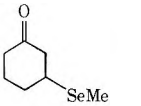
The transformation of a variety of exemplary methyl and ethyl esters to their corresponding selenol esters was found to be complete within 1 h (30 min at 0 °C, followed by an additional 30 min with warming to room temperature)!

The reaction mixtures were quenched with moist sodium sulfate and the products extracted with ether. Concentration of the organic extracts under reduced pressure and bulb-to-bulb distillation of the yellow oils gave the desired products in high yield and high purity as ascertained by NMR, IR, and mass spectral analysis (Table I).

The use of related aluminum reagents and their reactions with esters have previously been explored by Y. Ishii[2] (Et_2AlSEt) and E. J. Corey ($Me_2AlS(CH_2)_3SAlMe_2$, Me_2AlSPh, Me_2AlSCH_2Ph).[3] In addition, S. Weinreb and R. Hatch have recently reported the preparation of *tert*-butyl thioesters by reaction of dimethylaluminum 2-methyl-2-propanethiolate with *O*-alkyl esters.[4] Two equivalents of this aluminum reagent and a reaction time of 4–24 h were required for complete conversion of ester to *tert*-butyl thioester. In contrast, only 1.1 equiv of the selenium reagent **1** are required in most cases for the preparation of the selenol esters.

As is evidenced from Table I, methyl and ethyl esters react with equal facility. The ethyl ester of cyclopropanecarboxylate undergoes reaction without concomitant opening of the strained carbocycle. Only for 4-carboethoxyoxindole (**8**), which possesses a very acidic proton at C-3, is it essential to employ 2 equiv of **1** for complete conversion to the selenol ester

Table I. Reactions of Dimethylaluminum Methylselenolate (1)

starting material[a]	product[b]	isolated yield, %
$CH_3(CH_2)_5CO_2CH_3$ (**2**)	$CH_3(CH_2)_5COSeMe$ (**3**)	95
 (**4**)	 (**5**)	99
 (**6**)	 (**7**)	93
 (**8**)	 (**9**)	80
 (**10**)	 (**11**)	96
$EtO_2C(CH_2)_3CO_2Et$ (**12**)	$MeSeCO(CH_2)_3COSeMe$ (**13**)	95
 (**14**)	$HO(CH_2)_4COSeMe$ (**15**)	78
 (**16**)	 (**17**)	80
 (**18**)	 (**19**)	93
 (**20**)	 (**21a**, ~3:1; **21b**)	92
 (**22**)	 (**23**)	96
 (**24**)	 (**25**)	87

[a] All starting materials were distilled prior to reaction. [b] All products with the exception of **9** were purified by bulb-to-bulb distillation under reduced pressure. Compound **9**, which was obtained in near quantitative yield as the crude product, was recrystallized from methanol. [c] Prepared by the method of A. P. Kozikowski and M. Kuniak, *J. Org. Chem.*, **43**, 2083 (1978).

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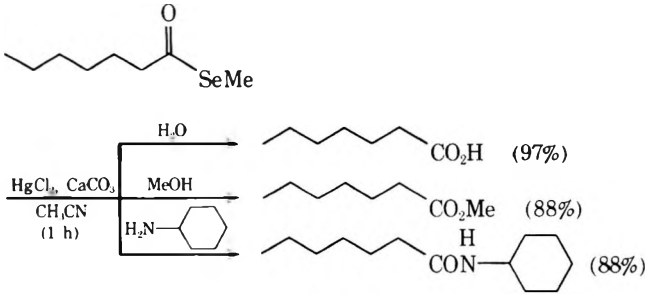
9. In contrast to the high reactivity of *O*-methyl and *O*-ethyl esters, the *tert*-butyl ester of octanoic acid fails to react under the standard conditions and is converted only in low yield to its selenol ester after prolonged heating with 2 equiv of **1**. While δ-valerolactone (**14**) is smoothly transformed to the δ-hydroxyselenol ester **15**, γ-butyrolactone is recovered unchanged on exposure to **1**, even after heating at the reflux temperature of methylene chloride for 24 h.[5] The fused γ-lactone **16**, on the other hand, is transformed to the hydroxyselenol ester **17** in 80% yield. At the temperature required to effect Kugelrohr distillation of this compound [118 °C (23 mm)], it was noted that substantial reversion of this selenol ester to starting lactone occurred.

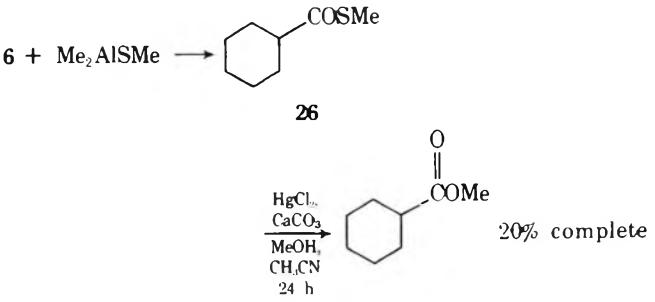
N-Methyl-3-cyclohexenylcarboxamide exhibits no evidence of conversion to selenol ester on reaction with either 1 or 2 equiv of **1** at room temperature. With the ethylene ketal of methyl levulinate (**18**) as reactant, conversion to selenol ester **19** proceeds without competing cleavage of the dioxolane group. Cyclohexene epoxide (**22**) undergoes facile ring opening with dimethylaluminum methylselenolate to furnish 2-methylseleno-1-cyclohexanol (**23**). With ethyl epoxybutyrate (**20**), opening of the epoxide ring takes place in preference to selenol ester formation. Reaction of **1** with 2-cyclohexenone furnishes **25**, the product of 1,4-conjugate addition. These latter observations thus serve to set some limits on the use of **1** for the preparation of selenol esters of polyfunctional molecules.

Finally, the ability of the selenol esters to serve as active acyl-transfer agents was readily demonstrated by the conversion of **3** to its corresponding acid, ester, or amide. This was accomplished by simply stirring the selenol ester with H_2O/CH_3CN, $MeOH/CH_3CN$, or cyclohexylamine/CH_3CN, respectively, at room temperature for 1 h in the presence of mercuric chloride and calcium carbonate.



The reactivity of the selenol esters was anticipated to be higher than that of the thiol esters as a consequence of the weak carbon–selenium bond.[6] In accord with this expectation, methanolysis of the 2-methylpropane-2-thiol ester of cyclohexanecarboxylic acid has been reported by Masamune to require 3 h of reflux in acetonitrile with $HgCl_2/CdCO_3$ present.[7] In contrast, the methylselenol ester **7** of this acid was transformed to *O*-methyl ester in 15 min at room temperature on treatment with $HgCl_2/CaCO_3$ in $MeOH/CH_3CN$.[8]

Since these rate differences may to some extent reflect the different steric demands of the substituents bound to the group 6A element (*tert*-butyl vs. methyl), the methylthiol ester of cyclohexanecarboxylic acid was also prepared. Methyl cyclohexanecarboxylate was treated with Me_2AlSMe (prepared from Me_3Al and S in refluxing toluene)[1] to give **26**, which was then reacted with methanol in the presence of $HgCl_2/CaCO_3/CH_3CN$. After 24 h at room temperature, the reaction mixture was found to consist of 80% starting thiol ester plus only 20% *O*-methyl ester by ^1H NMR analysis. This result clearly affirms the enhanced reactivity of selenol esters as acyl-transfer agents.



A typical experimental procedure is illustrated by the preparation of the methylselenol ester of heptanoic acid. To a 50-mL side-arm flask containing 4.1 g (0.052 mol) of selenium powder was added 25.2 mL (0.05 mol) of a 17.0% solution of trimethylaluminum in toluene. The reaction mixture was heated at reflux for 2 h, then cooled to room temperature, allowing the unreacted selenium to settle from solution. A 1.1-mL (2.2 mmol) aliquot of **1** was transferred by syringe to a solution of methyl heptanoate (288 mg, 2.0 mmol) in 5 mL of argon-degassed dichloromethane at 0 °C. After 30 min at this temperature, the yellow solution was warmed to room temperature over 30 min and then treated with moist sodium sulfate. The resulting mixture was extracted with ether and the isolated crude product purified by bulb-to-bulb distillation (95 °C oven temperature, 30 mm) to yield 393 mg (95%) of **3** as a yellow oil: IR (film) 1729 cm^{-1}; NMR (CCl_4) δ 2.54 (t, 2 H), 2.16 (s, 3 H), 0.63–2.00 (br m, 11 H); mass spectrum (70 eV) m/e 204, 205, 206, 208, 210 (M^+), 113 (base peak).

The methanolysis of **3** was carried out as follows. A mixture of 109 mg (0.525 mmol) of *Se*-methyl selenoheptanoate, 293 mg (1.07 mmol) of freshly sublimed mercuric chloride, and 214 mg (2.14 mmol) of calcium carbonate in 2.75 mL of dry acetonitrile and 0.04 mL of dry methanol was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was then extracted with pentane, the organic extracts were filtered through Celite, and the isolated crude product was purified by bulb-to-bulb distillation to yield 67 mg (88%) of methyl heptanoate.

Reagent **1** thus offers a convenient method for the single-step generation of active acyl-transfer agents from *O*-alkyl esters. The use of powdered sulfur and selenium for the preparation of aluminum thiolates and selenolates also extends the utility of these reagents in organic synthesis, for this method avoids the use of toxic and disagreeable thiols and selenols. The utility of dimethylaluminum methylselenolate in macrolactam and macrolactone construction and peptide synthesis must await further investigations. Studies to assess the reactivity of the aluminum enolates generated by conjugate addition of **1** to α,β-unsaturated carbonyl systems are also underway.

Acknowledgment. We are grateful to the National Institutes of Health (Grant No. R01-HL2059-01) and the donors of the Petroleum Research Foundation, administered by the American Chemical Society, for support of these investigations. We also thank Dr. Steven Weinreb for preprints of his publications.

References and Notes

(1) Two previous accounts of the preparation of aluminum selenolates ($Et_2AlSeEt$ and $i\text{-}Bu_2AlSe\text{-}i\text{-}Bu$) and thiolates by this method are present in the literature: L. I. Zakharkin and V. V. Gavrilenko, *Bull. Acad. Sci. USSR (Engl. Transl.)* 1294 (1960); Kali-Chemie, German Patent 1 031 306; *Chem. Abstr.*, **54**, 17269g (1960); see also T. Mole and E. A. Jeffery, "Organoaluminum Compounds", Elsevier, Amsterdam, 1972.
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(5) Failure to observe reaction in this case may be attributable either to competing enolate formation or to a facile back reaction converting hydroxyselenol ester to lactone. This question will be resolved in future studies.
(6) For a review of selenol acids and esters, see K. A. Jensen in "Organic Selenium Compounds: Their Chemistry and Biology", D. L. Klayman and W. H. Günther, Ed., Wiley, New York, N.Y., 1973, pp 263–272.
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(8) Preliminary experiments indicate the Cu(II) salts are equally effective in promoting the methanolysis of the selenol esters.

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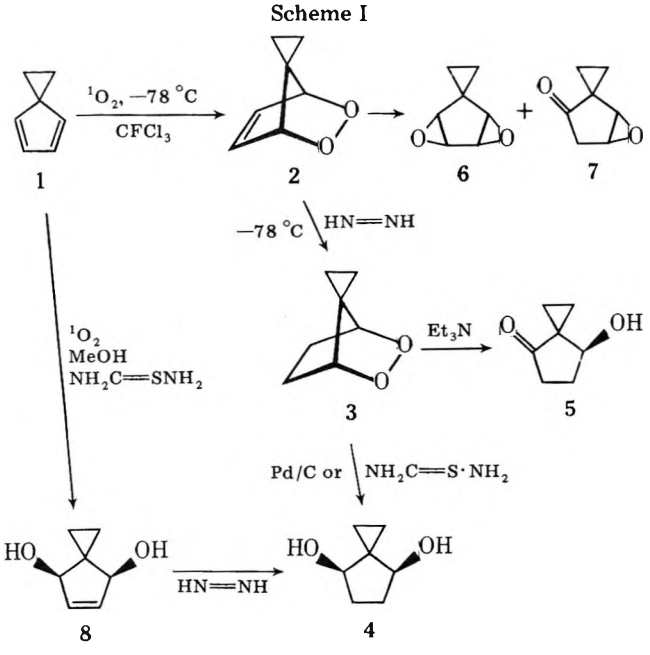
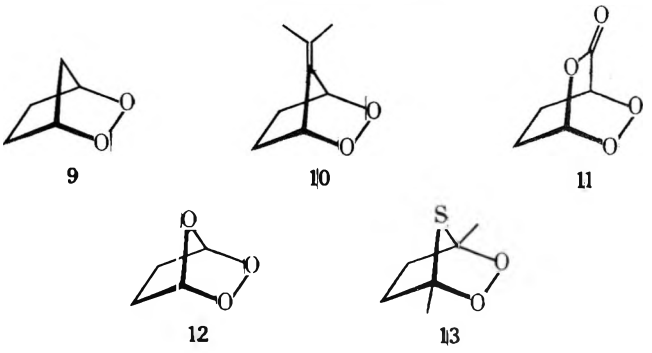
Synthesis and Characterization of 7-Spirocyclopropyl-2,3-dioxabicyclo[2.2.1]hept-5-ene[1]

Summary: The title compound, **3**, was prepared by diimide reduction of the unstable endoperoxide **2** which was obtained by photooxygenation of spiro[2.4]hepta-4,6-diene (**1**) and characterized by catalytic reduction to its diol **4** and base-catalyzed rearrangement to its ketol **5**.

Sir: Although the singlet oxygenation of spiro[2.4]hepta-4,6-diene (**1**) has been reported,[2] the intermediacy of the expected endoperoxide **2** could only be inferred from the formation of the diepoxide **6** and ketoepoxide **7** as the major rearrangement products (cf. Scheme I). Recently we have been successful in trapping the unstable singlet oxygen adducts derived from cyclopentadiene,[3] 6,6-dimethylfulvene, α-pyrone,[5] furan,[6] and 2,5-dimethylthiophene[7] by diimide reduction to their respective bicyclic peroxides **9**–**13**. In view of this convenient peroxide bond-preserving technique, we have reinvestigated the singlet oxygenation of the spirodiene **1** and established the intervention of its unstable endoperoxide **2** by direct NMR monitoring and reductive trapping in the form of the stable bicyclic peroxide **3**.

Scheme I





The photooxygenation of **1** in $CFCl_3$ at −78 °C with tetraphenylporphyrin (TPP) as sensitizer using a General Electric 400-W sodium lamp gave after warm-up to room temperature the reported[2] rearrangement products **6** and **7**. However, when the singlet oxygenation was monitored by subambient (−50 °C) NMR analysis, after 5 h of irradiation the characteristic spirodiene **1** resonances at δ 1.50 (singlet, cyclopropyl, 4 H) and δ 5.85 and 6.30 (multiplets, olefinic, 4 H) had been completely replaced by new resonances at δ 0.90 (broad singlet, cyclopropyl, 4 H), 4.58 (triplet, J = 2.0 Hz, bridgehead, 2 H), and 6.53 (triplet, J = 2.0 Hz, olefinic, 2 H), ascribed to the unsaturated endoperoxide **2** as the expected singlet oxygenation adduct of **1**. Not even traces of the diepoxide **6** and ketoepoxide **7** rearrangement products of **2** could be detected by NMR at −50 °C in $CFCl_3$. Warming of the reaction mixture to 0 °C promoted rapid replacement of the above signals assigned to **2** by those reported[2] for **6** and **7**. Furthermore, photooxygenation of the spirodiene **1** in MeOH with Rose Bengal as sensitizer in the presence of thiourea afforded the unsaturated diol **8** in 60% yield, liquid, n^{20}_D 1.4930 (after VPC collection on a 5 ft × ¼ in. aluminum column packed with 5% SE 30 on Chromosorb P and operated at a column temperature of 125 °C). Its characterization rests on satisfactory elemental analysis, ^1H NMR ($CDCl_3$, Me_4Si) resonances at δ 0.85 (s, cyclopropyl, 4 H), 2.60 (broad s, OH, exchanged with D_2O, 2 H), 3.98 (s, OCH, 2 H), and 6.05 (s, olefinic, 2 H), and IR ($CHCl_3$) bands at 3710–3125 (OH), 3070–3020 (cyclopropyl CH and olefinic CH), 2990–2900 (aliphatic CH), and 1710 cm^{-1} (C═C).

Treatment of the photooxygenate with excess diimide, generated in situ from potassium azodicarboxylate as described previously,[3] at −78 °C in $CFCl_3$ afforded the stable saturated endoperoxide **3** in 68% yield, pale yellow needles, mp 32 °C [after sublimation at 30 °C (0.15 mmHg)]. The bicyclic peroxide **3** gave a satisfactory elemental analysis and exhibited ^1H NMR (CCl_4) resonances at δ 0.85 (m, cyclopropyl, 4 H), 1.87 (broad s, methylenic, 4 H), and 3.80 (broad s bridgehead, 2 H) and IR (CCl_4) bands at 3080 (cyclopropyl CH), 2980–2940 (aliphatic CH), 1460 (CH_2 bending), and 1018 cm^{-1} (peroxide). The following chemical transformations confirm this structure assignment. Thus, catalytic hydrogenation of **3** over 10% Pd/C as well as thiourea reduction in MeOH gave the *cis*-diol **4** in 92% yield, n^{20}_D 1.4935 (after VPC collection under the conditions described for diol **8**). Diol **4** gave a satisfactory elemental analysis and exhibited ^1H NMR ($CDCl_3$) resonances at δ 0.30–1.00 (m, cyclopropyl, 4 H), 1.95 (broad s, CH_2, 4 H), 2.39 (broad s, –OH, exchanged with D_2O, 2 H), and 3.48 (m, OCH, 2 H) and IR ($CHCl_3$) bands at 3710–3200 (OH), 3065 (cyclopropyl CH), 2995–2860 (aliphatic CH), 1420 (CH_2 bending), and 1040 cm^{-1} (CO). Diol **4** could also be obtained by diimide reduction of the unsaturated diol **8** in MeOH at 0 °C, showing identical spectral data. Finally, treatment of the saturated endoperoxide **3** with triethylamine in CH_2Cl_2 at 0 °C gave the ketol **5** in 87% yield, n^{20}_D 1.4856 (after VPC collection under the conditions described for diol

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4). Ketol **5** exhibited a satisfactory elemental analysis and showed ^{1}H NMR ($CDCl_3$) resonances at δ 1.18 (broad s, cyclopropyl, 4 H), 1.72 (broad s, OH, exchanged with D_2O, 1 H), 1.90–2.70 (m, CH_2, 4 H), and 4.11 (m, OCH, 1 H) and IR ($CHCl_3$) bands at 3700–3240 (OH), 3060 (cyclopropyl CH), 2995–2940 (aliphatic CH), 1720 (C=O), 1446 and 1412 (CH_2 bending), and 1070 and 1050 (CO).

On the basis of the spectral data and chemical transformations (cf. Scheme I) the intervention of the strained unsaturated endoperoxide **2** in the photooxygenation of spirodiene **1** is confirmed. Its reductive trapping with diimide offers a convenient synthetic entry to the saturated bicyclic peroxide **3**, difficult to come by via alternatives routes. We are extending this synthetic methodology to prepare otherwise inaccessible bicyclic peroxides in order to explore their thermal and photochemical behavior.

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(8) NIH Career Development Awardee (1975–1980).

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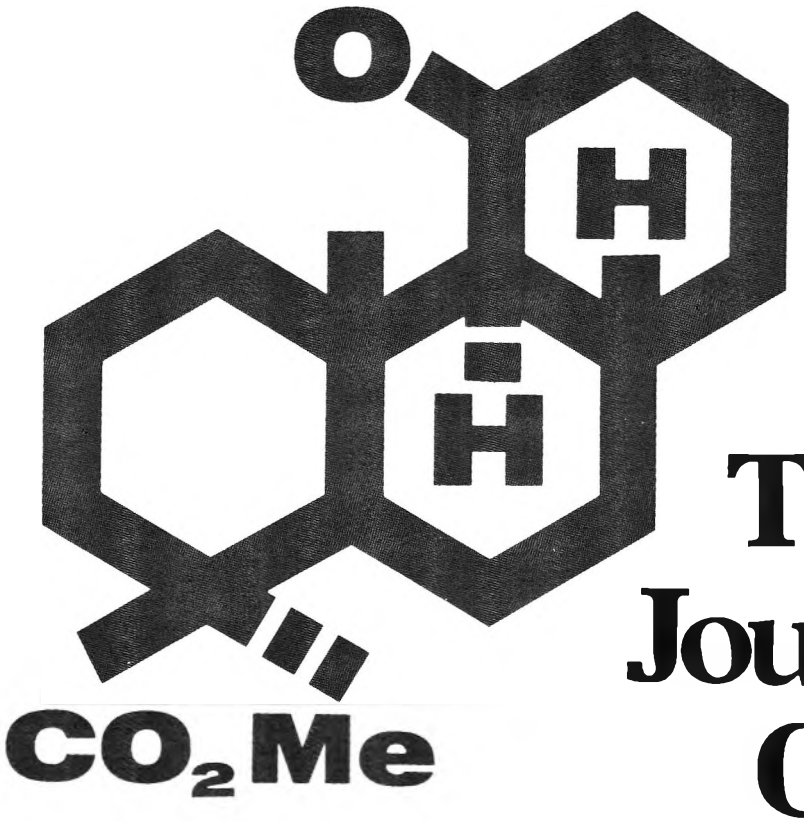

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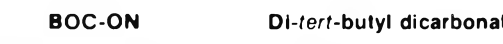

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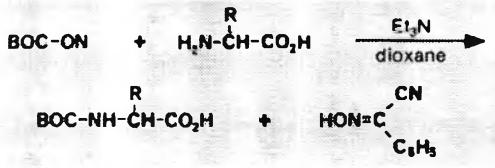
simply and rapidly with amino acids to provide the protected derivatives in excellent yields.

tert-Butoxycarbonylation with **BOC-ON**[2,3] is accomplished by stirring a dioxane solution of the amino acid with a 10% excess of the reagent and a 50%

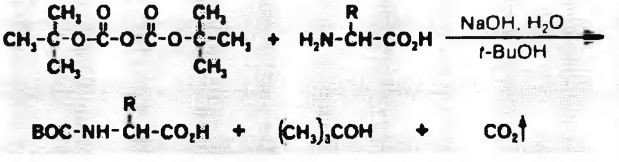


excess of triethylamine at room temperature for several hours. Several *t*-BOC-amino acids prepared in this manner are given in Table 1.[3]

Table 1

Amino acid	Yield (%)
Gly	87
Leu	72
Met·DCHA	82
Phe·DCHA	98
Thr·DCHA	100
Tyr·DCHA	82

tert-Butoxycarbonylation with **di-*tert*-butyl dicarbonate**[4,5,6] involves the treatment of the sodium or amine salts of amino acids with **di-*tert*-butyl dicarbonate** at room temperature for 10-30 minutes. Only *tert*-butyl alcohol and carbon dioxide are formed as by-products.



Some of the *t*-BOC-amino acids which have been prepared in this manner are given in Table 2.[4]

Table 2

Amino acid	Yield (%)
Ala·DCHA	84-88
MeAla	74
Val·DCHA	88
$(Lys)_2Cu$	94
$(Orn)_2Cu$	95
Asp(OBzl)	83
Glu(OBzl)·DCHA	86

Aldrich is pleased to offer a choice between two excellent reagents for the introduction of the *t*-BOC protecting group. To each his own!

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20,524-9 Di-*tert*-butyl dicarbonate, 99% **10g $10.00; 50g $45.00**

19,913-3 Di-*tert*-butyl dicarbonate, 97% **25g $12.00; 100g $45.00**

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