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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 14

JULY 8, 1977

The Maytansinoids. Isolation, Structural Elucidation, and Chemical Interrelation of Novel Ansa Macrolides[1a,2]

S. M. Kupchan,[1b] Yasuo Komoda, Alan R. Branfman, Albert T. Sneden,* William A. Court, Gareth J. Thomas, H. P. J. Hintz, Roger M. Smith, Aziz Karim, Gary A. Howie, Ashok K. Verma, Yoshimitsu Nagao, Richard G. Dailey, Jr., Virginia A. Zimmerly, and William C. Sumner, Jr.

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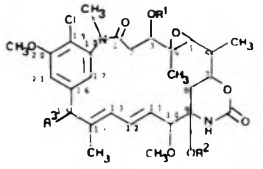
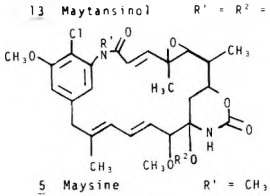
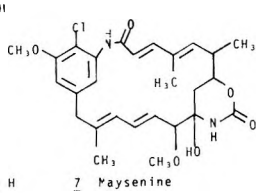
The details of the isolation and structural elucidation of the potent antileukemic ansa macrolide principles maytansine (**1**), maytanprine (**2**), maytanbutine (**3**), maytanvaline (**4**), and maytanacine (**12**), and the companion maytansides, maysine (**5**), normaysine (**6**), maysenine (**7**), and maytansinol (**13**), are reported. The isolation and characterization of a new antileukemic principle, maytanbutacine (**8**), is also reported. **1**, **2**, **3**, and **4** were shown to be *N*-acyl amino acid esters of **13**, and **12** was found to be the acetate ester of **13**. Reductive cleavage of **3** and **12** afforded **13** as well. **8** was found to contain two acyl ester groups, a C-3 isobutyrate ester and a C-15 acetate ester. **5**, **6**, and **7** all lack the C-3 ester moiety, but retain the ansa macrolide ring system.

In the course of a continuing search for tumor inhibitors from plant sources, we found that an alcoholic extract of *Maytenus serrata* (Hochst. ex A. Rich.) R. Wilczek[3a,b] showed significant inhibitory activity in vitro against cells derived from human carcinoma of the nasopharynx (KB) and in vivo against five standard animal tumor systems.[4] Our preliminary communications[5-7] described the isolation and structural elucidation of the potent antileukemic (PS) maytanside esters, maytansine (**1**), maytanprine (**2**), maytanbutine (**3**), and maytanvaline (**4**), as well as the maytansides, maysine (**5**), normaysine (**6**), and maysenine (**7**). Chemical[8,9] and biological[10-17] interest in the maytansinoids continues and maytansine is currently undergoing clinical trials under the auspices of the National Cancer Institute. In this paper we present in detail the isolation and structural elucidation of the maytansinoids, and, in addition, the characterization of a new maytanside diester, maytanbutacine (**8**), is described.



1	Maytansine	$R^1 = COCH(CH_3)N(CH_3)COCH_3$; $R^2 = R^3 = H$
2	Maytanprine	$R^1 = COCH(CH_3)N(CH_3)COCH_2CH_3$; $R^2 = R^3 = H$
3	Maytanbutine	$R^1 = COCH(CH_3)N(CH_3)COCH(CH_3)_2$; $R^2 = R^3 = H$
4	Maytanvaline	$R^1 = COCH(CH_3)N(CH_3)COCH_2CH(CH_3)_2$; $R^2 = R^3 = H$
8	Maytanbutacine	$R^1 = COCH(CH_3)_2$; $R^2 = H$; $R^3 = OCOCH_3$
9	Desacetylmaytanbutacine	$R^1 = COCH(CH_3)_2$; $R^2 = H$; $R^3 = OH$
10	Colubrinol acetate	$R^1 = COCH(CH_3)N(CH_3)COCH(CH_3)_2$; $R^2 = H$; $R^3 = OCOCH_3$
11	Maytansine bromopropyl ether	$R^1 = COCH(CH_3)N(CH_3)COCH_3$; $R^2 = CH_2CH_2CH_2Br$; $R^3 = H$
12	Maytanacine	$R^1 = COCH_3$; $R^2 = R^3 = H$
13	Maytansinol	$R^1 = R^2 = R^3 = H$





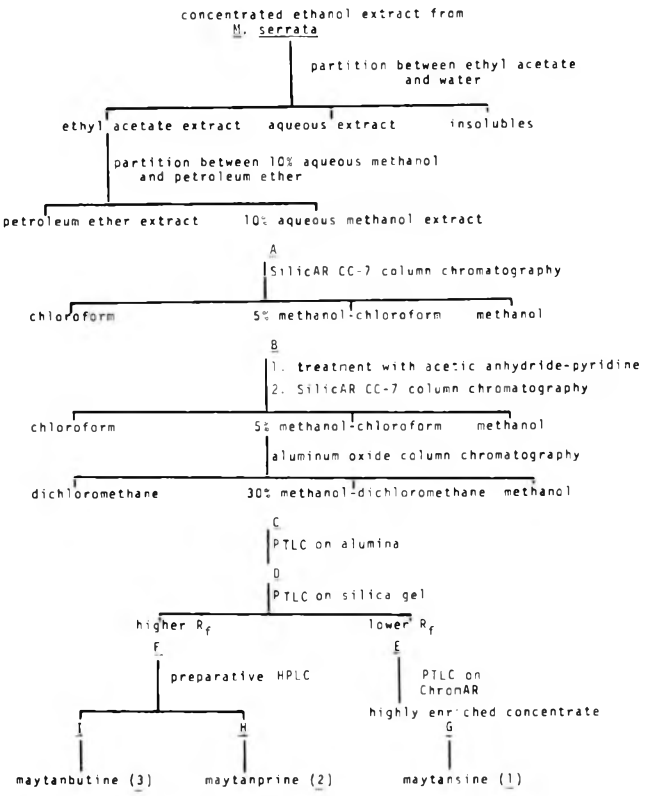
5	Maysine	$R^1 = CH_3$; $R^2 = H$
6	Normaysine	$R^1 = R^2 = H$
14	Maysine methyl ether	$R^1 = R^2 = CH_3$

7 Maysenine

Elemental analysis of fraction G indicated the presence of three nitrogen atoms. Partitioning between 2 N hydrochloric acid and ether, with the active principle remaining in the ether, indicated that none of the nitrogen atoms was strongly basic. Attempts to prepare a quaternary salt derivative from fraction G revealed that a common crystalline product, apparently a methyl derivative, was formed in methanolic solution in low yield (<1%). Similar experiments in ethanolic

Fractionation (Chart I) of the ethanolic extract, guided by assay against KB tissue culture and PS leukemia in mice, revealed that the inhibitory activity was concentrated, successively, in the ethyl acetate layer of an ethyl acetate–water partition and in the methanol layer of a 10% aqueous methanol–petroleum ether partition. Column chromatography of the aqueous methanol solubles on SilicAR CC-7 was followed by treatment of the 5% methanol–chloroform eluent with acetic anhydride–pyridine,[18] and the resulting residue was subjected to extensive column chromatography first on SilicAR and then on alumina. The fraction eluted with 30% methanol–chloroform from the alumina column was then subjected to preparative thin layer chromatography (PTLC) on alumina to give fraction D. Further purification of fraction D by PTLC on silica gel yielded fraction F (high R_f) and fraction E (low R_f), both of which showed high biological activity. PTLC of fraction E on ChromAR 7GF afforded a highly enriched concentrate (fraction G, 1 mg/kg of plant) as a solid residue which was homogeneous by both silica gel and alumina TLC yet resisted all attempts at crystallization.

Chart I. Fractionation of the Active Extract from *Maytenus serrata*



solution afforded a common crystalline ethyl derivative also in low yield. Accordingly, when fraction G was treated with 3-bromopropanol and *p*-toluenesulfonic acid in dichloromethane at room temperature, the crystalline 3-bromopropyl derivative, **11**, $C_{37}H_{51}BrClN_3O_{10}$, was obtained in 10% yield. Treatment of **11** with 2 N hydrochloric acid in aqueous methanol afforded a crystalline hydrolysis product which was used to seed a solution of fraction G and yield crystalline maytansine (**1**, 0.2 mg/kg of plant, 0.00002%). On the basis of elemental analysis and high-resolution mass spectrometry, maytansine was assigned the molecular formula $C_{34}H_{46}ClN_3O_{10}$ [mass spectrum *m/e* 630.2680, $C_{33}H_{43}ClN_2O_8$ [M − 61 (H_2O + HNCO)][19] = 630.2708].

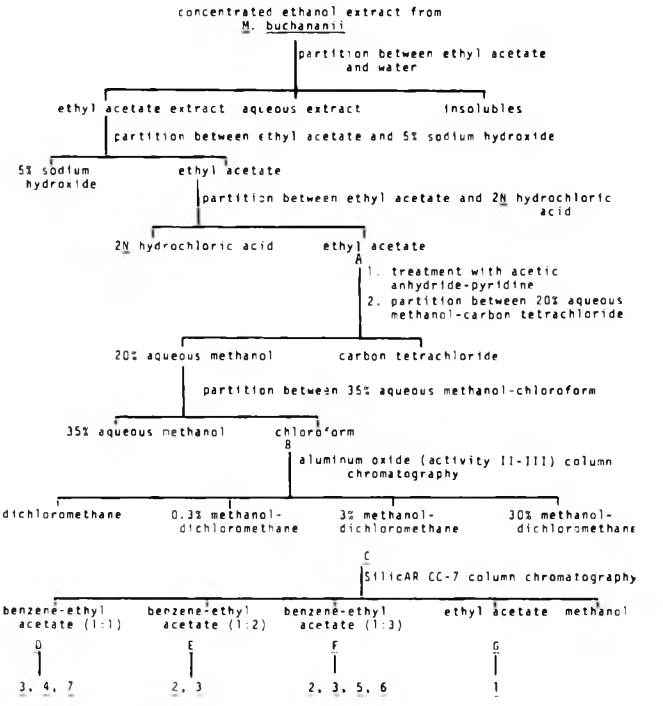
Owing to the extremely small quantity of maytansine obtained and the reversible interrelation of maytansine (**1**) and 3-bromopropyl derivative **11**, the latter compound was an attractive target for x-ray crystallographic analysis. The structure of **11** was solved by the heavy-atom method,[5,20] and led to structural assignment **1** for maytansine. The absolute configurations of **11** were found to be 3*S*, 4*S*, 5*S*, 6*R*, 7*S*, 9*S*, 10*R*, and 2′*S*.

Fraction F (Chart I) was purified further by preparative high-pressure liquid chromatography (HPLC) to give fractions H and I. These fractions were crystallized by seeding each with the crystalline hydrolysis product obtained from their respective alkyl ether derivatives, to give maytanprine (**2**, 0.031 mg/kg) and maytanbutine (**3**, 0.036 mg/kg).

A search for a better source of maytansine revealed that *Maytenus buchananii* (Loes.) R. Wilczek, collected in Kenya in 1970 and 1972[3a] and fractionated by the same procedure as *M. serrata*, gave higher yields of maytanprine (1.2 mg/kg) and maytanbutine (0.9 mg/kg) as well as maytansine (1.5 mg/kg).

Additional extracts of *Maytenus buchananii* were fractionated by an improved procedure as shown in Chart II. The active principles were concentrated, successively, in the ethyl acetate layers of an ethyl acetate–water partition, an ethyl acetate–5% sodium hydroxide partition, and an ethyl ace-

Chart II. Fractionation of the Active Extract from *Maytenus buchananii*



tate–2 N hydrochloric acid partition to give fraction A. After treatment of fraction A with acetic anhydride–pyridine,[18] the active components were further concentrated in the aqueous methanol layer of a 20% aqueous methanol–carbon tetrachloride partition and in the chloroform layer of a 35% aqueous methanol–chloroform partition to afford fraction B. Column chromatography of fraction B over alumina (activity II–III) concentrated the activity in fraction C (3% methanol–dichloromethane) which was then subjected to column chromatography over SilicAR CC-7 to yield fractions D–G. PTLC in several systems gave maytansine (**1**) from fraction G, maytanprine (**2**) from fractions E and F, maytanbutine (**3**) from fractions D, E, and F, maytanvaline (**4**) from fraction D, maysine (**5**) and normaysine (**6**) from fraction F, and maysenine (**7**) from fraction D.

The relationship of compounds **2**–**7** to maytansine (**1**) was established from the spectral and analytical data. The ultraviolet (UV) spectra of all the compounds were almost identical with that of maytansine, with characteristic absorptions at 233, 243, 254, 282, and 290 nm. The infrared (IR) spectra of **2**–**4** were also virtually identical with that of maytansine, and **5**–**7** differed primarily in the disappearance of the ester carbonyl absorption at 5.75 μ and the appearance of a carbonyl band in the 6.12–6.21-μ region. The respective empirical formulas were assigned based on microanalyses and high-resolution mass spectral measurements. The mass spectral fragmentation patterns (Table I) also gave valuable structural information.

The four maytanside esters (**1**–**4**) possess the same mass spectral peaks at *m/e* 485, 470, and 450. The ion at *m/e* 485 results from the initial loss of H_2O and HNCO from the carbinolamide moiety (a) and subsequent elimination of the ester side chains as carboxylic acids (b). The ion at *m/e* 470 is *m/e* 485 minus a methyl group and the ion at *m/e* 450 is *m/e* 485 minus the chlorine atom. The principal peaks derived from side chain cleavage (Table I) correspond to (b) − (OH) and (b) − (COOH), and between each of the side chain acids of compounds **1**–**4** there is one methylene group difference, respectively. Each compound also has major ions at *m/e* 58 and 44 derived from the (b) − (COOH) fragment which correspond to $C_3H_8N^+$ and $C_2H_6N^+$, respectively. These mass spectral

Table I[a]

Compd	M⁺ − (a)	M⁺ − (a + b)	485 − (CH_3)	485 − (Cl)	b − (OH)	b − (COOH)
1	630	485	470	450	128	100
2	644	485	470	450	142	114
3	658	485	470	450	156	128
4	672	485	470	450	170	142
12	545	485	470	450		
13	503	485	470	450		

Compd	M⁺ − (a)	M⁺ − (a + CH_3)	M⁺ − (a + Cl)
5	485	470	450
6	471	456	436
7	455	440	420

Compd	M⁺ − (a)	M⁺ − (a + c)	M⁺ − (a + c + b)	483 − (CH_3)	483 − (Cl)
8	631	571	483	468	448
9	589	571	483	468	448

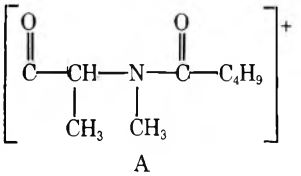
[a] (a) = H_2O + HNCO; (b) = R′OH; (c) = R^3H.

characteristics indicated that **2–4** have ansa macrolide structures similar to **1** except for differences in the *N*-acyl group of the ester side chains.

The chemical relationships among compounds **1–4** were confirmed by comparison of their nuclear magnetic resonance (NMR) spectra. The NMR spectra of **2–4** differed from that of **1** solely in the signals attributed to the terminal *N*-acyl group, as expected from the mass spectral fragmentation patterns. The NMR signals for the *N*-acyl group of maytanprine (**2**) [δ 1.18 (3 H, t, J = 7 Hz), 2.37 (1 H, m), 2.41 (1 H, m)] indicated a $-CH_2CH_3$ group with nonequivalent methylene protons. This was confirmed by spin-decoupling studies.[21,22]

The NMR signals for the *N*-acyl group of maytanbutine (**3**) [δ 1.12 (3 H, d, J = 7 Hz), 1.19 (3 H, d, J = 7 Hz), 2.80 (1 H, m)] suggested a $-CH(CH_3)_2$ moiety with two nonequivalent methyl groups. This was supported by a combination of spin decoupling experiments and solvent shift studies. The two signals for the C-2′ N-CH_3 group [δ 2.87 (0.75 H, s) and 2.92 (2.25 H, s)] in the NMR of **3** indicated that the rate of rotation about the carbonyl to nitrogen bond was reduced by steric interaction of the isopropyl group and the aromatic ring.[21,22]

The mass spectral data for maytanvaline (**4**) suggested a molecular weight of 170 for the ester fragment, consistent with structure A. Hydrolysis of **4** with sodium carbonate in



A

50% aqueous methanol at room temperature yielded maysine (**5**) and *N*-isovaleryl-*N*-methyl-L-alanine, characterized as its methyl ester by comparison with a synthetic sample prepared by acylation of *N*-methyl-L-alanine methyl ester with isovaleryl chloride.[23]

The mass spectral characteristics of maytansides **5–7** (Table I) indicated that these compounds have ansa macrolide structures similar to **1–4** but lack the ester side chains. The NMR spectrum of maysine (**5**) showed the presence of a trans α,β-unsaturated amide [δ 5.65 (1 H, d, J = 16 Hz), 6.37 (1 H, d, J = 16 Hz)] with no proton in the γ position. Treatment of maytansine with sodium carbonate in 50% aqueous methanol at room temperature gave one major product which was identical with maysine in all respects. This information, along with the disappearance of the carbonyl IR absorptions of the C_3 ester, established structure **5** for maysine.

The mass spectral fragmentation pattern of normaysine (**6**) with M⁺ − (a) at *m/e* 471, M⁺ − (a + CH_3) at *m/e* 456, and M⁺ − (a + Cl) at *m/e* 436 indicated that normaysine is the *N*-demethyl homologue of maysine. The NMR spectrum of **6** showed a signal corresponding to the proton on C-1 nitrogen [δ 7.38 (1 H, br s), exchangeable with D_2O] and lacked the NCH_3 signal of maysine.

The mass spectrum of maysenine (**7**) showed that **7** is a deoxy derivative of **6**. The NMR spectrum of **7** showed signals for a vinyl methyl group [δ 1.56 (3 H, br s)] and vinyl proton [δ 5.50 (1 H, br d, J = 10 Hz)] instead of the signals for the 4-methyl and 5-H protons of the 4,5-epoxide system of **6** and a downfield shift of the C-2 and C-3 protons relative to **6**. The structure of **7** was supported also by the bathochromic shift of its UV and IR carbonyl absorption bands in comparison with those of **6**. Chemical interrelation was effected by reductive elimination of the epoxide of **6** with chromous chloride in acetic acid to give maysenine (**7**).[24]

The relationships established for maytansinoids **1–7** aided the structural elucidation of a previously unreported active maytansinoid from *M. serrata*, maytanbutacine (**8**). The plant material was fractionated as in Chart I to give fraction E which was separated into two bands by PTLC on alumina. PTLC of the lower R_f band on silica gel again gave two bands, and HPLC of the higher R_f band gave a fraction enriched in maytanbutacine (**8**). Further purification of this fraction by PTLC on ChromAR and then crystallization from dichloromethane–diethyl ether yielded maytanbutacine (**8**) (0.115 mg/kg plant, 0.0000115%).

The structure of maytanbutacine (**8**) differs from that of colubrinol acetate (**10**)[25] only in the C-3 side chain ester. The UV spectrum was typical of a maytanside ester. The IR spectrum was also similar to those of maytanside esters **1–4**, but the band at 5.73 μ attributed to the ester carbonyl was more intense than in the spectra of **1–4**.

The mass spectral data (Table I) provided an important indication of the structure. A weak parent ion was observed at *m/e* 692, and a strong ion at *m/e* 631 resulted from the typical loss of H_2O and HNCO from the carbinolamide moiety of the parent compound. The next major ion expected for a normal maytanside ester would be at *m/e* 485 (loss of the side chain acid). However, the next major ion observed was at *m/e*

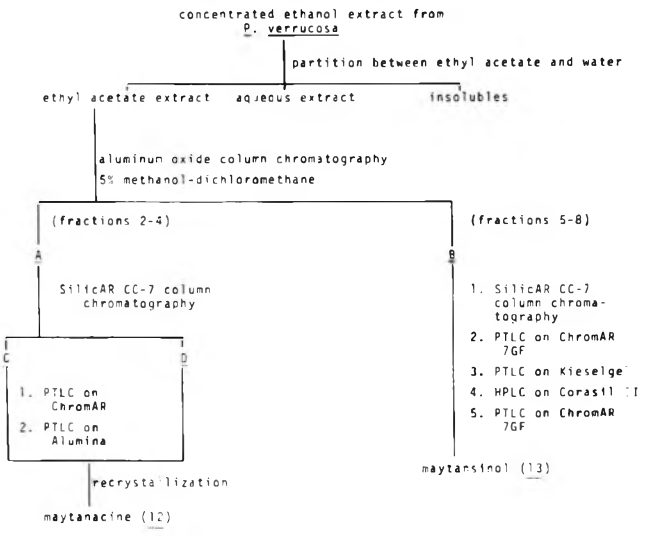
571, a loss of 60 mass units and typical of the loss of CH_3COOH. A further loss of 88 mass units, corresponding to loss of $C_4H_8O_2$, gave a major ion at *m/e* 483. The next two major ions, *m/e* 468 and 448, resulted from the loss of CH_3 and Cl, respectively, from the *m/e* 483 ion. The latter three ions thus fit the typical fragmentation pattern of maytansinoids but each ion was two mass units less than expected. This, taken together with the ions at *m/e* 631 and 571, indicated that there were two side chain esters, one of which was an acetate.

The relative positions of the two esters and the identity of the second ester were established by NMR and chemical means. The NMR spectrum revealed that there was no *N*-methyl in the side chain ester. There was, however, a six-proton doublet centered at δ 1.28 and multiple signals from δ 2.6 to 2.0 containing three protons, two which could be assigned to the C-2 protons and one which could be assigned to the second ester. These data suggested that the second ester was an isobutyrate. In addition, the two doublets corresponding to the C-15 protons which should appear at δ 3.7 and 3.1 were absent. Instead signals were observed for an acetate methyl singlet at δ 2.23 and a one-proton singlet at δ 6.21. Mild hydrolysis of maytanbutacine with sodium bicarbonate in aqueous methanol removed the acetate, and in the NMR spectrum the one-proton singlet at δ 6.21 shifted upfield to δ 5.37. This behavior was similar to that observed in colubrinol acetate[25] and indicated that the isobutyrate ester was at C-3, since it was not affected by the hydrolysis. The acetate was, therefore, at C-15. This latter fact was confirmed by oxidation of the deacetyl compound (**9**) with Jones reagent to form a conjugated enone system, as indicated by UV.

The biological activity of the extracts of both *M. serrata* and *M. buchananii* prompted a search of other related Celastraceae plants as potential sources of the maytansinoids. Thus, *Putterlickia verrucosa* Szyszyl. was found to be the best source of maytansine to date.[8] A 1-kg ethanolic extract of *P. verrucosa*[26] was fractionated by a modification of the procedure developed for *M. serrata* (Chart I) guided both by assay against PS and KB and by analytical TLC using authentic materials as references. The ethanolic extract was partitioned between ethyl acetate and water, and the ethyl acetate soluble material was subjected to column chromatography over SilicAR CC-7. The fraction which was eluted with 5% methanol–chloroform was treated with acetic anhydride–pyridine, and the residue from this reaction was subjected to column chromatography over SilicAR CC-7. The fraction which was eluted with 5% methanol–chloroform from this column was then subjected to PTLC first over alumina and then over ChromAR to give three homogeneous solids which upon crystallization yielded maytansine (**1**, 12.3 mg/kg), maytanbutine (**3**, 4.5 mg/kg), and maytanprine (**2**, 8.5 mg/kg).[27] PTLC of a higher R_f band on ChromAR and subsequent crystallization yielded a new maytansinoid, maytanacine (**12**, ~0.2 mg/kg).

The high yield of maytansine and the isolation of maytanacine, apparently an acetyl derivative, prompted fractionation of *P. verrucosa* on a larger scale. To eliminate the possibility that maytanacine was an artifact arising from the acetylation step, an alternative procedure was employed. A 10-kg ethanolic extract of *P. verrucosa* (Chart III) was fractionated by a modification of the procedure developed for *M. buchananii*, again guided by biological assays and by analytical TLC using authentic materials for references. The ethanolic extract was first partitioned between ethyl acetate and water. The active ethyl acetate solubles were then subjected to column chromatography over deactivated alumina (activity II–III). The fractions which were eluted with 5% methanol–chloroform were examined by HPLC, and similar fractions were combined to give fractions A (fractions 2–4) and B (fractions 5–8).

Chart III. Fractionation of the Active Extract from *Putterlickia verrucosa*



Fraction A was subjected to column chromatography over SilicAR CC-7 with increasing amounts of ethyl acetate in benzene as eluent. The fractions which were eluted with 66% ethyl acetate in benzene were examined by HPLC, and similar fractions were combined to give fractions C and D, both of which contained maytanacine (**12**). PTLC of each fraction on ChromAR with 5% methanol–chloroform followed by PTLC of the band corresponding to **12** on alumina with 10% methanol–ethyl acetate gave pure **12**. Crystallization from dichloromethane–hexanes yielded a total of 0.18 mg/kg of maytanacine (**12**).

The presence of such a variety of C-3 esters prompted an effort to isolate a possible common precursor, the C-3 alcohol. To aid in the isolation, synthetic maytansinol (**13**) was prepared by reductive cleavage of maytanbutine (**3**). Treatment of **3** with lithium aluminum hydride in dry tetrahydrofuran[28] gave, after extensive PTLC of the products, maytansinol (**13**) in 40% yield. This synthetic material was then used as a reference in the isolation of the naturally occurring maytansinol.

Fraction B was subjected to column chromatography over SilicAR CC-7 and eluted with increasing amounts of methanol in chloroform. The material eluted with 5% methanol–chloroform was then chromatographed on ChromAR developed with 5% methanol–ethyl acetate. The band corresponding to synthetic maytansinol was isolated and subjected to preparative TLC on Kieselgel plates developed with 15% ethanol–ether. Further preparative HPLC and TLC gave pure maytansinol (**13**) (0.025 mg/kg), identical in every respect with synthetic **13**.

To confirm the chemical relationship between maytanacine and maytansinol, maytanacine (**12**) was treated with lithium aluminum hydride to give maytansinol (**13**). This maytansinol was converted back to maytanacine (53%) by treatment with acetic anhydride and pyridine[29] and was identical with the natural product in all respects.

The structures of maytanacine and maytansinol were confirmed by their spectra. The UV spectra of both **12** and **13** were typical of maytansinoids, with maxima at 233, 242, 252, 281, and 289 nm. The IR spectra confirmed the principal difference between **12** and **13**; **12** had the absorptions (5.70, 5.80, 6.00 μ) expected for a maytanside ester, while **13** had only two carbonyl bands (5.85 and 6.06 μ). The absence of the band at 5.70 μ indicated that **13** was missing the side chain ester moiety at C-3.

The mass spectral data (Table I) corroborated differences

between **12** and **13**. The mass spectrum of **12** had fragments at *m/e* 545 [$M^+ - (H_2O + HNCO)$] and 485 [$M^+ - (H_2O + HNCO)$ − side chain acid]. The loss of 60 mass units, which corresponded to loss of the side chain acid, indicated that the ester was an acetate. The fragmentation pattern of **13** showed ions at *m/e* 503 [$M^+ - (H_2O + HNCO)$] and 485 [$M^+ - (H_2O + HNCO)$ − side chain acid]. Loss of 18 mass units as the "side chain acid" corresponded to loss of water, as would be expected for **13**.

The NMR spectrum of maytanacine lacked signals for the C-2′ H, C-2′ CH_3, and NCH_3 of the amino ester side chain, but had an acetate methyl singlet at δ 2.18. The NMR spectrum of maytansinol lacked signals due to a side chain ester; the C-3 proton signal was shifted upfield and obscured by other peaks, and the C-3 hydroxyl proton appeared as a singlet at δ 3.44.

The spectral evidence taken in conjunction with the chemical evidence provided by the lithium aluminum hydride reductive cleavage and subsequent acylation thus established the structure of maytanacine as **12** and that of maytansinol as **13**.

We would like to acknowledge with thanks the preparation of many large scale extracts of the plant material by Mr. Barry R. Sickles.

Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Ultraviolet absorption spectra were determined on Beckman Model DK-2A and Coleman Hitachi Model EPS-3T recording spectrophotometers. Infrared spectra were determined on a Perkin-Elmer Model 257 recording spectrophotometer. Nuclear magnetic resonance spectra were determined on either a Varian HA-100 spectrometer or a JEOL PS-100 pulsed FT NMR spectrometer interfaced to a Texas Instrument JEOL 980A computer, with tetramethylsilane as the internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS902 spectrometers at the University of Virginia. Additional mass spectra were obtained at the Mass Spectrometry Laboratories of Battelle Memorial Institute and Research Triangle Institute. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 polarimeter. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Analytical high-pressure liquid chromatography was performed on Waters Associates Models ALC-100 and ALC-202 employing a Corasil II column (4 ft × 0.125 in.) with 1.5% methanol–dichloromethane as the eluent and a flow rate of 1 mL/min. Gas–liquid chromatography was carried out on a Varian Model 1860-1 aerograph moduline gas chromatograph. Petroleum ether refers to the fraction with bp 60–68 °C. All thin layer chromatography was carried out on prepared plates (E. Merck and Mallinckrodt).

Maytenus serrata. The ground dried fruit (10 kg) of *M. serrata* was extracted in Soxhlet extractors with 80 L of 95% ethanol for 6 h. The plant material was extracted again with 80 L of fresh 95% ethanol for 15 h. After a third extraction of 24 h, the extracts were combined and concentrated at 40–50 °C in vacuo to give a dark gum (1.35 kg). The concentrated alcoholic extract was partitioned between ethyl acetate (3 L) and water (1.5 L) by stirring vigorously with a mechanical stirrer for 12 h. The suspension was filtered and the insoluble material was treated two more times with ethyl acetate (1 L) and water (0.5 L), followed by filtration. The aqueous layers were combined and washed with ethyl acetate (2 × 0.5 L). The combined ethyl acetate layers were washed with water (0.5 L) and concentrated to a dark gum (220 g). This residue was partitioned between 10% aqueous methanol (1.5 L) and petroleum ether (1 × 1.5 L, 2 × 0.5 L). The combined petroleum ether layers were washed with 10% aqueous methanol (300 mL) and concentrated to a dark green oil (60 g). Concentration of the aqueous methanol layers gave a dark green gum (A, 160 g).

Fraction A was dissolved in 250 mL of 30% methanol–chloroform and adsorbed on 320 g of SilicAR. The mixture was thoroughly dried and placed on top of a column prepared from 1.28 kg of SilicAR in chloroform, and 3.2-L fractions were collected. Fractions 1–5 were eluted with chloroform, fractions 6–15 with 5% methanol–chloroform, and fractions 16–18 with methanol. The PS and KB active fractions 7 and 8 were combined (B, 18 g). A solution of fraction B in 108 g of pyridine–acetic anhydride (1:2) was stirred at room temperature for 15 h, then concentrated to a dark oil.

The dark oil was chromatographed on a column of SilicAR (100 g), collecting 200-mL fractions. Fractions 1–5 were eluted with chloroform, fractions 6–10 with 5% methanol–chloroform, and fractions 11–13 with methanol. The PS and KB active fractions 7–10 were concentrated, then chromatographed on a column of alumina (Woelm, activity I) collected 18-mL fractions. Fractions 1–3 were eluted with dichloromethane, fractions 4–8 with 30% methanol–chloroform, and fractions 9–11 with methanol. The PS and KB active fractions 5–8 were combined (C, 720 mg).

PTLC of fraction C on alumina developed with 7% methanol–ethyl acetate gave a band (R_f 0.5) in which most of the activity was concentrated (D, 120 mg). PTLC of fraction D on silica gel developed with 3% methanol–ethyl acetate gave a band (R_f 0.2) corresponding to fraction E (19 mg) and all bands of higher R_f than fraction E were combined to afford fraction F (57 mg). Fraction E was further purified by PTLC on ChromAR developed with 5% methanol–ethyl acetate to give a highly enriched concentrate of maytansine (**1**) (R_f 0.25, fraction G, 10 mg).

Maytansine Bromopropyl Ether (11). Method A. A mixture of fraction G (20.2 mg), 3-bromopropanol (234 mg), and *p*-toluenesulfonic acid (0.6 mg) in 1.0 mL of dichloromethane was allowed to stand at room temperature for 7 h, then quenched with 3 mL of 5% sodium bicarbonate solution and 10 mL of dichloromethane. The water layer was extracted with dichloromethane (2 × 5 mL) and the combined dichloromethane layers were washed with water and concentrated to dryness. PTLC of this residue on ChromAR developed with ethyl acetate gave a product (11.6 mg) which crystallized from a mixture of dichloromethane–hexane. Two recrystallizations gave 3.7 mg (~15%) of maytansine 3-bromopropyl ether (**11**): mp 176–178 °C; IR (KBr) 5.76, 6.01, 6.34, 8.42, 9.29 μ. Recrystallization of **11** from methanol by slow evaporation gave crystals suitable for x-ray analysis.

Method B. A 1-dram vial containing maytansine (4.8 mg), 3-bromopropanol (60 μL, Aldrich 98%, purified by PTLC on silica gel 60 F-254 using ethyl acetate as the eluent and visualization with iodine), benzene (300 μL, dried over 3 Å molecular sieves), and trifluoroacetic acid (4 drops) was allowed to stand for 3 days under nitrogen in a sealed 1-oz jar containing 3 Å molecular sieves. PTLC on silica gel 60 F254 plates developed with ethyl acetate followed by crystallization (twice) from methylene chloride–ether–hexanes gave **11** (3.1 mg, 55%, 71% based on maytansine recovered).

Acid Hydrolysis of Maytansine Bromopropyl Ether (11). A solution of **11** in 10% aqueous methanol (0.1 mL) and 1 drop of 2 N hydrochloric acid was allowed to stand at room temperature for 2.5 h, then quenched with 1 mL of 5% sodium bicarbonate solution and 5 mL of dichloromethane. The water layer was extracted with dichloromethane (2 × 2 mL) and the combined organic layer was purified by PTLC on ChromAR developed with ethyl acetate. Crystallization twice from dichloromethane–hexane gave the hydrolysis product (**1**).

Maytansine (1). A solution of fraction G (54.9 mg) in dichloromethane–hexane was seeded with the crystalline hydrolysis product of **11** to induce crystallization. Several recrystallizations from this system and finally from dichloromethane–ether gave maytansine (**1**, 11.0 mg, 0.2 mg/kg of plant): mp 171–172 °C; $[\alpha]^{26}_D$ − 145° (*c* 0.055, $CHCl_3$); UV max (EtOH) 233 nm (ε 29 800), 243 (sh, 27 100), 254 (27 200), 282 (5690), 290 (5520); IR (KBr) 5.75, 5.80, 6.02, 6.34, 8.42, 9.26 μ; NMR ($CDCl_3$) δ 0.87 (3 H, s, C-4 CH_3), 1.34 (3 H, d, J = 6 Hz, C-6 CH_3), 1.37 (3 H, d, J = 7 Hz, C-2′ CH_3), 1.69 (3 H, br s, C-14 CH_3), 2.15 (3 H, s, C-2′ $NCOCH_3$), 2.21 (1 H, dd, $J_{2,2}$ = 15, $J_{2,3}$ = 3 Hz, C-2 H), 2.65 (1 H, dd, $J_{2,2}$ = 15, $J_{2,3}$ = 12 Hz, C-2 H), 2.89 (3 H, s, C-2′ NCH_3), 3.04 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.13 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 3.22 (3 H, s, C-1 NCH_3), 3.38 (3 H, s, C-10 OCH_3), 3.50 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.53 (1 H, s, C-9 OH), 3.67 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 3.99 (3 H, s, C-20 OCH_3), 4.28 (1 H, m, C-7 H), 4.79 (1 H, dd, $J_{2,3}$ = 12, 3 Hz, C-3 H), 5.35 (1 H, q, J = 7 Hz, C-2′ H), 5.66 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 6.24 (1 H, br s, C-9 NH), 6.42 (1 H, dd, $J_{11,12}$ = 15, $J_{12,13}$ = 11 Hz, C-12 H), 6.70 (1 H, br d, $J_{12,13}$ = 11 Hz, C-13 H), 6.75, 6.84 (2 H, d, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H), 0.80–2.50 (3 H, C-6 H, C-8 H_2); mass spectrum *m/e* 630.2680, $C_{33}H_{43}ClN_2O_8$ [$M - 61 (H_2O + HNCO)$] = 630.2708.

Anal. Calcd for $C_{34}H_{46}ClN_3O_{10}\cdot H_2O$: C, 57.50; H, 6.98; Cl, 4.99; N, 5.91. Found: C, 57.34; H, 7.42; Cl, 4.81; N, 6.38.

Isolation of Fraction F from *Maytenus buchananii*. Fraction D (296 mg) was obtained from stem barks (5.6 kg) and roots (4.0 kg) of *M. buchananii* (Loes.) R. Wilczek collected in Kenya in 1970. PTLC of fraction D on silica gel developed with ethyl acetate followed by 3% methanol–ethyl acetate gave fraction E (72 mg) which yielded 13.5 mg of maytansine (0.00015%) after further purification, and fraction F (110 mg). Preparative HPLC (Corasil II, 3 ft × 0.375 in., 2% methanol–dichloromethane, 1.4 mL/min) of fraction F gave fractions H (16 mg) and I (20 mg).

Maytanprine (2). Fraction H was crystallized by seeding with the crystalline hydrolysis product of the ethyl ether derivative of fraction H, and recrystallized three times from dichloromethane–ether to afford maytanprine (2, 0.00012%): mp 169–170 °C; $[\alpha]^{30}_D$ − 125° (*c* 0.056, $CHCl_3$); UV max (EtOH) 234 nm (ε 30 700), 243 (sh, 28 200), 254 (27 800), 282 (5870), 290 (5800); IR (KBr) 5.73, 5.80, 6.03, 6.33, 8.43, 9.26 μ; NMR ($CDCl_3$) δ 0.87 (3 H, s, C-4 CH_3), 1.18 (3 H, t, *J* = 7 Hz, C-4′ CH_3), 1.35 (3 H, d, *J* = 7 Hz, C-6 CH_3), 1.36 (3 H, d, *J* = 7 Hz, C-2′ CH_3), 1.70 (3 H, br s, C-14 CH_3), 2.19 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 3 Hz, C-2 H), 2.37 (1 H, m, C-4′ H), 2.41 (1 H, m, C-4′ H), 2.64 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 12 Hz, C-2 H), 2.86 (3 H, s, C-2′ NCH_3), 3.04 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.12 (1 H, d, $J_{15,15}$ = 12 Hz, C-15 H), 3.21 (3 H, s, C-1 NCH_3), 3.38 (3 H, s, C-10 OCH_3), 3.50 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.55 (1 H, s, C-9 OH), 3.68 (1 H, d, $J_{15,15}$ = 12 Hz, C-15 H), 4.00 (3 H, s, C-20 OCH_3), 4.28 (1 H, m, C-7 H), 4.79 (1 H, dd, $J_{2,3}$ = 12, 2.5 Hz, C-3 H), 5.40 (1 H, q, *J* = 7 Hz, C-2′ H), 5.67 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 6.26 (1 H, br s, C-9 NH), 6.42 (1 H, dd, $J_{11,12}$ = 15, $J_{12,13}$ = 11 Hz, C-12 H), 6.76 (1 H, br d, $J_{12,13}$ = 11 Hz, C-13 H), 6.66, 6.82 (2 h, d, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H), 0.80–2.00 (3 H, C-6 H, C-8 H_2); mass spectrum *m/e* 644.2810, $C_{34}H_{45}ClN_2O_8$ [M − 61 (H_2O + HNCO)] = 644.2864.

Anal. Calcd for $C_{35}H_{48}ClN_3O_{10}$: C, 59.52; H, 6.85; N, 5.95. Found: C, 59.31; H, 6.78; N, 5.89.

Maytanbutine (3). Fraction I was crystallized by seeding with the crystalline hydrolysis product of the 3-bromopropyl ether derivative of fraction I, and recrystallized three times from dichloromethane–ether to afford maytanbutine (3, 0.00009%): mp 170–171 °C; $[\alpha]^{30}_D$ − 122° (*c* 0.049, $CHCl_3$); UV max (EtOH) 234 nm (ε 33 100), 243 (sh, 30 400), 254 (30 500), 282 (6430), 290 (6380); IR (KBr) 5.72, 5.79, 6.04, 6.06, 6.34, 8.44, 9.28 μ; NMR ($CDCl_3$) δ 0.88 (3 H, s, C-4 CH_3), 1.12 (3 H, d, *J* = 7 Hz, C-4′ CH_3), 1.19 (3 H, d, *J* = 7 Hz, C-4′ CH_3), 1.35 (3 H, d, *J* = 6 Hz, C-6 CH_3), 1.36 (3 H, d, *J* = 6 Hz, C-2′ CH_3), 1.70 (3 H, br s, C-14 CH_3), 2.20 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 3 Hz, C-2 H), 2.65 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 12 Hz, C-2 H), 2.80 (1 H, m, C-4′ H), 2.87 (0.75 H, s) and 2.92 (2.25 H, s, C-2′ NCH_3), 3.04 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.12 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 3.20 (3 H, s, C-1 NCH_3), 3.37 (3 H, s, C-10 OCH_3), 3.51 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.52 (1 H, s, C-9 OH), 3.68 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 4.00 (3 H, s, C-20 OCH_3), 4.29 (1 H, m, C-7 H), 4.78 (1 H, dd, $J_{2,3}$ = 12, 3 Hz), 5.39 (1 H, q, *J* = 7 Hz, C-2′ H), 5.64 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 6.25 (1 H, br s, C-9 NH), 6.43 (1 H, dd, $J_{11,12}$ = 15, $J_{12,13}$ = 11 Hz, C-12 H), 6.79 (1 H, br d, $J_{12,13}$ = 11 Hz, C-13 H), 6.66, 6.82 (2 H, d, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H), 0.80–2.00 (3 H, C-6 H, C-8 H_2); NMR ($CDCl_3$ + C_6D_6) δ 1.17 (3 H, d, *J* = 7 Hz, C-4′ CH_3), 1.22 (3 H, d, *J* = 7 Hz, C-4′ CH_3); mass spectrum *m/e* 658.3030, $C_{35}H_{47}ClN_2O_8$ [M − 61 (H_2O + HNCO)] = 658.3021.

Anal. Calcd for $C_{36}H_{53}ClN_3O_{10}$: C, 60.03; H, 7.00; N, 5.83. Found: C, 59.87; H, 7.11; N, 5.87.

***Maytenus buchananii*, Improved Fractionation Procedure.** The ground dried stems and bark (19.8 kg) of *M. buchananii* were extracted in three batches in a Soxhlet extractor with 8 L of 95% ethanol for 6 h for each batch. The plant material was extracted again with 8 L of fresh 95% ethanol for 15 h. After a third extraction of 24 h, the extracts were combined and concentrated at 40–50 °C in vacuo to give a dark gum (963 g). The concentrated alcoholic extract was partitioned between ethyl acetate (4 L) and water (3 L) by stirring vigorously with a mechanical stirrer for 12 h. The suspension was filtered and the insoluble material was treated two more times with ethyl acetate (2 L) and water (1 L), followed by filtration. The aqueous layers were combined and washed with ethyl acetate (2 × 1 L).

The combined ethyl acetate layer was partitioned with a cold 5% sodium hydroxide solution (1 × 4 L, 4 × 1 L). The combined aqueous layer was washed with ethyl acetate (5 × 600 mL), acidified with 3 N hydrochloric acid, and extracted with ethyl acetate to give the acidic fraction which was devoid of biological activity. The combined ethyl acetate layer was then partitioned with cold 2 N hydrochloric acid (5 × 600 mL). The combined aqueous layer was washed with ethyl acetate (3 × 600 mL), basified with sodium bicarbonate, and extracted with ethyl acetate to give the alkaloidal fraction which was devoid of biological activity. The combined ethyl acetate layer was washed with water until neutral pH and concentrated to afford fraction A (135 g).

A solution of fraction A in 400 mL of pyridine–acetic anhydride (1:1) was stirred at room temperature for 15 h, then concentrated to a dark oil. The dark oil was partitioned between aqueous methanol (50 mL) and carbon tetrachloride (1 × 50 mL, 4 × 20 mL). The combined carbon tetrachloride layer was extracted with 20% aqueous methanol (7 × 20 mL) and concentrated to dryness. Water was added to the combined aqueous methanol layer to give 35% aqueous methanol layer which was partitioned with chloroform (1 × 50 mL, 4 × 20 mL). The combined chloroform layer was dried over sodium sulfate and concentrated to give fraction B (20.8 g).

Fraction B was chromatographed on a column of alumina (600 g, activity II–III), collecting 3-L fractions. Fractions 1–3 were eluted with dichloromethane, fractions 4–6 with 0.3% methanol–dichloromethane, fractions 7–10 with 3% methanol–dichloromethane, and fraction 11 with 30% methanol–dichloromethane. The PS and KB active fractions 7–11 were combined to give fraction C (4.9 g) which was chromatographed on a column of SilicAR, collecting 1-L fractions. Fractions 1–41 were eluted with benzene–ethyl acetate (1:1), fractions 42–49 with ethyl acetate, and fraction 50 with methanol. The eluent was monitored by analytical HPLC. Fractions 6–10 were combined to give fraction D (514 mg), fractions 11–17 to give fraction E (246 mg), fractions 18–41 to give fraction F (723 mg), and fractions 42–49 to give fraction G (666 mg).

Maytanvaline (4). PTLC of the appropriate portion of fraction D on alumina, developed with 5% methanol–ethyl acetate, gave crude 4 which was separated from a higher R_f maytansinoid by PTLC on ChromAR developed with 20% benzene–ethyl acetate × 2. Partition chromatography (20% aqueous methanol/20% chloroform–heptane) over Celite, followed by PTLC on ChromAR, developed with 5% methanol–chloroform, gave homogeneous material which was crystallized from dichloromethane–ether to give 4 (6.9 mg, 0.0000035%): mp 175–176.5 °C; $[\alpha]^{26}_D$ −135° (c 0.950, $CHCl_3$); UV (EtOH) 233 nm (ε 29 100), 243 (sh, 26 400), 254 (26 800), 281 (5300), 288 (5360); IR (KBr) 5.72, 5.80, 6.02, 6.34, 8.48, 9.27 μ; NMR ($CDCl_3$) δ 0.81 (3 H, s, C-4 CH_3), 0.92 (3 H, d, *J* = 7 Hz, C-5′ CH_3), 0.95 (3 H, d, *J* = 7 Hz, C-5′ CH_3), 1.29 (3 H, d, *J* = 6 Hz, C-6 CH_3), 1.32 (3 H, d, *J* = 7 Hz, C-2′ CH_3), 1.65 (3 H, s, C-14 CH_3), 2.14 (2 H, d, *J* = 7 Hz, C-4′ H_2), 2.24 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 3 Hz, C-2 H), 2.68 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 11 Hz, C-2 H), 2.86 (3 H, s, C-2′ NCH_3), 3.03 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.12 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 3.20 (3 H, s, C-1 NCH_3), 3.35 (3 H, s, C-10 OCH_3), 3.49 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.52 (1 H, s, C-9 OH), 3.67 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 3.98 (3 H, s, C-20 OCH_3), 4.30 (1 H, m, C-7 H), 4.78 (1 H, dd, $J_{2,3}$ = 11, 3 Hz, C-3 H), 5.34 (1 H, q, *J* = 7 Hz, C-2′ H), 5.66 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 6.24 (1 H, s, C-9 NH), 6.48 (1 H, dd, $J_{11,12}$ = 15, $J_{12,13}$ = 10 Hz, C-12 H), 6.71 (1 H, d, $J_{12,13}$ = 10 Hz, C-13 H), 6.70, 6.83 (2 H, 2 d, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H), 1.0–2.0 (4 H, C-6 H, C-8 H_2, C-5′ H).

Anal. Calcd for $C_{37}H_{52}ClN_3O_{10}$: C, 60.51; H, 7.14; N, 5.72. Found: C, 60.43; H, 7.20; N, 5.71.

Conversion of Maytanvaline to Maysine and Isolation of *N*-Isovaleryl-*N*-methyl-L-alanine Methyl Ester. A mixture of maytanvaline (19.8 mg) and sodium carbonate (15 mg) in 2 mL of 50% aqueous methanol containing 0.2 mL of tetrahydrofuran was allowed to stir at room temperature for 3 h. The reaction mixture was acidified in the cold and extracted with ethyl acetate (3 × 5 mL) to give 22.2 mg of yellow solid. This solid was purified by PTLC on ChromAR, developed with ethyl acetate, to give a fraction corresponding in R_f to maysine (3.8 mg) and 4.2 mg of recovered maytanvaline. All fractions (separations made based on UV detection) of higher R_f than maysine were dissolved separately in methanol and each one was treated with ethereal diazomethane. Preparative GLC of the appropriate fractions gave 1.2 mg of *N*-isovaleryl-*N*-methyl-L-alanine methyl ester characterized by mixture GLC (E307 and 3% SE-30), IR, NMR, and mass spectrum with an authentic sample of the synthetically prepared amino acid ester. The maysine isolated was further purified by PTLC on alumina, developed with 10% methanol–ethyl acetate, to give 1.4 mg of maysine which was identical with an authentic sample by mixture TLC and HPLC, IR, NMR, and mass spectrum.

***N*-Isovaleryl-*N*-methyl-L-alanine Methyl Ester.** A methanolic solution of *N*-methyl-L-alanine (103 mg, 1 mmol) was treated with ethereal diazomethane at 0 °C. The reaction mixture was allowed to warm to room temperature over a 2-h period and most of the solvent was removed under a stream of nitrogen gas. A mixture of the crude methyl ester and potassium carbonate (500 mg) in chloroform–water (4 mL, 1:1) was cooled to 0 °C and an excess of isovaleryl chloride (prepared from isovaleric acid and benzoyl chloride)[30] was added. The mixture was allowed to warm to room temperature and stirred vigorously for 18 h. Water was added and the aqueous layer was thoroughly extracted with chloroform. Preparative GLC (E307 Chromosorb W 60/80 glass column, He 40 mL/min, column temperature 105 °C, injection port 187 °C, t_R 6.24 min) gave 75 mg (37%) of *N*-isovaleryl-*N*-methyl-L-alanine methyl ester as a colorless liquid: IR (neat) 3.36, 3.48, 5.72, 6.07 μ; NMR ($CDCl_3$) δ 0.95 (6 H, d, *J* = 6 Hz, 2 CH_3), 1.36 (3 H, d, *J* = 7.6 Hz, $CHCH_3$), 2.16 (1 H, m, CH_2CH), 2.17 (2 H, d, *J* = 2 Hz, CH_2CH), 2.77, 2.89 (0.5 H, 2.5 H, NCH_3), 3.62 (3 H, s, $COOCH_3$), 5.16 (1 H, q, *J* = 7.6 Hz, $CHCH_3$); mass spectrum *m/e* 202.1434, $C_{10}H_{19}NO_3$ (M + H^+) = 202.1438.

Maysine (5). PTLC of fraction F on alumina, with 5% methanol–ethyl acetate × 3 as eluent, gave **5** (9.9 mg, 0.000005%): mp 137–141 °C; $[\alpha]^{30}_D$ −173° (c 0.023, EtOH); UV (EtOH) 226 nm (ε 29 100), 241 (sh, 23 300), 252 (sh, 17 500), 280 (4280), 289 (sh, 3900); IR (KBr) 5.85, 6.01, 6.14, 6.34, 9.19 μ; NMR ($CDCl_3$) δ 1.06 (3 H, s, C-4 CH_3), 1.30 (3 H, d, J = 6 Hz, C-6 CH_3), 1.68 (3 H, br s, C-14 CH_3), 2.62 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.02 (1 H, d, $J_{15,15}$ = 12 Hz, C-15 H), 3.22 (3 H, s, C-1 NCH_3), 3.28 (3 H, s, C-10 OCH_3), 3.39 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.42 (1 H, d, $J_{15,15}$ = 12 Hz, C-15 H), 3.92 (3 H, s, C-20 OCH_3), 4.24 (1 H, m, C-7 H), 5.43 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 5.65 (1 H, d, $J_{2,3}$ = 16 Hz, C-2 H), 6.02 (1 H, br d, $J_{12,13}$ = 11 Hz, C-13 H), 6.29 (1 H, s, C-9 NH), 6.34 (1 H, dd, $J_{12,13}$ = 11, $J_{11,12}$ = 15 Hz, C-12 H), 6.37 (1 H, d, $J_{2,3}$ = 16 Hz, C-3 H), 6.62, 6.74 (2 H, d, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H), 3.20–3.50 (1 H, C-9 OH), 0.70–2.50 (3 H, C-6 H, C-8 H_2); mass spectrum m/e 485.1974, $C_{27}H_{32}ClNO_5$ [M − 61 (H_2O + HNCO)] = 485.1969.

Normaysine (6). The PTLC which gave maysine also gave normaysine (**6**, 13.8 mg, 7 × 10^{-6}%): mp 187–188 °C (acetone); $[\alpha]^{30}_D$ −217° (c 0.051, EtOH); UV (EtOH) 229 nm (ε 44 500), 242 (sh, 36 400), 252 (sh, 27 300), 280 (sh, 5770), 290 (sh, 5200); IR (KBr) 5.92, 6.01, 6.12, 6.34, 9.24 μ; NMR ($CDCl_3$) δ 1.21 (3 H, s, C-4 CH_3), 1.32 (3 H, d, J = 6 Hz, C-6 CH_3), 1.69 (3 H, br s, C-14 CH_3), 2.67 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.05 (1 H, d, $J_{15,15}$ = 12 Hz, C-15 H), 3.20 (3 H, s, C-10 OCH_3), 3.43 (1 H, d, $J_{15,15}$ = 12 Hz, C-15 H), 3.44 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.58 (1 H, s, C-9 OH), 3.88 (3 H, s, C-20 OCH_3), 4.28 (1 H, m, C-7 H), 5.48 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 6.03 (1 H, br d, $J_{12,13}$ = 11 Hz, C-13 H), 6.05 (1 H, d, $J_{2,3}$ = 16 Hz, C-2 H), 6.35 (1 H, s, C-9 NH), 6.41 (1 H, dd, $J_{12,13}$ = 11, $J_{11,12}$ = 15 Hz, C-12 H), 6.52 (1 H, d, $J_{2,3}$ = 16 Hz, C-3 H), 6.58, 6.63 (2 H, d, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H), 7.38 (1 H, s, C-1 NH), 1.00–2.00 (3 H, C-6 H, C-8 H_2); mass spectrum m/e 471.1807, $C_{26}H_{30}ClNO_5$ [M − 61 (H_2O + HNCO)] = 471.1812.

Anal. Calcd for $C_{27}H_{33}ClN_2O_7 \cdot \frac{1}{2}H_2O$: C, 59.83; H, 6.32; N, 5.17. Found: C, 59.24; H, 6.25; N, 5.22.

Maysenine (7). PTLC of fraction D on alumina developed with 5% methanol–ethyl acetate gave a major component which was submitted to PTLC on ChromAR, with 10% benzene–ethyl acetate × 2 as the eluent, to afford maysenine (**7**, 5.1 mg, 0.0000026%): mp 184–185 °C (acetone); $[\alpha]^{30}_D$ −57° (c 0.056, EtOH); UV max (EtOH) 234 nm (sh, ε 44 000), 243 (53 400), 252 (sh, 41 400), 271 (23 500), 300 nm (sh, 9470); IR (KBr) 5.87, 6.01, 6.21, 6.31, 9.26 μ; NMR ($CDCl_3$) δ 1.25 (3 H, d, J = 6 Hz, C-6 CH_3), 1.56 (3 H, br s, C-4 CH_3), 1.65 (3 H, br s, C-14 CH_3), 3.07 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 3.10 (1 H, s, C-9 OH), 3.29 (3 H, s, C-10 OCH_3), 3.40 (1 H, d, $J_{15,15}$ = 13 Hz, C-15 H), 3.45 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.88 (3 H, s, C-20 OCH_3), 4.11 (1 H, m, C-7 H), 5.42 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 14 Hz, C-11 H), 5.50 (1 H, br d, $J_{5,6}$ = 10 Hz, C-5 H), 5.82 (1 H, d, $J_{2,3}$ = 16 Hz, C-2 H), 6.00 (1 H, br d, $J_{12,13}$ = 10 Hz, C-13 H), 6.16 (1 H, s, C-9 NH), 6.37 (1 H, dd, $J_{12,13}$ = 10, $J_{11,12}$ = 14 Hz, C-12 H), 6.51, 6.57 (2 H, d, $J_{17,21}$ = 1 Hz, C-17 H, C-21 H), 7.15 (1 H, s, C-1 NH), 7.28 (1 H, d, $J_{2,3}$ = 16 Hz, C-3 H), 1.00–2.00 (3 H, C-6 H, C-8 H_2); mass spectrum m/e 455.1844, $C_{26}H_{30}ClNO_4$ [M − 61 (H_2O + HNCO)] = 455.1863.

Anal. Calcd for $C_{27}H_{33}ClN_2O_6 \cdot \frac{1}{2}H_2O$: C, 61.65; H, 6.51; N, 5.33. Found: C, 61.29; H, 6.74; N, 5.45.

Methyl Maysine (14). A mixture of crude maysine (16.7 mg) and *p*-toluenesulfonic acid (one small crystal) in dry methanol (0.5 mL) was allowed to stand at room temperature for 17 h. The reaction mixture was quenched by the addition of 1 drop of 5% sodium bicarbonate and purified by PTLC on ChromAR, developed with ethyl acetate to give 13.0 mg of crystalline product which was recrystallized from dichloromethane–ether–hexane to give methyl maysine (2.3 mg, 13%): mp 178–179 °C; IR (KBr) 5.80, 6.00, 6.13, 6.33, 9.20 μ; NMR ($CDCl_3$) δ 3.21 (6 H, s, C-1 NCH_3, C-9 OCH_3); mass spectrum m/e 528.2031, $C_{28}H_{33}ClN_2O_6$ (M − CH_3OH) = 528.2027.

Hydrolysis of Methyl Maysine. A mixture of methyl maysine (2.0 mg), 50% aqueous methanol (0.2 mL), and 2 N hydrochloric acid (1 drop) was allowed to stand at room temperature for 1 h. The reaction mixture was quenched by the addition of 1 drop of 5% sodium bicarbonate and purified by PTLC on alumina, developed with 10% methanol–ethyl acetate, to give **5** which was identical with natural maysine in all respects.

Conversion of Maytansine to Maysine. A mixture of maytansine (18.0 mg) and sodium carbonate (20 mg) in 2 mL of 50% aqueous methanol was allowed to stir at room temperature for 4 h. The reaction mixture was extracted with dichloromethane (3 × 5 mL) to give a solid residue which was purified by PTLC on alumina, developed with 10% methanol–ethyl acetate. In addition to the major product (2.3 mg), which was identical with natural maysine in all respects, 1.8 mg of maytansine was recovered. The product was further characterized by preparation of the methyl ether derivative which was identical with an authentic sample by IR and mixture melting point.

Conversion of Normaysine (6) to Maysenine (7). A mixture of normaysine (3.8 mg), chromous chloride (2 drops), and acetic acid (3 drops) was allowed to stand at room temperature for 1 h. The reaction mixture was diluted with water and extracted with dichloromethane (three times). The organic layer was washed with water (twice), 5% sodium bicarbonate, and again with water (three times). PTLC on alumina, developed with 10% methanol–ethyl acetate × 2, gave 1.2 mg of an unknown product and 1.2 mg of maysenine, mp 184–185 °C, identical with an authentic sample by UV, IR, and mixture melting point.

Maytanbutacine (8). PTLC of fraction E from *Maytenus serrata* on alumina with 5% methanol–ethyl acetate gave two bands. The lower R_f band was separated and subjected to PTLC on silica gel in ethyl acetate. Again two bands resulted and the higher R_f band was isolated. Preparative HPLC of this band on a Corasil II column (3 ft × 0.375 in., 1 mL/min, 1 faction/2 min) using 1% methanol–dichloromethane gave fraction H (fractions 74–94). PTLC of fraction H on SilicAR in ethyl acetate (twice) gave a concentrated band of maytanbutacine (R_f 0.67). Repeated crystallization from dichloromethane–ether afforded crystals of maytanbutacine (0.115 mg/kg plant, 0.0000115%): mp 253–255 °C; $[\alpha]^{33}_D$ −90° (c 0.055, EtOH); UV (EtOH) 233 (ε 27 200), 253 (24 200), 282 (5050), 290 nm (5080); IR (KBr) 5.73, 5.82, 6.00, 6.32, 8.16, 9.17 μ; NMR ($CDCl_3$) δ 0.79 (3 H, s, C-4 CH_3), 1.20 (3 H, d, J = 7 Hz, C-2′ CH_3), 1.28 (3 H, d, J = 7 Hz, C-2′ CH_3), 1.28 (3 H, d, J = 7 Hz, C-6 CH_3), 1.67 (3 H, s, C-14 CH_3), 2.23 (3 H, s, C-15 $OCOCH_3$), 2.43 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 11 Hz, C-2 H), 2.47 (1 H, dd, $J_{2,2}$ = 14, $J_{2,3}$ = 3 Hz, C-2 H), 2.95 (1 H, d, $J_{5,6}$ = 8.5 Hz, C-5 H), 3.16 (3 H, s, C-1 NCH_3), 3.35 (3 H, s, C-10 OCH_3), 3.51 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 4.02 (3 H, s, C-20 OCH_3), 4.26 (1 H, m, C-7 H), 4.79 (1 H, dd, $J_{2,3}$ = 11, 3 Hz, C-3 H), 5.60 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 14 Hz, C-11 H), 6.21 (1 H, s, C-15 H), 6.30 (1 H, dd, $J_{12,13}$ = 10 Hz, C-12 H), 6.39 (1 H, s, C-9 NH), 6.44 (1 H, d, $J_{12,13}$ = 10 Hz, C-13 H), 6.85 (1 H, d, $J_{17,21}$ = 1.5 Hz, C-21 H), 7.09 (1 H, d, $J_{17,21}$ = 1.5 Hz, C-17 H), 1.0–2.0 (3 H, C-6 H, C-8 H_2), 2.0–2.6 (1 H, m, C-2′ H); mass spectrum m/e 631.2540, $C_{33}H_{42}ClNO_9$ [M − 61 (H_2O + HNCO)] = 631.2548, m/e 571.2331, $C_{31}H_{38}ClNO_7$ [M − 61 − 60(CH_3COOH)] = 571.2337.

Anal. Calcd for $C_{34}H_{45}ClN_2O_{11}$: C, 58.91; H, 6.54; N, 4.04. Found: C, 58.90; H, 6.67; N, 3.92.

Deacetylmaytanbutacine (9). Maytanbutacine (**8**, 17 mg) was treated with 80 mg of sodium bicarbonate in 4 mL of methanol–water (1:1) at room temperature for 43 h. The solvent was evaporated, and PTLC of the residue on ChromAR developed with ethyl acetate (twice) gave two major bands, one corresponding to **8**. Isolation of the lower band (R_f 0.38) gave 8.3 mg of homogeneous material. Crystallization of this material from dichloromethane–ether–*n*-hexane gave 4.9 mg of **9** (30%): mp 227–228 °; $[\alpha]^{25}_D$ −94° (c 0.053, EtOH); UV (EtOH) 233 nm (ε 24 700), 252 (21 700), 281 (4540), 289 (4540); IR (KBr) 5.76, 5.89, 6.02, 6.35, 9.22 μ; NMR ($CDCl_3$ + acetone-d_6) δ 0.88 (3 H, s, C-4 CH_3), 1.19 (3 H, d, J = 7 Hz, C-2′ CH_3), 1.21 (3 H, d, J = 7 Hz, C-2′ CH_3), 1.27 (3 H, d, J = 7 Hz, C-6 CH_3), 1.68 (3 H, s, C-14 CH_3), 2.1–2.3 (1 H, m, C-2′ H), 2.40 (1 H, dd, $J_{2,2}$ = 15, $J_{2,3}$ = 11 Hz, C-2 H), 2.67 (1 H, dd, $J_{2,2}$ = 15, $J_{2,3}$ = 3 Hz, C-2 H), 2.88 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.15 (3 H, s, C-1 NCH_3), 3.37 (3 H, s, C-10 OCH_3), 3.47 (1 H, d, J = 7 Hz, C-15 H), 3.57 (1 H, s, C-9 OH), 3.59 (1 H, d, J = 9 Hz, C-10 H), 4.03 (3 H, s, C-20 OCH_3), 4.29 (1 H, m, C-7 H), 4.80 (1 H, dd, $J_{2,3}$ = 11, 3 Hz, C-3 H), 5.37 (1 H, s, C-15 H), 5.63 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 5.82 (1 H, d, $J_{12,13}$ = 11 Hz, C-13 H), 6.40 (1 H, s, C-9 NH), 6.63 (1 H, dd, $J_{11,12}$ = 15, $J_{12,13}$ = 11 Hz, C-12 H), 6.89 (1 H, d, $J_{17,21}$ = 1.5 Hz, C-21 H), 7.49 (1 H, d, $J_{17,21}$ = 1.5 Hz, C-17 H), 1.0–2.0 (3 H, C-6 H, C-8 H_2); mass spectrum m/e 589 [M − 61 (H_2O + HNCO)], 571 [M − 61 − 18 (H_2O)], 554 [M − 61 − 35 (Cl)], 501 [M − 61 − 88 ($C_4H_8O_2$)], 486 [M − 61 − 88 − 15 (CH_3)], 466 [M − 61 − 88 − 35 (Cl)].

Oxidation of Deacetylmaytanbutacine. Deacetylmaytanbutacine (0.7 mg) was dissolved in 3 drops of acetone and treated with 1 drop of Jones reagent at room temperature for 3 min. Three drops of water were added, the mixture was extracted with ethyl acetate, and the ethyl acetate was evaporated. PTLC of the residue on alumina in 10% methanol–ethyl acetate gave three bands. Isolation of the band with R_f 0.31 gave an unsaturated ketone: UV (MeOH) 285 nm; mass spectrum m/e 587 [M − 61 (H_2O + HNCO)], 562 [M − 61 − 15 (CH_3)], 552 [M − 61 − 35 (Cl)], 499 [M − 61 − 88 ($C_4H_8O_2$)], 484 [M − 61 − 88 − 15 (CH_3)], 464 [M − 61 − 88 − 35 (Cl)].

***Putterlickia verrucosa*. Procedure A.** The ground dried stem wood and bark (1 kg) of *P. verrucosa* was extracted in Soxhlet extractors with 8 L of 95% ethanol for 6 h. The plant material was extracted two additional times with 8 L of fresh 95% ethanol for 15 and 24 h. The extracts were combined and concentrated at 40–50 °C in

vacuo to give a dark gum which was partitioned between ethyl acetate (300 mL) and water (150 mL). The insoluble material was removed by filtration and washed again with ethyl acetate (2 × 200 mL) and water (2 × 100 mL). The combined aqueous layers were washed with an additional 200 mL of ethyl acetate and the combined ethyl acetate layers were then concentrated in vacuo to give 12.4 g of a dark gum. This material was subjected to column chromatography over SilicAR CC-7 (62 g) packed in chloroform. The column was eluted with chloroform (140 mL), 5% methanol–chloroform (1600 mL), and methanol (280 mL). The fraction which was eluted with 5% methanol–chloroform (10.1 g) was treated with 60 mL of acetic anhydride–pyridine (1:1) at room temperature for 18 h. The residue from the acetylation step (11.5 g), after removal of the excess acetic anhydride–pyridine, was subjected to column chromatography over SilicAR CC-7 (57 g) eluted first with chloroform (550 mL) and then with 5% methanol–chloroform (900 mL). The 5% methanol–chloroform eluate (1.8 g) was subjected to PTLC on alumina developed with 5% methanol–ethyl acetate. The bands corresponding to the maytansinoids were isolated (60 mg) and again subjected to PTLC using the same conditions. The bands corresponding to the maytansinoids (R_f 0.3–0.6) were isolated (47 mg), and subjected to PTLC on ChromAR developed with ethyl acetate (twice). Isolation and crystallization of the appropriate bands gave maytansine (**1**, 12.3 mg, 0.0012%), maytanprine (**2**, 8.5 mg, 0.00085%), and maytanbutine (**3**, 4.5 mg, 0.00045%).

PTLC of a band with R_f 0.55 from the previous step on ChromAR developed with 10% benzene–ethyl acetate gave <200 μg of a crystalline maytansinoid identical with maytanacine (**12**) isolated from a large-scale extraction (procedure B).

Procedure B. The ground dried wood stems and stem bark (10.0 kg) of *P. verrucosa* were extracted in Soxhlet extractors with 80 L of 95% ethanol for 6 h. The plant material was extracted again with 80 L of fresh 95% ethanol for 15 h. After a third extraction of 24 h, the extracts were combined and concentrated at 40–50 °C in vacuo to give a dark gum (277 g). The concentrated alcoholic extract was shaken between ethyl acetate (1 L) and water (500 mL). The suspension was filtered and the insoluble material was treated two more times with ethyl acetate (250 mL), followed by filtration. The aqueous layer was washed with an additional 250 mL of ethyl acetate.

The combined ethyl acetate layers (93 g) were chromatographed on a column of alumina (1 kg, activity II–III), packed in dichloromethane. Beginning with 5% methanol–dichloromethane, 250-mL fractions were collected and analyzed by HPLC for maytansinoid content. Fractions 2–4 were combined to give fraction A (9.3 g) and fractions 5–8 were combined to give fraction B (1.7 g).

Maytanacine (12). Fraction A was chromatographed on a column of SilicAR CC-7 (1 kg), packed in 50% ethyl acetate–benzene, with each 1-L fraction being analyzed by HPLC. Elution with 66% ethyl acetate–benzene gave fractions C (100 mg) and D (124 mg). PTLC of fraction D on ChromAR, developed with 5% methanol–chloroform, gave a band (7.4 mg) corresponding in R_f to the maytanacine standard. Further PTLC of this material on alumina, developed with 10% methanol–ethyl acetate, gave 1.5 mg of crystalline material. Identical purification of fraction C gave an additional 0.3 mg of crystalline isolate. The combined crystalline material (1.8 mg) was found to be identical by mixture HPLC, TLC, and mass spectrum with the synthetic sample prepared from maytansinol.

Maytansinol (13). Fraction B was chromatographed on a column of SilicAR CC-7 (170 g), packed in chloroform, and eluted with increasing amounts of methanol in chloroform. Elution with 5% methanol–chloroform gave 240 mg of material which was submitted to PTLC on ChromAR, developed with 5% methanol–ethyl acetate. The band (46 mg) corresponding to maytansinol was chromatographed further on Kieselgel plates, developed with 15% ethanol–ether, to give 5.7 mg of material with the same R_f as maytansinol. Preparative HPLC, collecting the component with the proper retention time, followed by PTLC on ChromAR, developed with 5% methanol–chloroform × 2, yielded 0.25 mg of isolate. This material was found to be identical by mixture HPLC, TLC, and mass spectrum with an authentic sample of maytansinol prepared by lithium aluminum hydride treatment of maytanbutine.

Maytansinol (13). A mixture of maytanbutine (**3**, 40 mg, 0.0556 mmol) and excess lithium aluminum hydride was stirred in dry tetrahydrofuran (4 mL) at −23 °C (carbon tetrachloride–dry ice bath) for 3 h. Ethyl acetate (10 mL) was added, followed by 10 mL of pH 6.8 phosphate buffer,[31] and the mixture was further extracted with ethyl acetate (4 × 10 mL). The extracts were combined, dried over sodium sulfate, and brought to dryness. The residue (45 mg) was submitted to PTLC on ChromAR, developed with 5% methanol–chloroform × 2, to give 21 mg of material which was further purified by PTLC on ChromAR, developed with 3% isopropyl alcohol–ethyl acetate × 2. The major band (17.2 mg) was chromatographed over a very short column of aluminum oxide (activity II–III), packed in dichloromethane with the product eluted with 5% methanol–dichloromethane, to give 16.0 mg of maytansinol. Precipitation from dichloromethane–hexane afforded white, solid **13** (12.5 mg, 40%): mp 173–174.5 °C; $[\alpha]^{23}_D$ −309° (*c* 0.110, $CHCl_3$); UV (EtOH) 232 nm (ε 32 700), 244 (sh, 30 800). 252 (31 600), 281 (5810), 288 (5700); IR (KBr) 5.85, 6.06, 6.35 μ; NMR ($CDCl_3$) δ 0.84 (3 H, s, C-4 CH_3), 1.32 (3 H, d, J = 6 Hz, C-6 CH_3), 1.68 (3 H, s, C-14 CH_3), 3.20 (3 H, s, C-1 NCH_3), 3.36 (3 H, s, C-10 OCH_3), 3.44 (1 H, br s, C-3 OH), 3.64 (1 H, br s, C-9 OH), 3.98 (3 H, s, C-20 OCH_3), 4.36 (1 H, m, C-7 H), 5.53 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 6.19–6.39 (3 H, C-12 H, C-13 H, C-9 NH), 6.81, 7.05 (2 H, d, $J_{17,21}$ = 1.5 Hz, C-17 H, C-21 H), 1.30–3.55 (10 H, C-2 H_2, C-3 H, C-5 H, C-6 H, C-8 H_2, C-10 H, C-15 H_2); mass spectrum *m/e* 503.2075 ($M^+ - H_2O$ − HNCO) (calcd, 503.2074).

Maytanacine (12). Maytansinol (**13**, 1.5 mg, 0.0027 mmol) prepared from maytanacine under the same conditions used for maytanbutine was treated with 1 mL of acetic anhydride–pyridine (1:1) at 53 °C for 18 h. The reaction mixture was brought to dryness and the residue was chromatographed on ChromAR developed with 5% methanol–chloroform. The major band was removed, eluted with 10% methanol in ethyl acetate, and evaporated to a white solid. Crystallization from dichloromethane–hexanes gave **12** (0.8 mg, 48%): mp 234–237 °C; $[\alpha]^{23}_D$ −119° (*c* 0.100, $CHCl_3$); UV (EtOH) 233 nm (ε 30 300), 242 (sh, 28 000), 252 (27 900), 281 (5360), 289 (5360); IR (KBr) 5.70, 5.80, 6.00, 6.34 μ; NMR ($CDCl_3$) δ 0.84 (3 H, s, C-4 CH_3), 1.28 (3 H, d, J = 6 Hz, C-6 CH_3), 1.69 (3 H, s, C-14 CH_3), 2.18 (3 H, s, C-3 $OCOCH_3$), 2.05–2.30 (1 H, C-2 H), 2.46 (1 H, dd, $J_{2,3}$ = 12, $J_{2,2}$ = 14 Hz, C-2 H), 2.89 (1 H, d, $J_{5,6}$ = 9 Hz, C-5 H), 3.18 (3 H, s, C-1 NCH_3), 3.36 (3 H, s, C-10 OCH_3), 3.52 (1 H, d, $J_{10,11}$ = 9 Hz, C-10 H), 3.10–3.60 (3 H, C-9 OH, C-15 H_2), 3.99 (3 H, s, C-20 OCH_3), 4.16 (1 H, m, C-7 H), 4.92 (1 H, dd, $J_{2,3}$ = 3, 12 Hz, C-3 H), 5.48 (1 H, dd, $J_{10,11}$ = 9, $J_{11,12}$ = 15 Hz, C-11 H), 6.10–6.59 (3 H, C-9 NH, C-12 H, C-13 H), 6.84, 6.76 (2 H, s, C-17 H, C-20 H), 0.80–2.50 (3 H, C-6 H, C-8 H_2); mass spectrum *m/e* 545.2180 ($M^+ - H_2O$ − HNCO) (calcd, 545.2180), 485.1969 ($M^+ - H_2O$ − HNCO − CH_3COOH) (calcd, 485.1969).

Anal. Calcd for $C_{30}H_{39}ClN_2O_9$: C, 59.35; H, 6.48; N, 4.61. Found: C, 59.19; H, 6.39; N, 4.69.

Registry No.—**1**, 35846-53-8; **2**, 38997-09-0; **3**, 38997-10-3; **4**, 52978-27-5; **5**, 52978-28-6; **6**, 52978-29-7; **7**, 52978-30-0; **8**, 62414-95-3; **9**, 62414-96-4; **11**, 36482-96-9; **12**, 57103-69-2; **13**, 57103-68-1; **14**, 62414-97-5; 3-bromopropanol, 627-18-9; *N*-isovaleryl-*N*-methyl-L-alanine methyl ester, 62414-98-6; *N*-methyl-L-alanine, 3913-67-5; isovaleryl chloride, 108-12-3; unsaturated ketone, 62414-99-7.

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(2) Supported by grants from the National Cancer Institute (CA-11718) and the American Cancer Society (T-275, T-541, and CI-102K) and a contract with the Division of Cancer Treatment, National Cancer Institute (NIH-71-2099, N01-CM-12099, N01-CM-67002). A.R.B. was a NIH Postdoctoral Fellow, 1972–1975.

(3) (a) We thank Dr. Robert E. Perdue, Jr., USDA, Beltsville, Md., for supplying the plant material in accordance with the program developed by the National Cancer Institute. (b) Fruits were collected in Ethiopia in Jan 1962. Roots and the wood of stems from Ethiopia and Kenya also yielded active extracts.

(4) Activity was noted against sarcoma 180, Lewis lung carcinoma, and L-1210 and P-388 leukemias in the mouse and Walker 256 intramuscular carcinosarcoma in the rat. Cytotoxicity and in vivo activity were assayed as in *Cancer Chemother. Rep.*, **25**, 1 (1962), and by the procedures described by R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972).

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(26) Stem wood and stem bark were collected in South Africa in 1972. We again acknowledge with thanks receipt of the dried plant material from Dr. Robert E. Perdue, Jr.
(27) Later collections of *P. verrucosa* have also been assayed for maytansine yield and have been found to average 8–9 mg/kg.
(28) We thank Professor a. I. Meyers, Colorado State University, for unpublished information concerning $LiAlH_4$ reductive cleavage of esters in synthetic model compounds.
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Studies of Resin Acids. 10. Approaches to the Synthesis of Podocarpic and Dehydroabietic Acids†[1]

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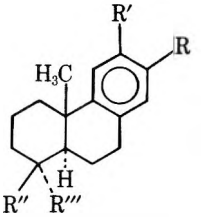
In a new stereoselective synthesis of the tricyclic nucleus of the resin acids, 2-(2-phenylethyl)cyclohexane-1,3-dione is cyclized to a tricyclic enone (**5**). Conjugate addition of lithium dimethylcuprate gives a mixture of the 5α and 5β isomers of 18,19-dinorpodocarpa-8,11,13-triene (**6**), which reacts with methylenetriphenylphosphorane to give as a major product olefin **7**, which is also prepared from podocarpic acid (**2**). A new stereoselective synthesis of dehydroabietic acid (**1**) from the dinorketone **9** via the sequence methylenetriphenylphosphorane to olefin **10**, conversion of **10** to aldehyde **17**, alkylation with allyl bromide to **22**, is presented. Wolff–Kishner reduction of **22** followed by oxidation affords homodehydroabietic acid (**24**), which has been converted previously to acid **1**.

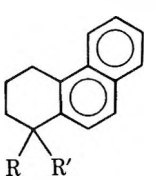
Although a number of syntheses of diterpenoid acids, such as dehydroabietic acid (abieta-8,11,13-trien-18-oic acid, **1**) and podocarpic acid (12-hydroxypodocarpa-8,11,13-trien-19-oic acid, **2**) have been described,[3] all of these syntheses are rather lengthy and many are nonstereoselective. Also, in none of these syntheses could a single intermediate well along the synthetic route be used to obtain stereoselectively both epimeric C-4 carboxylic acids. Either the reaction sequence gave a mixture of epimers at this center, or the synthesis was designed in such a way that it provided only one epimer from the outset.

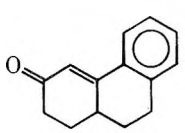
In an effort to overcome both of these shortcomings a new approach to the total synthesis of these diterpenoid acids has been devised which is a modification of an earlier synthesis, reported from this laboratory, which resulted in a short, stereoselective synthesis of eudesmol and several related sesquiterpenes.[4] The modified synthetic sequence as applied to the diterpene acids is shown in Scheme I. In order to utilize readily available starting materials, this approach was to be applied to the syntheses of podocarpa-8,11,13-trien-18-oic (**3**) and -19-oic (**4**) acids, both of which have been converted to naturally occurring compounds.[3e,5]

The key steps of the synthesis were first, the conjugate addition of lithium dimethylcuprate to enone **5**, and second, the reaction of methylenetriphenylphosphorane with ketone **6** to give selectively the 5α olefin (**7**). Olefin **7** could easily be transformed to aldehyde **8**, which then could, hopefully, be utilized to synthesize acids **3** and **4**.

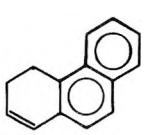


1, R = $CH(CH_3)_2$; R′ = H; R″ = CH_3; R‴ = CO_2H
2, R = H; R′ = OH; R″ = CO_2H; R‴ = CH_3
3, R,R′ = H; R″ = CH_3; R‴ = CO_2H
4, R,R′ = H; R″ = CO_2H; R‴ = CH_3
11, R = $CH(CH_3)_2$; R′,R‴ = H; R″ = CH_3
18, R = $CH(CH_3)_2$; R′ = H; R″ = CO_2H; R‴ = CH_3
20, R = $CH(CH_3)_2$; R′ = H; R″ = CHO; R‴ = CH_3
21, R = $CH(CH_3)_2$; R′ = H; R″,R‴ = CH_3
22, R = $CH(CH_3)_2$; R′ = H; R″ = CHO; R‴ = $CH_2CH{=}CH_2$
23, R = $CH(CH_3)_2$; R′ = H; R″ = CH_3; R‴ = $CH_2CH{=}CH_2$
24, R = $CH(CH_3)_2$; R′ = H; R″ = CH_3; R‴ = CH_2CO_2H





14



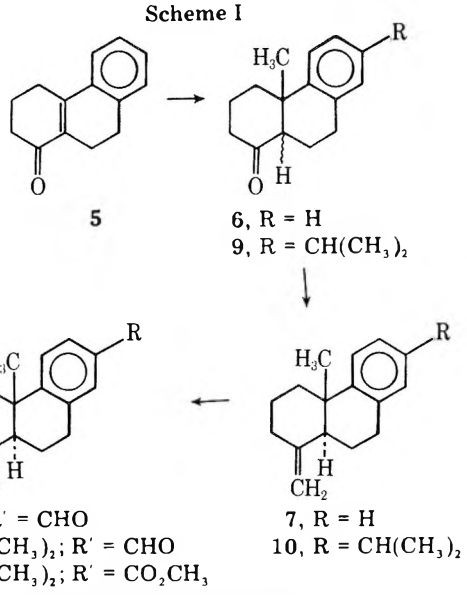
16

12, R,R′ = O
13, R,R′ = H
15, R = OH; R′ = H

In order to ascertain the feasibility of the trans-selective Wittig reaction which had worked well in other cases,[4,6] the

† Dedicated to Professor R. B. Woodward on the occasion of his 60th birthday.

Scheme I



5

6, R = H
9, R = $CH(CH_3)_2$

8, R = H; R′ = CHO
17, R = $CH(CH_3)_2$; R′ = CHO
19, R = $CH(CH_3)_2$; R′ = CO_2CH_3

7, R = H
10, R = $CH(CH_3)_2$

model reaction of ketone **9**, readily obtainable as a mixture of 5α and 5β isomers by degradation of dehydroabietic acid,[7] with methylenetriphenylphosphorane was investigated. The preparation of ketone **9** was modified by first separating the precursor olefin (**10**) from the mixture of olefins obtained from the lead tetraacetate oxidation of dehydroabietic acid[8] by means of selective epoxidation[9] and then cleaving the olefin by oxidation with periodate–permanganate.

In contrast to earlier reports,[4,6] the Wittig reaction of ketone **9** with methylenetriphenylphosphorane under a variety of conditions was found not to be completely stereoselective with the product containing 90% of the desired 5α isomer (**10**). The structure and stereochemistry of the major product of the Wittig reaction were confirmed by hydrogenation to 18-norabieta-8,11,13-triene (**11**).[8] Based on spectral data, the balance of the hydrocarbon fraction was the undesired 5β isomer. Following the completion of this phase of the work, Ziegler reported the reaction of a very similar ketone with methoxymethylenetriphenylphosphorane to give the 5α isomer with unspecified stereoselectivity.[10]

The second key step in the synthesis was the conjugate addition of lithium dimethylcuprate[11] to tricyclic enone **5**. This enone had been prepared some years ago from 2-(2-phenylethyl)cyclohexane-1,3-dione on treatment with polyphosphoric acid.[12] Repetition of this synthesis, under conditions which apparently duplicated those published, gave a complex mixture of **5**, 1,2,3,4-tetrahydro-1-phenanthrone (**12**), phenanthrene, and 1,2,3,4-tetrahydrophenanthrene (**13**), apparently resulting from complex hydride transfer reactions.

In one reaction a small quantity of 1,2,3,9,10,10a-hexahydro-3-phenanthrone[13] (**14**) was obtained. This material is undoubtedly an artifact arising from the cyclization of 4-(2-phenylethyl)cyclohexane-1,3-dione present as a contaminent in the dione precursor to enone **5**.[14]

Some effort was made to ascertain the course of the hydride transfer reactions in these cyclization reactions of 2-(2-phenylethyl)cyclohexane-1,3-dione. From these experiments the following conclusions could be reached: (1) The use of purified 2-(2-phenylethyl)cyclohexane-1,3-dione almost completely suppressed the hydride transfer reactions. (2) Carrying out the cyclization under relatively dilute conditions suppressed the hydride transfer reactions. (3) Once formed, enone **5** is stable to hot polyphospheric acid. In addition, two probable intermediates in the hydride transfer reactions, 1,2,3,4-tetrahydro-1-phenanthrol[15] (**15**) and 3,4-dihydrophenanthrene (**16**), were prepared in order to investigate their possible role in this reaction.

Although 3,4-dihydrophenanthrene has been reported previously, in one case the compound was not characterized[16] and in the other[17] the physical properties did not agree with those of material prepared by the dehydration of alcohol **15**. In order to clarify this situation, olefin **16** was oxidized to the corresponding diacid, which was identical with a sample prepared from ketone 12,[18] thus confirming that our material had the assigned structure. Based on the published data, it appears that the dihydrophenanthrene reported by Paquette from the pyrolysis of "benzosnoutene"[17] is actually 1,2-dihydrophenanthrene.

Treatment of alcohol **15** or dihydrophenanthrene **16** with hot polyphosphoric acid gave low to modest yields of mixtures of phenanthrene and tetrahydrophenanthrene (**13**). While a mechanism can be proposed which accounts for most of these data, some points remain obscure.[19] It was finally found that by carrying out the cyclization under moderately dilute conditions, using purified diketone acceptable yields of recrystallized enone **5** could be obtained.

The conjugate addition of lithium dimethylcuprate to enone **5** gave a mixture of both isomers of **6**, which contained a preponderance (88%) of the 5β ketone. Isomerization of this mixture with dilute acid gave the equilibrium mixture containing approximately 67% of the 5β isomer.[20] Reaction of ketone **6** with methylenetriphenylphosphorane in Me_2SO gave olefin **7** with the same degree of selectivity observed in the reaction of ketone **9** under similar conditions. This racemic material was identical in its spectral properties with a sample prepared from podocarpic acid (**2**), by removal of the phenolic hydroxyl group,[21] to give acid **4**, which was decarboxylated with lead tetraacetate to give a mixture of olefins.[7a,8] Pure olefin **7** was separated from its isomers by selective epoxidation of the more substituted Δ^3 and Δ^4 olefins.[9]

Some efforts were made to increase the selectivity of the Wittig reaction; however, the best results (86% of olefin **7**, 14% of the apparent 5β isomer) were obtained under the usual conditions for dimsyl ion catalyzed generation of the phosphorus ylide.[4,6] The use of excess sodium hydride gave only recovered ketone, while carrying out the condensation of the ketone with the ylide at room temperature led to a mixture containing only 70% of the desired olefin (**7**).

Although a new synthetic path to the tricyclic nucleus of the diterpenoid acids had been developed, in view of the lack of complete trans selectivity in the Wittig reaction the original plan of using completely synthetic material to synthesize acids **3** and **4** was abandoned. Instead an alternative system was selected for the development of methodology for the introduction of the carboxylic acid group at C-4. The substrate chosen was olefin **10**, an analogue of olefin **7**, but which is readily available in quantity from dehydroabietic acid.[8,22]

The conversion of olefin **10**, via 19-norabieta-8,11,13-trien-18-al (**17**) to 4-epidehydroabietic acid (callitrisic acid, **18**) has been reported by Pelletier,[23] and a similar transformation has been reported by Ziegler.[10] Thus, a method for the introduction of an axial carboxyl group from olefin **10** is available. In an effort to improve this sequence aldehyde **17** was converted to methyl ester **19** by oxidation, followed by esterification. This ester afforded the methyl ester of 4-epidehydroabietic acid (**18**) on treatment with lithium diisopropylamide followed by methyl iodide; however, the yield of isolated product from this sequence was very low (2%) and could not be improved by varying the reaction conditions. An improvement in the published method for converting aldehyde **17** to acid **18** was made when it was found that methylation of aldehyde **17** with potassium triphenylmethide[24] afforded abieta-8,11,13-trien-19-al (**20**) in 91% isolated yield. The oxidation of aldehyde **20** to acid **18** has been reported.[23]

Although the stereoselective conversion of aldehyde **17** to

the axial carboxylic acid is quite routine, the introduction of an equatorial carboxyl group is less straightforward, owing to the stereochemical course of alkylation at C-4 which invariably leads to the introduction of an equatorial alkyl group.[23] A conversion of ketone **6** to either C-4 epimer would appear to be possible using the combination of an elegant, but lengthy, sequence developed recently by Trost[25] with a sequence devised by Wenkert;[26] however, a direct, short, stereoselective conversion of aldehyde **17** to a compound having the correct stereochemistry and functionality at C-4 proved to be feasible. The key step of this sequence was the reduction of a highly sterically hindered aldehyde, such as **20** to the corresponding alkane. That this reduction was feasible was realized when aldehyde **20** was subjected to the Wolff–Kishner reduction to afford abieta-8,11,13-triene (**21**).[27]

The conversion of aldehyde **17** to a 4α-carboxylic acid precursor was accomplished by alkylation with potassium triphenylmethide–allyl bromide to give aldehyde **22** followed by Wolff–Kishner reduction to hydrocarbon **23**. Periodate–permanganate oxidation afforded homodehydroabietic acid **24**, identical in all respects with a sample prepared by homologation of dehydroabietic acid.[3b] This compound has been degraded to dehydroabietic acid **1** by both Stork[3b] and Ireland.[3c] In view of the fact that ketone **9** has been synthesized,[28] the conversion of ketone **9** to acid **24** constitutes a formal total synthesis of dehydroabietic acid.

Experimental Section[29]

18-Norabieta-4(19),8,11,13-tetraene (10). To a solution of 21.28 g (83.77 mmol) of the mixture of olefins obtained by the lead tetraacetate oxidation of dehydroabietic acid[7a,8] in 900 mL of methylene chloride was added 10.47 g (51.6 mmol) of *m*-chloroperbenzoic acid (85%) in 100 mL of methylene chloride. The solution was stirred at room temperature for 0.75 h and excess 10% aqueous sodium iodide was added. The organic layer was drawn off and washed twice with excess 10% aqueous sodium bisulfite and twice with 10% aqueous sodium carbonate. The methylene chloride was dried and evaporated to give 20.28 g of a clear yellow oil. The crude product was taken up in hexane and chromatographed on 1000 g of activity I neutral alumina. Elution with hexane gave 6.98 g (75%) of olefin, the spectral properties of which agreed with those reported previously.[8]

18,19-Dinorabieta-8,11,13-trien-4-one (9). To a solution of 0.19 g (1.20 mmol) of potassium permanganate and 12.12 g (80.0 mmol) of sodium periodate in 350 mL of water was added 13.2 g of potassium carbonate. To this mixture was added 2.00 g (7.87 mmol) of olefin **10** dissolved in 350 mL of *tert*-butyl alcohol and the mixture was stirred for 72 h at room temperature. The mixture was filtered by gravity and the *tert*-butyl alcohol removed on the steam bath at water-pump pressure. The aqueous residue was extracted with ether and the combined ether extracts were dried and evaporated to give a yellow oil. This oil was dissolved in 4:1 hexane–benzene and chromatographed on 70 g of silica gel. Elution with 1:1-benzene–ethyl acetate afforded 0.843 g (42%) of pure trans ketone (**9**, 5α-H) as a yellow oil: IR 5.85 μ; NMR δ 0.99 (s, 3 H, C-10 methyl), 1.21 (d, J = 7 Hz, 6 H, isopropyl methyl), 6.90–7.20 (m, 3 H, ArH). Chromatography on alumina afforded the equilibrium mixture containing 67% of the 5β isomer.[7]

Heating a solution of 0.501 g of the 5α ketone in 25 mL of diglyme with 2.5 mL of 2 M hydrochloric acid on the steam bath for 0.5 h gave the same mixture of cis and trans ketones.

Wittig Reaction of 18,19-Dinorabieta-8,11,13-trien-4-one. A. To 0.200 g (4.17 mmol) of sodium hydride (50% dispersion in mineral oil), which had been washed repeatedly with hexane, and which was kept under dry nitrogen, was added 6 mL of freshly distilled dimethyl sulfoxide. The mixture was stirred at 65–72 °C until the sodium hydride had dissolved and cooled to room temperature and a solution of 1.428 g (4.00 mmol) of methyltriphenylphosphonium bromide in 4 mL of dimethyl sulfoxide was added and the mixture stirred for 5 min. A solution of 0.256 g (1.00 mmol) of 18,19-dinorabieta-8,11,13-trien-4-one (**9**) in 4 mL of dimethyl sulfoxide was added and the mixture stirred and heated for 16 h under nitrogen at 62–65 °C. The mixture was cooled to room temperature, poured into water, and extracted with hexane. The hexane extracts were washed with water, dried, and evaporated to give a colorless oil which was dissolved in hexane and chromatographed on 20 g of basic alumina. Elution with hexane afforded 0.080 g (32%) of colorless oil. GLC (OV-17, 235 °C) showed the product to contain 92.5% of the 4(19) olefin (**10**) and 7.5% of another compound, presumably the 5β olefin.

B. When 0.323 g (6.73 mmol) of sodium hydride as a 50% oil dispersion was reacted as described above with 10 mL of dimethyl sulfoxide, 2.285 g (6.40 mmol) of methyltriphenylphosphonium bromide in 8 mL of dimethyl sulfoxide, and 0.410 g (1.60 mmol) of the equilibrium mixture of ketones **9** in 8 mL of dimethyl sulfoxide, 0.120 g (30%) of a colorless oil was obtained after chromatography. GLC (OV-17, 235 °C) showed the product to contain 89% of the 5α olefin (**10**) and 11% of the 5β isomer.

18-Norabieta-8,11,13-triene (11). A solution of 0.038 g of 18-norabieta-4(19),8,11,13-tetraene (**10**) from the Wittig reaction in 15 mL of 95% ethanol was hydrogenated at 50 psig using Adams' catalyst. The catalyst was filtered off using Celite and the solvent evaporated to give 0.033 g (86%) of hydrocarbon **11** as a colorless oil. The product had identical spectral data with those of a sample prepared earlier.[8]

Cyclizations of 2-(2-Phenylethyl)cyclohexane-1,3-dione. A. To 100.0 g of polyphosphoric acid at 120 °C was added with stirring 7.793 g of crude, crystalline 2-(2-phenylethyl)cyclohexane-1,3-dione.[12] The temperature was increased at 160 °C and the mixture stirred at that temperature for 0.75 h. After cooling to 90 °C, the mixture was poured into water, cooled, and extracted with ether. The ether extracts were combined, washed with water, dried, and evaporated to give 5.039 g of dark yellow oil. The crude product was dissolved in hexane and chromatographed on Camag activity I acid-washed alumina. Elution with 1:1 hexane–benzene gave 1.495 g of 1,2,3,4-tetrahydrophenanthrene **13**, as a colorless oil which was identical with an authentic sample. Repeated rechromatography using Woelm activity I neutral alumina and elution with benzene gave 0.034 g of 1,2,3,4-tetrahydro-1-ketophenanthrene **12**, which was identical with an authentic sample. Further elution with benzene gave a yellow oil which crystallized on standing. Recrystallization from 30–60 °C petroleum ether gave 0.400 g of 1,2,3,4,9,10-hexahydro-1-ketophenanthrene (**5**), mp 48–48.5 °C (lit. 48–49 °C[12]) as light yellow plates: IR 6.00 μ; NMR δ 1.78–3.45 (m, 10 H, aliphatic H), 7.15–7.85 (m, 4 H, ArH); UV 288 nm (log ϵ 4.12), 235 (4.13), 298 (4.12). The 2,4-dinitrophenylhydrazone had mp 260–262 °C (lit. 262–263 °C[12]). Rechromatography and elution with benzene afforded 0.070 g of 1,2,3,9,10,10a-hexahydro-3-ketophenanthrene (**14**), which was identical with the material described below.

In another reaction, 0.150 g of crude, crystalline 2-(2-phenylethylcyclohexane)-1,3-dione was heated in 15.0 g of polyphosphoric acid in the manner described above to give 0.110 g of brown oil. The crude product was dissolved in hexane and chromatographed on 8.0 g of Camag activity I acid-washed alumina. Elution with 2:1 hexane–benzene gave 0.022 g of phenanthrene which was twice sublimed (80 °C, 0.025 mm) to give white crystals, mp 94–97 °C, mixture melting point with a commercial sample 97.5–99 °C.

B. In a typical analytical run in which the products were not isolated, 0.50 g of unrecrystallized diketone was added with stirring to 30 g of polyphosphoric acid at 120 °C. The mixture was stirred at 160 °C for 0.75 h. After cooling to 80 °C, the reaction mixture was poured into water, cooled, and extracted with ether. The combined ether extracts were washed with water, dried, and evaporated to give a brown oil. GLC of the crude product (SE-30, 210 °C) showed the mixture to contain 5% 1,2,3,4-tetrahydrophenanthrene (**13**), 4% phenanthrene, 78% 1,2,3,4,9,10-hexahydro-1-ketophenanthrene (**5**), and 14% of a mixture of 1,2,3,4-tetrahydro-1-ketophenanthrene (**12**) and enone **14**.

When this reaction was carried out using 0.150 g of crude, crystalline diketone in 15 g of polyphosphoric acid, the reaction mixture contained 42% tetrahydrophenanthrene (**13**), 21% phenanthrene, 29% of enone **5**, and 8% of ketone **12**.

C. For the preparation of quantities of enone **5**, the cyclization of recrystallized (mp 149–151 °C) 2-(2-phenylethyl)cyclohexane-1,3-dione was carried out as described above. From 15.0 g of diketone in 2500 g of polyphosphoric acid there was obtained 13.8 g of crude enone as a dark brown oil. GLC (SE-30, 210 °C) indicated that this material was contaminated with ca. 5% of the hydride transfer products. Recrystallization from petroleum ether gave 10.6 g (77%) of pale yellow needles of sufficient purity to carry out the succeeding reactions.

1,2,3,4-Tetrahydro-1-phenanthrone (12). This material was prepared by the polyphosphoric acid catalyzed cyclization of 4-(1-naphthyl)butanoic acid,[30] and was obtained as crystals from hexane, mp 96–96.5 °C (lit. 96–97 °C[31]). This material was identical in all respects with the material described above.

1,2,3,4-Tetrahydrophenanthrene (13). This material was prepared by the Wolff–Kishner reduction of the semicarbazone of

1,2,3,4-tetrahydro-1-ketophenanthrene. From 0.414 g of semicarbazone there was obtained 0.309 g (97%) of hydrocarbon **13** as a colorless oil which crystallized on standing in the freezer: NMR δ 1.80 (m, 4 H, H-1 and H-4), 2.82 (m, 4 H, H-2 and H-2), 6.85–7.80 (m, 6 H, ArH); UV 280 nm (log ϵ 3.74), 308 (2.97), 315 (2.76), 325 (2.94). The picrate has mp 109–110 °C (lit. 111 °C[31]), mixture melting point with the picrate from the cyclization of the dione 110–111 °C.

1,2,3,9,10,10a-Hexahydro-3-ketophenanthrene (14). This material was prepared by a modification of the published procedure.[13,19] From 5.00 g of 1-tetralone there was obtained, following condensation with ethyl formate and annelation with methyl vinyl ketone, 0.953 g (14%) of enone **14** as pale yellow crystals from cyclohexane. This material had mp 82–83 °C (Mousseron reports mp 103 °C[13]); mixture melting point with the material described above from the cyclization reaction 80–81 °C; IR 5.99 μ; NMR δ 1.40–3.10 (m, 9 H, aliphatic H), 6.60–6.65 (d, J = 3 Hz, 1 H, H-4), 7.18–7.25 (m, 3 H, ArH), 7.65–7.82 (m, 1 H= H-5); UV 228 nm (log ϵ 3.97), 235 (3.92), 300 (4.25).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 85.05; H, 7.28.

3,4-Dihydrophenanthrene (16). A. To a solution of 0.100 g of 1,2,3,4-tetrahydro-1-phenanthrol (**15**)[32] dissolved in 20 mL of toluene was added a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was heated at reflux for 2.75 h, cooled, washed with water, and dried and the solvent was evaporated leaving 0.075 g of light yellow solid. The crude product was dissolved in hexane and chromatographed on Camag activity I basic alumina. Elution with hexane gave 0.050 g (55%) of clear plates: mp 65–66 °C; IR 6.20 μ; NMR δ 2.45 (m, 2 H, H-4), 3.18 (t, J = 8 Hz, 2 H, H-3), 6.12 (m, 1 H, H-2), 6.55 (q, J = 1 and 6 Hz, 1 H, H-1), 7.10–8.15 (m, 6 H, ArH).

Anal. Calcd for $C_{14}H_{12}$: C, 93.33; H, 6.66. Found: C, 93.12; H, 6.56.

B. To 0.198 g of 1,2,3,4-tetrahydro-1-phenanthrol (**15**) in 4 mL of pyridine was slowly added 0.35 mL of phosphoryl chloride. The solution was heated on the steam bath for 1 h, cooled slightly, and poured into water. The aqueous mixture was extracted with ether; the ether extract was washed with cold 10% aqueous hydrochloric acid and water, dried, and evaporated, giving 0.025 g (14%) of light yellow oil. This material was identical with that described in part A above.

3-(2-Carboxy-1-naphthyl)propanoic Acid. To a solution of 0.012 g (0.07 mmol) of potassium permanganate, 1.70 g (7.94 mmol) of sodium periodate, and 1.75 g of potassium carbonate dissolved in 40 mL of water was added 0.144 g (0.80 mmol) of 3,4-dihydrophenanthrene dissolved in 40 mL of *tert*-butyl alcohol, the reaction mixture was stirred for 20 h at room temperature, the *tert*-butyl alcohol was removed on the steam bath at water pump pressure, and the aqueous residue was acidified with 10% aqueous sulfuric acid and extracted with ether. The ether solution was extracted with 2.5% aqueous potassium hydroxide and the combined alkaline extracts were washed with ether and acidified with 10% aqueous hydrochloric acid. The product was isolated by extraction. Recrystallization from ether/petroleum ether gave 0.083 g (42%) of white needles, mp 202–203 °C (lit. 203 °C[18]), mixture melting point with material prepared by the method of Meyer[18b] 203 °C.

4a-Methyl-1,2,3,4,4a,9,10,10a-octahydro-1-ketophenanthrene (6). To a rapidly stirred mixture of 23.05 g (121.0 mmol) of cuprous iodide and 165 mL of anhydrous ether in a Morton flask at 0 °C under nitrogen was slowly added 198 mL (256.4 mmol) of methyllithium (1.30 M in ether). The mixture was stirred for 5 min and 6.00 g (30.3 mmol) of 1,2,3,4,9,10-hexahydro-1-ketophenanthrene (**5**) in 165 mL of anhydrous ether was slowly added. The yellow, heterogeneous mixture was stirred at 0 °C for 2 h. The mixture was slowly poured into a rapidly stirred solution of cold 1.2 M hydrochloric acid and the resulting mixture was repeatedly extracted with ether. The combined ether extracts were washed twice with 10% aqueous sodium bisulfite and once with saturated aqueous sodium chloride, dried, and evaporated to give 6.067 g of brown oil. The oil was dissolved in benzene and chromatographed on 300 g of Woelm activity I silica gel. Elution with 100:1 benzene–ethyl acetate gave 2.861 g (44%) of yellow oil. By comparison of NMR peak heights, the product was found to contain 12% of 5α ketone and 88% of the 5β isomer.

A solution of 0.545 g of this ketone mixture in 26 mL of diglyme containing 2.5 mL of 2 M hydrochloric acid was heated on the steam bath for 0.5 h. The mixture was diluted with water, cooled, and extracted several times with hexane. The combined hexane extracts were washed several times with water, dried, and evaporated to give a yellow oil. The oil was dissolved in 1:1 hexane–benzene and filtered through 25 g of activity I silica gel. Elution with 2:1 benzene–ethyl acetate afforded 0.365 g (67%) of ketone mixture as a yellow oil. By NMR integration the mixture was found to contain 34% of the 5α isomer and 66% of the 5β compound: IR 5.85 μ; NMR, trans isomer, δ 1.00 (s, 3 H, C-10 methyl); cis osimer, δ 1.24 (s, 3 H, C-10). These properties agree with those reported by Stork and Burgstahler.[28]

19-Norpodocarpa-4(18),8,11,13-tetraene (4aβ-Methyl-1-methylene-1,2,3,4,4a,9,10,10aα-octahydrophenanthrene, 7). A. To 0.3472 g (7.23 mmol) of sodium hydride (50% oil dispersion which had been repeatedly washed with hexane and maintained in a helium atmosphere was added 10 mL of dimethyl sulfoxide, freshly distilled from calcium hydride, and the mixture was stirred at 65–72 °C until solution occurred. The flask was cooled to room temperature and a solution of 2.295 g (6.43 mmol) of methyltriphenylphosphonium bromide in 8 mL of dimethyl sulfoxide was added. The mixture was stirred for 5 min and a solution of 0.344 g (1.61 mmol) of 4a-methyl-1,2,3,4,4a,9,10,10a-octahydro-1-ketophenanthrene (**6**) in 5 mL of dimethyl sulfoxide was added. The mixture was cooled to room temperature, poured into water, and extracted with ether. The ethereal solution was washed with water, dried, and evaporated to give a light yellow oil. The oil was taken up in hexane and filtered through 20 g of Camag activity I basic alumina. Elution with hexane gave 0.140 g (41%) of colorless oil which contained 86% of the 5α olefin and had an identical infrared spectrum with that of the material described in B below.

B. To a solution of 1.00 g (3.88 mmol) of podocarpa-8,11,13-trien-19-oic acid[21] dissolved in 15 mL of dry benzene and 1 mL of dry pyridine was added 2.00 g (4.51 mmol) of lead tetraacetate. The mixture was stirred for 1 h at room temperature, then for 3 h at reflux, cooled, filtered through Celite, and washed several times with benzene. The filtrate and washings were combined and concentrated. The resulting yellow oil was dissolved in hexane, washed twice with dilute hydrochloric acid and twice with water, and dried and the hexane evaporated. The product was taken up in hexane and filtered through 30 g of acid-washed alumina to give 0.717 g (87%) of clear, colorless oil which contained 34% 19-norpodocarpa-4(18),8,13-tetraene (**7**) and 66% of a mixture of 19-norpodocarpa-4,8,11,13-tetraene plus 19-norpodocarpa-3,8,11,13-tetraene (analysis by NMR). To a solution of this olefin mixture in 53 mL of methylene chloride was added 0.502 g (2.47 mmol) of *m*-chloroperbenzoic acid (85%) and the mixture was stirred at room temperature for 0.75 h. Excess 10% aqueous sodium iodide was added, and the organic layer drawn off and washed twice with excess 10% aqueous sodium bisulfite and twice with 10% aqueous sodium carbonate. The methylene chloride was dried and evaporated to give 0.637 g of colorless oil. The crude product was taken up in hexane and chromatographed on 32 g of Camag activity I basic alumina. Elution with hexane gave 0.134 g (57%) of clear oil: IR 6.09 μ; NMR δ 1.02 (s, 3 H, C-10 methyl), 4.70–4.95 (m, 2 H, CCH_2), 7.10–7.50 (m, 4 H, ArH). The infrared and NMR spectra were identical with those of the racemate described in part A.

Anal. Calcd for $C_{16}H_{20}$: C, 90.51; H, 9.49. Found: C, 90.68; H, 9.54.

Methyl 19-Norabieta-8,11,13-trien-18-oate (19). To a stirred solution of 5.70 g (21.11 mmol) of 19-norabieta-8,11,13-trien-18-al (**17**) prepared by the method of Pelletier[23] in 285 mL of acetone at room temperature was added dropwise 12 mL (24.0 mmol) of Jones reagent over a 1-min period. After 20 min, 8 mL of methanol was added, and the mixture was diluted with brine and extracted with ether. The ether extracts were combined, dried, and evaporated to give a yellow oil. The crude acid was dissolved in 10% aqueous potassium hydroxide, washed twice with ether, and precipitated with dilute sulfuric acid. The precipitate was taken up in ether and the ether was dried and evaporated to give 3.28 g (54%) of acid as a yellow foam: IR 5.85 μ; NMR δ 1.11 (s, 3 H, C-10 methyl), 6.85–7.25 (m, 3 H, ArH), 10.37 (s, 1 H, COOH).

A solution of 3.43 g (12.00 mmol) of this material in methylene chloride was treated with an excess of ethereal diazomethane. The solvent was removed under vacuum to give 3.466 g of crude ester as a yellow solid. Recrystallization from methanol gave 2.87 g (80%) of white needles: mp 88–89 °C; IR 5.72 μ; NMR δ 1.10 (s, 3 H, C-10 methyl), 1.23 (d, J = 7 Hz, isopropyl methyl), 3.68 (s, 3 H, $COOCH_3$), 6.82–7.30 (m, 3 H, ArH).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 80.14; H, 9.40.

Methyl Abieta-8,11,13-trien-19-oate. To a flame-dried flask at 0 °C under helium was added 0.460 g (4.55 mmol) of diisopropylamine and then dropwise, over a 4-min period, 2.1 mL (4.55 mmol) of 2.2 M *n*-butyllithium. After stirring at 0 °C for 0.25 h, the lithium diisopropylamide precipitated as a white solid. A cold solution of one crystal of triphenylmethane in 3 mL of hexamethylphosphoramide, freshly distilled from calcium hydride, was added and to the resulting bright red solution was added a solution of 0.667 g (2.22 mol) of methyl 19-norabieta-8,11,13-trien-18-oate (**19**) in 4 mL of hexamethyl-

phosphoramide. The reaction mixture remained bright red after stirring for 1 h at 0 °C. To the cold mixture was then added 4.72 g (33.24 mmol) of methyl iodide in one portion. The mixture was stirred and heated at 40 °C for 2 h and cooled to room temperature and 12 mL of petroleum ether was added. Sufficient 10% aqueous hydrochloric acid was added until the mixture became acidic and the aqueous layer was then drawn off and twice extracted with petroleum ether. The organic layers were combined and washed repeatedly with 10-mL portions of 10% aqueous hydrochloric acid, water, and saturated brine. The solvent was dried and evaporated to give 0.416 g of light yellow foam. The product was dissolved in 6:1 hexane–benzene and chromatographed on 20 g of activity I acid-washed alumina. Elution with 5:1 hexane–benzene afforded 0.014 g (2%) of oil which crystallized on the addition of methanol; recrystallization from methanol gave white crystals, mp 78–78.5 °C (lit.[33] 79–80 °C), mmp 74.5–77 °C. The infrared spectrum was identical with that of an authentic sample.

Abieta-8,11,13-trien-19-al (20). To 1.13 g of potassium hydride (6.75 mmol, 24% oil dispersion), which had been thoroughly washed with dry hexane and anhydrous ether and which was maintained in an atmosphere of helium, was added 3 drops of dry dimethyl sulfoxide. Following the cessation of the evolution of hydrogen, a solution of 1.647 g (6.75 mmol) of triphenylmethane in 6.5 mL of dimethyoxyethane (freshly distilled from lithium aluminum hydride) was added and the mixture stirred for 0.25 h at 40 °C. The tritylpotassium was added slowly to a solution of 0.450 g (1.66 mmol) of 19-norabieta-8,11,13-trien-18-al (17) dissolved in 2.0 mL of dimethoxyethane under helium until a permanent red color was obtained. The mixture was stirred for 10 min and 2.5 mL of methyl iodide was added all at once, with the immediate discharge of the red color and the formation of a precipitate. The heterogeneous mixture was stirred overnight at room temperature; the reaction mixture was poured into cold water and acidified with concentrated hydrochloric acid and the product extracted with several portions of ether. The etheral extracts were combined, washed thoroughly with water, and dried and the solvent was evaporated to give a mixture of a yellow oil and a solid. The product was taken up in hexane and chromatographed on 50 g of silica gel. Elution with benzene gave 0.433 g (91%) of a light yellow oil: IR 3.65, 5.82 μ; NMR δ 1.08 (s, 3 H, C-18 methyl), 1.11 (s, 3 H, C-10 methyl), 1.28 (d, J = 7 Hz, 6 H, isopropyl methyl), 7.15–7.46 (m, 3 H, ArH), 10.20 (d, J = 1 Hz, CHO). These spectral properties agree with those reported by Pelletier.[23]

Abieta-8,11,13-triene (21). To the semicarbazone from 0.433 g (1.52 mmol) of abieta-8,11,13-trien-19-al (20) was added a solution of 3.66 g of potassium hydroxide in 25 mL of diethylene glycol and enough water to effect solution. The mixture was distilled until a temperature of 185 °C was reached and then heated at reflux for 5 h. The reaction mixture was cooled to 90 °C, poured into water, and extracted several times with hexane. The combined hexane extracts were washed with water, dried, and evaporated to give a yellow oil. The oil was taken up in hexane and chromatographed on 50 g of acid-washed alumina. Elution with hexane gave 0.129 g (31%) of a clear, colorless oil which crystallized on standing in the freezer. The oil had identical spectral properties with those reported.[27]

18-Dihomoabieta-8,11,13,18a-tetraen-19-al (22). A solution of tritylpotassium prepared as described above was added slowly to a solution of 0.981 g (3.63 mmol) of 19-norabieta-8,11,13-trien-18-al (17) dissolved in 2.0 mL of dimethoxyethane under helium until a permanent red color was obtained. The mixture was stirred for 10 min and 3.0 mL of allyl bromide was added all at once, with the immediate discharge of the red color and the formation of a precipitate. The mixture was stirred at room temperature overnight, poured into cold water, and acidified with concentrated hydrochloric acid and the product was extracted with several portions of ether. The ethereal extracts were combined, washed thoroughly with water, and dried and the solvent was removed at reduced pressure to give a mixture of a yellow oil and a solid. The product was taken up in hexane and chromatographed on silica gel. Elution with benzene gave 1.078 g (96%) of light yellow oil: IR 3.65, 5.82, 6.10, 6.22 μ; NMR δ 1.05 (s, 3 H, C-10 methyl), 1.25 (d, J = 7 Hz, 6 H, isopropyl methyl), 4.95–6.00 (m, 3 H, C-18a and C-18b, CH=CH_2), 7.00–7.50 (m, 3 H, ArH), 10.00 (s, 1 H, CHO). The 2,4-dinitrophenylhydrazone had mp 192–193 °C.

Anal. Calcd for $C_{28}H_{34}N_4O_4$: C, 68.55; H, 6.99; N, 11.42. Found: C, 68.70; H, 7.10; N, 11.24.

18-Dihomoabieta-8,11,13,18a-tetraene (23). To a solution of 1.063 g (3.43 mmol) of 18-dihomoabieta-8,11,13,18a-tetraen-19-al dissolved in 40 mL of diethylene glycol was added 3.0 mL of 99% hydrazine and the mixture was heated at reflux for 1 h. The mixture was cooled and a solution of 3.0 g of potassium hydroxide in 15 mL of diethylene glycol and enough water to effect solution was added. The mixture was distilled until a temperature of 185 °C was reached and then heated at reflux for 4.5 h, cooled, poured into water, and extracted several times with hexane. The combined hexane extracts were washed with water, dried, and evaporated to give a yellow oil. The oil was taken up in hexane and chromatographed on 50 g of Camag activity I basic alumina. Elution with hexane afforded 0.537 g (53%) of clear, colorless oil: IR 6.10, 6.20 μ; NMR δ 0.92 (s, 3 H, C-10 methyl), 1.20 (s, 3 H, C-19 methyl), 2.22 (d, J = 7 Hz, 6 H, isopropyl methyl), 2.62–2.97 (m, 2 H, C-18 CH_2), 4.72–5.75 (m, 3 H, C-18a and C-18b $CH{=}CH_2$), 6.72–7.70 (m, 3 H, ArH).

Anal. Calcd for $C_{22}H_{32}$: C, 89.12; H, 10.88. Found: C, 89.33; H, 10.92.

18-Homo-8,11,13-trien-18a-oic Acid (Homodehydroabietic Acid, 24). To a solution of 0.325 g (1.10 mmol) of 18-dihomoabieta-8,11,13,18a-tetraene (23) in 50 mL of *tert*-butyl alcohol was added a solution of 0.045 g of potassium permanganate, 2.59 g of sodium periodate, and 1.98 g of potassium carbonate in 50 mL of water. The reaction mixture was stirred at room temperature for 22 h and filtered and the solvent removed at water-pump pressure. The aqueous residue was acidified with 10% sulfuric acid and the product extracted with 1:1 hexane–ether. The combined organic extracts were washed with 10% aqueous potassium hydroxide. The basic extract was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water, dried, and evaporated to give a colorless oil which was twice recrystallized from aqueous methanol to give 0.095 g (28%) of white needles, mp 142–144 °C, mixture melting point with material prepared by Stork's method[3b] 143–144 °C. The infrared spectra of samples prepared by both procedures were identical.

Registry No.—**1**, 6980-63-8; **2**, 15292-90-7; **4**, 10178-11-7; **5**, 62264-34-0; 5α**H-6**, 54170-97-7; 5β**H-6**, 62318-99-4; **7**, 62319-00-0; 5α**H-9**, 62319-01-1; 5β**H-9**, 62319-02-2; 5α**H-10**, 62319-03-3; 5β**H-10**, 62319-04-4; **12** semicarbazone, 62264-35-1; **13**, 1013-08-7; **14**, 53023-33-9; **15**, 62264-36-2; **16**, 38399-10-9; **17**, 62319-05-5; **19**, 62264-37-3; 19 free acid, 62264-38-4; **20**, 62319-06-6; **22**, 62288-64-6; **22** hydrazone, 62264-39-5; **23**, 62264-40-8; 2-(2-phenylethyl)cyclohexane-1,3-dione, 62264-41-9.

References and Notes

(1) Presented at the Southeastern–Southwestern Regional Meeting of the American Chemical Society, Oct 29–31, 1975.
(2) Tennessee Eastman Fellow, 1973–1974.
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Synthesis of 2-Alkylcyclopentenones. Jasmone, Dihydrojasmone, and a Prostaglandin Precursor

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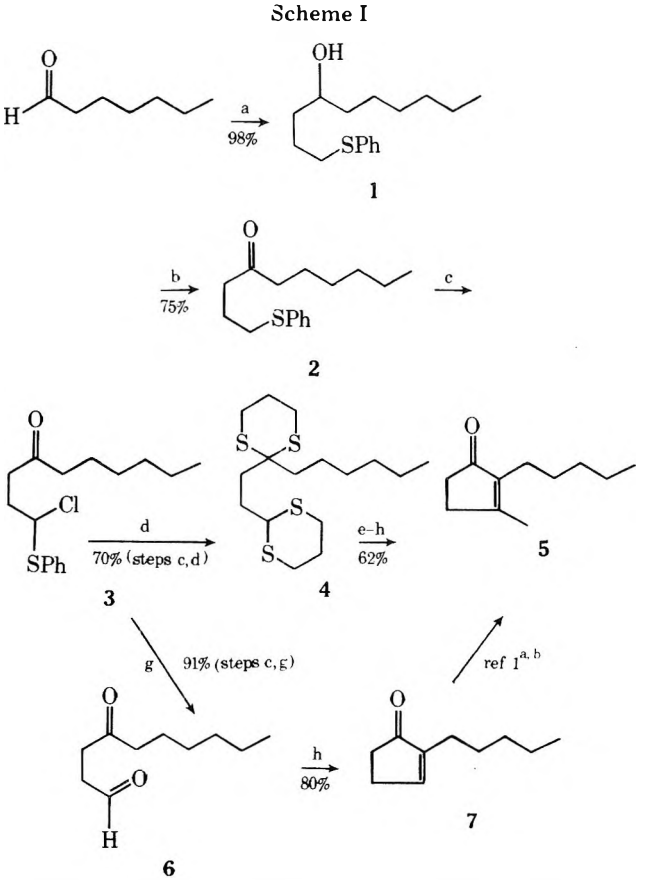
Jasmone (**15**), dihydrojasmone (**5**), and 2-(6-carboxyhexyl)cyclopent-2-en-1-one (**10**) were prepared in several steps from acyclic precursors. Thus, levulinic acid was transformed into a sulfide which was oxidized with *N*-chlorosuccinimide and hydrolyzed to the diketo aldehyde **13**. A chemoselective Wittig reaction, followed by base-catalyzed cyclization, gave jasmone (**15**). Similarly, **5** was prepared from heptanal, while **10** was prepared from azelaic acid monomethyl ester.

2-Alkylcyclopentenones are important intermediates in the preparation of natural products such as jasmones,[1] prostaglandins,[2] steroids,[3] and triterpenes.[4] One method of preparing such compounds is the base-catalyzed cyclization[5] of 1,4-dicarbonyl[6] compounds. While there are many methods of preparing 1,4-diketones,[6a] there are relatively few methods for preparing γ-keto aldehydes.[6b,c] We would like to report a simple sequence of reactions, from readily available starting materials, that permits the synthesis of the 1,4-dicarbonyl precursors of the title compounds.

Grignard reagents prepared from β-halo acetals are known to be unstable,[7] although they have been used for the preparation of alcohols[8] and ketones.[6b] Grignard and lithium reagents prepared from protected bromopropanols and butanols are useful for the preparation of alcohols, ketones, functional homologations, and 1,4-additions to unsaturated systems.[9] However, the preparation of both of these reagents by inexperienced workers is not easy, and the latter reagents are prepared from expensive starting materials. Recently, we showed that Grignard reagents prepared from bromoalkyl phenyl sulfides (easily prepared from the readily available dibromo alkanes) can be used for functional homologations.[10] In this report we present our results on the application of these compounds to the preparation of carbonyl compounds.

While the two sequences outlined in Scheme I for the preparation of dihydrojasmone are longer than the best present method,[11] they illustrate some of the potential of the $PhS(CH_2)_nMgBr$ reagents. Hydroxy sulfide **1**, prepared from heptanal in near-quantitative yields, was oxidized selectively to the carbonyl compound **2** with pyridinium chlorochromate.[12] The key intermediate **3**, prepared by oxidation of **2** with *N*-chlorosuccinimide,[10,13] was transformed into the dithiane **4** and then, by the usual methods[14] of alkylation, hydrolysis, and cyclization, into dihydrojasmone (**5**). Alter-

Scheme I

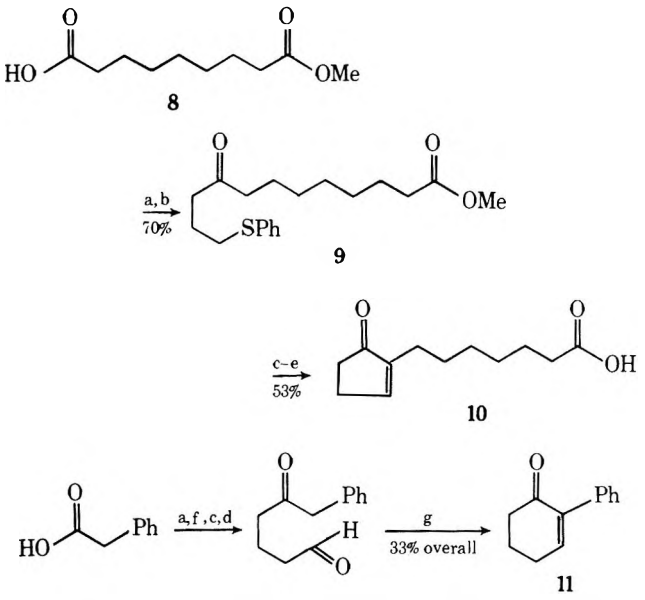


a, $BrMg(CH_2)_3SPh$; b, $PyHCrO_3Cl$; c, NCS; d, $HS(CH_2)_3SH/BF_3{\cdot}Et_2O$; e, *n*-BuLi; f, CH_3I; g, Cu(II)/H_2O; h, NaOH/H_2O/Δ.

nately, the chloro sulfide **3** could be hydrolyzed[10,13,15] to keto aldehyde **6**[6b,16] and cyclized[16] to 2-pentylcyclopentenone (**7**). Cyclopentenone **7** has been transformed[1a,b] into dihydrojasmone.

Scheme II shows additional applications of the method for

Scheme II

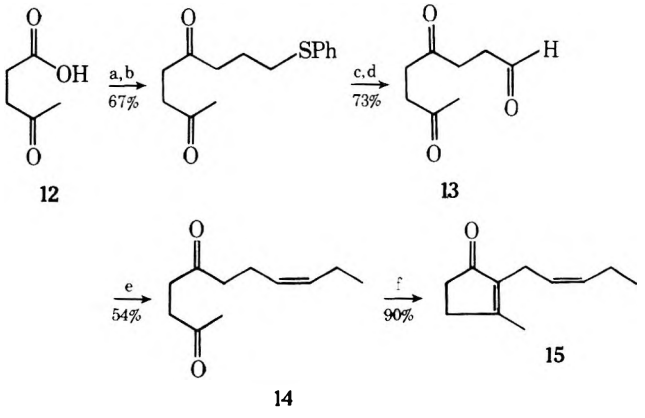


a, *t*-BuCOCl/NEt_3; b, $BrMg(CH_2)_3SPh$; c, NCS; d, Cu(II)/H_2O; e, NaOH/H_2O/Δ; f, $BrMg(CH_2)_4SPh$; g, NaOH/H_2O/room temp

synthesis of 2-alkylcycloalkenones. Thus, cyclopentenone **10**,[17] an important intermediate[2] in the synthesis of prostaglandins, was prepared in 37% overall yield from the commercially available azelate **8**. The key intermediate **9** was prepared in a one-pot sequence via the mixed anhydride[11] formed from pivaloyl chloride. Similarly, phenylacetic acid was transformed into 2-phenylcyclohexenone (**11**)[18] in 33% overall yield. (For an additional example of the preparation of a keto sulfide, 7-phenylthio-3-heptanone, see the Experimental Section.)

Scheme III outlines the synthesis of *cis*-jasmone (**15**). Thus, levulinic acid (**12**) was transformed into the diketo aldehyde

Scheme III



a, *t*-BuCOCl/NEt_3; b, $BrMg(CH_2)_3SPh$; c, NCS; d, Cu(II)/H_2O; e, $Ph_3P{=}CHCH_2CH_3$; f, NaOH/H_2O/Δ

13 in 49% overall yield by a sequence of reactions similar to that discussed in Scheme II. A chemoselective Wittig reaction transformed tricarbonyl compound **13** into the key intermediate **14**[19] in 54% yield without requiring protection of the two ketone groups. The stereochemistry of the double bond was assigned cis (>90%) in analogy to known[9e,19b,c] reactions under comparable conditions.[20] Confirmation of this assignment came from the spectra of the cyclized product, *cis*-jasmone (**15**), which showed no absorption in the infrared at 10.32 μ, characteristic of *trans*-jasmone.[21]

Experimental Section

All reactions were run under an atmosphere of N_2. THF was freshly distilled from $LiAlH_4$. Chlorinations of sulfides were found to give erratic results, even when reagent grade CCl_4 was used as solvent. However, reproducible results were obtained by purifying reagent grade CCl_4 by washing with concentrated H_2SO_4, aqueous base, and H_2O, drying over Na_2SO_4, and distilling. The crude chloro sulfides and the derived aldehydes were unstable and thus used immediately after preparation.

Procedure for the Preparation of γ-and δ-Keto Sulfides. Methyl 9-Oxo-12-phenylthiododecanoate (9). To a solution of 1.60 g (7.9 mmol) of azelaic acid monomethyl ester (**8**) in 15 mL of THF at −15 °C was added 1.15 mL (8.3 mmol) of NEt_3 and 1.03 mL (8.4 mmol) of pivaloyl chloride. After stirring at −15 °C for 1 h, the suspension was filtered and the precipitate was washed with 15 mL of THF. To the combined liquid phases, at −78 °C, was added, dropwise, a Grignard solution prepared from 0.19 g (7.8 mmol) of magnesium and 2.28 g (9.8 mmol) of 3-bromopropyl phenyl sulfide[10] in 17 mL of THF. After stirring at −78 °C for 20 min, the solution was allowed to come to room temperature, hydrolyzed with 10% NH_4Cl, and extracted with ether. The organic layer was washed with 10% NaOH and H_2O and dried over Na_2SO_4. The crude product was chromatographed on 90 g of silica gel, 1% ethanol in benzene eluting 1.86 g (70%) of methyl 9-oxo-12-phenylthiododecanoate (**9**). An analytical sample was prepared by bulb-to-bulb distillation: IR (neat) 5.78, 5.82, 6.3, 6.98, 8.52, 13.53, 14.49 μ; ^1H NMR (CCl_4) δ 7.21 (m, 5 H), 3.6 (s, 3 H), 2.88 (t, J = 7 Hz, 2 H). Anal. Calcd for $C_{19}H_{28}O_3S$: C, 67.82; H, 8.39. Found: C, 67.74. H, 8.39.

The ketones could also be prepared without filtration of the precipitated $HCl{\cdot}NEt_3$. In these cases, the original quantity of THF was doubled.

7-Phenylthio-3-heptanone. From 40.8 mmol of propanoic acid and 40.8 mmol of 4-bromobutyl phenyl sulfide[10] a 61% yield of pure keto sulfide was obtained: IR (neat) 5.83, 6.3, 13.53, 14.50 μ; ^1H NMR (CCl_4) δ 7.20 (m, 5 H), 3.0–2.7 (m, 2 H), 2.5–2.0 (m, 4 H), 1.9–1.4 (m, 4 H), 0.97 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 70.18; H, 8.03.

6-Phenylthio-1-phenyl-2-hexanone. From 20 mmol of phenylacetic acid and 20 mmol of 4-bromobutyl phenyl sulfide a 65% yield of pure keto sulfide was obtained: IR (neat) 5.82, 6.3, 13.5, 14.3, 14.5 μ; ^1H NMR (CCl_4) δ 7.17 (m, 10 H), 3.53 (s, 2 H), 2.76 (t, J = 7 Hz, 2 H), 2.33 (t, J = 7 Hz, 2 H), 1.79–1.42 (m, 4 H). Anal. Calcd for $C_{18}H_{20}OS$: C, 76.01; H, 7.09. Found: C, 75.76; H, 6.93.

8-Phenylthio-2,5-octadione. From 50 mmol of levulinic acid (**12**), 50 mmol of Mg, and 83 mmol of 3-bromopropyl phenyl sulfide a 67% yield of pure diketo sulfide was obtained: IR (neat) 7.83, 6.3, 13.5, 14.5 μ; ^1H NMR (CCl_4) δ 7.24 (m, 5 H), 2.89 (t, J = 7 Hz, 2 H), 2.55 (s, 4 H), 2.09 (s, 3 H); mol wt 250.1033 (calcd for $C_{14}H_{18}O_2S$, 250.1027).

Preparation of 1-Phenylthio-4-decanone (2). This compound could be prepared from heptanoic acid and 3-bromopropyl phenyl sulfide, but separation from by-products was difficult and therefore the following two-step procedure was developed. To a Grignard solution at room temperature, prepared from 0.64 g of magnesium and 7.7 g of 3-bromopropyl phenyl sulfide in 50 mL of diethyl ether, was added, dropwise, 2.28 g of *n*-heptanal. After stirring for 2 h, the mixture was hydrolyzed with dilute HCl, and the organic layer was washed with water and dried over Na_2SO_4. The crude product was chromatographed on 300 g of silica gel, benzene eluting 0.16 g of heptanal and 8% ether/benzene eluting 4.86 g of 1-phenylthio-4-decanol (**1**) (93%, based on unrecovered heptanal). An analytical sample was prepared by bulb-to-bulb distillation, the sample crystallizing upon cooling: mp 41.5–42.5 °C; IR (neat) 2.95, 6.29, 13.57, 14.5 μ; ^1H NMR (CCl_4) δ 7.22 (m, 5 H), 3.25–3.69 (m, 1 H), 2.9 (t, J = 6.5 Hz, 2 H). Anal. Calcd for $C_{16}H_{26}OS$: C, 72.12; H, 9.84. Found: C, 72.30; H, 9.63.

A mixture of 2.78 g of the alcohol **1**, prepared above and 3.55 g of pyridinium chlorochromate[12] in 50 mL of CH_2Cl_2 was stirred at room temperature for 2 h. After dilution with 50 mL of ether, the mixture was filtered and the filtrate was washed with 10% NaOH solution, 4% HCl solution, and water and dried over Na_2SO_4. The crude product was chromatographed on 75 g of silica gel, elution with benzene giving 2.08 g (75%) of 1-phenylthio-4-decanone (**2**). Continued elution with 8% ether/benzene gave 0.52 g of starting alcohol (**1**). An analytical sample of the ketone was prepared by bulb-to-bulb distillation, the sampling crystallizing upon cooling: mp 33–34 °C; IR (neat) 5.83, 6.29,

13.55, 14.5 μ; ^{1}H NMR (CCl_4) δ 7.2 (m, 5 H), 2.86 (t, J = 7 Hz, 2 H). Anal. Calcd for $C_{16}H_{24}OS$: C, 72.67; H, 9.15. Found: C, 72.62; H, 8.92.

Procedure for the Transformation of γ- and δ-Keto Sulfides into 2-Alkylcycloalkenones. 2-(6-Carboxyhexyl)cyclopent-2-en-1-one (10). A mixture of 484 mg of methyl 9-oxo-12-phenylthiododecanoate (**9**) and 210 mg of NCS in 10 mL of CCl_4 was stirred of 0 °C for 4 h. After the mixture was filtered and the solvent removed, the residue was refluxed for 15 min in a mixture of 450 mg of CuO, 450 mg of $CuCl_2$·$2H_2O$, 0.2 mL of H_2O, and 10 mL of acetone. After cooling rapidly, the mixture was diluted with 50 mL of benzene and filtered, and the filtrate was dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on 30 g of silica gel using 2% ethanol/benzene as eluent to give 292 mg (84%) of methyl 9,12-dioxododecanoate: IR (neat) 3.62, 5.74, 5.82 μ; ^{1}H NMR (CCl_4) δ 9.73 (s, 1 H), 3.59 (s, 3 H), 2.65 (s, 4 H).

Cyclization and hydrolysis of this unstable oil was carried out immediately after isolation. Thus, 829 mg of the oil in 15 mL of EtOH was added, over 25 min, to a degassed solution of 700 mL of 1% NaOH at 75 °C. After stirring for an additional 15 min, the solution was cooled, acidified with concentrated HCl, saturated with NaCl, and extracted with ether (3 × 120 mL). The crude product was chromatographed on 25 g of silica gel, 15–25% ether/benzene eluting 451 mg (63%) of the acid (**10**):[17] IR (neat) 5.85, 6.12 μ; ^{1}H NMR (CCl_4) δ 9.21 (s, 1 H), 7.32 (m, 1 H), 2.8–1.9 (m, 8 H), 1.9–1.1 (m, 8 H).

2-Pentylcyclopentenone (7). From 10 mmol of 1-phenylthio-4-decanone (**2**) and 11 mmol of NCS in 70 mL of CCl_4, at room temperature for 2 h, followed by hydrolysis and column chromatography as above, was obtained a 91% yield of 4-oxodecanal (**6**):[6b,16] IR (neat) 3.65, 5.80, 5.83 μ; ^{1}H NMR (CCl_4) δ 9.75 (s, 1 H), 2.65 (s, 4 H), 2.43 (t, J = 6.5 Hz, 2 H). Cyclization[16] of the keto aldehyde gave 2-pentyl-2-cyclopentenone (**7**):[16] IR (neat) 5.86, 6.10 μ; ^{1}H NMR (CCl_4) δ 7.20 (m, 1 H).

2-Phenylcyclohexenone (11). From 2.6 mmol of 6-phenylthio-1-phenyl-2-hexanone and 3.4 mmol of NCS in 12 mL of CCl_4, at room temperature for 2 h, followed by hydrolysis as above, was obtained an ether solution of crude keto aldehyde which was not isolated. The ethereal layer was washed with 10% HCl solution and then shaken with a 10% NaOH solution until the organic phase became colorless (in a few minutes). After drying and removal of solvent, the residue was chromatographed on 15 g of silica gel, 1:1 petroleum ether/benzene eluting 1.3 mmol (50%) of 2-phenylcyclohexenone (**11**):[18] mp 93.5–94.5 °C (lit.[18] 93–94 °C); IR (KBr) 6.0, 6.21 μ; ^{1}H NMR (CCl_4) δ 7.24 (s, 5 H), 6.92 (t, J = 3.5 Hz, 1 H).

Preparation of Dihydrojasmone (5). A mixture of 1.145 g of 1-phenylthio-4-decanone (**2**) and 0.735 g of NCS, in 30 mL of CCl_4, was stirred at room temperature for 3 h. After filtration and removal of the solvent, the residue was dissolved in 15 mL of CH_2Cl_2 and to this solution, at 0 °C, was added 2.65 mL of 1,3-propanedithiol and 0.25 mL of BF_3·Et_2O. After 5 min, the cooling bath was removed and the mixture was stirred overnight at room temperature and then diluted with ether and poured onto ice. The organic phase was washed three times with 10% NaOH solution and once with brine, and dried over Na_2SO_4. After removal of solvent, the residue was chromatographed on 60 g of silica gel, 1:1 petroleum ether/benzene eluting 1.06 g (70%) of 2-[2-(1,3-dithian-2-yl)ethyl]-2-hexyl-1,3-dithiane (**4**). An analytical sample was prepared by bulb-to-bulb distillation: IR (neat) 6.90, 7.05, 7.86, 8.08, 11.0, 12.46 μ; ^{1}H NMR (CCl_4) δ 3.96 (t, J = 6 Hz, 1 H), 3.2–2.4 (m, 8 H). Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.80; H, 8.62. Found: C, 54.79; H, 8.42.

To a solution of 0.56 g of the above dithiane in 5 mL of THF, at −15 °C, was added, via syringe, 2 mL of 1.3 M n-BuLi in hexane. After stirring for 1 h, the solution was cooled to −78 °C and 0.5 mL of CH_3I was added dropwise, After 1 h, the mixture was allowed to come to room temperature slowly, kept at this temperature for 0.5 h, and then diluted with ether. The ethereal solution was washed with water and dried over Na_2SO_4 and solvent was removed. The residue was chromatographed on 30 g of silica gel, 1:1 petroleum ether/benzene eluting 0.55 g (95%) of 2-[2-(2-methyl-1,3-dithian-2-yl)ethyl]-2-hexyl-1,3-dithiane:[14] IR (neat) 6.88, 7.04, 7.85, 10.99, 12.65 μ; ^{1}H NMR (CCl_4) δ 3.3–2.4 (m, 8 H), 2.04 (s, 4 H), 1.52 (s, 3H).

A mixture of 0.21 g of the above di-dithiane, 0.41 g of $CuCl_2$·$2H_2O$, 0.38 g of CuO, 0.1 mL of H_2O, and 10 mL of acetone was refluxed for 2 h. After cooling, the mixture was diluted with 50 mL of benzene and filtered, and the filtrate was dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on 15 g of silica gel, 1% ethanol/benzene eluting 0.080 g (72%) of 5-oxo-2-undecanone:[1,22] IR (neat) 5.8 μ; ^{1}H NMR (CCl_4) δ 2.58 (s, 4 H), 2.37 (t, J = 6.5 Hz. 2 H), 2.11 (s, 3 H). Dihydrojasmone (**5**)[1] was prepared in the usual way[1] by base-catalyzed cyclization of the diketone (90% yield): IR (neat) 5.88, 6.07 μ; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H).

Preparation of Jasmone (15). A mixture of 263 mg of 8-phenylthio-2,5-octadione and 155 mg of NCS in 10 mL of CCl_4 at −20 °C was stirred for 4 h. After filtration and removal of the solvent, the residue was hydrolyzed by refluxing, for 15 min, with 360 mg of $CuCl_2$·$2H_2O$, 335 mg of CuO, 0.2 mL of H_2O, and 10 mL of acetone. After cooling, the mixture was diluted with 100 mL of benzene and filtered, and the filtrate was dried over Na_2SO_4. After removal of solvent, the residue was chromatographed on 15 g of silica gel, 1.5% ethanol/benzene eluting 28 mg of starting sulfide and 3% ethanol/benzene eluting 107 mg (73%) of 4,7-dioxooctanal (**13**): unstable oil; IR (neat) 3.60, 5.83 μ; ^{1}H NMR (CCl_4) δ 9.65 (s, 1 H), 2.67 (s, 4 H), 2.63 (s, 4 H), 2.10 (s, 3 H).

To a suspension of 770 mg of n-propyltriphenylphosphonium bromide in 25 mL of toluene at room temperature was added, dropwise, 1.4 mL of 1.5 M n-butyllithium in hexane. After stirring for 1 h, the bright red suspension was cooled to −50 °C and to it was added, dropwise, 270 mg of diketo aldehyde **13**, prepared as above, in 2 mL of toluene. After the resulting black-brown suspension was sistirred at −45 to −50 °C for 20 min, the temperature was raised to −15 °C, and the suspension was stirred for 1 h and then allowed to come to room temperature and left overnight. The crude mixture was chromatographed on 30 g of silica gel, benzene eluting 171 mg (54%) of *cis*-8-undecene-2,5-dione (**14**):[19] IR (neat) 5.82 μ (no absorption at 10.3 μ); ^{1}H NMR (CCl_4) δ 5.25 (m, 2 H), 2.57 (s, 4 H), 2.09 (s, 3 H), 0.95 (t, J = 7.5 Hz, 3 H). ^{1}H NMR spectra in $CDCl_3$ at 100 MHz and in benzene at 60 MHz gave no evidence for the presence of the trans isomer. Cyclization of the enedione under the usual conditions[19] gave *cis*-jasmone (**15**):[19] IR (neat) 5.87, 6.05 μ (no absorption[21] at 10.3 μ); ^{1}H NMR ($CDCl_3$) δ 5.34 (m, 2 H), 2.95 (t, J = 5 Hz, 2 H), 2.07 (s, 3 H), 0.98 (t, J = 7.5 Hz, 3 H).

Acknowledgment. We would like to thank Professor Baker of CPPN, Rio de Janeiro, for spectral determinations. The partial support of this work by CNPq and CAPES is gratefully acknowledged.

Registry No.—**1**, 62358-93-4; **2**, 62358-94-5; **4**, 62358-95-6; **5**, 1128-08-1; **6**, 43160-78-7; **7**, 25564-22-1; **8**, 2104-19-0; **9**, 62358-96-7; **10**, 5239-43-0; **11**, 4556-09-6; **12**, 123-76-2; **13**, 62358-97-8; **14**, 4868-21-7; **15**, 4907-07-7; 3-bromopropyl phenyl sulfide, 3238-98-0; 7-phenylthio-3-heptanone, 62358-98-9; propanoic acid, 79-09-4; 4-bromobutyl phenyl sulfide, 17742-54-0; 6-phenylthio-1-phenyl-2-hexanone, 62358-99-0; phenylacetic acid, 103-82-2; 8-phenylthio-2,5-octadione, 62359-00-6; heptanal, 111-71-7; methyl 9,12-dioxododecanoate 50266-44-9; 1,3-propanedithiol, 109-80-8; 2-[2-(2-methyl-1,3-dithian-2-yl)ethyl]-2-hexyl-1,3-dithiane, 62414-94-2; 5-oxo-2-undecanone, 7018-92-0.

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Factors Governing the Relative Stabilities of the C/D Cis and Trans Ring Junctures in Δ^8-11-Keto Steroids

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Pure 14α and 14β epimers of Δ^8-11-keto steroids with different 17β-alkyl groups were prepared and the position of their base-catalyzed equilibrium established by gas-liquid phase chromatography. In contrast to 15-keto steroids, where the nature of the 17β substituents crucially affects the cis/trans hydrindanone equilibrium, the 14β (C/D cis) isomer is greatly favored in the present series irrespective of the nature of the C-17 substituent. Using a previously described force-field method, the energies and conformations of the cis and trans isomers of the Δ^8-11-keto steroids were calculated and found to be in reasonable agreement with the experimentally established values.

One of the most interesting problems in steroid conformational analysis lies in the variation of the relative stabilities of the cis and trans (C/D) ring juncture, notably in steroidal hydrindanone systems.[1] Numerous variations observed in these systems led to a whole series of explanations.[1,2] A detailed experimental study using optical rotatory dispersion measurements of 17β-alkyl-5α,14ξ-androstan-15-ones[3] and a subsequent theoretical study using a force-field method[4] were in good agreement.[5] The data generated by this force-field method made it possible to understand the exact nature of the interactions which led to the observed energy differences.[5]

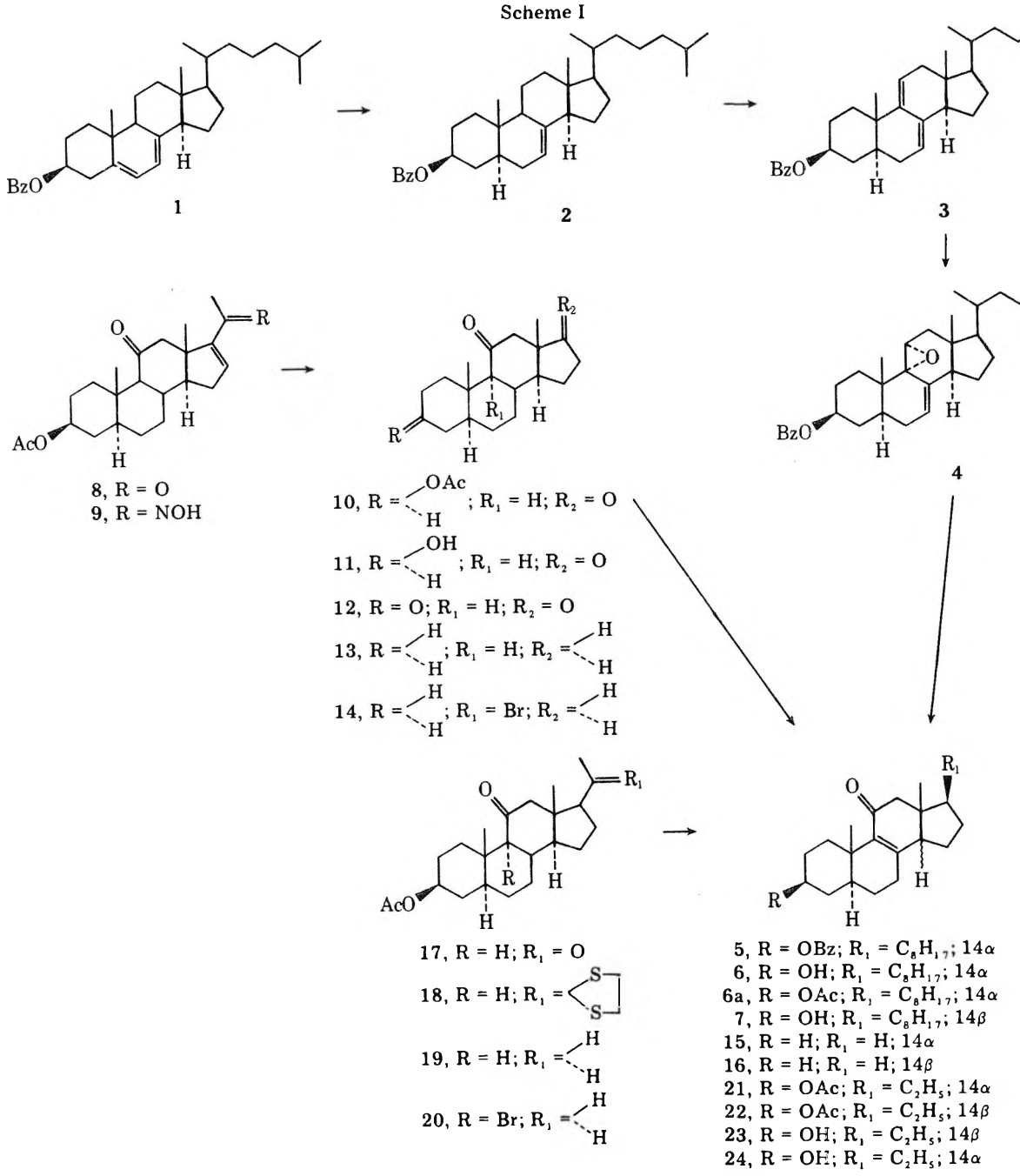
In the 8-methylhydrindane system the cis compound is the more stable one.[2a,5,6] The greater stability of the cis compound can be applied to steroid systems[2a] and Dreiding[7] summarized examples showing trans to cis isomerization of the C/D rings. Most of these compounds had either an isolated or aromatic double bond between C-8 and C-9. Djerassi and co-workers were able to isomerize a Δ^8-11-ketone in the sapogenin series from the 14α to the 14β epimer[8] and Eardley et al.[9] were able to effect a similar change with a Δ^8-11-ketone possessing a 17β-C_9H_{19} substituent.

The object of the present study was to investigate the base-catalyzed equilibration of 17β-alkyl-Δ^8-5α,14ξ-androsten-11-ones, in order to determine what role the size of the 17β-alkyl substituent plays in the relative stabilities of the cis and trans (C/D) ring juncture. In addition, theoretical calculations using the 1973 force-field method[10] were carried out in order to provide insight into the nature of the interactions involved. The results of the experimental study (Table I) are in accord with the theoretical predictions.

Synthesis of Δ^8-11-Keto Steroids. The synthesis of the various Δ^8-11-keto steroids is depicted in Scheme I. Hydrogenation (W-5 Raney nickel) of $\Delta^{5,7}$-cholestadien-3β-ol benzoate (**1**) gave in nearly quantitative yield the known[11] alkene **2**, which upon mercuric acetate oxidation in acetic acid afforded in 69% yield the known[12] $\Delta^{7,9(11)}$-5α-cholestadien-3β-ol benzoate (**3**). Oxidation at 0 °C with *m*-chloroperbenzoic acid gave the known[13] monoepoxide **4**, which was smoothly rearranged in the presence of boron trifluoride etherate to give a 74% yield of Δ^8-5α-cholesten-3β-ol-11-one benzoate (**5**). Owing to the facile alkaline isomerization at C-14, the benzoate **5** was saponified under mild conditions[8] to give the corresponding alcohol **6** which could be acetylated under normal conditions to give the known[14] Δ^8-5α-cholesten-3β-ol-11-one acetate (**6a**). Alternatively, saponification (5% methanolic KOH) of the benzoate **5** afforded in 83% yield the C-14 epimeric alcohol Δ^8-5α,14β-cholesten-3β-ol-11-one (**7**). Base-catalyzed equilibration of pure Δ^8-5α,14α (**6**) and Δ^8-5α,14β (**7**) gave an equilibrium mixture (see Table I) consisting of 96–97% of the 14β (**7**) and 3–4% of the 14α (**6**) epimers.

The versatile starting material Δ^{16}-5α-pregnene-11,20-dion-3β-ol acetate (**8**)[15,16] was chosen for the desired Δ^8-11-one compounds in the androstane and pregnane series. Beckmann rearrangement[17] of the oxime **9** gave 64% of 5α-androstane-11,17-dion-3β-ol acetate (**10**). Saponification to **11** followed

Scheme I



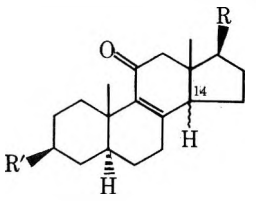
by oxidation to 5α-androstane-3,11,17-trione (**12**) and Wolff–Kishner reduction gave a 46% overall yield of 5α-androstan-11-one (**13**). Bromination[18] to the 9α-bromide **14** and subsequent dehydrobromination[9,18] for *30 s* afforded the desired Δ^8-5α-androsten-11-one (**15**). Alternatively, dehydrobromination of **14** for *2 min* gave the C-14 epimeric Δ^8-5α,14β-androsten-11-one (**16**). Base-catalyzed equilibration of Δ^8-5α,14α (**15**) and Δ^8-5α,14β (**16**) gave an equilibrium mixture (see Table I) consisting of 99 to <100% of the 14β (**16**) and ~1% of the 14α (**15**) epimers.

Hydrogenation (10% palladium on carbon) of Δ^{16}-5α-pregnene-11,20-dion-3β-ol acetate (**8**)[15,16] gave a quantitative yield of **17** which was converted quantitatively with ethanedithiol and boron trifluoride etherate[19] to the 20-ethylene thioketal **18**. Raney nickel[20] (W-7) desulfurization proceeded in 85% yield to 5α-pregnan-3β-ol-11-one acetate (**19**). Bromination in acetic acid[18] led to the 9α-bromo derivative **20** which furnished in 97% yield Δ^8-5α-pregnen-3β-ol-11-one acetate (**21**) upon dehydrobromination for *30 s* with calcium carbonate in refluxing dimethylacetamide. Alternatively, dehydrobromination of 9α-bromo-5α-pregnan-3β-ol-11-one acetate (**20**) for *20 min* furnished the C-14 epimeric acetate Δ^8-5α,14β-pregnen-3β-ol-11-one acetate (**22**) which was then saponified to the desired alcohol Δ^8-5α,14β-pregnen-3β-ol-11-one (**23**). Base-catalyzed equilibration of the 14β alcohol **23** gave an equilibrium mixture (see Table 1) consisting of 98% of the 14β (**23**) and 2% of the 14α (**24**) epimers. Mild saponification[8] of the 14α-acetate **21** furnished Δ^8-5α-pregnen-3β-ol-11-one (**24**) which was also subjected to base-catalyzed equilibration (see Table I).

Results and Discussion

Table II summarizes the calculated[21] stabilities of tricyclic models[22] of 15-keto steroids and Δ^8-11-keto steroids. In the saturated tricyclic ketone **25a**, the trans isomer is slightly more stable (by 0.3 kcal/mol). Adding a bridgehead methyl (**25b**) makes a major change, so that the cis isomer is now very strongly stabilized. On the other hand, placing a methyl substituent at the 17 position (steroid numbering) produces a trend in the opposite direction; nevertheless, in **25c** the cis isomer remains the preferred one. When an isopropyl group is attached at C-17 (**25d**), the order inverts again, and the trans

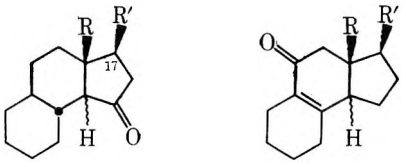
Table I. Position of Base-Catalyzed Equilibrium of 17β-R-Δ⁸-5α,14ξ-Androsten-3β-R'-11-one



R	R'	% 14β epimer	ΔG_{65}°, kcal/mol
H	H	99[a] to <100[b]	3.2
C_2H_5	OH	98[a,b]	2.6
C_8H_{17}	OH	96[a]–97[b]	2.2

[a] Base-catalyzed equilibration from the 14α epimer. [b] Base-catalyzed equilibration from the 14β epimer.

Table II. Calculated Enthalpies (kcal/mol) for Conformational Equilibria: 14β (Cis) ⇋ 14α (Trans)



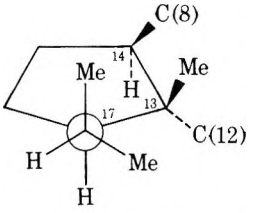
25 26

25	ΔH_{25}°	R	R'	26	ΔH_{26}°
a	−0.33	H	H	a	+0.70
b	+2.08	Me	H	b	+2.69
c	+1.01	Me	Me	c	+1.41
d	−1.14	Me	*i*-Pr	d	+1.14

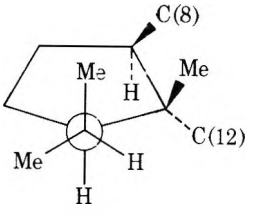
isomer is now preferred. Similar results have been encountered experimentally in a study of 17-alkyl-15-keto steroids.[3] This inversion of stability has been suggested to be mainly due to an unfavorable interaction between a C-20 methyl and the 14β hydrogen which are only 2.35 Å apart.[5]

If we now consider the Δ^8-11-keto steroids, in the simple tricyclic case (**26a**) the cis isomer is more stable by 0.7 kcal/mol. This inversion of stability from **25a** to **26a** can be attributed to the well-known effect of a cyclohexene system in stabilizing a five-membered ring fused cis at the observed position in the compounds under discussion.[7,23] This "cyclohexene effect" contributes about 1 kcal toward stabilizing the cis isomer when comparing **25a** and **26a.** Proceeding down the series from **26a** to **26d** the energy differences are consistently positive relative to those in the series **25a** to **25d.** The calculations (Table II) for the tricyclic unsaturated ketone indicate that the cis isomer is strongly favored irrespective of the side chain and this is what is found experimentally (Table I) for the Δ^8-11-keto steroids. The calculations also indicate that there are basically two different kinds of conformations for the C/D system when the juncture is cis. These two conformations **27** and **28** (Table III)[24] correspond to the two different half-chair conformations of the cyclohexene in ring C. In conformation **28,** models show that the 15α hydrogen interacts unfavorably (by about 1 kcal according to the calculation) with the 7α hydrogen. This unfavorable repulsion, and distortions imposed in an attempt to relieve it, seem to be the main source of the increase in relative stability of conformation **27.** In addition, for each of these conformations there are two separate conformations which differ mainly by twisting ring D in the pseudorotational itinerary.[25]

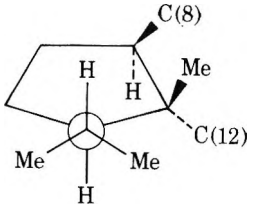
It is apparent from Table II that the same general trend is found in both the 15-ketone series (**25b** to **25d**) and the Δ^8-11-ketone series (**26b** to **26d**): the relative stability of the (C/D)-cis isomer decreases as the size (C-20) of the β-alkyl group attached to C-17 increases. The effect of the 17β-isopropyl group in the 15-ketone series was to actually invert the relative stability at the C/D ring juncture from the cis to the trans configuration.[3,5] The isopropyl group does not have the same effect in the Δ^9-11-ketone (**26d**) where the cis compound is still the overwhelming favorite (Table II). There are three orientations that the isopropyl group can assume, and their energies (relative to the best conformation of the cis isomer) are shown below along with values in parentheses for the corresponding saturated 15-ketones as recalculated with the 1973 force-field method.[10] The conformation with E = 1.14



E = 4.46 (3.77)



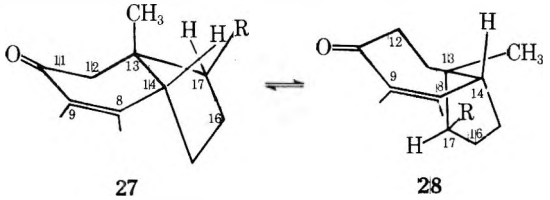
E = 3.12 (2.02)



E = 1.14 (0.00)

is the best conformation for the (C/D)-trans isomer of the Δ^8-11-ketone **26d** as well as for the (C/D)-trans isomer of the 15-ketone **25d.** The other conformations suffer from an extremely unfavorable interaction between the angular 18-methyl group and a methyl group of the isopropyl substituent. This interaction is similar to the syn-diaxial dimethyl interaction in a 1,3-dimethylcyclohexane.[26]

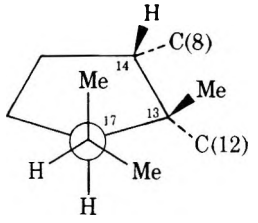
Table III. Calculated Energies for the Two Half-Chair Conformations of Ring C in the Δ^8-11-Keto Steroids



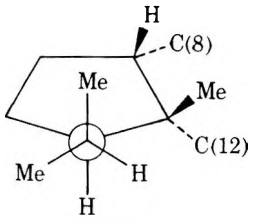
27 28

Conformer 27	Angle 8-14-13-17	Angle 12-13-14-15	ΔE, kcal/mol	R	Conformer 28	Angle 8-14-13-17	Angle 12-13-14-15	ΔE, kcal/mol
a	163.7	80.7	0.00	H	a	85.3	156.5	1.82
b	163.5	80.6	2.26	Me	b	78.6	165.4	3.21
c	150.9	98.6	6.54	*i*-Pr	c	78.4	167.6	7.57

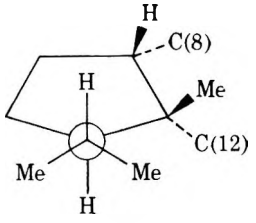
In the (C/D)-cis Δ^8-11-one (**26d**), surprisingly, the stable conformation (E = 0.00) has an extremely unfavorable interaction between the angular 18-methyl group and the isopropyl Me group. However, this conformation lacks the interaction between the C-20 methyl group and the 14β hydrogen which was apparently the major interaction responsible for the inversion of stability in going from a 17-methyl (**25c**) to a 17-isopropyl (**25d**) substituent in the 15-ketone series.[5] That the conformation of the isopropyl side chain in the most stable conformation of the cis isomer is different in the 15-ketones as compared to the Δ^8-11-ketones was not anticipated. From looking at plots of the structures and the accompanying tables of numbers obtained as computer output, the following observations were made.



E = 2.91 (2.81)



E = 1.53 (1.14)



E = 0.00 (3.48)

Since there are many interactions which differ in energy when the different series and conformations are compared, the interpretation is neither complete nor unambiguous, but rather is suggestive. The dihedral angle between the side chain and the 18-methyl group differs in the two systems. In the most stable conformation for the cis 11-ketone (E = 0.00) this dihedral angle is 21°. In the corresponding 15-ketone conformation (E = 3.48), the angle is only 15° and the interaction of the side chain and the 18-methyl is more serious. Thus in the 15-ketone the conformation where the methyl–side chain interaction is minimized (E = 1.14) will be preferred. The presence of the 15-ketone group introduces different torsional and angular interactions in the five-membered ring and apparently affects the crucial dihedral angle. In addition, the presence or absence of the unsaturation in the B ring may lead to further small distortions, and, probably more importantly, changes in the ease of distortions.

Experimental Section

General Information. Microanalyses were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. All melting points are uncorrected and were taken with a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained for solutions in chloroform with a Perkin-Elmer 700 spectrometer. NMR spectra were recorded under the supervision of Dr. L. J. Durham on a Varian Associates T-60 of XL-100 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal reference. Ultraviolet spectra were recorded for solutions in absolute methanol with a Cary Model 14 spectrometer using 1-cm quartz cells. Routine optical rotations were recorded with a Perkin-Elmer Model 141 spectropolarimeter for solutions in chloroform. Circular dichroism curves were determined for solutions in absolute methanol by Mrs. R. Records with a JASCO J-40 circular dichrometer. Low-resolution mass spectra were determined by Mr. R. G. Ross with an AEI MS9 spectrometer operating at 70 eV by use of the direct inlet system. Exact masses were determined by Miss Annemarie Wegmann on a Varian-Mat 711 high-resolution mass spectrometer.

The progress of all reactions and column chromatographies was monitored by thin layer chromatography on silica gel (HF-254) microplates. The spots were detected by spraying with a 2% solution of cerium(IV) sulfate in 2 N sulfuric acid, followed by heating. Preparative thin layer chromatoplates had a thickness of 0.75 mm of silica gel (HF-254) and the bands were detected either visually or by viewing under ultraviolet light. Gas–liquid phase chromatography (GLC) was performed on a Hewlett-Packard Model 402 high-efficiency instrument using 6-ft glass columns packed with 1% OV-25 on Gas-Chrom Q (100–120 mesh) using helium as the carrier gas.

Δ^8-5α-Cholesten-3β-ol-11-one Benzoate (5). The epoxide[13] (**4**, 213 mg, 0.422 mmol) was dissolved in 30 mL of dry, thiophene-free benzene and 20 drops of freshly distilled boron trifluoride etherate[8] was added to the reaction mixture which was allowed to stand at room temperature for 70 h. The solution was then extracted with ether and washed with sodium bicarbonate and water. After drying over $MgSO_4$ and purification by thin layer chromatography on silica gel (10% ether–hexane) a white, crystalline material was obtained (**5**, 157.6 mg, 0.31 mmol, 74%). Crystallization from aqueous acetone afforded clear needles: mp 181–182 °C; $[\alpha]^{21.7}_D$ +117° (c 0.52); IR 5.82, 6.03 μ; NMR δ 4.97 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.80 (d, 1 H, 12β-H, J = 14 Hz), 2.33 (d, 1 H, 12α-H, J = 14 Hz), 1.17 (s, 3 H, 19-CH_3, calcd[27] 1.11), 0.71 (s, 3 H, 18-CH_3, calcd[27] 0.68); UV 230 nm (ϵ 16 000), 257 (9200); CD $[\theta]_{215}$ −24 000, $[\theta]_{254}$ +42 000, $[\theta]_{332}$ −7400; mass spectrum m/e (rel intensity) 504.3602 [M^+ (92), calcd for $C_{34}H_{48}O_3$, 504.3603], 382 (61), 367 (36), 352 (100), 297 (100), 161 (29), 105 (86).

Anal. Calcd for $C_{34}H_{48}O_3$: C, 80.91; H, 9.58. Found: C, 80.65; H, 9.70.

Δ^8-5α,14α-Cholesten-3β-ol-11-one (6). The benzoate (**5**, 200 mg, 0.396 mmol), 320 mg of K_2CO_3, 4 mL of water, 40 mL of methanol, and 15 mL of chloroform were allowed to stand at room temperature for 49 h. After concentration under reduced pressure, dilution with water, and filtration, the product was chromatographed on silica gel (100% ether) and the early fractions provided 61 mg of the starting benzoate **5**. Further development provided 76.0 mg of the desired alcohol **6** which was crystallized from aqueous methanol to give fine needles: mp 132–133 °C; $[\alpha]^{20}_D$ +154° (c 0.26); IR 2.93 6.08, 6.29 μ; NMR δ 3.60 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.78 (d, 1 H, 12β-H, J = 14 Hz), 2.30 (d, 12α-H, J = 14 Hz), 1.10 (s, 3 H, 19-CH_3, calcd[27] 1.09), 0.70 (s, 3 H, 18-CH_3, calcd[27] 0.68); UV 255 nm (ϵ 8500); CD $[\theta]_{216}$ −30 700, $[\theta]_{254}$ +46 800, $[\theta]_{332}$ −8200; mass spectrum m/e (rel intensity) 400.3321 [M^+ (100), calcd for $C_{27}H_{44}O_2$, 400.3341] 248 (61), 193 (60).

Acetylation under normal conditions of the alcohol **6** afforded the acetate **6a**: mp 105–106 °C (lit.[14] mp 104–106 °C); IR 5.82, 6.08, 6.28 μ.

Δ^8-5α,14β-Cholesten-3β-ol-11-one (7). The benzoate (**5**, 924 mg, 1.82 mmol) was heated under reflux in an atmosphere of nitrogen for 130 min with 100 mL of 5% methanolic KOH. After concentration under reduced pressure, the reaction mixture was diluted with water and extracted into ether. The extracts were washed four times with water followed by drying over $MgSO_4$ and evaporation to give 742.5 mg (~100%) of slightly yellow, glassy solid. Column chromatography on silica gel (100% ether) afforded material which was again subjected to column chromatography on 12% $AgNO_3$ impregnated silica gel (30% acetone–hexane) to give 613 mg (83%) of the alcohol **7** which was crystallized from aqueous methanol to give white plates: mp 72–74 °C (presoftens): $[\alpha]^{20}_D$ +170°; IR 3.02, 6.03, 6.22 μ; NMR δ 3.61 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.48 (d, 1 H, 12β-H, J = 14 Hz), 2.14 (d, 1 H, 12α-H, J = 14 Hz), 1.13 (s, 3 H, 19-CH_3), 1.01 (s, 3 H, 18-CH_3); UV 250 nm (ϵ 8700); CD $[\theta]_{209}$ −11 020, $[\theta]_{245.5}$ +19 320, $[\theta]_{333.5}$ −1162; GLC (265 °C) relative retention time (rrt) 0.69 (rrt of **6**, 1); mass spectrum m/e (rel intensity) 400.3354 [M^+ (100), calcd for $C_{27}H_{44}O_2$, 400.3341], 248 (18), 193 (14).

5α-Androstane-11,17-dion-3β-ol Acetate (10). Δ^{16}-5α-Pregnene-11,20-dion-3β-ol acetate (**8**) was reacted under conditions described in the literature[18] to give a 79% yield of the oxime **9** which was crystallized from absolute methanol to give small, white flakes: mp 219–224 °C (lit.[18] mp 217–222 °C); M^+ m/e 387; IR 2.95, 5.82, 5.88 μ (lit.[18] IR 5.82, 5.88 μ); NMR δ 8.43 (s, 1 H, =NOH, D_2O labile), 1.03 (s, 3 H, 19-CH_3), 0.85 (s, 3 H, 18-CH_3).

Beckmann rearrangement[17] of the oxime **9** afforded a 65% yield of the desired ketone **10** which was crystallized from acetone–hexane to give needles: mp 163–164.5 °C (lit.[18] mp 161–163 °C); M^+ m/e 346; IR 5.75, 5.79, 5.86, 8.0, 9.7 μ (lit.[18] IR 5.74, 5.78, 5.88, 8.06, 9.7 μ); NMR δ 1.05 (s, 3 H, 19-CH_3, calcd[27] 1.07), 0.82 (s, 3 H, 18-CH_3, calcd[27] 0.83).

5α-Androstane-11,17-dion-3β-ol (11). The acetate (**10**, 1.1 g, 3.17 mmol) and 50.72 g (63.4 mmol, 20-fold excess) of 5% methanolic KOH were allowed to stand at room temperature for 80 min followed by concentration under reduced pressure and dilution with water. Ether

extraction, washing (H_2O), drying ($MgSO_4$), and evaporation gave the desired alcohol (**11**, 965 mg, 100%) which was crystallized twice from ether–hexane to give needles: mp 169–170 °C; M^+ *m/e* 304; IR 2.82, 5.76, 5.86 μ; NMR δ 1.03 (s, 3 H, 19-CH_3, calcd[27] 1.06), 0.81 (s, 3 H, 18-CH_3, calcd[27] 0.83).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.92; H, 9.32.

5α-Androstane-3,11,17-trione (12). Jones oxidation of the alcohol (**11**, 829 mg, 2.72 mmol) gave the desired trione (**12**, 760 mg, 93%) which was crystallized from acetone–hexane to give white plates: mp 180–181 °C (lit.[13] mp 180.5–181.2 °C); M^+ *m/e* 302; NMR δ 1.23 (s, 3 H, 19-CH_3, calcd[27] 1.27), 0.85 (s, 3 H, 18-CH_3, calcd[27] 0.87).

5α-Androstan-11-one (13). The trione (**12**, 250 mg, 0.82 mmol) was dissolved in 22 mL of diethylene glycol and 1.8 mL of 85% hydrazine hydrate and the mixture heated under reflux for 1 h. Upon cooling to about 100 °C, 500 mg of KOH dissolved in 1 mL of water was added and heating was continued without a reflux condenser until the temperature reached 200 °C. After heating under reflux between 200 and 215 °C for an additional 195 min the reaction mixture was cooled and poured into water (110 mL). The aqueous phase was extracted five times with ether and the ether extracts washed with water, dried ($MgSO_4$), and evaporated to give 227 mg (100%) of a slightly yellow oil. Column chromatography on silica gel (50% benzene–hexane) provided the desired ketone (**13**, 114 mg, 50%) which was crystallized from aqueous methanol to give fine white needles: mp 51.5–53 °C (lit.[28] mp 49–50 °C); $[\alpha]^{20}_D$ +55° (lit.[28] $[\alpha]_D$ +65°); M^+ *m/e* 274; IR 5.89 μ (lit.[28] IR 5.89 μ).

9α-Bromo-5α-androstan-11-one (14). Bromination[18] of the ketone (**13**) gave after preparative TLC and crystallization in absolute methanol a 21% yield of **14** as small, white, soft needles: mp 74–75.5 °C (lit.[18] mp 71–72 °C); M^+ *m/e* 352/354; IR 5.90 μ. The chromatography also afforded 4.0 mg of pure starting ketone **13**.

Δ^8-5α,14α-Androsten-11-one (15). 9α-Bromo-5α-androstan-11-one (**14**, 60 mg, 0.17 mmol) was dehydrobrominated for 30 s with calcium carbonate (51 mg, 0.51 mmol) in refluxing dimethylacetamide (1.5 mL, which had been stirred with KOH and distilled from CaO). The mixture was then poured into water and ether. The ether extracts were washed, dried ($MgSO_4$), and evaporated to give semicrystalline material which was purified by thin layer chromatography on silica gel (50% benzene–hexane) to give after crystallization in aqueous methanol (20.0 mg, 43%) fine white needles: mp 112–113.5 °C (lit.[18] mp 113–114 °C); $[\alpha]^{20}_D$ +168° (*c* 0.16) [lit.[18] $[\alpha]_D$ +180° (c 1.3)]; IR 6.07, 6.28 μ (lit.[15] IR 6.07, 6.24 μ); NMR δ 2.54 (d, 1 H, 12β-H, *J* = 14 Hz), 2.26 (d, 1 H, 12α-H, *J* = 14 Hz), 1.10 (s, 3 H, 19-CH_3, calcd[27] 1.075), 0.73 (s, 3 H, 18-CH_3, calcd[27] 0.725); UV 255 nm (ε 8900) [lit.[18] UV 253 nm (ε 8300)]; CD $[\theta]_{220}$ −13 940, $[\theta]_{255}$ +29 570, $[\theta]_{335}$ −6337; mass spectrum *m/e* (rel intensity) 272.2138 [M^+ (100), calcd for $C_{19}H_{28}O$, 272.2140], 257 (84), 243 (56), 177 (47), 161 (41).

Δ^8-5α,14β-Androsten-11-one (16). Crude 9α-bromo-5α-androstan-11-one (**14**, 458 mg, 1.29 mmol) was dehydrobrominated for 2.0 min with calcium carbonate (387 mg, 3.87 mmol) in refluxing dimethylacetamide (10.0 mL, which had been stirred with KOH and distilled from CaO). The reaction mixture was then poured into water and extracted with ether. The ether extracts were washed, dried ($MgSO_4$), and evaporated to give 354.6 mg of semicrystalline material which was purified by thin layer chromatography on silica gel (50% benzene–hexane) to give after crystallization in aqueous methanol (142.4 mg) fine white needles: mp 64–65.5 °C; $[\alpha]^{20}_D$ +192° (c 0.13); IR 6.04, 6.22 μ; NMR δ 2.53 (d, 1 H, 12β-H, *J* = 14 Hz), 1.92 (d, 1 H, 12α-H, *J* = 14 Hz), 1.12 (s, 3 H, 19-CH_3, calcd[27] 1.05), 1.05 (s, 3 H, 18-CH_3, calcd[27] 1.025); UV 251 nm (ε 8700); CD $[\theta]_{210}$ −11 210, $[\theta]_{247.5}$ +17 390, $[\theta]_{325}$ −2445; GLC (205 °C) rrt 0.74 (rrt of **15**, 1); mass spectrum *m/e* (rel intensity) 272.2128 (M^+ (100), calcd for $C_{19}H_{28}O$, 272.2140], 257 (76), 243 (43), 177 (11), 161 (18).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.76; H, 10.36. Found: C, 83.70; H, 10.33.

5α-Pregnane-11,20-dion-3β-ol Acetate (17). Δ^{16}-5α-Pregnene-11,20-dion-3β-ol acetate (**8**, 5 g, 13.4 mmol) was hydrogenated over 10% palladium on carbon in ethyl acetate to give white, crystalline **17**: mp 134–135 °C (lit.[16] mp 143–145 °C); $[\alpha]^{20}_D$ +78° (lit.[16] $[\alpha]^{20}_D$ +86.5°); M^+ *m/e* 374; IR 5.75, 5.85 μ (lit.[29] IR 5.75, 5.85 μ); NMR δ 1.02 (s, 3 H, 19-CH_3, calcd[27] 1.05), 0.56 (s, 3 H, 18-CH_3, calcd[27] 0.58).

5α-Pregnan-3β-ol-11-one Acetate (19). Boron trifluoride etherate (3.0 mL) was added to a solution of the acetate (**17**, 1.68 g, 4.49 mmol) in 3.0 mL of ethanedithiol. The stirred mixture became hot and deposited a thick paste within 2 min. After being kept at room temperature for a further 7 min, methanol (20 mL) was added with stirring and the solid material filtered, washed with methanol, and dried under reduced pressure to give 1.95 g (97%) of the thioketal **18** which was crystallized from 95% ethanol–methylene chloride to give white plates: mp 234.5–235.5 °C; $[\alpha]^{20}_D$ +22°; M^+ *m/e* 450; IR 5.80, 5.85 μ; NMR δ 4.69 (3α-H, $W_{1/2}$ ca. 22 Hz), 3.28 (m, 4 H, SCH_2CH_2S), 2.02 (s, 3 H, OAc), 1.83 (s, 3 H, 21-CH_3) 1.03 (s, 3 H, 19-CH_3), 0.77 (s, 3 H. 18-CH_3).

Anal. Calcd for $C_{25}H_{38}S_2O_3$: C, 66.62; H, 8.50; S, 14.23. Found: C, 66.48; H, 8.51; S, 14.42.

The thioketal (**18**, 1.1 g, 2.44 mmol) which was dissolved in 95% ethanol (100 mL) was heated under reflux with fresh W-7 Raney nickel[20] (prepared from 30 g of alloy) for 5.5 h. The catalyst was removed by filtration and washed well with ethanol. To the ethanol solution was added 100 mL of benzene and the solvents evaporated to give 987 mg of crude material which was dissolved in ether, hexane added, and the product allowed to crystallize in the freezer to give the desired ketone (**19**, 664 mg, 85%) as white plates: mp 163–165 °C; M^+ *m/e* 360; IR 5.82, 5.87 μ; NMR δ 4.68 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.53 (dt, 1 H, 1β-H, *J* = 13.5, 3.5, 3.5 Hz), 2.31 (d, 1 H, 12β-H, *J* = 12 Hz), 2.12 (d, 1 H, 12α-H, *J* = 12 Hz), 2.01 (s, 3 H, OAc), 1.04 (s, 3 H, 19-CH_3, calcd[27] 1.05), 0.52 (s, 3 H, 18-CH_3, calcd[27] 0.52).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.26; H, 10.23.

A second crop was obtained, 101 mg, mp 145–160 °C cloudy, 162 °C clear.

9α-Bromo-5α-pregnan-3β-ol-11-one Acetate (20). A solution of 32% hydrogen bromide in acetic acid (8 drops) was added to a solution of the ketone (**19**, 140.5 mg, 0.38 mmol) in acetic acid (2.0 mL) followed by the dropwise addition of 0.022 mL (0.43 mmol, 0.069 g, 1.1 mol %) of bromine in acetic acid (0.6 mL). After keeping the solution for 225 min at room temperature in the dark under a current of nitrogen, the crude product (171 mg), isolated by dilution with water and ether extraction followed by drying ($MgSO_4$) and evaporation, was purified by thin layer chromatography on silica gel (40% ether–hexane). The product (**20**, 91.8 mg, 55%) was crystallized from absolute methanol to give 60.3 mg of large leaflets: mp 178.5–180 °C; $[\alpha]^{20}_D$ +158° (c 0.85); IR 5.83, 5.88 μ; NMR δ 4.68 (3α-H, $W_{1/2}$ ca. 24 Hz), 3.25 (broadened d, 1 H, 12α-H, *J* = 13.5 Hz), 2.52 (broad d, 1 H, 1β-H, *J* = 13 Hz), 2.25 (d, 1 H, 12β-H, *J* = 13.5 Hz), 2.01 (s, 3 H, OAc), 1.20 (s, 3 H, 19-CH_3, calcd[27] 1.18), 0.54 (s, 3 H, 18-CH_3, calcd[27] 0.55); CD $[\theta]_{235}$ −5707, $[\theta]_{325}$ +16 000; mass spectrum *m/e* (rel intensity) 438/440 (M^+, 5), 299 (100), 246 (28), 205 (24), 152 (92), 147 (35).

Anal. Calcd for $C_{23}H_{35}BrO_3$: C, 62.86; H, 8.03; Br, 18.18. Found: C, 62.76; H, 8.20; Br, 18.20.

A second crop of 10.0 mg, mp 177–177.5 °C, as well as 35.5 mg of the unreacted starting material **19**, was also obtained.

Δ^8-5α,14α-Pregnen-3β-ol-11-one Acetate (21). 9α-Bromo-5α-pregnan-3β-ol-11-one acetate (**20**, 250 mg, 0.56 mmol) was dehydrobrominated for 30 s with calcium carbonate (168 mg, 1.68 mmol) in refluxing dimethylacetamide (8.0 mL). The same workup as before afforded 214 mg of white, semicrystalline material which was purified by thin layer chromatography on silica gel (50% ether–hexane) to give the desired acetate (**21**, 195 mg, 97%) as a white, crystalline material. Crystallization twice from ether–hexane furnished rosettes of small needles which was greater than 97% the 14α isomer by GLC: mp 144–146 °C (presoftens); IR 5.82, 6.07, 6.29 μ; NMR δ 4.72 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.91 (dt, 1 H, 1β-H, *J* = 14, 3.5, 3.5 Hz), 2.56 (d, 1 H, 12β-H, *J* = 14 Hz), 2.19 (d, 1 H, 12α-H, *J* = 14 Hz), 2.03 (s, 3 H, OAc), 1.12 (s, 3 H, 19-CH_3, calcd[27] 1.12), 0.62 (s, 3 H, 18-CH_3, calcd[27] 0.591); mass spectrum *m/e* (rel intensity) 358.2501 [M^+ (71), calcd for $C_{23}H_{34}O_3$, 358.2508], 298 (73), 290 (100), 283 (64), 269 (21), 235 (97), 230 (22), 175 (42), 161 (54), 121 (35), 109 (37).

Δ^8-5α,14β-Pregnen-3β-ol-11-one Acetate (22). 9α-Bromo-5α-pregnan-3β-ol-11-one acetate (**20**, 250 mg, 0.56 mmol) was dehydrobrominated for 20 min with $CaCO_3$ (125 mg, 1.25 mmol) in refluxing dimethylacetamide (8 mL). The usual workup afforded 200 mg of a clear, thick oil. purification twice by column chromatography on silica gel (40% ether-hexane) afforded 100 mg (50%) of semicrystalline **22**: M^+ *m/e* 358; IR 5.82, 6.03, 6.22 μ; NMR δ 4.68 (3α-H. $W_{1/2}$ ca. 22 Hz), 2.45 (d, 1 H, 12β-H, *J* = 14 Hz), 1.98 (d, 1 H, 12α-H, *J* = 14 Hz), 1.98 (s, 3 H, OAc), 1.10 (s, 3 H, 19-CH_3), 0.90 (s, 3 H, 18-CH_3); GLC (265 °C) rrt 0.78 (rrt of **21**, 1).

Δ^8-5α,14β-Pregnen-3β-ol-11-one (23). To the acetate (**22**, 50 mg, 0.13 mmol) was added 8.0 g (10 mmol) of 5% methanolic KOH. The reaction mixture was left at room temperature for 80 min followed by dilution with water, ether extraction, washing, drying ($MgSO_4$), and evaporation. This material was purified by column chromatography on silica gel (100% ether) to give after two recrystallizations from aqueous methanol the desired alcohol (**23**, 14 mg, 34%) as white plates: mp 169–170 °C; $[\alpha]^{20}_D$ +183°; IR 2.75, 6.03, 6.20 μ; NMR δ 3.62 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.71 (dt, 1 H, 1β-H, *J* = 14, 3.5, 3.5 Hz), 2.47 (d, 1 H, 12β-H, *J* = 14 Hz), 2.04 (d, 1 H, 12α-H, *J* = 14 Hz), 1.12 (s, 3 H. 19-CH_3, calcd[27] 1.075), 0.92 (s, 3 H, 18-CH_3, calcd[27] 0.891); UV 250

nm (ε 9700); CD $[\theta]_{207}$ −15 200, $[\theta]_{246}$ +21 580, $[\theta]_{334}$ −2225; GLC (262 °C) rrt 0.77 (rrt of **24**, 1); mass spectrum *m/e* (rel intensity) 316.2408 [M^+ (100), calcd for $C_{21}H_{32}O_2$, 316.2402], 301 (12), 298 (13), 288 (15), 283 (37), 269 (12), 257 (8), 248 (11), 193 (9), 161 (18), 109 (20), 91 (21).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.69; H, 10.10.

Δ^8-5α,14α-Pregnen-3β-ol-11-one (24). A mixture of the acetate (**21**, 20.4 mg, 0.056 mmol), 41 mg (0.3 mmol) of K_2CO_3, 0.15 mL of water, 7.5 mL of methanol, and 1 mL of ether was allowed to stand at room temperature for 20 h. After concentration under reduced pressure, dilution with water, ether extraction, washing, drying ($MgSO_4$), and evaporation, the product was purified by thin layer chromatography on silica gel (100% ether) and crystallized (**24**, 16.4 mg, 93%) from aqueous acetone to give white plates; mp 159–163 °C (presoftens); IR 6.07, 6.28 μ; NMR δ 3.59 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.86 (dt, 1 H, 1β-H, J = 14, 3.5, 3.5 Hz), 2.54 (d, 1 H, 12β-H, J = 14 Hz), 2.16 (d, 1 H, 12α-H, J = 14 Hz), 1.10 (s, 3 H, 19-CH_3, calcd[27] 1.10), 0.60 (s, 3 H, 18-CH_3, calcd[27] 0.591); UV 255 nm (ε 8800); CD $[\theta]_{215}$ −21 710, $[\theta]_{255}$ +31 330, $[\theta]_{331}$ −6187; mass spectrum *m/e* (rel intensity) 316.2406 [M^+ (100), calcd for $C_{21}H_{32}O_2$, 316.2402], 301 (16), 298 (13), 288 (7), 283 (34), 269 (15), 257 (6), 248 (96), 193 (92), 161 (32), 109 (28), 91 (35).

Equilibration of the Δ^8-11-Ones 6, 7, 15, 16, 23, and 24. The Δ^8-11-ketones were dissolved in excess 5% methanolic KOH and the resulting mixtures heated under reflux. The equilibrations were followed by GLC analysis of aliquots and when the equilibration appeared to be complete the solution was poured into water followed by ether extraction, washing (H_2O), drying ($MgSO_4$), and concentration under reduced pressure.

Analysis of Equilibrium Mixtures. The analysis of the reaction mixtures was carried out by GLC. The recorder was run at the highest chart speed (2 in./min) in order to maximize the peak areas. The relative product ratios were obtained by cutting out and weighing the appropriate peaks. Each equilibration value given in Table I is the average of three to five separate injections and the average reproducibility in the ratios of peak weights for successive injections of the same mixture was ±1.2%.

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Registry No.—**4**, 62250-87-7; **5**, 62250-88-8; **6**, 62250-89-9; **6a**, 40225-72-7; **7**, 62279-64-5; 8, 2724-68-7; **9**, 2800-40-0; **10**, 4731-15-1; **11**, 7090-90-6; **12**, 1482-70-8; **13**, 1755-32-4; **14**, 5976-21-6; **15**, 54498-82-7; **16**, 62318-96-1; **17**, 3684-81-9; **18**, 62250-90-2; **19**, 62250-91-3; **20**, 62250-92-4; **21**, 62250-93-5; **22**, 62279-65-6; **23**, 62250-94-6; **24**, 62279-66-7; 14α-**25a**, 62250-95-7; 14β-**25a**, 62250-96-8; 14α-**25b**, 62250-97-9; 14β-**25b**, 62250-98-0; 14α-**25c**, 62250-99-1; 14β-**25c**, 62251-00-7; 14α-**25d**, 62251-01-8; 14β-**25d**, 62251-02-9; 14α-**26a**, 62251-03-0; 14β-**26a**, 35841-06-6; 14α-**26b**, 62251-04-1; 14β-**26b**, 62251-05-2; 14α-**26c**, 62251-06-3; 14β-**26c**, 62251-07-4; 14α-**26d**, 62251-08-5; 14β-**26d**, 62251-09-6.

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(21) The numbers in Table II are not exactly the same as those published earlier (see ref 5). The reason for this is mainly that the computer program now has more stringent requirements for determining an energy minimum. Small changes in the force field were also made in the interim (see ref 10). These results are now more reliable (although not necessarily better insofar as agreement with experiment).

(22) In the case of compound **26b** only, ring A was added and the calculation was repeated for the actual steroid. It was noted that there was an interference between the C-11 oxygen and the equatorial C-1 hydrogen which was substantially worse in the trans isomer than in the cis (0.22 kcal/mol in the fully relaxed structure). Thus the energy difference of 2.69 kcal/mol in the tricyclic analogue was increased to 3.19 kcal/mol in the tetracyclic steroid. Similar increases would be expected for the other compounds **26a–d**, in Table II.

(23) For a discussion of this "cyclohexene effect" see N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968), and references cited therein.

(24) The conformation with C-13 above the plane of the double bond (**27**) appears to be the most stable for each compound. It is possible to get a stable conformation with the cyclohexene geometry such that C-12 is above the plane and C-13 is below the plane. The potential well in which the molecule finds itself in this case is apparently not very deep, as it changes rather easily to the conformation **27**.

(25) It is not certain whether these two pseudorotational conformations correspond to discrete energy minima or whether they are just different places at opposite ends of a wide, flat potential well. If an actual energy maximum does separate them it is probably small. In most cases these two conformations have essentially the same energy, but with the isopropyl group the energies are quite different. The latter occurs because the pseudorotational motion involved causes the isopropyl group to interact with other parts of the molecule.

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Synthetic Approaches to Adriamycin Involving Diels–Alder Reactions of Photochemically Generated Bisketenes. Total Synthesis of Islandicin and Digitopurpone

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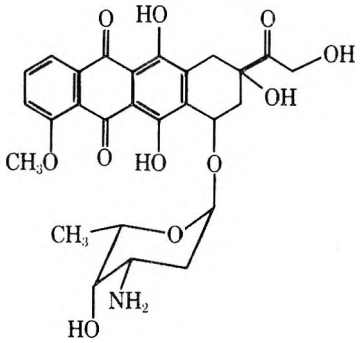
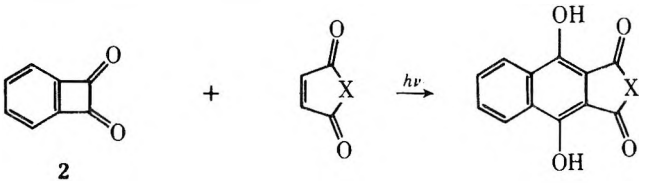
Oxidation of 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (**7**), prepared from 3-nitrophthalic acid in four steps in 67% overall yield, with lead tetraacetate in the presence of anthracene afforded the Diels–Alder adduct **9** (R = H) in good yield. Protection of the phenolic hydroxyl group could be easily accomplished under base-catalyzed conditions to furnish the methoxymethyl **9** (R = CH_2OCH_3) and methyl **9** (R = CH_3) ethers. Vapor phase pyrolysis of these two compounds afforded the corresponding 3-alkoxybenzocyclobutene-1,2-diones, **2** (R = CH_2OCH_3 and CH_3). Hydrolysis of the former afforded the phenol **2** (R = H) in high yield. As a test of the utility of these systems in a photochemical synthetic approach to the potent antineoplastic agent, adriamycin (**1**), the ether **2** (R = CH_2OCH_3) was photolyzed in the presence of several quinones **10a–e**. The desired anthraquinone products **11** and **12** were obtained (as a regiochemical mixture where possible) in low yields. The use of 2-methylbenzoquinone (**10b**) and 2-hydroxymethylbenzoquinone (**10c**) permitted a straightforward total synthesis of the natural products, islandicin (**11b**) and digitopurpone (**12b**).

The broad spectrum of antineoplastic activity and effectiveness in combination chemotherapy of adriamycin (**1**) make



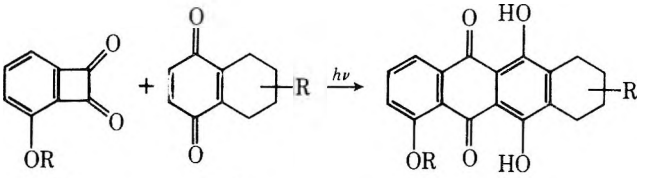
1

it one of the most useful chemotherapeutic agents available.[1] The principal limit on its utility is its high cardiotoxicity.[2] This fact, combined with an inefficient biosynthetic process for its production,[3] has stimulated considerable work recently on the synthesis of adriamycin and its analogues.[4] Some time ago, Staab and Ipaktschi reported that benzocyclobutene-1,2-dione (**2**) undergoes Diels–Alder reactions with electron-deficient olefins [maleic anhydride (**3a**) and naphthoquinone (**3b**)] upon irradiation to afford the Diels–Alder adducts **4a** and **4b**, respectively.[5] Despite the low yield in the case of



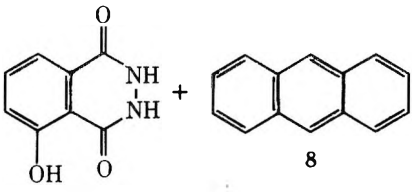
2 **3a**, X = O; **b**, X = *o*-C_6H_4 **4a**, 67%; **b**, 13.5%

naphthoquinone, which the authors attribute to having to terminate the irradiation prematurely due to the intense absorption by the product, it seemed possible that an appropriately substituted benzocyclobutene-1,2-dione **2** might undergo Diels–Alder reaction with an appropriately substituted quinone **5** to produce a compound **6** which might be easily converted into the aglycone of adriamycin, adriamycinone. We now report our initial results in this area, to include (1) the synthesis of 3-substituted benzocyclobutene-1,2-diones **2**, (2) their photoreactions with quinones, and (3) the total synthesis of islandicin (**11b**) and digitopurpone (**12b**).[6]

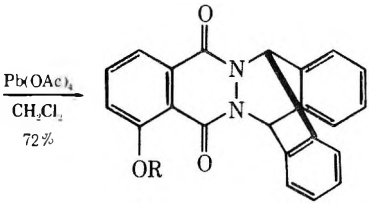


2 **5** **6**

The synthesis of the requisite benzocyclobutene-1,2-diones **2** was accomplished via McOmie's modification[7] of Rees' procedure.[8] Thus the readily available 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (**7**), prepared from 3-nitrophthalic acid in four steps in 67% overall yield, was treated with lead tetraacetate in the presence of anthracene (**8**)[10] to furnish the Diels-Alder adduct **9** (R = H). The adduct **9** (R = H) could be

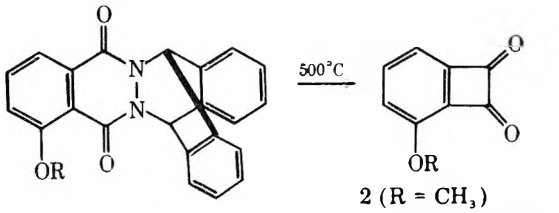


7 **8**



9

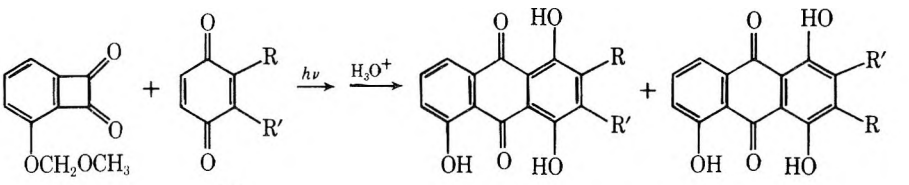
protected as its methyl or methoxymethyl ether (in yields of 67 and 89%, respectively) and then pyrolyzed in the vapor phase at 500 °C to furnish the required 3-alkoxybenzocyclobutene-1,2-dione **2** in up to 61% yield. The free phenol, **2** (R



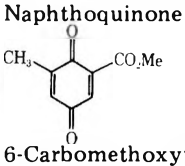
9 (R = CH_3)
9 (R = CH_2OCH_3)

2 (R = CH_3)
2 (R = CH_2OCH_3)

Table I. Photolysis of 2 with Quinones



2 10 11 12

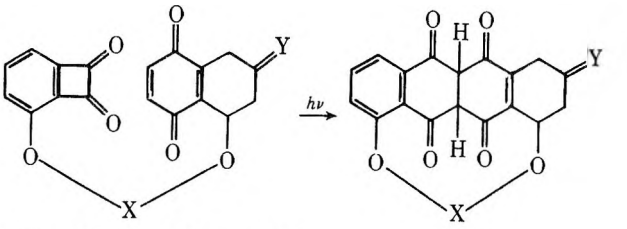
Quinone 10	Time,[a] h	Products	Yield,[b] %
a, R = R′ = H Benzoquinone	9	11a[c]	4, 8[g]
b, R = Me; R′ = H 2-Methylbenzoquinone	12	11b[d] + 12b[d] (1:1)	8
c, R = CH_2OH; R′ = H 2-Hydroxymethylbenzoquinone	9	11b[e] + 12b[e] (1:1)	9
d, R = R′ = −CH=CHCH=CH− Naphthoquinone	12	11d[f]	13.5
e  6-Carbomethoxytoluquinone	3.5		

[a] The length of time irradiation was carried out. [b] Yields are given for isolated purified products, all of which exhibit spectral data in accord with their structures. [c] Identified by comparison with melting point and IR spectrum as given in H. Brockmann and B. Franck, *Chem. Ber.*, **88**, 1792 (1955). [d] Identified as the triacetates by comparison with NMR of authentic samples of the triacetates and as given in Y. Ogihara, N. Kobayashi, and S. Shibata, *Tetrahedron Lett.*, 1881 (1968). [e] Identified as in c, following hydrogenolysis with 10% Pd/C and 1 atm H_2 at 25 °C for 4 h. [f] Identified by comparison with melting point and UV spectrum as given in H. Brockmann and W. Müller, *Chem. Ber.*, 92, 1164 (1959). [g] Using the free phenol, 2 (R = H), in the presence of triethylamine.

= H), could be obtained by acid hydrolysis of the methoxymethyl ether **2** (R = CH_2OCH_3), or, more conveniently, by treating the crude pyrolysis product with acid and isolating the phenol by extraction with aqueous bicarbonate [overall yield of **2** (R = H) from **9** (R = CH_2OCH_3) is 56%].[11] Interestingly, the phenol **2** (R = H) exhibits a pK_a value of 5.8 ± 0.2, making it a very acidic phenol, though not quite as acidic as 4,5-dihydroxybenzocyclobutene-1,2-dione (pK_a = 4.48).[7]

Irradiation of the methoxymethyl ether **2** (R = CH_2OCH_3) in CH_2Cl_2 in the presence of various quinones **10a–e** furnished the expected adducts (**11a–d, 12b**) as listed in Table I. After hydrolysis of the protecting group, the products were isolated by preparative thin layer chromatography and compared with melting points and spectra given in the literature or from authentic samples. While the yield of adduct **11d**, a compound possessing marked activity against the solid form of Ehrlich carcinoma,[12] was the same as that reported by Staab for the parent compound, the yields of the other adducts were somewhat lower and there was no starting material left to be recovered. In the case of the 2-methylbenzoquinone **10b** and the 2-hydroxymethylbenzoquinone **10c**, the products after hydrolysis (and hydrogenolysis of the benzylic hydroxyl function in the case of **10c**) were a 1:1 mixture of the natural products, islandicin (**11b**) and digitopurpone (**12b**). We detect no directing effect of methyl or hydroxymethyl on the regiochemistry of this Diels–Alder reaction. The last entry in Table I reflects an attempt to overcome the intense absorption by the product as a possible problem by blocking the usually facile aromatization with an ester function. However, irradiation in the presence of 6-carbomethoxy-1,4-toluquinone[13] (**10e**) followed by acidic or basic hydrolysis failed to produce any of the desired anthraquinone. Also, irradiation of the phenol **2** (R = H) in the presence of triethylamine (via the phenolate ion) and benzoquinone gave only 8% yield of the desired adduct, **11a**.

Thus, although we have demonstrated the viability of the proposed synthetic scheme, the yields obtained are far too low



13 (X = CO, CH_2, $SiMe_2$, etc.) 14

to be synthetically useful, especially inasmuch as no starting material is left to be recycled. The possibility that other absorbing chromophores besides the benzocyclobutene-1,2-dione might be causing harmful side reactions is suggested by preliminary experiments which indicate that maleic anhydride gives an appreciably better yield. Therefore research is continuing to explore reaction with other dienophiles in order to improve the synthetic utility of the photoprocess. Especially interesting is the possibility of photolyzing bridged intermediates, e.g., **13**, which might then afford products, e.g., **14**, with the correct regiochemical placement of groups in significantly higher yields.

Experimental Section

General. Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 137B spectrophotometer. NMR spectra were measured on a Varian T-60 spectrometer and are reported in parts per million downfield from internal tetramethylsilane, except for the spectra of **11b** and **12b**, which were measured as the triacetates at 251 MHz. Mass spectra were recorded on an MS-9 instrument. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Anthracene Adduct of 5-Hydroxyphthalazine-1,4-dione (9, R = H). To a stirring solution of 0.64 g (3.60 mmol) of 5-hydroxy-2,3-dihydro-1,4-phthalazinedione (**7**),[9] 0.71 g (4.00 mmol) of anthracene, and 0.5 mL of acetic acid in 35 mL of CH_2Cl_2 at 25 °C under N_2 was added 1.60 g (3.60 mmol) of lead tetraacetate in small portions every 15 min for 1.5 h. To the final dark brown mixture was added 4

g of activity V neutral alumina (Merck) and the mixture rotary evaporated to dryness. The solids were placed atop a column of 70 g of activity V neutral alumina (Merck) and eluted with CCl_4 to remove anthracene. Elution with CH_2Cl_2 gave 916 mg (72%) of nearly white, crystalline solid: mp 288–290 °C dec; IR (KBr) $\nu_{C=O}$ 1630, 1600 cm^{-1}; ν_{OH} 3400 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 354 (5), 179 (21) and 178 (100). Anal. Calcd for $C_{22}H_{14}N_2O_3$: C, 74.56; H, 3.98. Found: C, 74.50; H, 3.98.

Anthracene Adduct of 5-(Methoxymethyloxy)phthalazine-1,4-dione (9, R = CH_2OCH_3). To a stirring suspension of 623 mg (1.76 mmol) of adduct **9** (R = H) in 40 mL of dry THF at 25 °C under N_2 was added 790 mg (7.05 mmol) of potassium *tert*-butoxide. The mixture was stirred at 25 °C for 40 min, and then 0.51 mL (7.05 mmol) of chloromethyl methyl ether was added with gradual formation of a white precipitate as it was stirred at 25 °C for 3 h. Partitioning between CH_2Cl_2 and H_2O and evaporation of the CH_2Cl_2 layer left 0.67 g of crude solid which was chromatographed on SiO_2 eluting with mixtures of CH_2Cl_2 and ether to give 625 mg (89%) of white, crystalline solid: mp 244–246 °C dec; IR (KBr) $\nu_{C=O}$ 1635 cm^{-1}, ν_{C-O} 1025 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 398 (9), 192 (3), 191 (4), 179 (16), 178 (100), 177 (6), and 176 (5); NMR ($CDCl_3$) δ 3.52 (3 H, s), 5.30 (2 H, s), 7.7–7.2 (13 H, m). Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55. Found: C, 72.29; H, 4.63.

Anthracene Adduct of 5-Methoxyphthalazine-1,4-dione (9, R = CH_3). To a stirring suspension of 403 mg (1.14 mmol) of adduct **9** (R = H) in 40 mL of dry THF at 25 °C under N_2 was added 512 mg (4.56 mmol) of potassium *tert*-butoxide. The mixture was stirred at 25 °C for 40 min, and then 0.28 mL (4.56 mmol) of iodomethane was added and the mixture heated at reflux for 40 h. It was then cooled and rotary evaporated, and the solids chromatographed on SiO_2, eluting with mixtures of CH_2Cl_2 and Et_2O to give 280 mg (67%) of white, crystalline solid: mp 297–299 °C dec; IR (KBr) $\nu_{C=O}$ 1630 cm^{-1}, ν_{C-O} 1065 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 368 (6), 179 (26), 178 (100), 134 (15), 133 (5), and 104 (8). Anal. Calcd for $C_{23}H_{16}N_2O_3$: C, 74.98; H, 4.38. Found: C, 75.00; H, 4.36.

3-(Methoxymethyloxy)benzocyclobutene-1,2-dione (2, R = CH_2OCH_3). The pyrolysis apparatus was a horizontal 1.7-cm diameter quartz tube wrapped with nichrome wire over a 20-cm length. Pyrolyses were carried out at 500 °C (±20 °C) by reducing the pressure to 7 μ (±3 μ) and heating the anthracene adduct **9** (R = CH_2OCH_3) until it sublimed and passed through the tube. The solids that were trapped were chromatographed on SiO_2. Elution with CH_2Cl_2 furnished the product. From 137 mg (0.344 mmol) of **9** (R = CH_2OCH_3) there was obtained 40 mg (61%) of yellow solid: mp 80.5–82 °C; IR (KBr) $\nu_{C=O}$ 1780 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (3 H, s), 5.52 (2 H, s), 7.5–7.2 (1 H, m), 7.8–7.6 (2 H, m); UV λ_{max} 413 nm (ϵ 53), 296 (3960); mass spectrum (70 eV) *m/e* (rel intensity 192 (1), 191 (2), 164 (9), 163 (12), 162 (9), 161 (90), 147 (4), 136 (2), 135 (5), 134 (57), 133 (13), 132 (4), 120 (3), 119 (14), 106 (12), 105 (100), 104 (20), 103 (8), 93 (2), 92 (3), and 91 (14). Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.19. Found: C, 62.53; H, 4.12.

3-Methoxybenzocyclobutene-1,2-dione (2, R = CH_3). Pyrolysis of anthracene adduct **9** (R = CH_3) was carried out as for **9** (R = CH_2OCH_3) and the crude solids were chromatographed on SiO_2. Elution with CH_2Cl_2 gave the product. From 126 mg of **9** (R = CH_3) there was obtained 18 mg (33%) of yellow solid: mp 112.5–113.5 °C; IR (KBr) $\nu_{C=O}$ 1780 cm^{-1}; NMR ($CDCl_3$) δ 4.16 (3 H, s), 7.6–7.0 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 162 (14), 135 (3), 134 (65), 133 (25), 106 (6), 105 (10), 104 (31), 91 (5), 78 (8), 77 (11), 76 (100), 75 (9), and 74 (8); UV λ_{max} 411 nm (ϵ 78), 299 (3690). Anal Calcd for $C_9H_6O_3$: C, 66.66; H, 3.73. Found: C, 66.59; H, 3.94.

3-Hydroxybenzocyclobutene-1,2-dione (2, R = H). A solution of 40 mg (0.208 mmol) of 3-(methoxymethyloxy)benzocyclobutene-1,2-dione (**2**, R = CH_2OCH_3), 1 mL of concentrated HCl, and 4 mL of H_2O in 30 mL of MeOH was stirred at reflux for 3 h. The solution was cooled and partitioned between CH_2Cl_2 and H_2O. The phases were separated and the aqueous layer washed with 2 × 10 mL of CH_2Cl_2. The combined organic phase was washed with 3 × 15 mL of saturated aqueous $NaHCO_3$ solution and the aqueous layer washed with 2 × 15 mL of CH_2Cl_2. The aqueous layer was then acidified with concentrated HCl to pH 1 and extracted with 3 × 15 mL of CH_2Cl_2. The organic phase was dried over Na_2SO_4 and rotary evaporated to leave 25 mg (81%) of pale yellow solid: mp 177–178 °C dec; IR (KBr) $\nu_{C=O}$ 1760 cm^{-1}, ν_{OH} 3340 cm^{-1}; NMR (acetone-d_6) δ 7.3–7.6 (m); mass spectrum (70 eV) *m/e* (rel intensity 148 (17), 121 (9), 120 (100), 119 (6), and 92 (56); UV λ_{max} 411 nm (ϵ 53), 297 (3610); pK_a = 5.8 ± 0.2. Anal. Calcd for $C_8H_4O_3$: C, 64.87; H, 2.72. Found: C, 64.69, H, 2.69.

The same procedure was utilized with the crude pyrolysate to give 56% overall yield of the phenol **2** (R = H) from **9** (R = CH_2OCH_3).

Photoreactions of 3-(Methoxymethyloxy)benzocyclobutene-1,2-dione (2, R = CH_2OCH_3). Irradiation was carried out in a Pyrex flask, placed approximately 5 cm from a 550-W Hanovia medium-pressure Hg arc, in approximately 10^{-2} M solutions of CH_2Cl_2, for the period indicated in Table I. The products were generally hydrolyzed as in the preparation of 3-hydroxybenzocyclobutene-1,2-dione and isolated by preparative TLC.

Acknowledgments. We wish to thank Dr. A. S. Kende for authentic samples of digitopurpone trimethyl ether and triacetate and islandicin, Dr. R. Helgeson for helpful advice, and Dr. F. A. L. Anet and Mr. M. Squillacote for 251-MHz NMR spectra. We also wish to thank the University of California Cancer Research Coordinating Committee for partial support of this work.

Registry No.—**1**, 23214-92-8; **2** (R = H), 62416-21-1; **2** (R = Me), 62416-22-2; **2** (R = CH_2OMe), 62416-23-3; **7**, 7600-08-0; **9** (R = H), 62416-24-4; **9** (R = Me), 62416-25-5; **9** (R = CH_2OMe), 62416-26-6; **10a**, 106-51-4; **10b**, 553-97-9; **10c**, 644-17-7; **10d**, 130-15-4; **10e**, 62416-27-7; **11b**, 476-56-2; **12b**, 34425-57-5; anthracene, 120-12-7; chloromethyl methyl ether, 107-30-2; iodomethane, 74-88-4.

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Photocycloaddition of Dimethyl Acetylenedicarboxylate and Methyl Propiolate to Benzo[b]furans

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The sensitized photochemical [$_{\pi}2_s + {}_{\pi}2_s$] cycloaddition of dimethyl acetylenedicarboxylate to benzo[b]furan (Ia) leads to four cyclobutene derivatives in which carboxymethyl groups occupy vicinal positions. We suggest that 1,7-dicarboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (IIIa) arises via the initially formed 6,7-dicarboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (IIa) or from the 5,6-dicarboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (IVa). Compound IVa is shown to be formed both from IIa and from IIIa via a postulated 1,2-cyclobutenospiro[2.5]octadiene as intermediate. Compound IVa could rearrange to 1,5-dicarboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (Va). Sensitized addition of methyl propiolate to Ia produces both the adduct with the carboxymethyl group attached to the 2 position of the benzo[b]furan nucleus and the unrearranged 1:1 adduct, suggesting that the excited state of benzo[b]furan is highly polarized. The cyclobutenes IIIa and IVa rearrange to the corresponding 1-benzoxepins by heating at 180–210 °C. The photocycloaddition of dimethyl acetylenedicarboxylate to 2-methylbenzo[b]furan is more complicated but shows the cycloaddition to be general.

Thermal additions of acetylenic esters to fused heteroaromatic compounds have been extensively investigated[2] and appear to be of great value in the synthesis of fused heterocyclic seven-membered ring systems, e.g., benzo[b]azepine, benzo[b]oxepin, and benzo[b]thiepin. Cyclobutene intermediates could be isolated[3-5] in some cases.

A similar reaction has been reported for the photocycloaddition of acetylenes to benzo[b]thiophene.[6,7] The only alkyne from which an unrearranged 1:1 adduct to benzo[b]thiophene could be isolated was diphenylacetylene while only rearranged cyclobutenes were found when dimethyl acetylenedicarboxylate, methyl propiolate, and methyl phenylpropiolate were used.

We have now investigated the photochemical addition of dimethyl acetylenedicarboxylate and methyl propiolate to benzo[b]furan. It will be shown that the normal rearrangement of the first formed 1:1 photoadduct is followed by a more complex type of photorearrangement.

Results

Irradiation, at $\lambda > 300$ nm, of a mixture of benzo[b]furan (Ia) and dimethyl acetylenedicarboxylate dissolved in deaerated benzene, for 70 h in the presence of the sensitizer, acetophenone, gave a complex reaction mixture. By column chromatography on Florisil, four products could be isolated (IIa–Va) in 9, 8, 7, and 1.5% yield, respectively (Table I). A similar irradiation in benzene without added acetophenone did not lead to substantial photoconversion. However, on irradiation of Ia (E_T = 70 kcal/mol[8a]) in the presence of benzophenone as sensitizer only oxetanes were obtained.[8]

In view of the known direct and photosensitized additions of acetylene derivatives to benzo[b]thiophene,[6,7] it could be supposed that IIa and IIIa also are cyclobutenes. The NMR spectrum of IIIa (Table II) revealed a broad singlet at δ 4.50 ppm, whereas that of product IIa exhibited an AB pattern (J_{AB} = 6.0 Hz) at δ 4.52 and 5.63 ppm. The former values are in good agreement with the chemical shift values of H_5 in 2-thiabenzo[b]bicyclo[3.2.0]hepta-3,6-dienes,[7] while the latter value corresponds to the chemical shift of H_1 in the corresponding 5-pyrrolidino derivative.[4] The mass spectra of these adducts include, as is expected,[7,10] ions from retro-cleavage in a direction such that the benzo[b]furan nucleus remains as the major peak, *m/e* 118 and 176, respectively. Further, the IR spectrum contained an absorption at about 1635 cm^{-1}, within the region expected for the olefinic double bond in annelated cyclobutenes.[4,5,7,11a]

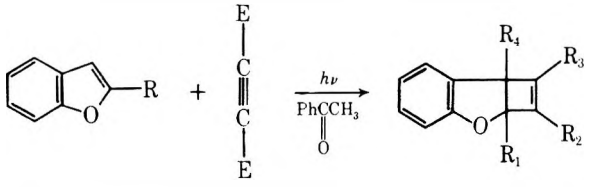
The base peak in the mass spectrum of IVa, *m/e* 176, loss of HC≡CCOOCH$_3$ fragment, pointed out that IVa also should be a cyclobutene adduct. The NMR spectrum showed two singlets at δ 5.51 and 6.78 ppm, fitting in with H_1 and H_7, respectively. It is not surprising that H_1 and H_7 are very weakly coupled ($J \ll 1$ Hz), an observation characteristic of vinyl and allylic protons in cyclobutenes.[7] The UV and IR data of IVa were quite similar to those found for IIIa.

Finally, in analogy to the photoproduct IIIa, product Va is expected to be 1,5-dicarboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene. The NMR spectrum (Table II) was clearly consistent with structure Va.

Compound IVa was isolated as a major product and was shown to derive from either IIa or IIIa by rearrangement (Table III). As a matter of fact, all isomers IIa–Va derived from each of the other isomers when irradiated in the presence of acetophenone as sensitizer.

To gain more insight into the mechanism of this rearrangement the sensitized addition of dimethyl acetylenedi-

Table I. Products of Photocycloaddition of Dimethyl Acetylenedicarboxylate to Benzo[b]furans

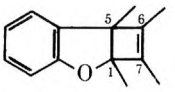


Ia,b, R = H, CH$_3$ E = COOCH$_3$

	Compd	R_1	R_2	R_3	R_4	Yield, %
R = H[a]	IIa	H	E	E	H	9
	IIIa	E	E	H	H	8
	IVa	H	H	E	E	7
	Va	E	H	H	E	1.5
R = CH$_3$[b]	IIb	CH$_3$	E	E	H	5
	IIIb	E	E	CH$_3$	H	15
	IVb	H	CH$_3$	E	E	6
	Vb	E	CH$_3$	H	E	*c*
	IIc	H	E	E	CH$_3$	1
	IIIc	E	E	H	CH$_3$	*c*
	IVc	CH$_3$	H	E	E	2
	Vc	E	H	CH$_3$	E	*c*

[a] Compounds IIa, IIIa, IVa, and Va equilibrate under the conditions of the experiment. The relative yields, therefore, depend on the irradiation time. [b] A photoequilibrium exists among isomers IIb–Vc. The relative yields may therefore vary. [c] These isomers are likely in reaction mixture but were not definitively identified.

Table II. NMR Spectra of Substituted Cyclobutene Systems, Measured in $CDCl_3$ (δ, ppm)



Registry no.	Compd	H_5	H_6	H_7	H_1	$COOCH_3$	$COOCH_3$	CH_3
62250-75-3	IIa	4.52			5.63	3.82	3.84	
62250-76-4	IIIa	4.50	<6.80			3.78	3.88	
62250-77-5	IVa			6.78	5.51	3.79	3.82	
62250-78-6	Va		6.28	6.93		3.82	3.84	
62279-99-6	IIb	4.16				3.84	3.84	1.82
62250-79-7	IIIb	4.35				3.75	3.85	2.19
62250-80-0	IVb				5.40	3.80	3.83	2.09
62250-81-1	IIc				5.28			2.05
62250-82-2	IVc			6.56		3.79	3.89	1.81
62250-83-3	VI	4.62		6.71	5.50		3.82	
62250-84-4	VII	4.57	6.23	6.82			3.88	

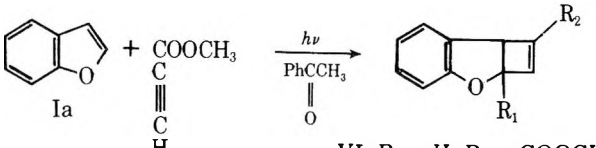
Table III. Rearrangement of Dicarboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-dienes[a]

$h\nu$, h	Starting material	Products[b] IIa	IIIa	IVa	Va
20	IIa	6	50	44	>0
84	IIIa	>0	75	19	6
63	IVa	>0	36	52	12

[a] Irradiated in a solution of benzene (70–115 mg/8 mL), under nitrogen, with acetophenone (20 mol %). [b] Relative yields (%), obtained by NMR analysis (±5%).

carboxylate was also carried out under the same conditions with 2-methylbenzo[b]furan. Of the eight possible isomers (vide infra) at least seven cyclobutene derivatives could be shown in the vapor phase chromatogram of the crude reaction mixture. Five of them could be characterized by NMR spectroscopy (Tables I and II).

Sensitized addition of methyl propiolate to benzo[b]furan (Ia) proceeds similarly to that reported for benzo[b]thiophene[7] (eq 1). Only two photoproducts could be isolated, VI and VII,



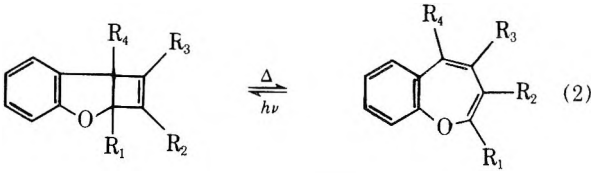
(1)

VI, R_1 = H; R_2 = $COOCH_3$
VII, R_2 = H; R_1 = $COOCH_3$

in 2 and 4% yield, respectively. The IR spectra again showed an olefinic double bond in an annelated cyclobutene, while the UV spectra were similar to those of IIIa and IVa. The NMR spectrum of VI showed an AB quartet between the allylic protons at δ 4.62 and 5.50 ppm, weakly coupled with the vinylic proton at δ 6.71 ppm, whereas that of VII revealed a broad singlet at δ 4.57 ppm and an AB quartet between the vinylic protons. Irradiation of pure VI in the presence of acetophenone yields the isomer VII as the only new-formed product. Moreover, the alternate 7-carboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene could be dismissed because of the less likely opposite mode of cycloaddition. Nevertheless, a vapor phase chromatogram of the crude reaction mixture shows the presence of this isomer in only a few percent.

The cyclobutene adduct prepared from dimethyl acetylenedicarboxylate and 3-pyrrolidinobenzo[b]furan is thermally only moderately stable and can be converted in refluxing dioxane to give the corresponding benzo[b]oxepine. Prolonged heating in p-xylene (138 °C) gave the isomeric 7-naphthol.[4]

A chemical proof for the structures of the products IIIa and IVa was obtained by thermolysis of the pure compounds at 185 and 210 °C, respectively. This resulted in the 1-benzo[b]-oxepins VIII and IX (eq 2). The NMR spectra[12] for both



(2)

IIIa, R_3 = R_4 = H
IVa, R_1 = R_2 = H

VIII, R_1 = R_2 = $COOCH_3$
IX, R_3 = R_4 = $COOCH_3$

compounds contained an AB pattern at δ 6.08 and 6.51 ppm (J_{AB} = 6.0 Hz) and at 6.39 and 7.06 ppm (J_{AB} = 11.5 Hz), respectively. The UV absorptions of both VIII and IX showed a long-tailed absorption into the visible region, caused by the oxepin chromophore.[12b-d]

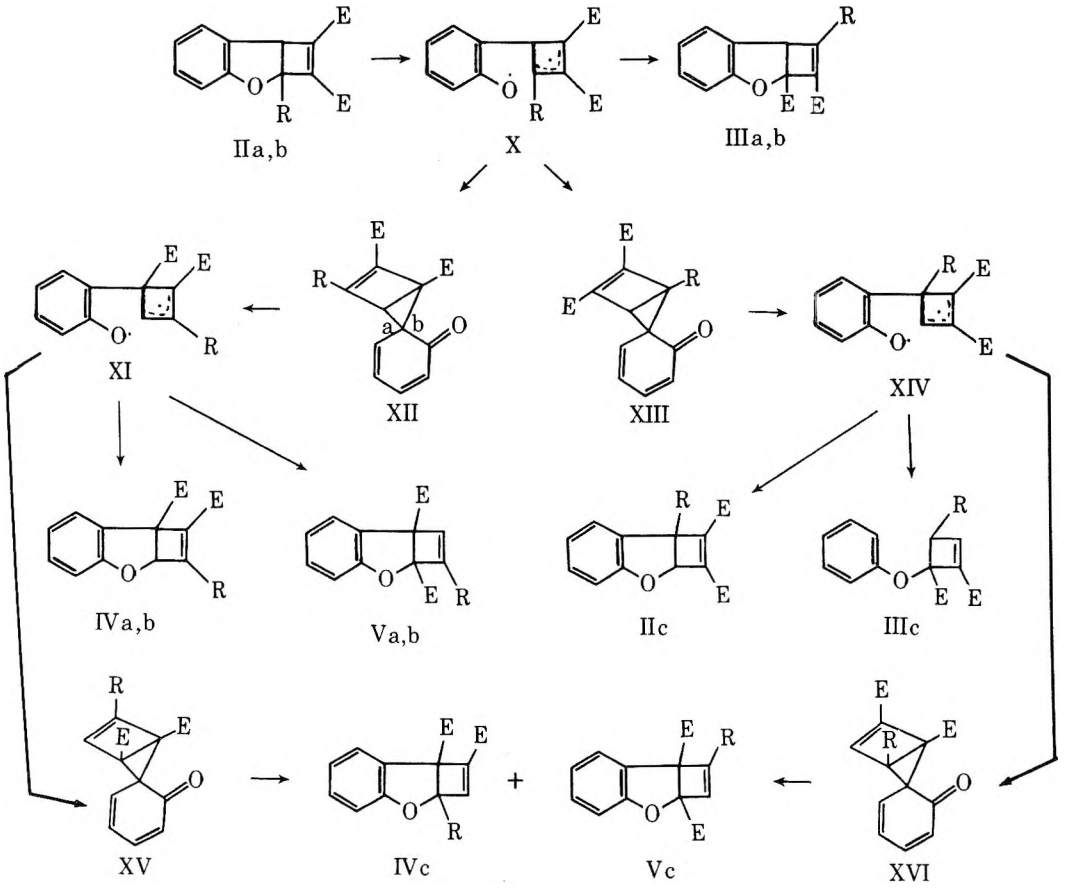
As expected, upon irradiation at $\lambda > 300$ nm, the 1-benzo[b]oxepins VIII and IX are reconverted into the corresponding cyclobutenes IIIa and IVa, respectively (eq 2). This reaction, an electrocyclic ring closure of the diene system, has been observed for other heterocyclic compounds as well.[13] It results from a symmetry-allowed disrotatory reaction which leads to cis annelation of the two rings.

Discussion

The UV spectrum of benzo[b]furan[14] possesses a sharp absorption maxima in the 266–281-nm region, with a maximum absorption at 281 nm (ϵ 3300). Above 286 nm (ϵ 155) almost no light is absorbed. The absorption maxima of dimethyl acetylenedicarboxylate and methyl propiolate lie below the position of the absorption maxima of benzo[b]furan and are weaker. The reaction of benzo[b]furan and the acetylenic esters does not occur in the absence of the sensitizer acetophenone. Thus, as in similar systems,[15] it appears that sensitized formation of the benzo[b]furan triplet state is the initial photochemical act involved in the addition. Charge distribution in the excited benzo[b]furan derives from the direction of addition of the unsymmetrical acetylene (eq 1). The charged excited state of benzo[b]furan might select the carbon of the carboxymethyl group in methyl propiolate.[16,7]

From our results it may be concluded that, by the addition of 1 mol of the acetylene to the benzo[b]furan, a photolabile cyclobutene (IIa,b) is produced (Scheme I). It is obvious that these products must have the cis configuration.[17] In all cases, these cyclobutenes are further converted, by a second light quantum, into a 7-substituted cyclobutene (IIIa,b) which is usually the main product under the conditions used. Rearrangement of IIa,b → IIIa,b likely proceeds via rupture of the

Scheme I



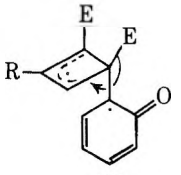
R = CH_3 or H; E = $COOCH_3$

C_1–O bond to give a stabilized diradical X (Scheme I) which can further react to form a new C_6–O bond. This result is in accord with formation of rearranged photoadducts in the reaction of acetylenes with benzo[*b*]thiophene observed in previous studies.[5,7] We suppose that another possibility for the biradical X is that it either forms 1,2-cyclobutenospiro-[2.5]octadienone XII or XIII. Similar intermediates have earlier been postulated in abnormal Claisen rearrangements[18] and in the rearrangement of flavanone.[19] Bond rupture at (a) in XII gives the biradical XI. By bond formation between the original C_5 or C_7 and the oxygen, O, the abnormal rearranged cyclobutenes IVa,b and Va,b arise. With 2-methylbenzo-[*b*]furan the formation of the (possible) photoproducts IIc and IIIc can be similarly explained. The biradical XI (XIV) can also form the spirocyclopropyl intermediate XV (XVI) from which can arise the photoproducts IVc and Vc.

Product distribution derives from the relative stabilities of the biradical intermediates, and polar effects on the ring closures of these intermediates as well as on the steric effects which operate in the ring closure. Thus, IIa,b and Va,b are always minor products because the biradicals leading to their formation are less stable. IIIa,b and IVa,b are major products both because they derive from more stable biradicals and because the polar effects leading to their formation are more favorable.

In all cases the formation of IVa,b (IIc) is preferred over Va,b (IIIc). A reason could be the fact the less steric hindrance of the former compounds. Another reason could be the fact that the intermediate biradical obeys the "principle of least motion".

For getting from the biradical XI into a conformation from which after ring closure products Va,b can arise, there has to be approximately a 90° rotation around the C_{ar}–C_6 axis.



XI

Possibly this rotation is much slower than C_5–O bond formation giving IVa,b.

The rearrangements of the cyclobutenes occur also in the absence of sensitizer, although there is no observed photochemical oxepin formation under these conditions. These reactions are much less efficient than the sensitized process.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded either in chloroform solution or in KBr disks using a Perkin-Elmer 337 infrared spectrophotometer. NMR spectra were recorded on a Varian A-60 spectrometer with deuteriochloroform as the solvent and tetramethylsilane as the internal reference. UV spectra were determined in methanol using a Beckman Acta MIV spectrophotometer. Mass spectra were obtained using a Varian MAT Model CH7 mass spectrometer. Analytical gas–liquid chromatography was carried out using a Varian Aerograph 1200, column 8 ft × 0.125 in., UCON LB 10% on Chromosorb P 60/90. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind. Photolyses were carried out using a 450-W Hanovia medium-pressure mercury lamp. Samples were contained in sealed 13-mm o.d. Pyrex tubes under nitrogen atmosphere and irradiated on a merry-go-round apparatus immersed in a thermostated water bath (13 ± 1 °C).

Addition of Dimethyl Acetylenedicarboxylate to Benzo-[*b*]furan. A solution of 1.18 g (0.010 mol) of benzo[*b*]furan, 4.45 g (0.032 mol) of dimethyl acetylenedicarboxylate, and 0.24 g (0.002 mol)

of acetophenone in 80 mL of benzene was irradiated for 70 h. After evaporation of the solvent the unreacted benzo[b]furan, the dimethyl acetylenedicarboxylate, and a part of the acetophenone were distilled in vacuo. To prevent rearrangements of the cyclobutene derivatives to the corresponding 1-benzoxepins, one should not use a higher pot temperature than 130 °C. The red-orange colored residue was chromatographed over a Florisil column (100–200 mesh) with CCl_4 as elution agent. Changing solvents carefully from CCl_4 to $CHCl_3$ gave four products, respectively.

1,5-Di(carboxymethyl)-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (Va), yield 1.5%. This product could not be isolated in pure form. The pale yellow oil always contained some of the isomer IVa.

5,6-Di(carboxymethyl)-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (IVa): yield 7%; mp 161–162 °C (methanol); λ_{max} 279 nm (ϵ 2560); NMR δ 3.79 (s, 3 H, $COOCH_3$), 3.82 (s, 3 H, $COOCH_3$), 5.51 (s, H_1), 6.78 (s, H_7), 6.76–7.67 (m, 4 H); IR 1637 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity, fragment) 260 (65), 229 (19, OCH_3), 213 (16), 201 (27, CO_2CH_3), 176 (100, $HC{\equiv}CCO_2CH_3$), 163 (14), 158 (11), 145 (74), 130 (15), 118 (3, $H_3CO_2CC{\equiv}CCO_2CH_3$). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.20; H, 4.68.

1,7-Di(carboxymethyl)-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (IIIa): yield 8%; mp 122–123 °C (methanol; λ_{max} 283 nm (ϵ 2600); NMR δ 3.78 (s, 3 H, $COOCH_3$), 3.88 (s, 3 H, $COOCH_3$), 4.50 (broad s, H_5), 6.78–7.42 (m, 5 H); IR 1633 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity, fragment) 260 (81), 229 (21, OCH_3), 213 (15), 201 (27, CO_2CH_3), 186 (7), 176 (100, $CH{\equiv}CCO_2CH_3$), 163 (10), 158 (10), 145 (79), 130 (13), 118 (19, $H_3CO_2CC{\equiv}CCO_2CH_3$). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.61; H, 4.53.

6,7-Di(carboxymethyl)-2-oxabenzo[b]bicyclo[3.2.0]hepta-3.6-diene (IIa): yield 9%; oil; NMR δ 3.82 (s, 3 H, $COOCH_3$), 3.84 (s, 3 H, $COOCH_3$), 4.52 and 5.63 (AB, H_5 and H_1, J_{AB} = 3.8 Hz), 6.83–7.51 (m, 4 H); IR 1667 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity, fragment) 260 (65), 229 (23, OCH_3), 213 (8), 201 (23, CO_2CH_3), 186 (8), 176 (6, $HC{\equiv}CCO_2CH_3$), 157 (6), 145 (11), 142 (11), 129 (7), 118 (100, $H_3CO_2CC{\equiv}CCO_2CH_2$). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.80; H, 4.82.

Addition of Dimethyl Acetylenedicarboxylate to 2-Methylbenzo[b]furan. A solution of 6.60 g (0.050 mol) of 2-methylbenzo[b]furan, prepared according to Suu, Buu-Hoi, and Xuong[20] by formation of 2-formylbenzo[b]furan followed by reduction by the Huang-Minlon modification of the Wolff–Kishner reduction, 27.23 g (0.192 mol) of dimethyl acetylenedicarboxylate, and 1.06 g (0.009 mol) of acetophenone in 480 mL of benzene was irradiated for 143 h. The reaction mixture was worked up as described above.

Addition of Methyl Propiolate to Benzo[b]furan. A solution of 3.20 g (0.027 mol) of benzo[b]furan, 6.50 g (0.077 mol) of methyl propiolate, and 0.54 g (0.0045 mol) of acetophenone in 100 mL of benzene was irradiated for 160 h. After evaporation of the unreacted benzo[b]furan, the methyl propiolate and a part of the acetophenone were removed by distillation in vacuo. The dark-colored residue was chromatographed over a Florisil column with $CCl_4/CHCl_3$ (7:3) as eluent to give 700 mg of a pale yellow oil. Repeated column chromatography over Florisil with $CCl_4/CHCl_3$ mixtures of increasing ratio as eluent followed by crystallization from methanol gave two products.

6-Carboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (VI): yield 2%; mp 60–61 °C; λ_{max} 279 nm (ϵ 2300); NMR δ 3.82 (s, 3 H, $COOCH_3$), 4.62 and 5.50 (AB, H_5 and H_1, $J_{1,5}$ = 3.8, $J_{5,7}$ = 1.6 Hz), 6.71 (d, H_7), 6.75–7.55 (m, 4 H); IR 1630 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity, fragment) 202 (88), 174 (9, CO), 171 (17, OCH_3), 159 (11, $COCH_3$), 143 (32, $COOCH_3$), 131 (19), 118 (100, $H_3COOCC{\equiv}CH$), 115 (74). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.18; H, 4.95.

1-Carboxymethyl-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene (VII): yield 4%; mp 143–145 °C; λ_{max} 279 nm (ϵ 2400); NMR δ 3.88 (s, 3 H, $COOCH_3$), 4.57 (br s, H_5), 6.23 (q, H_6, $J_{6,7}$ = 2.8, $J_{6,5}$ = 1.2 Hz), 6.82 (d, H_7), 6.77–7.43 (m, 4 H); IR 1635 cm^{-1} (C=C); mass spectrum *m/e* 202.

Photorearrangements of VI and VII. Product VII appeared to be photostable on irradiation for 63 h of a solution of VII in benzene, in the presence of acetophenone as a sensitizer. No rearranged products could be detected by NMR or GC analysis. However, on irradiation of VI for 112 h, VII was obtained (34%) as the only photoproduct.

Thermal Rearrangement of the Di(carboxymethyl)-2-oxabenzo[b]bicyclo[3.2.0]hepta-3,6-diene Derivatives to the Corresponding Di(carboxymethyl)-1-benzoxepins. 4,5-Dicarboxymethyl-1-benzoxepin (IX). IVa (400 mg) was, in its pure form, heated up in an oil bath thermostated at 210 °C for 4 h. After cooling, the dark mixture was chromatographed over Florisil using petroleum ether (bp 20–40 °C)–chloroform (8:2) as eluent, yielding 340 mg (85%) of the benzoxepin IX. After crystallization from methanol an analytical pure sample was obtained: mp 73–74 °C; λ_{max} 297 nm (ϵ 5260); NMR δ 3.87 (s, 3 H, $COOCH_3$), 3.96 (s, 3 H, $COOCH_3$), 6.08 and 6.51 (AB, H_2 and H_3, J_{AB} = 5.0 Hz), 6.95–7.58 (m, 4 H); mass spectrum *m/e* (rel intensity) 260 (100), 229 (33), 217 (26), 201 (31), 176 (21), 163 (26), 158 (21), 145 (30), 142 (10), 130 (31), 118 (76). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.90; H, 4.58. Upon irradiation of a solution of IX in benzene for 65 h, compound IVa was obtained in 85% yield, with the same spectroscopic and physical data as described above.

2,3-Dicarboxymethyl-1-benzoxepin (VIII). IIIa (150 mg) was treated in the same way as described above at 185 °C for 1 h. The dark residue was purified by column chromatography over Florisil using petroleum ether–chloroform (8:2) as eluent, yielding 122 mg (81%) of the benzoxepin VIII: mp 67–68 °C (methanol); λ_{max} broad absorption maximum in the 302–330-nm region with two distinct absorption maxima at 306 and 328 nm (ϵ 3700); NMR δ 3.84 (s, 3 H, $COOCH_3$), 3.91 (s, 3 H, $COOCH_3$), 6.39 and 7.06 (AB, H_4 and H_5, J_{AB} = 11, 5 Hz), 7.07–7.60 (m, 4 H); mass spectrum *m/e* (rel intensity) 260 (100), 232 (20), 229 (25), 217 (12), 201 (28), 185 (27), 170 (20), 157 (26), 145 (41), 130 (22), 129 (23), 118 (83). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.58; H, 4.64. Upon irradiation of a solution of VIII in benzene for 65 h, compound IIIa was obtained (and some traces of IVa) with the same spectroscopic and physical data as described above.

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Registry No.—Ia, 271-89-6; Ib, 4265-25-2; VIII, 62250-85-5; IX, 62250-86-6; dimethyl acetylenedicarboxylate, 762-42-5; methyl propiolate, 922-67-8.

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Photochemical Transformations. 14. Photochemical Reactions of Ketones with Some Aliphatic Ureas[1]

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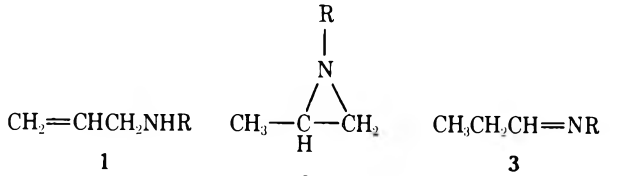
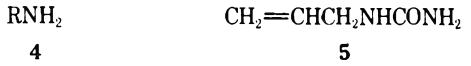
Irradiation of mixtures of aliphatic ureas and ketones led to ureido alcohols, bisureas, or mixtures of these products. Formation of these products is rationalized mechanistically.

Our research group has been interested in the photochemistry of allylic compounds for some time.[2] It has been reported[3] that irradiation of allylamine derivatives **1** gives mixtures of aziridines **2**, Schiff bases **3**, as well as deallylation products **4**, when R is aliphatic or hydrogen, while that of allylanilines (R = Ar) gave deallylation **4** or rearrangement products,[4] presumably via bond-homolysis precursors. The photochemical deallylation reaction seemed of considerable interest to us, particularly if it could be induced by photosensitization, as it offered the possibility of using an allylic group as a protecting group, say in peptide synthesis, with photochemical "deblocking" rather than chemical deblocking.



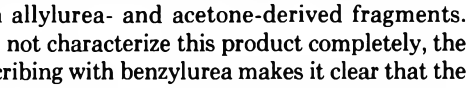
1 **2** **3**



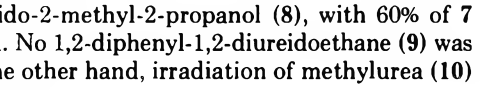
4 **5**

We therefore decided to irradiate allylurea **5** in acetone, as a model system. With a Pyrex light filter a precipitate formed rapidly upon irradiation. Investigation showed that it was not urea, but rather that it was a low molecular weight polymer containing both allylurea- and acetone-derived fragments. Although we did not characterize this product completely, the work we are describing with benzylurea makes it clear that the polymer may be described essentially as **6**. We did not find any evidence for an aziridine or imine product, or for urea (cleavage product) itself.

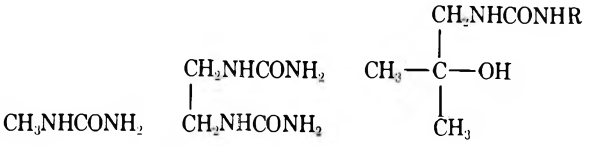
In order to investigate the photochemical reaction in more simple systems, we chose to study a number of other ureas. Irradiation of 0.16 M benzylurea (**7**) in acetone gave 39% of 1-phenyl-1-ureido-2-methyl-2-propanol (**8**), with 60% of **7** being recovered. No 1,2-diphenyl-1,2-diureidoethane (**9**) was detected. On the other hand, irradiation of methylurea (**10**) in acetone gave a good yield of 1,2-diureidoethane (**11**), without detectable amounts of the ureido alcohol **12**-H being formed. Similarly, *N*,*N*′-dimethylurea (**13**) gave **14** and no **12**-CH_3. Preliminary results indicated that *n*-propylurea and *n*-butylurea behaved like methylurea.



6 **7**



8 **9**



10 **11** **12**

13 **14**

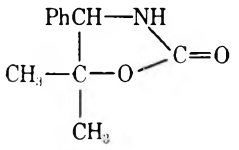
Benzylurea (**7**) was irradiated directly in acetonitrile and in *tert*-butyl alcohol solutions, using either quartz or Vycor tubes, for extended periods of time, and was recovered unchanged. Attempted sensitization with benzonitrile gave largely unchanged **7** with no evidence for cleavage products. Deaeration had little effect on any of the results.

The products of the photoreactions are readily rationalized mechanistically. n-π^* excited states of ketones are reactive hydrogen-atom abstractors,[5] and it seems clear that, instead of the triplet excitation transfer we had hoped for, excited acetone abstracted hydrogen from the α position of the alkyl group of the urea to give a 2-hydroxy-2-propyl radical **15** and a ureidoalkyl radical **16**. Combination of **15** and **16** in the benzylurea case gave **8**, while combination of two **16** radicals gave the bisureas observed in the other systems. We are unable to rationalize the failure to observe ureido alcohols from the methylureas, propylurea, or butylurea, as one might anticipate that geminate combination of **15** and **16** would occur more readily with R aliphatic or H rather than with the more stable **16** (R = Ph).

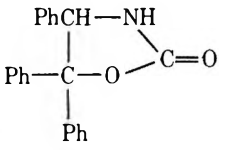
15 **16** **17** **18**

As it seemed likely that **8** formed, in large part at least, from geminate combination of **15** and **16** (R = Ph), we thought that use of a ketone which would give a more stable radical might permit the formation of bisurea **9**. Indeed when an equimolar solution of benzylurea (**7**) and benzophenone in acetonitrile was irradiated, besides the ureido alcohol **18**, there was formed 10–15% of a mixture of the meso and *dl* isomers of **9**, as well as benzopinacol from the dimerization of **17**.

The ureido alcohols **8** and **18** were unstable at their melting points and were found to eliminate ammonia and to give the



19



20

known oxazolidones **19**[6] and **20**,[6,7] respectively, in about 80% yield.

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer. Mass spectra were obtained on a Varian MAT Model CH-7 spectrometer. Irradiations were carried out using a Hanovia 450-W mercury arc lamp (Engelhardt-Hanovia, Inc., Newark, N.J., Model L679A-36) inserted into a water-cooled quartz immersion probe.

Ureas used in irradiation experiments were either commercial products or were prepared from potassium cyanate or the corresponding amine.[8]

Irradiation procedure involved irradiating 10 mL of solution in a 25 cm × 10 mm Pyrex tube sealed with a serum stopper and immersed in a water bath. Large-scale irradiations were carried out using 125 mL of solution in a water-jacketed probe immersion well. Reaction temperatures were kept constant at about 15 °C. Analyses were by Galbraith Laboratories.

Irradiation of Benzylurea (7)–Acetone Solutions. A solution of 3.0 g (0.02 mol) of **7** in 125 mL of acetone was irradiated through quartz for 2 h. A precipitate formed (1.65 g, 39%) which was almost pure 1-phenyl-1-ureido-2-methyl-2-propanol (**8**): mp after recrystallization from ethanol 202 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.97 (s, CH_3), 1.10 (s, CH_3), 4.48 (s, OH), 4.50 (d, J = 10 Hz, CH), 5.52 (m, NH_2), 6.58 (d, J = 10 Hz, NH), 7.25 (s, C_6H_5).

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.43; H, 7.75. Found: C, 63.60; H, 7.90.

When the solvent was evaporated from the mother liquor, 1.80 g (60%) of **7** was recovered.

Irradiation of Methylurea (10)–Acetone Solutions. A solution of 1.07 g (0.014 mol) of **10** in 45 mL of acetone was irradiated through Pyrex for 35 h. A precipitate formed (0.434 g, 40%) which was almost pure 1,2-diureidoethane (**11**): mp after recrystallization from propylene carbonate and ethyl acetate 192–195 °C dec (lit.[9] mp 193–194 °C); ^{1}H NMR (Me_2SO-d_6) δ 3.0 (m, CH_2), 5.45 (m, NH), 5.95 (m, NH_2).

The mother liquors were evaporated to dryness and dissolved in Me_2SO-d_6. The ^{1}H NMR spectrum had absorption peaks largely attributable to starting material **10** with smaller peaks attributable to **11**. No peaks attributable to **12** were observed.

Irradiation of *N,N'*-Dimethylurea (13)–Acetone Solutions. A solution of 2.3 g (0.026 mol) of **13** in 50 mL of acetone was irradiated through Pyrex for 29 h. A precipitate formed (0.62 g, 27%) which was almost pure 1,2-bis(3-methylureido)ethane (**14**): mp after recrystallization from ethanol 218–219 °C (lit.[10] mp 218–219 °C); ^{1}H NMR (Me_2SO-d_6) δ 2.59 (d, J = 5 Hz, CH_3), 3.01 (m, CH_2), 5.86 (m, 2 NH).

Anal. Calcd for $C_6H_{14}N_4O_2$: C, 41.10; H, 8.05. Found: C, 41.31; H, 7.68.

The mother liquors were evaporated to dryness and dissolved in Me_2SO-d_6. The ^{1}H NMR spectrum had peaks largely attributable to **13** and smaller peaks attributable to **14**. Not more than a trace of ureido alcohol could have been present.

Irradiation of Benzophenone and Benzylurea (7) in Acetonitrile. A solution of 3.0 g (0.02 mol) of **7** and 3.64 g (0.02 mol) of benzophenone in 125 mL of acetonitrile was irradiated through quartz for 2 h. A precipitate formed (0.30 g, 12.5%) which was a mixture of *meso*- and *dl*-1,2-diphenyl-1,2-diureidoethane (**9**). The meso and *dl* diastereoisomers were separated on a silica preparative TLC plate (E-M Reagents, F-254) using acetone, eluting three times and drying the plate completely between each elution. The ratio of *rac*- to *meso*-**9** was 2.1:1.0. ^{1}H NMR spectra for these diastereoisomers were obtained on a JEOL 100-MHz spectrometer.

meso-1,2-Diphenyl-1,2-diureidoethane (**9**) hardly moved on the TLC plate. It was recrystallized from ethanol: mp 221–222 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 5.01 (s, CH), 5.57 (m, NH_2), 7.16 (s, C_6H_5), NH too broad to detect readily.

Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.36; H, 6.08. Found: C, 64.35; H, 6.06.

dl-1,2-Diphenyl-1,2-diureidoethane (**9**) had been prepared previously.[11] It was recrystallized from ethanol: mp over 360 °C (lit.[11] mp over 360 °C); ^{1}H NMR (Me_2SO-d_6) δ 4.86 (s, CH), 5.57 (m, NH_2), 7.16 (C_6H_5).

The solvent was evaporated from the mother liquor and the residue was washed twice with 100-mL portions of boiling water. When the water extract was evaporated 1.2 g (40%) of **7** was recovered. The water-insoluble solid was then washed with two 100-mL portions of diethyl ether. When the ether extract was evaporated 2.2 g (74%) of benzopinacol was recovered. The dried ether-insoluble solid (2.71 g, 50%) was almost pure 1,1,2-triphenyl-2-ureidoethanol (**18**): mp after recrystallization from methanol 193–194 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 5.58 (m, CH), 5.75 (s, OH), 6.00 (m, NH), 6.62 (m, NH_2), 7.0–7.6 (C_6H_5).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88, H, 6.02. Found: C, 75.70; H, 6.17.

Irradiations of Allylurea (5)–Acetone Solutions. A typical experiment was conducted as follows. A solution of 1.20 g of **5**, mp 88–90 °C, in 10 mL of acetone was irradiated for 35 h, following deaeration. A white solid (1.37 g) collected on the sides of the tube. The acetone solution was decanted and evaporated to dryness; an additional 0.48 g of oily solid remained. In various experiments the amounts of acetone-insoluble material varied slightly, but generally represented (in weight) more than the initial allylurea. This material was a granular, hygroscopic solid. It was soluble in water, methanol, ethanol, dimethylformamide, and dimethyl sulfoxide; it was insoluble in acetone, ethyl acetate, acetonitrile, benzene, tetrahydrofuran, and chloroform. Dissolution in methanol and precipitation with acetone led to almost complete recovery of product, but without significant change of properties. It melted over a wide range, beginning to decompose at 70 °C, and giving vigorous evolution of volatile materials at 100 °C. Analysis indicated that the material was an impure substance, which might be largely a low molecular weight polymer having a structure approximating **6**.

Anal. Calcd for $(C_7H_{14}N_2O_2)_n$: C, 53.1; H, 8.9; N, 17.7. Found: C, 51.1; H, 8.1; N, 17.9.

Thermal Cyclization of 1-Phenyl-1-ureido-2-methyl-2-propanol (8). **8** (2.9 g, 0.015 mol) was heated to 210 °C under a nitrogen atmosphere until the evolution of ammonia ceased. After initial purification in a Kugelrohr oven at reduced pressure (4 Torr) the residue formed (1.87 g, 80%) was almost pure 5,5-dimethyl-4-phenyl-2-oxazolidone (**19**): mp after recrystallization from acetone 129.5–130 °C (lit.[6] mp 125–127 °C); ^{1}H NMR (Me_2SO-d_6) δ 0.82 (s, CH_3), 1.55 (s, CH_3), 4.7 (s, CH), 7.4 (s, C_6H_5), 8.05 (m, NH).

Thermal Cyclization of 1,1,2-Triphenyl-2-ureidoethanol (18). **18** (2.0 g, 0.006 mol) was heated to 200 °C under a nitrogen atmosphere until the evolution of ammonia ceased. After initial purification on a Kugelrohr oven at reduced pressure (4 Torr), the residue formed (1.29 g, 78%) was almost pure 4,5,5-triphenyl-2-oxazolidone (**20**): mp after recrystallization from ethanol–water 230–231 °C (lit.[7] mp 229.5–231 °C); ^{1}H NMR (Me_2SO-d_6) δ 5.70 (s, CH), 7.05 (s, C_6H_5), 7.40 (m, 2 C_6H_5), 7.90 (m, NH).

Acknowledgment. This investigation was supported by Grant CA13199, awarded by the National Cancer Institute, DHEW.

Registry No.—**5**, 557-11-9; **6**, 62183-25-9; **7**, 538-32-9; **8**, 62183-18-0; *meso*-**9**, 62183-19-1; *dl*-**9**, 62183-20-4; **10**, 598-50-5; **11**, 1852-14-8; **13**, 96-31-1; **14**, 62183-21-5; **18**, 62183-22-6; **19**, 33664-93-6; **20**, 62183-23-7; acetone, 67-64-1; benzophenone, 119-61-9.

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A New Preparation of Acetylenic Ketones and Application to the Synthesis of *exo*-Brevicomin, the Pheromone from *Dendroctonus brevicomis*[1]

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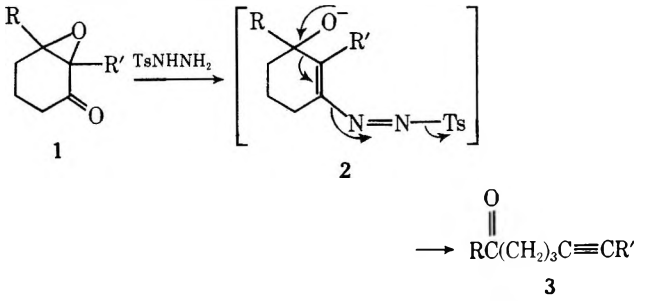
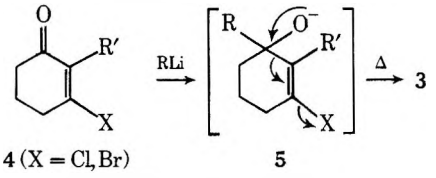
A new synthesis of acetylenic ketones has been developed. This involves addition of alkyllithium reagents to the carbonyl group of β-halo-α,β-unsaturated ketones and thermal cleavage of the intermediate alkoxides to give good yields of acetylenic ketones. This method provides a straightforward, versatile synthesis of several acetylenic ketones. An application of this method is given to the synthesis of *exo*-brevicomin (**19**), the pheromone from *Dendroctonus brevicomis*. The addition of lithium dimethylcuprates to β-halo-α,β-unsaturated ketones is shown.

In 1967 Eschenmoser[2] and Tanabe[3] and their co-workers developed a method for converting α,β-epoxy ketones to acetylenic ketones or aldehydes[4] by reaction of epoxy ketones such as **1** with tosylhydrazine to give intermediate **2** which spontaneously cleaves to the final ketone **3**. In some systems this method has the disadvantage of low yields or difficulty of preparing the starting material **1**.



1 **2** **3**

We have developed an alternate scheme for the preparation of compounds like **3**. Our method is based on the construction of an intermediate similar to **2**, i.e., an allylic alkoxide with a vinyl leaving group in the proper position to allow cleavage of the carbon–carbon bond. This scheme can be illustrated by the reaction of β-halo-α,β-unsaturated ketone **4** with an alkyllithium reagent to generate intermediate **5** which is then pyrolyzed to give acetylenic ketone **3**.

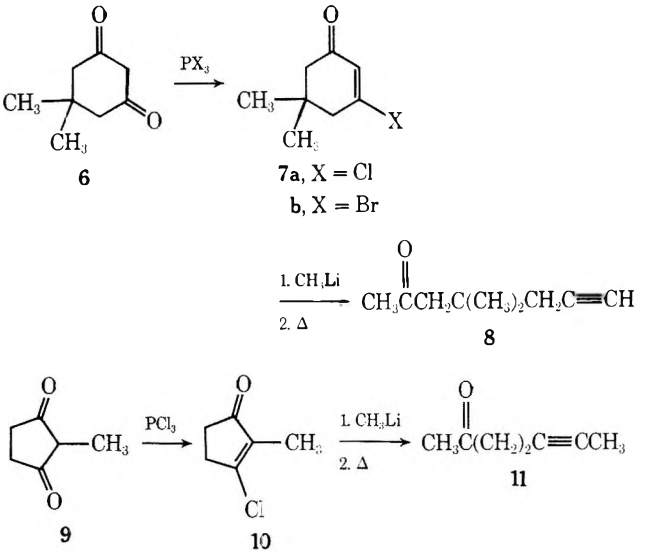


4 (X = Cl, Br) **5**

Among the variables which make this method versatile is the ability to vary each of the two R groups. Another variable is the ring size which in turn controls the number of methylene groups separating the ketone and acetylene groups in the final product. It should be noted that the cleavage reactions of intermediates **2** and **5** are examples of a very general kind of elimination–cleavage reaction, other types of which have been reviewed.[5]

Exploratory work is shown in Chart I. Dimedone was converted to the corresponding vinyl chloride **7a** and vinyl bromide **7b**, both of which were found to give good yields (70–75%) of the acetylenic ketone **8** upon reaction with methyllithium followed by pyrolysis of the intermediate alkoxide. There were some impurities in the crude pyrolysis product which we have not yet identified but it is interesting to note that similar impurities seem to be absent in other examples when the alkyllithium reagent is used in hexane solution. Chloride **7a** is the preferred reagent because it is cheaper to prepare and gives as good a yield as the bromide. Similarly, 2-methyl-1,3-cyclopentanedione (**9**) was converted to the corresponding vinyl chloride **10**, reacted with methyllithium, and the intermediate alkoxide was subjected to pyrolysis to give acetylenic ketone **11** in 32% yield.[6]

Chart I

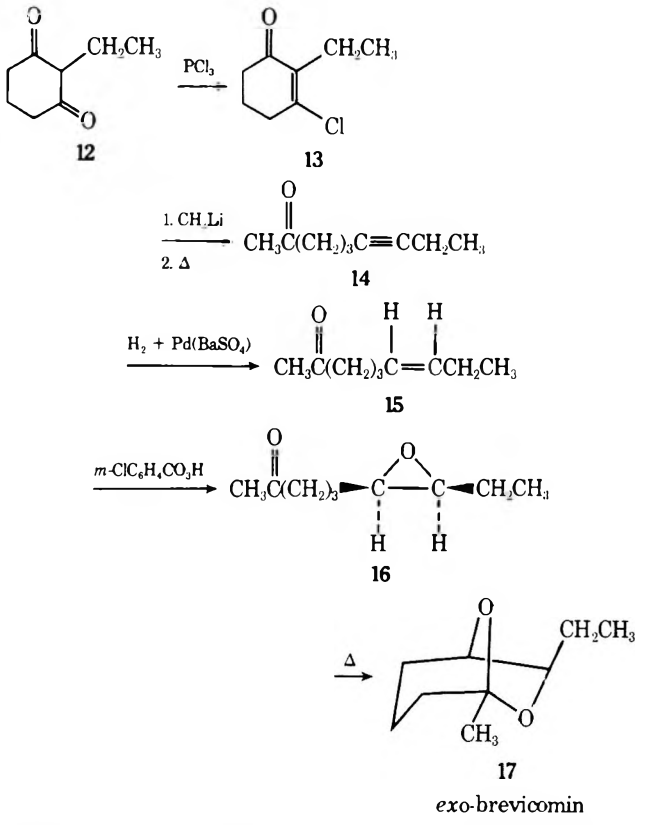


6 **7a**, X = Cl; **b**, X = Br **8** **9** **10** **11**

Acetylenic ketones are useful intermediates in the synthesis of several insect pheromones as exemplified by the synthesis of brevicomin (Chart II). Preparation of the necessary diketone involved alkylation of dihydroresorcinol[7] with ethyl iodide and base to give 2-ethyl-1,3-cyclohexanedione (**12**).[8] Compound **12** was treated with phosphorus trichloride to give chloride **13**, which was allowed to react with methyllithium. The resulting alkoxide was subjected to pyrolysis to give 6-nonyn-2-one (**14**).[9] The acetylenic ketone **14** was reduced to the corresponding cis olefin **15**,[10] which was converted to epoxide **16**[10] using *m*-chloroperbenzoic acid. *exo*-Brevicomin, the pheromone from *Dendroctonus brevicomis*, was formed by simple thermolysis of epoxide **16** by the procedure of Wasserman and Barber[10] giving a mixture of about 90% *exo*-brevicomin (**17**) and 10% *endo*-brevicomin. A sample of the *exo*-brevicomin, isolated by gas chromatography, was identical with an authentic sample.[11] Brevicomin has been synthesized by a number of methods,[9,10,12,13] including one synthesis of optically active material.[14]

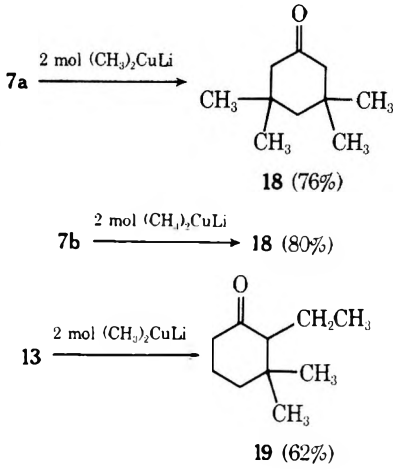
Structures involving a β-halo-α,β-unsaturated ketone are bifunctional and should be capable of adding electrophiles at the carbonyl carbon (above) or at the β position as shown by the addition of cuprates to similar compounds having β substituents such as sulfides[15] or acetoxy groups.[16] On the basis of work by House and Umen[17] and the known σ_p constants of

Chart II



halides[18] one can predict that structures such as **4** should add dialkyl cuprates and we have observed this (Chart III). On reaction with 2 mol of lithium dimethylcuprate compounds

Chart III



7a and **7b** give good yields of **18** and compound **13** gives **19**. Since the initial report of our work,[1] there have appeared two other accounts of this type of reaction[19] showing its general usefulness.

Experimental Section[20]

Preparation of 1,3-Diketones. Dimedone (**6**) was purchased from Aldrich Chemical Co. and 2-methyl-1,3-cyclopentanedione (**9**) was prepared according to the procedure of Schick and Lehman.[21]

2-Ethyl-1,3-cyclohexanedione (12). Compound **12** was prepared in 35% yield by the method of Schick and Lehmann[21] but a better method was the following. Dihydrorescorcinol (**7**, 11 g, 0.1 mol) was added to a solution of 24 mL of water, 7 mL of dioxane, and 4 g (0.1 mol) of sodium hydroxide. A total of 15 g (0.1 mol) of ethyl iodide was added and the mixture was stirred at reflux for 6 h. An additional 4 g of ethyl iodide was added and heating was continued for 12 h. The solution was basified with 4 g of sodium hydroxide, cooled in ice, extracted with ether, and acidified to Congo red. The yellow solid which formed was collected and recrystallized from water (using charcoal) to give 5 g (36%) of 2-ethyl-1,3-cyclohexanedione, mp 174–176 °C (lit.[8] mp 178 °C).

Preparation of β-Halo-α,β-unsaturated Ketones. The general procedure used was that of Crossley and LeSueur[22] with minor modifications. A mixture of 0.1 mol of diketone, 0.3 mol of phosphorus tribromide or trichloride, and 500 mL of chloroform was heated at reflux with stirring for 3 h and was then cooled and poured over ice. The chloroform layer was separated and the water layer was extracted with chloroform. The chloroform solutions were combined, washed with 10% sodium bicarbonate and water, and dried and evaporated. Distillation of the residue gave the β-halo-α,β-unsaturated ketone.

3-Chloro-5,5-dimethyl-2-cyclohexen-1-one (7a). The procedure, using 56 g (0.4 mol) of dimedone (**6**), gave 50 g (79%) of **7a**, bp 98 °C (14 mm), n^{25}D 1.5168 [lit.[23] bp 105 °C (20 mm), n^{20}D 1.4942].

3-Bromo-5,5-dimethyl-2-cyclohexen-1-one (7b). The above procedure using 14 g (0.1 mol) of dimedone (**6**) gave 15.5 g (76%) of **7b**, bp 92–95 °C (7 mm), n^{25}D 1.4912 [lit.[22] bp 129 °C (25 mm)].

3-Chloro-2-methyl-2-cyclopenten-1-one (10). The above procedure using 22.4 g (0.2 mol) of **9** gave 9.7 g (37%) of **10**, bp 67–68 °C (6 mm) [lit.[19b] bp 43 °C (1.6 mm)].

3-Chloro-2-ethyl-2-cyclohexen-1-one (13). The above procedure using 14 g (0.1 mol) of **12** gave 11.1 g (76%) of **13**, bp 100 °C (15 mm), n^{25}D 1.5083.

Anal. Calcd for $C_8H_{11}ClO$: C, 60.57; H, 6.99; Cl, 22.35. Found: C, 60.18; H, 7.03; Cl, 22.18.

Reaction of β-Halo-α,β-unsaturated Ketones with Methyllithium and Pyrolysis to Give Acetylenic Ketones.[24] The general procedure for this cleavage reaction was as follows. A solution of 0.07 mol of β-substituted α,β-unsaturated ketone in 50 mL of dry ether was cooled to −20 °C under nitrogen. A total of 0.1 mol of methyllithium in ether was added slowly and the solution was stirred for 10 min. The resulting solution was then slowly introduced into a Pyrex pyrolysis tube at 200 °C under 15 mm of nitrogen pressure. The distillate was collected at −78 °C and the solvent was removed under vacuum. Distillation of the residue gave the acetylenic ketones.

4,4-Dimethyl-6-heptyn-2-one (8). By the above procedure compound **8** was formed in 70% yield from 15.8 g (0.1 mol) of chloride **7a** and in 75% yield from 20.3 g (0.1 mol) of bromide **7b**.[25] Compound **8** was purified by distillation, bp 80 °C (6 mm), n^{25}D 1.4408.

Anal. Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 78.23; H, 10.15.

5-Heptyn-2-one (11). By the above procedure, except that pyrolysis was carried out in a round-bottom flask,[6] compound **11** was formed in 32% yield from 2.6 g (0.02 mol) of chloride **10**. Compound **11** was purified by distillation in a Kugelrohr, bp 60 °C (10 mm), 2,4-DNP derivative mp 121 °C [lit.[26] bp 58–60 °C (10 mm), 2,4-DNP derivative mp 122–122.5 °C].

6-Nonyn-2-one (14).[27] By the above procedure compound **14** was formed in 60% yield[25] from 11 g (0.07 mol) of chloride **13**. Compound **14** was purified by distillation to give 4.2 g (44% isolated yield), bp 98 °C (6 mm), n^{25}D 1.4595 [lit.[9] bp 50–51 °C (0.5 mm)].

***cis*-6-Nonen-2-one (15).** A solution of 1.39 g (1 mmol) of 6-nonyn-2-one (**14**) in 10 mL of methanol containing 3 drops of quinoline was hydrogenated with 50 mg of 10% palladium on barium sulfate, at atmospheric pressure, until 1 mmol of hydrogen had been absorbed (40 min). The mixture was filtered and evaporated under vacuum and the residue was distilled in a Kugelrohr to give 1.2 g (86%) of *cis*-6-nonen-2-one (**15**), bp 56 °C (6 mm), having spectral properties identical with those of an authentic sample[10,11] [lit.[10] bp 92–92 °C (20 mm)].

***cis*-6,7-Epoxynonan-2-one (16).** The procedure of Wasserman and Barber was used.[10] A solution of 2 g (14.3 mmol) of **15** in 12 mL of methylene chloride was added to a stirred solution of 5.69 g (28.6 mmol) of 87% *m*-chloroperbenzoic acid in 60 mL of methylene chloride at 0 °C. The mixture was maintained at 0 °C for 3 h and was then filtered and washed with sodium bisulfite and water. The solution was dried and evaporated and the residue was distilled in a Kugelrohr to give 1.7 g (76%) of epoxide **16**, bp 45–46 °C (0.1 mm), identical with an authentic sample[10,11] [lit.[10] bp 45–46 °C (0.1 mm)].

***exo*-Brevicomin (17).**[10] Pyrolysis of 100 mg (0.64 mmol) of epoxide **16** in a base-washed Pyrex tube for 48 h at 210 °C gave 90 mg of brevicomin which by gas chromatography was found to be 10% *endo*-brevicomin and 90% *exo*-brevicomin. A pure sample of *exo*-brevicomin[10,11] (shorter retention time) was collected by preparative gas chromatography on a 10% Carbowax 20M on Chromosorb column.

Lithium Dimethylcuprate Addition to β-Halo-α,β-unsaturated Ketones. The general procedure used was to add 1 equiv of the unsaturated ketone in ether to a stirred solution of 3 equiv of lithium dimethylcuprate[28] in ether at 0 °C. The mixture was stirred for 2 h

at 0 °C and was then poured over ice containing 2 N hydrochloric acid (4 equiv). The product was then extracted into ether. The ether solution was dried and evaporated under vacuum, and the product was distilled.

3,3,5,5-Tetramethylcyclohexanone (18). By the above procedure compound 18 was formed in 76% yield from 16 g (0.1 mol) of chloride **7a** and in 80% yield from 20 g (0.1 mol) of bromide **8b**. Compound **18** was purified by distillation, bp 82–83 °C (9 mm), n^{20}D 1.4521 [lit.[29] bp 59–61 °C (5.5 mm), n^{20}D 1.4520].

2-Ethyl-3,3-dimethylcyclohexanone (19). By the above procedure compound **19** was formed in 62% yield from 4 g (0.026 mol) of chloride **13** and was purified by distillation, bp 86 °C (6 mm), n^{25}D 1.4556.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 78.17; H, 11.87.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and also to the University Research Council, University of North Carolina, for partial support.

Registry No.—**7a**, 17530-69-7; **7b**, 13271-49-3; **8**, 17520-15-9; **10**, 35173-23-0; **11**, 22592-18-3; **13**, 61426-12-8; **14**, 57237-89-5; **15**, 34019-86-8; **16**, 57238-62-7; **17**, 60018-04-4; **18**, 14376-79-5; **19**, 61426-13-9.

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Selective Reductive Cleavage of the Propargyl Oxygen Bond of Acetylenic Epoxides. A General Synthesis of 2-Ethynylcycloalkanones

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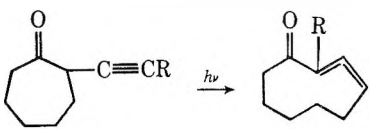
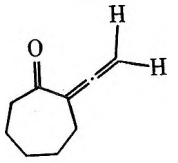
The reduction of the acetylenic epoxides **9** with lithium in liquid ammonia leads to the selective cleavage of the propargyl oxygen bond and produces a mixture of *cis*- and *trans*-2-ethynylcycloalkanols. The 2-ethynylcycloalkanols can be oxidized to 2-ethynylcycloalkanones which are useful substrates for photochemical ring expansions.

2-Alkynylcycloalkanones, e.g., **1**, on photolysis undergo a novel two-atom ring expansion to produce the interesting cyclic allenones **2**.[1,2] Although the cyclopentyl, cyclohexyl, and cycloheptyl analogues of **1** are readily prepared by reaction of acetylide anion or a substituted acetylide anion with the corresponding cycloalkene oxide and careful oxidation of the resulting alcohol,[1,2] this method fails with higher homologues because of the inertness of the cycloalkene oxides to carbon nucleophiles. Consequently, we sought a general method for the preparation of 2-ethynylcycloalkanones which would be applicable to a variety of ring sizes and which would use the readily available cyclic ketones as starting materials. Fur-

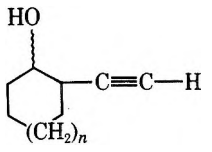


1 2

thermore, because 2-alkynylcycloalkanones such as 1 undergo a facile acid- or base-catalyzed isomerization to the conjugated allenones 3, we preferred to generate them as needed by oxidation of the corresponding alcohols 4.

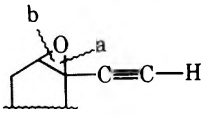


3



4

In considering potential routes to the required 2-ethynylcycloalkanols 4 we considered the possibility that an acetylenic epoxide 5, potentially readily available from the corresponding

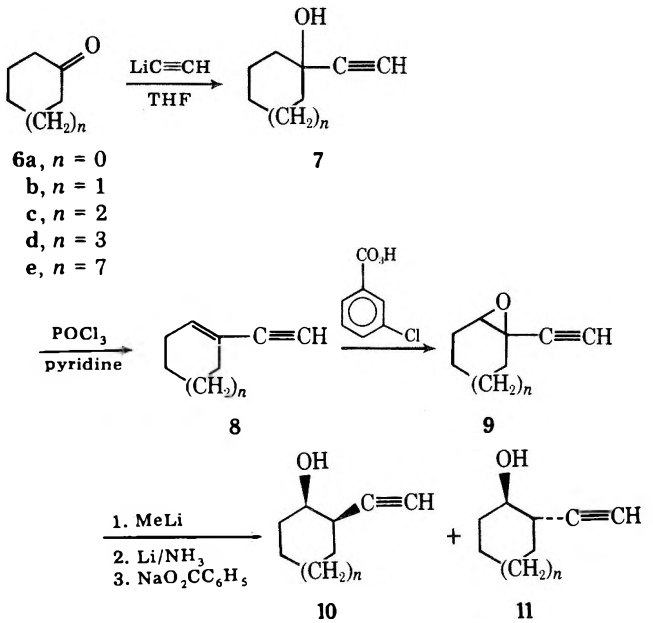


5

cycloalkanone, might undergo selective reductive cleavage of bond a when treated with an alkali metal in liquid ammonia. Although such reductive openings of epoxides are well known,[3] two problems were anticipated in the case of 5. First, the reductive opening of unsymmetrical epoxides usually proceeds to give the more substituted alcohol (cleavage of bond b), and secondly, acetylenes themselves are readily reduced under similar conditions. However, we felt that the acetylene functional group might provide sufficient activation of the propargyl C–O bond that the reductive cleavage might proceed in the desired direction and this would overcome the first of the anticipated problems. It also seemed likely that the second problem could be overcome by prior formation of the acetylide anion, a standard method used to prevent reduction of acetylenes when other functional groups are reduced by alkali metals in liquid ammonia.[4]

The required acetylenic epoxides 5 were readily prepared by the general route shown in Scheme I. This route to the

Scheme I



6a, n = 0
b, n = 1
c, n = 2
d, n = 3
e, n = 7

7 8 9 10 11

acetylenic epoxides utilized standard methods and the overall yields were very good except in the case in which $n = 0$, where the high volatility of some of the intermediates led to loss of material.

Initial studies of the reduction of the epoxy acetylenes 9 were conducted with the cyclohexyl analogue 9b because one of the expected reduction products, *trans*-2-ethynylcyclohexanol (11b), is a known compound. Treatment of 9b with lithium in liquid ammonia produced a mixture of alcohols in good yield which contained the desired *cis*- and *trans*-2-ethynylcyclohexanols. The NMR spectrum of the product, however, indicated that overreduction had occurred and ~15% olefinic alcohols had been produced as well.

Table I. Reduction of Epoxy Acetylenes (9 → 10 + 11)

Epoxy acetylene (9) *n*	Yield, %[a]	Cis/trans
0	63	1:3
1	92	7:3
2	81	4:6
3	90	
7	85	

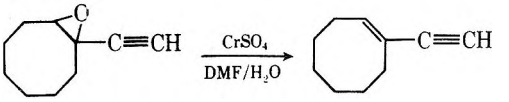
[a] Yields are isolated yields of purified materials.

It was found that the overreduction could readily be prevented by converting the terminal acetylene to its anion prior to reduction. The optimum procedure involved the cautious addition of 1 equiv of methyllithium in ether to a solution of the acetylenic epoxide in liquid ammonia–ether prior to reduction. With this procedure 9b was smoothly reduced with no overreduction, and a 7:3 mixture of *cis*- and *trans*-2-ethynylcyclohexanols was obtained in 92% distilled yield. Sodium benzoate was used to destroy excess lithium in these reductions because of indications in the literature that ammonium chloride will protonate anions more rapidly than it destroys excess lithium.

Table I summarizes the purified yields of alcohols obtained by this procedure. In each case a mixture of *cis*- and *trans*-acetylenic alcohols was obtained as indicated in Scheme I and Table I. The fact that a mixture is obtained presents no difficulty in our work because oxidation of either isomer produces the same acetylenic ketone.

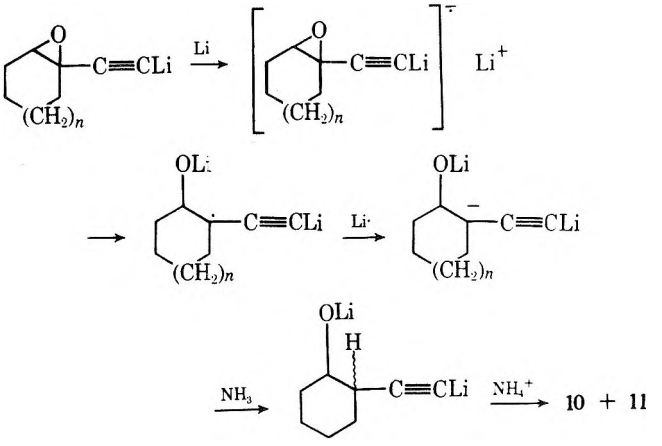
When the reduction was carried out on the cyclododecyl system 9e a 6% yield of ethylidenecyclododecane was obtained in addition to an 85% yield of a mixture of *cis*- and *trans*-2-ethynylcyclododecanols. This product presumably arises by deoxygenation of the epoxide[3a] to the enyne and subsequent reduction.

We also examined the use of chromium(II) sulfate[5] as a reagent for the reduction of the epoxy acetylenes. However, the reduction of epoxy acetylene 9d gave only the enyne 8d.

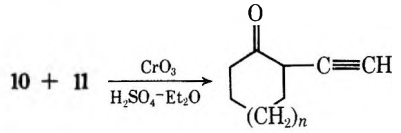


9d 8d

A possible mechanism for these reductions is shown below.



The mixtures of alcohols obtained were oxidized to the sensitive 2-ethynylcycloalkanones (**12**) by a modification of Brown's procedure.



12

Although we have examined only five systems for this selective reductive opening of acetylenic epoxides, it should provide a general route to cyclic and acyclic β-hydroxy acetylenes which cannot be prepared by direct opening of an epoxide with acetylide anion.

Experimental Section

All boiling points are uncorrected. Melting points were determined in Pyrex capillary tubes using a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on Beckman IR-8 or Acculab 3 spectrometers. Nuclear magnetic resonance spectra were obtained on Varian Associates Models A-60, A-60A, EM-360, T-60, and HA-100 instruments. Mass spectra were obtained on a MAT CH-5 mass spectrometer at 70 eV. Exact molecular weights were obtained by peak matching on the parent ion in the mass spectrum. Gas chromatographic analyses were conducted on an F & M Model 700 and a Bendix Model 2300 gas chromatographs. Elemental analyses were performed by the analytical service of the Department of Medicinal Chemistry, University of Kansas, Lawrence, Kans. Ultraviolet spectra were recorded on a Beckman DB spectrometer using isooctane as a solvent.

1-Ethynylcycloalkanols (7). 1-Ethynylcyclopentanol (**7a**) and 1-ethynylcyclohexanol (**7b**) were purchased from Aldrich Chemical Co.

1-Ethynylcyclododecanol (7e). In a three-necked, round-bottom flask equipped with a serum cap, a gas inlet tube, and stopper was placed 250 mL of dry tetrahydrofuran. The vessel was purged with nitrogen and cooled in a dry ice–acetone bath, and acetylene (purified by passing through concentrated sulfuric acid and solid potassium hydroxide) was introduced into the flask (ca. 2–3 mL/min) for 30 min. A solution of 60 mL of 2.0 M *n*-butyllithium in hexane (0.12 mol) was added via a syringe over a 30-min period. The stopper was replaced with an addition funnel and a solution of 18.2 g (0.10 mol) of cyclododecanone in 30 mL of tetrahydrofuran was added to the lithium acetylide solution over a 5-min period. The reaction mixture was stirred for 20 min at −78 °C and allowed to warm to room temperature (ca. 1 h) and 30 mL of water was added. The layers were separated, the water layer extracted with ether, and the organic layers dried ($MgSO_4$) and concentrated under vacuum to afford the crude product which was recrystallized from hexane to give 17.85 g (86%) of white crystals: mp 95.5–96 °C (lit.[6] mp 98–98.5 °C); IR (CCl_4) 3610, 3470, 3310, 2940, 2860, 1465, 1440, 1345, 1160, 1060, and 1000 cm^{-1}; NMR (CCl_4) δ 2.34 (s, 1 H) and 1.20–1.90 (m, 23 H); mass spectrum *m/e* (rel abundance) 208 (M^+, 0.3), 55 (100).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.73; H, 11.85.

1-Ethynylcyclooctanol (7d). Using the procedure described for the preparation of **7e**, 12.60 g (0.10 mol) of cyclooctanone gave 15.10 g of a clear liquid which was recrystallized from pentane to afford 12.80 g (84%) of white needles: mp 44–44.5 °C (lit.[7] mp 47 °C); IR (CCl_4) 3600, 3470, 3310, 2920, 2860, 2700, 2110, 1465, 1445, 1325, 1260, 1140, 1060, 1000, and 980 cm^{-1}; NMR δ 3.15 (br s, 1 H), 2.33 (s, 1 H), and 1.20–2.10 ppm (m, 14 H).

1-Ethynylcycloheptanol (7c). To 25 g (0.25 mol) of lithium acetylide–ethylenediamine complex suspended in 200 mL of tetrahydrofuran which had been saturated with acetylene gas for 20 min at 0 °C was slowly added 22.4 g (0.20 mol) of cycloheptanone in 20 mL of tetrahydrofuran. The reaction mixture was maintained at 0 °C for 36 h and quenched with water and 10% hydrochloric acid. The mixture was extracted with ether, and the ether extracts washed with 10% hydrochloric acid and brine, dried ($MgSO_4$), and concentrated to give 28.20 g of a yellow liquid. Distillation gave 21.10 g (76%) of a clear liquid: bp 56–60 °C (0.65 Torr) [lit.[8] bp 80–81 °C (10 Torr)]; IR (CCl_4) 3600, 3470, 3300, 2950, 2860, 2700, 2110, 1460, 1445, 1330, 1205, and 1030 cm^{-1}; NMR (CCl_4) δ 3.30 (m, 1 H), 2.36 (s, 1 H), and 1.30–2.10 (m, 12 H).

General Procedure for the Preparation of 1-Ethynylcycloalkenes (8). 1-Ethynylcyclooctene (8d). To a cold (0 °C) solution of 19.30 g (0.13 mol) of 1-ethynylcyclooctanol in 70 mL of pyridine maintained under nitrogen was added, with stirring, 20 mL (0.20 mol) of phosphorus oxychloride over a 30-min period. The reaction mixture was allowed to warm to room temperature, stirred for 15 h, and then heated to 70 °C for 0.75 h. After cooling 200 g of ice was added, the layers were separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid, water, and saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$), and concentrated to give 13.81 g of a yellow liquid. Kugelrohr distillation gave 13.23 g (78%) of a colorless liquid: bp 92–93 °C (23 Torr); IR (CCl_4) 3310, 3030, 2950, 2875, 2690, 2100, 1630, 1470, and 1445 cm^{-1}; NMR (CCl_4) δ 6.14 (t, 1 H, J = 8 Hz), 2.63 (s, 1 H), 2.00–2.60 (m, 5 H), and 1.50 (br s, 7 H); mass spectrum *m/e* (rel intensity) 134 (M^+, 29), 91 (100).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.59; H, 10.71.

1-Ethynylcyclopentene (8a). Using the procedure described for the preparation of **8d**, 11.16 g (0.10 mol) of 1-ethynylcyclopentanol was dehydrated with 15 mL (0.15 mol) of phosphorus oxychloride in 80 mL of pyridine. The crude product was distilled to give 5.17 g (56%) of a colorless liquid: bp 60–62 °C (100 Torr) (lit.[9] bp 144 °C); IR (CCl_4) 3310, 3060, 2960, 2860, 2110, 1450, and 960 cm^{-1}; NMR (CCl_4) δ 6.02 (m, 1 H), 2.81 (s, 1 H), and 1.60–2.70 (m, 6 H).

1-Ethynylcyclohexene (8b). Using the procedure described for the preparation of **8d**, 32.00 g (0.25 mol) of 1-ethynylcyclohexanol was dehydrated with 40 mL (0.40 mol) of phosphorus oxychloride in 200 mL of pyridine. The crude product was distilled to give 21.74 g (82%) of a colorless liquid: bp 71–72 °C (60 Torr) [lit.[8] bp 60 °C (30 Torr)]; IR (CCl_4) 3300, 3030, 2940, 2860, 2840, 2100, 1630, 1440, and 930 cm^{-1}; NMR (CCl_4) δ 6.10 (m, 1 H), 2.65 (s, 1 H), 1.85–2.28 (m, 4 H), and 1.40–1.85 (m, 4 H).

1-Ethynylcycloheptene (8c). Using the procedure described for the preparation of **8d**, 8.41 g (0.061 mol) of 1-ethynylcycloheptanol was dehydrated with 10 mL (0.10 mol) of phosphorus oxychloride in 30 mL of pyridine. Distillation of the crude product gave 4.91 g (67%) of a colorless liquid: bp 50–52 °C (1.00 Torr) [lit.[8] bp 65 °C (10 Torr)]; IR (CCl_4) 3310, 3030, 2930, 2860, 2100, 1630, 1455, 1445, and 863 cm^{-1}; NMR (CCl_4) δ 6.25 (t, 1 H, J = 6 Hz), 2.64 (s, 1 H), 2.00–2.45 (m, 4 H), and 1.35–1.90 (m, 6 H).

***cis*- and *trans*-1-Ethynylcyclododecene (8e).** Using the procedure described above for the preparation of **8d**, 20.8 g (0.10 mol) of 1-ethynylcyclododecanol was dehydrated with 15 mL (0.15 mol) of phosphorus oxychloride in 70 mL of pyridine. The crude product was distilled in a Kugelrohr apparatus to afford 13.04 g (79%) of a colorless liquid which was a 1:1 mixture of isomers by VPC[10] analysis: bp 61–62 °C (0.08 Torr); IR (CCl_4) 3310, 3020, 2960, 2860, 2100, 1460, and 1445 cm^{-1}; NMR (CCl_4) δ 5.80 (t, 1 H, J = 8 Hz), 2.94 (s, ~0.5 H), 2.54 (s, ~0.5 H), 2.00–2.40 (m, 4 H), and 1.10–1.80 (m, 16 H); mass spectrum *m/e* (rel intensity) 190 (M^+, 15), 79 (100).

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.54; H, 11.78.

General Procedure for the Preparation of Acetylenic Epoxides 9. 1-Ethynyl-9-oxabicyclo[6.1.0]nonane (9d). To a solution of 12.59 g (0.094 mol) of **8d** in 30 mL of methylene chloride at 0 °C was added over a 30-min period a solution of 19.1 g (0.094 mol) of 85% *m*-chloroperbenzoic acid in 150 mL of methylene chloride. The reaction mixture was stirred at 0 °C for 0.25 h and at room temperature for 1.2 h. Sodium sulfite solution (10%) was added until the reaction mixture gave a negative test to starch–iodide paper. Aqueous sodium bicarbonate solution was carefully added, the layers separated, and the organic layer washed with saturated aqueous sodium bicarbonate and water, dried (Na_2SO_4), and concentrated under vacuum to give 13.88 g of a yellow liquid which was distilled in a Kugelrohr apparatus to give 12.24 g (87%) of a colorless liquid: bp 37 °C (0.08 Torr); IR (CCl_4) 3300, 2940, 2870, 2680, 1465, 1445, 1250, and 940 cm^{-1}; NMR (CCl_4) δ 2.91 (dd, 1 H, J = 11, 4.5 Hz), 2.19 (s, 1 H), 1.95–2.20 (m, 2 H), and 1.10–1.80 (m, 10 H); mass spectrum *m/e* (rel intensity) 150 (M^+, 27), 79 (100).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.06; H, 9.47.

1-Ethynyl-6-oxabicyclo[3.1.0]hexane (9a). Using the procedure described for the preparation of **9d**, 4.04 g (0.044 mol) of 1-ethynylcyclopentene and a slight excess of 85% *m*-chloroperbenzoic acid gave, upon distillation, 3.01 g (58%) of a colorless liquid: bp 60–62 °C (30 Torr); IR (CCl_4) 3300, 3020, 2950, 2920, 2850, 1440, 1400, 1300, 935, and 855 cm^{-1}; NMR (CCl_4) δ 3.48 (s, 1 H), 2.30 (s, 1 H), and 1.20–2.30 ppm (m, 6 H); mass spectrum *m/e* (rel intensity) 108 (M^+, 59), 79 (100).

Anal. Calcd for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.70; H, 7.44.

1-Ethynyl-7-oxabicyclo[4.1.0]heptane (9b). Using the procedure described for the preparation of **9d,** 15.9 g (0.15 mol) of 1-ethynylcyclohexene and a slight excess of 85% *m*-chloroperbenzoic acid gave, after distillation, 14.91 g (81%) of a colorless liquid: bp 70–72 °C (15 Torr); IR (CCl_4) 3300, 2910, 2870, 2690, and 1440 cm^{-1}; NMR (CCl_4) δ 3.22 (t, 1 H, J = 4.5 Hz), 2.23 (s, 1 H), 2.00 (m, 4 H), and 1.40 (m, 4 H); mass spectrum *m/e* (rel intensity) 122 (M^+, 11), 78 (100).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.62; H, 8.43.

1-Ethynyl-8-oxabicyclo[5.1.0]octane (9c). Using the procedure described for the preparation of **9d,** 9.00 g (0.075 mol) of 1-ethynylcycloheptene and a slight excess of 85% *m*-chloroperbenzoic acid gave after distillation 8.21 g (80%) of a colorless liquid: bp 42–44 °C (0.6 Torr); IR (CCl_4) 3300, 3020, 2930, 2860, 2100, and 1235 cm^{-1}; NMR (CCl_4) δ 3.14 (br t, 1 H, J = 5 Hz), 2.17 (s, 1 H), and 1.00–2.30 ppm (m, 10 H); mass spectrum *m/e* (rel intensity) 136 (M^+, 24), 91 (100).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.46; H, 9.10.

***cis*- and *trans*-1-Ethynyl-13-oxabicyclo[10.1.0]tridecane (9e).** Using the procedure described for the preparation of **9d,** 12.92 g (0.068 mol) of a mixture of *cis*- and *trans*-**8e** and a slight excess of 85% *m*-chloroperbenzoic acid gave, after Kugelrohr distillation (92–94 °C, 0.10 Torr), 10.87 g (78%) of a colorless liquid containing both geometrical isomers in approximately equal amounts (as determined by NMR analysis): IR (CCl_4) 3310, 2940, 2870, 1470, 1450, and 1120 cm^{-1}; NMR (CCl_4) δ 2.90 (m, 1 H), 2.30 (s, ~0.5 H), 2.15 (s, ~0.5 H), and 1.00–2.00 ppm (m, 20 H); mass spectrum *m/e* (rel intensity) 206 (M^+, 36), 82 (100).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.46; H, 10.75. Found: C, 81.25; H, 10.93.

General Procedure for the Reduction of the Acetylenic Epoxides 9. *cis*- and *trans*-2-Ethynylcyclohexanol (10b and 11b). To 30 mL of dry ammonia under argon in a three-necked flask equipped with a serum cap, a mechanical stirrer with a glass stirring blade, and a dry ice condenser topped with an argon inlet were added a few crystals of triphenylmethane and 1.92 g (15.7 mmol) of **9b** in 5 mL of ether. Methyllithium in ether (1.8 M) was added via a syringe (*Caution*: extremely vigorous reaction!) until a red triphenylmethane end point was achieved. Small pieces of lithium wire were then added until the blue color persisted, enough sodium benzoate[15] was added to dissipate the blue color, and 5.3 g (0.1 mol) of ammonium chloride was added. The ammonia was allowed to evaporate, the residue taken up in ether and water, the layers separated, and the ether layer washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated under vacuum to give 1.91 g (98%) of a yellow liquid. Vacuum transfer (25–45 °C, 0.02 Torr) gave 1.78 g (92%) of a colorless liquid which VPC analysis[11,12] indicated was a 7:3 mixture of **10b** and **11b:** IR (CCl_4) 3580, 3300, 2940, 2870, 2120, 1455, 1405, and 1080 cm^{-1}; NMR (CCl_4) δ 3.50 (m, ~2.5 H), 2.75 (m, ~0.5 H), 2.10 (d, 1 H, J = 2 Hz), and 1.00–2.00 ppm (m, 8 H).

***cis*- and *trans*-2-Ethynylcyclopentanol (10a and 11a).** Using the procedure described for the reduction of **9b,** 1.26 g (11.7 mmol) of **9a** was reduced to give 1.09 g (85%) of a yellow liquid. The crude product was shown to consist of a 1:3 mixture of the cis and trans alcohols by VPC[12,13] analysis. The crude product was chromatographed on 60 g of activity grade II Woelm silica gel, eluting with hexane–ether mixtures. The total amount of **10a** and **11a** obtained was 0.68 g (63%). Some fractions contained either pure cis or trans alcohol. *cis*-2-Ethynylcyclopentanol (**10**), which eluted first, was a colorless liquid: IR (CCl_4) 3560, 3300, 2960, 2900, 2870, 2110, 1465, 1445, 1370, 1340, 1255, 1200, 1095, and 1025 cm^{-1}; NMR (CCl_4) δ 4.10 (m, 1 H), 2.55 (m, 1 H), 2.11 (d, 1 H, J = 2 Hz), and 1.50–2.10 (m, 7 H). *trans*-2-Ethynylcyclopentanol (**11a**) was a colorless liquid: IR (CCl_4) 3600, 3490, 3310, 2960, 2880, 2120, 1470, 1450, 1205, 1090, and 1025 cm^{-1}; NMR (CCl_4) δ 4.08 (m, 2 H), 2.02 (d, 1 H, J = 2.5 Hz), and 1.40–1.80 (m, 6 H).

***cis*- and *trans*-2-Ethynylcycloheptanol (10c and 11c).** Using the procedure described above for the reduction of **9b,** 0.98 g (7.2 mmol) of **9c** was reduced to give, after vacuum transfer into a dry ice trap (60–75 °C, 0.1 Torr), 0.81 g (82%) of a colorless liquid which was a 6:4 mixture of cis and trans isomers as determined by VPC analysis:[12,14] IR (CCl_4) 3670, 3300, 2930, 2860, 2690, 2120, 1460, 1450, 1400, 1260, and 1050 cm^{-1}; NMR (CCl_4) δ 3.70 (m, 1 H), 3.25 (br s, 1 H), 2.85 (m, ~0.5 H), 2.50 (m, ~0.5 H), 2.14 (d, ~0.5 H), 2.12 (d, ~0.5 H), and 1.20–2.00 ppm (m, 10 H).

***cis*- and *trans*-2-Ethynylcyclooctanol (10d and 11d).** Using the procedure described above for the reduction of **9b,** 4.50 g (0.03 mmol) of **9d** was reduced to give, after vacuum transfer into a dry ice trap (60–75 °C, 1.0 Torr), 4.08 g (90%) of a colorless liquid which was shown to be a 6:4 mixture of cis and trans isomers (isomers unassigned) by VPC[10] analysis: IR (CCl_4) 3580, 3300, 2960, 2860, 2120, 1470, 1050, and 1030 cm^{-1}; NMR (CCl_4) δ 3.75 (m, 1 H), 3.10 (m, ~1 H), 2.80 (m, ~0.5 H), 2.50 (m, ~0.5 H), 2.06 (d, ~0.5 H), 2.04 (d, ~0.5 H), and 1.20–2.10 ppm (m, 12 H); mass spectrum *m/e* (rel intensity) 152 (M^+, 7), 54 (100).

Anal. Calcd for $C_{10}H_{16}O$: C, 81.46; H, 10.75. Found: C, 81.25; H, 10.93.

***cis*- and *trans*-2-Ethynylcyclododecanol (10e and 11e).** This reduction was carried out using the procedure described above for **9b,** except that a 1:2 mixture of ether–ammonia (120 mL total) was used as the solvent. Reduction of 2.952 g (0.013 mol) of **9e** gave 2.952 g (95%) of a colorless liquid. Chromatography of this crude mixture on 150 g of activity grade I Woelm silica gel and eluting with hexane and increasing amounts of ether gave three compounds. The first, 0.17 g (6%) of a colorless liquid eluted with 100% hexane, was identified as ethylidenecyclododecane: IR (CCl_4) 2940, 2850, 1470, and 1440 cm^{-1}; NMR (CCl_4) δ 5.22 (q, 1 H, J = 7 Hz), 2.00 (m, 4 H), 1.56 (d, 3 H, J = 7 Hz), and 1.30–1.70 ppm (m, 18 H); irradiation of the quartet at δ 5.22 collapsed the doublet at δ 1.56 to a singlet; mass spectrum *m/e* (rel intensity) 194 (M^+, 14), 56 (100).

Anal. Calcd for $C_{14}H_{26}$: C, 86.51; H, 13.49. Found: C, 86.54; H, 13.35.

Further elution gave 2.50 g (85%) of a 6:4 mixture of the *cis*- and *trans*-2-ethynylcyclododecanol **10** and **11e** (isomers unassigned). Fractions containing both pure isomers were obtained. The minor and more polar isomer was a liquid. The major and less polar isomer was a solid (mp 69–69.5 °C). The mixture gave the following spectral data: IR (CCl_4) 3580, 3310, 2940, 2870, 2120, 1470, 1445, and 1110 cm^{-1}; NMR (CCl_4) δ 3.75 (m, 1 H), 2.60 (m, 1 H), 2.00 (d, ~0.4 H, J = 2 Hz), 1.95 (d, ~0.6 H, J = 2 Hz), and 1.20–1.80 ppm (m, 20 H). An analytical sample of the less polar isomer was prepared by sublimation at 60–80 °C (0.03 Torr): mp 69–69.5 °C; mass spectrum *m/e* (rel abundance) 208 (M^+, 1), 54 (100).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.76; H, 11.61.

General Procedure for the Oxidation of *cis*- and *trans*-2-Ethynylcycloalkanols (10 and 11).[16] 2-Ethynylcyclododecanone (12e). To a cold (−5 to −10 °C) solution of 1.03 g (5.0 mmol) of **10e** and **11e** in 10 mL of ether in a 25-mL, three-necked flask equipped with a drying tube, a thermometer, and a serum cap was added, over a 5-min period, 5.5 mL (2.2 equiv) of *cold* 0.67 M sodium dichromate in sulfuric acid. The reaction mixture was stirred for 1.5 h at −5 to −10 °C, the layers separated, and the ether washed once with aqueous saturated sodium bicarbonate and several times with brine, dried (Na_2SO_4), and concentrated under vacuum to give 0.94 g (92%) of a colorless liquid: IR (CCl_4) 3310, 2940, 2870, 2120, 1715, 1465, and 1440 cm^{-1}; NMR (CCl_4) δ 3.10–3.30 (m, 1 H), 2.60 (m, 2 H), 2.14 (d, 1 H, J = 2 Hz), and 1.00–2.00 (m, 18 H); UV (isooctane) λ_{max} 276 nm (ϵ 99); mass spectrum *m/e* (rel intensity) 206 (M^+, 10), 79 (100).

Exact molecular weight. Calcd for $C_{14}H_{22}O$: 206.167. Found: 206.167.

2-Ethynylcyclooctanone (12d). Procedure A. Using the procedure described above for the preparation of **12e,** 0.46 g (3.0 mmol) of **10d** and **11d** was oxidized to give 0.23 g (81%) of a light yellow oil which contained some allenone and alcohol by IR analysis, but otherwise gave the same spectral data as that recorded for the compound prepared by procedure B.

2-Ethynylcyclooctanone (12d). Procedure B. To 2.1 mL (2.1 equiv) of 0.67 M sodium dichromate in sulfuric acid and 10 mL of ether at −10 °C was added dropwise a solution of 0.31 g (2.0 mmol) of **10d** and **11d** in 10 mL of ether over a 5-min period. The solution was maintained at −5 to −10 °C for 1.25 h, and the ether layer decanted, washed once with saturated aqueous sodium bicarbonate and several times with brine, dried (Na_2SO_4), and concentrated to give 0.27 g (88%) of a colorless liquid: IR (CCl_4) 3300, 2930, 2860, 2690, 2120, 2100, 1715, 1450, and 1250 cm^{-1}; NMR (CCl_4) δ 3.25 (dt, 1 H, J = 2.5, 7 Hz), 2.20 (d, 1 H, J = 2.5 Hz), and 1.00–3.00 (m, 12 H); UV (isooctane) λ_{max} 276 nm (ϵ 81); mass spectrum *m/e* (rel intensity) 150 (M^+, 55), 94 (100).

Exact molecular weight. Calcd for $C_{10}H_{14}O$: 150.104. Found: 150.104.

Acknowledgments. We are indebted to the National Science Foundation (Grant MPS 73-08764) and the General Research Fund of the University of Kansas for partial support of this work.

Registry No.—**7a,** 17356-19-3; **7b,** 78-27-3; **7c,** 2809-78-1; **7d,** 55373-76-7; **7e,** 14519-31-4; **8a,** 1610-13-5; **8b,** 931-49-7; **8c,** 2809-83-8; **8d,** 61967-54-2; *cis*-**8e,** 61967-55-3; *trans*-**8e,** 61967-56-4; **9a,**

34329-47-0; **9b**, 932-03-6; **9c**, 61967-57-5; **9d**, 61967-59-7; *cis*-**9e**, 61967-58-6; *trans*-**9e**, 62014-82-8; **10a**, 61967-60-0; **10b**, 61967-61-1; **10c**, 61967-62-2; **10d**, 61967-63-3; **10e**, 61967-64-4; **11a**, 61967-50-8; **11b**, 55506-28-0; **11c**, 25127-83-7; **11d**, 61967-51-9; **11e**, 62057-82-3; **12d**, 61967-52-0; **12e**, 61967-53-1; acetylene, 74-86-2; cyclododecanone, 830-13-7; cyclooctanone, 502-49-8; cycloheptanone, 502-42-1; ethylidenecyclododecane, 56888-86-9.

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(10) A 6 ft × 0.25 in. column packed with 10% Dow 710 silicone oil on 60/80 mesh Chromosorb W was employed for this analysis.
(11) A 6 ft × 0.25 in. column packed with 15% Carbowax 20M/NaOH on 60/80 mesh Chromosorb W was employed for this analysis.
(12) The trans isomer was identified by coinjection with an authentic sample.
(13) A 6 ft × 0.25 in. column packed with 15% SF-96 silicone oil on 60/80 mesh Chromosorb W was employed for this analysis.
(14) A 6 ft × 0.25 in. column packed with 15% Carbowax 20M on 60/80 mesh Chromosorb W was employed for this analysis.
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Chlorocarbonylbis(triphenylphosphine)iridium-Catalyzed Isomerization, Isoaromatization, and Disproportionation of Some Cycloalkanones Having Exocyclic Double Bonds

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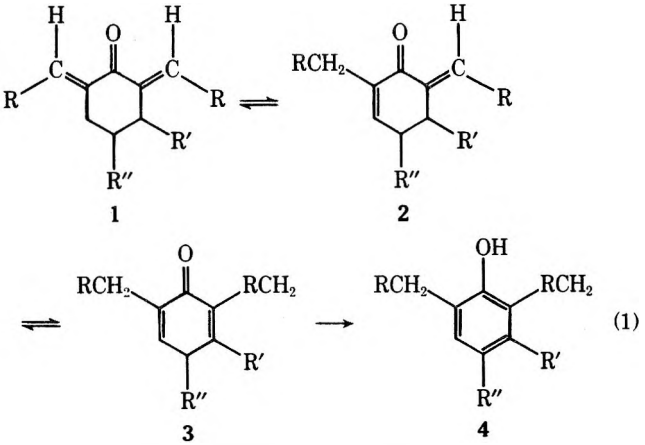
Chlorocarbonylbis(triphenylphosphine)iridium has been shown to be an efficient catalyst at 250 °C for isoaromatization of 2,6-diarylidenecyclohexanones. A stepwise migration of the exocyclic double bonds takes place followed by thermal tautomerization of the cyclohexa-2,5-dienone system. 2-Arylidene-1-tetralones undergo similar transformations to the corresponding naphthols. 2,7-Dibenzylidenecycloheptanone, which cannot form an aromatic system without loss of H_2, exhibits only *E–Z* isomerization. 3,7-Dibenzylidenecycloheptane-1,2-dione is partly converted into 3,7-dibenzyltropolone, and partly disproportionates to dibenzylcycloheptanedione and to polymer precursor. Unsaturated cyclopentanones react to give disproportionation products along with double bond migration into the five-membered ring.

2-Benzylphenols and naphthols have been known for many years to possess specific bacteriostatic and fungistatic activities.[1] They are, however, of little practical value since most of their present syntheses are inefficient and low yielding processes. Direct benzylation of phenols give, in general, mixtures of isomers.[2] Isomerization of benzylidenecyclohexanones[3-7] by acids (PPA, HOAc–HBr) is often accompanied by skeletal rearrangements[8] and ring expansion,[9] whereas heterogeneous transition metal catalysts (Ni, Pd/C, PtO_2)[10] frequently cause oxygen extrusion[11] or, in alcoholic media, result in transfer hydrogenation of the carbon–carbon double bonds.[12]

In a preliminary communication[13] we reported that isoaromatization of 2,6-dibenzylidenecyclohexanones to 2,6-dibenzylphenols can be accomplished in excellent yields by the versatile iridium catalyst, $IrCl(CO)(PPh_3)_2$. We have now extended this study to include further arylidenecyclohexanones, as well as some derivatives of α-tetralone, cyclopentanone, cycloheptanone, and cycloheptanedione.

Isomerization of Diarylidenecyclohexanones. As described in the Experimental Section, (*E,E*)-2,6-dibenzylidenecyclohexanone (**1**, R = C_6H_5; R′ = R″ = H) is converted to 2,6-dibenzylphenol (**4**, R = C_6H_5; R′ = R″ = H) simply by heating the ketone and the catalyst (a high boiling solvent may be used) for 1.5–2 h at 230–250 °C. The reaction is stepwise (vide infra) as shown in eq 1.



1 2 3 4 (1)

The catalysis proceeds equally well (though at different rates) when the phenyl moieties in **1**, R = C_6H_5; R′ = R″ = H, are exchanged by substituted aryl groups, provided the substituents neither coordinate irreversibly to the catalyst (as does NO_2) nor extend serious steric effects (e.g., ortho substituents).

A summary of some representative experiments using $IrCl(CO)(PPh_3)_2$ as catalyst is given in Table I.

The application of some other typical catalysts, viz., $RhCl_3 \cdot 3H_2O$, $RhCl(PPh_3)_3$, and $RuCl_2(PPh_3)_3$, gives less satisfactory results.

The stepwise nature of reaction 1 follows directly from its kinetic curves (Figure 1).[14] While the equilibration of **1** and **2** and of **2** and **3** is assisted by the iridium catalyst, the tau-

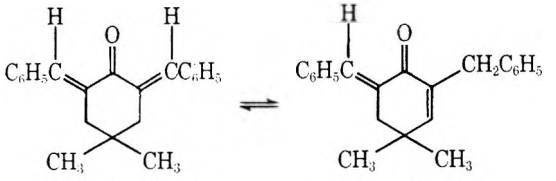
Table I. Isoaromatization of Bis(arylmethylene)cyclohexanones (1) by $IrCl(CO)(PPh_3)_2$ at 250 °C[a]

Registry no.	Expt	R	R′	R″	Solvent	Reaction time, h	Yield, %
42052-61-9	1	C_6H_5	H	H	Ph_2O	2.5	98
	2	C_6H_5	H	H	none	2	76
62085-69-2	3	C_6H_5	CH_3	H	Ph_2O	2.5	87
	4	C_6H_5	CH_3	H	none	2.2	78
42792-77-8	5	C_6H_5	H	$C(CH_3)_3$	Ph_2O	2	92
42792-79-0	6	4-$CH_3C_6H_4$	H	H	Ph_2O	0.5	97
62085-70-5	7	2-$CH_3OC_6H_4$	H	H	Ph_2O	15	52
62085-71-6	8	4-$CH_3OC_6H_4$	H	H	Ph_2O	0.3	98
62085-72-7	9	2-ClC_6H_4	H	H	Ph_2O	24	<1
62085-73-8	10	3-ClC_6H_4	H	H	Ph_2O	4	90
42792-80-3	11	4-ClC_6H_4	H	H	Ph_2O	3.5	98
62085-74-9	12	4-FC_6H_4	H	H	Ph_2O	4	85
62085-75-0	13	2-Furyl	H	H	Ph_2O	2	98
62085-76-1	14	1-$C_{10}H_7$	H	H	Ph_2O	24	0
62085-77-2	15	2-$C_{10}H_7$	H	H	Ph_2O	15	95

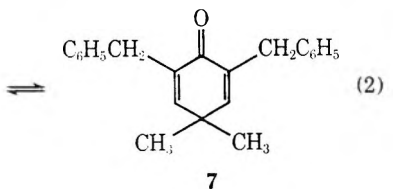
[a] Except in expt 2 and 4, the reaction mixture consisted of 2×10^{-3} mol of ketone, 1.28×10^{-5} mol of catalyst, and 1 mL of diphenyl ether. The yields in these experiments were determined by GLC (5% SE-30 on Chromosorb W). In expt 2 and 4, 3.65×10^{-2} mol of ketone and 1.28×10^{-4} mol of catalyst were reacted and the product was isolated by distillation.

tomerization 3 → 4 is not. It is merely a thermal rearrangement.[15] In this concern it is noteworthy that $IrCl(CO)(PPh_3)_2$, as well as $RhCl(PPh_3)_3$ and $RuCl_2(PPh_3)_3$, are also inactive in other keto to enol transformations such as in anthrone and 2-acetyl-1-tetralone.[16]

2-Benzyl-6-benzylidenecyclohex-2-enone (**2**, R = C_6H_5; R′ = R″ = H) and the substituted analogues are fairly stable. They can be isolated from the reaction mixtures of the uncompleted catalyses by preparative GLC. Diene **3**, R = C_6H_5; R′ = R″ = H, however, is labile. It isomerizes in part and cannot be obtained by this method free of phenol **4**. A stable diene of type **3**, viz., 2,6-dibenzyl-4,4-dimethylcyclohexa-2,5-dienone (**7**), is formed when the two hydrogen atoms in **3**, R = C_6H_5; R′ = R″ = H, are substituted by methyl groups. Upon blocking the final enolization step, **5** gives at 230 °C (without a solvent) an equilibrium mixture of 94.1% **5**, 1,8% **6**, and 4.1% **7**. In diphenyl ether (250 °C) **6** and **7** accumulate in substantial amounts (yields of **5**, **6**, and **7** 1.5, 18, and 74%, respectively). From this mixture **6** and **7** were isolated.



5 **6**



(2)

7

Both electronic and steric factors affect reaction 1. In experiments with 1 in diphenyl ether at 250 °C, for which R′ = R″ = H and R represents (a) 4-$CH_3OC_6H_4$, (b) 4-$CH_3C_6H_4$, (c) C_6H_5, and (d) 4-FC_6H_4 a Hammett σ–ρ relationship is obtained for the initial reaction rates. (The corresponding values for the consumption of 1 are 6.7, 3.3, 1.1, and 0.5% min^{-1}.) The initial rate for **1**, R = 4-ClC_6H_4; R′ = R″ = H, is 0.72% min^{-1}. This value is somewhat higher than expected, owing to the complication involved in the activation of aryl chlorides by $IrCl(CO)(PPh_3)_2$.[17] In the absence of diphenyl ether, however, the order of rates no longer parallels with the order of electronegativities of the substituents. The initial rates for isomerization of the *E,E* series of 2,6-dibenzylidene-, 2,6-bis(*p*-methylbenzylidene)-, 2,6-bis(*p*-methoxybenzylidene)-, 2,6-bis(*m*-chlorobenzylidene)-, 2,6-bis(*p*-chlorobenzylidene)-, and 2,6-bis(*p*-fluorobenzylidene)cyclohexanone are 1.80, 0.73, 0.71, 0.49, 0.47, and 0.21% min^{-1}, respectively (230 °C, substrate to catalyst ratio 100:1). This may imply that the solvent serves in our reaction as hydrogen donor for a Harrod–Chalk type mechanism.[18] In fact the application of deuterium labeled diphenyl ether leads to partially deuterated dibenzylphenols. In the absence of the ether the required hydrogen atom is abstracted either from the substrate itself or, less probably, from the ortho position of the triphenylphosphine ligand of the catalyst.[19]

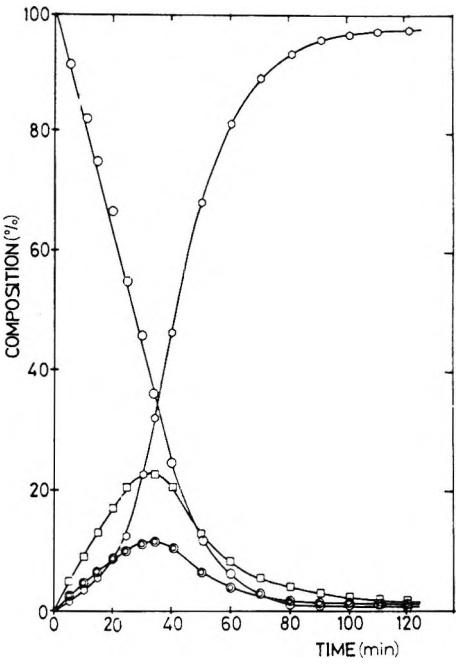


Figure 1. Isoaromatization of (*E,E*)-2,6-dibenzylidenecyclohexanone (2.0 mmol) at 230 °C in the presence of $IrCl(CO)(PPh_3)_2$ (1.28×10^{-2} mmol) under N_2; ○, ketone **1**, R = C_6H_5, R′ = R″ = H; □, **2**, R = C_6H_5, R′ = R″ = H; ⊙, **3**, R = C_6H_5, R′ = R″ = H; ○, **4**, R = C_6H_5, R′ = R″ = H.

In contrast to some Rh(I)- and Rh(III)-catalyzed isomerization reactions,[20] the isoaromatization is not affected by

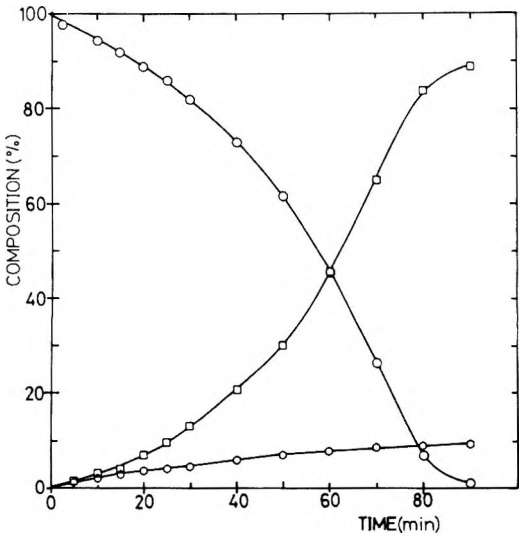


Figure 2. Concentration–time profiles for the reactant and products in $IrCl(CO)(PPh_3)_2$-catalyzed conversion of (*E*)-2-benzylidene-1-tetralone: (○) (**8**, R = R′ = H) into 2-benzyl-1-naphthol (□) (**11**, R = R′ = H) and 2-benzyl-1-tetralone (○). Reaction system: 10^{-3} mol of **8**, 10^{-5} mol of catalyst, 0.5 mL of Ph_2O; 255 °C.

hydrogen chloride. It is thus unlikely that hydrogen chloride transfer (Cramer's mechanism[20]) is of importance to reaction 1.

When the catalyses listed in Table I have been interrupted after a short period, freed from iridium compounds, and analyzed by GLC, 1 mol of PPh_3 per each mole of catalyst could be isolated.[21] However, since neither the liberated phosphine nor that added externally has any significant effect on the reaction rate [as does, e.g., PPh_3 on $RhCl(PPh_3)_3$-catalyzed isomerization[22]], it seems unlikely that $IrCl(CO)(PPh_3)_2$ is activated by reversible dissociation. $IrCl(CO)(PPh_3)_2 \rightleftharpoons$ "$IrCl(CO)(PPh_3)$" + PPh_3.

2-Arylidene-1-tetralones. Isoaromatization of (*E*)-2-benzylidene-1-tetralone (**8**, R = R′ = H) by $IrCl(CO)(PPh_3)_2$ in boiling diphenyl ether gives 2-benzyl-1-naphthol (**11**, R = R′ = H) in high yield. The only by-product is 2-benzyl-1-tetralone (up to 10%) resulting from a slow hydrogen transfer from the solvent to the activated double bond in **8**.[23]

The conversion **8** → **10** proceeds without substantial accumulation of reaction intermediates. The exocyclic double bond migrates into the ring and compound **9**, which is probably formed, either tautomerizes immediately to **11** or undergoes first isomerization to the conjugated species **10**.

A typical reaction curve for the isoaromatization of **8**, R = R′ = H, is shown in Figure 2.

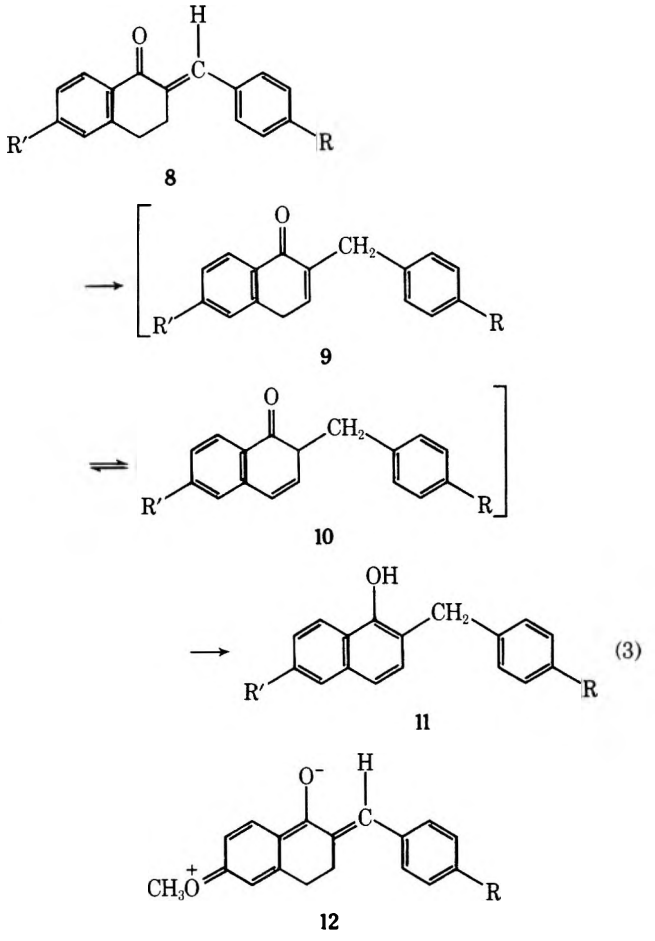
Introduction of CH_3 or Cl into the benzylidene moiety of **8** causes an effect similar to that noted in the diarylidenecyclohexanone series. The electropositive methyl group, which is expected to promote coordination of the carbonyl group and an exocyclic double bond to the iridium atom, enhances the reaction rate, and vice versa, electron-attracting chlorine atoms slow down the catalysis (see Table II). Substitution at C-6 position of the tetralone residue has a similar effect: 6-acetoxy-2-arylidene-1-tetralones react considerably slower than the corresponding unsubstituted 2-arylidene-1-tetralones (Table II). The reactivities of the 6-methoxy derivatives are, however, somewhat lower than expected and are not quite understood. It should be recalled that in the absence of a powerful driving force, $IrCl(CO)(PPh_3)_2$ is a very poor catalyst for exo- to endocyclic double bond migration in some alkylidenecycloalkanes.[24]

The kinetic curves for the $IrCl(CO)(PPh_3)_2$-catalyzed isoaromatization of the additional eight substituted arylidenetetralones listed in Table II resemble those shown in Figure 2. Induction periods of 40–60 min that precede the maximum rates are typical for all the tetralones. (In the dibenzylidenecyclohexanone series no measurable induction periods have been observed.)

Table II. Maximum Rates for $IrCl(CO)(PPh_3)_2$-Catalyzed Isoaromatization of 2-Arylidene-1-tetralones (% Consumption of 8 per min)[a]

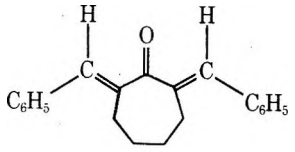
	R		
R′	CH_3	H	Cl
H	2.07	1.88	0.70
CH_3O	1.75	1.65	0.63
CH_3COO	1.20	0.92	0.20[b]

[a] Reaction conditions: 1 mmol of tetralone derivative and 10^{-2} mmol of catalyst in 0.5 mL of diphenyl ether at 255 °C. [b] The reaction seems to stop after 90 min.



Isomerization of (*E,E*)-2,7-Dibenzylidenecycloheptanone. Leonard et al.[25] reported the conversion of 2,7-dibenzylidenecycloheptanone (**13**) into 16% 2,7-dibenzyltropone (**15**) by 10% Pd/C catalyst in triethylene glycol at 280 °C. The starting ketone, **13**, is assumed to isomerize first to **14** and then, at the elevated temperature, to lose a molecule of hydrogen.

We were, however, unable to duplicate Leonard's experiments. We found instead that Pd/C[26] catalyzes hydrogen transfer from the glycol to **13** to give a mixture of the two isomeric 2,7-dibenzylcycloheptanones (**14**)[27] in almost quantitative yield.[28] Similar transfer hydrogenation is observed when the palladium catalyst is replaced by $IrCl(CO)(PPh_3)_2$ or by some other transition metal complexes.[29] When the reaction is conducted in boiling diphenyl ether or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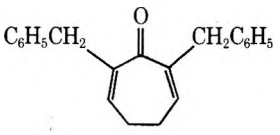
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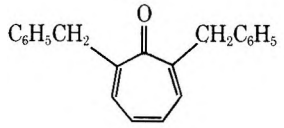
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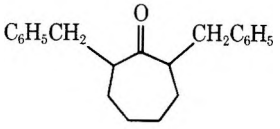
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in the absence of any solvent, neither double bond migration (to give **14** or **15**) nor transfer hydrogenation takes place. The iridium catalyst promotes merely *Z–E* interconversion of the exocyclic C=C bonds to give an equilibrium mixture of 66% *E,E*, 33% *E,Z*, and <1% *Z,Z* isomer **13**. In fact, the inability of $IrCl(CO)(PPh_3)_2$ to catalyze double bond migration in **13** is not unexpected. In contrast to the two previous systems, in which the conversion of the unsaturated ketones into aromatic phenols (or naphthols) is associated with a substantial gain in energy, there is no such driving force in **13** to cause introduction of exocyclic double bonds into the cycloheptanone ring. It is, however, remarkable that *Z–E* interconversion is *not* observed to any significant extent during isoaromatization of the above (*E,E*)-2,6-diarylidenecyclohexanones (reaction 1) and (*E*)-2-arylidene-1-tetralones (reaction 3); geometric isomerization is quite common in other $IrCl(CO)(PPh_3)_2$-catalyzed transformations of unsaturated systems (see, e.g., ref 24).

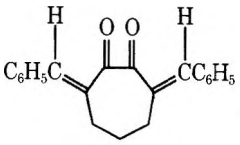
While (*Z,Z*)-**13** is found only in small amounts in the iridium(I)-catalyzed reaction mixture, it can be obtained in 55% yield (together with 40% of the *E,Z* compound) upon irradiation of (*E,E*)-**13** in EtOH for 4 h with a 450-W high-pressure mercury lamp.

The three isomeric 2,7-dibenzylidenecycloheptanones have essentially the same mass spectra;[30] however, their structures could easily be elucidated from their characteristic NMR. The resonances of both vinylic and aromatic protons of (*E,E*)-**13** coincide to give a broad singlet at 7.32 ppm.[31] The corresponding peaks of the *Z,Z* isomer appear at 6.62 and 7.19 ppm. The *E,Z* compound has a vinylic absorption at 6.44 ppm and two aromatic ones centered at 7.15 and 7.31 ppm. The second vinylic peak coincides with the aromatic resonance at 7.31 ppm. (Cf. the NMR of (*E,Z*)-2,5-dibenzylidenecyclopentanone[32].)

Each of the three isomers can be converted by $IrCl(CO)(PPh_3)_2$ (at 230 °C) into the above equilibrium mixture. The *Z,Z* compound undergoes also thermal isomerization and gives (*E,Z*)-**13** in the absence of the organometallic catalyst.

(*E,E*)-3,7-Dibenzylidenecycloheptane-1,2-dione. Unlike in the previous monoketone, migration of the exocyclic double bonds in **17** may result in formation of a pseudoaromatic compound. The gain in energy associated with the formation of the tropolone structure suffices to drive reaction 4 toward the right.

Continuous analysis of the reaction system by our standard methods (GLC and GLC–MS) proved difficult owing to the low mobility of the tropolone derivative on the GLC columns (see Experimental Section). We have partly overcome this difficulty by silylation of each sample withdrawn from the reaction mixture prior to injection but not without reducing the accuracy of the results. The qualitative results indicate that the features of reaction 4 resemble those of reactions 1 and 3 only in the initial period of the catalysis. As the catalysis proceeds two side reactions, viz., disproportionation[33] and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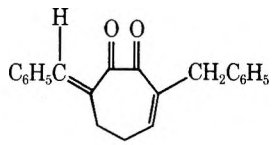
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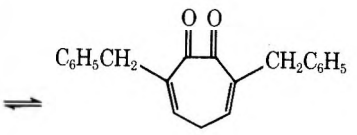
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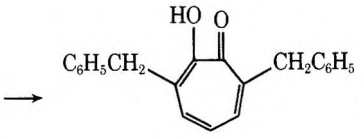
(4)

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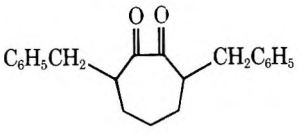
polymerization, become of importance. In a typical run the starting diketone **17** disappeared completely within 2 h, although the intermediate **18** was consumed only after a further 60 min. By that time the reaction mixture consisted of 40% 3,7-dibenzyltropolone (**20**), 30% 3,7-dibenzylcycloheptane-1,2-dione (**21**), and 30% resinous material. Before completion of the reaction two transient compounds of *m/e* 304 could be identified (not isolated) in the GLC–MS chromatogram. These are presumably the precursors **22** and **23** of the saturated diketone **21**.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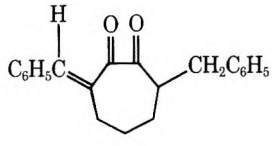
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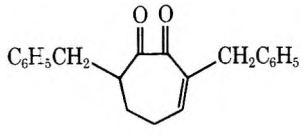
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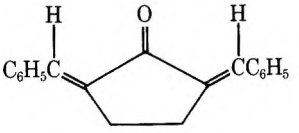
Aryl- and Alkylmethylenecyclopentanones. The reaction of (*E,E*)-2,5-dibenzylidenecyclopentanone (**24**) and Vaska's catalyst was compared with those of the unsaturated cyclohexanone, cycloheptanone, and cycloheptanedione derivatives. Inspection of the kinetic curves obtained at 230 °C (Figure 3) indicates that **24** was not isomerized over a period of 15 min. Then rapid conversion (19.5% min^{-1}) of **24** into the known 2-benzyl-6-benzylidenecyclopent-2-enone (**25**)[34,35] and polymeric material started. Formation of the semireduced compounds, 2-benzyl-5-benzylidenecyclopentanone (**27**) and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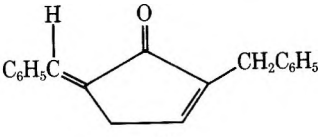
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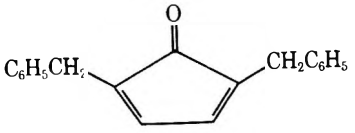
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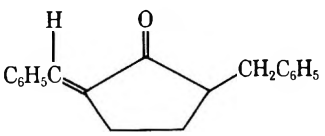
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Table III. Yields, Melting Points, and NMR Spectra of (*E,E*)-α,α′-Diarylidenecyclohexanones

Compd	Yield, %	Mp, °C	NMR, δ, ppm ($CDCl_3$)	Ref
1, R = C_6H_5; R′ = R″ = H	90	118	1.76 (m, 2), 2.92 (t-d, 4 *J* = 3 and 1 Hz), 7.35 (m, 10), 7.91 (br s, 2)	31, 45
1, R = 2-ClC_6H_4; R′ = R″ = H	47	110	1.80 (m, 2), 2.83 (t-d, 4 *J* = 3 and 1 Hz), 7.33 (m, 8), 7.70 (br s, 2)	46
1, R = 3-ClC_6H_4; R′ = R″ = H	81	106	1.80 (m, 2), 2.90 (t-d, 4 *J* = 3.5 and 1 Hz), 6.78–7.52 (m, 8), 7.73 (br s, 2)	*a*
11, R = 4-ClC_6H_4; R′ = R″ = H	80	147	1.77 (m, 2), 2.85 (t-d, 4 *J* = 3.5 and 1 Hz), 7.40 (AB q, 8), 7.70 (m, 2)	45, 46
1, R = 4-FC_6H_4; R′ = R″ = H	78	155–156	1.75 (q, 2 *J* = 3 Hz), 2.84 (t, 4 *J* = 3 Hz), 6.80–7.52 (m, 8), 7.71 (s, 2)	47
1, R = 4-$CH_3C_6H_4$; R′ = R″ = H	63	169–170	1.78 (m, 2), 2.37 (s, 6), 2.90 (t-d, 4 *J* = 3 and 1 Hz), 7.25 (AB q, 8), 7.77 (s, 2)	48
1, R = C_6H_5; R′ = CH_3; R″ = H	87	126	1.24 (d, 3 *J* = 4 Hz), 1.80 (m, 2), 2.96 (m, 2), 3.43 (m, 1), 7.28 (m, 10), 7.46 (s, 1), 7.63 (br s, 1)	49
1, R = 2-$CH_3OC_6H_4$; R′ = R″ = H	65	139–140	1.90 (m, 2), 2.92 (t-d, 4 *J* = 3 and 1 Hz), 3.91 (s, 6), 6.80–7.55 (m, 8), 7.98 (br s, 2)	*b*
1, R = 4-$CH_3OC_6H_4$; R′ = R″ = H	80	160	1.90 (q, 2 *J* = 3 Hz), 2.93 (t, 4 *J* = 3.5 Hz), 3.82 (s, 6), 7.18 (AB q, 8), 7.72 (br s, 2)	49
1, R = C_6H_5; R′ = H; R″ = $C(CH_3)_3$	40	145	0.95 (s, 9), 2.49 (d, 4 *J* = 6 Hz), 3.12 (d, 1 *J* = 6 Hz), 7.28 (m, 10), 7.63 (m, 2)	50
1, R = 1-$C_{10}H_7$; R′ = R″ = H	52	212[c]	1.60 (m, 2), 2.70 (t, 4 *J* = 3 Hz), 7.25–7.90 (m, 16)	7
1, R = 2-$C_{10}H_7$; R′ = R″ = H	50	150	1.60 (m, 2), 2.70 (t, 4 *J* = 3 Hz), 7.05–7.95 (m, 16)	*d*
1, R = 2-C_5H_3O; R′ = R″ = H	82	148	1.89 (m, 2), 3.18 (t, 4 *J* = 3 Hz), 6.41 (m, 4), 7.36 (br s, 4)	51
5	52	123	0.98 (s, 6), 2.76 (d, 4 *J* = 1.5 Hz), 7.42 (m. 10), 7.82 (br s, 2)	52, 53

[a] Anal. Calcd for $C_{20}H_{16}Cl_2O$: C, 70.0; H, 4.7; Cl, 20.7. Found: C, 69.7; H, 4.7; Cl, 20.7. [b] Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.0; H, 6.6. Found: C, 79.2; H, 6.4. [c] Lit.[7] mp 194–205 °C. [d] Anal. Calcd for $C_{28}H_{22}O$: C, 89.8; H, 5.9. Found: C, 89.5; H, 5.7.

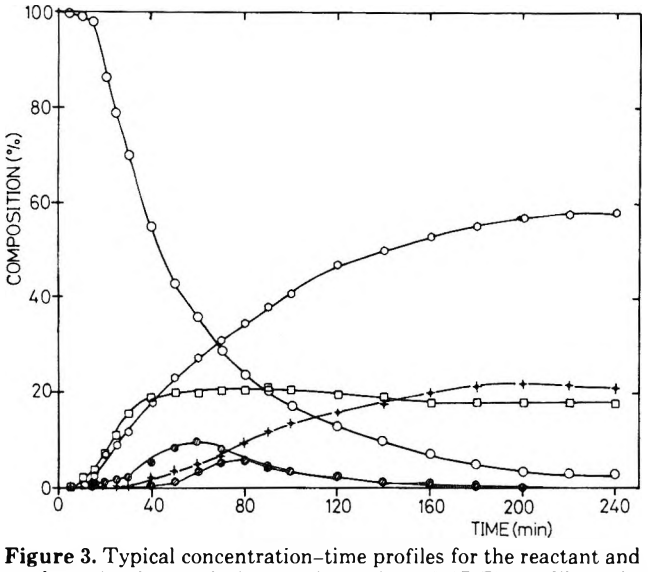
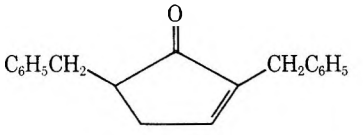


Figure 3. Typical concentration–time profiles for the reactant and products in the catalytic transformation of (*E,E*)-2,5-dibenzylidenecyclopentanone (**24**) (3.66 mmol) by $IrCl(CO)(PPh_3)_2$ (3.87 × 10^{-2} mmol) at 230 °C. ○, **24**; □, **25**; ✦, **28**; ⊛ and ⊛, $C_{19}H_{18}O$ isomers; ○, polymers.



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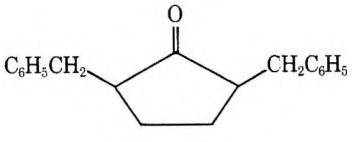

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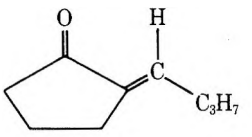
2,6-dibenzylcyclopent-2-enone (**28**),[35] became substantial only some 15 min later, but at rates which soon permit the concentration of **28** to surpass that of **25**.

It is interesting to note that none of the fully hydrogenated ketone **29** of *m/e* 264 was obtained in the catalysis, though it is easily accessible by $RuCl_2(PPh_3)_3$-promoted transfer hydrogenation of **22** in ethylene glycol.[28]

The internal diene **26** did not appear either in the GLC chromatogram. We assume, however, that it is formed as a transient compound and responsible for the formation of part of the polymers. Some support for this assumption could be found in an experiment in which **26** was trapped with benzyne. Diphenyliodonium 2-carboxylate (80 mg) was treated together with 200 mg of **24** and 6 mg of iridium catalyst for 90 min at 230 °C. Mass spectral analysis of the reaction mixture indicated the formation of an adduct of benzyne to **24** (probably rearranged) of *m/e* 336. No peak of this mass appeared in control experiments to which either no catalyst or no diphenyliodonium 2-carboxylate was added.

Since polymerization of **26** can account only for part of the isolated macromolecular product, the remaining part must arise from disproportionation of **24** and, at advanced stages of the catalysis, from the dibenzylcyclopentenone **28** (see Figure 3).

Competition between double bond migration and disproportionation seems to occur generally when methylenecyclopentanone derivatives are subjected to Vaska's catalyst. 2-Butenylidenecyclopentanone (**30**), e.g., yields 2-butylcyclopent-2-enone (**31**) and 2-butylcyclopentanone (**32**) in a ratio 5:4 when 1 mmol is refluxed for 3.5 h with 10^{-2} mmol of catalyst. Prolonged heating causes some deterioration of the cyclopentenone derivative **31**. The facile separation of **31** and **32** on $AgNO_3$-activated Florisil provides thus a convenient route to **31** and to other valuable precursors for jasmone-like plant inhibitors[36] recently synthesized in our department.[37]



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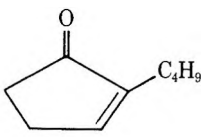

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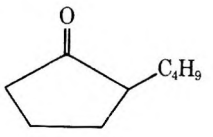

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Table IV. GLC Separation of Starting Material, Reaction Intermediates, and Products of Reaction 1

R	R′	R″	Column and conditions[a]	Retention time, min 1	2	3	4
4-FC_6H_4	H	H	A	11.5	10.0	9.6	8.3
3-ClC_6H_4	H	H	A	16.6	14.4	13.1	10.5
4-ClC_6H_4	H	H	A	16.6	14.4	13.0	9.9
4-$CH_3C_6H_4$	H	H	B	23.2	19.5	18.7	16.5
2-$CH_3OC_6H_4$	H	H	C	14.3	9.7	*b*	6.4
4-$CH_3OC_6H_4$	H	H	B	20.5	17.8	17.1	15.0
2-Furyl	H	H	C	7.5	4.5	*b*	2.7
C_6H_5	CH_3	H	C	3.8	2.5	*b*	2.0
C_6H_5	H	$C(CH_3)_3$	C	5.5	3.5	*b*	2.4

[a] A, 3.16 × 2000 mm stainless steel column packed with 5% OV-101 on 60–80 mesh Chromosorb W, operated between 200 and 285 °C programmed to 6 °C/min, initial hold 1 min, carrier gas (N_2) 30 mL/min, injector and detector temperature 305 °C. B, column as A operated between 200 and 290 °C programmed to 5 °C/min. C, 6.32 × 500 mm copper column packed with 15% SE-30 on 60–80 mesh Chromosorb W, 180 °C, injector and detector 300 °C, carrier gas (He) 50 mL/min. [b] Under these conditions 2 and 3 are not separated.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not correlated. Infrared spectra were measured with either Perkin-Elmer Models 137 or 257 spectrophotometers. Ultraviolet spectra were obtained on a Unicam SP-800 spectrophotometer. Proton magnetic resonance spectra were run using Varian T-60, EM-360, and HA-100 spectrometers. Mass spectra were recorded with a Varian MAT-311 spectrometer or directly from a gas chromatograph using a Varian MAT-111 instrument.[30] Preparative gas-liquid phase chromatography was performed with Aerograph 90-P, Varian 920, and F & M 720 instruments. Analytical GLC was performed with a Packard 4700 (800 series) instrument.

The catalysts $RuCl_2(PPh_3)_3$,[38] $RhCl(PPh_3)_3$,[39] and $IrCl(CO)(PPh_3)_2$[40] were prepared as previously described.

(*E,E*)-α,α′-Diarylidenecyclohexanones[32,41–45] were prepared by the following general procedure. A mixture of 0.2 mol of freshly distilled aldehyde, 9.8 g (0.1 mol) of cyclohexanone, 12 g of NaOH, 100 mL of EtOH, and 50 mL of water was stirred vigorously for 4 h. Water was added and the unsaturated ketone was recrystallized from MeOH. The yields and physical data of the products are given in Table III.[30]

***Z–E* Isomerization of (*E,E*)-2,6-Diarylidenecyclohexanones.** Photoisomerization of the above *E,E* isomers to the corresponding *E,Z* and *Z,Z* compounds was accomplished by irradiation of the methanolic solutions with a Hanovia 450-W UV lamp through quartz essentially as described for (*E*)-2-benzylidenecyclohexanone.[4] The conditions described by George and Roth[32] for (*E,E*)-2,5-dibenzylidenecyclopentanone led to polymers in the cyclohexanone series.

Rearrangement of (*E,E*)-2,6-Diarylidenecyclohexanones to Phenols. A. In a typical experiment a mixture of 10.0 g (3.65×10^{-2} mol) of **1**, R = C_6H_5; R′ = R″ = H, and 100 mg (1.28×10^{-4} mol) of $IrCl(CO)(PPh_3)_2$ was heated under N_2 at 250 °C for 2 h. Distillation afforded 7.6 g (76%) of 2,6-dibenzylphenol: bp 210 °C (3 mm); mp 30 °C;[10] ν_{OH} 3560 cm^{-1}; UV max (EtOH) 280 nm (ε 2000); NMR ($CDCl_3$) δ 3.95 (s, 4), 6.98 ppm (m, 14).

The same result was obtained when the reaction was conducted at ambient atmosphere.

B. A modified reaction tube equipped with gas inlet and outlet was immersed in a thermostat at 250 °C and charged (under N_2) with 500 mg (1.82×10^{-3} mol) of ketone **1**, R = C_6H_5; R′ = R″ = H, 1 mL of freshly chromatographed diphenyl ether (Al_2O_3), and a small amount of *n*-$C_{28}H_{58}$ (internal standard for GLC analysis). After 20 min, 25 mg (3.2×10^{-5} mol) of $IrCl(CO)(PPh_3)_2$ was added at once. Samples (1–2 μL) were withdrawn and immediately frozen (−20 °C) every 5 min for the first 40 min, and every 10 min thenceforth. GLC analysis was performed on a 3.16 × 2000 mm stainless steel column packed with 5% OV-101 on 60–80 mesh Chromosorb W, operated between 200 and 285 °C programmed to 6 °C/min, initial hold 1 min, carrier gas (N_2) 30 mL/min, injector and detector temperature 305 °C. The compounds having retention times of 8.2, 9.5, 10.0, and 11.6 min proved to be **4**, **3**, **2**, and **1** (R = C_6H_5; R′ = R″ = H), respectively.

2-Benzyl-6-benzylidenecyclohex-2-enone (**2**, R = C_6H_5; R′ = R″ = H) was isolated by preparative GLC as a viscous liquid: UV max (MeOH) 290 nm (ε 6850); NMR ($CDCl_3$) δ 1.86–2.96 (m, 4), 3.66 (s, 2), 6.64 (m, 1), 7.24–7.61 ppm (m, 11). Anal. Calcd for $C_{20}H_{18}O$: C, 87.6; H, 6.6. Found: C, 87.7; H, 6.6.

Attempts to isolate phenol-free 2,6-dibenzylcyclohexa-2,5-dienone (**3**, R = C_6H_5; R′ = R″ = H) were unsuccessful. The NMR spectrum of the impure endocyclic diene (that had correct elemental analysis) confirmed, however, the proposed structure: ($CDCl_3$) δ 3.47 (br s, 2 diallylic), 3.70 (br s, 4 benzylic), 6.78 (s, 2 vinylic), 7.20 ppm (m, 10 aromatic).

Substituted 2,6-dibenzylidenecyclohexanones were isomerized to the corresponding phenols[53] and reaction intermediates as described for **1**, R = C_6H_5; R′ = R″ = H. The sequence of peaks in the gas–liquid chromatograms parallels that of the unsubstituted compound as shown in Table IV.

The isoaromatization experiments were repeated in the absence of diphenyl ether at 230 °C. All control experiments without $IrCl(CO)(PPh_3)_2$ gave negative results.

2-Benzyl-6-benzylidene-4,4-dimethylcyclohex-2-enone (6) and 2,6-dibenzyl-4,4-dimethylcyclohexa-2,5-dienone (7) were obtained by heating a mixture of 2×10^{-2} mol of **5**, 10^{-4} mol of $IrCl(CO)(PPh_3)_2$, and 10 mL of Ph_2O for 24 h under N_2 at 250 °C. Separation of the isomers was afforded by a 0.5-m long GLC column packed with 15% SE-30 on 60–80 mesh Chromosorb W operated at 180 °C. The first compound, having retention time 170 s, was **7**: $\nu_{C=O}$ 1675 cm^{-1}; UV max (EtOH) 290 nm (ε 10^4); NMR ($CDCl_3$) δ 1.12 (s, 6), 3.61 (s, 4), 6.57 (s, 2), 7.14–7.26 ppm (m, 10). Anal. Calcd for $C_{22}H_{22}O$: C, 87.4; H, 7.3. Found: C, 87.2; H, 7.1. The intermediate **6**, retention time 270 s; $\nu_{C=O}$ 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (s, 3), 0.97 (s, 3), 2.76 (d, 2 *J* = 2 Hz), 3.59 (s, 2), 6.38 (s, 1), 7.12–7.66 ppm (m, 11). Anal. Calcd for $C_{22}H_{22}O$: C, 87.4; H, 7.3. Found: C, 87.3; H, 7.0.

(*E*)-2-Benzylidene-1-tetralone (8, R = R′ = H), mp 105–106 °C;[54] **(*E*)-2-(*p*-chlorophenylmethylene)-1-tetralone (8, R = Cl; R′ = H)**, mp 137 °C;[55] and **(*E*)-2-benzylidene-6-methoxytetralone (8, R = H; R′ = OCH_3)**, mp 97–98 °C,[56] were prepared as described in the literature.

(*E*)-2-(*p*-Methylphenylmethylene)-1-tetralone (8, R = CH_3, R′ = H) was obtained by stirring a solution of 7.3 g (0.05 mol) of 1-tetralone and 6 g (0.05 mol) of *p*-tolualdehyde in 50 mL of 4% ethanolic KOH for 2 h. Acidification (AcOH) and dilution with water afforded 11.2 g (90%) of yellow plates: mp 123 °C (from aqueous EtOH); $\nu_{C=O}$ (Nujol) 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.41 (s, 3), 3.04 (m, 4), 7.13–7.57 (m, 7), 7.87 (br s, 1), 8.14 ppm (d-d, 1, $J_{6,8}$ = 2.5 and $J_{7,8}$ = 7 Hz). Anal. Calcd for $C_{18}H_{16}O$: C, 87.1; H, 6.5. Found: C, 87.2; H, 6.2.

(*E*)-2-(*p*-Methylphenylmethylene)-6-methoxy-1-tetralone (8, R = CH_3; R′ = OCH_3) was obtained in the same manner: pale yellow needles, mp 133 °C; $\nu_{C=O}$ (Nujol) 1653 cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3), 3.03 (m, 4), 3.87 (s, 3), 6.70–7.42 (m, 6), 7.82 (t, 1, *J* = 1.5 Hz), 8.12 ppm (d, 1, $J_{7,8}$ = 8 Hz). Anal. Calcd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5. Found: C, 82.2, H, 6.5.

(*E*)-2-(*p*-Chlorophenylmethylene)-6-methoxy-1-tetralone (8, R = Cl; R′ = OCH_3) from 6-methoxy-1-tetralone and *p*-chlorobenzaldehyde: pale yellow needles, mp 123 °C; $\nu_{C=O}$ (Nujol) 1645 cm^{-1}; NMR ($CDCl_3$) δ 3.00 (m, 4), 3.88 (s, 3), 6.68–7.42 (m, 6), 7.80 (t, 1, *J* = 1 Hz), 8.15 ppm (d, 1, $J_{7,8}$ = 8 Hz). Anal. Calcd for $C_{18}H_{15}ClO_2$: C, 72.4; H, 5.0; Cl, 11.9. Found: C, 72.2; H, 5.2; Cl, 12.1.

(*E*)-6-Acetoxy-2-arylidene-1-tetralones. The following general procedure was applied. A mixture of 0.05 mol of 6-hydroxy-1-tetralone (prepared from 6-methoxy-1-tetralone according to Haberland[57]),

Table V. GLC Separation of 2-Arylidene-1-tetralones, 2-Arylmethyl-1-naphthols, and the Corresponding 2-Arylmethyl-1-tetralones

R	R′	Column and conditions[a]	Retention time, min: 8	11	2-Arylmethyl-1-tetralone	Registry no.
H	H	D	17.5	16.3	14.4	27019-08-5
CH_3	H	E	18.1	16.8	15.0	62085-78-3
Cl	H	F	11.8	10.7	9.5	62085-79-4
H	OCH_3	G	20.7	19.3	17.7	62085-80-7
CH_3	OCH_3	G	23.4	21.3	19.9	62085-81-8
Cl	OCH_3	H	14.1	12.3	12.0	62085-82-9
H	$OCOCH_3$	G	22.1	21.5	19.3	62085-83-0
CH_3	$OCOCH_3$	I	20.7	19.5	17.1	62085-84-1
Cl	$OCOCH_3$	J	18.7	16.0	*b*	

[a] D, 6.32 × 2600 mm glass column packed with 30% SE-30 on Chromosorb W (AW), operated between 190 and 275 °C, programmed to 3 °C/min, initial hold 2 min, injector and detector temperature 300 °C, carrier gas (N_2) 40 mL/min. E, as for D, temperature increase programmed to 4 °C/min. F, 6.32 × 2600 mm glass column 3% SE-30 on Gaschrom Q, operated between 190 and 270 °C, initial hold 1 min, other conditions as for D. G, as E, initial hold 1 min. H, as F, column temperature 200–270 °C. I, as E, column temperature 210–275 °C. J, as D, column temperature 219–285 °C, programmed to 5 °C/min. [b] No reduction product formed.

0.05 mol of the appropriate benzaldehyde, and 50 mL of Triton B (40% in MeOH) was refluxed for 4 h. The reaction mixture was acidified to pH 5 with AcOH and diluted with water. Extraction with $CHCl_3$ and evaporation of the solvent afforded almost pure 2-arylidene-6-hydroxy-1-tetralone. The crude ketone was dissolved in 15 mL of dry pyridine; 10 mL of acetic anhydride was added and the mixture was allowed to stand at room temperature for 24 h. The solvents were evaporated in vacuo and the crystalline residue was recrystallized from aqueous EtOH. The yields of the acetoxytetralone derivatives were 90–92%.

(*E*)-6-Acetoxy-2-benzylidene-1-tetralone (8, R = H; R′ = $OCOCH_3$): mp 109–110 °C; $\nu_{C=O}$ (Nujol) 1752, 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (s, 3), 3.03 (m, 4), 7.03 (s, 1), 6.9–7.4 (m, 6), 7.87 (br s, 1), 8.19 ppm (d, 1, $J_{7,8}$ = 9 Hz). Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.1; H, 5.5. Found: C, 78.1; H, 5.4.

(*E*)-6-Acetoxy-2-(*p*-methylphenylmethylene)-1-tetralone (8, R = CH_3; R′ = $OCOCH_3$): mp 122 °C; $\nu_{C=O}$ (Nujol) 1750, 1655 cm^{-1}; NMR ($CDCl_3$) δ 2.31 (s, 3), 2.39 (s, 3), 3.03 (m, 4), 7.00 (s, 1), 7.05–7.32 (m, 5), 7.83 (br s, 1), 8.14 ppm (d, 1, $J_{7,8}$ = 9 Hz). Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.5; H, 6.0.

(*E*)-Acetoxy-2-(*p*-chlorophenylmethylene)-1-tetralone (8, R = Cl; R′ = $OCOCH_3$): mp 142–143 °C; $\nu_{C=O}$ (Nujol) 1755, 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (s, 3), 3.02 (m, 4), 6.85–7.40 (m, 6), 7.80 (s, 1), 8.17 ppm (d, 1, $J_{7,8}$ = 8.5 Hz). Anal. Calcd for $C_{19}H_{15}ClO_3$: C, 69.8; H, 4.6; Cl, 10.9. Found: C, 69.5; H, 4.90; Cl, 11.2.

Isoaromatization of 2-Arylidene-1-tetralones. In a typical example 2.48 g (10^{-2} mol) of 8 (R = CH_3; R′ = H), 7.8 mg (10^{-4} mol) of $IrCl(CO)(PPh_3)_2$, and 5 mL of freshly purified diphenyl ether was gently refluxed (bath temperature 260 °C) for 2 h. The reaction mixture was cooled, diluted with benzene, and chromatographed over silica gel (70–230 mesh). Using benzene as eluent there was obtained 2.01 g (81%) of colorless **11** (R , CH_3; R′ = H): mp 66–67 °C (from cyclohexane); ν_{OH} (Nujol) 3290–3350 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (s, 3), 4.66 (s, 2), 5.20 (s, 1), 7.15–8.22 ppm (m, 10). Anal. Calcd for $C_{18}H_{16}O$: C, 87.1; H, 6.5. Found: C, 86.9; H, 6.3.

Attempts to purify the naphthol derivatives by extraction into aqueous alkali led in general to deterioration of the product.

Reaction rate measurements were followed by GLC analyses. The experimental conditions and retention times are listed in Table V.

(*E,E*)-2,7-Dibenzylidenecycloheptanone (13) was obtained in 78% yield according to Cornubert et al.:[58] mp 108 °C; $\nu_{C=O}$ (CCl_4) 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.94 (m, 4), 2.66 (m, 4), 7.32 ppm (m, 12).[31]

Isomerization of (*E,E*)-13. A. By Photolysis. A solution of 1.2 g of the above ketone in 300 mL of absolute EtOH was irradiated under N_2 through quartz with a Hanovia 450-W high-pressure mercury lamp. After 4 h the solution was concentrated and separated on a 2-m long column packed with 3% OV-101 on 60–80 mesh Chromosorb W operated between 150 and 285 °C, programmed to a 6 °C increase/min, initial hold 1 min, injector 305 °C, gas flow (N_2) 38 mL/min. The retention times (and yield) for the *E,E*, *E,Z*, and *Z,Z* isomers were 1160 (5%), 1060 (40%), and 997 s (55%), respectively. NMR of *E,Z* isomer ($CDCl_3$) δ 1.91 (m, 4), 2.43 (m, 2), 2.71 (m, 2), 6.44 (s, 1), 7.05–7.40 ppm (m, 11). NMR of *Z,Z* isomer ($CDCl_3$) δ 1.90 (m, 4), 2.70 (m, 4), 6.62 (s, 2), 7.19 ppm (m, 10). The mass spectra of the three isomers proved to be identical (see ref 30), *m/e* 288 (M^+·).

B. By $IrCl(CO)(PPh_3)_2$. A mixture of 576 mg (2×10^{-3} mol) of **13** and 10 mg (1.28×10^{-5} mol) of the iridium catalyst was heated under N_2 with the aid of a thermostat at 230 °C. GLC analysis on 3% OV-101 inicated that after 7 min an equilibrium mixture of 66% (*E,E*)-, 33% (*E,Z*)-, and 0.9% (*Z,Z*)-**13** resulted. The three isomers were directly compared with the corresponding compounds from the above photolysis. The same results were obtained when 1 mL of Ph_2O was added to the reaction mixture.

On repetition of the reaction with either the *E,Z* or the *Z,Z* compounds (for 30 min) the same mixture of isomers resulted.

Transfer Hydrogenation of 13. Under the exact conditions described by Leonard et al.[25] for the *isomerization–aromatization* of 2,7-diarylidenecycloheptanone, a mixture of 806 mg (2.8 mmol) of **13**, 500 mg of 10% Pd/C,[26] and 25 mL of triethylene glycol was refluxed for 30 min. Column chromatography on alumina afforded 695 mg (85%) of (*E*)- and (*Z*)-2,7-dibenzylcycloheptanone (**16**) identical with a sample prepared from **13** according to Irvine et al.:[27] *m/e* 292 (M^+·); NMR ($CDCl_4$) δ 1.70 (m, 8), 2.4–3.6 (m, 6), 7.0–7.5 ppm (m, 10). No 2,7-dibenzyltropone (**16**) (prepared for comparison by dehydrobromination of 2,7-dibromobenzylcycloheptanone[25]) was obtained in this and in similar[26] experiments.

(*E,E*)-3,7-Dibenzylidenecycloheptane-1,2-dione (17) was obtained in two steps from cycloheptanone:[59] mp 191–193 °C (from acetone); $\nu_{C=O}$ ($CHCl_3$) 1683 cm^{-1}; NMR ($CDCl_3$) δ 2.14 (m, 2), 2.90 (t, 4 *J* = 3 Hz), 7.40 (s, 10), 7.86 (s, 2); mol wt 302 (mass spectrum).[30]

Isomerization and Disproportionation of 17. Each of 15 reaction tubes was charged with 121 mg (4×10^{-4} mol) of **17** and 3 mg (3.9×10^{-6} mol) of $IrCl(CO)(PPh_3)_2$ and heated at 230 °C. One tube was removed from the thermostat after 2, 5, 10, 15, 20, 30, 40, 60, 80, 100, 120, 150, 180, 210, and 240 min. Each was treated with 5 mL of dry THF, 2.5 mL of hexamethyldisilazane, and 50 μL of trimethylsilyl chloride, and heated at 55 °C for 30 min. The ammonium chloride was allowed to precipitate. The clear solution was then analyzed on a 2-m long column packed with 3% OV-101 on Chromosorb W, operated between 200 and 285 °C, 6 °C increase/min, initial hold 1 min, injector temperature 300 °C, gas flow 35 mL/min. The peaks observed at the initial stages of the reaction (<100 min) were the starting diketone **17** (retention time 13.6 min), the silylized 3,7-dibenzyltropolone (11.5 min), (*E*)- and (*Z*)-3,7-dibenzylcycloheptane-1,2-dione (**21**) (7.5 and 10.4 min) of *m/e* 306 (M^+·), and a small peak (12.2 min) of *m/e* 302, presumably **18**, and two of *m/e* 304 (10.9 and 12.8 min) attributed to compounds **22** and **23**. After 2 h the only compounds detectable by GLC were **21** (30%) and the silylized tropolone derivative (40%).

When the reaction mixtures were not silylized **20** was fully absorbed on the GLC column.

Isolation of **20** by extraction of the reaction mixture with $CHCl_3$ followed by fractional crystallization from MeOH was associated with substantial losses. The tropolone proved identical with an authentic sample:[59] IR (CH_3Cl) 2990 and 1605 cm^{-1};[59] mass spectrum (70 eV, 120 °C) *m/e* (rel intensity) 302 (100, M^+), 195, (20), 193 (8), 183 (12), 181 (8), 165 (18), 152 (7), 91 (24).

(*E,E*)-2,5-Dibenzylidenecyclopentanone (24): 90%; mp 190 °C;[31]

$\nu_{C=O}$ (KBr) 1695 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (s, 4), 7.46 (m, 10), 7.60 ppm (m, 2).[31,32]

Catalytic Transformations of 24 by $IrCl(CO)(PPh_3)_2$. As described for **1**, 952 mg (3.7 mmol) of **24**, 30 mg (3.9×10^{-2} mmol) of $IrCl(CO)(PPh_3)_2$, and tetracosane (internal standard) were heated at 230 °C, and samples withdrawn from the reacting mixture. GLC analysis was best carried out on a 6.32 × 2600 mm glass column packed with 3% SE-30 on Chromosorb Q operated between 190 and 255 °C, 4 °C increase/min. The reaction profiles of the products[35] are shown in Figure 3.

The various isomers of 2-benzyl-5-benzylidene- and 2,5-dibenzylcyclopentanone (**27** and **29**, respectively) were prepared by partial and complete transfer hydrogenation of **24** in the presence of $RuCl_2(PPh_3)_3$ and ethylene glycol as described for the reduction of diarylidenecyclohexanones.[13,29]

2-Butylidenecyclopentanone (**30**, 400 mg, 2.90 mmol) reacted with $IrCl(CO)(PPh_3)_2$ (20 mg, 2.58×10^{-2} mmol) at reflux temperature. The products were analyzed on a 2-m long column packed with 10% Carbowax on Chromosorb W operated between 70 and 170 °C, 6 °C increase/min.

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Registry No.—**1** (R = R′ = R″ = H), 62085-85-2; **2** (R = R′ = R″ = H), 62085-86-3; **2** (R = C_6H_5; R′ = R″ = H), 62085-87-4; **2** (R = 4-FC_6H_4; R′ = R″ = H), 62085-88-5; **2** (R = 3-ClC_6H_4; R′ = R″ = H), 62085-89-6; **2** (R = 4-ClC_6H_4; R′ = R″ = H), 62085-50-1; **2** (R = 4-$CH_3C_6H_4$; R′ = R″ = H), 62085-51-2; **2** (R = 2-$CH_3OC_6H_4$; R′ = R″ = H), 62085-52-3; **2** (R = 4-$CH_3OC_6H_4$; R′ = R″ = H), 62085-53-4; **2** (R = 2-furyl; R′ = R″ = H), 62085-54-5; **2** (R = Ph; R′ = CH_3; R″ = H), 62085-55-6; **2** (R = Ph; R′ = H; R″ = $C(CH_3)_3$), 62085-56-7; **3** (R = R′ = R″ = H), 62085-57-8; **3** (R = Ph; R′ = R″ = H), 62085-58-9; **3** (R = 4-FC_6H_4; R′ = R″ = H), 62085-59-0; **3** (R = 3-ClC_6H_4; R′ = R″ = H), 62085-60-3; **3** (R = 4-ClC_6H_4; R′ = R″ = H), 62085-61-4; **3** (R = 4-$CH_3C_6H_4$; R′ = R″ = H), 62085-62-5; **3** (R = 2-$CH_3OC_6H_4$; R′ = R″ = H), 62085-63-6; **3** (R = 4-$CH_3OC_6H_4$; R′ = R″ = H), 62085-64-7; **3** (R = furyl; R′ = R″ = H), 62085-65-8; **3** (R = Ph; R′ = CH_3; R″ = H), 62085-66-9; **3** (R = Ph; R′ = H; R″ = $C(CH_3)_3$), 62085-67-0; **4** (R = R′ = R″ = H), 576-26-1; **4** (R = Ph; R′ = R″ = H), 47157-01-7; **4** (R = 4-FC_6H_4; R′ = R″ = H), 62085-68-1; **4** (R = 3-ClC_6H_4; R′ = R″ = H), 62126-69-6; **4** (R = 4-ClC_6H_4; R′ = R″ = H), 31480-69-0; **4** (R = 4-$CH_3C_6H_4$; R′ = R″ = H), 51866-65-0; **4** (R = 2-$CH_3OC_6H_4$; R′ = R″ = H), 53376-41-3; **4** (R = 4-$CH_3OC_6H_4$; R′ = R″ = H), 53376-42-4; **4** (R = 2-furyl; R′ = R″ = H), 15341-61-4; **4** (R = Rh; R′ = Me; R″ = H), 4732-03-0; **4** (R = Ph; R′ = H; R″ = $C(CH_3)_3$), 53376-43-5; **6**, 62085-34-1; **7**, 53376-46-8; **8** (R = R′ = H), 57558-64-2; **8** (R = Me; R′ = H), 59082-26-7; **8** (R = Cl; R′ = H), 59082-24-5; **8** (R = H; R′ = OMe), 50558-94-6; **8** (R = CH_3; R′ = OMe), 62085-35-2; **8** (R = Cl; R′ = OMe), 62085-36-3; **8** (R = H; R′ = $OCOCH_3$), 62085-37-4; **8** (R = CH_3; R′ = $OCOCH_3$), 62085-38-5; **8** (R = Cl; R′ = $OCOCH_3$), 62085-39-6; **11** (R = R′ = H), 36441-32-4; **11** (R = CH_3; R′ = H), 62085-40-9; **11** (R = Cl; R′ = H), 62085-41-0; **11** (R = H; R′ = OMe), 62085-42-1; **11** (R = CH_3; R′ = OMe), 62085-43-2; **11** (R = Cl; R′ = OMe), 62085-44-3; **11** (R = H; R′ = $OCOCH_3$), 62085-45-4; **11** (R = CH_3; R′ = $OCOCH_3$), 62085-46-5; **11** (R = Cl; R′ = $OCOCH_3$), 62085-47-6; (*E,E*)-**13**, 62085-48-7; (*E,Z*)-**13**, 62085-49-8; (*Z,Z*)-**13**, 62085-25-0; (*Z*)-**16**, 34403-31-1; (*E*)-**16**, 34410-06-5; **17**, 62085-26-1; **18**, 62085-27-2; (*Z*)-**21**, 62085-28-3; (*E*)-**21**, 62085-29-4; **22**, 62085-30-7; **23**, 62085-31-8; **24**, 34611-43-3; **25**, 62085-32-9; **28**, 23923-54-8; $IrCl(CO)(PPh_3)_2$, 14871-41-1; 1-tetralone, 529-34-0; *p*-tolualdehyde, 104-87-0; 6-methoxy-1-tetralone, 1078-19-9; *p*-chlorobenzaldehyde, 104-88-1; 6-hydroxy-1-tetralone, 3470-50-6; cycloheptanone, 502-42-1; trimethylsilyl-3,7-dibenzyltropolone, 62085-33-0.

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Mass Spectrometric Fragmentation of Some Arylidenecycloalkanones

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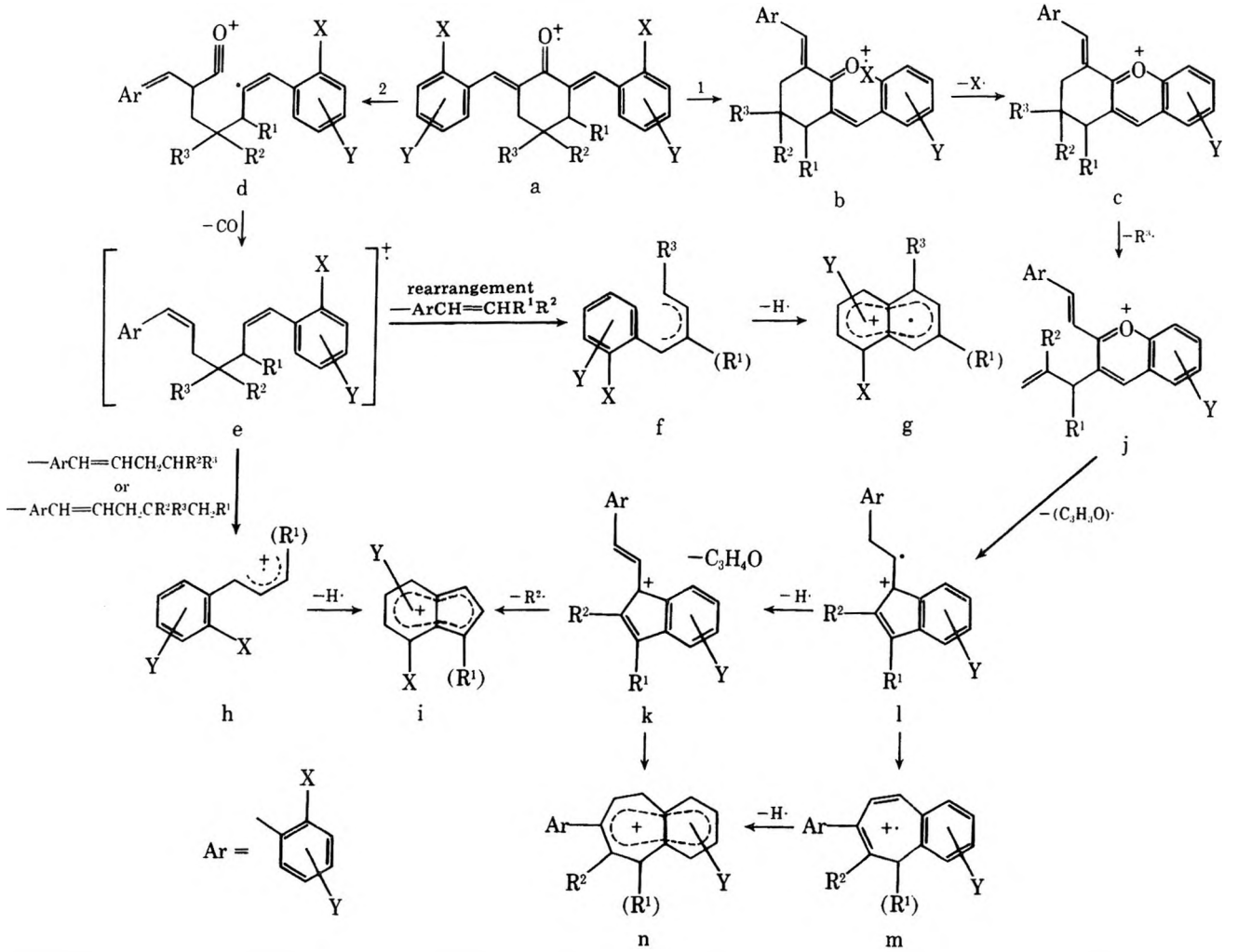
The mass spectra of (*E,E*)-α,α'-dibenzylidenecyclopentanone, -hexanone, -heptanone, and (*E*)-2-benzylidene-1-tetralone are reported. The main feature in these spectra is *E–Z* isomerization of the parent ions followed by production of stable benzopyrilium ions. A competing but less important fragmentation mode involves α-cleavage and CO extrusion as initial steps. The latter route dominates in the mass spectrum of (*E,E*)-3,5-dibenzylidenetetrahydro-4*H*-pyran-4-one. The mass spectrum of (*E,E*)-3,7-dibenzylidenecycloheptane-1,2-dione differs from that of the lower cyclohexanone derivative only by M and M − CO ions. At 70 eV benzopyrilium ion formation is virtually independent of the electronic nature of the benzylidene moieties, but is promoted by electron-donating groups and reduced by electron-attracting substituents attached to the fused aromatic ring in 2-arylidene-1-tetralones.

In the course of our study on $IrCl(CO)(PPh_3)_2$-catalyzed isomerization, isoaromatization, and disproportionation of arylidenecycloalkanones,[1] we found that the mass spectra of these ketones may be utilized not only for unequivocal location of the double bonds, but also as a convenient method for estimation of the exo- to endocyclic C=C bond migration in these systems.

The mass spectrum of (*E,E*)-2,6-dibenzylidenecyclohexanone (1) has been reported previously by Smith, Dimmock, and Turner.[2] The present investigation extends this study to include various substituted diarylidenecyclohexanones and arylidene derivatives of other cyclic structures.

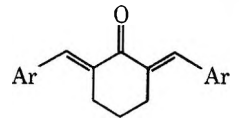
General fragmentation patterns for (*E,E*)-2,6-diarylidenecyclohexanones are suggested in Scheme I, and the

Scheme I[a]

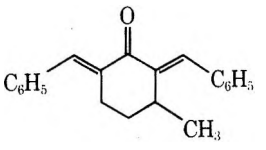


[a] The fragments shown correspond only to the most intense peaks of the 70-eV spectra. Usually no attempts were made to evaluate peaks of relative intensities lower than 5%

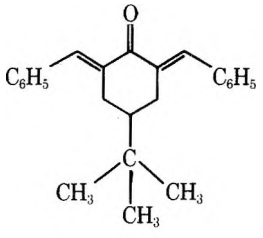
masses and relative intensities of the principal fragments are assembled in Table I. The most significant fragment in route 1 is the benzopyrilium ion (c), formed by initial *E* to *Z* isomerization of at least one arylidene group (a → b) followed by an intramolecular substitution that involves the ortho function X of the aryl moiety. The *E*–*Z* transformation is temperature dependent, as shown, e.g., by an increase in the (M − 1)/M ratio in **6** from 1.0 to 1.4 upon raising the source temperature from 70 to 130 °C. Cleavage of the α bond to the carbonyl followed by CO extrusion and McLafferty rearrangement (route 2, a → d → e, etc.) ("normal" cyclohexanone fragmentation[3]) is usually less pronounced than fragmentation 1 or even completely absent (e.g., in ortho-substituted benzylidenecyclohexanones). A semiquantitative measure for the relative amount of fragmentation by either route is given by the ratio of ion abundances h/i, since i is formed by both routes and h only by route 2. Compounds that cleave predominantly via benzopyrilium ion have small h peaks, while those that follow mainly the decarbonylation pathway have large ones. (See, e.g., the spectrum of **13** below.)



1, Ar = C_6H_5
2, Ar = *p*-$CH_3C_6H_4$
3, Ar = *o*-$CH_3OC_6H_4$
4, Ar = *p*-$CH_3OC_6H_4$
5, Ar = *o*-ClC_6H_4
6, Ar = *m*-ClC_6H_4
7, Ar = *p*-ClC_6H_4
11, Ar = 2-$C_{10}H_7$
12, Ar = 2-C_4H_3O



8



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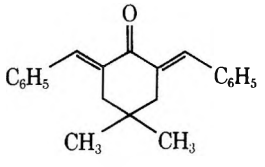
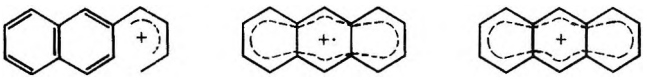


10

Although the formation of the relatively stable ion c is associated with intramolecular aromatic substitution, the data given in Table I indicate no Hammett-like correlation. E.g., both the electron-attracting Cl and the electron-donating OCH_3 cause the (M − X)/M ratio to be larger than that obtained by introduction of a CH_3 group. In fact this is not unexpected as previous studies[4,5] have shown that at 70 eV (M − fragment)/M is not an exact reflection of the formation of the two ions. With the exception of the anisyl derivative **4**, 1 < (M − 1)/M > 2 at 70 °C and 70 eV. The parent ion M in the spectrum of **4** is somewhat less abundant than M − 1. Smith et al.[2] suggested two possible explanations for the low (M − 1)/M ratio in the spectrum of the related 2-(*p*-dimethylaminophenylmethylene)cyclohexanone: (a) The stabilizing effect of the electron-donating group on the parent ion is making the attack of the carbonyl oxygen onto the aromatic ring less favored. (b) Charge location on either of the heteroatoms may stabilize pseudoquinone structures which do not tend to undergo much further fragmentations. Neither of these suggestions can be employed in our system. Compound **2**, e.g., which has an electron-donating CH_3 group, exhibits the highest (M − 1)/M ratio recorded, and the fragmentation of methoxyl containing **4** is not less than that of unsubstituted **1**.

When one ortho position in each aromatic ring in **1** is substituted by either electronegative Cl or electropositive OCH_3, elimination of the substituents, rather than the ortho hydrogen atom, takes place. The ortho-substituted compounds undergo very little fragmentation and the abundance of any but the benzopyrilium ion is very low.

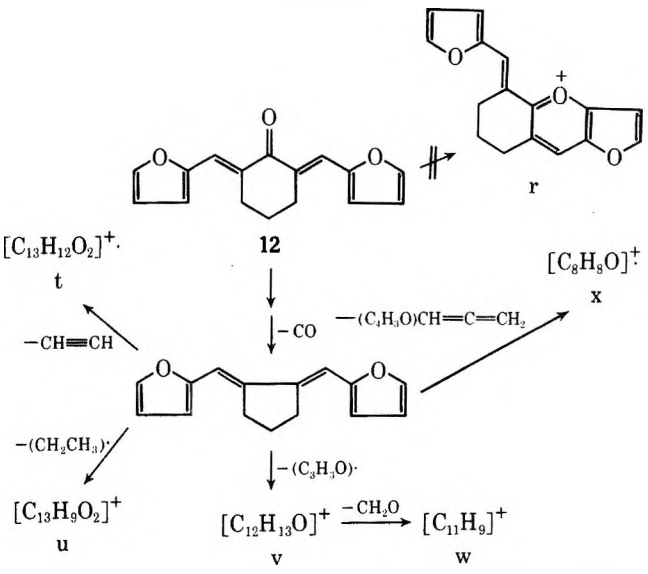
Fragmentation of (*E,E*)-2,6-bis(2-naphthylmethylene)-cyclohexanone (**11**) follows the same patterns outlined for the lower benzologs. However, apart from the intense M and M − 1 peaks [*m/e* 375 (92), 373 (100)] the peaks of the low energy species o, p, and q (that correspond to f, g, and i in Scheme I) are unusually strong [*m/e* 179 (98), 178 (64), and 165 (68), respectively].



o p q

Substitution of the aryl groups of **1** by a function which is not strictly aromatic suppresses the formation of stable oxonium ions and route 1 describes no longer the fragmentation of the dienone. Thus, (*E,E*)-2,6-bis(2-furfurylidene)cyclohexanone (**12**) does not form a furanopyrilium ion, but undergoes, instead, rapid decarbonylation followed by "normal" furfurylidene–cycloketone cleavages[6] (Scheme II).

Scheme II



The corresponding masses and relative intensities of the parent ion and fragments s and t–x (70 °C, 70 eV) are *m/e* 254 (100), 226 (28), 200 (14), 197 (17), 171 (13), 141 (15), 120 (10).

When an oxygen atom is introduced into the central cycloalkanone ring as, e.g., in (*E,E*)-3,5-dibenzylidenetetrahydro-4*H*-pyran-4-one (**13**), the formation of a benzopyrilium ion (z) is greatly diminished by the existing of a competing fragmentation pathway which involves cleavage of the C_2–C_3 (α to carbonyl) and the etheric C_2–O bonds. Carbon monoxide extrusion from ion dd, so formed, followed by loss of H· gives fragments h and i as shown in Scheme III.

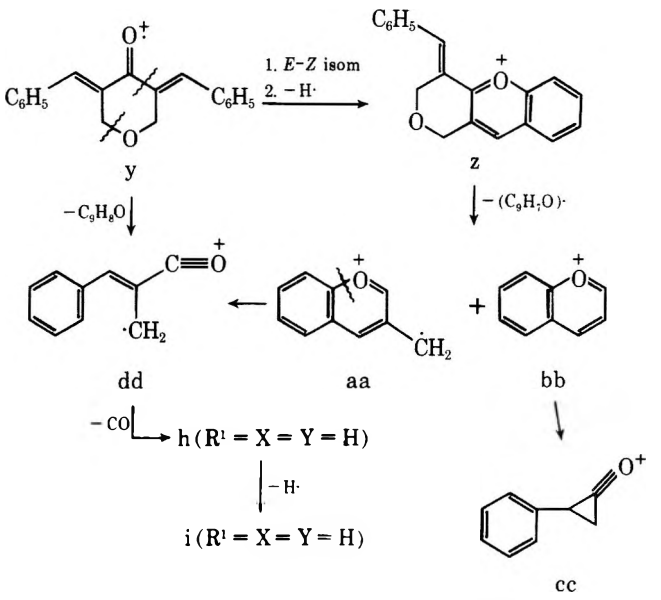
The benzopyrilium ion z cleaves at the α position to the carbonyl group, and to the ring oxygen to yield aa and bb. The latter may rearrange into the relatively stable phenlcyclopropanonium ion cc. Ion aa may open up to dd and thus contribute to the abundances of h and i. The major peaks in the mass spectrum of **13** are *m/e* y 276 (79), z 275 (44), aa and dd 144 (12), bb and cc 131 (8), h (R^1 = X = Y = H) 116 (100), i (R^1 = X = Y = H) 115 (60). All other peaks are extremely weak,

Table I. Summary of Major Fragment Ions of (*E*, *E*)-2,6-Diarylidenecyclohexanones[a]

Compd	Substituents as referred to Scheme I	*m/e* values for fragment ions (rel intensity, %)									
		a (M)	c (M − X)	e (M − CO)	f[b]	g[b]	i[b]	l and/or m[c]	k and/or n[c]	Y − $C_7H_6^+$, $C_7H_7^+$	Other significant ions
1	$R^1 = R^2 = R^3 = X = Y = H$	274 (65)	273 (100)	246 (7)	129 (12)	128 (13)	115 (27)	218 (11)	217 (22)	91 (13)	C_6H_5-c-$C_3H_5{\equiv}O^+$, 131 (13),[d] h, 116 (7)
2	$R^1 = R^2 = R^3 = X = H$; Y = *p*-CH_3	302 (26)	301 (50)	274 (2)	143 (5) 129 (16)[e]	142 (7) 128 (21)	115 (21)	246 (4) 232 (4)	245 (9) 231 (16)	105 (14) 91 (14)	M − CH_2, 288 (26); M − CH_3, 287 (100); e − CH_3, 259 (10); $C_{11}H_9^+$, 141 (8)
3	$R^1 = R^2 = R^3 = Y = H$; X = OCH_3	334 (<1)[f]	303 (100)				115 (2)		277 (1) 247 (1)	121 (4) 91 (8)	c − O, 287 (4); c − $CH_3OC_6H_4$, 297 (8)
4	$R^1 = R^2 = R^3 = X = H$; Y = *p*-OCH_3	334 (100)	333 (72)	306 (9)	159 (16) 129 (19)	128 (74)	145 (26) 115 (32)		277 (16) 247 (18)	121 (10) 91 (43)	M − OCH_3, 303 (16); e − OCH_3, 275 (14)
5	$R^1 = R^2 = R^3 = Y = H$; X = Cl	344 (<1) 342 (<1)	309 (33) 307 (100)				149 (10) 115 (29)	254 (6) 252 (19)			c − HCl, 271 (19)
6	$R^1 = R^2 = R^3 = X = H$; Y = *m*-Cl	344 (13) 342 (38)	343 (13) 341 (39)	316 (<1) 314 (<1)	155 (4) 153 (13) 129 (10)	154 (8) 152 (13) 128 (30)	151 (6) 149 (10) 115 (50)	288 (1) 286 (2) 254 (1) 252 (4)	287 (1) 285 (2) 253 (5) 251 (15)	91 (5)	M − Cl, 309 (33), 307 (100); e − Cl, 281 (9), 279 (26); e − 2Cl, 244 (30)
7	$R^1 = R^2 = R^3 = X = H$; Y = *p*–Cl	344 (36) 342 (55)	343 (57) 341 (86)	316 (3) 314 (5)	155 (9) 153 (27) 129 (38)	154 (16) 152 (43) 128 (55)	151 (23) 149 (35) 115 (100)	288 (7) 286 (22) 254 (4) 252 (12)	287 (11) 285 (11) 253 (11) 251 (32)	91 (48)	M − Cl, 309 (33), 307 (100); e − Cl, 281 (21), 279 (62); e − 2Cl, 244 (56)
8	$R^1 = CH_3$; $R^2 = R^3$ = X = Y = H	288 (79)	287 (100)	260 (5)	143 (6) 129 (30)[e]	142 (6) 128 (28)	115 (44)	218 (20)	217 (28)	91 (35)	h, 116 (20)
9	$R^1 = R^3 = X = Y = H$; $R^2 = C(CH_3)_3$	330 (62)	329 (100)	302 (10)	129 (28)	128 (24)	115 (59)	218 (18)	273 (10)[g] 217 (28)	91 (78)	M − CH_3, 316 (9); M − CH_3 − CH_2, 301 (11); h, 116 (21); $C(CH_3)_3^+$, 57 (51)
10	$R^1 = X = Y = H$; $R^2 = R^3 = CH_3$	302 (60)	301 (100)	274 (4)	143 (13) 129 (14)	142 (14) 128 (15)	115 (42)	233 (7)		91 (50)	e − CH_3, 259 (9); l or m − CH_3 + H, 218 (10); k or n − CH_3 + H, 217 (12), h, 116 (15)

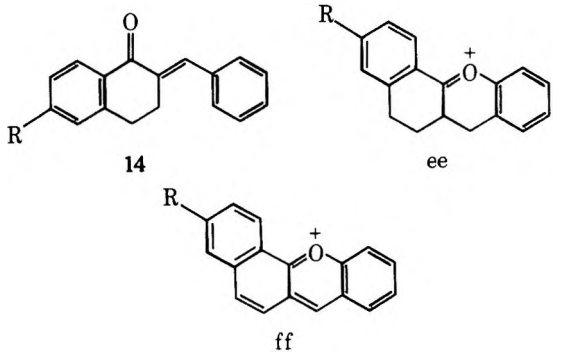
[a] All spectra were recorded at 70 °C; electron energy 70 eV. [b] Also this fragment −Y and H transfer. [c] Also these ions −Y, −2Y, and $-R^1$ coupled with H transfer. [d] For the formation of this ion see Scheme III. [e] *m/e* 129 corresponds to i as well. [f] Ratio of intensities of M (*m/e* 334): M − 1 (*m/e* 333) is 4:5. [g] *m/e* 273 is also M − $C(CH_3)_3$.

Scheme III



thus indicating that **13** hardly cleaves to give the analogous of ions j–n of Scheme I.

(*E*)-2-Arylidene-1-tetralones (**14**) were included in our study[1] as representative cyclohexanone derivatives with one exocyclic and one endocyclic bond. These compounds readily undergo *E–Z* isomerization and produce benzopyrilium ions ee, and the even more stable naphthobenzoperylium ions ff,



by loss of two hydrogen atoms. Fragmentation via the decarbonylation pathway is extremely small in this series.

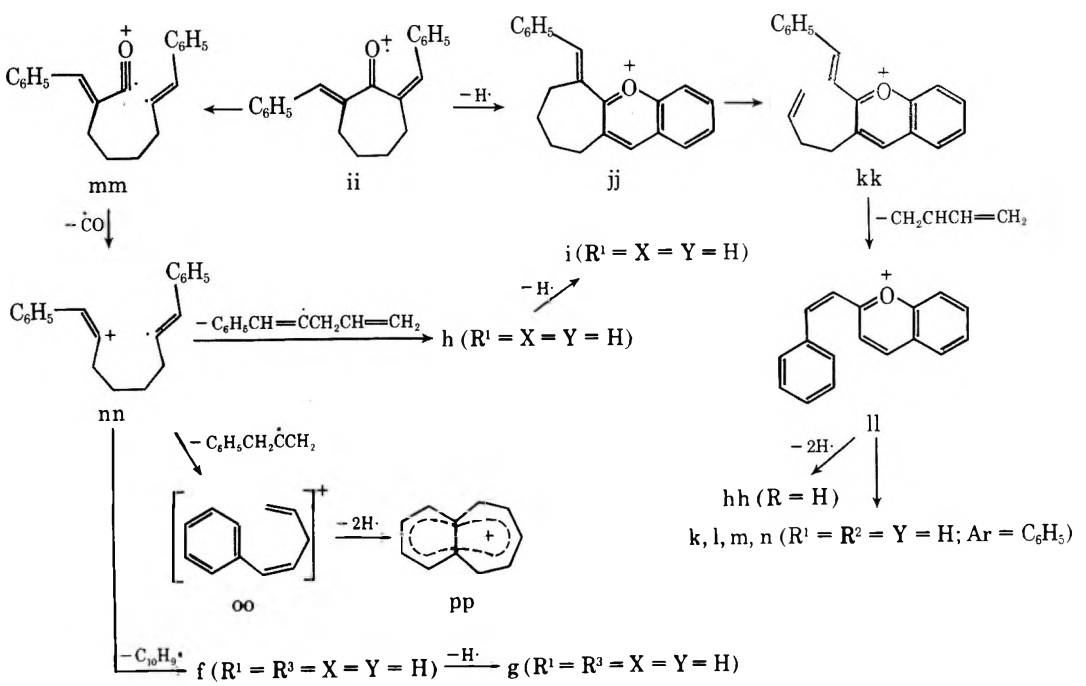
Although no correlation of the substituents with the ratio (M − 1)/M could be observed in (*E,E*)-2,6-diarylidenecyclohexanones, in **14** the substituents R attached to the fused aromatic ring affect this ratio in accord with expectations. Electron-donating substituents that stabilize structure ee cause the ratio to increase, and vice versa with electron-attracting groups. The corresponding *m/e* values and relative intensities for ions M, M − 1, and M − 3 of (a) **14**, R = OCH_3; (b) **14**, R = H; (c) **14**, R = $OCOCH_3$, are (a) 264 (33), 263 (100), 261 (5); (b) 234 (60), 233 (100), 231 (19); (c) 292 (38), 291 (26), 290 (1). [(M − 1)/M for (a), (b), and (c) are 3.03, 1.66, and 0.68, respectively]. Two further strong peaks, *m/e* 249 (29) and 248 (100), appear in the mass spectrum of 6-acetoxy-2-benzylidene-1-tetralone (**14**, R = $OCOCH_3$) owing to loss of acetoxyl or acetic acid from the parent ion.

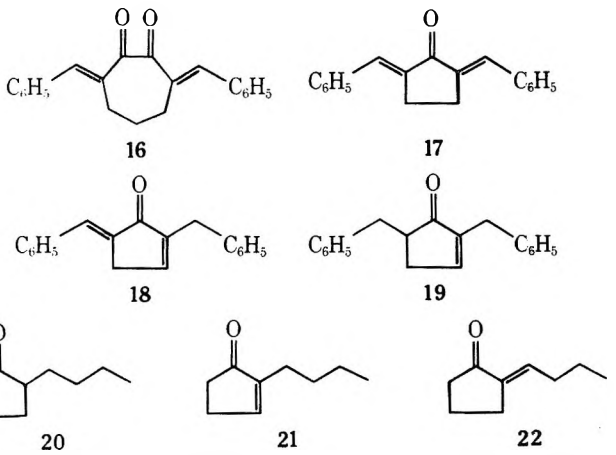
The tendency to form benzopyrilium ions is not limited to derivatives of six-membered cycloalkanones. Expansion of the central ring in **1** by one carbon unit gives (*E,E*)-2,7-dibenzylidenecycloheptanone (**15**), which behaves similarly to **1** under electron impact. The fragmentation patterns suggested for **15** in Scheme IV resemble, therefore, those shown in Scheme I except for the features that are associated with the cycloheptane ring. The masses, assignments, and relative abundances (80 eV) are as follows: $M^{+}\cdot$ 288 (90), jj 287 (100), nn 260 (14), hh 231 (14), e and m 218 (20), k and n 217 (40), pp 141 (49), f (R¹ = R³ = X = Y = H) 129 (40), g (R¹ = R³ = X = Y = H) 128 (51), i (R¹ = X = Y = H) 115 (81), $C_7H_7^{+}$ 91 (65).

It is most remarkable that the mass spectra of (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-**15** are essentially identical for a broad range of electron energies (30–80 eV). This suggests that under electron impact rapid interconversion of the three geometric isomers takes place.

(*E,E*)-3,7-Dibenzylidenecycloheptane-1,2-dione (**16**), as a typical 1,2-diketone, ejects one molecule of CO prior to further fragmentation.[7] By this process the parent ion of 2,6-dibenzylidene*cyclohexanone* is formed (not necessarily as the closed structure a). One could, therefore, anticipate the resemblance of the mass spectra of **16** and **1** and expect a small parent peak for **16**. The recorded masses and relative inten-

Scheme IV

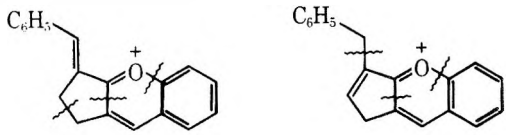




16 17 18 19 20 21 22

sities [*m/e* (120 °C, 70 eV) 302 (<1), 274 (73), 273 (100), 218 (14), 217 (24), 129 (20), 128 (27), 115 (59), 91 (25)] confirm these assumptions.

(*E,E*)-2,5-Dibenzylidenecyclopentanone (17) follows almost entirely the "benzopyrilium" mode of fragmentation. The mass spectrum [*m/e* (70 eV) $M^{+\cdot}$ 260 (33), rr 259 (56.5), $C_{11}H_9^+$ 141 (7.5), i 115 (100), $C_7H_7^+$ 91 (20)] indicates no α-cleavage of the parent ion and CO abstraction. The intense indenyl ion i (*m/e* 115) may be produced by two independent routes from the benzopyrilium ion rr: one involves α- and β-cleavage followed by hydrogen transfer, and the other route proceeds via ion dd as shown in Scheme III.



rr ss

An isomer of 17 with only one exocyclic double bond, 2-benzyl-5-benzylidenecyclopent-2-enone (18), has the following mass spectrum: *m/e* (70 eV) $M^{+\cdot}$ 260 (65), ss 259 (50), $[M - C_7H_7]^+$ 169 (21), $[M - C_7H_7 - CO]^+$ 141 (20), i 115 (44), $C_7H_7^+$ 91 (100), $C_6H_5^+$ 77 (20). The spectrum differs from that of 17 in two respects: (a) The intensities of ion M and M − 1 are no longer in favor of M − 1. (b) The base peak corresponds to the tropylium ion (*m/e* 91) due to facile benzyl ion abstraction from the parent ion and from ss. The latter fragment may, however, undergo α- and β-cleavage in the same manner as rr and give some indenyl cation i as well.

When the exocyclic double bond in 18 is selectively reduced to form 2,5-dibenzylcyclopent-2-enone (19), naturally, the M − 1 peak disappears. The base peak (*m/e* 91) results from the *two* available benzyl groups. The only other intense peaks correspond to M [*m/e* 262 (36)], M − C_7H_7 [*m/e* 171 (30)], and M − C_7H_7 − H_2O [*m/e* 153 (19)].

It may thus be concluded that benzopyrilium ion production is feasible only when *exocyclic* double bonds are available, and that the ratio of intensities (M − 1)/M is proportional to the number of benzylidene functions. On the basis of these features we were able to locate by mass spectrometry the position of double bonds in the various reaction products obtained from 17 and $IrCl(CO)(PPh_3)_2$ described in the preceding paper.[1] Moreover, upon recording the intensities of peaks *m/e* 260, 259, 115, and 91 throughout the catalytic process, we could calculate the rate of disappearance of 17 and rate of product formation in accuracy comparable with the usual GLC method.[1,8]

Finally, the mass spectra of 2-alkyl- and 2-alkylidenecycloalkanones **20–22** were recorded for comparison with those of the aryl-containing compounds. The spectrum of 2-*n*-butylcyclopentanone (**20**) resembles that of the lower homologue.[9-11] The molecular ion [*m/e* 140 (7)] undergoes McLafferty rearrangements, mainly with γ-hydrogen shift, to give cyclopentanol ion [*m/e* 84 (100)] that reketonizes to $C_5H_7O^+$ [*m/e* 83 (26)]. McLafferty rearrangement with δ-hydrogen shift is less important. It yields the 2-methylenecyclopentanol ion [*m/e* 97 (15)].

The cyclopentenone derivative (**21**) undergoes likewise McLafferty rearrangements; however, the main feature of this compound is α-cleavage (side chain) and H-transfer to give an unsaturated enol ion *m/e* 96 (100) which reketonizes [*m/e* 95 (50)]. Other intense peaks in the spectrum of 21 result from ethyl abstraction and the complete rupture (α-cleavage) of the side chain [*m/e* 109 (44) and 81 (45), respectively].

The side chain of 2-butylidenecyclopentanone (**22**) is gradually cleaved off to give fragment ions *m/e* 123 (40), 109 (15), and 95 (60). α-Cleavage of the parent ion [*m/e* 138 (65)] followed by decarbonylation affords ion *m/e* 110 (11), which, upon α-cleavage, gives the base ion $C_5H_7^+$ (*m/e* 67). As no significant M − 1 ion appears in the spectrum, it may be concluded that stable perylium ion formation from cycloalkanones is conditioned by the presence of an *arylidene* group at the α position.

Experimental Section

The preparations of compounds 1–12 and 14–19 are described or referred to in the preceding paper.[1] 3,5-Dibenzylidenetetrahydro-4*H*-pyran-4-one[12] and 2-butylidenecyclopentanone[13] were synthesized according to the literature. The latter was isomerized and reduced to 2-butylcyclopent-2-enone and 2-butylcyclopentanone, respectively, by $IrCl(CO)(PPh_3)$ under the condition described for 2,5-dibenzylidenecyclopentanone.[1] All liquid samples were purified by gas chromatography and solids by recrystallization prior to mass spectrometric analysis.

The mass spectra were measured with a double focusing Varian MAT-311 spectrometer. The exact masses of all ambiguous ions were determined by high resolution, $R = M/\Delta M > 10\,000$.

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Registry No.—1, 42052-61-9; 2, 42792-79-0; 3, 62085-70-5; 4, 62085-71-6; 5, 62085-72-7; 6, 62085-73-8; 7, 42792-80-3; 8, 62085-69-2; 9, 42792-77-8; 10, 62085-90-9; 11, 62085-77-2; 12, 62085-75-0; 13, 62085-91-0; 14a, 50558-94-6; 14b, 57558-64-2; 14c, 62085-37-4; 15, 62085-48-7; 16, 62085-26-1; 17, 34611-43-3; 18, 62085-32-9; 19, 23923-54-8; 20, 934-42-9; 21, 5561-05-7; 22, 56292-42-3.

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Synthesis and Structure of Perhydrotriptycene Stereoisomers

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Six of the nine stereoisomers of perhydrotriptycene were obtained by hydrogenation of triptycene over Pd and Ru and identified by spectroscopic and x-ray diffractometric techniques. Of them, one has D_3 symmetry, another C_{3h} symmetry. Five other partially hydrogenated compounds were isolated and identified mainly by ^{13}C NMR spectroscopy. Several reaction steps have been checked by selective hydrogenation of the single intermediates and a satisfactory reaction course is given for both catalysts. In the case of Pd, stereochemical data support a mechanism of hydrogen approach from the "gas phase", in contrast to the mechanism most commonly accepted for catalytic hydrogenation. From the equilibrium composition of saturated stereoisomers it is possible to deduce the presence of a considerable strain in all stereoisomers; the compounds with cyclohexane rings in a boat conformation and those with rings in a chair conformation have almost the same energy owing to the predominance of transannular interactions.

The pioneering work of Hückel on decalin[1] has highlighted the role of saturated polycyclic hydrocarbons in the development of conformational analysis.[2]

Such hydrocarbons exist in different stereoisomeric forms, and their relative energies may be accurately determined by catalytic equilibration. The conformational energy of decalin,[3] hydrindan,[4] perhydrophenanthrene,[5] and perhydroanthracene[6] has been studied by means of this method. In the recent past, new techniques such as ^{13}C NMR and GC have been successfully applied to test molecular structure,[7,8] and the relationship between stereochemistry and catalytic hydrogenation has been investigated in naphthalene.[9]

In our laboratory we have developed a program of research on compounds having a symmetry number (σ) higher than 2, and lacking any element of mirror symmetry.[10]

After the first organic molecule with D_3 symmetry ($\sigma = 6$) synthesized in our laboratory,[11-14] we focused our attention on the hexasubstituted derivatives of bicyclo[2.2.2]octane and in particular to the perhydro derivatives of triptycene.[15] The bicyclo[2.2.2]octane skeleton is the ideal framework on which to build high symmetry molecules featuring threefold symmetry. The fusion of bicyclo[2.2.2]octane and three cyclohexane rings leads to interesting conformational problems; nevertheless, the structure of the several stereoisomers involved in the hydrogenation process gave interesting information on the mechanism of catalysis.

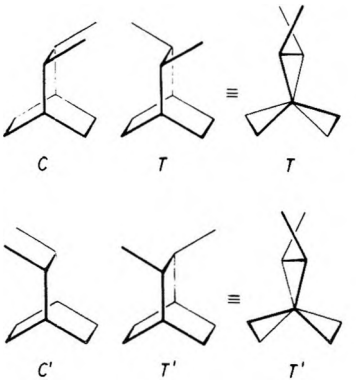
The Stereochemical Problem. A number of investigations have been carried out concerning the conformation of bicyclo[2.2.2]octane, of its 1- and 1,4-substituted derivatives, and of its nitrogen analogues, quinuclidine and triethylenediamine. The bicyclic portion of these molecules may have either a mirror symmetry (D_{3h} and C_{3v} depending on the cases) or may be twisted, with D_3 or C_3 symmetry.

On the basis of diffraction methods, Dunitz states that bicyclo[2.2.2]octane shows an actual D_{3h} symmetry at all temperatures, whereas molecular mechanics calculations show two energy minima corresponding to slightly twisted conformations, though with a very low interconversion barrier (~100 cal/mol).[16] Fournier and Waegell obtained analogous results, although the deformation and potential barrier are much lower than those calculated by Dunitz.[17]

However, nothing is known about the stereochemistry of homosubstituted bicyclo[2.2.2]octanes, such as 2,3,5,6,7,8-hexamethylbicyclo[2.2.2]octane.

These compounds are characterized according to the arrangement of the substituents along every bridge of the bicyclooctane nucleus. The terms cis (C) and trans (T) are used when, on examining the compound in its undistorted conformation, the substituents are eclipsed or placed at 120° from each other, respectively. In order to distinguish between the two opposite dispositions, letters C and T are used when the substituent bound to the front part of the molecule is arranged clockwise; in the opposite case we use the terms C′ and T′ (see Chart I). The steric notations (C, C′, T, T′) concerning the three bridges of the molecule are indicated in a clockwise succession.

Chart I. Nomenclature Used for Stereoisomers of Substituted Bicyclo[2.2.2]octanes



The number of stereoisomers and their symmetry are systematically determined in the Appendix. As for hexamethylbicyclooctane, we predict the existence of nine isomers, seven of which are chiral. Table I reports the nomenclature that is adopted for them hereafter.

We can apply the same kind of analysis and the same nomenclature to pentacyclic compounds like perhydrotriptycene, provided that the conditions for ring closure are taken into account. From this standpoint, we believe that isomers TT′T and TT′C have high energy content owing to the opposite deformations necessary to join a cyclohexane ring clockwise (T) and a second ring counterclockwise (T′). Therefore we will consider only seven out of nine isomers. Their formulas are reported in **1-7** (only one enantiomer for each chiral form), in a twisted conformation if T junctions are present, and in an eclipsed conformation if all rings are C or C′. In the former case cyclohexanes are represented in the chair form, and in the latter in the boat form.

Isomer TTT has D_3 symmetry and constitutes the high symmetry chiral compound that is the main object of our re-

Table I. Stereoisomers of Hexasubstituted Bicyclooctanes[a]

Predicted Symmetry		
	A. Chiral Stereoisomers	
D_3	TTT	(T′T′T′)
C_1	TTC = TTC′	(T′T′C = T′T′C′)
C_1	TCC = TC′C′	(T′CC = T′C′C′)
C_2	TT′T	(T′TT′)
C_1	TT′C = TC′T′	(T′TC = T′C′T)
C_2	TC′C	(T′C′C)
C_2	TCC′	(T′CC′)
	B. Achiral Stereoisomers	
C_{3h}	CCC = C′C′C′	
C_s	CC′C = C′CC′	

[a] The preferred nomenclature for every stereoisomer is reported on the left, in parentheses that of the corresponding enantiomer. Triplets related by the sign = are equivalent according to rule 2 in the Appendix.

search. It has chirality *S* for all asymmetric atoms (its enantiomer is T′T′T′). It may be noticed that our nomenclature defines the absolute configuration of chiral isomers and is simpler than that of Cahn, Ingold, and Prelog;[18] as a matter of fact, it requires only three letters (and possibly some primes) and not ten letters and six numbers.[26]

Isomer CCC in the eclipsed conformation has C_{3h} symmetry, whereas in the twisted conformation it should have C_3 symmetry. In a previous communication we called the TTT and CCC isomers respectively iso-*trans*- and iso-*cis*-perhydrotriptycene.[15]

From a conformational point of view, perhydrotriptycene isomers constitute a quite complex system, in which opposite factors are involved and do not allow any simple prediction of stability. On the basis of qualitative reasoning, two subgroups may be indicated, which have an increasing energy content, namely, TTT < TTC < TCC < CCC and TC′C < CC′C < TCC′, where TC′C is approximately placed close to CCC. However, in order to show the difficulty and the limits of such predictions, we anticipate that the expected large difference in stability between TTT and CCC (corresponding to the energy of three boat conformations) does not occur.[15]

Table II. Triptycene Derivatives with a Different Degree of Hydrogenation[a]

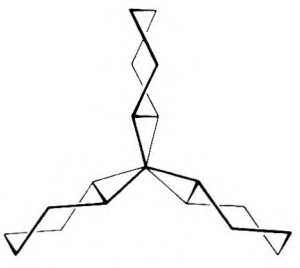
General formula	Mol wt	No. of isomers
AAA	254	1
AAU	258	1
AAS	260	2
AUU	262	1
AUS	264	3
ASS	266	7
UUU	266	1
UUS	268	2
USS	270	7
SSS	272	9

[a] Enantiomeric pairs are considered as a single isomer. Restrictions due to ring closure are not taken into account in the table

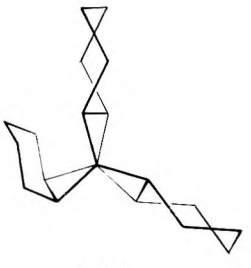
This topic will be further discussed with the aid of experimental data.

Going back to nomenclature, we have used the same method for the products of partial hydrogenation of triptycene. In that case, letter A indicates an aromatic ring and U an unsaturated one. The number of stereoisomers is obtained by applying—after minor corrections—the rules given in the Appendix for saturated compounds. As for the unsaturated compounds, only the isomers with a tetrasubstituted double bond shared by two rings have been taken into consideration. Table II shows the number of the possible isomers. For the sake of simplicity, the four different stereochemistries present in the saturated rings (C, C′, T, T′) are all indicated by the letter S (saturated).

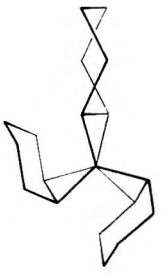
In order to identify the single atoms of triptycene and its derivatives, we do not use the official nomenclature, but a method that more easily allows the detection of analogies and symmetry. As indicated in 8, such a method consists in using a number (1, 2, 3) distinguishing the three outer rings, a Greek letter (α, β, γ, δ) depending on the distance from the bicyclooctane axis, and a prime, if the atom considered is placed in the opposite side of the molecule with respect to the point of observation. The ring called 1 has the chemical or stereochemical constitution indicated by the first letter of the triplet identifying the compound (A in AC′C, T in TCC, etc.).



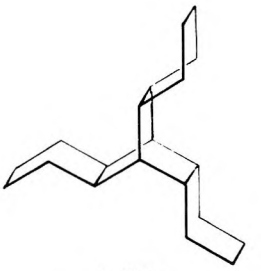
1 TTT



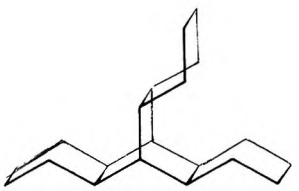
2 TTC



3 TCC

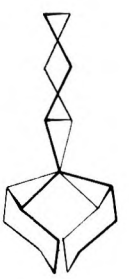


4 CCC



5 CC′C

5 TC′C



7 TCC′

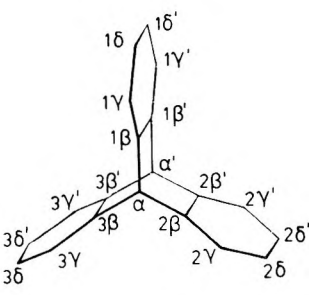


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Table III. Properties of Triptycene and of Its Hydrogenated Derivatives

Compd	Mol wt	Mp, °C	Kovats indices I OV-101 200°	OV-101 $\delta I/10°$	Carbowax 20M 200 °C	Carbowax 20M $\delta I/10°$	Symmetry	No. of obsd ^{13}C NMR resonance lines
TTT	272	195	2025.2	12.2	2240.4	17.7	D_3	4
TTC	272	138	2096.4	13.1	2374.4	20.1	C_1	20
TCC	272	nd[a]	2152.3	14.2	2474.0	22.0	C_1	20
CCC	272	166	2193.3	14.0	2532.6	22.7	C_{3h}	4
TC'C	272	nd	nd[b]	nd	2487.5	22.7	C_2	nd
CC'C	272	82	2228.6	15.7	2606.0	25.4	C_s	10
UCC	270	nd	2087.6	14.0	2395.2	21.5	C_s	10
UC'C	270	107	2072.6	16.0	2377.5	22.9	C_{2v}	7
ACC	266	128	2129.1	14.4	2606.8	23.9	C_s	10
AC'C	266	144	2082.3	14.8	2526.5	23.3	C_{2v}	7
AUC[c]	264	nd	2077.5	12.3	nd	nd	C_s	nd
AAC	260	167	2119.9	13.8	nd[d]	nd	C_s	nd
AAA	254	259	2146.0	12.4	nd[d]	nd	D_{3h}	4

[a] A mixture containing TCC (85%) and TC'C (15%) melts at 111 °C. [b] On the OV-101 column it cannot be distinguished from TCC. [c] Or ACU. [d] Kovats indices of AAC and AAA have not been determined on the Carbowax 20M column because the retention times of the two compounds are excessively long.

Structure of Saturated and Unsaturated Compounds. The number and relative abundance of the hydrogenation products of triptycene directly depend on the experimental conditions. Twelve compounds can be detected by GLC by considering only the pentacyclic products present in amounts above 0.5%. The complexity of the mixtures of hydrogenation products decreases on increasing the reaction time. As a matter of fact, only five saturated stereoisomers are present at the equilibrium. All substances formed were characterized by GLC; Kovats indices were determined on WCOT columns having different polarities at different temperatures. Information on the molecular weights and on the characteristic fragmentations was obtained via GC/MS. Eight components were isolated in a high purity grade by absorption LC, preparative GC, or fractional crystallization. Their structures were determined on the basis of their MS, IR, ^1H NMR, and ^{13}C NMR spectra; in five cases a complete x-ray analysis was performed. Two further components (TCC and UCC) were enriched up to above 80%, whereas minor components were exclusively examined by GC or GC/MS.

Some physical and structural data are reported in Table III. GC/MS shows six perhydrogenated compounds (mol wt 272), two hexadecahydro derivatives (mol wt 270), two dodecahydro derivatives (mol wt 266), one hexahydrotriptycene (mol wt 260), unreacted triptycene (mol wt 254), and traces of other compounds with different molecular weight. We have purposely neglected the products with a molecular weight higher than 272, derived from hydrogenolysis of a C–C bond, as well as those with molecular weight far lower than 254, due to ring cleavage (mainly perhydroanthracene with mol wt 192).

As is well known, proton-decoupled ^{13}C NMR spectra allow a direct determination of molecular symmetry. Properly speaking, they enable us to determine the number of the nonequivalent carbon atoms contained in the "submolecular asymmetric unit".[10,19] Moreover, the relative intensity of the resonance lines is related to symmetry, because it shows if the corresponding atoms lie on some element of symmetry or not (atoms in a special or in a general position, respectively).[19] In the specific case, the highest symmetry allowed when four resonance lines exist is D_3 or C_{3h} (D_{3h} for triptycene); with seven lines, the corresponding symmetry is C_{2v}, with ten lines it is C_s or C_2, whereas 20 lines indicate the absence of symmetry (point group C_1).

Isomers TTT and CCC. The compounds melting at 195 and 166 °C, both exhibiting four resonance lines in the ^{13}C NMR spectrum in the approximate ratio 3:3:3:1, were assumed to have TTT and CCC structure, respectively, as demonstrated by x-ray analysis.[15] The molecular conformation in the solid state is nearly that indicated in 1 and in 4.

TTT exhibits a twisted bicyclo[2.2.2]octane nucleus and the outer cyclohexanes in chair conformation, whereas CCC is eclipsed. Such conclusions have also been proved by ^1H NMR spectra. In TTT apical hydrogens give rise to a singlet at 0.85 ppm having a half-height width of 1.4 Hz (area 2). The examination of molecular models shows that the dihedral angle Hα–Cα–Cβ–Hβ approaches 90° and therefore hydrogen couplings are virtually absent.

In its turn, the ^1H NMR spectrum of CCC shows an unresolved peak at 0.87 ppm having a half-height width of about 4.5 Hz (area 2). The two apical hydrogens are equivalent and are coupled to the vicinal hydrogens, the value of the dihedral angle in the eclipsed conformation being near 60°. Spectra recorded in a wide range of temperature (−80 to 130 °C) do not give evidence for any equilibrium involving twisted conformers.

Table IV shows the ^{13}C NMR spectra of these series of compounds. A considerable upfield shift is observed going from TTT to CCC. In agreement with Grant,[20] the phenomenon was interpreted as indicating a high steric crowding in CCC. The value of the β-carbon resonance, which is predominantly determined from the geometry of the γ or γ' carbon atom of one of the adjacent rings, is particularly meaningful for the following discussion.

Isomers TTC and TCC. The compounds melting at 138 and 111 °C (see footnote in Table III) were assumed to have structures TTC (2) and TCC (3), respectively; their ^{13}C NMR spectra show 20 lines, and therefore they do not possess any element of symmetry. This is also proved by the nonequivalence of apical hydrogen in the ^1H NMR spectra; two peaks at 0.82 and 1.08 ppm are observed in TTC, whereas TCC shows a peak with area 1 at 0.75 ppm, while the second one is hidden by other peaks.

We distinguished the two structures by examining the chemical shift of β carbons. In TTC the atom 1β strongly interacts with 3γ' and therefore it should be shifted upfield; in TCC a similar situation takes place three times (1β, 3β, 3β'). Actually, in the ^{13}C NMR spectrum of the compounds melting at 138 °C, only one signal is observed at high field for β carbons

Table IV. ^{13}C NMR Spectra of Hydrogenated Derivatives of Triptycene[a]

Carbon	TTT	TTC	TCC	CCC	CC'C	ACC	UCC	AC'C	UC'C
α	42.9	43.6 α	43.5 α	40.8	42.1	46.0	46.5	47.2	47.7
		50.8 α'	49.6 α'						
β	43.3	34.3 1β	33.0 1 β	32.4	32.8 1β	143.4 1β	135.2 1β	140.5 1β	132.6 1β
		41.0	33.0 3β		39.7	32.4 3β	37.4 3β	39.5	40.3
		42.0	34.4 3β'		40.9	37.2 2β	41.8 2β		
		42.0	40.0						
		42.3	41.2						
		42.5	42.5						
γ	30.6	28.1 1γ'	24.1 2γ'	22.9	23.1	125.4 1γ	29.1 1γ	126.9 1γ	31.1 1γ
		28.8 3γ'	25.7 3 γ'		25.5	22.4 2γ	23.7	24.0	24.2
		31.0	28.3		25.7	24.3 3γ	24.4		
		31.1	29.1						
		31.3	32.1						
		33.5 2γ'	33.8						
δ	28.0	20.7	20.8	21.3	21.2	124.9 1δ	22.7 1δ	125.2 1δ	23.4 1δ
		21.8	21.0		22.0	20.1	20.4	20.0	20.0
		22.8	21.4		22.0	20.5	20.8		
		26.3	21.8						
		28.1	22.6						
		28.1	23.0						

[a] Chemical shift in parts per million from internal Me_4Si, room temperature, deuteriobenzene.

(TTC isomer), whereas in the second compound, peaks corresponding to three atoms appear between 33 and 35 ppm (isomer TCC).

These attributions agree both with the elution order from a GC nonpolar column and with the results of kinetic and thermodynamic investigations. More recently our assignments have been confirmed by x-ray analysis.[21]

Isomers CC'C and TC'C. GC/MS analysis shows that two further isomers exist with mol wt 272. One may be obtained in large amounts and in pure form by operating under convenient experimental conditions (ruthenium catalyst), and melts at 82 °C. The other is present always in small amount, and its isolation can be hardly performed, because of its GC behavior very similar to that of TCC. Its existence was evidenced only by the use of an efficient column filled with Apiezon L.

The ^{13}C NMR spectrum of the compound melting at 82 °C exhibits ten resonance lines and is consistent with structures CC'C (**5**), TC'C (**6**), and TCC' (**7**), the increasing order of energy reasonably being TC'C < CC'C < TCC'. To this compound we attributed stereochemistry CC'C on the basis of the following considerations.

(1) It is formed within a short time and in good yields in the presence of ruthenium, which is a catalyst with poor isomerizing properties.[22]

(2) It is rapidly transformed into CCC over palladium.

(3) It does not exist at equilibrium, where, on the contrary, small amounts of the other mentioned compound (TC'C) are present.

The ^{13}C NMR spectrum is consistent with the proposed structure. The chemical shifts of β carbons indicate for two atoms (identified as 1β and 1β', equivalent by symmetry) a strong steric crowding, analogous to that existing in the CCC isomer; the other two resonance lines at lower fields correspond to 2β (= 2β') and to 3β (= 3β'). This structure has been subsequently proved by a crystallographic analysis by Allegra and Bruckner.[21]

Structure TC'C (**6**) was attributed to the nonisolated isomer present at equilibrium. The only other possible choice, TCC' (**7**), was excluded for the presence in **7** of a strong transannular interaction between atoms 2γ and 3γ, which is higher than that existing between atoms 1γ and 2γ in CC'C (which is not even present at equilibrium). Such considerations have been fully supported by molecular mechanics calculations by Allegra and Bruckner[21] on the whole series of perhydrotriptycenes.

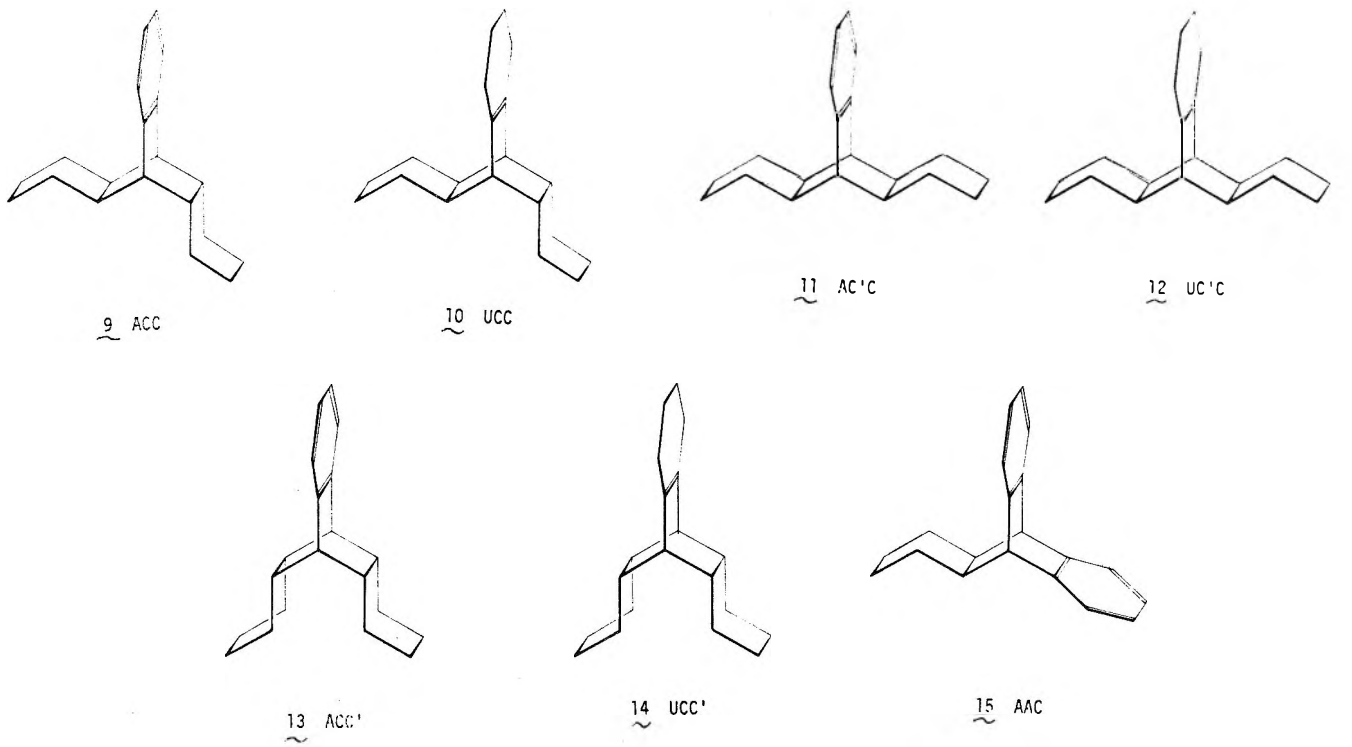
Compounds ACC, UCC, AC'C, UC'C. Among the partially hydrogenated compounds that are present in large amounts in the first stages of reaction, we have in particular studied four products which involve interesting stereochemical problems and play an important role during hydrogenation. MS, ^1H NMR, and IR spectra show for two of them the presence of an aromatic ring (*m/e* 266, multiplets between 6.9 and 7.0 ppm, absorption bands between 3100 and 3000, 1603, 1478, 755 cm^{-1} for AC'C and between 3100 and 3000, 1582, 1481, 760 cm^{-1} for ACC). The spectra of the other two show the presence of an unsaturation between atoms 1β and 1β' (*m/e* 270, absence of ethylenic hydrogens and equivalence of α and α' hydrogens in ^1H NMR spectra, stretching band C=C at 1672 cm^{-1} in UC'C and at 1659 cm^{-1} in UCC).

These compounds may be divided in two series, both consisting of an aromatic and of an olefinic compound with the same stereochemistry. Their ^{13}C NMR spectra show seven resonance lines (point group C_{2v}) in one case, and ten lines (point group C_s)[27] in the other.

As for the compounds with ten resonance lines [for which structures ACC (**9**), UCC (**10**), ATT, and UTT could be considered), cis stereochemistry is clearly indicated in the aromatic compound from the chemical shift of 3β carbon, coincident in value with the β carbons of CCC. Moreover, such compounds are already present in the initial stage of the reaction (when the existence of structures with two trans junctions is unlikely) and are strictly connected with the formation of CCC, to which they must be structurally related.

As for the compounds giving rise to seven resonance lines, the structures may be chosen between AC'C (**11**) and UC'C (**12**) on one side and ACC' (**13**) and UCC' (**14**) on the other side. The structures C'C were chosen on the basis of the chemical shift of saturated β-carbons, coincident with that of 2β and 3β in CC'C. The structure of AC'C was subsequently proved by x-ray analysis.[21]

Compound AAC. On the basis of the most probable reaction course, structure AAC (**15**) was attributed to the compound having *m/e* 260 and melting point 167 °C, which is present in large amount in the first hour of reaction. This compound is the precursor of both AAC and AC'C, and represents an important intermediate in the interpretation of the hydrogenation of triptycene.



Other Compounds. In some fractions enriched by adsorption LC or preparative GC, we detected some minor components. Among them, we particularly recall a product with *m/e* 264, whose structure might be either AUC or ACU. Another product has *m/e* 270 and might be UCC′ (**14**) or a positional isomer with a nonsymmetrically substituted double bond.

The Course of Hydrogenation. Triptycene was hydrogenated over palladium or ruthenium at 150–200 °C and 50–80 atm in a hydrocarbon solvent. In both cases we observed the presence of two series of compounds having a different stereochemistry as well as the appearance of scarcely reactive aromatic and olefinic intermediates and the fall of hydrogen absorption rate when the 85–90% of the stoichiometric value has been absorbed.

However, some differences are observed in the two cases. In the presence of palladium the predominant saturated product is CCC, which is subsequently epimerized until the thermodynamic equilibrium is reached after long times. At this point five saturated stereoisomers are present.

In the presence of ruthenium, hydrogenation is slower, and the predominant saturated isomer after short times is CC′C, although the unsaturated intermediates are the same. Moreover, since the beginning, compounds with an anomalous molecular weight are observed, deriving from hydrogenolysis or thermolysis of one or more C–C bond (perhydroanthracene, 9-cyclohexylperhydroanthracene in various stereoisomeric forms and their less hydrogenated precursors). The subsequent epimerization is far slower than in the case of Pd and the study is complicated by the ever increasing presence of hydrogenolysis products.

In order to clarify the course of these complex reactions, we isolated most intermediate compounds and examined their behavior under reaction conditions. Such selective hydrogenations were carried out with the main purpose to determine the first reaction product obtained from each compound. As is well known, such a product is characterized by an initial formation rate differing from zero.

Palladium-Catalyzed Hydrogenation. Figure 1 shows the typical behavior of triptycene hydrogenation over palladium. Although the reaction cannot be strictly reproduced

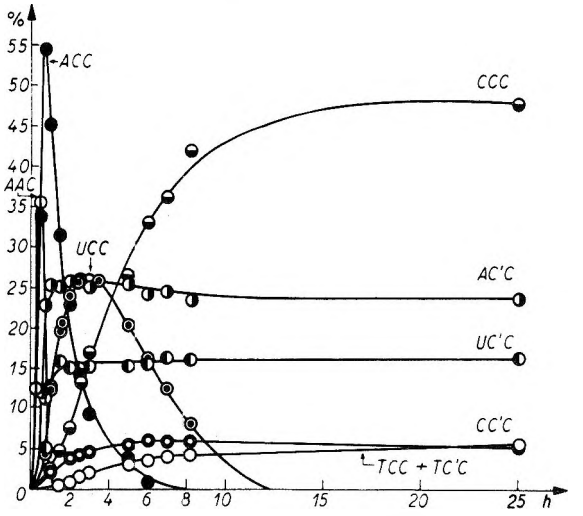


Figure 1. Hydrogenation of triptycene over palladium at 150 °C and 60 atm H_2. Other conditions are reported in the Experimental Section (semimicro hydrogenations).

from the quantitative standpoint, the discrepancies observed are not such as to invalidate our interpretation.

Triptycene rapidly disappears (after 45 min it cannot be detected any longer), while the transient appearance of AAC may be observed: in the first 0.5 h it reaches its highest concentration and disappears within the first 1 h of reaction. AAC is the only product that directly derives from triptycene at an appreciable rate, as demonstrated by drawing samples a few minutes after the reaction starts. This leads to exclusion of the simultaneous hydrogenation of two aromatic rings.

The composition/time curves concerning compounds AAC, ACC, UCC, and CCC indicate the existence of a series of consecutive reactions. A selective hydrogenation test shows that in addition to the predominant path ACC → UCC → CCC, a minor parallel reaction occurs giving rise to small amounts of CC′C.

With regard to the C′C series, a rapid formation of AC′C and UC′C is observed. These compounds are quite resistant to

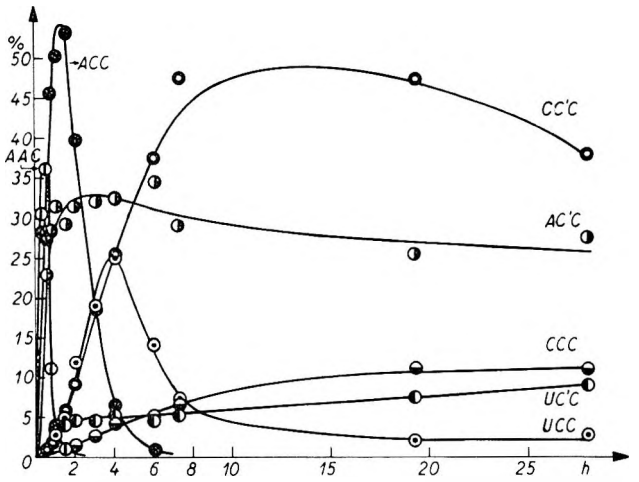


Figure 2. Hydrogenation of triptycene over ruthenium at 150 °C and 60 atm H_2.

hydrogenation and last for a long time, even after the disappearance of any other unsaturated compounds. The lack of reactivity of AC'C and UC'C is related to the difficult approach to the reactive site, which is shielded on both sides by saturated rings.

Selective hydrogenations showed that AC'C is quite slowly transformed into UC'C and that the latter is even more resistant to hydrogenation. By forcing the condition, and in particular, by increasing the catalyst/substrate ratio, UC'C gives rise to CC'C, CCC, and TC'C, but also to a small amount of AC'C. However, the reversibility of the reaction AC'C ⇄ UC'C observed in very particular conditions (catalyst/substrate ratio 10/1) does not seem to exert a determinant influence on the overall process of hydrogenation of triptycene. In our opinion the formation routes of AC'C and UC'C are mostly independent and they both derive from a less hydrogenated substance (AAC) either directly or through short-life intermediates (e.g., ACU).

Clear evidences exist that the precursor of CC'C is neither AC'C nor UC'C. The ratio between the amount of compounds ACC + UCC + CCC + TCC (series CC) and of compounds AC'C + UC'C + CC'C + TC'C (series C'C) is the highest at the very beginning of the reaction. Its value is about 2.7 after 0.5 h, 1.5 after 1 h, and becomes stable at about 1.15 after a few hours. This indicates that a nonnegligible fraction of the CC series is converted into C'C. In this period of time ACC is the compound showing the greatest decrease in concentration; moreover, it is absent when the CC/C'C ratio becomes constant; hence it is the most probable precursor of CC'C. The role of UCC in this reaction could not be determined, owing to the difficulties of obtaining this compound in the pure state.

Once formed, CC'C is transformed into CCC and into its epimerization products.

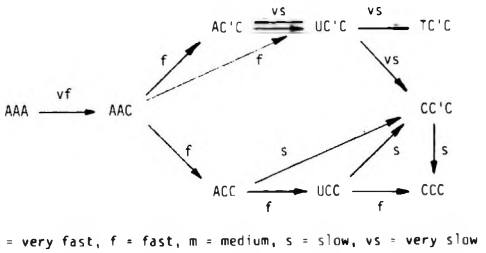
TC'C was observed in the direct hydrogenation of AC'C and UC'C. On the other hand, it is related to TCC, into which it is reversibly transformed. The ratio TC'C/TCC becomes constant within a relatively short time and remains unchanged during the subsequent epimerization processes.

The above remarks on palladium-catalyzed hydrogenation of triptycene are summarized in Chart II.

Ruthenium-Catalyzed Hydrogenation. Figure 2 shows the product composition as a function of time. Also in this case compounds with CC and C'C stereochemistries are present; however, unlike the case of palladium, C'C series predominates.

After the transient appearance of AAC and ACC, the predominant compound after short reaction times is AC'C. It

Chart II. Palladium-Catalyzed Hydrogenation of Triptycene



vf = very fast, f = fast, m = medium, s = slow, vs = very slow

Chart III. Ruthenium-Catalyzed Hydrogenation of Triptycene

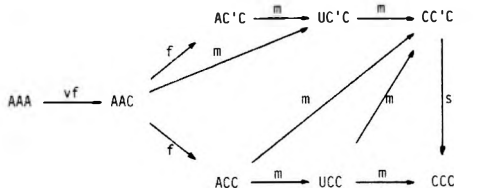
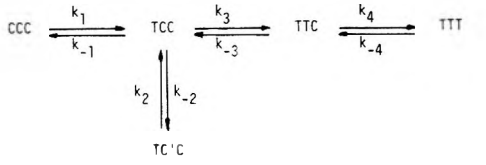


Chart IV. Palladium-Catalyzed Epimerization of Perhydrotriptycenes



reaches a maximum after 2–5 h, then it decreases mainly in favor of UC'C and CC'C. The reaction yielding UC'C independently of AC'C is less pronounced than in the case of palladium.

Ruthenium also differs from palladium in the way of formation of CC'C. Selective hydrogenations indicate that this isomer is formed from both AC'C and ACC. In the latter case the data may be interpreted by assuming the existence of the following reactions: ACC → UCC, ACC → CC'C, UCC → CCC, UCC → CC'C, and CC'C → CCC. Also a slight contribution of the direct reaction ACC → CCC is not excluded.

The general scheme of reaction over ruthenium is reported in Chart III.

Palladium-Catalyzed Epimerization. With the formation of CCC, CC'C, and TC'C the quite complex process of hydrogenation of triptycene is completed. As already mentioned, the above isomers epimerize to other stereoisomers. Since the transformation of CC'C into CCC is fast over palladium (with respect to the subsequent reactions) and the amount of TC'C is always small, we are able to observe the fate of CCC only (Figure 3 and Chart IV). CCC is transformed through a series of reversible consecutive and parallel reactions into TCC, TC'C, TTC, and TTT. Equilibrium is reached after more than 2 months reaction at 445 K with a high catalyst/hydrocarbon ratio. The values of the concentration, the equilibrium constants, and $\Delta G°$ are reported in Table V.

The epimerization course was interpreted quantitatively (according to the scheme of Chart IV), by taking into account the values of the equilibrium constants of the single reactions. An excellent agreement with the experimental data was obtained by giving the following relative values to the rate constants: $k_1 = k_3 = 28$, $k_{-1} = 13$, $k_{-3} = 7.5$, $k_4 = 2.25$, $k_{-4} = 1$, k_2 whatever value, $k_{-2} = 0.15k_2$.

Discussion

Among the many interesting points arising from the study of the catalytic hydrogenation of triptycene, we wish to tackle

Table V. Equilibrium Composition, Equilibrium Constants, and Standard Free Energy of the Reaction TTT ⇄ Less Stable Isomers, in Liquid Phase at 445 K

Isomer	Mol %	K_{eq}	$\Delta G°$, cal/mol
TTT	61.2		
TTC	27.0	0.44	720
TCC	7.3	0.12	1900
CCC	3.4	0.055	2550
TC′C	1.1	0.018	3550
CC′C	<0.05	$<10^{-3}$	>6000

two groups of problems, one connected with the reaction mechanism, the other concerning structure and thermodynamics.

Hydrogenation of unsaturated compounds proceeds by the well-established cis or *suprafacial* addition. Trans compounds are produced by subsequent epimerization which requires long reaction times.

As already mentioned, the hydrogenation of triptycene occurs by steps, involving just one aromatic ring at a time. Only in this way, the formation of AAC and its transformation into ACC and AC′C is explained. A simultaneous reaction on the two rings would directly convert AAA into AC′C or ACC′ and, were it somehow formed, AAC into CC′C in contrast with the experimental findings. It is worthwhile to notice the appreciable amount of cyclic olefins present in the reaction mixture at the first stages, confirming that also the benzene ring is reduced step by step.

Furthermore, the stereochemical data better agree, in the case of palladium, with an approach of hydrogen from the top side (or from the gas phase), if the molecule is adsorbed on the catalyst in the most favorable arrangement. This statement is based on the higher rate of the reaction ACC → CCC with respect to ACC → CC′C, together with the nonreactivity of AC′C.[23] This result contrasts with the most common hypothesis of addition of hydrogen from the bottom side and supports the Rideal mechanism of hydrogenation.

With regard to thermodynamics the most significant result consists in the small free-energy difference between TTT and CCC and in general among the five most stable stereoisomers of perhydrotriptycene (Table V).

TTT has a slightly twisted bicyclo[2.2.2]octane frame, about 20°, and the outer cyclohexanes have a deformed chair conformation. CCC, on the contrary, is substantially eclipsed, with cyclohexanes in boat conformation. As a consequence, the enthalpy difference between the two isomers should be about 15 kcal/mol.[24] Since the entropic contribution due to symmetry and to enantiomer mixing is essentially balanced in the two cases, analogous values should be found for the free-energy difference, in contrast with the experimental value.

Such a discrepancy between qualitative conformational analysis and the experimental value is due to an underestimation of transannular interactions. Calculations of molecular mechanics, carried out by Allegra and Bruckner,[21] justify the entire set of data on the basis of the conformational parameters proposed by Boyd.[25] The enthalpy difference calculated between TTT and CCC is 1.8 kcal/mol, in good agreement with our result.

A further proof of the complex steric interactions existing in the series of compounds is drawn from the examination of the reaction AC′C ⇄ UC′C. At 150 °C and under 60 H_2 atm, about 3–5% of AC′C is obtained from UC′C. This indicates a lower value of $\Delta G°$ (more than 4 kcal/mol) with respect to the analogous reaction benzene ⇄ cyclohexene at the same temperature. The high energy content of UC′C must be related to the considerably large transannular interactions of allyl hydrogens 1γ and 1γ′ with the saturated rings 2 and 3.

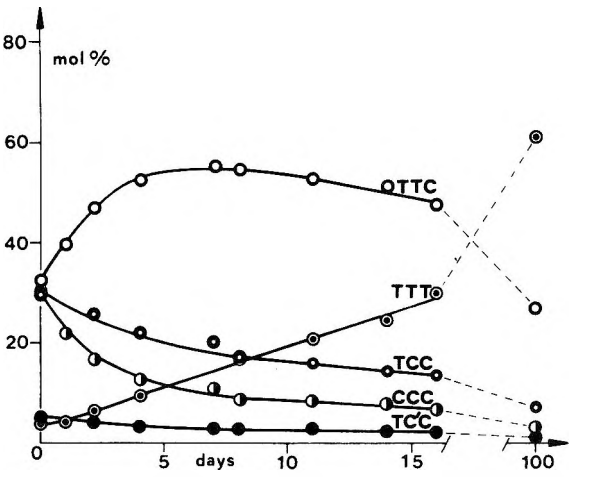


Figure 3. Epimerization of perhydrotriptycenes over palladium at 445 K and 60 atm H_2.

Experimental Section

General. Melting points were determined on a Leitz hot-stage microscope and are uncorrected.

Hewlett-Packard Model 5750 research gas chromatographs equipped with TC and FID detectors were used for analytical studies. The following columns (stainless steel, unless otherwise specified) and conditions were used: A, 10% diethylene glycol succinate (LAC-3R-728) on 100–120 mesh Chromosorb W AW-DMCS, 2 m × 0.125 in., 160 °C, 30 mL/min He; B, 3% Apiezon L on 100–120 mesh Chromosorb W AW-DMCS, 4 m × 0.125 in., 220 °C, 20 mL/min He; C, 2% Silicone OV-17 on 100–120 mesh Chromosorb W AW-DMCS, 2 m × 0.125 in., 185 °C, 27 mL/min He; D, 2% Silicone rubber SE-52 on 100–120 mesh Chromosorb W AW-DMCS, 5 m × 0.125 in., 220 °C, 30 mL/min He; E, Carbowax 20M, stainless steel capillary column 50 m × 0.25 mm i.d., 180–200 °C, 2 mL/min He; F, Silicone OV-101, stainless steel capillary column, 50 m × 0.25 mm i.d., 200–220 °C, 2 mL/min He; G, Ucon LB 550 X, glass capillary column, 30 m × 0.3 mm i.d., 160 °C, 2 mL/min He. Columns A, B, C, and D are suitable for the analysis of the mixtures of saturated isomers, but in the presence of olefinic or aromatic compounds some overlapping of peaks or excessively long retention time was observed. Only column B was convenient for the separation of TCC and TC′C. Retention indices were measured on columns E and F. Quantitative analysis was performed on column G, which is a general purpose column, with the aid of a Hewlett-Packard 3380 A recording integrator.

A F and M Model 770 preparative gas chromatograph equipped with a TC detector was used for preparative separations on the following columns: H, 20% Silicone rubber SE-30 on 45–60 mesh Chromosorb W, 2.3 m × 19 mm o.d., 230 °C, 400 mL/min He; K, 20% Silicone rubber SE-52 on 60–80 mesh Diatoport S, glass, 2 m × 10 mm o.d., 260 °C, 250 mL/min He.

Infrared spectra were recorded on Perkin-Elmer Model 457 and Model 125 spectrophotometers (KBr pellets).

Mass spectra were determined on a 5930 A Hewlett-Packard dodecapole mass spectrometer connected with a 5700 Hewlett-Packard gas chromatograph equipped with columns B, C, and D quoted above. A 5932 Hewlett-Packard data system provided the acquisition and reduction of GC/MS data.

^1H NMR spectra were obtained on a Varian HA-100 spectrometer in CCl_4 or CS_2 with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Bruker HFX/10 spectrometer in deuteriobenzene with internal standard Me_4Si.

Reagents. Triptycene (Aldrich Chemical Co.) was crystallized twice from toluene, mp 259 °C. Palladium (10% on charcoal) and ruthenium (5% on charcoal, dry) were purchased from Engelhard Industries Inc. *n*-Heptane was a high-purity product from Esso. Pure (99.95%) dry hydrogen was used.

Procedures. Hydrogenations were carried out in an oscillating 500-mL stainless steel pressure reactor equipped with a needle sampling valve. Temperature was controlled ±5 °C. Reactions were carried out on a semimicro scale (0.05–0.1 g of starting compound in 100 mL of *n*-heptane) or on a preparative scale (0.5–10 g of reagent in 100 mL of *n*-heptane).

Semimicro Hydrogenations. A breakable small glass vial containing triptycene (50 mg) was sealed under nitrogen and introduced into the reactor with Pd/C (250 mg) [or with Ru/C (500 mg)] and *n*-

heptane (100 mL). Air was replaced with nitrogen, the reactor was heated to 150 °C, hydrogen (60 atm) was introduced, and stirring was started.

Samples (0.5–1 mL) were withdrawn from the reactor at suitable times, taking care to purge the valve with the reaction solution (1 mL at least) before every drawing. After filtration from the catalyst, the composition was determined by gas chromatography.

Preparative Hydrogenation and Isolation of Pure Products. Hydrogenation conditions were selected in such a way as to optimize the yield of every product and to simplify the successive isolation procedure. The single products were isolated by preparative gas chromatography, by adsorption liquid–solid chromatography, and/or by fractional cyrstallization from different solvents.

TTT, TTC, TCC, and CCC. Triptycene was hydrogenated at 150–190 °C and 60–80 atm over 10% Pd/C (usually 1:1 by weight). The reaction time ranged from 2 to 3 days (for CCC) to 20 days and more (for TTT) at 150 °C. At 190 °C the time was considerably reduced, but some perhydroanthracene was formed.

Isolation of single isomers was best accomplished by preparative GC on column H. Preparation of pure TTC required the absence of UCC and UC′C due to the similar value of their Kovats indices on most columns. Separation of TCC from TC′C proved very difficult; in the best case an 85:15 mixture was obtained. In the other isomers, purity reached 98–99% (GC).

CC′C. Triptycene was hydrogenated over 5% Ru/C (1:1 by weight) at 150 °C and 80 atm. After 15 h the yield of CC′C reached 40–50%. After filtration from the catalyst, the compound was obtained by preparative GC on column H, purity 98.5% (GC).

UCC. Mixtures containing 20–25% of UCC were easily obtained by triptycene hydrogenation over Pd or Ru (2–4 h). However, the presence of a comparable amount of UC′C made its separation impossible. After repeated crystallizations from pentane, a purity of 70% was obtained.

A possible way to prepare pure UCC consists in the hydrogenation of ACC over Ru (1:1 by weight). After 5–8 h the mixture contains 20–25% UCC, 25–35% CC′C, 10–20% CCC, but not UC′C. UCC can be purified by adsorption chromatography.

UC′C. AC′C was hydrogenated over Pd (1:1) at 150 °C and 60 atm. After 8 days, the amount of UC′C reached 50%. The product was purified by repeated crystallization from acetone, purity 99% (GC).

ACC, AC′C, and AAC. Triptycene (contained in a breakable glass vial) was hydrogenated over Pd (1:1) at 150 °C and 60 atm. After 15–45 min, pressure was released and the reactor was rapidly cooled. The filtered solution was eluted through a silica gel column with *n*-heptane, then with toluene, and finally with acetone. Products were collected in the following order: saturated compounds, UC′C, UCC, AC′C, ACC, AAC, and AAA. Each fraction was repeatedly crystallized from *n*-heptane. Purity reached 98–99% (GC).

Equilibration of Perhydrotriptycene Stereoisomers. A mixture of saturated isomers was heated in the presence of 10% Pd/C (1:2 by weight) to 172 °C under 60 atm of hydrogen, until the composition remained constant (2 months). Equilibration was further continued with fresh catalyst for 1 month. After filtration from the catalyst, the mixture was analyzed by GC.

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Appendix

Determination of the Number and Symmetry of Hexasubstituted Bicyclo[2.2.2]octane Stereoisomers. Each stereoisomer is indicated by a triplet of letters chosen among T, T′, C, and C′, the meaning of which is defined in the text. By using simple element of combinatorial analysis and by considering the internal symmetry of the letters, the following rules are established.

(1) All triplets generated by cyclic permutation are identical (e.g., TCC′ = CC′T).

(2) The replacement of C by C′ and vice versa (leaving T and T′ unchanged), followed by an exchange of the position of two letters, produces a triplet equivalent to the primitive one (e.g., TCT′ = TT′C′). Such an operation corresponds to the inversion of the way of observation of the same compound.

(3) The replacement of T by T′ and vice versa (leaving C and C′ unchanged) converts a triplet into its mirror image (e.g., TTC is the antipode of T′T′C).

(4) A stereoisomer has a plane of symmetry perpendicular to the bicyclo[2.2.2]octane axis if, by performing the operation described in 3, a triplet is generated that is identical with or equivalent to the primitive one, according to 1 and 2 (e.g., CC′C (3) → CC′C).

(5) A stereoisomer has a threefold axis of symmetry coincident with the bicyclooctane axis, if the related triplet consists of three equal letters (e.g., TTT and CCC).

(6) A stereoisomer has (at least) a twofold axis perpendicular to the bicyclooctane axis, if, by performing the operation described in 2, a triplet is generated which is identical (according to 1) with the primitive one, e.g.,

$$TC'C \xrightarrow{2} C'CT \xrightarrow{1} TC'C$$

Application of rules 1–6 leads to the following results:

(I) Sixty-four triplets exist consisting of letters T, T′, C, and C′.

(II) Twenty-four distinct triplets exist according to rule 1.

(III) Sixteen distinct triplets exist according to rules 1 and 2.

(IV) Seven pairs of enantiomers exist according to rules 2 and 3.

(V) Two meso compounds exist according to rules 2 and 4.

(VI) Three stereoisomers with a threefold symmetry exist according to rules 2 and 5. Two of them (TTT and T′T′T′) form, according to 3, an enantiomeric pair and have, according to 6, (at least) a twofold axis. The only possible symmetry group is D_3. The third stereoisomer (CCC) possesses, according to 4, a mirror plane perpendicular to the axis. The only possible symmetry group is C_{3h}.

(VII) Six further stereoisomers with a twofold axis exist, according to rules 2 and 6; according to rule 3, they form three pairs of enantiomers. Symmetry group: C_2.

In conclusion, apart from the presence of optical antipodes, the stereoisomers of hexasubstituted bicyclo[2.2.2]octane are nine (see IV and V). The preferred nomenclature and symmetry of each isomer are indicated in Table I.

Registry No.—TTT, 41841-41-2; TTC, 62211-78-3; TCC, 62211-79-4; CCC, 41841-40-1; CC′C, 62182-20-1; TC′C, 62211-80-7; ACC, 62182-19-8; UCC, 62183-41-9; AC′C, 61897-81-2; UC′C, 62211-82-9; AAC, 62211-83-0; AAA, 477-75-8; AUC, 62183-42-0.

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(26) According to the Cahn–Ingold–Prelog rules, and to the official numbering system, the absolute configurations of the isolated chiral stereoisomers follow: TTT = 4a*S*,8a*S*,9a*S*,10a*S*,11*S*,12*S*; TTC = 4a*S*,8a*R*,9a*S*,10a*S*,11*S*,12*S*; TCC = 4a*S*,8a*R*,9a*R*,10a*S*,11*S*,12*S*;TC'C = 4a*R*,8a*R*,9a*R*,10a*S*,11*S*,12*S*.
(27) As for the olefinic compounds, the indicated symmetry corresponds to the apparent symmetry or the maximum allowed symmetry, related to the fast averaging of the conformation of the cyclohexene ring.

Synthesis and Rearrangement of *tert*-Butylanthracenes

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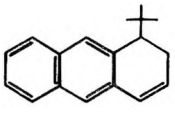
Dehydrogenation of a series of mono- and di-*tert*-butyldihydroanthracenes is investigated as a potential synthetic route to the corresponding *tert*-butylanthracenes. Synthesis of 1- and 2-*tert*-butylanthracene is accomplished through dehydrogenation with DDQ and o-chloranil, respectively. Dehydrogenations with the reagent trityl trifluoroacetate generated in situ from trityl alcohol in trifluoroacetic acid lead to rearrangement and disproportionation to afford anthracene, 2-*tert*-butylanthracene, and 2,6-di-*tert*-butylanthracene. Similar rearrangements of the fully aromatic *tert*-butylanthracenes occur in trifluoroacetic acid neat. Reaction of anthracene with *tert*-butyltrifluoroacetate affords 2,6-di-*tert*-butylanthracene directly in high yield. The mechanism of these reactions and structural assignments of the *tert*-butylarenes by NMR analysis are discussed.

Despite the voluminous literature on polycyclic hydrocarbons, remarkably few *tert*-butylarenes have ever been synthesized.[1] At the inception of this research, 1-*tert*-butylanthracene and 9,10-di-*tert*-butylanthracene were unknown, and 2- and 9-*tert*-butylanthracene were obtainable only through multistep syntheses.[2,3] Since the related mono-*tert*-butyldihydroanthracene compounds **1–3** are obtainable through addition of *tert*-butyllithium to anthracene,[4,5] and the di-*tert*-butyldihydro compounds **4** and **5** can be synthesized through alkylation of **3**,[5] dehydrogenation of **1–5** appears



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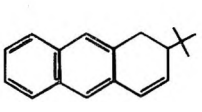

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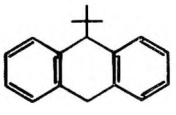

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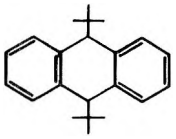

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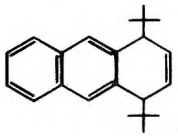


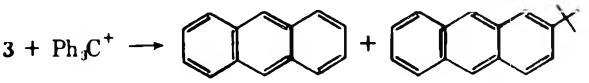
5

to offer a convenient route to the corresponding mono- and di-*tert*-butylanthracenes. In this study the synthetic utility of this and other approaches to *tert*-butyl substituted anthracenes is examined, and the products and mechanisms of rearrangements encountered are investigated.

Results

Dehydrogenation of 1-*tert*-butyl-1,2-dihydroanthracene (**1**) with DDQ gave 1-*tert*-butylanthracene, readily distinguished from its isomers by its NMR spectrum (cf. summary of NMR results presented later in this section). Similar reaction of 2-*tert*-butyl-1,2-dihydroanthracene (**2**) with DDQ afforded only tarry products, but when the milder reagent o-chloranil was employed, 84% of 2-*tert*-butylanthracene was obtained. Its NMR spectrum and other physical properties match those of an authentic sample.[2] In contrast, 9-*tert*-butyl-9,10-dihydroanthracene (**3**) resisted dehydrogenation by o-chloranil in refluxing benzene. Analogous reaction with DDQ gave a complex mixture of products containing less than 2% of the desired product, 9-*tert*-butylanthracene.

Attempted dehydrogenation of **3** with trityl trifluoroacetate generated from trityl alcohol in refluxing trifluoroacetic acid[6] furnished a mixture of anthracene, 2-*tert*-butylanthracene (**6**), and 2,6-di-*tert*-butylanthracene (**7**) in the approximate



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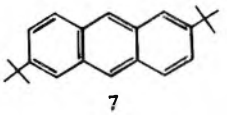
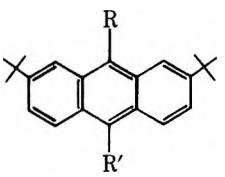
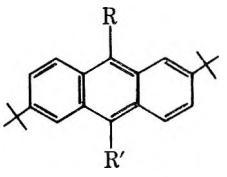


7

ratio of 2:1:1. All attempts to separate the components of this mixture by conventional chromatographic techniques on columns or thin layers of silica gel, alumina, or Florisil failed. Efficient separation was achieved, however, by chromatography on silica gel impregnated with 2% trinitrofluorenone.[7] The structural assignment of the 2,6-di-*tert*-butyl isomer **7** was made initially through analysis of its NMR spectrum in comparison with those of other *tert*-butylanthracene derivatives, as discussed later in this section. This assignment was confirmed and the alternative isomeric 2,7-di-*tert*-butylanthracene (**8a**) structure excluded through bromination to a monobromo derivative.[13] The NMR spectrum of the latter was entirely consistent with the structure **9a** anticipated to be formed from **7** and incompatible with either **8b** or **8c** expected to be formed from **8a**.



8a, R = R' = H
b, R = Br; R' = H
c, R = H; R' = Br



9a, R = Br; R' = H
b, R = R' = CH_3

Table I. Dehydrogenation and Rearrangement of Mono- and Di-*tert*-butyldihydroanthracene with Trityl Trifluoroacetate Generated in Situ[a]

Registry no.	Compd	Amount, mg	Time, h	Yield, %[b] Anthracene	6	7
62337-61-5	1	20	16	45	35	20
62337-62-6	2	15	20	35	50	15
13387-48-9	3	25	24	55	25	20
54974-11-7	*trans*-4	383	24	5	15	80
54974-12-8	5	82	20	20	25	55
54974-10-6	*cis*-4[c]	30	15	0	0	0

[a] Conditions are described in the Experimental Section. In all experiments, a 5% molar excess of trityl alcohol was employed. [b] Yields are based on the integrated NMR spectra and represent product percentage composition rather than isolated yields of pure products. The estimated error is in the range of ±5%. [c] Only TFAA (5 mL) without trityl alcohol was employed.

Analogous reaction of **1** or **2** with trityl trifluoroacetate in trifluoroacetic acid also afforded anthracene, **6**, and **7** as the principal products (Table I). Reaction of *trans*-9,10-di-*tert*-butyl-9,10-dihydroanthracene (**4**) with trityl trifluoroacetate under similar conditions led to formation of 2,6-di-*tert*-butylanthracene (80%) accompanied by lesser amounts of anthracene (5%) and **6** (15%). Similar reaction of the *cis*-1,4-di-*tert*-butyl compound **5** gave the same three products in somewhat different ratio (Table I).

The rearranged products apparently arise via an anthracenonium ion formed by initial hydride abstraction. Thus, the di-*tert*-butyl compounds **4** and **5** when refluxed in trifluoroacetic acid in the absence of trityl alcohol gave no reaction. Since dehydrogenation (i.e., loss of a proton from the intermediate) may conceivably precede rearrangement, reactions of the *tert*-butylanthracenes in trifluoroacetic acid were investigated. When 9-*tert*-butylanthracene was heated at reflux in trifluoroacetic acid for 24 h, a mixture of anthracene, **6**, and **7** was obtained in similar ratio to that isolated from dehydrogenation and rearrangement of **3** (Table I). Analogous reaction of 2-*tert*-butylanthracene in trifluoroacetic acid gave a mixture of the same three products (Table I). While this result apparently supports the idea that dehydrogenation precedes rearrangement, it is inconclusive since protonation of a *tert*-butylanthracene derivative in strong acid can afford the same carbonium ion intermediate as hydride abstraction from a *tert*-butyldihydroanthracene (cf. Discussion).

As discussed in greater detail in the following section, *tert*-butyl trifluoroacetate appears to be the active intermediate species which *tert*-butylates anthracene and its derivatives regiospecifically in the 2 position during these rearrangements. To test this hypothesis, reaction of anthracene with *tert*-butyl alcohol in trifluoroacetic acid was investigated and found to furnish the 2,6-di-*tert*-butyl isomer virtually quantitatively (Table II). Even with short reaction time and low ratios of the reagent, no more than traces of the mono-*tert*-butyl derivative **6** could be detected, indicating the second *tert*-butylation step to be much more rapid than the first.

In view of the efficiency of this synthesis, additional examples were examined to extend its generality. Analogous reactions of 2-methylanthracene and 9,10-dimethylanthracene furnished 2-methyl-6-*tert*-butylanthracene (**10**) and 9,10-dimethyl-2,6-di-*tert*-butylanthracene (**9b**), respectively, in good yields.

The NMR spectra of the *tert*-butylanthracene compounds exhibit characteristic chemical shift patterns in the aromatic region which are consistent with the assigned structures. The meso (γ) protons of anthracene appear as a singlet at lowest field (δ 8.38), and the α and β protons appear as multiplets at δ 8.02 and 7.43, respectively.[8] The NMR spectrum of 1-*tert*-butylanthracene shows one less α proton, and the meso proton adjacent to the *tert*-butyl group appears downfield at δ 8.98 ($\Delta\delta$ = 0.60 ppm). This relatively large deshielding effect of the *tert*-butyl group in the adjacent peri proton is consistent with values found previously for other *tert*-butyl substituted arenes.[8,9] The spectrum of 9-*tert*-butylanthracene shows a single proton at δ 8.22 shifted upfield ($\Delta\delta$ = 0.16) from the meso protons of anthracene. One pair of α protons (H_4, H_5) appears in the anthracene region, while the remaining pair (H_1, H_8) is found ~0.60 ppm downfield, consonant with their location in the positions peri to the *tert*-butyl group. The chemical shift pattern of 2-*tert*-butylanthracene differs little from that of the parent hydrocarbon except for the absence of one β proton. Although a shift of the ortho protons of *tert*-butylbenzene[10] and 2,7-di-*tert*-butylpyrene[11] to lower field has been noted, this effect appears relatively insignificant in 1- and 2-*tert*-butylanthracene.

Table II. *tert*-Butylation of Anthracene with *tert*-Butyl Alcohol in TFAA[a]

Molar ratio $(CH_3)_3COH/C_{14}H_{10}$	Time, h	Product composition, %[b] Anthracene	6	7
1	0.25	>99	Tr	0
1	24	50	0	50
2	24	0	0	100
3	24	0	0	100

[a] Experimental details are described in the Experimental Section. [b] Product compositions are determined from the integrated NMR spectra of the products isolated according to the procedure described.

The NMR spectrum of 2,6-di-*tert*-butylanthracene exhibits a relatively simple pattern consonant with the symmetry of the assigned structure. The β protons (H_3, H_7) appear as a doublet at δ 7.48 (J_{ortho} = 9.0, J_{meta} = 2.0 Hz), while the α protons ortho to the *tert*-butyl groups (H_1, H_5) appear as a singlet at δ 7.84, and the remaining pair of α protons (H_4, H_8) occur as a doublet at δ 7.90 (J_{ortho} = 9.0 Hz); the meso protons appear as a singlet at δ 8.29. This spectral pattern, while consistent with structure **7**, does not rule out the alternative 2,7-di-*tert*-butyl structure **8a**. However, the spectrum of the monobromo derivative obtained through reaction with cupric bromide[12] is consistent only with structure **9a**, proof of its origin from **7**. Most significant are the markedly different chemical shifts of the two α protons at H_1 and H_5. The peak at δ 8.21 assigned to H_1 is strongly displaced downfield ($\Delta\delta$ = 0.37) relative to that of the parent hydrocarbon **7**, while the H_5 signal (δ 7.75) is only slightly shifted, clear evidence for the location of the bromine at C-9 adjacent to H_1. Similarly, the remaining two α protons (H_4 and H_8) appear as doublets (J = 9 Hz), one of which exhibits a major downfield shift ($\Delta\delta$ = 0.42) relative to **7**, while the other signal (δ 7.90) is only slightly shifted. Therefore, the former can be assigned to H_8 which must also be located adjacent to the bromine atom. All four α protons are, therefore, different, a structural feature characteristic of the unsymmetrical structure **9a** and inconsistent with the symmetrical isomers **8b** and **8c**. Thus, structures **9a** and **7** can be assigned unequivocally to the monobromo compound and the parent hydrocarbon, respectively.

The chemical shifts of the *tert*-butyl protons of the mono-*tert*-butylanthracenes exhibit marked dependence on the site of substitution. The *tert*-butyl protons of 2-, 1-, and 9-*tert*-butylanthracene appear as singlets at δ 1.42, 1.73, and 1.85, respectively. The observed order $\beta < \alpha < \gamma$ corresponds to the known relationship of the chemical shifts of protons or methyl

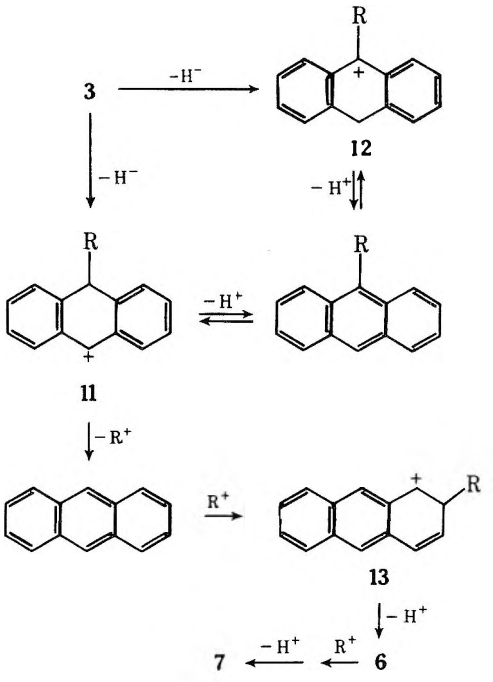
groups in these positions[9] which is considered primarily a consequence of the aromatic ring current effect. The chemical shifts of the *tert*-butyl protons of compounds **7**, **9a**, **9b**, and **10** corresponded closely to that of the 2-*tert*-butyl isomer, confirming the assigned location of this group in β positions in all cases. The two *tert*-butyl groups of **9a** exhibited slightly different chemical shifts (δ 1.47, 1.50), further evidence for the unsymmetrical isomeric structure assigned.

Discussion

Synthesis of 1- and 2-*tert*-butylanthracene through addition of *tert*-butyllithium to anthracene followed by dehydrogenation of the resulting 1,2-dihydroanthracene adducts with DDQ and o-chloranil, respectively, provides a relatively convenient route to these difficulty accessible compounds. Attempted analogous synthesis of 9-*tert*-butyl- and 9,10-di-*tert*-butylanthracene proved unsatisfactory. Alternative approaches involving either dehydrogenation with trityl trifluoroacetate or direct *tert*-butylation of anthracene with *tert*-butyl alcohol in trifluoroacetic acid also failed to furnish the desired 9-*tert*-butylanthracene derivatives. Instead, the rearranged products of **6** and/or **7** were obtained. From a purely synthetic viewpoint, direct *tert*-butylation with *tert*-butyl alcohol in trifluoroacetic acid provides a convenient and efficient synthesis of 2,6-di-*tert*-butylanthracene and related compounds such as **9b** and **10**. This reagent, first reported by Svanholm and Parker,[13] holds considerable promise as a generally useful reagent for the direct *tert*-butylation of other polycyclic hydrocarbons in ring positions of minimum steric hindrance.

All the reactions described in this report, despite their superficial differences, may be interrelated through a common mechanistic scheme (Chart I). This may be illustrated for **3**,

Chart I



R = $(CH_3)_3C$

the conformation of which has been shown to be a flattened boat structure with the bulky *tert*-butyl group oriented axially as a consequence of the steric interaction with the peri hydrogens in the 1 and 8 positions.[4] Hydride abstraction from the 10 position of **3** by trityl cation, DDQ, or chloranil affords the carbonium ion **11**. Although hydride abstraction could conceivably also take place at the 9 position of **3** to afford **12**, attack in this region is less probable since the hydrogen atom at C-9 is equatorial and highly hindered. In any case, it is known that **12** undergoes facile conversion to **11** in the presence of acid.[3] The intermediate **11** can undergo loss of either a proton or a *tert*-butyl ion. The latter is favored due to the strong steric resistance to formation of 9-*tert*-butylanthracene. The *tert*-butyl carbonium ion produced can recombine with anthracene, possibly without prior dissociation, to provide the new intermediate **13**. Aromatization of the latter is energetically favorable, since the peri steric interaction present in **11** is lacking. Dehydrogenation of **2** under similar conditions is expected to provide directly the intermediate **13** which collapses to 2-*tert*-butylanthracene (**6**) without involvement of rearrangement. Subsequent reaction of **6** with a second *tert*-butyl cation, probably as *tert*-butyl trifluoroacetate, takes place at the equivalent position on the other side of the molecule, i.e., the 6 position, to furnish **7**. Reaction stops at this stage, since there remain no positions unhindered by either peri hydrogen or a *tert*-butyl group.

Similar reaction of **1** presumably involves initial formation of an intermediate analogous to **13** bearing the positive charge in the 2 position. Aromatization of this intermediate, since there is a peri hydrogen on only one side of the carbon atom bearing the *tert*-butyl group, is expected to occur with greater facility than **11** and slower than **13**.

Reactions of the disubstituted compounds **4** and **5** are presumed to proceed via analogous pathways.

Prolonged heating of any of the isomeric mono- or di-*tert*-butylanthracenes in TFAA may be expected, according to this mechanism, to result in eventual conversion to anthracene and **7**. It is likely also that loss of the *tert*-butyl group as isobutylene could become seriously competitive under such conditions.

Finally, the technique of "charge-transfer chromatography" on silica gel impregnated with 2,4,7-trinitrofluorenone[7] is deserving of further comment. A mixture of anthracene, the three isomeric mono-*tert*-butylanthracenes, and 2,6-di-*tert*-butylanthracene which migrated together as a single spot on silica gel, Florisil, and alumina was clearly separated into its individual components on a TNF–silica gel plate. Moreover, each compound exhibited a distinctive color characteristic of its charge-transfer complex. These follow in order of R_f value: 9-*tert*-butyl- (brown) > 2,6-di-*tert*-butyl (blue-gray) > 1-*tert*-butyl- (red-violet) > 2-*tert*-butyl- (violet-red) > anthracene (maroon). This powerful technique is routinely employed in our laboratory to effect many difficult separations of hydrocarbon isomers and derivatives. It is highly recommended for general use.

Experimental Section

Physical Data. ^{1}H NMR spectra were obtained on Varian T-60 and Bruker 270 MHz spectrometers; chemical shifts are reported relative to Me_4Si in CCl_4. Integration was consistent with all assignments. Gas chromatographic analyses were performed on a Varian 2700 chromatograph employing a 5.5 ft × 0.25 in. 10% SE-30 60–80 mesh Chromosorb WA column, with 21 psig helium pressure. Thin layer plates of silica gel impregnated uniformly with 2,4,7-trinitrofluorenone (TNF) were prepared as described previously[7] and developed with benzene in hexane (1:2).

Materials. Benzene was dried over lithium aluminum hydride and redistilled from this reagent. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and o-chloranil were purchased from Araphahoe and Upjohn, respectively. Anthracene, 2-methylanthracene, and 9,10-dimethylanthracene were crystallized before use. The dihydroanthracene derivatives **1**–**5** were prepared as described previously.[4,5] Trityl alcohol, *tert*-butyl alcohol, and trifluoroacetic acid (TFAA) were obtained from commercial sources and used without purification.

Dehydrogenation of 1-*tert*-Butyl-1,2-dihydroanthracene (1) with DDQ. A solution of **1** (54 mg, 0.23 mmol) and DDQ (120 mg, 0.53 mmol) in benzene (10 mL) was refluxed for 1 h. After removal of benzene, the residue was chromatographed over silica gel. Elution with

hexane–benzene (4:1) gave 1-*tert*-butylanthracene (10 mg, 19%) as a colorless oil: NMR (CCl_4) δ 1.73 (s, 9, CH_3), 7.42 (m, 4, H_2, H_3, H_6, and H_7), 7.92 (m, 3, H_4, H_5, and H_8), 8.40 (s, 1 H_{10}), and 8.98 ppm (s, 1, H_9); GLC retention time 12 min.

Dehydrogenation of 2-*tert*-Butyl-1,2-dihydroanthracene (2) with o-Chloranil. A solution of 2 (70 mg, 0.3 mmol) and o-chloranil (75 mg, 0.3 mmol) in benzene (10 mL) was refluxed for 50 min. After removal of benzene by rotatory evaporator, the dark brown-black residue was extracted with 20 mL of hot hexane. The filtrate was then chromatographed on silica gel. Elution with hexane–benzene (9:1) gave a colorless solid (63 mg) which was identified as 2-*tert*-butylanthracene (6) containing a trace of anthracene by TLC on silica gel impregnated with TNF. Recrystallization from methylene chloride–petroleum ether (bp 30–60 °C) gave pure **6** as a colorless solid, 58 mg (84%), mp 146–147 °C (lit.[2] 145.5–146.5 °C). The NMR spectrum, TLC, and GLC retention time (13.2 min) were identical with those of an authentic sample, provided by Dr. L. H. Klemm.

Dehydrogenation and Rearrangement of Mono- and Di-*tert*-butyldihydroanthracene with Trityl Alcohol in TFAA. A mixture of *trans*-9,10-di-*tert*-butyl-9,10-dihydroanthracene (**4**, 383 mg, 1.31 mmol), trityl alcohol (360 mg, 1.38 mmol), and TFAA (6 mL) was heated at reflux for 1 day. The solution was cooled, quenched with water, neutralized with sodium bicarbonate, and partitioned between ethyl ether and water. The ethereal layer was separated, dried over magnesium sulfate, and evaporated to dryness to yield 719 mg of a brown solid. Analyses by NMR and TLC on TNF–silica gel revealed the presence of anthracene, **6**, and **7** in the ratio 5:15:80, together with triphenylmethane, and a trace of recovered **4**. Chromatography on a column of silica gel (2.5 × 25 cm) eluted with hexane gave pure **7** as a colorless solid, 278 mg, mp 150–152 °C.

Analogous reactions with **1**, **2**, **3**, and **5** furnished the products summarized in Table I.

Rearrangement of 9-*tert*-Butylanthracene. 9-*tert*-Butylanthracene (100 mg, 0.43 mmol) in 7 mL of TFAA was refluxed for 22 h. TFAA was removed under vacuum to afford a light brown solid (89 mg). Analysis of the NMR spectrum confirmed by TLC on TNF–silica gel indicated the product to contain anthracene, **6**, and **7** in the ratio 55:20:25.

In a separate experiment, 20 mg of 9-*tert*-butylanthracene in 5 mL of TFAA heated at reflux for 20 min gave a product containing anthracene, **6**, and **7** in the ratio of 85:10:5.

Rearrangement of 2-*tert*-Butylanthracene (6). A solution of **6** (30 mg, 0.13 mmol) in 5 mL of TFAA was heated at reflux for 30 min. Analysis of the product obtained following the usual workup revealed unchanged **6** containing only trace amounts of anthracene and **7**. A similar reaction for 4 h gave 85% recovered **6** accompanied by equal amounts of anthracene and **7**.

Nonrearrangement of 2,6-Di-*tert*-butylanthracene (7). A solution of **7** (100 mg) refluxed in 10 mL of TFAA for 4 h gave no reaction.

***tert*-Butylation of Anthracene.** A mixture of anthracene (1.78 g, 10 mmol), *tert*-butyl alcohol (2.22 g, 30 mmol), and TFAA (10 mL) was heated at reflux for 24 h. The resulting dark brown solution was allowed to cool to room temperature, and water (50 mL) was added. The solution was neutralized with sodium bicarbonate and extracted with ethyl ether. The ethereal layer was separated and dried over magnesium sulfate, and ether was removed, giving a brownish solid (3.18 g). NMR analysis confirmed by TLC showed the presence of only **7**. Chromatography on a silica gel column eluted with hexane gave **7** which was recrystallized twice from methanol to afford the analytical sample of **7** as light yellow plates, 2.09 g (72%): mp 151–152.5 °C; NMR (CCl_4) δ 1.42 (s, 18, CH_3), 7.48 (d, 2, J = 9.0 Hz, H_3 and H_7), 7.84 (s, 2, H_1 and H_5), 7.90 (d, 2, J = 9.0 Hz, H_4 and H_8), and 8.29 ppm (s, 2, H_9 and H_{10}).

Anal. Calcd for $C_{22}H_{26}$: C, 90.76; H. 9.24. Found: C, 90.95; H, 9.03.

***tert*-Butylation of 2-Methylanthracene.** Analogous reaction of 2-methylanthracene (960 mg, 5 mmol) in *tert*-butyl alcohol (2.22 g, 30 mmol) and TFAA (10 mL) for 16 h, followed by conventional workup, gave a brown solid (1.67 g). Chromatography on a column of Florisil (2.5 × 20 cm) eluted with hexane, followed by recrystallization from methylene chloride–petroleum ether (bp 30–60 °C), gave pure 2-methyl-6-*tert*-butylanthracene (**10**) as a yellow solid (843 mg, 68%): mp 173–175 °C; NMR (CCl_4) δ 1.44 (s, 9, *tert*-butyl), 2.57 (s, 3, CH_3), 7.08–7.44 (m, 2, H_3 and H_7), 7.50–7.98 (m, 4, H_1, H_4, H_5, and H_8), 8.20 (apparent s, 1, H_9), and 8.23 ppm (apparent s, 1, H_{10}).

Anal. Calcd for $C_{19}H_{20}$: C, 91.88; H, 8.12. Found: C, 91.73; H, 8.15.

***tert*-Butylation of 9,10-Dimethylanthracene.** Analogous reaction of 9,10-dimethylanthracene (515 mg, 2.5 mmol) in *tert*-butyl alcohol (0.74 g, 10 mmol) and TFAA (8 mL) for 16 h, followed by similar workup and recrystallization from methylene chloride–petroleum ether, gave pure 2,6-di-*tert*-butyl-9,10-dimethylanthracene (**9b**) as yellow-green plates (5.72 mg, 72%): mp 245–247 °C; NMR (CCl_4) δ 1.46 (s, 18, *tert*-butyl), 3.03 (s, 6, CH_3), 7.48 (d of d, 2, J_{ortho} = 9.0, J_{meta} = 2.0 Hz, H_3 and H_7), 8.08 (s, 2, H_1 and H_5), and 8.17 ppm (d, 2, J = 9.0 Hz, H_4 and H_8).

Anal. Calcd for $C_{24}C_{30}$: C, 90.51; H, 9.49: Found: C, 90.42; H, 9.50.

9-Bromo-2,6-di-*tert*-butylanthracene (9a). A solution of **7** (320 mg, 1.1 mmol) and cupric bromide (507 mg, 2.27 mmol) in distilled carbon tetrachloride (20 mL) was refluxed for 20 h under N_2. After cooling to room temperature, the solution was filtered to remove an insoluble residue and washed with carbon tetrachloride. The filtrate was then chromatographed on a column of Florisil (2 × 20 cm). Elution with hexane–benzene (3:1) gave a yellow oil (393 mg). HPLC on a Li-Chromosorb silica gel column (10 μm, 1.5 × 35 cm) at 125 psig eluted with hexane cleanly separated the product into two components, both of which were collected and identified. The starting material **7** (retention time 20 min) was not detected. The minor component (retention time 10 min) was identified as 9,10-dibromo-2,6-di-*tert*-butylanthracene mainly by mass spectral analysis [*m/e* (70 eV) 448]. The major component (retention time 14.5 min) was **9a**: mp 148–150 °C; NMR (CCl_4) δ 1.47 (s, 9, 6-*tert*-butyl), 1.50 (s, 9, 2-*tert*-butyl), 7.49 (d of d, 1, J_o = 9, J_m = 2 Hz, H_3), 7.59 (d of d, 1, J_o = 9, J_m = 2 Hz, H_7), 7.75 (s, 1, H_5), 7.80 (d, 1, J = 9 Hz, H_4), 8.21 (s, 1, H_1), 8.32 (s, 1, H_{10}), and 8.32 ppm (d, 1, J = 9 Hz, H_8).

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Registry No.—**6**, 18801-00-8; **7**, 62375-58-0; **9a**, 62337-63-7; **9b**, 62337-64-8; **10**, 62375-59-1; 1-*tert*-butylanthracene, 62337-65-9; anthracene, 120-12-7; 2-methylanthracene, 613-12-7; *tert*-butyl alcohol, 75-65-0; 9,10-dimethyanthracene, 781-43-1; 9-*tert*-butylanthracene, 13719-97-6.

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Carbon-13 Nuclear Magnetic Resonance Examination of Naphthalene Derivatives. Assignments and Analysis of Substituent Chemical Shifts

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The natural abundance ^{13}C NMR spectra of a number of substituted naphthalenes have been obtained and assigned by utilization of some or all of the following criteria: (a) specific ^{2}H incorporation and spectral consequences thereof, (b) fully proton coupled spectra, (c) fluoro substitution, and (d) approximate additivity of substituent effects on chemical shifts for certain dispositions. For crucial sets of 1- and 2-substituted naphthalenes, spectra have been obtained under dilute conditions in chloroform and acetone, and the substituent chemical shifts have been treated by the dual substituent parameter equation (DSP analysis) to provide further insight into the transmission of substituent effects in the naphthyl system.

Recently we reported[1,2] some initial studies of the ^{13}C spectra of substituted naphthalenes, and emphasized the beneficial effects of specific ^{2}H substitution, regarding spectral assignments. Subsequently, we and others have explored[2-9] other strategies for assignment purposes, and in particular fully proton coupled spectra have been most informative, yielding information on the number and kind of vicinal ^{1}H–^{13}C interactions, and the characteristic differences in "resonance shapes" for Cα and Cβ resonances in an ortho-disubstituted benzo fragment.[10] The availability of a large number of fluoro-substituted benzenes and naphthalenes[11] has permitted study of the value of fluoro substitution as an assignment aid. We employed this approach in our study of the benzocycloalkenes[3,4] and the results were quite definitive. In this research, we have further utilized this approach, and other aspects of additivity of substituent effects.

Many of our original spectra[1] were obtained at 15.086 MHz in the CW mode, and ^{2}H incorporation, off-resonance noise decoupling (to identify quaternary carbon signals), and chemical shift arguments were employed to assign the spectra. Since that report, we have synthesized and examined the spectra of a large number of naphthalene derivatives, and it was apparent that several of our (and other)[5] assignments required modification. These changes are embodied in this report. While our program was being executed, Ernst[7,8] was also examining selected naphthalene compounds and his report drew attention to some of the previous incorrect assignments alluded to above. While there is some overlap with the published work of Ernst as far as final assignments are concerned, the procedures employed for assignments are in general different, but complementary. In contrast to Ernst's approach,[7,8] we have generally examined at least one specifically ^{2}H-substituted naphthalene, synthesized by standard organic transformations, to provide a completely unambiguous start to the assignment problem. It is gratifying to note that where duplication of effort has occurred with Ernst, agreement in assignment sequence has resulted. (What appear to be systematic differences in the chemical shifts can occur, however.)

As a logical extension of our efforts toward understanding substituent effects in naphthalene by ^{19}F chemical shifts,[11] we have recorded the spectra of a basic set[12,13] of 1- and 2-substituted naphthalenes in chloroform at low dilution (~5%). Ernst has published data for a range of compounds using 10% solutions in acetone,[7,8] and we have completed this solvent series for the 1- and 2-methyl- and -methoxynaphthalenes. Substituent chemical shifts have been calculated and fitted to the dual substituent parameter equation[12,13] to provide substituent parameters. Conclusions based on these ^{13}C results are compared where possible with previous ^{19}F data.[11,12]

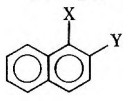
Results and Discussion

A. Assignments. A number of techniques are now available for the assignment of the ^{13}C spectra of aromatic molecules, and details and applications of these strategies have been reported.[1-10] Rather than provide a detailed discussion of the application of these techniques to individual naphthalene compounds, we have indicated in Table I the methods employed for each compound. In almost every case, the different techniques yielded harmonious assignments. Quaternary carbons in these molecules were located by off-resonance noise decoupling, and additionally were usually of relatively low intensity in the PFT spectra. While chemical shifts alone can be unsatisfactory and misleading, they were always considered and can be of much value when the aromatic system is perturbed by substituents capable of substantial resonance interactions, e.g., CN, OCH_3, NH_2, etc.

The following code has been employed in Table I (in the formula column) to indicate the assignment techniques employed for individual compounds, and the chemical shifts of all compounds examined are in Tables I and II. These assignments, together with those of Ernst,[7,8] should be regarded as established for these compounds: A ≡ consideration of ^{13}C–^{19}F couplings; B ≡ specific ^{2}H incorporation at position 4; C ≡ fully ^{1}H coupled spectrum; D ≡ consideration of specifically fluorinated derivatives; E ≡ specific ^{2}H incorporation at position 5; F ≡ specific ^{2}H incorporation at position 6; G ≡ specific ^{2}H incorporation at position 7.

B. Substituent Effects. The substituent effects exerted in aromatic systems frequently are gauged by NMR chemical shift changes (substituent chemical shifts), and it is now realized that full appreciation of such substituent effects involves examination of aromatic systems other than benzene,

Table I. Carbon-13 Chemical Shifts[a] of Some Naphthyl Compounds

Registry no.	Compd 	Carbon no. 1	2	3	4	5	6	7	8	9	10	Others	Shift sequence of aromatic carbons
	Y = H, X =												
321-38-0	$F^{A,B,C}$	159.5	109.8	126.0	124.2	128.1	127.3	126.6	120.9	124.3	135.7		2, 8, 4, 9, 3, 7, 6, 5, 10, 1
		(253.6)	(19.8)	(8.0)	(4.6)	(3.0)	(~1.0)	(~2.0)	(5.0)	(17.2)	(5.0)		
		157.2	108.27	124.31	122.42	126.22	125.50	124.88	119.29	123.82	133.59		2, 8, 4, 9, 3, 7, 6, 5, 10, 1
90-11-9	$Br^{B,C}$	122.73	129.7	125.75	127.7	128.1	126.4*	126.9*	127.0*	132.0	134.6		
86-53-3	$CN^{B,C,D}$	108.83	131.05	123.53	131.78	127.28	126.12	127.1	123.53	130.75	131.38	116.5	1, 3, 8, 6, 7, 5, 9, 2, 10, 4
		109.94	132.08	124.78	132.39	128.55	127.38	128.39	124.78	132.06	132.70	117.6	1, 3, 8, 6, 7, 5, 9, 2, 4, 10
3163-27-7	$CH_2Br^{B,C,E}$	132.0	127.4	125.0	129.3	128.5	125.8	126.2	123.4	130.8	133.7	31.5	8, 3, 6, 7, 2, 5, 4, 9, 1, 10
4780-79-4	CH_2OH^{E}	136.2	125.0	125.3	128.1	128.5	125.6	126.0	123.5	131.0	133.6	62.8	8, 2, 3, 6, 7, 4, 5, 9, 10, 1
134-32-7	NH_2^{E}	142.2	109.5	126.3	118.6	128.4	125.7	124.6	120.9	123.6	134.3		2, 4, 8, 9, 7, 6, 3, 5, 10, 1
17085-91-5	$C(CH_3)_3^{B,D}$	145.9	123.1	125.0	127.4	129.6	124.5	124.5	126.8	132.0	135.8	31.6, 35.7 (q)	2, 6, 7, 3, 8, 4, 5, 9, 10, 1
6301-54-8	$C(CH_3)_2OH^{B,D}$	143.5	122.6	124.6	128.5	128.9	125.2*	125.0*	127.3	130.9	134.8	31.4, 73.8 (q)	2, 3, 7*, 6*, 8, 4, 5, 9, 10, 1
1855-47-6	$C(=CH_2)CH_3^{B}$	144.7	124.5	125.2	127.2	128.3	125.6*	125.8*	125.8*	131.0	133.9	25.1, 116.1, 142.3	2, 3, 6*, 7*, 8*, 4, 5, 9, 10, 1
941-98-0	$COCH_3^{B,D}$	134.9	128.8	124.2	132.9	128.3	126.3	127.9	126.0	130.1	133.8	29.6, 201.3	3, 8, 6, 7, 5, 2, 9, 4, 10, 1
86-55-5	$COOH^{B,C,D}$	126.5	129.49	123.45	132.29	127.44	125.04	126.5	124.82	130.35	132.78	168.97	3, 8, 6, 1, 7, 5, 2, 9, 4, 10
	X = H, Y =												
323-09-1	$F^{A,C,F,G}$	110.9	161.0	116.2	130.5	128.1	125.2	127.0	127.5	134.7	130.8		1, 3, 6, 7, 8, 5, 4, 10, 9, 2
		(21.0)	(248.8)	(25.9)	(10.1)	(~0)	(2.8)	(1.2)	(5.1)	(9.9)	(~0)		
		109.73	158.98	115.00	128.93	126.55	123.77	125.52	125.52	132.79	129.11		1, 3, 6, 7, 8, 5, 4, 10, 9, 2
580-13-2	$Br^{C,F}$	130.0	119.9	129.4	129.6	127.9	126.3	126.9	127.1	134.3	131.6		2, 6, 7, 8, 5, 3, 4, 1, 10, 9
2876-35-9	$C(CH_3)_3^{C,D}$	122.9	148.4	124.7	127.6	128.0	125.2	125.7	127.4	134.0	132.3	31.3 (CH_3), 34.8 (q)	1, 3, 6, 7, 8, 4, 5, 10, 9, 2
18052-85-2	$Si(CH_3)_3^{D}$	133.8	137.8	129.8	127.0	128.1	126.2	125.7	128.1	133.1	133.8	−1.1	7, 6, 4, 5, 8, 3, 1, 9, 10, 2
91-59-8	$NH_2^{C,F,D}$	107.4	142.65	117.0	127.82	126.39	121.2	125.0	124.5	133.5	126.60		1, 3, 6, 8, 7, 5, 10, 4, 9, 2
135-19-3	$OH^{C,F}$	108.42	151.7	116.54	128.57	126.47	122.40	125.25	125.12	133.21	127.65		1, 3, 6, 8, 7, 5, 10, 4, 9, 2
93-04-9	$OCH_3^{D,F}$	105.82	157.7	118.79	129.45	127.73	123.67	126.43	126.82	134.65	129.03	55.27	1, 3, 6, 7, 8, 5, 10, 4, 9, 2
93-08-3	$COCH_3^{C,D}$	130.06	134.45	123.79	128.29	127.70	128.34	129.49	132.46	135.48	135.48	26.45, 197.65	3, 7, 5, 4, 6, 8, 1, 9, 2, 10
93-09-4	$COOH^{C,D}$	131.67	128.56	125.76	128.45	128.07	128.56	126.95	129.65	133.00	136.08	169.56	3, 7, 5, 4, 2, 6, 8, 1, 9, 10
613-46-7	$CN^{C,D,F}$	133.79	109.16	126.03	128.97	127.85	128.89	127.50	128.21	131.97	134.34	119.11	2, 3, 7, 5, 8, 6, 4, 9, 1, 10
581-90-8	CF_3^{D}	126.0	nl	121.7	129.1**	128.1*	128.3*	127.4	129.2**	132.5	134.9		3, 1, 7, 5, 6, 4, 8, 9, 10
		(4.5)		(3.2)	u	u	u	u	u	u	(~0.7)		

[a] Relative to Me_4Si. Asterisked signals indicate possible interchange; nl, not located; u, unresolved or negligible splitting; A, B, C, D, F, G indicate assignment techniques applied. See text.

Table II. Carbon-13 Chemical Shifts of Some Substituted 1- and 2-Fluoronaphthalenes[a]

Registry no.	Compd	Carbon no. 1	2	3	4	5	6	7	8	9	10	Other
59080-27-2	5-F-1-CN-N	110.1	~133.4	125.3	125.7	158.7	111.30	128.6	120.90	~133.4	123.3	117.3
		(3.75)		(2.44)	(6.09)	(253.90)	(19.53)	(8.55)	(4.89)		(17.1)	

	1-CN-N (calcd)	109.7	131.9	124.5	132.7	127.1	127.2	128.4	124.6	135.9	132.6	
59080-30-7	6-F-1-CN-N	nl	131.9	126.1	132.6	112.0	nl	119.0	127.8	nl	nl	nl
			nr	nr	(4.89)	(20.75)		(25.63)	(8.53)			
	1-CN-N (calcd)		132.5	124.9	133.0	129.0		128.5	125.2			
	1-CN-N (obsd)	109.9	132.1	124.8	132.4	128.6	127.4	128.4	124.8	132.1	132.7	117.6
55831-09-9	1-(7-F-1-N)1-Methylethanol	143.3	123.5	124.0	128.3	131.00	115.4	159.9	111.4	nl	131.9	
						(9.73)	(25.54)	(246.1)	(23.19)		nd	
	1-N-1-Methylethanol (calcd)	143.7	122.3	124.6	128.1	128.4	125.0	124.7	128.4			
	1-N-1-Methylethanol (obsd)	143.5	122.6	124.6	128.5	128.9	125.2	125.0	127.3	130.9	134.8	73.8; 31.4
13916-91-1	6-F-2-NH_2-N	107.6	142.1	118.1	127.1	109.6	157.1	115.3	126.5	130.5	126.8	
					(3.66)	(20.14)	(238.0)	(23.8)	(7.32)		(7.32)	
	2-NH_2-N (calcd)	107.4	142.7	116.9	127.5	126.6	121.9	124.8	123.9	133.3	125.7	
	2-OCH_3-N (obsd)	106.25	158.1	119.1	129.9	128.15	124.0	126.8	127.2	135.3	129.6	
33627-02-0	6-F-2-$COCH_3$N	128.62	132.66	123.69	126.33	109.92	160.48	116.00	130.77	128.14	135.19	26.22; 195.49
						(20.14)	(249.02)	(25.63)	(9.16)		(9.16)	
	2-$COCH_3$-N (calcd)	129.97	134.69	123.97	128.71	128.09	127.3	126.8	129.74	132.6	136.0	
33718-09-1	3-F-2-$COCH_3$-N	131.08	124.5	157.02	111.17	125.47	127.73 (?)	124.67	128.22	128.22	134.73	30.9 (7.32)
		(nr)	(25.63)	(249.02)	(21.97)						(9.15)	193.87 (3.66)
	2-$COCH_3$N (calcd)	130.05	135.3	123.84	129.34	127.85	128.01	126.7	129.57	134.49	135.54	
	2-$COCH_3$N (obsd)	130.06	134.45	123.79	128.29	127.70	128.34	126.65	129.49	132.46	135.48	26.45; 197.65
5043-01-6	6-F-2-COOH-N	130.22	126.44	125.55	126.44	110.14	160.79	116.16	130.96	128.62	135.61	167.46
						(20.14)	(247.19)	(25.63)	(9.16)		(10.99)	
	2-COOH-N (calcd)	131.22	128.45	125.81	128.77	128.26	127.59	126.94	129.88	132.98	136.29	
5043-10-7	7-F-2-COOH-N	129.45	127.92	123.90	127.11	129.23	117.59	159.67	111.32	132.41	131.59	167.49
		(5.49)		(br)		(9.16)	(25.63)	(245.36)	(20.14)	(9.16)		
	2-COOH-N (calcd)	131.78	128.18	125.91	128.41	128.15	128.37	126.47	129.44	133.09	135.95	
5043-22-1	8-F-2-COOH-N	122.93	127.28	125.47	126.84	122.56	127.21	109.33	158.17	122.03	135.24	167.22
		(br)				(br)	(9.15)	(20.15)	(250.85)	(16.48)		
	2-COOH-N (calcd)	131.49	128.18	125.75	128.47	127.89	128.68	126.84	128.81	131.67	135.12	
	2-COOH-N (obsd)	131.67	128.56	125.76	128.45	128.07	128.56	126.95	129.65	133.00	136.08	169.56
62078-75-5	7-F-2-CN-N	131.89	109.56	124.52	127.92	129.37	118.32	159.79	110.46	131.89	130.32	117.67
		(?)				(9.16)	(25.54)	(247.14)	(?)			
	2-CN-N (calcd)	134.22	109.78	126.53	129.22	128.29	129.10	126.59	128.58	132.57	134.67	
	2-CN-N (obsd)	133.79	109.16	126.03	128.97	127.85	128.89	127.50	128.21	131.97	134.34	119.11
62078-76-6	7-F-2-NH_2-N	106.7	143.7	116.1	127.9	128.7	111.3	159.8	107.7	134.8	123.55	
		(3.66)				(10.99)	(25.64)	(241.7)	(20.14)	(9.16)	(~0)	
	2-NH_2-N (calcd)	107.1	142.5	116.7	127.7	126.1	120.9	124.5	124.7	133.4	126.2	
	2-NH_2-N (obsd)	107.4	142.7	117.0	127.8	126.4	121.2	125.0	124.5	133.5	126.6	
575-08-6	6-F-1-COOH-N	127.57	128.73	124.85	131.55	110.59	159.31	116.70	127.96	130.73	134.17	168.49
					(5.49)	(20.14)	(245.36)	(25.63)	(9.15)		(9.15)	
	1-COOH-N (calcd)	128.92	130.76	125.13	133.93	128.76	126.11	127.5	126.93	135.23	134.98	
575-06-4	7-F-1-COOH-N	125.77	130.84	122.99	132.43	130.04	115.62	160.71	109.27	131.75	130.19	168.24
						(9.16)	(25.64)	(243.5)	(23.80)	(11.00)		
	1-COOH-N (calcd)	128.1	131.1	125.00	133.73	128.96	126.4	127.51	127.39	132.43	134.55	
	1-COOH-N (obsd)	126.5	129.49	123.45	132.29	127.44	125.04	126.5	124.82	130.35	132.78	
5471-32-9	2-F-1-$COCH_3$-N	121.64	156.78	114.52	131.71	126.98	124.36	126.98	123.51	129.16	129.38	32.63; 198.53
		(14.65)	(245.36)	(25.63)	(9.15)				(5.49)	(3.67)		
	1-$COCH_3$N (calcd)	139.81	123.6	125.32	130.68	128.33	126.39	127.26	125.9	130.0	133.9	
33718-11-5	8-F-1-$COCH_3$-N	133.96	122.77	124.79	128.08	123.1	125.27	110.36	156.30	118.13	136.03	(9.15); 202.79
							(9.16)	(21.97)	(249.02)			
	1-$COCH_3$N (calcd)	142.57	123.69	125.09	129.76	128.66	126.76	127.89	127.00	~129.6	136.19	
	1-$COCH_3$N (obsd)	134.9	128.4	124.2	132.9	128.3	126.3	127.9	126.00	130.1	133.8	29.6; 201.3
62078-77-7	7-F-2-OCH_3-N	104.24	156.94	116.76	128.03	128.64	112.44	159.71	108.89	134.30	124.63	54.59
		(3.66)				(9.16)	(25.64)	(243.53)	(20.14)	(9.16)		
	2-OCH_3-N (calcd)	106.62	157.22	118.79	129.38	128.19	123.24	126.53	127.06	135.1	129.12	

Table III. ^{13}C Substituent Chemical Shifts (SCS)[a,b] of Substituted Naphthalenes

Registry no.	Substituent	Carbon no. 1	2	3	4	5	6	7	8	9	10
		A. 1-Substituted Naphthalenes									
86-57-7	NO_2	+18.58	−1.95	−1.95	+6.62	+0.58	+1.40	+3.51	−4.90	−8.48	+0.74
	CN	−17.83	+6.66	−0.84	+5.23	+0.58	+1.59	+2.66	−3.12	−1.27	−0.42
	$COCH_3$	+7.39	+2.66	−0.64	+4.92	+0.35	+0.43	+2.04	−2.05	−3.49	+0.35
26458-04-8	CF_3		−1.08	−1.48	+5.04	+1.04	+1.02	+2.02	−3.56	−3.85	+1.05
2216-69-5	OCH_3	+27.54	−22.07	+0.04	−7.70	−0.46	+0.57	−0.68	−5.92	−7.86	+1.02
	NH_2	+14.06	−16.27	+0.39	−9.10	+0.52	−0.13	−1.13	−7.21	−9.94	+0.78
90-12-0	CH_3	+6.34	+0.55	−0.30	−1.37	+0.61	0.00	−0.13	−3.81	−0.88	+0.06
	F	+30.95	−16.42	−0.24	−4.26	−0.38	+0.98	+0.32	−7.37	−8.01	+1.44
	Br	−5.08	+4.04	+0.32	−0.01	+0.38	+0.85	+1.28	−0.61	−1.49	+1.14
	OCH_3[c]	+27.57	−21.85	+0.43	−7.82	−0.43	+0.43	−0.81	−6.09	−8.38	+1.08
	CH_3[c]	+6.15	+0.59	−0.33	−1.40	+0.59	−0.32	−0.32	−3.88	−0.92	+0.16
		B. 2-Substituted Naphthalenes									
581-89-5	NO_2	−3.42	+19.55	−6.70	+1.49	−0.04	+3.80	+1.98	+1.95	−1.66	+2.20
	CN	+6.10	−16.56	+0.35	+1.17	+0.03	+3.08	+1.72	+0.39	−1.37	+1.00
	$COCH_3$	+2.21	+8.67	−1.99	+0.44	−0.16	+2.56	+0.87	+1.64	−1.01	+2.01
581-90-8	CF_3	−1.96		−4.18	+1.14	+0.14	+2.42	+1.52	+1.24	−1.05	+1.35
	OCH_3	−22.14	+31.82	−7.09	+1.49	−0.23	−2.21	+0.55	−1.14	+1.10	−4.52
	NH_2	−19.35	+18.30	−7.61	+1.26	−0.20	−3.38	+0.52	−2.12	+1.43	−5.53
91-57-6	CH_3	−1.08	+9.62	+2.30	−0.66	−0.30	−0.88	+0.03	−0.30	+0.19	−1.79
	F	−17.04	+34.84	−9.58	+2.39	−0.05	−0.75	+1.01	−0.57	+0.70	−3.93
	Br	+1.66	−6.18	+3.41	+2.01	−0.07	+0.42	+1.04	−1.04	+1.01	−1.66
	OCH_3[c]	−22.12	+29.93	−7.23	+1.35	−0.27	−2.43	+0.43	−1.13	+1.30	−4.53
	CH_3[c]	−1.13	+9.38	+2.11	−0.61	−0.21	−0.91	−0.05	−0.21	+0.27	−1.73

[a] Defined as the difference (ppm) between the ^{13}C chemical shift of the substituted compound and that of the appropriate carbon in the parent hydrocarbon. Positive values indicate decreased shielding. [b] Unless otherwise specified, all compounds were run in deuteriochloroform (0.5–1.0 M). Naphthalene ($DCCl_3$, relative to Me_4Si): 127.96 (C1); 125.88 (C2); 133.55 (C9). [c] Solvent, deuterioacetone (0.5 M). Naphthalene [$(CD_3)_2CO$; relative to Me_4Si]: 128.66 (C1); 126.67 (C2); 134.38 (C9).

e.g., naphthalenes or anthracene. With the definite assignments for a number of key naphthyl compounds now available, we are in a position to report analysis of spectra recorded at low concentrations, so that meaningful appraisal of intramolecular effects on ^{13}C shifts in this system can be made. These results are discussed below.

The ^{13}C substituent chemical shift (SCS) data for 1- and 2-substituted naphthalenes ($DCCl_3$ solvent) together with the results for the methyl- and methoxy-substituted naphthalenes (acetone-d_6 solvent) are listed in Table III. A wide variety of substituents exhibiting a range of electronic characteristics was chosen in order to provide a meaningful correlative analysis by the Taft dual substituent parameter (DSP)[12,13] equation

$$p^i = \rho_I{}^i\sigma_I + \rho_R{}^i\sigma_R = \rho_I{}^i(\sigma_I + \lambda\sigma_R) \quad (1)$$

where p^i = substituent effect property; σ_I and σ_R are the substituent polar and resonance effect parameters, respectively; ρ_I and ρ_R represent the susceptibilities of the property to each of the substituent properties; the ratio or blend $\rho_R/\rho_I \equiv \lambda$.

Table IV gives the results of the best fits of the SCS data ($DCCl_3$ and acetone-d_6) to eq 1. The SCS for CH_3 and OCH_3 in acetone-d_6 (Table III) were combined with the recently published data of Ernst[7,8] to provide an adequate basis set of substituents (NO_2, CN, CHO, $COCH_3$, F, Cl, Br, I, CH_3, and OCH_3)[12,13] for the correlative analysis for this solvent. However, because acetone is a fairly basic solvent, the data for substituents (NH_2, OH, and COOH) whose electronic properties are markedly perturbed by hydrogen-bonding interactions were excluded. The discriminatory precision of fit achieved with the σ_R° parameters over that obtained with the σ_R (BA) parameters is not highly significant and in two dispositions (Table IV, 4α and 8β, acetone-d_6) the latter scale provided the best fit. An important feature of the analyses in the two vastly different solvent systems is that the DSP parameters are mutually consistent regarding the overall precision and pattern of fits. Thus intermolecular interactions (solute–solute and solute–solvent) are not grossly distorting the picture as far as intramolecular effects in the various dispositions are concerned.

It should be noted that the results for the proximate carbon sites (C1, C2, and C9 in 1-substituted naphthalenes; C1, C2, and C3 in 2-substituted naphthalenes) are not given because of the extremely poor precision of fits. This was expected as it is well known that carbon sites close to the point of substitution are markedly affected by steric, neighboring group, magnetic anisotropy, and bond order effects as well as electronic phenomena.[14] The ^{13}C nucleus can be a reliable monitor of total charge density at remote carbon centers only since here the above mentioned proximity factors are considered negligible. This proposition is exemplified by a number of successful empirical and theoretical correlations which have clearly established that para ^{13}C SCS of monosubstituted benzenes accurately reflect the charge density at that position.[15]

Bearing in mind that a ^{13}C NMR study of monosubstituted naphthalenes provides information for three more nonproximate sites than a corresponding substituent effect study which employs a side chain probe or detector (^{19}F NMR and chemical reactivity studies), a cursory examination of the results set out in Table VI indicates that the overall analysis provides some distinct similarities with the DSP results for the ^{19}F SCS data[11,12] when compared with the analysis of reactivity data at the corresponding dispositions. Although some discussion of the ^{19}F NMR situation has been presented,[11,12] it is instructive to note the salient features. The overall precision of fits achieved by the DSP equation is significantly worse than those reported for reactivity data.[12] Further, the shielding data display different λ blending factors, i.e., SCS

Table IV. Best Fit Parameters of Dual Substituent Parameter Equation for Substituent ^{13}C NMR Shielding Effects in Naphthalene

Carbon no.[a] (disposition)	Type	Solvent	ρ_I	ρ_R	λ	SD[b]	f[c]	n[d]
	A. 1-Substituted Naphthalenes							
3 (4β)	σ_R°	$DCCl_3$	−1.80	−1.63	0.91	0.44	0.49	9
4 (4α)	σ_R°	$DCCl_3$	5.92	19.98	3.38	0.66	0.12	9
5 (5α)	σ_R°	$DCCl_3$	0.82	0.59	0.72	0.46	0.80	9
6 (5β)	σ_R°	$DCCl_3$	2.23	0.41	0.18	0.17	0.18	9
7 (8β)	σ_R°	$DCCl_3$	4.10	3.89	0.95	0.27	0.15	9
10	σ_R°	$DCCl_3$	1.36	−1.66	−1.22	0.40	0.46	9
3 (4β)	σ_R°	Acetone	−0.70	−2.25	3.22	0.52	0.69	10
4 (4α)	σ_R°	Acetone	6.87	18.90	2.75	0.88	0.18	10
4 (4α)	σ_R(BA)	Acetone	7.11	15.66	2.20	0.45	0.10	10
5 (5α)	σ_R°	Acetone	1.56	1.27	0.81	0.34	0.46	10
6 (5β)	σ_R°	Acetone	2.68	0.57	0.21	0.18	0.16	10
7 (8β)	σ_R°	Acetone	4.98	4.26	0.85	0.38	0.18	10
7 (8β)	σ_R(BA)	Acetone	4.90	3.30	0.67	0.25	0.12	10
10	σ_R°	Acetone	1.36	−1.95	−1.54	0.40	0.45	10
	B. 2-Substituted Naphthalenes							
4 (3α)	σ_R°	$DCCl_3$	2.95	−2.00	−0.68	0.31	0.21	9
5 (6α)	σ_R°	$DCCl_3$	−0.04	0.36	−9.70	0.13	0.78	9
6 (6β)	σ_R°	$DCCl_3$	4.01	7.74	1.93	0.14	0.06	9
7 (7β)	σ_R°	$DCCl_3$	2.85	0.37	0.13	0.19	0.16	9
8 (7α)	σ_R°	$DCCl_3$	1.28	4.32	3.39	0.52	0.40	9
9	σ_R°	$DCCl_3$	−1.30	−3.80	2.91	0.34	0.30	9
10	σ_R°	$DCCl_3$	0.41	11.23	27.11	0.38	0.12	9
4 (3α)	σ_R°	Acetone	3.72	−1.43	−0.39	0.39	0.23	10
5 (6α)	σ_R°	Acetone	0.27	0.45	1.65	0.12	0.66	10
6 (6β)	σ_R°	Acetone	4.50	7.63	1.70	0.15	0.07	10
7 (7β)	σ_R°	Acetone	3.21	1.04	0.32	0.12	0.09	10
8 (7α)	σ_R°	Acetone	1.34	4.62	3.45	0.55	0.44	10
9	σ_R°	Acetone	−0.73	−4.08	5.61	0.47	0.44	10
10	σ_R°	Acetone	0.63	10.03	15.88	0.32	0.13	10

[a] The Greek letter indicates the position of the detector, the numeral that of the substituent. This nomenclature has been used for specifying the various dispositions of substituted fluoronaphthalenes. [b] The standard deviation of the fit. [c] The fit parameter, $f \equiv$ SD/rms, where rms is the root mean square of the data points. Correlations of excellent precision are those for which $f \leq 0.1$. [d] The number of substituents in the data set.

consist of distinctly different blends of polar and mesomeric effects as compared to reactivity substituent effects. However, while the positional dependencies of ρ_I values differ markedly, the positional dependencies of ρ_R values appear to display essentially similar patterns for the appropriate comparisons between these two kinds of measurements. This is particularly the case for the formally conjugated dispositions.

We believe that the most important aspect of the correlative analysis of the ^{13}C NMR shielding data concerns the several significant differences, when compared with the corresponding ^{19}F NMR DSP results. Firstly, it can be seen from Table IV that the susceptibility coefficients (ρ_I and ρ_R) at C5 (5α) and C5 (6α) in 1- and 2-substituted naphthalenes, respectively, indicate very feeble polar and resonance effects at these positions. However, because the precision of fits for these dispositions is extremely poor, this feature is best exemplified by examining the ^{13}C SCS for these two dispositions listed in Table III. It can be seen for a series of substituents covering a wide range of electronic effects that the SCS at these positions (5α and 6α) are confined to a very narrow range and generally show no obvious correlation with the electronic properties of the substituent.[16] The 5α disposition, which is formally a conjugated position, is slightly but more irregularly affected than the unconjugated 6α orientation, but this probably has its origin in structural factors of the kind previously alluded to for the corresponding ^{19}F SCS, rather than specific electronic effects.[11,17] Hence it is very reasonable that, as a good first approximation, polar and resonance effects can be considered negligible at the 5α and 6α dispositions in monosubstituted naphthalenes as determined by the ^{13}C probe. However, the situation is significantly different when monitored by ^{19}F chemical shifts.[11,18] Now substantial residual polar effects at both dispositions are observed and, although mesomerism is indicated to be virtually zero in the 5α disposition, significant secondary mesomeric effects are observed for the unconjugated 6α orientation.[18,19] Two important conclusions follow. Firstly, the nature of polar substituent effects as determined by the two probes is completely different. Recent studies[4,20,21] of geometrically well-defined model systems indicate quite unambiguously that electrostatic field induced π polarization is the dominant, if not exclusive, long-range mechanism transmitting the influence of the primary inductive substituent effect as indicated by aryl ^{13}C chemical shifts. More recently, this has been further confirmed by Reynolds and Hamer,[22] who have shown that the pattern of ρ_I values from a DSP analysis of the ^{13}C SCS for 4-substituted biphenyls is very similar to the SCS for 4-ammoniobiphenyl (relative to 4-methylbiphenyl)[23] and to the chemical shift and π electron density patterns in phenylalkane derivatives. Further confirmation is achieved from the current study by noting (Chart I) the similar pattern displayed by the ρ_I values (Table IV, $DCCl_3$) for the two monosubstituted naphthalenes and the ^{13}C chemical shifts for 1- and 2-ammonionaphthalenes relative to the chemical shifts for 1- and 2-methylnaphthalene (Table V, CF_3CO_2H as solvent), respectively. The significantly larger ρ_I values in acetone compared to $DCCl_3$ (Table III) suggests that field-induced π polarization is increased when substituent polarity is enhanced

Table VA. Carbon-13 Chemical Shifts[a] of Amino- and Methyl-Substituted Naphthalenes in CF_3CO_2H[b]

Compd	Carbon no. 1	2	3	4	5	6	7	8	9	10	Other
1-Naphthylamine	124.22	121.30	124.96	131.4	129.38	127.97	128.71	118.99	126.17	134.77	
2-Naphthylamine	122.01	125.60	119.04	131.24	128.17	128.17	127.85	128.17	133.68	133.27	
1-Methylnaphthalene	134.95	126.56	125.94	126.82	128.70	125.94	125.94	124.32	133.09	134.10	19.38
2-Methylnaphthalene	127.01	136.47	128.54	127.57	127.92	125.29	126.20	127.92	134.26	132.28	21.72
Naphthalene	128.07	126.12	126.12	128.07	128.07	126.12	126.12	128.07	133.68	133.68	

[a] Relative to Me_4Si. [b] CF_3 (quartet): 96.55, 108.94, 121.33, 133.68; COOH (quartet): 159, 160.89, 162.81, 164.69.

Table VB. Carbon-13 Chemical Shifts[a] of Some Fluoro-Substituted Naphthylamines in CF_3CO_2H

Registry no.	Compd	Carbon no. 1	2	3	4	5	6	7	8	9	10
438-32-4	4-F-1-NH_2		120.19 (8.71)	109.02 (23.25)	160.19 (253.57)	121.77 (5.09)	128.48 (~2)	129.79	119.42 (2.47)	127.77 (5.83)	125.13 (17.39)
62078-78-8	6-F-1-NH_2	124.79	121.29	126.33	130.53	112.80 (19.59)	161.52 (246.77)	118.84 (26.13)	122.59 (7.99)	123.40	136.05 (8.69)
	6-F-2-NH_2	121.67	125.09 (2.93)	120.07	129.67	110.81 (21.97)	160.94 (244.66)	117.87 (24.90)	129.67	129.67	133.62 (9.52)
	7-F-2-NH_2	121.79	127.41	119.12	131.12	131.34 (10.2)	118.69 (18.93)	162.30 (246.06)	111.61 (21.85)	134.66 (10.2)	131.12

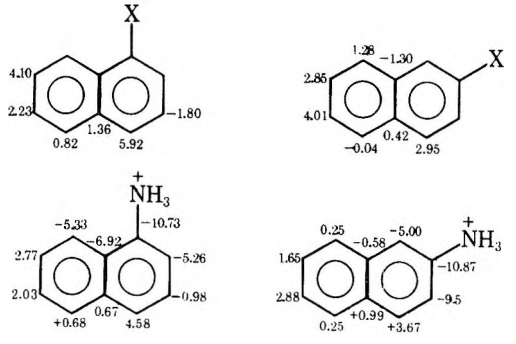
[a] Relative to Me_4Si.

Table VC. Calculated Chemical Shifts[a,b] for 1- and 2-Naphthylamine in CF_3CO_2H

Compd	Carbon no. 1	2	3	4	5	6	7	8	9	10
4-F-1-NH_2		120.43	125.44	129.24	129.14	128.16	128.81	119.80	126.33	133.14
6-F-1-NH_2	124.84	122.04	125.23	131.10	129.84	126.67	128.42	120.29	127.33	135.35
6-F-2-NH_2	121.72	125.84	119.84	130.24	127.85	126.10	127.45	127.28	133.60	132.90
7-F-2-NH_2	122.36	126.40	119.87	131.17	128.95	128.27	127.46	128.65	133.96	133.05

[a] Relative to Me_4Si. [b] Calculated by utilizing the ^{13}C SCS for fluorine (Table III).

Chart I



by a more polar solvent.[24]

Thus, since the $\rho_I\sigma_I$ terms for ^{13}C NMR shielding effects are dominated by field-induced π polarization, and since this effect is negligible at the 5α and 6α disposition, it follows that the observed ^{19}F NMR polar substituent effects at these dispositions must have their origin in the through-space component (direct field effect) of the electrostatic-field vector acting on the potential π component of the C–F bond.[25,26] Assuming a common effective dielectric constant and by utilizing readily determined angle/distance relationships,[27] the polar effect values in the 5α and 6α orientations can be used to estimate direct electric-field contributions to the ^{19}F SCS at the various dispositions in substituted fluoronaphthalenes[11,25] as well as in para-substituted fluorobenzenes[28] and 10-substituted 9-fluoroanthracenes.[29] Calculated contributions for fluorine as the substituent are given in Table VI. This substituent was chosen because of its steric size (similar to hydrogen) and hence its ^{19}F SCS at the 5α disposition (−2.15 ppm, DMF)[11] should be uncomplicated by potential structural factors and therefore be only a manifestation of substituent polarity. The results listed in Table VI indicate that although direct field effects are clearly dominant in fluorobenzenes,[30] this is not the case in many of the dispositions of substituted fluoronaphthalenes and fluoroanthracenes where field-induced π polarization is apparently important. This may be the reason for the observed variable ρ values when the FMMF treatment is applied to the ^{19}F SCS of aryl fluorides[31] as the method treats only direct field effects. Reynolds and Hamer[22] have recently drawn attention to this limitation of the FMMF method in connection with Schulman and co-workers'[32] erroneous conclusions concerning the relative importance of polar field effects on aryl ^{13}C chemical shifts.

These workers[22] have also presented estimates of direct field contributions to the ^{19}F SCS for para-substituted fluorobenzenes and 10-substituted 9-fluoroanthracenes, 45 and 25%, respectively, using the NO_2 group as an example, which are significantly different from the percentage dissections listed in Table VI. Their estimates are based on the Buckingham equation[33] for linear electric field effects in which the coefficient (A) was evaluated from the ^{19}F chemical shifts of 4-substituted β,β-difluorostyrenes.[34] However, we believe that our determinations probably are more realistic for aryl fluorides since a recent study[35] of a new model system suggests that the response of ^{19}F chemical shifts to an applied electric field is markedly determined by the electronic structure of the chemical bonds in the immediate vicinity of the fluorine atom. A full discussion on the nature of ^{19}F NMR polar substituent effects must await the completion of a study of new model

Table VI. Estimates of Direct Field Effects to ^{19}F SCS of Aryl Fluorides for Fluorine as Substituent in DMF

Aromatic system	Disposition[a]	Cos θ/r^2 [b]	Total polar field effect, ppm[c]	Direct field contribution, ppm[d]	% direct field contribution
Benzene	Para	1	−4.68	−3.61 (−3.31)	77 (71)
Anthracene	9,10	1	−8.33	−3.61 (−3.31)	43 (40)
Naphthalene	4α	1	−6.81	−3.61 (−3.31)	53 (49)
Naphthalene	5α	0.65	−2.15	−2.15	100
Naphthalene	6α	0.37	−1.34	−1.34	100
Naphthalene	7α	0.22	−1.81	−0.79 (−0.73)	44 (40)
Naphthalene	6β	0.42	−3.65	−1.52 (−1.39)	42 (38)
Naphthalene	7β	0.41	−2.34	−1.48 (−1.36)	63 (58)
Naphthalene	8β	0.65	−4.49	−2.35 (−2.15)	52 (48)

[a] The Greek letter indicates the position of the detector, the numeral that of the substituent. [b] Relative values. θ is the angle between a line of length r drawn between the midpoints of the CF bonds. [c] Dissected by DSP equation ($\rho_I\sigma_I$). Values for ρ_I were taken from the literature (ref 11 and 28) while σ_I for fluorine was taken as 0.50 (ref 13). The sign convention commonly employed for ^{19}F chemical shifts is generally opposite to that for ^{13}C chemical shifts. [d] Estimated from the direct field effect at the 6α disposition and the appropriate relative angle/distance relationships. The values in parentheses are similar estimates derived from the 5α orientation.

systems[36] which should help to illuminate the overall situation.

The second significant conclusion that can be made from a comparison of the ^{13}C and ^{19}F SCS in the 6α disposition is that the latter parameter is much more sensitive to mesomeric-field effects.[25,31,37] This is exemplified further by the fact that in the 7β disposition the electronic effect of the *amino* substituent leads to a slight *downfield* shift (0.15 ppm, acetone-d_6)[7b] as monitored by ^{13}C NMR while the corresponding shift by ^{19}F NMR is significantly *upfield* (1.03 ppm, DMF).[38]

Secondly, it can be seen from Table IV that all the formally conjugated positions (C4 in 1-X-naphthalenes; C6, C8, and C10 in 2-X-naphthalenes) are reasonably well correlated by eq 1 except for the 5α and 7α dispositions. Although the poor correlation for the 5α disposition was expected on the basis of the ^{19}F NMR DSP results,[11] the result for the 7α orientation was surprising given that the corresponding ^{19}F SCS are well fitted by the DSP equation.[11] We are unable to offer an explanation for this apparent anomaly. However, we should point out that serious discrepancies between ^{13}C and ^{19}F SCS have recently been noted within a series of benzocycloalkenes.[3,30c] Here bond-order effects within the carbocyclic ring appear to be implicated. Interestingly, Ernst[8] has demonstrated an approximate linear correspondence between ^{13}C SCS at the 7 position of 1-X-naphthalenes and electron densities calculated by INDO MO theory. Nevertheless, the correlation for this disposition was poor, and substantially worse than those for other formally conjugated positions.

Conclusions

Three main conclusions follow from this study. Firstly, it is abundantly clear that shielding data involve similar factors of a different order of complexity, and factors different from, those encountered in the study of substituent effects on conventional chemical properties. Hence attempts to interpret these single state properties in terms of chemical reactivity parameters may fail depending on the substrate and disposition in question. However, it is apparent that shielding parameters from the 6β and 7β orientations of 2-substituted naphthalenes are well correlated by eq 1 and, thus, where structural and stereochemical factors may be a problem with the less rigid benzene system,[11] these two naphthalene dispositions may be usefully employed for estimating σ_I and σ_R° for certain substituents.[11] We are currently investigating this proposition with respect to a reevaluation of the electronic characteristics of various groups.[39]

Secondly, ^{19}F NMR polar and mesomeric effects are somewhat more complicated than the corresponding effects determining ^{13}C SCS due to significant contributions by direct field and mesomeric-field effects. Previously, Adcock and Dewar[25] had noted from SCF MO calculations for benzaldehyde and the naphthaldehydes that the negative charge in the formally meta positions varied considerably. The negative charge in the 4 position of β-naphthaldehyde was considerably greater than that at the 3 position in α-naphthaldehyde and the meta position in benzaldehyde. This was the basis for the suggestion that direct mesomeric effects were responsible for the unusual ^{19}F SCS in the 4β position of naphthalene. However, the ρ_I values (Chart I) and the chemical shifts for $^+NH_3$ (relative to CH_3) (Chart I) indicate unambiguously that the origin of this phenomenon is field induced π polarization and not mesomerism.

Hence, it now appears that the anomalously small ^{19}F SCS previously observed for +F+M substituents (NO_2, CN, COOH, CF_3) in the 4β disposition is a situation where direct field and field-induced π polarization effects are opposed, leading to a small net polar field response. These results for the 4β disposition are not in accord with expectations based on the polarity parameter (σ_I), and the possibility therefore arises that DSP analyses for such dispositions may break down due to a failure to distinguish between primary inductive and mesomeric phenomena, which distinction is the basis of the DSP approach. The surprisingly poor correlation for the 7α ^{13}C data may be due, at least in part, to considerations of this type. In this connection, Ernst[8] has noted for the nonproximate conjugative positions in benzene and naphthalene that, although ^{13}C SCS correlate reasonably well with formal charge densities computed by INDO MO theory, the slopes ($\Delta\delta/\Delta\rho$) for the various dispositions differ widely (187–324 ppm/e). (Slopes are in the sequence 6β > 4α ~ para > 7α ~ 8β > C_{10}.) This sequence was noted previously[40,31] for the FMMF treatment of ^{19}F SCS of aryl fluorides giving rise to variable ρ values, attributed by us (vide supra) to nonincorporation of field-induced π polarization in the FMMF treatment. There seems every reason to believe that the INDO MO method also suffers from this defect, and while good correlations may result for dispositions where resonance effects (ρ_R) dominate, poor correlations (7α!) may result where there is not a fortuitous reflection of field-induced π polarization in the calculated formal charge.

Thirdly, the established importance of field-induced π polarization and direct mesomeric effects as the dominant mechanisms determining ^{13}C SCS in aromatic systems suggests that a simple two-parameter treatment of the kind recently proposed by Sardella[41] will be of limited generality.

The apparent success of the Sardella formulation[41] for strongly polar substituents rests on a somewhat fortuitous correspondence between atom–atom polarizabilities and field-induced π polarization effects in some dispositions. However, it should be noted that there are many dispositions in 1- and 2-substituted naphthalenes where such a correspondence does not hold.

Finally, in view of recent semantic confusion surrounding π-inductive effects, we feel compelled to clarify our past and present usage of the term "π-inductive effect". This term may be traced to Jaffé[42] and Dewar[43] and was envisaged as an inductomesomeric (or inductoelectromeric) phenomenon, and in semiempirical treatments[40,31,37] was incorporated into the mesomeric constant for a substituent as the transmission factors to various ring sites would be identical.[37] We have employed the term in this fashion and hence interposition of a methylene group between an electronegative atom or group and the aryl ring essentially ensures a feeble π-inductive effect. The classic field effect[44] of a substituent is conceptually clear and not in dispute, but we have consistently regarded field-induced π polarization as distinct from the π-inductive effect as the transmission factors for the former can be quite different from these for the latter and not readily determined by any a priori treatment. Recently, some authors[20,22,30b,45] have grouped inductomesomeric and field-induced π polarization under the general term "π-inductive effect" on the basis that both mechanisms involve no charge transfer between the aryl ring and the substituent. We believe that this approach complicates unnecessarily any attempt at a semiempirical treatment of substituent effects.

Experimental Section

Spectra. Spectra were recorded in the pulse Fourier transform mode at 22.625 or 67.89 MHz on Bruker spectrometers. Some spectra were also recorded at 15.086 MHz in the CW mode. The solutions were ca. 10–15 mol % in the compounds for assignment purposes and somewhat less (5%) for the careful evaluation of substituent effects. This level of concentration has been considered by others[24,46,47] to be of satisfactory dilution for meaningful appraisal of intramolecular effects. For acquisition of ^{1}H coupled spectra, solutions were somewhat more concentrated, but checks indicated that for $CDCl_3$ solvent, differential concentration effects on chemical shifts were not a complication. For comparisons at different field strengths, the standard compounds (e.g., naphthalene, and the fluoronaphthalenes) were examined under the appropriate conditions, as some systematic differences in chemical shifts did occur for the different situations.

Compounds. The (nondeuterated) monosubstituted naphthalenes were generally commercially available. The substituted fluoronaphthalenes represent part of the collection of one of us (W.A.), while the specifically deuterated naphthalenes were synthesized by standard organic transformations. The coincidence of their spectra (and other physical properties), other than for the effects of ^{2}H substitution, with those of authentic ^{1}H specimens confirms their constitution. "Scrambling" of deuterium in the synthesis was not anticipated, and did not occur as judged by the ^{13}C spectra.

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An Electrochemical Synthesis of 2-Acetoxy-2-amino Acid and 3-Acetoxy-3-amino Acid Derivatives

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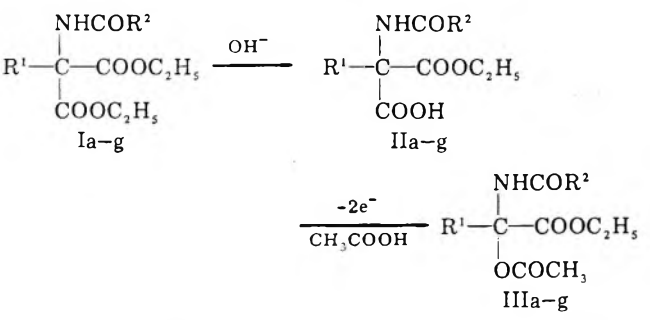
2-Acetoxy-2-amino acid derivatives, which are useful synthetic intermediates, have been synthesized in good yields by anodic oxidation of acylaminomalonic acid monoesters in acetic acid containing sodium acetate. This electrochemical method has been extended to a synthesis of 3-acetoxy-3-amino acid derivatives from 3-alkoxycarbonylalanine derivatives. The mechanism of these electrode reactions is also discussed.

Amino acids which contain a functional group in the 2 position, i.e., 2-hydroxy-2-amino acids,[1] 2-methoxy-2-amino acids,[2a-e] etc., have recently received much attention as useful synthetic intermediates for a preparation of a novel class of amino acids.[3a-c] Ben-Ishai et al.[4a-c] have shown the rich synthetic potentiality of 2-hydroxyglycinate and 2-methoxyglycinate which effectively react with a variety of nucleophiles under Lewis acid catalysts to afford physiologically important 2-substituted 2-amino acids. Most recently, the possible importance of 2-acetoxy-2-amino acid in amino acid chemistry has been recognized by Olsen et al.:[5] this amino acid is more susceptible to nucleophilic substitution under neutral or basic condition than are 2-hydroxy- and 2-methoxy-2-amino acids. Thus, from the viewpoint of the potential value as a synthetic intermediate[6a,b] for amidoalkylation, 2-acetoxy-2-amino acid is considered to be superior over 2-hydroxy- and 2-methoxy-2-amino acids. In spite of the superiority of the former amino acid, however, this amino acid has not been utilized as yet. Limited studies[5,7] of syntheses of 2-acetoxy-2-amino acid have indicated a synthetic difficulty of this amino acid in which the unstable *N,O*-acetal skeleton is involved. For example, *N*-acetyl-2-acetoxy-3-chloroalaninate was synthesized by the treatment of 2-acetamidoacrylate with *N*-chlorosuccinimide/HCl/LiOAc.[5] However, this method lacks versatility for a preparation of all types of 2-acetoxy-2-amino acids.

Recently, on the other hand, functionalization of the methine or methylene group attached to the acylamino group has been one of the interesting themes in synthetic chemistry in relationship to a synthesis of physiologically important natural products such as 7-methoxycephalosporin,[8] bicyclomycin,[9] ergotamine,[10a-c] etc., and excellent methods for the functionalization have been developed.[11a-c] In the previous communication from this laboratory,[12] the electrochemical method has been shown to be highly efficacious in functionalization at the 2 positions of *N*-acylamino acids, especially in the preparation of *N*-acyl-2-methoxy-2-amino acids. In the present paper, we wish to report a synthesis of 2-acetoxy-2-amino acid derivatives[13] by anodic oxidation of substituted and nonsubstituted acylaminomalonic acid monoesters. 3-Acetoxy-3-amino acid derivatives were synthesized in a similar way from 3-alkoxycarbonylalanine derivatives.

A synthesis of 2-acetoxy-2-amino acids (III) was carried out according to Scheme I. Monoesters (II) were prepared by the saponification of the one ester group of the corresponding acylaminomalonic acid diethyl esters (I) in ethanol–potassium hydroxide. The anodic oxidation of compounds II was carried out at 15–20 °C using graphite anode–graphite cathode in a nondivided cell. On electrolysis of monoesters IIa–e in acetic acid containing 0.25 molar equiv of sodium acetate to that of IIa–e, the corresponding *N*-acetyl-2-acetoxy-2-amino acid ethyl esters (IIIa–e) were obtained in 81–94% yield. The current efficiencies of these reactions were about 75%. The side reactions due to oxidation of the benzyl moieties[14] of

Scheme I



a, $R^1 = R^2 = CH_3$ b, $R^1 = C_2H_5$; $R^2 = CH_3$
c, $R^1 = (CH_2)_3CH_3$; $R^2 = CH_3$ d, $R^1 = CH_2Ph$; $R^2 = CH_3$
e, $R^1 = CH_2CH{=}CH_2$; $R^2 = CH_3$ f, $R^1 = H$; $R^2 = OCH_2Ph$
g, $R^1 = H$; $R^2 = CH_3$

monoester IId and the product IIId were not observed. Furthermore, the reduction of the products IIIa–e at the cathode which are sensitive to cathodic reduction[15] did not occur in this electrolysis system. The use of a larger amount of sodium acetate made the current efficiencies decrease: concurrent oxidation of acetate ion presumably took place. The electrolysis of *N*-benzyloxycarbonyl derivative IIf was carried out under the same condition as above to afford ethyl *N*-benzyloxycarbonyl-2-acetoxyglycinate (IIIf) in a good yield without appreciable oxidative cleavage of the benzyl group.[16] In the preparation of *N*-acetyl-2-acetoxyglycinate (IIIg), the potassium salt of monoester IIg was oxidized in acetic acid. The current efficiency of this electrode reaction was lower than those described above. The structural elucidation of these 2-acetoxy-2-amino acid derivatives was carried out based on IR, NMR, and mass spectra and elemental analyses. The yields and the characterizations of the products are summarized in Table I.

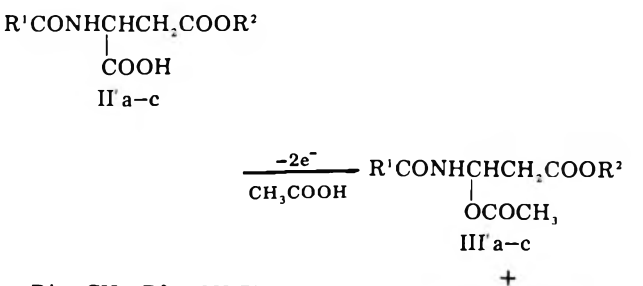
A facile elimination reaction to *N*-acyl-2,3-dehydroalaninate has been observed in *N*-acyl-2-methoxyalaninate[17] and *N*-acyl-2-chloroalaninate.[3a,13a,b] These 2-acetoxy 2-amino acid derivatives (IIIa–e) are so labile that a considerable amount of 2,3-dehydro-2-amino acid derivatives formed by elimination of acetic acid was detected on TLC on treating these amino acids with acetic acid at 50 °C. Accordingly, in the preparation of such unstable 2-acetoxy-2-amino acid derivatives, the electrolysis temperature was kept as low as possible, at least below 25 °C, and the workup procedure was also made carefully to avoid the formation of the dehydroamino acids.

The electrolysis of *N*-acyl-3-alkoxycarbonylalanine (II'a–c) was carried out at 5 °C in acetic acid–tetrahydrofuran (3:1) containing 0.33 molar equiv of sodium acetate to that of (II'a–c). *N*-Acetyl-3-benzyloxycarbonylalanine (II'a), *N*-benzoyl-3-methoxycarbonylalanine (II'b), and *N*,3-dibenzyloxycarbonylalanine (II'c) afforded the corresponding *N*-

Table I. Yields and Spectral Data

Registry no.	Compd	Yield %	IR, cm^{-1}	NMR ($CDCl_3$), δ
62183-00-0	IIIa	91	3300, 1765, 1740, 1670, 1550	1.28 9t, 3 H), 1.98 (s, 3 H), 2.03 (s, 3 H), 2.08 (s, 3 H), 4.26 (q, 2 H), 7.5 (broad s, 1 H)
62183-01-1	IIIb	81	3400, 1755, 1740, 1700, 1520	0.80 (t, 3 H), 1.28 (t, 3 H), 2.03 (s, 3 H), 2.08 (s, 3 H), 1.7–2.4 (m, 1 H), 2.7–3.3 (m, 1 H), 4.26 (q, 2 H), 7.13 (broad s, 1 H)
62183-02-2	IIIc	85	3300, 1750 (broad), 1680, 1510	0.7–1.6 (m, 7 H), 1.24 (t, 3 H), 2.02 (s, 3 H), 2.08 (s, 3 H), 2.4–3.2 (m, 2 H), 4.25 (q, 2 H), 7.1 (broad s, 1 H)
59223-92-6	IIId	94	33000,1770,1750, 1670, 1520	1.20 (t, 3 H), 1.94 (s, 3 H), 2.06 (s, 3 H), 3.26 and 4.30 (AB q, 2 H, J = 13.5 Hz), 4.18 (q, 2 H), 7.0–7.4 (m, 6 H, C_6H_5 + NH)
62183-03-3	IIIe	87	3400, 1755, 1740, 1705, 1540	1.28 (t, 3 H), 2.03 (s, 3 H), 2.09 (s, 3 H), 2.75 (m, 1 H), 3.80 (m, 1 H), 4.27 (q, 2 H), 5.0–6.0 (m, 3 H), 7.4 (broad s, 1 H)
62183-04-4	IIIf	87	3350, 1770, 1740, 1720, 1520	1.25 (t, 3 H), 2.09 (s, 3 H), 4.22 (q, 2 H), 5.25 (s, 2 H), 6.30 (broad s, 2 H, NH + CH), 7.36 (s, 5 H)
62183-05-5	IIIg	82	3300, 3100, 1765, 1740, 1550	1.30 (t, 3 H), 2.10 (s, 3 H), 2.12 (s, 3 H), 4.26 (q, 2 H), 6.40 (d, 1 H), 7.73 (broad d, 1 H)
62183-06-6	IIIh	79	3400, 1740, 1715	1.18 (t, 3 H), 1.88 (s, 3 H), 2.04 (s, 3 H), 3.11 (s, 3 H), 4.11 (q, 2 H), 5.11 (s, 2 H), 7.30 (s, 5 H)
62183-07-7	III'a	40	3300, 1750–1710 (broad), 1670	1.95 (s, 6 H), 2.87 (d, 2 H), 5.14 (s, 2 H), 6.60 (m, 1 H), 7.2–7.5 (m, 6 H, C_6H_5 + NH)
62183-08-8	III'b	54	3300, 1750–1730 (broad), 1655	2.05 (s, 3 H), 2.98 (m, 2 H), 3.77 (s, 3 H), 6.82 (m, 1 H), 7.2–8.0 (m, 5 H), 8.20 (broad d, 1 H)
62183-09-9	III'c	76	3340, 1735, 1720–1700 (broad)	2.05 (s, 3 H), 2.7–3.1 (m, 2 H), 5.10 (s, 2 H), 5.13 (s, 2 H), 6.4–6.6 (m, 1 H), 7.30 (s, 10 H), 10.42 (broad s, 1 H)

Scheme II



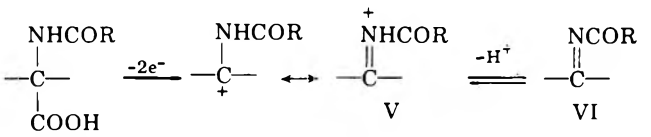
acyl-3-acetoxy-3-amino acid esters (III'a–c) in 40–76% yield. The spectral data of these 3-acetoxy-3-amino acids are shown in Table I. The amount of current passed with 2 Faradays/mol, which was insufficient to consume all the starting materials. A trace amount of products other than the 3-acetoxy-3-amino acid III'b were found on TLC of the electrolyzed solution. The products isolated by preparative TLC were assigned to be *trans*- and *cis*-*N*-acyl-2,3-dehydro-3-amino acids (IV'b) which were presumably formed by elimination of acetic acid from the acetoxyamino acid III'b but not by direct electrode reaction. The electrolysis at a temperature above 20 °C afforded a fair amount of the dehydroamino acid other than the acetoxyamino acid. *N*-Acyl-3-acetoxy-3-amino acids (III'a–c) obtained here are less stable to heat in acetic acid than *N*-acyl-2-acetoxy-2-amino acids (IIIa–e).

In anodic decarboxylation, it is well known that the possible product-forming intermediates are radical and carbonium ion: Kolbe-type reaction involves the former; Hofer–Moest reaction the latter.[19a–c] In these anodic oxidations reported here, no Kolbe dimers were observed. Furthermore, the current efficiencies were fairly good. The results suggest that the carbonium ion intermediate generated via a two-electron transfer is favored over the radical intermediate in these electrode reactions. If the radical intermediate formed by decarboxylation of the monoesters reacts with acetoxy radical, a lower current efficiency would be observed, because the lifetime of acetoxy radical, which is of the order of 10^{-10} s,[20] is too short to give such an efficiency. Furthermore, no elimination and rearrangement took place in these reactions. Thus, the presence of the acylamino group would lead to stabilization of the carbonium ion and allow the formation of only the acetoxy compound. A similar carbonium ion process stabilized by acylamino group has been documented in anodic replacement of carboxylate by methoxy group[12,21a,b] or acetoxy group.[21a] On the other hand, anodic oxidation of alkylated malonic acid monoesters makes the product distribution more complex owing to simultaneous occurrence of elimination, rearrangement, and Kolbe-type reactions.[22a,b]

It has recently been proposed that *N*-acylimine would be an intermediate rather than *N*-acylimmonium both in displacement reaction on 2-substituted *N*-acylalaninate[5,23] and

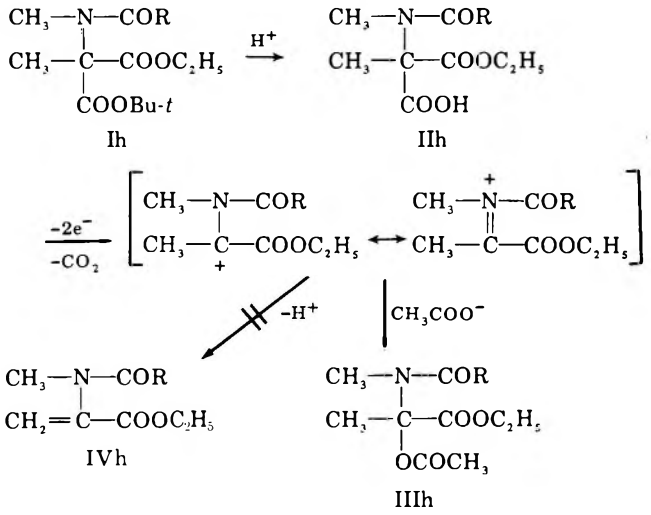
in electrophilic addition reaction[5,18b] to *N*-acyl-2,3-dehydroalaninate; the *N*-methyl analogue of *N*-acyl-2,3-dehydroalaninate, which cannot form *N*-acylimine, did not afford the corresponding 2-substituted alaninate but 2-substituted alaninate produced by Michael addition reaction.[5] The same intermediates, *N*-acylimmonium (V) and *N*-acylimine (VI),

Scheme III



are possible as an intermediate in this electrode reaction. In order to compare the electrode reaction with the electrophilic addition reaction as referenced above, methyl(*N*-methyl-*N*-benzyloxycarbonylamino)malonic acid monoethyl ester (IIh) was synthesized from diester Ih. Anodic oxidation of IIh

Scheme IV



was carried out in acetic acid–tetrahydrofuran (3:1) at 5 °C to afford only the corresponding acetoxy compound (IIIh) but not the elimination product (IVh). This result, which is in contrast with the addition reaction, indicates that the lifetime of the immonium ion (V) is long enough for it to be susceptible to nucleophilic attack of acetate ion, although the immonium ion (V) would be destabilized by inductive effect of the electron-withdrawing acyl group. It is, therefore, suggested that *N*-acylimmonium (V) may be involved in the anodic oxidation of monoesters II and II′. It has also been noted that anodic oxidation of *N,N*-dialkylformamides,[24a,b] trialkylamines,[25a,b] and *N,N*-dialkylcarbamates[26] in methanol proceeds through the immonium intermediates to afford the corresponding α-methoxylated products.

Experimental Section

Equipment. Melting points were measured using the Yamato melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. NMR spectra were obtained using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as internal standard. The electrolyses were carried out by the use of a Hokuto Potentio-Galvanostat HA 104 (1A-55V) attached to a Hokuto HA-108A coulomb meter.

Preparation of Substituted Acylaminomalonic Acid Diesters (Ia–h). Compound Ig was recrystallized from ethanol–ethyl acetate. Compounds Ia–e were prepared by the reaction of Ig with the corresponding alkyl halides in ethanol containing sodium ethoxide. The yields of these reactions were usually good (70–95%). The physical constants of these compounds have appeared elsewhere.[27] The *N*-benzyloxycarbonyl derivative (If) was prepared according to the reported method.[28]

Compound Ih. *N*-Benzyloxycarbonylaminomalonic acid monoethyl ester (10.0 g) was dissolved in 150 mL of methylene chloride containing 1 mL of concentrated sulfuric acid. This solution was saturated with isobutene at 0 °C. The reaction mixture was allowed to stand overnight at room temperature, washed several times with 1% aqueous sodium bicarbonate and with water, then dried over magnesium sulfate. The solution was evaporated to dryness in vacuo and the resulting residue was purified on silica gel chromatography using chloroform–ethyl acetate (4:1) as eluate to afford 11.6 g (97%) of *N*-benzyloxycarbonylaminomalonic acid *tert*-butyl ethyl diester as a colorless syrup: IR (film) 3360 (NH), 1755, 1740, 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.27 (t, 3 H), 1.47 (s, 9 H), 4.26 (q, 2 H), 5.90 (d, 1 H, J = 6 Hz). 5.16 (s, 2 H), 5.89 (broad d, 1 H), 7.39 (s, 5 H). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.48; H, 6.86; N, 4.30. Anhydrous dimethylformamide (130 mL) was added to a mixture of the diester (11.0 g) obtained above and commercially available silver oxide (purchased from Nakarai Kagaku Co. Ltd.) (25 g). To this was added 40 mL of methyl iodide at 0 °C under vigorous stirring. The stirring was continued for 16 h at room temperature. The above procedure[29] was performed in a dark room. After the reaction was over, insoluble materials were filtered off and the filtrate was evaporated to dryness in vacuo. To the resulting residue was added 200 mL of ethyl acetate and insoluble materials were filtered off. The filtrate was washed five times with 50 mL of 10% aqueous sodium thiosulfate, washed with water, then dried over magnesium sulfate. The solution was evaporated to dryness in vacuo and the residue was purified on silica gel chromatography using chloroform–ethyl acetate (4:1) as eluate to afford 11.5 g (97%) of methyl(*N*-methyl-*N*-benzyloxycarbonylamino)malonic acid *tert*-butyl ethyl diester as a light yellow syrup: IR (film), 1750, 1731, 1708 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.23 (t, 3 H), 1.47 (s, 9 H), 1.71 (s, 3 H), 2.96 (s, 3 H), 4.28 (q, 2 H), 5.17 (s, 2 H), 7.35 (s, 5 H). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.36; H, 7.37; N, 3.73.

Preparation of Monoesters (IIa–g) (General Procedure). Diester I (0.1 mol) was dissolved in 70 mL of ethanol. To this was added dropwise a solution of potassium hydroxide (0.12 mol) dissolved in 6 mL of water at 20–25 °C under vigorous stirring. The reaction mixture was allowed to stand for 1 week at the same temperature, and then the solvent was evaporated under reduced pressure below 35 °C. The residue was dissolved in 10–30 mL of water and the solution was washed with ethyl acetate. The aqueous layer was acidified to Congo red with 12 N hydrochloric acid at 0 °C. The acidified solution was shaken with five 100-mL portions of ethyl acetate, and the combined ethyl acetate layer was washed twice with 20 mL of water, dried over magnesium sulfate, then evaporated to dryness in vacuo below 30 °C. The resulting crystals were recrystallized with ethyl acetate-*n*-hexane. This procedure gave monoesters IIa–e,g in good yields. Analytical data are as follows.

Compound IIa (76% yield), mp 135–136 °C (lit.[30] mp 136–136.5 °C). Anal. Calcd for $C_3H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.10; H, 6.51; N, 6.93.

Compound IIb (78% yield): mp 138–140 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.82 (t, 3 H), 1.27 (t, 3 H), 2.05 (s, 3 H), 2.34 (q, 2 H), 4.24 (q, 2 H), 7.08 (broad s, 1 H), 11.10 (broad s, 1 H). Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.75; H, 6.86; N, 6.51.

Compound IIc (73% yield): mp 128–130 °C; NMR (Me_2SO-d_6) δ 0.7–1.5 (m, 7 H), 1.24 (t, 3 H), 2.02 (s, 3 H), 2.1–2.7 (m, 2 H), 4.19 (q, 2 H), 7.12 (s, 1 H). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81; N, 5.71. Found: C, 53.50; H, 7.52; N, 5.74.

Compound IId (79% yield): mp 130–131 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.28 (t, 3 H), 2.01 (s, 3 H), 3.59 (s, 2 H), 4.23 (q, 2 H), 6.8–7.5 (m, 6 H, C_6H_5 + NH), 11.65 (broad s, 1 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.01; H, 6.21; N, 5.09.

Compound IIe (82% yield), mp 123–124 °C (lit.[31] mp 121–122 °C). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.15; H, 6.72; N, 6.21.

Compound IIf (78% yield): mp 65–67 °C; NMR (Me_2SO-d_6) δ 1.20 (t, 3 H), 4.15 (q, 2 H), 4.82 (d, 1 H), 5.08 (s, 2 H), 7.36 (s, 5 H), 8.03 (d, 1 H). Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.62; H, 5.41; N, 4.82.

In the case of monoester IIg, the following procedure was employed. Diethyl acetamidomalonate (Ig) was saponified as described above. The reaction mixture was evaporated to dryness in vacuo, and the resulting residue was triturated with acetone. The crystals were collected by filtration and used without purification.

Compound IIh. Compound Ih (8.0 g) was dissolved in 50 mL of 20% hydrogen chloride in dioxane and the reaction mixture was allowed to stand at room temperature for 4 h. The solvent was evaporated

under reduced pressure and the resulting residue was purified on silica gel chromatography with chloroform–ethyl acetate (1:1) as eluate to afford 3.3 g (49%) of IIh: mp 77–78 °C; IR (Nujol) 1760, 1736, 1569 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.19 (t, 3 H), 1.73 (s, 3 H), 3.12 (s, 3 H), 4.20 (q, 2 H), 5.18 (s, 2 H), 7.35 (s, 5 H), 9.1 (broad s, 1 H). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53. Found: C, 57.96; H, 6.27; N, 4.71.

Compounds II'a–c. Compounds II'a (mp 107–109 °C) and II'c (mp 93–95 °C) were prepared from 3-benzyloxycarbonyl-L-alanine, according to the known method.[32] Compound II'b (mp 125–126 °C) was synthesized from 3-methoxycarbonyl-L-alanine as reported previously.[33]

Reagent and Apparatus for Electrolysis. Acetic acid was purified as follows. Acetic acid (2 L) was refluxed with 70 mL of acetic anhydride for 5 h, and distilled under dried nitrogen gas (bp 115 °C). Special grade sodium acetate was purchased from Katayama Kagaku Co. Ltd., and used without further purification. The electrolysis cell used is an ordinary beaker which is 4 cm in diameter and 10 cm in height. A graphite anode (3 × 4 cm) was placed 1–3 mm apart from a graphite cathode in a nondivided cell.

Electrolysis. Method A. Monoester II (0.02 mol) and sodium acetate (0.005 mol) were dissolved in 50 mL of acetic acid. The solution was put in an electrolysis cell and electrolyzed at a constant current of 250 mA at 20–25 °C. The amount of current passed was 80 mFaradays. After the electrolysis was over, the electrolyzed solution was evaporated to dryness in vacuo below 30 °C. To the residue was added 50 mL of benzene and the mixture was evaporated to dryness in vacuo. This evaporation procedure was repeated at least five times until acetic acid was completely removed. The residue was extracted with ethyl acetate. The extract was washed once with water, dried over magnesium sulfate, then evaporated to dryness in vacuo. The resulting syrup was crystallized by standing at −30 °C in a refrigerator and the crystals were recrystallized from ethyl acetate–*n*-hexane.

Method B. Monoester II or II' (0.01 mol) and sodium acetate (0.0033 mol) were dissolved in a mixture of 30 mL of acetic acid and 10 mL of tetrahydrofuran. The electrolysis was carried out at a constant current of 125 mA at 5–7 °C. The reaction was discontinued when 20 mFaradays was passed. The electrolyzed solution was evaporated to dryness in vacuo below 15 °C, and the resulting residue was treated with benzene as described in method A. To the residue was added 20 mL of dry ethyl ether, and insoluble materials were filtered off. The filtrate was treated with 1 g of activated charcoal, and insoluble materials were filtered off. The treatment with activated charcoal was repeated three times. The filtrate was evaporated to dryness in vacuo. The resulting syrup was allowed to stand at −30 °C, and the crystals formed were collected by filtration. The acetoxyamino acids obtained by method A or method B should be stored below −30 °C; otherwise these decompose to the dehydroamino acids by elimination of acetic acid.

Compound IIIa. This compound was obtained by method A, mp 72–73 °C. Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.49; H, 7.09; N, 6.55.

Compound IIIb. Electrolysis of IIb by method A afforded this compound, mp 71–72 °C. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.74; H, 7.39; N, 6.12.

Compound IIIc. This compound prepared by method A was resistant to crystallization, but analytical data support IIIc: colorless syrup; mass spectrum *m/e* 259 (M^+), 200 (M^+-$OCOCH_3$). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.32; H, 8.22; N, 5.31.

Compound IIId. This compound was prepared by method A, mp 69–70 °C. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.35; H, 6.53; N, 4.74.

Compound IIIe. Treatment of IIe by method A gave this compound: mp 61–62 °C; mass spectrum *m/e* 243 (M^+), 184 ($M^+ - OCOCH_3$). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 53.88; H, 7.02; N, 5.57.

Compound IIIf. After electrolysis by method A, the crude product was purified on silica gel chromatography with chloroform–ethyl acetate (3:1) as eluate to afford IIIf as a colorless syrup. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.82; H, 5.94; N, 4.83.

Compound IIIg. The potassium salt of IIg was electrolyzed in acetic acid to afford IIIg: mp 61–62 °C; mass spectrum *m/e* 203 (M^+), 144 ($M^+ - OCOCH_3$). Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.28; H, 6.39; N, 6.94.

Compound IIIh. Method B was applied to this compound: mp −7 to −8 °C; mass spectrum *m/e* 295 (M^+), 236 ($M^+ - OCOCH_3$). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.34; H, 6.55; N, 4.33. Found: C, 59.41; H, 6.57; N, 4.56.

Compounds III'a–c. These compounds were treated by method B. Compound III'a, mp 78–79 °C (from ethyl acetate–*n*-hexane). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.11; H, 5.98; N, 5.11. Compound III'b, mp 88–89 °C (from ethyl acetate–*n*-hexane). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.42; H, 5.74; N, 5.42.

Compound II'c was electrolyzed at 5 °C. The workup procedure was also performed below 10 °C to afford pure III'c as a colorless syrup which was confirmed by IR and NMR spectra (Table I). This compound is so unstable that the elemental analysis and mass spectrum did not show reasonable values. When this compound was allowed to stand at room temperature, the spot of this compound on TLC almost vanished to afford the elimination product IV'c.

Electrolysis of II'b at 25 °C. Compound II'b was electrolyzed in acetic acid–tetrahydrofuran (3:1) at 25 °C. Two spots, R_f 0.48 and 0.94, other than the acetoxyamino acid III'b (R_f 0.55) were observed on TLC using chloroform–acetic acid–methanol (95:5:3) as a developing solvent. The spots were isolated by preparative TLC and assigned to be the trans form of IV'b (R_f 0.48) and the cis form of IV'b (R_f 0.94). *trans*-IV'b: mp 137–139 °C; IR (Nujol) 3350, 1690, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (s, 3 H), 5.70 (d, 1 H, J = 14 Hz), 7.2–8.0 (m, 5 H), 8.23 (dd, 1 H, J = 11, 14 Hz), 9.25 (broad d, 1 H, J = 11 Hz). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.45; H, 5.52; N, 6.55. *cis*-IV'b: mp 61–62 °C; IR (Nujol) 3330, 1700, 1685, 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.78 (s, 3 H), 5.27 (d, 1 H, J = 9 Hz), 7.2–8.1 (m, 6 H), 11.0–12.0 (broad s, 1 H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.53; H, 5.61; N, 6.54.

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Registry No.—Ia, 55166-91-1; Ib, 32819-24-2; Ic, 62183-10-2; Id, 3235-26-5; Ie, 14109-62-7; If, 3005-66-1; Ih, 62183-11-3; IIa, 59223-81-3; IIb, 59223-82-4; IIc, 62183-12-4; IId, 59223-84-6; IIe, 2584-73-8; IIf, 7682-49-7; IIg potassium salt, 62183-13-5; IIh, 62183-14-6; II'a, 10144-33-9; II'b, 39741-26-9; II'c, 62813-15-7; *trans*-IV'b, 62813-16-8; *cis*-IV'b, 62813-17-9; *N*-benzyloxycarbonylaminomalonic acid *tert*-butyl ethyl diester, 61016-16-8; isobutene, 115-11-7.

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Reaction of 2,3-Di(*p*-anisyl)-2,3-butanediol with Acetyl Bromide

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The reaction of *meso*-di(*p*-anisyl)-2,3-butanediol (**1**) with acetyl bromide in the presence of a small amount of *N*-phenyl-β-naphthylamine at room temperature is different from the literature,[1,2] and gives *cis*- and *trans*-2,3-di(*p*-anisyl)-2-butene (**6** and **2**) and 2-*p*-anisyl-3-methyl-6-methoxyindene (**5**) together with another isomeric butene, 2,3-di(*p*-anisyl)-1-butene (**7**) and pinacol rearrangement product, 3,3-di(*p*-anisyl)-2-butanone (**4**), but the yield of expected product, 2,3-di(*p*-anisyl)-1,3-butadiene (**3**), is very low. Addition of a small amount of HBr and KI promotes the formation of the butenes with simultaneous decrease in the content of the indene and the butanone. The time–conversion curves for the reaction of **1** and **4** with acetyl bromide were drawn and a mechanism involving dianisyl-3-methylallyl cation (**9**) is suggested.

2,3-Diaryl-1,3-butadiene was reported to be prepared by the dehydration of *meso*-2,3-diaryl-2,3-butanediol with acetyl bromide in the presence of a small amount of *N*-phenyl-β-naphthylamine.[1,2] In the course of our attempt to prepare 2,3-di(*p*-anisyl)-1,3-butadiene (**3**) according to this procedure, however, we found that by long duration of reaction the yield of butadiene **3** was very low and that *trans*-2,3-di(*p*-anisyl)-2-butene (**2**) and 2-*p*-anisyl-3-methyl-6-methoxyindene (**5**) were obtained together with a certain amount of 3,3-di(*p*-anisyl)-2-butanone (**4**) and other products. The easy formation of pinacolone **4** is anticipated under these acidic conditions, because the *p*-anisyl group has a high migratory aptitude in the pinacol rearrangement[3] and the substituted butadiene **3** can be converted to the substituted indene **5** by acid catalysts,[1] but the substituted butene **2** is an unexpected product. We tried to confirm the reaction products and to elucidate the mechanism for this abnormal formation of **2** and other products.

Results and Discussion

When the reaction of pinacol **1** with acetyl bromide in the presence of a little *N*-phenyl-β-naphthylamine was carried out at 0 °C for 2 h according to the literature procedure,[2] the main products were pinacolone **4** and indene **5** together with minor products such as butadiene **3** and butenes **2, 6,** and **7,** as shown in Table I.

The products were identified by NMR, IR, and MS, and GLC products **2, 3, 4,** and **5** were isolated by column chromatography using silicic acid as an adsorbent and benzene–petroleum ether as an eluent. The yields of butenes **2, 6,** and **7** were low after 2-h reaction at 0 °C (run 1), but at higher temperature (run 2), longer reaction time (run 3) or addition of KI and HBr (runs 4 and 6) caused an increase in the contents of the butenes with a simultaneous decrease in the content of pinacolone **4** and indene **5.** These results suggest that reducing agents such as HBr and HI promote the formation of butenes **2, 6,** and **7.** Acetyl bromide which can give HBr by the reaction with pinacol **1** is effective in the butene formation and, as expected, acetyl chloride is also effective in the presence of KI (run 9).

Acetic anhydride as well as acetyl chloride as a diluent suppressed the butene formation (runs 7 and 8). The amine acts to increase the amount of butadiene **3** but decreases that of indene **5** (runs 10 and 11). Excess acetyl bromide tends to increase the amount of **5** and pinacolone **4,** but decreases those of other products (runs 2 and 5).

Figure 1 shows the time–conversion curves in the reaction of pinacol **1** with acetyl bromide. Figure 1 implies the initial formation and then gradual consumption of indene **5** and diene **3** to butenes **2, 6,** and **7.** The total recovery decreases to 70%, probably because of the formation of tarry material; the decrease of indene **5** seems to be parallel to the decrease of whole products.

Since pinacol **1** under these acidic reaction condition can be converted to pinacolone **4** at an early stage of the reaction, the reaction of **4** with acetyl bromide was examined. On addition of acetyl bromide to the pinacolone, the same products and the similar time–conversion curve as Figure 1 were obtained, but the reaction with pinacolone **4** was much slower than pinacol **1.** Hence, the reaction of **1** to give butenes **2, 6,** and **7** would not proceed mainly via pinacolone **4.** Also, addition to KI to the system of **4**–AcBr accelerated the reaction of pinacolone **4,** giving the butenes **2** and **6.**

Figure 1 might suggest a pathway **1** → **5** → **2, 6,** and **7,** but it is less plausible, since the treatment of indene **5** with acetyl bromide alone, aqueous HBr, acetic anhydride, or acetyl

Table I. Products Distribution for the Reaction of 2,3-Di(*p*-anisyl)-2,3-butanediol (1) with Acetyl Bromide

	Run, % composition										
Product	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]	10[j]	11[k]
6	6	25	37	45	4	32	Trace	Trace	11	4	3
2	6	21	32	36	8	51	Trace	Trace	22		
7	2	5	19	11			Trace	Trace		4	1
3	12	4	3	1	1	2	15	20	2	7	18
4 (+1)	51	6	0	1	25	3	72	9	44	61	65
5	24	39	9	6	63	13	13	71	21	22	10

[a] A reaction in an ice bath for 2 h (1, 4 g; AcBr, 12.5 mL; amine, 0.25 g). [b] A reaction of the mixture in footnote *a* in an ice bath for 0.5 h and at ambient temperature (~15 °C) for 1.5 h. [c] A reaction of the mixture in footnote *a* in an ice bath for 0.5 h and at ambient temperature (~15 °C) for 4.5 h. [d] A reaction in an ice bath for 0.5 h (1, 2 g; AcBr, 4 mL; amine 0.13 g; KI, 1.1 g). [e] A reaction in an ice bath for 0.5 h and at ambient temperature for 1 h (~25 °C) (1, 0.5 g; AcBr, 3 mL). [f] A reaction in an ice bath for 5 min and at ambient temperature (~25 °C) for 55 min (1, 0.5 g; AcBr, 4.5 mL; 47% aqueous HBr, 0.5 mL). [g] A reaction at ambient temperature for 2 h (1, 1 g; AcBr, 1 mL; Ac_2O, 4 mL). [h] A reaction at ambient temperature (~25 °C) for 16 h (1, 3 g; AcBr, 15 mL; Ac_2O, 3 mL). [i] A reaction at ambient temperature (~25 °C) for 20 min (1, 0.2 g; AcCl, 2 mL; KI, 0.2 g). [j] A reaction in an ice bath for 2 h (1, 2 g; AcBr, 6.2 mL). [k] A reaction in an ice bath for 2 h (1, 2 g; AcBr, 6.2 mL; amine, 0.65 g).

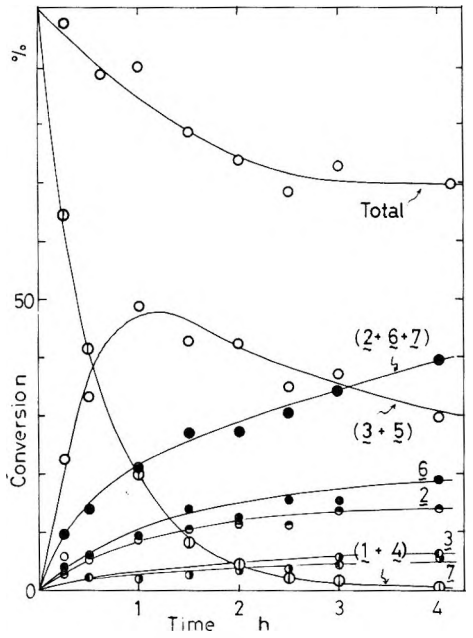


Figure 1. Reaction of pinacol 1 (0.91 g) with acetyl bromide (8.3 g) in the presence of *N*-phenyl-β-naphthylamine (0.03 g) at ambient temperature (~18 °C).

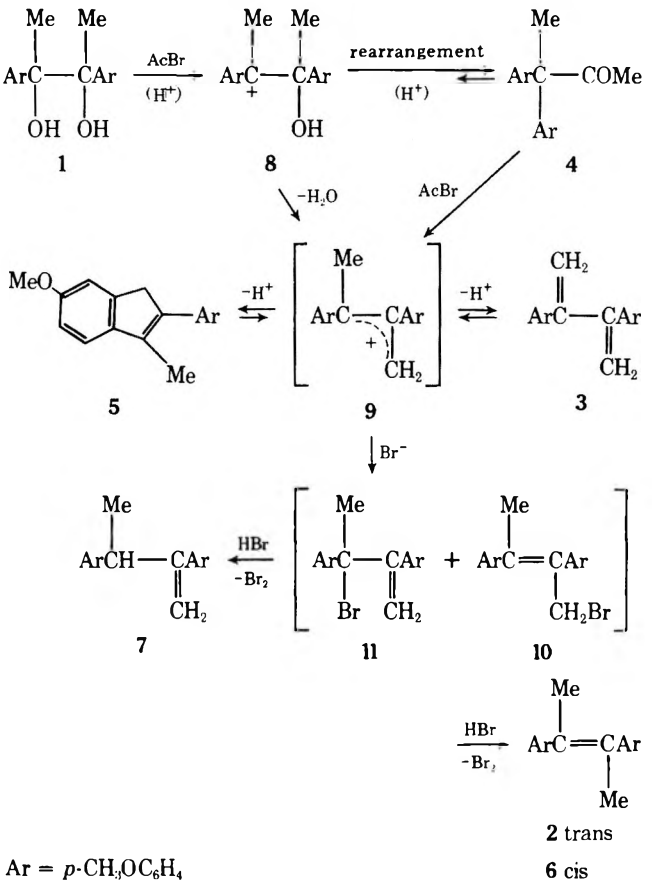
bromide–KI for over 15 h gave only a small amount of butenes **2, 6,** and **7** with recovery of most of indene **5.** These observations suggest a tentative mechanism of Scheme I for the reaction, where a shorter arrow means the slower rate.

Intermediary carbonium ion **8** is well established in the pinacol rearrangement. Dehydration of this cation leads to allyl cation **9** which may be a key intermediate in this reaction. The scheme is supported by the fact that butadiene **3** reacted with acetyl bromide to give indene **5** (70%) together with butenes **2** (7%) and **6** (3%) with recovery of **3** (21%). A facile acid-catalyzed cyclization of 2,3-diphenyl-1,3-butadiene (**3**, Ar = Ph) to the corresponding indene has been reported.[1]

The observation that pinacolone **4** reacted with difficulty with HBr, but reacted with acetyl bromide to give indene **5** and butenes **2, 6,** and **7,** suggests that the reaction of **4** proceeds via the enol ester followed by the elimination of acetate ion and rearrangement to give cation **9.**

HBr[4] and HI[5] have been shown to be effective agents for the reduction of olefins, alcohols, and alkyl halides, and these reductions were suggested to proceed via alkyl bromides and iodides.[6] Similarly, the pathway to **2, 6,** and **7** from **9** probably

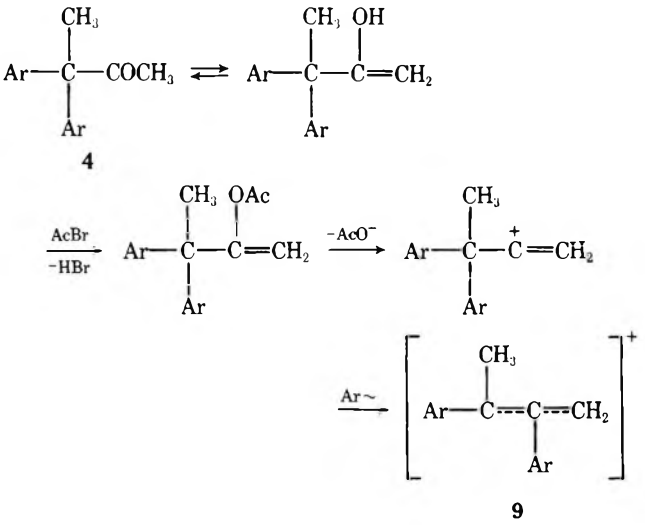
Scheme I



Ar = *p*-$CH_3OC_6H_4$

involves the formation of 1- and 3-butenyl bromides, while a direct hydride transfer from HBr to **9** is inconceivable because of the instability of formed Br^+. Addition of iodide, which is a reducing agents more effective than bromide, promotes the reduction to the butenes.

Since cyclization of cation **9** to **5,** deprotonation to **3,** and reduction to **2, 6,** and **7** compete with each other, as shown in Scheme I, addition of HBr or KI should favor butenes **2, 6,** and **7,** but not favor the formation of indene **5** and butadiene **3,** which was found to be the case. The use of acetyl chloride or acetic anhydride as a diluent, which retards the reduction, favors the formation of **5** and **3** as was observed (runs 7 and 8). Detection of molecular bromine by sodium thiosulfate and the monobromo derivative of *N*-phenyl-β-naphthylamine by



GLC–MS (*m/e* 299, 297, and 219) from the products mixture is an additional support to the conversion of HBr to Br_2 in the reaction system.

Another possible mechanism is that involving the reduction of pinacolone **4** with hydrogen bromide to 3,3-di(*p*-anisyl)-2-butanol followed by a retropinacol-type rearrangement to form butenes **2, 6,** and **7.** This is less plausible, since the pinacolone reacted under similar conditions much slower than the pinacol and does not undergo facile reduction by HBr to the butanol.

$$MeCO{=}CMeAr_2 \xrightarrow{HBr} MeCH(OH){-}CMeAr_2$$

$$\xrightarrow{H^+} MeCH{-}\overset{+}{C}MeAr_2$$

$$\xrightarrow{\sim Ar} MeCHAr{-}\overset{+}{C}MeAr \xrightarrow{-H^+} \textbf{2, 6, and 7}$$

In conclusion, pinacol **1** can be easily converted to butenes **2, 6,** and **7** with an acetyl bromide–KI mixture in one operation. It is preferentially converted to pinacolone **4,** indene **5,** and butadiene **3** with acetyl bromide–acetic anhydride mixture. Indene **5** (mp 112.5 °C) might be wrongly assigned by Sisido et al.[2] the isomeric structure **3** (mp 110 °C) on the basis of its melting point and elemental analysis alone.

Experimental Section

Materials. Butanediol **1** was prepared by the reductive coupling of *p*-methoxyacetophenone with amalgamated aluminum foil in a mixture of absolute ethanol and dry benzene:[2] meso isomer, mp 165–167 °C (lit.[7] 168–169 °C); *dl* isomer, mp 125–127 °C (lit.[7] 122–123 °C). Ketone **4** was prepared according to the literature,[2] mp 72–73 °C (lit.[2] 69–70 °C). Acetyl bromide, bp 74.5–75 °C, acetyl chloride, bp 50–51 °C, acetic anhydride, bp 114–116 °C, and *N*-phenyl-β-naphthylamine were guaranteed grade commercial reagents.

Reaction of Butanediol 1 with Acetyl Bromide. According to the Sisido's procedure,[2] acetyl bromide was added dropwise to a mixture of **1** and *N*-phenyl-β-naphthylamine in a flask equipped with a dropping funnel and a calcium chloride tube with stirring. After reaction at 0 °C for 2 h in an ice bath, the excess acetyl bromide was removed by distillation in vacuo, and then the mixture was poured into cold aqueous Na_2CO_3 (30%). The products were extracted with benzene, dried over $MgSO_4$, and separated by column chromatography with silicic acid using petroleum ether–benzene as a solvent, and determined by GLC on a Yanagimoto GCG-550 F gas chromatograph, employing a flame ionization detector and a 1.0 m × 2.5 mm stainless-steel column packed with silicone OV (5%) on Shimalite or PEG 20 M (2.5 %) on Chamelite CS using N_2 as a carrier gas at 150–280 °C.

The products were identified by IR, NMR, and mass spectra. Mass spectra were recorded on a Shimadzu Model GCMS 7000 mass spectrometer.

***trans*-2-Butene 2,** mp 128.5–130 °C (lit.[2] 126–128 °C), was identified by comparison of the IR spectrum with that of the authentic sample prepared according to ref 2: NMR (CCl_4) τ 8.17 (s, 6 H), 6.2 (s, 6 H), 3.23 (d, 4 H, J = 9 Hz), 2.92 (d, 4 H, J = 9 Hz); UV λ_{max}^{EtOH} 248 nm (log ε 4.2); mass spectrum *m/e* 268 (M^+), 253, 238. The mass spectrum of **6,** *m/e* 268, 253, and 238, and isomerization of trans-isomer **2** (100%) by iodine catalyst giving an equilibrium mixture of **6** (38%) and **2** (62%) indicate that **6** is a cis isomer of **2.** As shown below, the acid-catalyzed dehydration of 3,3-di(*p*-anisyl)-2-butanol gave **6** together with **2** and **7,** and this also supports the structure assigned for **2** and **6.** The mass spectrum of 1-butene **7** showed *m/e* 268 (M^+), 135, 133. The assignment for **7** is supported by the formation of **7** by dehydration of 3,3-di(*p*-anisyl)-2-butanol.

Butadiene 3: mp 109–110 °C (lit.[2] 108–109 °C); mass spectrum *m/e* 266 (M^+), 251, 236, 133; NMR ($CDCl_3$) τ 6.2 (s, 6 H), 4.67 (d, 2 H, J = 1.5 Hz), 4.43 (d, 2 H, J = 1.5 Hz), 3.13 (d, 4 H, J = 9 Hz), 2.55 (d, 4 H, J = 9 Hz).

Pinacolone 4: mp 72–73 °C (lit.[2] 69–70 °C); mass spectrum *m/e* 241 ($M^+ - CH_3O$); IR (cm^{-1}) 1700.

Indene 5: mp 112–112.5 °C; mass spectrum *m/e* 266 (M^+); λ_{max}^{EtOH} 301 nm (log ε 3.98), 270 (log ε 4.2); NMR ($CDCl_3$) τ 7.82 (t, 3 H, J = 1.9 Hz), 6.45 (q, 2 H, J = 1.9 Hz), 6.27 (s, 6 H), 2.6–3.4 (m, 7 H). The methylene at τ 6.45 has a long-range coupling with methyl at τ 7.82 to afford quartet and triplet, respectively.[8] Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found. C, 80.28; H, 6.76.

Other Reactions of Butanediol 1. In the other runs, acetyl bromide, acetyl chloride, or acetic anhydride–HBr was added at once to a mixture of **1** and other additives. The flask was stoppered and kept standing with occasional shaking for the appropriate length of time.

Time–Conversion Curves for Reaction of Butanediol 1 with Acetyl Bromide. For the time–conversion measurements, aliquots were pipetted out, treated with ice-cold aqueous Na_2CO_3, extracted with benzene, and dried over $MgSO_4$ and then the product contents were determined by GLC analysis using deoxybenzoin as an internal standard. **2** + **6** + **7** means the amount of butene isomers and **3** + **5** means that of isomers of butadienes.

Acid-Catalyzed Dehydration of 3,3-Di(*p*-anisyl)-2-butanol. The alcohol, which was prepared by the reduction of pinacolone **4** (3 g) with Na–EtOH in xylene,[2] was treated with acetic acid (16 mL)–H_2SO_4 (6 mL)–water (13 mL). After 5-h reaction time, a part of the mixture was poured into ice-cold aqueous Na_2CO_3, extracted with ether, and dried over $MgSO_4$. The GLC analysis of the extract showed that the reaction was not completed and it contained a mixture of **6** (22%), **2** (21%), **7** (10%), and unreacted alcohol (47%). After addition of acetic acid (10 mL) and H_2SO_4 (2 mL), the reaction was continued for 3 h. The mixture was treated with cold water and the resulting precipitate was recrystallized from methanol. Pure *trans*-butene **2** was obtained, 1 g (33%), mp 128.5–130 °C (lit.[2] 126–128 °C).

Registry No.—**1,** 62154-11-4; **2,** 17324-35-5; **3,** 52255-88-6; **4,** 22927-05-5; **5,** 62154-12-5; **6,** 54953-13-8; **7,** 15542-00-4; *p*-methoxyacetophenone, 100-06-1; acetyl bromide, 506-96-7; 3,3-di(*p*-anisyl)-2-butanol, 62154-13-6.

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Alkyl Nitrite–Metal Halide Deamination Reactions. 2. Substitutive Deamination of Arylamines by Alkyl Nitrites and Copper(II) Halides. A Direct and Remarkably Efficient Conversion of Arylamines to Aryl Halides[1]

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Alkyl nitrites and anhydrous copper(II) halides rapidly convert arylamines into aryl chlorides and bromides in high yield. One molar equivalent of alkyl nitrite and 0.5 molar equiv of copper(II) chloride or bromide are required for this direct substitutive deamination reaction, which results in the production of cupric oxide, nitrogen, and alcohol as well as aryl halide. Reactions of copper(II) halides and *tert*-butyl nitrite in acetonitrile with 15 representative arylamines are reported; results from this study exemplify the synthetic advantages of the direct substitution process and demonstrate the absence of side products that usually accompany similar syntheses using copper(I) halides and arenediazonium salts. A comparison of products and product yields from reactions of *tert*-butyl nitrite and aniline with copper(II) chloride and copper(I) chloride is presented; the unique role of copper(II) halides in substitutive deamination reactions with arylamines is indicated by these data. In reactions of arylamines with copper(II) bromide and *tert*-butyl nitrite a unique process that involves substitution of bromide at aromatic ring positions that are ortho or para to the original amine position competes with substitutive deamination. With arylamines that possess para substituents, orientation of bromine to the ortho position is the sole result of this competing deaminative pathway. The products from this competing process are identified and the extent of their formation is described.

The synthesis of aryl halides from arylamines by the conventional Sandmeyer procedure[3,4] involves initial diazotization of the arylamine followed by addition of the diazonium salt to the cuprous halide in an aqueous solution with the corresponding halogen acid. Although satisfactory yields of aryl halides are usually obtained, the Sandmeyer reaction (eq 1) is complicated by numerous competing reactions (eq 2–5). To minimize these side reactions prescribed procedures for the performance of the Sandmeyer reaction have been designed.

$$ArN_2^+CuX_2^- \rightarrow ArX + N_2 + CuX \quad (1)$$

$$2ArN_2^+CuX_2^- \rightarrow ArAr + 2N_2 + 2CuX_2 \quad (2)$$

$$2ArN_2^+CuX_2^- \rightarrow ArN{=}NAr + N_2 + 2CuX_2 \quad (3)$$

$$ArN_2^+X^- + H_2O \rightarrow ArOH + N_2 + HX \quad (4)$$

$$ArN_2^+X^- + SolH \rightarrow ArH + N_2 + SolX \quad (5)$$

Since the rates of formation of biaryl and azo compounds (eq 2, 3) depend on the square of the concentration of cuprous halide[5] and the rate of aryl halide production (eq 1) is inversely proportional to the square of the chloride ion concentration,[5] the optimum conditions for the conventional Sandmeyer reaction in aqueous halogen acid appear to require equimolar amounts of copper halide and arenediazonium salt.[3] However, effective control of competing processes transcends modification of the reaction stoichiometry. The mode of addition, the reaction temperature, and the nature of the diazonium salt are also prime determinants of the yield of aryl halide. For example, when the normal addition step is reversed and a dilute acid solution of cuprous halide is added to the diazonium salt, biaryl formation effectively competes with the production of aryl halide.[3a,6] With reactive diazonium salts reaction temperatures above 10 °C generally promote phenol formation in aqueous media (eq 4);[3] subsequent coupling of the phenol with undecomposed diazonium salt produces azophenols. In addition, reduction of the diazonium compound to the corresponding arene (eq 5) often competes with aryl halide formation,[7] particularly when the Sandmeyer reaction is performed in aqueous acetone or alcohol.[8]

Numerous variations of the conventional Sandmeyer reaction have been introduced to improve the yields of substitution products. Cuprous salts have been replaced by finely divided copper metal (the Gatterman method),[9] by copper(II) salts,[10] or by iron(III), cobalt(III), and zinc(II) salts,[3a] and examples have been reported in which these replacements have resulted in comparable or improved yields of Sandmeyer products.[3] Nitrosyl complexes of anhydrous copper(II) halides have recently been reported to effect a direct conversion of arylamines to aryl halides, presumably through an intermediate diazonium dihalocuprate salt (eq 6).[11]

$$ArNH_2 + CuX_2 \cdot NO \xrightarrow[(-H_2O)]{} [ArN_2^+CuX_2^-] \rightarrow ArX + N_2 + CuX \quad (6)$$

A similar direct replacement of the aromatic amino group by bromine through reactions of amine hydrobromides with dinitrogen trioxide, but without an added metal catalyst, has also been reported.[14] Although there are specific advantages to each of these methods, none of the variations has received wide application, and the preferred method for the synthesis of aryl halides from arylamines remains the conventional Sandmeyer procedure.

The recent successful uses of alkyl nitrites as nitrosating agents for alkyl-[16] and arylamines,[17] and our own observation of oxidative deamination of primary aliphatic amines by the combination of alkyl nitrites and anhydrous copper(II) halides,[18] prompted us to investigate the reactions of aromatic amines with alkyl nitrites in the presence of anhydrous copper(II) salts. In this paper we report the direct synthesis of aryl halides from arylamines by substitutive deamination.

Results

Treatment of arylamines with *tert*-butyl nitrite and anhydrous cupric halides (X = Cl, Br) in acetonitrile at 65 °C results in the rapid and quantitative evolution of nitrogen and in the formation of aryl halides, cupric oxide, and *tert*-butyl alcohol (eq 7).[19]

$$2ArNH_2 + 2RONO + CuX_2 \rightarrow 2ArX + 2ROH + CuO + H_2O + 2N_2 \quad (7)$$

The stoichiometry of this reaction, which was determined from experiments in which the molar ratios of both *tert*-butyl

Table I. Variation of Product Yields with the Molar Ratio of $CuCl_2$ to *p*-Nitroaniline in Reactions with *tert*-Butyl Nitrite at 65 °C [a]

$[CuCl_2]/[p\text{-}NO_2C_6H_4NH_2]$	Relative yield, %		Isolated yield, %
	$p\text{-}NO_2C_6H_4Cl$	$C_6H_5NO_2$	
2.0	100	0	99.5
1.0	>99.9	<0.1	90
0.50	98	2	86
0.26	85[b]	15	62

[a] Reactions were performed in acetonitrile using 10 mmol of *p*-nitroaniline and 15 mmol of *tert*-butyl nitrite. [b] A 53% isolated yield of *p*-nitrochlorobenzene was obtained which quantitatively accounts for the fate of the reactant chloride.

nitrite and cupric halide to arylamine were varied independently, requires 1 molar equiv of *tert*-butyl nitrite for complete reaction but necessitates the use of only sufficient cupric halide to quantitatively produce cupric oxide and aryl halide. The stoichiometric dependence of the yield of reaction products on cupric chloride is described by the data in Table I for the deamination of *p*-nitroaniline. There is a remarkable efficiency for halide utilization in this substitutive deamination procedure.

The major process competing with aryl halide formation when the molar ratio of CuX_2 to amine is equal to or less than 0.5 (Table I) is reduction of the arylamine to the corresponding arene. In the absence of copper(II) halide reaction of *tert*-butyl nitrite with *p*-nitroaniline in acetonitrile at 65 °C results in the formation of nitrobenzene in 40% yield;[20] cupric oxide has no measurable product orienting effect on this reduction process. Reaction times for complete evolution of nitrogen increase with decreasing CuX_2:$ArNH_2$ molar ratios. For example, with *p*-nitroaniline at 65 °C gas evolution is complete within 10 min when 1.0 molar equiv of $CuCl_2$ is employed, but requires nearly 30 min for complete nitrogen evolution when 0.5 equiv of the same cupric halide is used. Reduction of *p*-nitroaniline under the same reaction conditions, but in the absence of copper salts, requires reaction times comparable to those necessitated by the use of less than 0.5 molar equiv of $CuCl_2$. Thus reduction appears to be independent of substitutive deamination and is effectively minimized by the use of sufficient copper(II) halide so that the CuX_2:$ArNH_2$ molar ratio is greater than 0.5.

Copper(II) oxide was identified as the sole copper-containing product from reactions that employed less than a stoichiometric equivalent of cupric halide based on eq 7. The nature of the reaction products and the yields of these products did not depend on the presence or absence of air. For example, when the substitutive deamination procedure was performed under nitrogen with *p*-nitroaniline, *tert*-butyl nitrite, and copper(II) chloride, the products obtained were identical with those from reactions that were performed in an atmosphere open to air (Table I). No evidence was obtained by x-ray powder analysis for the presence of either copper(I) chloride or copper(I) oxide.

The isolated yields of aryl halides from reactions of representative arylamines with *tert*-butyl nitrite and copper(II) halides are given in Table II. The uniformly exceptionally high yields of aryl halides obtained by this method are comparable or superior to those obtained by the Sandmeyer procedure or its modifications.[3,9-11,14,21]

Lower reaction temperatures generally effect an increase in the yields of aryl halides from substitutive deamination reactions of arylamines bearing electron-donating substitutents. With *p*-anisidine, for example, the isolated yields of *p*-chloroanisole from reactions at 65 and 5 °C were 32 and 66%, respectively.[22] Similarly, the yields of aryl bromides from substitutive deamination reactions that employ the more reactive copper(II) bromide[23] are generally higher when the reaction temperature is at or below room temperature than at 65 °C.

The data in Table II indicate that substitutive deamination of arylamines by *tert*-butyl nitrite and copper(II) halides is general for the formation of aryl chlorides and bromides. However, arylamines possessing methyl substituents ortho to the amino group give low yields of aryl halides. For example, deamination of 2,4,6-trimethylaniline by *tert*-butyl nitrite and copper(II) chloride at 0–5 °C gave 2,4,6-trimethylchlorobenzene in only 32% yield; mesitylene, the product of reductive deamination, was the only other observed product (14% yield). Substitutive deaminations of 2-methyl-1-aminonaphthalene resulted in similar low yields of 2-methyl-1-halonaphthalenes. Amines with o-nitro, -chloro, and -carboxylate functional groups show no similar limitation.

Table II. Aryl Halide Product Yields from Reactions of Arylamines with *tert*-Butyl Nitrite and Copper(II) Halides in Acetonitrile [a]

Registry no.	$ArNH_2$	ArX	% yield ArCl[b]	% yield ArBr[b]
100-01-6	$p\text{-}NO_2C_6H_4NH_2$	$p\text{-}NO_2C_6H_4X$	99.5 (92)	90[c]
99-92-3	$p\text{-}CH_3COC_6H_4NH_2$	$p\text{-}CH_3COC_6H_4X$	98	92[c]
118-92-3	$o\text{-}HOOCC_6H_4NH_2$	$o\text{-}HOOCC_6H_4X$	95	
106-47-8	$p\text{-}ClC_6H_4NH_2$	$p\text{-}ClC_6H_4X$	74	88[d]
371-40-4	$p\text{-}FC_6H_4NH_2$	$p\text{-}FC_6H_4X$	61[c]	71[c]
455-14-1	$p\text{-}CF_3C_6H_4NH_2$	$p\text{-}CF_3C_6H_4X$	94[c]	78[c]
62-53-3	$C_6H_5NH_2$	C_6H_5X	66	47[c]
106-49-0	$p\text{-}CH_3C_6H_4NH_2$	$p\text{-}CH_3C_6H_4X$	96[c]	76[c]
104-94-9	$p\text{-}CH_3OC_6H_4NH_2$	$p\text{-}CH_3OC_6H_4X$	66[c]	71[c]
634-93-5	$2,4,6\text{-}Cl_3C_6H_2NH_2$	$2,4,6\text{-}Cl_3C_6H_2X$	84 (82)	93
88-05-1	$2,4,6\text{-}(CH_3)_3C_6H_2NH_2$	$2,4,6\text{-}(CH_3)_3C_6H_2X$	32[c]	26[d]
89-62-3	$2\text{-}NO_2\text{-}4\text{-}CH_3C_6H_3NH_2$	$2\text{-}NO_2\text{-}4\text{-}CH_3C_6H_3X$	(95)	98
92-87-5	Benzidine	$p\text{-}XC_6H_4C_6H_4X\text{-}p$	95	
134-32-7	1-Aminonaphthalene	$1\text{-}C_{10}H_7X$	82	96
2246-44-8	2-Methyl-1-aminonaphthalene	$2\text{-}CH_3\text{-}1\text{-}C_{10}H_6X$	15[d]	10[d]

[a] Reactions were performed by adding 10.0 mmol of the amine in 2 mL of anhydrous acetonitrile to 15.0 mmol of *tert*-butyl nitrite and, ordinarily, 12.0 mmol of copper(II) halide in 40 mL of acetonitrile. Reaction temperature was 65 °C unless indicated otherwise. [b] Absolute yield of the aryl halide after isolation of the organic product; yields were generally determined by GLC analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±1% of the reported values. Isolated yields after recrystallization are given in parentheses. [c] The reaction solution was cooled in an ice bath to 0–5 °C and was warmed to room temperature 2 h after complete addition of the amine. [d] Reaction temperature was 25 °C.

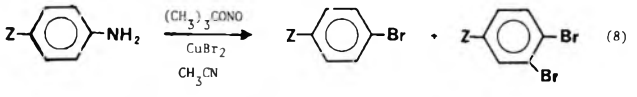
Table III. Mono- and Dibromide Products from Reactions of Arylamines with Copper(II) Bromide and *tert*-Butyl Nitrite in Acetonitrile [a]

$ArNH_2$	Relative yield, %			Isolated yield, %
	ArBr	*o*-$ArBr_2$	*p*-$C_6H_4Br_2$	
p-$NO_2C_6H_4NH_2$	92	8	0	98
p-$CH_3COC_6H_4NH_2$	94	6	0	98
p-$ClC_6H_4NH_2$	90	10	0	98
p-$FC_6H_4NH_2$	81	19	0	88
p-$CF_3C_6H_4NH_2$	79	21	0	99
$C_6H_5NH_2$	57	(3) [b]	40	82
p-$CH_3C_6H_4NH_2$	79	21	0	96
p-$CH_3OC_6H_4NH_2$	88	12	0	81

[a] Reaction conditions are those given in Table II for the same amines. [b] 1,2,4-Tribromobenzene; *o*-dibromobenzene is not a detectable product in the reaction with aniline.

Thorough examination of the product mixtures from reactions of *tert*-butyl nitrite and copper(II) chloride with the para-substituted arylamines reported in Table II showed a general absence of compounds that usually accompany aryl chlorides in the Sandmeyer reaction: biphenyls (eq 2), azobenzenes (eq 3), phenols (eq 4), arene reduction products (eq 5), and *N*-arylacetamides. Corresponding biphenyl, phenol, and arene compounds were not detected in the reaction mixtures from substitutive deamination of the series of arylamines: *p*-nitroaniline, *p*-aminoacetophenone, *p*-chloroaniline, *p*-fluoroaniline, *p*-trifluoromethylaniline, aniline, *p*-toluidine, and *p*-anisidine. Azobenzenes were found as minor products only from reactions with aniline (<1%), *p*-toluidine (1%), and *p*-anisidine (3%). *N*-Arylacetamides were constituents of product mixtures from reactions of copper(II) halide and *tert*-butyl nitrite with *p*-chloroaniline (5%) and *p*-toluidine (2%) but were absent in product mixtures from reactions with other amines. Identifiable side products (biphenyl, azobenzene, arene, phenol, and *N*-arylacetamide) were similarly absent in reaction mixtures from substitutive deaminations by copper(II) bromide and *tert*-butyl nitrite of those amines listed in Table II.

In reactions of arylamines with copper(II) bromide and *tert*-butyl nitrite a unique and, for the Sandmeyer process, previously unreported reaction accompanies the formation of aryl bromides. Substitution of bromide at aromatic ring positions that are ortho or para to the original amine position competes effectively with substitutive deamination (eq 7). With arylamines that possess para substituents, orientation of bromine to the ortho position is the sole result of this competing deaminative pathway (eq 8). With arylamines that



(8)

do not possess para substituents, however, orientation of bromine to the para position is highly favored. The yields of mono- and dibromide products from reactions of arylamines with copper(II) bromide and *tert*-butyl nitrite in acetonitrile are given in Table III. 2-Methyl-1-aminonaphthalene, which is not listed in Table III, formed 2-methyl-1,4-dibromonaphthalene (17%) as the only identifiable dibromonaphthalene derivative.

Deamination of aniline by *tert*-butyl nitrite and copper(II) bromide yielded only bromobenzene, *p*-dibromobenzene, and 1,2,4-tribromobenzene. o-Dibromobenzene, biphenyl, azobenzene, and phenol were not present in detectable amounts. The absence of *o*-dibromobenzene and the inertness of aryl halides to substitution reactions under the same reaction conditions point to a mechanistic pathway for deamination of aniline that involves para substitution prior to ortho substitution. Efforts are presently being directed toward determining the mechanism of this novel aromatic substitution process and its relationship to direct substitutive deamination (eq 7).

Of the arylamines listed in Table II only 1-aminonaphthalene, 2-methyl-1-aminonaphthalene, and aniline yielded dichloro compounds in detectable quantities when treated with copper(II) chloride and *tert*-butyl nitrite in acetonitrile. 1-Aminonaphthalene gave 1,4-dichloronaphthalene in 18% isolated yield with 1-chloronaphthalene as the only other constituent of the reaction mixture. 2-Methyl-1-aminonaphthalene yielded both 2-methyl-1-chloronaphthalene (15%) and 2-methyl-1,4-dichloronaphthalene (2%). Aniline gave *p*-dichlorobenzene in 2% yield (Table IV). Reaction conditions conducive to selective formation of dihaloarenes in high yields are currently being examined.

Since copper(II) halides are reduced to copper(I) halides in the formation of by-products that accompany deamination reactions, and low concentrations of copper(I) halides catalyze the Sandmeyer reaction,[5b,c,8b,24,25] the products and their percentage yields from copper(II) chloride and copper(I) chloride reactions with aniline and *tert*-butyl nitrite were compared. The unique role of copper(II) halides in substitutive deamination reactions with arylamines is indicated by the data in Table IV. Reactions that employ copper(II) chloride form chlorobenzene with only a minor amount of *p*-dichlorobenzene and a trace amount of azobenzene as by-products. By comparison, reactions of aniline–*tert*-butyl nitrite with copper(I) chloride result in a complex mixture of products. In addition, isolated product yields are 50% greater when copper(II) chloride is the reactant than when copper(I) chloride is used.

Discussion

Substitutive deamination by *tert*-butyl nitrite and copper(II) halides is a selective, synthetically valuable method for the direct formation of aryl halides from arylamines. Unlike the previously reported direct method for the conversion of arylamines to aryl halides by the use of copper halide nitrosyls,[11] the method that employs alkyl nitrites and copper(II) halides is not limited to anilines; for example, 1-chloronaphthalene is formed from 1-aminonaphthalene in 6% yield by the former method and in 82% yield by the latter procedure. In addition, the preparation of organic halides by copper(II) halide–alkyl nitrite reactions with amine compounds is not limited to arylamines. *p*-Chlorobenzenesulfonamide, for example, yields, *p*-chlorobenzenesulfonyl chloride in 95% yield when treated with copper(II) chloride and *tert*-butyl nitrite in acetonitrile at 65 °C. The general absence of side products that usually accompany aryl halides in the Sandmeyer procedure, the required use of copper(II) halides rather than air-sensitive copper(I) halides, and the convenient direct conversion of arylamine to aryl halide are particular synthetic advantages.

The marked differences in products and product yields between the substitutive deamination procedure that is reported here and the conventional Sandmeyer procedure suggests that the process that involves copper(II) halides is not a simple variation of the Sandmeyer reaction. In his comparison of copper salts, Sandmeyer reported that copper(II) salts do not have the same effect as copper(I) salts for the substitution of nitrogen by halide.[26] Considerable controversy concerning the effectiveness of the copper salt and the mechanism of its action on diazonium ions ensued,[3a,b] due principally to Hodgson's proposal that copper(II) salts also catalyze Sandmeyer reactions[27] and to his insistence that

Table IV. Deamination of Aniline by *tert*-Butyl Nitrite and Copper(II) Chloride or Copper(I) Chloride [a]

CuX_n	Temp, °C	C_6H_5Cl	Relative yield, %[b]				Isolated yield, %
			p-$C_6H_4Cl_2$	$C_6H_4C_6H_5$	$C_6H_5{=}NC_6H_5$	$C_6H_5NHCOCH_3$	
$CuCl_2$	25	>96	3	0	<1	0	68
$CuCl_2$	65	>96	3	0	<1	0	67
$(CuCl)_2$	25	53	4	1	14	28	44
$(CuCl)_2$	65	43	2.5	2.5	7	45	42

[a] Reactions were performed by adding 10.0 mmol of the aniline in 2 ml of anhydrous acetonitrile to 15.0 mmol of *tert*-butyl nitrite and 12.0 mmol of the anhydrous copper halide in 40 mL of acetonitrile. [b] Precision of analysis is ±1% from duplicate runs.

copper(I) salts are not unique in substitutive reactions with diazonium ions.

Current understanding of the Sandmeyer reaction holds that copper(I) plays an integral role in the substitution of nitrogen by halide.[3c,d,28] The previously reported effective use of copper(II) salts is explained by reduction of a portion of the copper(II) salt to copper(I) in processes that compete with the Sandmeyer reaction.[8b,24,25,29] Indeed, copper(I) chloride has been effectively employed in catalytic amounts for the decomposition of *p*-nitrobenzenediazonium chloride in the Sandmeyer reaction.[8a]

Four observations in this study point to a unique role for copper(II) halides in reactions of arylamines with alkyl nitrites: (1) the stoichiometry of these reactions that result in the conversion of copper(II) halides to cupric oxide, (2) the nearly complete absence of those side products that are usually obtained in the Sandmeyer procedure, (3) the comparatively high yield of aryl halide products from reactions of arylamines with alkyl nitrites and copper(II) halides, and (4) the substitution of halide at aromatic ring positions that are para and/or ortho to the original amine position. The nature of the role of copper(II) halides in the substitutive deamination reaction that is represented by eq 7 is presently under investigation.

Experimental Section

Instrumentation. Proton magnetic resonance spectra were obtained with a Varian Model A-60A spectrometer; chemical shifts are reported in δ units using tetramethylsilane as the internal standard. Infrared spectra were obtained on a Perkin-Elmer Model 621 grating spectrophotometer. Powder analyses were taken on a Norelco x-ray diffractometer. Analytical gas chromatographic analyses were performed on a Varian Aerograph Model 2720 gas chromatograph with thermal conductivity detectors; a Varian Model 485 digital integrator was used to determine peak areas. Use was made of 5–7-ft columns of 20% SE-30, 20% Carbowax 20M, and 10% DEGS, all on Chromosorb P. Melting points were obtained on a Thomas-Hoover apparatus and were uncorrected.

Materials. Anhydrous cupric chloride and cupric bromide were obtained commercially from Alfa and PCR, Inc., and were dried in an oven at 110 °C prior to use. Anhydrous cuprous chloride was prepared from cupric chloride dihydrate.[30] Reagent grade acetonitrile was distilled from calcium hydride prior to its use as a reaction solvent. 2-Methyl-1-aminonaphthalene was prepared from 2-methyl-1-bromonaphthalene by the procedure of Newman, Dhawan, and Tuncay.[31] Other amines that were used in this study were commercially available. Aniline and *p*-anisidine was purified prior to use. *tert*-Butyl nitrite was prepared from *tert*-butyl alcohol according to the procedure of Noyes.[32] Isoamyl nitrite was obtained commercially.

Substitutive Deamination of Arylamines. General Procedure. In the procedure employed for the reactions reported in Table II anhydrous copper(II) halide (12 mmol), *tert*-butyl nitrite (15 mmol), and anhydrous acetonitrile (40 mL) were added to a three-necked round-bottom flask that was equipped with a reflux condenser, addition funnel or solid inlet tube, and a gas outlet tube. The resulting rapidly stirred mixture was warmed (cooled) to the indicated reaction temperature (Table II). The amine (10 mmol) in 2 mL of acetonitrile (for liquid or acetonitrile-soluble amines) or as a solid was slowly added over a period of 5 min to the reaction solution. During this addition the reaction solution turned completely black from the initial green ($CuCl_2$) or black ($CuBr_2$) color as nitrogen was evolved. Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret; with the exception of reactions with 2,4,6-trimethylaniline, *p*-anisidine, and 2-methyl-1-aminonaphthalene, the yield of gaseous products in substitutive deamination reactions was 220 ± 20 mL (based on 10 mmol of the limiting reagent). At 65 °C gas evolution was generally complete within 10 min following the addition of the amine. After complete gas evolution the reaction temperature was allowed to reach room temperature, the reaction solution was then poured into 200 mL of 20% aqueous hydrochloric acid and extracted with 200 mL of ether, and the organic layer was washed once with 200 mL of 20% aqueous hydrochloric acid. The resulting ether solution was dried over anhydrous magnesium sulfate and the ether was removed under reduced pressure. Ether solutions containing volatile products were distilled at atmospheric pressure through a 12.5-cm Vigreux column.

Product Analyses. Structural assignments for the aryl halides produced in reactions of arylamines with alkyl nitrites and copper halides were made on the reaction solutions by ^1H NMR spectral comparisons and by GLC retention time and peak enhancement with authentic samples. The presence or absence of biphenyl, azobenzene, arene, phenol, and *N*-arylacetamide compounds in these reaction mixtures was confirmed by GLC retention time comparisons and by peak enhancement, if the compound was present, on two columns, generally 5-ft 20% SE-30 and 10% DEGS on Chromosorb P. Except for *p*-dichlorobenzene and *p*-dibromobenzene, which were identified by comparison to commercially available samples, the dihaloarenes produced from arylamines in this study were isolated by GLC separations and identified spectroscopically.

1,2-Dibromo-4-nitrobenzene: IR (KBr) 3095, 1592, 1564, 1525 (NO_2), 1448, 1370, 1340 (NO_2), 1280, 1245, 1122, 1015, 892, 871, 821, 745, and 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.50 (J_m = 2.3 Hz, H-3), 8.08 (J_o = 8.5, J_m = 2.3 Hz, H-5), and 7.82 (J_o = 8.5 Hz, H-6); mp 53.5–54.0 °C (lit.[33] mp 58–59 °C).

3,4-Dibromoacetophenone: IR (KBr) 3092, 3024, 3008, 2966, 1687 (C=O), 1580, 1548, 1464, 1423, 1392, 1367, 1353, 1321, 1270, 1247, 1135, 1120, 1108, 1079, 1019, 1010, 954, 894, 827, 793, 693, 653, and 607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.28–8.17 (1 H), 7.84–7.72 (2 H), and 2.60 (s, 3 H); mp 58.5–59.0 °C (lit.[34] mp 64 °C).

1,2-Dibromo-4-chlorobenzene: IR (KBr) 3080, 1560, 1487, 1450, 1407, 1365, 1248, 1090, 1072, 1013, 868, 809, and 778 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (J_m = 2.3 Hz, H-3), 7.57 (J_o = 9 Hz, H-6), and 7.15 (J_o = 9, J_m = 2.3 Hz, H-5); mp 35–36 °C (lit.[35] mp 35.5 °C).

1,2-Dibromo-4-fluorobenzene: IR (film) 3100, 1590, 1465, 1426, 1388, 1370, 1275, 1258, 1212, 1095, 1020, 889, 865, 810, 680, and 670 cm^{-1}. This IR spectrum corresponded to the similar Sadtler infrared spectrum of 1,2-dichloro-4-fluorobenzene.[36]

1,2-Dibromo-4-trifluoromethylbenzene: IR (film) 3090, 1600, 1520, 1380, 1320, 1250, 1170, 1070, 1050, 1010, 888, 820, 808, 707, and 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (J_m = 2 Hz, H-3), 7.60 (J_o = 13, J_m = 2 Hz, H-5), and 7.20 (J_o = 13 Hz, H-6).

3,4-Dibromotoluene: IR (film) 3050, 2925, 1590, 1460, 1375, 1256, 1210, 1108, 1012, 860, 840, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (H-2), 7.50 (J_o = 8 Hz, H-5), 6.98 (J_o = 8 Hz, H-6), and 2.30 (s, 3 H).

3,4-Dibromoanisole: IR (film) 3090, 3000, 2970, 2940, 2840, 1575, 1560, 1465, 1435, 1285, 1260, 1225, 1180, 1100, 1032, 1005, 845, 800, 740, and 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (J_o = 8.8 Hz, H-5), 7.18 (J_m = 2.8 Hz, H-2), 6.75 (J_o = 8.8, J_m = 2.8 Hz, H-6), and 3.81 (s, 3 H).

1,4-Dichloronaphthalene: ^1H NMR ($CDCl_3$) δ 8.4–8.1 (m, 2 H), 7.8–7.5 (m, 2 H), and 7.50 (s, 2 H); mp 56–59 °C (lit.[37] mp 67–68 °C).

1,4-Dichloro-2-methylnaphthalene: ^1H NMR ($CDCl_3$) δ 8.5–8.15 (m, 2 H), 7.8–7.5 (m, 2 H), 7.63 (broad s, 1 H), and 2.55 (s, 3 H).

1,4-Dibromo-2-methylnaphthalene: ^1H NMR ($CDCl_3$) δ 8.5–8.1 (m, 2 H), 7.8–7.5 (m, 2 H), 7.69 (broad s, 1 H), and 2.60 (s, 3 H).

1,2,4-Tribromobenzene was similarly isolated from reactions of

copper(II) bromide and *tert*-butyl nitrite with aniline, mp 42 °C (lit.[38] mp 44–45 °C).

Copper(II) oxide was isolated as a black, granular powder from reactions of copper(II) chloride with a stoichiometric excess of isoamyl nitrite and *p*-nitroaniline. The reaction mixture was filtered following complete gas evolution and prior to workup in aqueous acid. The isolated solid was dried in an oven for 2 h at 110 °C. The resulting black powder was subjected to x-ray analysis which confirmed its identity as copper(II) oxide and gave no evidence for the presence of either copper(I) oxide or copper(I) chloride.

The gaseous products from the reaction of copper(II) chloride and *tert*-butyl nitrite with *p*-nitroaniline were analyzed by GLC retention times on a 5-ft silica gel column and by infrared spectral analysis. Nitrogen was confirmed as the sole major product. Nitrous oxide was present as a minor constituent (<1% of the gaseous mixture) and no other gaseous product was detected.

Product yields were determined by GLC analyses for the vast majority of reactions reported in this study. Prior to workup a weighed amount of dibenzyl ether was added to the reaction mixture as an internal standard. The average integrated area ratio from at least two GLC traces was employed in each yield determination. Absolute yields were calculated with the use of experimentally determined thermal conductivities for each of the aryl halides examined by this method. Thermal conductivity ratios were determined immediately prior to product analyses to ensure accuracy in these determinations.

Product yields for naphthylamines were determined by ^{1}H NMR analyses through the use of 1,2-dibromoethane as the internal standard. Reaction products were analyzed by integration of the individual and characteristic absorption signals of each product and of the internal standard. The average values of at least five integrations were utilized in the calculation of absolute yields. Yields obtained by ^{1}H NMR analysis for reaction products from amines other than the naphthylamines confirmed those obtained by GLC methods.

4-Chloro-3-nitrotoluene. Solid 4-methyl-2-nitroaniline (15.2 g, 0.100 mol) was added slowly over 40 min to a rapidly stirred mixture of *tert*-butyl nitrite (15.5 g, 0.150 mol) and anhydrous copper(II) chloride (16.0 g, 0.120 mol) in 200 mL of acetonitrile which was heated at 65 °C in an oil bath. The rate of addition of 4-methyl-2-nitroaniline was determined by the rate of gas evolution; gas evolution was complete within 20 min following the last addition of the amine to the reaction mixture. After 16 h the black reaction mixture was cooled and then poured into 400 mL of 20% aqueous hydrochloric acid. The aqueous acetonitrile mixture was extracted twice with 200-mL portions of ether, the combined ether solution was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure. The resulting yellow liquid (16.3 g) was analyzed by ^{1}H NMR and GLC methods which showed the presence of only 4-chloro-3-nitrotoluene (0.095 mol, 95% yield).

1,2,3,5-Tetrachlorobenzene. 2,4,6-Trichloroaniline (19.65 g, 0.100 mol) was dissolved in 60 mL of acetonitrile and then added dropwise to a rapidly stirred mixture of *tert*-butyl nitrite (15.5 g, 0.150 mol) and anhydrous copper(II) chloride (13.65 g, 0.100 mol) in acetonitrile which was heated at 65 °C in an oil bath. Gas evolution was complete at 40 min following the start of addition. After 15 h the black reaction mixture was cooled and then worked up as described in the previous synthesis. Following the removal of ether, crude 1,2,3,5-tetrachlorobenzene was isolated as a brown solid (20.6 g). Recrystallization from absolute ethanol gave 17.6 g of pure 1,2,3,5-tetrachlorobenzene[39] (0.082 mol, 82% yield), mp 53.5–54.0 °C (lit.[40] mp 51 °C).

***p*-Chloronitrobenzene.** *p*-Nitroaniline (13.81 g, 0.100 mol) was dissolved in 100 mL of anhydrous acetonitrile and added dropwise over 40 min to the *tert*-butyl nitrite–copper(II) chloride mixture in acetonitrile. The reaction procedure and workup method were identical with those described in the previous syntheses. Following removal of ether, crude *p*-nitrochlorobenzene was isolated as a light yellow solid (16.8 g). Recrystallization from 50 mL of absolute ethanol gave 14.3 g of pure *p*-nitrochlorobenzene (0.092 mol, 92% yield), mp 82 °C (lit.[41] mp 83 °C).

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Registry No.—*tert*-Butyl nitrite, 540-80-7; copper(II) chloride, 7447-39-4; copper(I) chloride, 7758-89-6; $CuBr_2$, 7789-45-9; 1,2-dibromo-4-nitrobenzene, 5411-50-7; 3,4-dibromoacetophenone, 3114-30-5; 1,2-dibromo-4-chlorobenzene, 60956-24-3; 1,2-dibromo-4-fluorobenzene, 2369-37-1; 1,2-dibromo-4-trifluoromethylbenzene, 7657-08-1; 3,4-dibromotoluene, 60956-23-2; 3,4-dibromoanisole, 62415-74-1; 1,4-dichloronaphthalene, 1825-31-6; 1,4-dichloro-2-methylnaphthalene, 13577-15-6; 1,4-dibromo-2-methylnaphthalene, 62415-75-2.

References and Notes

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Alkyl Nitrite–Metal Halide Deamination Reactions. 3. Arylation of Olefinic Compounds in the Deamination of Arylamines by Alkyl Nitrites and Copper(II) Halides. A Convenient and Effective Variation of the Meerwein Arylation Reaction[1]

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Arylation of olefinic substrates occurs when arylamines are treated with alkyl nitrites and copper(II) halides in acetonitrile or acetone solutions that contain the olefin. The corresponding β-aryl-α-halo derivatives are formed in high yields by this direct procedure. Results from direct arylation reactions of representative arylamines with acrylonitrile and styrene in the presence of copper(II) chloride are reported; isolated yields of arylation products from these reactions are comparable or superior to those obtained by the Meerwein procedure. The yields of α-chloro-β-arylpropionitriles from deamination reactions of arylamines in the presence of copper(II) chloride and acrylonitrile closely match those of substitution products that are formed by direct substitutive deamination of arylamines with *tert*-butyl nitrite and copper(II) chloride. This similarity indicates that neither the Sandmeyer reaction nor potentially competitive processes that involve arylation intermediates adversely affect this Meerwein reaction, and that reactions that compete with the Sandmeyer reaction are of comparable importance in the Meerwein reaction. Reactions with acrylonitrile that employ copper(II) bromide, however, are complicated by a preponderance of products that result from competing substitutive deamination and ring substitution by bromine. In arylation reactions that involve the deamination of *p*-nitroaniline in the presence of copper(II) chloride and selected olefins the importance of the competing Sandmeyer reaction is dependent on the nature of the olefinic substrate.

The Meerwein reaction is the copper salt catalyzed arylation of olefinic compounds by arenediazonium halides (eq 1).[3]

$$ArN_2^+X^- + RCH{=}CR'Z \xrightarrow{CuX_n} \underset{\displaystyle Ar}{\overset{\displaystyle RCH}{|}}\!\!-\!\!\underset{\displaystyle X}{\overset{\displaystyle CR'Z}{|}} + N_2 \quad (1)$$

The olefinic components that are most suitable for this transformation are activated by electron-withdrawing groups or by conjugation with unsaturated functional groups (Z). Combination of the diazonium salt with the unsaturated compound and the copper salt results in the addition of the aryl component to the β carbon of the substituted olefin, with halide added to the α carbon. Elimination of hydrogen halide (eq 2) may occur under the reaction conditions of the Meerwein reaction or often results from a subsequent transformation.

$$\underset{\displaystyle Ar}{\overset{\displaystyle RCH}{|}}\!\!-\!\!\underset{\displaystyle X}{\overset{\displaystyle CR'Z}{|}} \xrightarrow{(-HX)} ArRC{=}CR'Z \quad (2)$$

Although cupric salts were promoted by Meerwein,[4] cuprous halides have been shown to be the effective catalysts for the arylation reaction.[5,6] However, both copper(I) and copper(II) oxidation states are utilized in the production of the Meerwein addition compound (eq 3–5).[7] Competing reactions, which in addition to formation of the Sandmeyer product include those processes that are most often associated with the Sandmeyer reaction, reinforce the widely held belief that the Meerwein reaction is initiated by copper(I)-catalyzed production of aryl radicals (eq 3).[3,7-9]

$$ArN_2^+ + CuX_2^- \longrightarrow Ar\cdot + N_2 + CuX_2 \quad (3)$$

$$Ar\cdot + RCH{=}CR'Z \longrightarrow \underset{\displaystyle Ar}{\overset{\displaystyle RCH}{|}}\!\!-\!\!CR'Z \quad (4)$$

$$ArRCH{-}CR'Z + CuX_2 \longrightarrow \underset{\displaystyle Ar}{\overset{\displaystyle RCH}{|}}\!\!-\!\!\underset{\displaystyle X}{\overset{\displaystyle CR'Z}{|}} + CuX \quad (5)$$

In the procedure normally employed for the Meerwein reaction[3] the arenediazonium halide is initially prepared in an aqueous halogen acid solution and then mixed with the unsaturated component in an appropriate solvent (water, acetone, or acetonitrile). Copper(II) halide is added to the homogeneous mixture and nitrogen evolution ensues, usually at temperatures at or below 25 °C. In this two-step procedure reaction variables, including the solution pH and the reaction solvent, are important determinants of the yield of the Meerwein arylation product. The Meerwein reaction is usually conducted in buffered solutions within the pH range of 2–4 to minimize side reactions.[10] Acetone is most often employed as the organic cosolvent but is reported to inhibit arylation in reactions with certain unsaturated compounds.[11]

The yields of arylation products are dependent on the structure of the diazonium salt and of the unsaturated compound, as well as on the previously mentioned reaction variables. For example, electron-donating substituents on the arenediazonium ion and the presence of ortho substituents generally adversely affect the yield of the Meerwein product.[3] Reactions that compete with the Meerwein reaction are often dominant and, consequently, the yield of the arylation product is low in many reactions.

Table I. Yields of α-Chloro-β-arylpropionitriles from Reactions of Arylamines and *tert*-Butyl Nitrite with Copper(II) Chloride and Acrylonitrile[a]

Registry no.	$ArNH_2$	Temp, °C	$ArCH_2CHClCN$	Isolated yield, %[b] (eq 6)	Reported yield, % (eq 7)
100-01-6	p-$NO_2C_6H_4NH_2$	25	p-$NO_2C_6H_4CH_2CHClCN$	(93)	48,[13] 83[14]
99-09-2	m-$NO_2C_6H_4NH_2$	25	m-$NO_2C_6H_4CH_2CHClCN$	74	38[13]
99-92-3	p-$CH_3COC_6H_4NH_2$	25	p-$CH_3COC_6H_4CH_2CHClCN$	83	
106-47-8	p-$ClC_6H_4NH_2$	25	p-$ClC_6H_4CH_2CHClCN$	78 (71)	76[5a]
62-53-3	$C_6H_5NH_2$	25	$C_6H_5CH_2CHClCN$	71	34[13]
106-49-0	p-$CH_3C_6H_4NH_2$	25	p-$CH_3C_6H_4CH_2CHClCN$	73	40[13]
104-94-9	p-$CH_3OC_6H_4NH_2$	65	p-$CH_3OC_6H_4CH_2CHClCN$	32	
		25		5	31[15]
634-93-5	2,4,6-$Cl_3C_6H_2NH_2$	25	2,4,6-$Cl_3C_6H_2CH_2CHClCN$	92	
88-05-1	2,4,6-$(CH_3)_3C_6H_2NH_2$	65	2,4,6-$(CH_3)_3C_6H_2CH_2CHClCN$	0	
		25		0	

[a] Reactions were performed by adding 10.0 mmol of the amine to 15.0 mmol of *tert*-butyl nitrite and 12.0 mmol of anhydrous copper(II) chloride in 20 mL (0.30 mol) of acrylonitrile and 20 mL of acetonitrile. [b] Absolute yield of the Meerwein product as determined by ^1H NMR analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±2% of the reported values. Isolated yield after purification by distillation or recrystallization is given in parentheses.

In the accompanying paper[1] alkyl nitrites are reported to react with arylamines and copper(II) halides to effect direct substitutive deamination which is remarkably free of the side reactions that usually accompany the Sandmeyer reaction. The high product yields obtained by this direct procedure and the mechanistic similarity between the Sandmeyer and Meerwein reactions[6,7a] suggest that a similar direct procedure for the arylation of olefinic compounds should have comparable synthetic advantages. If reactions that compete with the Sandmeyer reaction are assumed to be of equal importance in the Meerwein reaction, and if these processes are significantly minimized in the direct substitutive deamination procedure, then only the Sandmeyer reaction and side reactions of the arylation intermediate (the β-arylalkyl radical formed in eq 4) are expected to be competitive with production of the Meerwein product. In this paper we report the results of our investigation of the arylation of olefinic compounds by deamination of arylamines with alkyl nitrites in the presence of copper(II) halide and olefinic substrates.

Results and Discussion

Addition of an arylamine to an acetonitrile solution containing alkyl nitrite, anhydrous copper(II) chloride, and an olefinic substrate results in the evolution of nitrogen and in the formation of the arylation product from vicinal addition of the aryl group and halogen to the carbon–carbon double bond. Use of acrylonitrile, one of the most reactive olefinic substrates employed in the Meerwein reaction,[6] results in the formation of α-chloro-β-arylpropionitriles (eq 6). Isolated

$$ArNH_2 + H_2C{=}CHCN \xrightarrow[CuCl_2,\ CH_3CN]{RONO} ArCH_2\underset{Cl}{\underset{|}{C}}HCN + N_2 \quad (6)$$

yields of α-chloro-β-arylpropionitriles in representative reactions of arylamines, *tert*-butyl nitrite,[12] and anhydrous copper(II) chloride with acrylonitrile are presented in Table I.

A relatively large molar excess of acrylonitrile (30-fold) relative to the arylamine was employed in these reactions. Lower yields of the arylation product were obtained when only a twofold excess of acrylonitrile was used. For example, the isolated yield of α-chloro-β-(*m*-nitrophenyl)propionitrile from deamination of *m*-nitroaniline was only 40% when the molar ratio of acrylonitrile to *m*-nitroaniline was 2:1, whereas this same product was isolated in 74% yield when acrylonitrile was used as a cosolvent with acetonitrile. Optimum conditions for these reactions were not investigated with the individual substrates that were employed in this study; instead, since unreacted acrylonitrile could be conveniently separated from Meerwein arylation products, a general procedure was developed in which reactivity differences in arylation reactions with acrylonitrile would be effectively minimized. Polymerization of acrylonitrile, which would effect lower yields of α-chloro-β-arylpropionitriles, was not an obvious disadvantage in the operation of this experimental procedure.

The yields of α-chloro-β-arylpropionitriles in Table I closely match the yields of substitution products previously obtained for direct substitutive deamination of arylamines by *tert*-butyl nitrite and copper(II) chloride.[1] This similarity indicates that neither the Sandmeyer reaction nor potentially competitive processes involving the arylation intermediate adversely affect this Meerwein process, and that reactions that compete with the Sandmeyer reaction are of comparable importance in the Meerwein reaction. Indeed, *p*-chlornitrobenzene is not observed in the direct arylation of acrylonitrile that occurs with *p*-nitroaniline, and the Sandmeyer products from deamination of *p*-chloroaniline and 2,4,6-trichloroaniline in the presence of acrylonitrile are formed in 3 and 4% yield, respectively.

Low product yields in the direct substitutive deamination process[1] forecast comparably low yields of Meerwein products from reactions with acrylonitrile. *p*-Anisidine, for example, forms *p*-chloroanisole in 32% yield by direct substitutive deamination and yields α-chloro-β-(*p*-anisyl)propionitrile in 32% yield by the process that involves acrylonitrile. Furthermore, the restriction placed upon substitutive deamination reactions regarding the use of arylamines possessing *p*-methyl substituents is also applicable to the Meerwein reaction: 2,4,6-trimethylaniline does not form the Meerwein product with acrylonitrile and the chloride substitution product, 2,4,6-trimethylchlorobenzene, is not observed as a side product in attempted arylation reactions with this amine.

Yields from the direct arylation of acrylonitrile are compared in Table I with reported yields of the same compounds by the usual two step Meerwein procedure in which the amine is first diazotized and then added to a buffered aqueous acetone solution containing copper(II) chloride and acrylonitrile (eq 7).[3] Although the reported yields for arylation reactions that employ this procedure are highly variable,[16] the comparative data in Table I show that the direct method (eq 6) is clearly superior to the procedure previously employed for the

Table II. Product Yields from Reactions of Arylamines and *tert*-Butyl Nitrite with Copper(II) Bromide and Acrylonitrile[a]

$ArNH_2$	Temp, °C	Isolated yield, %[b] ArBr	$ArBr_2$	$ArCH_2CHBrCN$	$BrArCH_2CHBrCN$	Recovered product
$C_6H_5NH_2$	25	16	13[c]	57	7[e]	97[g]
p-$CH_3C_6H_4NH_2$	25	17	10[d]	39	16[f]	82
p-$CH_3C_6H_4NH_2$	5	25	9[d]	42	9[f]	84

[a] Reactions were performed as described in footnote *a* of Table I. [b] Absolute yield of products as determined by ^1H NMR and GLC analyses through comparison to an internal standard. [c] *p*-Dibromobenzene. [d] 3,4-Dibromotoluene. [e] α,*p*-Dibromo-β-(2-bromo-4-methylphenyl)propionitrile. [g] A 4% yield of 1,2,4-tribromobenzene was also obtained.

Table III. Yields of 2-Aryl-1-chloro-1-phenylethanes from Reactions of Arylamines and *tert*-Butyl Nitrite with Copper(II) Chloride and Styrene[a]

$ArNH_2$	$ArCH_2CHClC_6H_5$	Isolated yield, %[b] (eq 8)	Reported yield, % (eq 9)
p-$NO_2C_6H_4$-NH_2	p-$NO_2C_6H_4CH_2$-$CHClC_6H_5$	58	32[18]
p-ClC_6H_4-NH_2	p-$ClC_6H_4CH_2CHCl$-C_6H_5	57 (57)	41[18] (71)[19,c]
$C_6H_5NH_2$	$C_6H_5CH_2CHClC_6H_5$	53	23[18]
p-$CH_3C_6H_4$-NH_2	p-$CH_3C_6H_4CH_2$-$CHClC_6H_5$	51	

[a] Reactions were performed by adding 10.0 mmol of the amine to 15.0 mmol of *tert*-butyl nitrite and 12.0 mmol of anhydrous copper(II) chloride in 20 mL of styrene (0.175 mol) and 20 mL of acetonitrile. [b] Absolute yield of the Meerwein product as determined by ^1H NMR analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±2% of the reported values. Isolated yield after purification by recrystallization is given in parentheses. [c] Yield of 2-(*p*-chlorophenyl)-1-chloro-1-phenylethane.

$$ArNH_2 \xrightarrow[HCl]{NaNO_2} ArN_2^+Cl^- \xrightarrow[\substack{CuCl_2\\ acetone\text{-}H_2O}]{H_2C=CHCN} ArCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCN + N_2 \quad (7)$$

Meerwein reaction. The direct method shortcuts the preparation of the arenediazonium chloride, avoids the usual requirement for buffered solutions, and produces the Meerwein product in relatively high and predictable yield.

Use of the more reactive copper(II) bromide in place of copper(II) chloride for reactions of arylamines and *tert*-butyl nitrite with acrylonitrile gives mixtures of Sandmeyer and Meerwein products that include those from ring substitution by bromine.[1] Products and product yields from the arylation reactions that initiate from aniline and *p*-toluidine are given in Table II. In contrast to reactions that employ the anhydrous copper(II) chloride, those that use copper(II) bromide effect a high yield of Sandmeyer product and lead to substantial amounts of ring substitution products. Substitutive deamination is not effectively controlled by lowering the reaction temperature and, therefore, a general practical use of copper(II) bromide in arylation reactions by a direct procedure from arylamines and acrylonitrile is not presently feasible. However, the direct arylation procedure can be employed for deamination reactions of nitroanilines in the presence of copper(II) bromide and acrylonitrile; for example, *p*-nitroaniline yielded α-bromo-β-(*p*-nitrophenyl)propionitrile in 53% yield when reaction conditions identical with those described in Table I were used.

Variation of the reaction solvent from acetonitrile to acetone did not noticeably affect product yields in arylation reactions with acrylonitrile. In reactions run under conditions identical with those whose results are reported in Table I, but with acetone rather than acetonitrile as the solvent, aniline gave α-chloro-β-phenylpropionitrile in 65% yield and *p*-aminoacetophenone formed the corresponding Meerwein product in 78% yield.

Acrylonitrile is a reactive olefinic substrate and yields of the Meerwein products from arylations of acrylonitrile are generally high. Styrene, on the other hand, although not significantly affecting the rates of nitrogen evolution in the Meerwein reaction,[5b,6,7a] is a less reactive olefinic substrate. Product yields from arylation of styrene are significantly lower than those from arylation of acrylonitrile,[17,18] and this fact presents an identifiable synthetic challenge for the direct procedure of arylation. Reactions of arylamines with *tert*-butyl nitrite, copper(II) chloride, and styrene in acetonitrile at 25 °C result in the formation of 2-aryl-1-chloro-1-phenylethanes (eq 8). Isolated yields from representative reactions are presented in Table III. Noteworthy is the absence of stilbenes in these reactions; stilbenes are products normally obtained in the two-step Meerwein procedure.[18,19] Table III compares the yields of 2-aryl-1-chloro-1-phenylethanes (eq 8) with the

$$ArNH_2 + C_6H_5CH=CH_2 \xrightarrow[\substack{CuCl_2\\ CH_3CN}]{RONO} ArCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HC_6H_5 + N_2 \quad (8)$$

corresponding yields of stilbene products that are formed from arylamines by the scheme outlined in eq 9.

$$\begin{array}{ccccc} ArN_2^+Cl^- & + & C_6H_5CH=CH_2 & \xrightarrow{CuCl_2} & ArCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HC_6H_5 + N_2 \\ \uparrow & & & & \\ ArNH_2 & & & & \downarrow \\ & & & & ArCH=CHC_6H_5 \end{array} \quad (9)$$

Substitutive deamination is the major competing reaction in the direct process for arylation of styrene. The Sandmeyer products from deamination of *p*-nitroaniline (*p*-chloronitrobenzene, 23%) and *p*-chloroaniline (*p*-dichlorobenzene, 18%) in the presence of a 17.5 molar excess of styrene, for example, are the only compounds observed in greater than 3% yield. These data, when compared with similar results from arylation reactions with acrylonitrile, indicate that styrene is indeed a less reactive olefinic substrate than acrylonitrile. As was the case for reactions with acrylonitrile, polymerization of styrene does not occur in deamination reactions that employ anhydrous copper(II) chloride and *tert*-butyl nitrite.

Isolated yields of the Meerwein and Sandmeyer products from deamination reactions of *p*-nitroaniline in the presence of selected olefins are given in Table IV. The successful employment of acrylamide in the direct arylation procedure is notable since previous attempts to use this and related amides in the Meerwein procedure were unsuccessful.[3] These results indicate that the direct arylation procedure is potentially applicable to syntheses involving the wide range of olefinic substrates which have previously been successfully employed

Table IV. Product Yields from Reactions of *p*-Nitroaniline and *tert*-Butyl Nitrite with Copper(II) Chloride and Conjugated Olefins[a]

Registry no.	Olefin	Arylation product	Yield, %[b]	p-$NO_2C_6H_4Cl$ yield, %[c]
107-13-1	$H_2C{=}CHCN$	p-$NO_2C_6H_4CH_2CHClCN$	(93)	0
140-88-5	$H_2C{=}CHCOOCH_2CH_3$	p-$NO_2C_6H_4CH_2CHClCOOCH_2CH_3$	70	16
79-06-1	$H_2C{=}CHCONH_2$	p-$NO_2C_6H_4CH_2CHClCONH_2$	49[d]	18
100-42-5	$H_2C{=}CHC_6H_5$	p-$NO_2C_6H_4CH_2CHClC_6H_5$	58	23

[a] Reactions were performed by adding 10.0 mmol of the amine to 15.0 mmol of tert-butyl nitrite and 12.0 mmol of anhydrous copper(II) chloride in 20 mL of the olefinic substrate and 20 mL of acetonitrile. [b] Absolute yield of the Meerwein product as determined by ^1H NMR analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±2% of the reported values. Isolated yield after purification by recrystallization is given in parentheses. [c] Absolute yield of the Sandmeyer product as determined by GLC analysis through comparison to an internal standard. [d] Product recrystallized from chloroform, mp 143.0–144.5 °C.

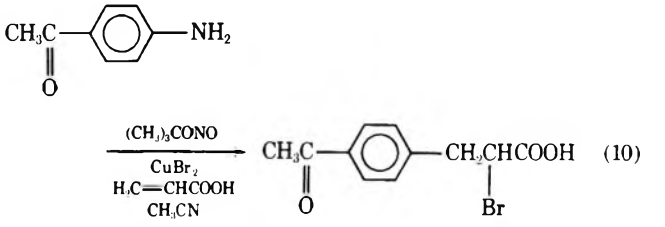
Table V. ^1H NMR Absorptions of Meerwein Products Formed by the Direct Arylation Procedure

Registry no.	$ArCH_2CHXZ$	Chemical shift, δ[a] Ar	CH_2	CH	Z
17849-31-9	p-$NO_2C_6H_4CH_2CHClCN$	8.40–8.15 (m, 2 H) 7.70–7.45 (m, 2 H)	3.47 (d)	4.72 (t)	
62448-25-3	p-$NO_2C_6H_4CH_2CHBrCN$	8.40–8.15 (m, 2 H) 7.70–7.45 (m, 2 H)	3.53 (d)	4.57 (t)	
17849-30-7	m-$NO_2C_6H_4CH_2CHClCN$	8.40–8.00 (m, 2 H) 7.80–7.30 (m, 2 H)	3.40 (d)	4.72 (t)	
62448-26-4	p-$CH_3COC_6H_4CH_2CHClCN$[b]	8.15–7.85 (m, 2 H) 7.60–7.30 (m, 2 H)	3.40 (d)	4.68 (t)	
17849-64-8	p-$ClC_6H_4CH_2CHClCN$	7.55–7.15 (m, 4 H)	3.28 (d)	4.58 (t)	
17849-62-6	$C_6H_5CH_2CHClCN$	7.45–7.30 (m, 5 H)	3.32 (d)	4.59 (t)	
62448-27-5	$C_6H_5CH_2CHBrCN$[c]	7.38 (s, 5 H)	3.38 (d)	4.42 (t)	
62448-28-6	p-$BrC_6H_4CH_2CHBrCN$[c]	7.70–7.10 (m, 4 H)	3.25 (d)	4.40 (t)	
3909-19-1	p-$HH_3C_6H_4CH_2CHClCN$[d]	7.22 (s 4 H)	3.17 (d)	4.48 (t)	
62448-29-7	p-$CH_3C_6H_4CH_2CHBrCN$[c,e]	7.21 (s, 4 H)	3.32 (d)	4.38 (t)	
62448-30-0	2-Br, 4-$CH_3C_6H_3CH_2CHBrCN$[c,d]	7.55–7.15 (m, 3 H)	3.48 (d)	4.75–4.45 (m)	
17849-23-9	p-$CH_3OC_6H_4CH_2CHClCN$[f]	7.40–6.80 (m, 4 H)	3.19 (d)	4.48 (t)	
27916-99-0	2,4,6-$Cl_3C_6H_2CH_2CHClCN$	7.43 (s, 2 H)	3.88–3.58 (m)	4.83 (t)	
4781-42-4	p-$NO_2C_6H_4CH_2CHClC_6H_5$	8.20–7.95 (m, 2 H) 7.45–7.20 (m, 2 H)	3.38 (d)	5.07 (t)	7.31 (s, 5 H)
4714-17-4	p-$ClC_6H_4CH_2CHClC_6H_5$	7.30–6.85 (m, 4 H)	3.28 (d)	5.00 (t)	7.31 (s, 5 H)
4714-14-1	$C_6H_5CH_2CHClC_6H_5$	7.50–7.30 (m, 5 H)	3.29 (d)	4.99 (t)	7.37 (s, 5 H)
4714-15-2	p-$CH_3C_6H_4CH_2CHClC_6H_5$[g]	7.41 (s, 4 H)	3.32 (d)	5.02 (t)	7.33 (s, 5 H)
57460-34-1	p-$NO_2C_6H_4CH_2CHClCOOCH_2CH_3$	8.30–8.00 (m, 2 H) 7.45–7.25 (m, 2 H)	3.45–3.25 (m)	4.38 (t)	OCH_2, 4.25 (g) CH_3, 1.27 (t)
18166-61-5	p-$NO_2C_6H_4CH_2CHClCONH_2$[h]	8.35–8.05 (m, 2 H) 7.75–7.45 (m, 2 H)	3.50–3.15 (m)	4.85–4.50 (m)	NH_2, 7.37 (broad δ)
18910-19-5	p-$CH_3COC_6H_4CH_2CHBrCOOH$[b]	8.05–7.85 (m, 2 H) 7.50–7.30 (m, 2 H)	3.55–3.25 (m)	4.47 (t)	

[a] Relative to internal Me_4Si in $CDCl_3$; temperature 37 °C. [b] CH_3CO at δ 2.58 (s). [c] Product isolated by GLC separation. [d] p-CH_3 at δ 2.33 (s). [e] p-CH_3 at δ 2.35 (s). [f] CH_3O at δ 3.83. [g] p-CH_3 at δ 2.29 (s). [h] Spectrum taken in Me_2SO-d_6.

in the Meerwein reaction.[3]

The synthesis of p-acetyl-α-bromohydrocinnamic acid was performed by the direct arylation procedure (eq 10) in order to provide a critical comparison of this method to that of the tested Meerwein procedure.[20] Use of 2 molar equiv of acrylic acid relative to p-aminoacetophenone resulted in the formation of p-acetyl-α-bromohydrocinnamic acid in 32% yield by the direct arylation procedure. However, when a 14.7-fold molar excess of acrylic acid was employed, the Meerwein product was isolated in 59% yield (55% yield after recrystallization). This same compound was prepared in 61–67% yield by sequential diazotization and reaction with copper(I) bromide and a 14.7-fold molar excess of acrylic acid (the Meerwein procedure).[20] Although results were presented earlier that showed copper(II) bromide to be inferior to copper(II) chloride in direct arylation reactions, and no attempt was made to optimize reaction conditions for the synthesis described by eq 10, the yields of p-acetyl-α-bromohydrocinnamic acid by these two procedures were comparable.



(10)

If copper(I) chloride is substituted for copper(II) chloride in the procedure for direct arylation, the Meerwein product is not obtained. In contrast, copper(I) halides have been successfully employed for Meerwein reactions that are performed in acetone.[5,6,21] However, for reactions of p-toluidine with *tert*-butyl nitrite in equal volumes of acrylonitrile and acetonitrile under conditions identical with those reported in Table I, the use of copper(I) chloride did not result in the

formation of the corresponding Meerwein product. Similarly, the Meerwein product is not obtained from reactions in which an aliphatic amine is substituted for an arylamine; benzylamine, for example, yields only those products that were previously observed in reactions with *tert*-butyl nitrite and copper(II) chloride that occurred in the absence of acrylonitrile.[22]

Experimental Section

General. Instrumentation has been previously described.[1] Anhydrous cupric chloride and cupric bromide were obtained commercially and were dried in an oven at 110 °C prior to use. Anhydrous cuprous chloride was prepared from cupric chloride dihydrate.[23] Aniline and *p*-anisidine were purified prior to use. *tert*-Butyl nitrite was prepared from *tert*-butyl alcohol according to the procedure of Noyes.[24] Reagent grade acetonitrile was distilled from calcium hydride prior to its use as a reaction solvent. Acetone, acrylonitrile, and acrylic acid were distilled prior to use.

Direct Arylation of Olefins. General Procedure. In the procedure employed for the reactions that were run on a small scale anhydrous copper(II) halide (12 mmol), *tert*-butyl nitrite or isopentyl nitrite (15 mmol), the olefinic substrate (20 mL), and anhydrous acetonitrile (20 mL) were added to a three-necked round-bottom flask that was equipped with a reflux condenser, addition funnel or solid inlet tube, and a gas outlet tube. The resulting mixture was rapidly stirred at room temperature (23 ± 2 °C). The amine in 2 mL of acetonitrile (for liquid or acetonitrile-soluble amines) or as a solid was slowly added over a period of 5 min to the reaction solution. During the amine addition the reaction temperature remained below 30 °C and the reaction solution turned completely black from the initial green ($CuCl_2$) or black ($CuBr_2$) color as nitrogen was evolved. Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret; with the exception of 2,4,6-trimethylaniline, the yield of gaseous products in these reactions was 220 ± 20 mL (based on 10 mmol of the limiting reagent). Gas evolution was generally complete within 15 min following the additon of the amine. After complete gas evolution the reaction solution was poured into 200 mL of 20% aqueous hydrochloric acid and extracted with 200 mL of ether, and the organic layer was washed once with 200 mL of 20% aqueous hydrochloric acid. The resulting ether solution was dried over anhydrous magnesium sulfate and the ether and excess of low-boiling olefinic substrate were removed under reduced pressure. Styrene was fractionally distilled through a 12.5-cm Vigreux column under reduced pressure.

Product Analyses. Reactions of copper(II) chloride with a two- to fourfold molar excess of *p*-nitroaniline or aniline, *tert*-butyl nitrite, and a corresponding excess of acrylonitrile produced a black, granular powder having a light green tint. The reaction mixtures were filtered following complete gas evolution and prior to workup in aqueous acid. The isolated solids were washed with benzene and then dried in an oven for 2 h at 110 °C. The resulting powders were subjected to x-ray powder analysis which gave no evidence for the presence of either of the structurally defined copper oxides or copper chlorides. No further attempt to define the structure of the copper product was made.

Structural assignments for the Meerwein products produced in reactions of arylamines with alkyl nitrites and copper(II) halides in the presence of olefinic substrates were made on the reaction solutions by ^1H NMR spectral analyses (Table V). Product yields for Meerwein products were determined through the use of either dibenzyl ether or 1,2-dibromoethane as the internal standard in ^1H NMR analyses. Absolute yields were calculated from integrations of the individual and characteristic absorption signals of the reaction products and of the internal standard; the average values of at least five integrations were utilized in these yield determinations.

Structural assignments for aryl halides produced in these arylation reactions were generally made on the reaction solutions by GLC retention time and peak enhancement comparisons with authentic samples.[1] *p*-Bromotoluene and 3,4-dibromotoluene were isolated by GLC separations and their identity was confirmed by ^1H NMR spectral analyses. The yields of aryl halides were determined by GLC analyses through the use of an internal standard. Absolute yields were calculated with the use of experimentally determined thermal conductivity ratios.

α-Chloro-β-(*p*-nitrophenyl)propionitrile. *p*-Nitroaniline (13.8 g, 0.100 mol) dissolved in 100 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) chloride (16.0 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 125 mL of acetonitrile and 125 mL of freshly distilled acrylonitrile (1.9 mol). The rate of addition of *p*-nitroaniline to the stirred mixture at room temperature was determined by the rate of gas evolution; gas evolution was complete within 30 min following the last addition of the amine to the reaction mixture. After complete gas evolution the black reaction mixture was poured into 400 mL of 20% aqueous hydrochloric acid and extracted twice with 200-mL portions of ether. The combined ether solution was dried over anhydrous magnesium sulfate and the organic layer was concentrated under reduced pressure to yield 21.9 g of a yellow-brown solid. Recrystallization from methanol gave 19.5 g of colorless needles of α-chloro-β-(*p*-nitrophenyl)propionitrile (0.093 mol, 93% yield) having mp 118–119 °C (lit.[13] mp 111–112 °C).

α,*p*-Dichloro-β-phenylpropionitrile. *p*-Chloroaniline (12.75 g, 0.100 mol) dissolved in 30 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) chloride (16.1 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 60 mL of acetonitrile and 100 mL of freshly distilled acrylonitrile (1.5 mol). The reaction flask was cooled by means of an ice bath during the addition in order to prevent the reaction temperature from rising above 30 °C. Gas evolution was complete within 10 min following the last addition of *p*-chloroaniline. After complete gas evolution the black reaction mixture was poured into 400 mL of 20% aqueous hydrochloric acid and extracted with 400 mL of ether. The organic layer was washed once with 400 mL of 20% aqueous hydrochloric acid, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 17.5 g of a brown liquid. Distillation of this liquid at 0.3 Torr yielded 0.6 g of *p*-dichlorobenzene (bp 60 °C) and 14.2 g (0.071 mol, 71% yield) of the yellow liquid α,*p*-dichloro-β-phenylpropionitrile, bp 130–135 °C (lit.[5a] bp 128–132 °C at 5 Torr).

2-(*p*-Chlorophenyl)-1-chloro-1-phenylethane. *p*-Chloroaniline (12.8 g, 0.100 mol) dissolved in 20 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) chloride (16.1 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 60 mL of acetonitrile and 150 mL of styrene (1.3 mol). The previous procedure was followed and, after removal of the ether and distillation of the excess styrene, 24.6 g of an orange liquid was obtained. Crystallization from pentane yielded 14.3 g of crystalline 2-(*p*-chlorophenyl)-1-chloro-1-phenylethane (0.057 mol, 57% yield),[25] mp 73–75 °C (lit.[5a] mp 75–76 °C).

***p*-Acetyl-α-bromohydrocinnamic Acid.** *p*-Aminoacetophenone (13.57 g, 0.100 mol) dissolved in 60 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) bromide (27 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 50 mL of acetonitrile and 100 mL of freshly distilled acrylic acid (1.47 mol). The reaction flask was cooled by means of an ice bath during the addition in order to maintain a reaction temperature of 25–26 °C. Gas evolution was complete within 10 min following the last addition of *p*-aminoacetophenone. After complete gas evolution the reaction mixture was poured into 500 mL of 20% aqueous hydrochloric acid and extracted with 500 mL of a 1:1 ether–benzene combination. The organic layer was washed twice with 200-mL portions of 20% aqueous hydrochloric acid and then was dried over anhydrous magnesium sulfate. The organic solvent was removed under reduced pressure to yield 36 g of an orange-yellow solid. This precipitate was filtered under vacuum and then recrystallized from a 2:3 (v/v) formic acid–water mixture to yield 15.0 g of light yellow needles of *p*-acetyl-α-bromohydrocinnamic acid (0.055 mol, 55% yield), mp 152–156 °C (lit.[20] mp 159–161 °C). The ^1H NMR spectrum of this solid (Table V) corresponded to the reported spectrum of *p*-acetyl-α-bromohydrocinnamic acid in trifluoroacetic acid.[20] An additional 1.7 g of impure product was obtained after concentration of the filtrate but was not further purified.

A similar reaction was performed using only 16 g of acrylic acid (0.22 mol) in 200 mL of anhydrous acetonitrile. However, only 8.3 g of the white, crystalline Meerwein product (32% yield) could be obtained when the above reaction procedure was employed.

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Registry No.—*tert*-Butyl nitrite, 540-80-7; copper(II) chloride, 7447-39-4; acrylonitrile, 107-13-1; copper(II) bromide, 7789-45-9.

References and Notes

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(25) This Meerwein product is heat sensitive and losses hydrogen chloride during distillation at 0.3 Torr. Similarly thermal decomposition to *trans*-stilbene occurs during GLC analysis of the reaction mixture.

Design of Chiral Derivatizing Agents for the Chromatographic Resolution of Optical Isomers. Asymmetric Synthesis of Some Chiral Fluoroalkylated Amines

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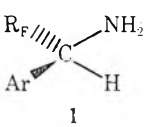
A general approach for the asymmetric synthesis of type 1 fluoroalkylated amines is described and an assignment of absolute configuration is made for 2,2,2-trifluoro-1-phenylethylamine (2). Amine 2 is obtained in high yield and >80% ee by reducing chiral imine 5 with sodium bis(2-methoxyethoxy)aluminum hydride with subsequent catalytic hydrogenolysis over palladium on charcoal. Catalytic hydrogenolysis of secondary amine 6 proceeds with complete regioselectivity owing to the retarding effect of the α-trifluoromethyl group upon the rate of hydrogenolysis of benzylamine. Fluoro amine 2 is evaluated as a chiral derivatizing agent (CDA) for the chromatographic resolution of racemic alcohols. Relative to the diastereomeric carbamates derived from menthol or 2-octanol and the nonfluorinated analogues of 2, those derived from 2 show greater chromatographic separability and an inverted elution order.

Recently, we reported the resolution of 2,2,2-trifluoro-1-(1-naphthyl)ethanol via the multigram chromatographic separation of diastereomeric carbamate derivatives[1] and in a subsequent paper elaborated a rationale which provides insight into the reasons underlying the chromatographic separability of diastereomeric carbamates.[2] On the basis of this rationale, we are endeavoring to design chiral derivatizing agents (CDA) that will confer still greater chromatographic separability upon the diastereomeric adducts of racemates. Although chiral type 1 fluoroalkylamines are of general in-



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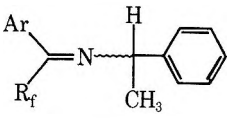
terest in this context, we specifically desired 2,2,2-trifluoro-1-phenylethylamine (**2**), since the aforementioned chromatographic rationale suggests strongly that diastereomeric carbamates derived from this amine should show greater chromatographic separability and inverted elution order when compared to those derived from nonfluorinated analogues, such as 1-phenylethylamine (3) or 1-(1-naphthyl)ethylamine (**3a**).[3]

We presently describe the asymmetric synthesis, assignment of absolute configuration, and preliminary chromatographic evaluation of **2** as a CDA and demonstrate that the synthetic scheme utilized is applicable for a series of structurally related amines.

Initial efforts to prepare racemic **2** from phenyl trifluoromethyl ketone (4) by Leuckart reductive amination or through the use of sodium cyanoborohydride and ammonium acetate in methanol[4] were fruitless. While ammonia readily adds to this ketone to afford the carbinolamine, the latter is very resistant to dehydration to the imine. Nevertheless, lithium aluminum hydride converts the carbinolamine to racemic **2** in ca. 30% yield. In an alternate approach, the tosylate of 2,2,2-trifluoro-1-phenylethanol was found to react with ammonia at 130 °C and 6 kbar pressure although it is resistant to aminolysis at ordinary pressures. The Curtius sequence on 3,3,3-trifluoro-2-phenylpropionic acid also affords **2**; however, the effort required, as well as the low overall yield (from **4**), makes this route unattractive.

A more direct approach to chiral **2** is shown in Scheme I and involves asymmetric reduction of imine **5**, derived from ketone **4** and the readily available chiral 1-phenylethylamine (**3**). This approach is similar to that of Overberger et al.,[5] who showed

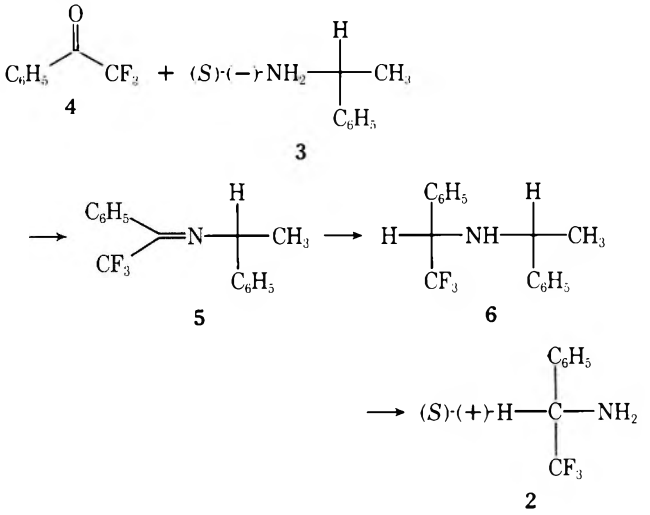
Table I. Asymmetric Reductions of Some Fluoroalkylated Imines



No.	R_F	Ar	Reducing agent	Solvent	Temp, °C	Time, h	Ratio of[a] amines	%
5	CF_3	Phenyl	$LiAlH_4$	Et_2O	25	24	60:40	90
5	CF_3	Phenyl	$LiAlH_4$	Et_2O	−78	24	70:30	95
5	CF_3	Phenyl	$LiAlH_4$	THF	25	24	65:35	90
5	CF_3	Phenyl	$LiAlH_4$	THF	−78	24	80:20	95
11	CF_3	Benzyl	$LiAlH_4$	Et_2O	25	24	65:35	80
11	CF_3	Benzyl	$LiAlH_4$	THF	−10	5	69:31	70
11	CF_3	Benzyl	$LiAlH_4$	THF	−78	36	85:15	95
5	CF_3	Phenyl	Red-Al	THF	25	18–20	70:30	65
5	CF_3	Phenyl	Red-Al	THF	−78	72	92:08	95
12	C_3F_7	Phenyl	Red-Al	THF	25	18–20	65:35	60
12	C_3F_7	Phenyl	Red-Al	THF	−78	72	90:10	80
5	CF_3	Phenyl	$NaBH_3CN$	THF	25	24	83:17	70
5	CF_3	Phenyl	$NaBH_3CN$	THF	0	72	96:04	67
5	CF_3	Phenyl	$NaBH_3CN$	THF	−78	72		*b*
5	CF_3	Phenyl	BH_3	THF	25	3–5	55:45	95
5	CF_3	Phenyl	BH_3	THF	−78	6–10	57:43	90
5	CF_3	Phenyl	$NaBH_4$	Et_2O	25	72		*b*
5	CF_3	Phenyl	$NaBH_4$	THF	25	72		*b*
5	CF_3	Phenyl	$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O	25	72		*b*
5	CF_3	Phenyl	$LiAl(O\text{-}t\text{-}Bu)_3H$	THF	25	72		*b*
5	CF_3	Phenyl	9-BBN	Et_2O	25	72		*b*
5	CF_3	Phenyl	9-BBN	THF	25	72		*b*
5	CF_3	Phenyl	H_2/Pd[c]	Cyclohexane	55	48	*d*	*d*
5	CF_3	Phenyl	H_2/Pd	THF	25	0.3	63:37	10
5	CF_3	Phenyl	H_2/Pd	THF	25	10	64:36	90

[a] The diastereomeric ratios were determined by examination of the nonequivalent ^1H or ^{19}F NMR spectra of these diastereomers. [b] No reaction. [c] Catalytic amount of dry HCl. [d] Racemic 2 is obtained in 95% yield.

Scheme I



that catalytic hydrogenation of the imine derived from acetophenone and chiral **3** preferentially affords the chiral rather than the meso diastereomer of the resultant secondary amine. Catalytic hydrogenation of fluoroalkylated imine **5** does not proceed as stereoselectively as might be desired; however, the ratio of the resultant diastereomeric secondary amines **6** can be more strongly biased by appropriate choice of other reducing agents as shown in Table I. Note that for all cases considered, reductions conducted in tetrahydrofuran give greater asymmetric induction than those similarly conducted in ether. From the standpoint of expense, degree of asymmetric induction, and overall yield, Red-Al[6] seems the optimum reducing agent among those surveyed.

Subsequent catalytic hydrogenolysis of **6** proceeds smoothly and in essentially quantitative yield to give exclusively fluoroalkylated amine **2** of the same enantiomeric composition as the diastereomeric composition of **6.** Although catalytic hydrogenolysis of benzylic carbon–nitrogen bonds is well known, we are unaware of prior reports concerning the retarding effect of α-perfluoroalkyl groups upon the rate of such hydrogenolyses. In the present instances, this retarding effect affords complete regioselectivity of hydrogenolysis of **6.**

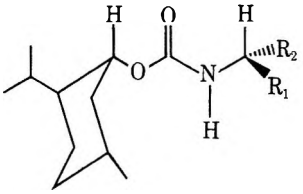
Obtained in enantiomeric purities ≥80%, amine **2** was totally resolved through recrystallization of the natural tartaric acid salt. When totally resolved, (*S*)-(+)-**2** exhibits $[\alpha]^{25}_D$ +24.11° (*c* 12.0, ethanol). The enantiomeric composition and absolute configuration of fluoro amine **2** were determined by NMR[7] using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol[8] as a chiral solvating agent.

This sequence of reactions is readily applicable to other fluorinated amines. For example, chiral 2,2,3,3,4,4,4-heptafluoro-1-phenylpentylamine (**7**) and 2,2,2-trifluoro-1-(1-benzyl)ethylamine (**8**) have been similarly prepared. Racemic fluoro amines **2, 7,** and **8** may be conveniently prepared from the imines of benzylamine by concomitant catalytic hydrogenation and hydrogenolysis.

Chromatographic Evaluation. Samples of (*S*)-(+)-enriched (80% ee) fluoro amine **2** were treated with the chloroformates derived from (*R*)-(−)-menthol and (*R*)-(−)-2-octanol, respectively. The diastereomeric ratios of the resulting carbamates were determined by ^{19}F NMR and corresponded closely with the initial enantiomeric composition of amine **2.** These diastereomeric carbamates were chromatographed upon silica gel with 1:1 methylene chloride–hexane and exhibited the expected inversion of elution order and improvement in chromatographic separability relative to the nonfluorinated analogues. Chromatographic data for these carbamates appear in Table II.[3]

It should be noted that incorporation of perfluoroalkyl

Table II. Comparative Data for Fluorinated vs. Nonfluorinated Carbamates



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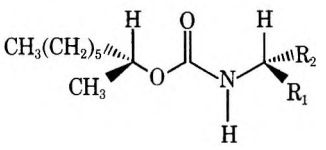

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Compd	R_2	R_1	K'	α
9a	α-Naph	CH_3	2.0	1.4
9b	CH_3	α-Naph	1.4	
9c	Ph	CF_3	1.6	1.5
9d	CF_3	Ph	2.4	
10a	α-Naph	CH_3	3.3	1.2
10b	CH_3	α-Naph	2.8	
10c	Ph	CF_3	2.3	1.4
10d	CF_3	Ph	3.1	

groups into CDA does not automatically confer great chromatographic separability upon diastereomeric derivatives. Although not originally described as chromatographic resolving agent, α-methoxy-α-trifluoromethylphenylacetic acid has found such application.[9] We have found that, for a given alcohol, diastereomeric esters derived from this acid are considerably more difficult to separate chromatographically than are the diastereomeric carbamates derived from amines 2 or 3. We ascribe this to a lesser degree of conformational preference in the esters than in the carbamates.[2,10] Although more extensive appraisal of fluoro amines is still underway, these initial results suggest that these amines will be quite useful for the chromatographic resolution of racemic alcohols. We also note that the carbamates derived from fluoro amine 2 and menthol (or 2-octanol) are rather more crystalline than their nonfluorinated counterparts, thus serendipitally enhancing the separability of these diastereomers by the classical approach.

Experimental Section

Melting points were taken on a Buchi apparatus and are uncorrected. Infrared spectra were obtained with a Beckman IR-12 or a Perkin-Elmer 237B spectrophotometer. ^1H and ^{19}F NMR spectra were obtained with Varian Associates A-60A, EM-390, HA-100, or HR-220 instruments. Mass spectra were determined using a Varian MAT CH-5 spectrometer. Microanalyses were performed by J. Nemeth and his colleagues.

Imines. All imines used in this study were prepared in the following manner. To a 100-mL round-bottom flask fitted with a Dean-Stark water trap and reflux condenser were added 10.6 mmol of fluoroalkylated ketone and (*S*)-(−)-α-Phenylethylamine (10.7 mmol, 1.29 g), along with 30 mL of dry toluene and ca. 3% by weight of *p*-toluenesulfonic acid. The mixture was refluxed until the theoretical amount of water had collected in the trap. The imine was collected and purified by distillation at reduced pressure; isolated yields ranged between 80 and 91%.

Imine 5 from phenyl trifluoromethyl ketone and (*S*)-(−)-1-phenylethylamine is a very pale yellow liquid: bp 99–101 °C (0.5 mm); NMR ($CDCl_3$) δ 1.40 (d, CCH_3), 4.59 (quartet, CH), 7.18–7.35 ppm (multiplet, $C_{12}H_{10}$); IR (neat) 3090, 3000, 1670 (C=N), 1500, 1460, 1380, 1340, 1220, 1150, 1020, 970 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 277 (5.4, M^+), 106 (8.7), 105 (100.0), 104 (4.6), 79 (9.6), 78 (4.3), 77 (14.2).

Anal Calcd for $C_{16}H_{14}F_3N$: C, 69.33; H, 5.05; N, 5.05. Found: C, 69.42; H, 5.06; N, 5.12.

Imine 11 from benzyl trifluoromethyl ketone and (*S*)-(−)-1-phenylethylamine is a very pale yellow liquid that was purified by molecular distillation: NMR ($CDCl_3$) δ 1.38 (d, CCH_3), 3.73 (AB multiplet, $=CCH_2$), 4.81 (quartet, CH), 7.00–7.46 ppm (multiplet, $C_{12}H_{10}$); IR (neat) 3095, 3000, 1670 (C=N), 1500, 1465, 1380, 1365, 1275, 1210, 1130, 925 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 291 (13.4, M^+), 107 (14.7), 106 (5.7), 105 (100.0), 104 (4.2), 79 (15.4), 78 (7.0), 77 (23.8).

Anal. Calcd for $C_{17}H_{16}F_3N$: C, 70.09; H, 5.54: N, 4.81. Found: C, 69.97: H, 5.42; N, 4.68.

Imine 12 from 1,1,2,2,3,3,3-heptafluoropropyl phenyl ketone and (*S*)-(−)-1-phenylethylamine is a very pale yellow liquid: bp 129–131 °C (1.5 mm); NMR ($CDCl_3$) δ 1.45 (d, CCH_3), 4.55 (quartet, CH), 7.13–7.78 ppm (multiplet, $C_{12}H_{10}$); IR (neat) 3070, 3000, 1655 (C=N), 1500, 1460, 1380, 1350, 1240, 1170, 1120, 980 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 377 (12.3, M^+), 107 (10.6), 106 (18.7), 105 (100.0), 104 (5.3), 103 (6.7), 79 (14.3), 78 (5.1), 77 (26.8).

Anal. Calcd for $C_{18}H_{14}F_7N$: C, 57.30; H, 3.74; N, 3.71. Found: C, 57.28; H, 3.71; N, 3.67.

Asymmetric Reductions. Diastereomeric secondary amines were produced by asymmetric reduction of imines in the following manner. A solution of 2.7 mmol of imine in 50 mL of dry tetrahydrafuran was placed in a three-necked 100-mL round-bottom flask equipped with overhead stirrer, vented dropping funnel, and nitrogen inlet. The reaction vessel was cooled in a −78 °C bath and Red-Al[6] (2.7 mmol) in 30 mL of dry tetrahydrofuran was slowly added over a 4-h period with continuous stirring. After addition was completed, stirring was continued for 72–96 h at −78 °C. The mixture was then slowly warmed to room temperature and hydrolyzed with cold, aqueous ammonium chloride and the entire mixture was extracted with three 25-mL portions of ether. The ether extracts were dried over magnesium sulfate prior to solvent evaporation. NMR data are given for the major diastereomer.

***N*-2,2,2-Trifluoro-1-phenylethyl-*N*-1′-(phenyl)ethylamine (6)** is a colorless liquid: bp 82–83 °C (0.4 mm); NMR ($CDCl_3$) δ 1.36 (d, CCH_3), 1.99 (broad s, NH), 4.01 (quartet, CH_3CH), 4.09 (quartet, CF_3CH), 7.16–7.45 ppm (multiplet, $C_{12}H_{10}$); IR (neat) 3500 (NH), 3180, 3060, 1495, 1480, 1380, 1255, 1175, 1130, 880 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 279 (3.3, M^+), 265 (16.4), 264 (100.0), 210 (6.6), 159 (58.1), 120 (2.3), 109 (34.5), 107 (31.1), 106 (15.6), 105 (35.3), 70 (31.1), 78 (7.3), 77 (29.5), 69 (2.2).

Anal. Calcd for $C_{16}H_{16}F_3N$: C, 68.80; H, 5.77; N, 5.02. Found: C, 68.71; H, 5.67; N, 4.97.

***N*-1,1,1-Trifluoro-3-phenylpropyl-*N*-1′-(phenyl)ethylamine (14)** is a colorless liquid: bp 119–121 °C (1.0 mm); NMR ($CDCl_3$) δ 1.20 (d, CCH_3), 2.01 (broad s, NH), 2.48 [doublet of doublets (J = 15, 10 Hz), CCH_2], 2.98 [doublet of doublets (J = 15, 5 Hz), CCH_2], 3.01 (multiplet, CF_3CH), 3.94 (quartet, CH_3CH), 7.06–7.38 ppm (multiplet, $C_{12}H_{10}$); IR (neat) 3490 (NH), 3080, 3000, 1490, 1460, 1375, 1270, 1200, 1150, 940 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 293 (8.2 (8.2, M^+), 278 (19.0), 202 (17.3), 109 (7.4), 106 (9.2), 105 (100.0), 103 (7.1), 91 (26.2), 79 (10.8), 77 (14.6).

Anal. Calcd for $C_{17}H_{18}F_3N$: C, 69.61; H, 6.19; N, 4.78. Found: C, 69.53; H, 6.07; N, 4.53.

***N*-4,4,4,3,3,2,2-Heptafluoro-1-phenylbutyl-*N*-1′-phenylethylamine (15)** is a colorless liquid, which was molecularly distilled; NMR ($CDCl_3$) δ 1.28 (d, CCH_3), 3.94 (quartet, CH_3CH), 4.14 (broad s, NH). 4.35 [doublet of doublets (J = 20, 10 Hz), CF_3CH], 7.08–7.43 ppm (multiplet, $C_{12}H_{10}$); IR (neat) 3495 (NH), 3090, 3005, 1492, 1475, 1380, 1240, 1180, 1130, 1095, 875 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 379 (5.4, M^+), 364 (100.0), 259 (61.7), 133 (2.7), 120 (4.5), 109 (31.4), 107 (30.4), 106 (10.1), 105 (41.4), 79 (27.7), 78 (4.3), 77 (34.6).

Anal. Calcd for $C_{18}H_{16}F_7N$: C, 56.99; H, 4.25; N, 3.69. Found: C, 56.74; H, 4.15; N, 3.52.

Hydrogenolysis. The following general procedure was utilized to conduct all hydrogenolysis. A solution of 1.5 mmol of secondary amine in 50 mL of absolute ethanol containing a trace of dry HCl was hydrogenated in a Parr shaker at ca. 60 °C and 40 psi for 24–48 h over ca. 3–5% by weight of 5% Pd on charcoal. After removal of the catalyst and evaporation of the ethanol, the mixture of amine–amine hydrochloride was treated with dilute aqueous sodium hydroxide. This mixture was extracted with three 25-mL portions of methylene chloride and the combined extracts were dried over magnesium sulfate prior to evaporation of the solvent and distillation of the primary amines, generally obtained in close to quantitative yields.

(*S*)-(+)-2,2,2-Trifluoro-1-phenylethylamine (2) is a colorless liquid: bp 88 °C (20 mm); NMR ($CDCl_3$) δ 1.80 (broad s, NH), 4.34 (quartet, CH), 7.23–7.41 ppm (multiplet, C_6H_5); IR (neat) 3390 (NH), 3000, 1595, 1500, 1460, 1340, 1255, 1170, 1120, 860 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 175 (13.2, M^+), 136 (4.2), 112 (4.8), 109 (11.7), 108 (4.9), 107 (64.4), 106 (100.0), 105 (7.1), 104 (8.5), 83 (6.4), 80 (5.7), 79 (85.1), 78 (12.2), 77 (56.4), 69 (7.4); $[\alpha]^{25}D$ +24.11° (c 12.0, ethanol).

Anal. Calcd for $C_8H_8F_3N$: C, 54.86; H, 4.60; N, 8.00. Found: C, 54.69; H, 4.52; N, 7.95.

Carbamates. The diastereomeric carbamates employed were prepared by a previously described method.[2]

Menthyl *N*-[1-(phenyl)-2,2,2-trifluoroethyl]carbamate (9c) and 9d as a 1:9 diastereomeric mixure is a colorless solid: mp 93–105 °C.

After separation of the carbamate diastereomers **9c** and **9d**, NMR, IR, and elemental analysis of each are consistent with the assigned structure.

9c: NMR ($CDCl_3$) δ 0.80–1.00 [multiplet, $C(CH_3)_2$ and $-CHCH_3$], 1.19–2.20 (multiplet, C_6H_8), 2.25 [heptet of doublets, $(CH_3)_2CH$], 4.69 (triplet of doublets, OCH), 7.38 ppm (broad s, C_6H_5); IR ($CDCl_3$) 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{26}F_3NO_2$: C, 63.85; H, 7.33; N, 3.92. Found: C, 63.92; H, 7.19; N, 3.85.

9d: NMR ($CDCl_3$) δ 0.80–1.00 [multiplet, $C(CH_3)_2$ and $-CHCH_3$], 1.19–2.20 (multiplet, C_6H_8), 2.25 [heptet of doublets, $(CH_3)_2CH$], 4.69 (triplet of doublets, OCH), 7.38 ppm (broad s, C_6H_5); IR ($CDCl_3$) 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{26}F_3NO_2$: C, 63.85; H, 7.33; N, 3.92. Found: C, 63.81; H, 7.24; N, 3.88.

2-Octyl *N*-[1-(phenyl)-2,2,2-trifluoroethyl]carbamate (10c) and 10d as a 1:9 diastereomeric mixture is a colorless solid: mp 105–106 °C.

After separation of **10c** and **10d**, NMR, IR, and elemental analysis of each were consistent with the assigned structure.

10c: NMR ($CDCl_3$) δ 0.91 [t, $(CH_2)_5CH_3$], 1.20–1.83 [multiplet, $CH_3C(CH_2)_5$], 4.85 (sextet, OCH), 5.40 (quintet, NCH), 5.53 (broad doublet, NH), 7.35 ppm (broad s, C_6H_5); IR ($CDCl_3$) 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{24}F_3NO_2$: C, 61.62; H, 7.30; N, 4.23. Found: C, 61.55; H, 7.24; N, 4.18.

10d: NMR ($CDCl_3$) δ 0.91 [t, $(CH_2)_5CH_3$], 1.20–1.83 [multiplet, $CH_3C(CH_2)_5$], 4.85 (sextet, OCH), 5.40 (quintet, NCH), 5.53 (broad doublet, NH), 7.35 ppm (broad s, C_6H_5); IR ($CDCl_3$) 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{24}F_3NO_2$: C, 61.62; H, 7.30; N, 4.23. Found: C, 61.82; H, 7.34; N, 4.28

Acknowledgment. This work has been partially supported by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—**2**, 62197-94-8; **3**, 2627-86-3; **4**, 434-45-7; **5**, 62197-91-5; **6** isomer 1, 62197-92-6; **6** isomer 2, 62197-93-7; **9a**, 17397-46-5; **9b**, 17397-45-4; **9c**, 62197-95-9; **9d**, 62197-96-0; **10a**, 62197-97-1; **10b**, 62197-98-2; **10c**, 62197-99-3; **10d**, 62198-00-9; **11**, 62198-01-0; **12**, 62198-02-1; **14** isomer 1, 62198-03-2; **14** isomer 2, 62198-04-3; **15** isomer 1, 62198-05-4; **15** isomer 2, 62198-06-5; benzyl trifluorometrhyl ketone, 350-92-5; 1,1,2,2,3,3,3-heptafluoropropyl phenyl ketone, 559-91-1.

References and Notes

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Photolysis and Thermolysis of 2,4,4-Trisubstituted Δ^2-Oxazolin-5-ones. Activation and Control by a Trifluoromethyl Group

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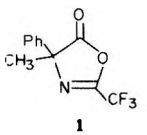
The photochemical and thermal reactivity of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (**1**) and 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (**2**) have been investigated. Photolysis of **1** in the presence of dipolarophiles gives Δ^1-pyrrolines presumably via carbon dioxide expulsion from **1** to give trappable nitrile ylides. However, photolysis of **2** (with or without dipolarophiles) gives *N*-(1-methylbenzylidene)acetamide (**6**) presumably via carbon monoxide expulsion. Thermally (refluxing xylene), **1** loses carbon monoxide to form *N*-(1-phenylvinyl)trifluoroacetamide (**10**); however, **2** is unreactive. A rationalization of the trifluoromethyl group's effect on the thermolysis of **1** is presented, and some points in possible photochemical reaction sequences at which a trifluoromethyl group may control photoreactivity are discussed.

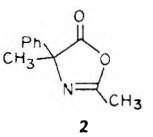
One of the most troublesome aspects of synthetic photochemistry is the capriciousness of many photorearrangements. Therefore, the investigation and development of possible photodirecting, photoactivating, or photoprotecting groups which may make photoreactions more predictable or even controllable are worthwhile, if difficult, goals.

A substituent which may show promise at directing the course of photoreactions is the trifluoromethyl group. For example, Wexler and Swenton[1] have recently reported that the acetone sensitized cycloaddition of 5-trifluoromethyluracil to isobutylene occurs with greater than 95% regioselectivity.

In connection with work to photochemically synthesize β-lactam systems,[2] we have synthesized 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (**1**).[3] Because the photochemistry of Δ^2-oxazolin-5-ones has been studied only to a limited extent[4] (see below), and because a comparison of the



1



2

photoreactivity of **1** with that of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (**2**)[5] would test the effect of the trifluoromethyl group, we have explored the photolytic and thermal behavior of **1** and **2**. The results of the study will follow a brief discussion of pertinent published work.

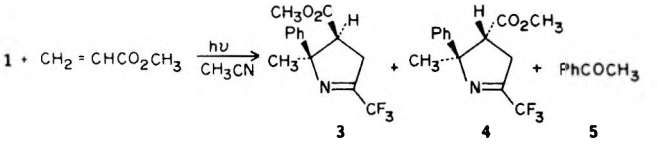
There are two reports of Δ^2-oxazolin-5-one photolysis.[4a,b] Padwa and Wetmore[4a] report that no Δ^1-pyrroline product is formed when a Δ^2-oxazolin-5-one is photolyzed in the presence of electron-deficient olefin dipolarophiles, but the products formed, if any, are not described.[6] The photolysis of one 2,4,4-trialkyl-Δ^2-oxazolin-5-one followed by acidic hydrolysis is reported by Slates et al.[4b] to yield a ketone de-

rived from carbon 4 and its substituents. Carbon monoxide loss to give an *N*-(dialkylmethylidene)acetamide which is subsequently hydrolyzed to the product ketone was postulated but not demonstrated. This behavior contrasts with that of Δ^3-oxazolin-5-ones which usually give Δ^1-pyrrolines in synthetically useful yields when photolyzed in the presence of appropriate dipolarophiles.[4a,c] Trappable nitrile ylide intermediates are evidently generated[4a] by carbon dioxide expulsion from the Δ^3-oxazolin-5-ones. However, photolysis of a 2-trifluoromethyl-Δ^3-oxazolin-5-one gives products derived from an *N*-acylimine which is presumably formed by carbon monoxide expulsion.[7] Photolysis of a trifluoromethyl derivative of Δ^2-oxazolin-5-one has not been reported.

Attempted thermolysis of 2,4,4-trisubstituted Δ^2-oxazolin-5-ones in refluxing xylene is reported to cause no reaction.[8] Huisgen and co-workers[8] have studied the reaction of 2,4-disubstituted Δ^2-oxazolin-5-ones with dipolarophiles and have found that oxazolium ion intermediates are formed and that subsequent carbon dioxide loss gives pyrrolines. Nitrile ylide intermediates are not involved in this case. Steglich and co-workers[9] and Schmid et al.[4c] have observed that higher temperatures and proper substituents allow the thermolysis of trisubstituted Δ^2-oxazolin-5-ones to give carbon dioxide loss and products expected from nitrile ylide intermediates. Carbon monoxide loss to give an enamide has also been observed,[10] but only when both a 2-trifluoromethyl and a 4-thiophenoxy group are present in a 2,4,4-trisubstituted Δ^2-oxazolin-5-one system. Compound **1** has been reported to be stable at 200 °C (but see below).[11] For comparison, trisubstituted Δ^3-oxazolin-5-ones studied by Steglich[9] lose carbon dioxide thermally and form products expected from nitrile ylide intermediates. Padwa reports[4a] that several 2,4-disubstituted Δ^3-oxazolin-5-ones are stable to thermolysis.

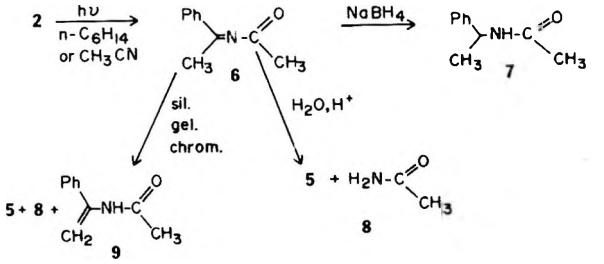
Results

Photolysis of 1 and 2. Photolysis of **1** and methyl acrylate in acetonitrile gives reasonable yields (26 to 17%, respectively) of *cis*- and *trans*-2-trifluoromethyl-4-carbomethoxy-5-methyl-5-phenyl-Δ^1-pyrrolines (**3** and **4** respectively), along with 7% acetophenone (**5**). Spectral and elemental analysis



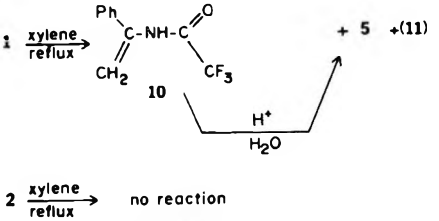
support the structures proposed. The stereochemical assignments are based on ^{1}H NMR spectra. Pyrroline **3** is assigned as the structure with phenyl and the carboxymethyl groups cis since the ester methyl group is more shielded in **3** as compared to **4**.[12] Also, the chemical shift of the C-5 methyl in **3** is at lower field than that of **4** as would be expected if **3** has the 5-methyl and 4-carbomethoxy group trans.[13] The reaction is evidently highly regioselective since there is no higher field multiplet which would have been evident in a C-4 unsubstituted Δ^1-pyrroline.[12] Starting material (**1**) was isolated unchanged from a dark control sample worked up by the procedure applied to the photolyzed solution; therefore, acetophenone is the result of photolysis.

Photolysis of **2** in acetonitrile or hexane gives a good yield of the relatively unstable *N*-(1-methylbenzylidene)acetamide (**6**). The assignment of the structure of **6** is based on its ^{1}H NMR spectrum (singlets at δ 2.1 and 2.3 and the aromatic signals expected for an imine *C*-phenyl) and on the observation that sodium borohydride reduction of **6** gives *N*-(1-phenylethyl)acetamide (**7**). Acid-catalyzed hydrolysis of **6** immediately gives acetophenone (**5**) and acetamide (**8**), and silica gel chromatography of **6**, which is not contaminated by **5**, **8**, or *N*-(1-phenylvinyl)acetamide (**9**), gives **5**, **8**, and **9** but



no **6**. Compound **9** was identified by its ^{1}H NMR spectrum and by comparison to a sample independently synthesized using the enamide synthesis of Padwa et al.[14] Since enamide **9** is easily hydrolyzed to **5** and **8**, it is possible but not necessary that **5** and **8** are formed from **6** via **9**. Irradiation of **2** in acetonitrile with methyl acrylate gives polymethyl acrylate as the only product in addition to those described above. The photoreactions of **1** and **2** are not quenched by piperylene added in concentrations such that excited states living for 10^{-7} s would have been 90% trapped.

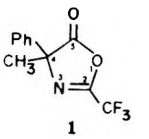
Thermolysis of 1 and 2. When **1** is refluxed in dry xylenes a good yield (66%) of *N*-(1-phenylvinyl)trifluoroacetamide (**10**) is obtained along with a small amount of **5** [presumably



trifluoroacetamide (**11**) is also formed]. The identification of **10** is based on its spectral data. The ^{1}H NMR indicated the presence of an exo methylene, an amide hydrogen, and a phenyl group. The mass spectrum is most helpful since it shows the correct parent and parent plus one peaks for $C_{10}H_8NOF_3$ and shows a loss of trifluoromethyl and also trifluoroacetamide fragments. Compound **10** is hydrolyzed readily to **5** and presumably **11**. Though **10** may have formed via an *N*-(1-methylbenzylidene)trifluoroacetamide (**12**) no evidence for it was found in the reaction mixture. When **2** was refluxed in xylenes with or without methyl acrylate for periods up to 15 h, it was recovered completely unchanged.

Discussion

Thermolysis. The most important feature of the results is the profound effect of the substitution of a trifluoromethyl group in place of a methyl group on the thermal and photochemical reactivity of a trisubstituted Δ^2-oxazolin-5-one. Considering the thermal reactivity first, the trifluoromethyl group greatly activates the Δ^2-oxazolin-5-one toward carbon monoxide loss when compared to a methyl group. The activation is selective and different from that of a 2-phenyl substituent which has been shown by Steglich and co-workers[9,10] to accelerate thermal carbon dioxide expulsion from trisubstituted Δ^2-oxazolin-5-ones. The trifluoromethyl group evidently encourages cleavage of the 4,5 bond, and possibly the 1,5 bond, while failing to activate or perhaps deactivating the system toward 1,2 bond breakage.



A consideration of the stability of diradicals which might be generated as intermediates, or which may resemble species on a concerted reaction pathway, helps rationalize the thermal results. Cleavage of the 1,2 bond in **1** would produce an iminoyl

σ radical[15] at carbon 2. Trifluoromethyl groups are known[16] to destabilize acyl radicals relative to methyl and phenyl groups. However, cleavage of the 4,5 bond would produce a π-type allyllike radical, with odd-electron density at centers 4 and 2, which would be more stabilized by a trifluoromethyl group than by a methyl group. Fluorine p–π interactions have been postulated to rationalize π-electron donation by trifluoromethyl groups to aromatic systems,[17] and these "interactions" have been invoked to rationalize the greatly enhanced stability of bis(trifluoromethyl) nitroxide as compared to dimethyl nitroxide.[18] Our experimental results do not indicate whether cleavage of the 1,5 bond is affected by the presence of a trifluoromethyl group.[19]

It is not possible to comment on the report[11] that **1** is stable to thermolysis because the conditions were not described. Contrary to an earlier hypothesis,[10] the presence of a 4-thiophenoxy group as well as a 2-trifluoromethyl group is not required for thermal carbon monoxide expulsion from Δ^2-oxazolin-5-ones. However, the extent to which substitution at C-4 can be varied without suppressing carbon monoxide expulsion is not known.

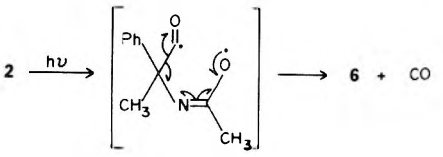
Photolysis. The very different photochemical behavior of **1** and **2** shows that the trifluoromethyl group can also strongly influence excited state behavior. The light-induced expulsion of carbon monoxide from a 2,4,4-trisubstituted Δ^2-oxazolin-5-one as observed for **2** apparently has precedent in the work of Slates et al.[4b,20] However, this is the first instance in which the postulated *N*-(methylidene)acetamide photoproduct (e.g., **6**) has been observed before hydrolysis. The substitution of a trifluoromethyl group for a methyl group (compound **1**) leads to the photoinduced loss of carbon dioxide to presumably give a nitrile ylide which is trapped by a dipolarophile. Such a reaction had not been observed for Δ^2-oxazolin-5-ones.[4a] Reactions of **1** and **2** probably involve singlet or very short-lived triplet states since the reactions were not quenched by piperylene.

The high regioselectivity in the reaction of the postulated nitrile ylide intermediate from **1** with electron-deficient dipolarophiles can be rationalized by the work of Houk and Caramella.[21] They attribute the greater nucleophilicity of the divalent carbon of the nitrile ylide (**15**) to the larger size of its HOMO coefficient.

The reaction pathways followed by **1** and **2** may not be completely exclusive, since the acetophenone (**5**) among the photolysis products of **1** could have come from hydrolysis of **10** derived by carbon monoxide expulsion. However, **5** could also have arisen via rearrangement of untrapped nitrile ylide to give an enamine which subsequently hydrolyzed. Carbon dioxide loss from **2** to give trappable nitrile ylides does not occur since photolysis of **2** in the presence of large amounts of dipolarophile failed to give Δ^1-pyrroline.

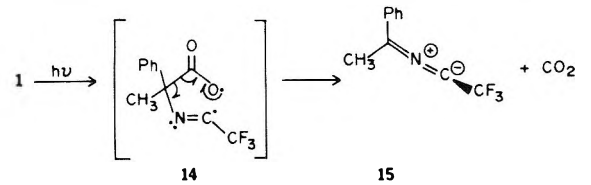
The Effect of a Trifluoromethyl Group. The means by which the trifluoromethyl group in **1** influences the reaction pathway is not clear. However, it is useful to consider stages in possible concerted or stepwise reaction sequences at which substitution of trifluoromethyl for methyl may alter the reaction course. The first potential point of control in photochemical processes involves the absorption of light. Compounds **1** and **2** may be considered to have one, two, or three chromophores, depending on the interaction of the phenyl, carbonyl, and imine systems. Though trifluoromethyl groups are known to red shift the n–π^* and π–π^* absorptions of ketones[22] (and presumably imines), the UV spectra of **1** and **2** have the same maxima. Both resemble the spectrum of toluene, but both have higher extinction coefficients than toluene in the 225–250-nm region as if absorption from the "ketone" and/or "imine" chromophores were tailing into that region. In the 250–280-nm region the extinction coefficient of **1** is approximately twice that of **2**. Absorption maxima do not shift as solvent polarity is changed, so the presence of n–π^* bands with energies lower than that of 250 nm light cannot be substantiated (or ruled out). The trifluoromethyl-induced changes in absorption seem to small to explain the difference in reactivity of **1** and **2**.

A second perhaps more likely point of control is the intramolecular energy transfer which may be necessary from phenyl to either the ester (anhydride)-like carbonyl or the imine. α-Phenyl to ester carbonyl energy transfer has been reported in studies of ester photochemistry by Morrison[23] et al. With methyl present as in **2**, energy transfer to the carbonyl may dominate and α-cleavage to give a diradical (**13**) like that



13

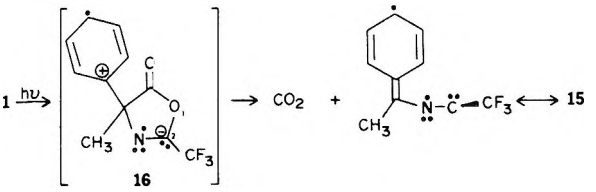
postulated for the photo-Fries[24] reaction may lead to carbon monoxide loss and the observed product **6** (Note that **2** is an analogue of a vinyl ester). The substitution of a trifluoromethyl for methyl as in **1** should lower the energy of the π–π^* and n–π^* levels of the imine,[22] and energy transfer to the imine followed by α-cleavage as postulated for azirines[4a] could lead to **14**. Loss of carbon dioxide would give nitrile ylide **15**,



14 **15**

which, when trapped by a dipolarophile, would give the observed Δ^1-pyrrolines. If the "imine" and "carbonyl" form a single excited state, the trifluoromethyl group could increase the importance of the "imine" description (by changing orbital weighting coefficients) and thus aid carbon dioxide expulsion.

A third possible point of control presupposes a different reaction mechanism: electron transfer from the photoexcited phenyl group to either the carbonyl or the imine group.[25] In the case of **2** a rational mechanism involving carbon monoxide loss leads from a species with phenyl radical cation and carbonyl radical anion character to **6**. When a trifluoromethyl replaces methyl as in **1**, electron transfer to the imine may lead to a species like **16**. A 1,2-bond fragmentation of **16** may be

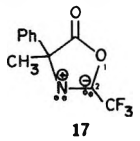


16

viewed as an analogue of α-elimination reactions which generate carbenes.[26] The carbene generated by carbon dioxide loss can be a resonance contributor for nitrile ylide **15**.[21] The importance of electron transfer in the photoreactions of **1** and **2** is not now known, and it is possible that electron transfer competes with energy transfer. Electron transfer may, for example, be important only for **1**.

In the points of possible control discussed thus far the trifluoromethyl and methyl groups are envisioned to influence major changes (energy or electron transfer) in excited state geometry and electron density. A consideration of surfaces[27] in regions related to specific "chromophore" excited states may also be useful. For example, trifluoromethyl perturbation (as in **1**) of the "imine" region of the surface might lower ac-

tivation barriers[28] and minima to favor 1,2-bond lengthening, and eventually 1,2-bond cleavage, by making a π–π^* or n–π^* excited state more zwitterionic (see **17** and note its relationship to **16**). The trifluoromethyl group at carbon 2 should have much less effect on the "carbonyl" region of the excited surface. Changes in the "imine" excited surface could control the reactivity of **1** as long as energy can be transferred to that "chromophore" (the transfer does not have to be irreversible or exclusive). If the "imine" and "carbonyl" form a single potential well in the excited state surface, the trifluoromethyl group may decrease barrier heights involving carbon dioxide loss.



17

A different potential point of control involves decay to the ground state surface in a region near the geometry of the primary photoproduct. This decay process is aided by a close approach of the ground and excited state surfaces.[27] Closer approach can be accomplished by decreasing excited state energy as discussed above, or by increasing the ground state energy near the desired product geometry. If carbon dioxide is lost from **1** or **2** a primary product may have radical character at carbon **2**. The trifluoromethyl destabilization of σ radicals, which may explain the thermal stability of the 1,2 bond in **1**, may help make a ground state σ-radical-like species photochemically accessible for **1** by raising the ground state energy surface and facilitating decay near a σ-radical-like geometry. The σ-radical stabilizing methyl group in **2** may not force the ground state surface to be as high at geometries involving carbon dioxide loss, as compared to **1**, and the excited state decays at geometries related to carbon monoxide loss instead.

At each of the possible points of control mentioned above the trifluoromethyl group seems to favor photochemical loss of carbon dioxide (at least by hindsight). This makes a determination of the actual control mechanism(s) difficult. However, the concurrence of several control points may rationalize the very sharp difference in reactivity of **1** and **2**.

Experimental Section

General. All solutions for photolysis were purged with argon for at least 15 min before and during the entire photolysis. NMR spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. UV spectra were recorded on a Cary 17 spectrophotometer. Mass spectra were taken on a Hitachi Perkin-Elmer RMV-6D spectrometer. Microanalyses were performed by Instranal Laboratory, Rensselaer, N.Y. Melting points are uncorrected.

Absorption Spectra of 1 and 2. UV absorption spectra of **1** and **2** were recorded in both hexane and acetonitrile, and are summarized here: [λ (ϵ) (an asterisk indicates maximum, λ in nm)], **1** (hexane), 268* (243), 263* (429), 261* (484), 257* (629), 251* (828), 245 (1036), 240 (1172), 230 (1930), 220 (3502), 210 (8183); **1** (acetonitrile), 268* (209), 263 (359), 261 (443), 257* (585), 251* (802), 245 (969), 240 (1130), 230 (1595), 220 (3174), 210 (7643); **2** (hexane), 268* (137), 263* (269), 261 (288), 257* (428), 251* (607), 245 (786), 240 (866), 230 (995), 220 (3731), 210 (8407); **2** (acetonitrile), 268* (98), 263* (197), 261 (208), 257* (384), 251 (519), 245 (711), 240 (909), 230 (1081), 220 (3091), 210 (8547).

Synthesis of 2,4-Dimethyl-4-phenyl-Δ^2-oxazolin-5-one (2).[5] A solution of 2.0 g (12.1 mmol) of α-phenylalanine in 15 mL of acetic anhydride was heated at reflux under a nitrogen atmosphere for 1 h. The solution was allowed to cool and excess acetic anhydride removed under reduced pressure. The residue was distilled under reduced pressure to yield 1.62 g (71%) of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (**2**): bp 62 °C (0.12 mm); NMR ($CDCl_3$) δ 1.7 (3 H, s), 2.2 (3 H, s), 7.1–7.6 (5 H, m).

Photolysis of 2,4-Dimethyl-4-phenyl-Δ^2-oxazolin-5-one (2). A solution of 205 mg (1.08 mmol) of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (**2**) in 330 mL of dry hexane was irradiated (Hanovia 450-W) through a Vycor filter for a period of 2.5 h. Solvent removal under reduced pressure gave a yellow liquid [presumably *N*-(1-methylbenzylidene)acetamide], which had an NMR spectrum containing singlets at δ 2.1 (3 H), and multiplets at δ 7.0–7.4 (4.5 H) and 7.6–7.8 (2 H), in addition to broad high-field signals attributed to polymeric material. No acetophenone or *N*-(1-phenylvinyl)acetamide were observed.[29] Treatment of an NMR sample of this material with slightly wet trifluoroacetic acid resulted in immediate formation of acetophenone and acetamide, identified by addition of authentic samples. Chromatography of 182 mg of the initial photolysis product on silica gel (Mallinckrodt CC-7), with methylene chloride elution, yielded a mixture containing 63 mg (54%) of acetophenone and 23 mg (15%) of *N*-(1-phenylvinyl)acetamide which had the following spectral data: NMR ($CDCl_3$) δ 2.1 (3 H, s), 5.1 (1 H, br s), 5.8 (1 H, br s), 6.8–7.2 (1 H, br s), 7.0–7.2 (5 H, m). Irradiation of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one in the presence of methyl acrylate gives, as the only additional product, polymethyl acrylate.

Similar irradiation of 167 mg of **2** in the presence of 86.6 mg (1.28 mmol) of *trans*-piperylene for 2.5 h followed by the same workup showed no starting material to be present. The combined yield of acetophenone and **9** was 53%. The concentration of piperylene was sufficient to reduce the quantum yield to 10% of its original value for a reactive lifetime of 10^{-7} s, assuming $k_{dif} = 2.7 \times 10^{10}$ for hexane.

Photolysis of 2,4-Dimethyl-4-phenyl-Δ^2-oxazolin-5-one and Reduction of Products. A solution of 192 mg (1.015 mmol) of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (**2**) in 320 mL of dry hexane was irradiated (Hanovia 450-W) through a Vycor filter for a period of 2 h. Solvent removal under reduced pressure gave 196 mg of a yellow oil. The oil was dissolved in 50 mL of dry tetrahydrofuran, 110 mg (2.9 mmol) of sodium borohydride was added, and the solution was heated at reflux temperature for 18 h. The solution was allowed to cool and quenched with water, and then methylene chloride and more water were added. The organic layer was removed, washed once with 0.1 M HCl, dried over sodium sulfate, and filtered, and the solvent was removed to yield 165 mg of a yellow oil. The oil was chromatographed on a silica gel column (Mallinckrodt CC-7) using 2% methanol/methylene chloride elution. One band came off, which consisted a mixture of *N*-(1-phenylethyl)acetamide (identified by its NMR spectrum[30]) and polymeric material. NMR analysis of the mixture using dioxane as an internal standard indicated a yield of 41% of *N*-(1-phenylethyl)acetamide, which had the following NMR spectrum ($CDCl_3$): δ 1.5 (3 H, d), 1.9 (3 H, s), 4.95 (1 H, quintet), 6.5–7.0 (1 H, br s), 7.1 (5 H, m).

Synthesis of *N*-Trifluoroacetyl-α-phenylalanine. In a slightly modified literature[3] procedure, a solution of 11.1 g (67.3 mmol) of α-phenylalanine and 10 mL (68 mmol) of trifluoroacetic anhydride in 30 mL of trifluoroacetic acid was stirred at room temperature for 8 h under a nitrogen atmosphere. The trifluoroacetic acid and anhydride used were previouly dried by distillation from phosphorus pentoxide. Solvent was removed under reduced pressure to yield a brown solid which was purified by filtration through a short silica gel column (Mallinckrodt CC-7), eluting with methylene chloride. Solvent removal yielded 14.6 g (83%) of *N*-trifluoroacetyl-α-phenylalanine: mp 131.5–132.5 °C (lit.[3] 126–128 °C); NMR ($CDCl_3$) δ 2.0 (3 H, s), 6.5 (2 H, br s), 7.3 (5 H, m); IR (Nujol) 1710 (vs), 1550 cm^{-1} (s).

Preparation of 4-Methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (1). In a modified literature[3] procedure a solution of 14.6 g (60 mmol) of *N*-trifluoroacetyl-α-phenylalanine in 30 mL of thionyl chloride (purified by distillation from triethyl phosphite) was heated to 60 °C and maintained at that temperatue for 1 h. Excess thionyl chloride was removed at room temperature using aspirator vacuum, and the residue distilled at reduced pressure to yield 12.6 g (92%) of 2-trifluoromethyl-4-methyl-4-phenyl-Δ^2-oxazolin-5-one: bp 52 °C (0.5 mm) [lit.[3] 53–57 °C (0.6 mm)]; NMR ($CDCl_3$) δ 1.9 (3 H, s), 7.2–7.6 (5 H, m); IR (neat) 1850 (vs), 1680 (s), 1370 cm^{-1} (vs).

Thermolysis of 4-Methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (1). A solution of 143 mg (0.588 mmol) of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (**1**) in 5 mL of dry xylenes was heated at reflux temperature for a period of 20 h under a nitrogen atmosphere. Solvent removal under reduced pressure yielded a mixture containing, by NMR analysis, 6.7 mg (9.6%) of acetophenone, 21 mg (15%) of starting material, and 83 mg (66%) of *N*-(1-phenylvinyl)trifluoroacetamide, which had the following spectral data: NMR ($CDCl_3$) δ 5.3 (1 H, br s), 5.8 (1 H, br s), 6.8–7.6 (1 H, br s), 7.2 (5 H, s) (signals assigned to acetophenone and starting material were also present); mass spectrum (70 eV) *m/e* (rel intensity)[31] 216, (11.5), 215 (100), 146 (75), 120, 118 (13), 105, 104 (38), 103

(96), 91 (58), 77, 69 (52), 51; IR (neat) 3300 (s), 3050 (m), 1720 (vs), 1310 (vs), 1160 cm^{-1} (vs). On standing for several weeks, the enamide hydrolyzed completely to acetophenone.

Photolysis of 4-Methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (1). A solution of 205 mg (0.843 mmol) of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (1) and 2 mL of methyl acrylate in 230 mL of dry acetonitrile was irradiated for 8 h through a Vycor filter with a Hanovia 450-W medium pressure lamp. Solvent removal at reduced pressure followed by silica gel chromatography (Mallinckrodt Silicar CC-7) with methylene chloride elution gave 105 mg of a mixture containing, by NMR analysis, 52 and 34% of the *cis*- and *trans*-2-trifluoromethyl-4-carbomethoxy-5-methyl-5-phenyl-Δ^1-pyrrolines, respectively. The remainder of the material, 14%, was acetophenone. By repeated silica gel chromatography, eluting with methylene chloride, a pure sample of the cis pyrroline was obtained, having the following spectral data: NMR ($CDCl_3$) δ 1.85 (3 H, s), 3.1 (3 H, s), 2.9–3.7 (3 H, m), 7.0–7.2 (5 H, m); IR (neat) 1740 (vs), 1440 (m), 1200 (vs), 1150 cm^{-1} (vs); mass spectrum (70 eV) *m/e* (rel intensity) 285 (28), 270 (11), 266 (6), 254 (6), 226 (42), 199 (57), 198 (25), 104 (100), 103 (88), 91 (15), 77 (57).

Anal. Calcd for $C_{14}H_{14}F_3NO_2$: C, 58.95; H, 4.95; N, 4.91. Found: C, 58.92; H, 5.07; N, 4.98.

By the same method a small portion of the pure trans isomer was also obtained, having the following spectral data: NMR ($CDCl_3$) δ 1.48 (3 H, s), 2.8–3.6 (3 H, m), 3.7 (3 H, s), 7.0–7.2 (5 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 285 (50), 270 (18), 266 (11) 254 (16), 226 (76), 199 (100), 198 (46), 179 (21), 104 (92), 103 (82), 91 (17), 77 (58).

Photolysis of 177.5 mg of **1** in the presence of 152.5 mg (2.24 mmol) of *trans*-piperylene in 230 mL of acetonitrile for 6.25 h followed by the same workup gave the same products in essentially identical yields. The concentration of quencher was sufficient to reduce the quantum yield to 10% of its original value if the reactive lifetime were 10^{-7} s, assuming $k_{diff} = 1 \times 10^{10}$ for acetonitrile.

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Registry No.—**1**, 62263-54-1; **2**, 4855-22-5; **3**, 62263-55-2; **4**, 62263-56-3; **6**, 52762-80-8; **7**, 6284-14-6; **9**, 57957-24-1; **10**, 62288-65-7; α-phenylalanine, 565-07-1; *N*-trifluoroacetyl-α-phenylalanine, 62318-98-3; trifluoroacetic anhydride, 407-25-0; methyl acrylate, 96-33-3.

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Reaction of Organic Azides with Ethoxycarbonylnitrene

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The reaction of *n*-hexyl azide with ethoxycarbonylnitrene generated by α-elimination from *N*-(*p*-nitrobenzenesulfonoxy)urethane in nitromethane generates *n*-hexaldehyde ethoxycarbonylhydrazone, which arises from the initial formation and rearrangement of ethyl *n*-hexylazocarboxylate. Ethyl phenylazocarboxylate is produced and isolated from a similar reaction with phenyl azide. Studies employing various organic azides, solvents, reaction conditions, and additives indicate *n*-hexyl azide to be reactive toward singlet ethoxycarbonylnitrene with a major competing reaction being the crossover of ethoxycarbonylnitrene from its singlet to its triplet state.

As part of a research program designed to explore the interaction of organic azides and reactive intermediates,[1-3] we have examined the reactions of organic azides with ethoxycarbonylnitrene. Azide–nitrene reactions have been observed in studies of the photolysis of alkyl[4] and aryl[5] azides, and the thermolysis of carbamoyl,[6] aryl,[7-11] and sulfonyl[12] azides. In each of these studies the focus of interest was the chemistry of the azide or the resulting nitrene rather than the reaction

of an azide with a nitrene intermediate. The specific purpose of this study, a preliminary report of which has appeared,[3] is the examination of the interaction of organic azides and ethoxycarbonylnitrene.

In numerous studies of azide decompositions, the formation of products, particularly azo compounds, can be explained either by the interaction of an azide with a nitrene intermediate or with some excited-state azide.[4,5,10,13] We have circumvented this ambiguity by using *N*-(*p*-nitrobenzenesulfonoxy)urethane[14] (NBSU) as a source of ethoxycarbonylnitrene (**4**).

$$\underset{\mathbf{1}}{ArSO_2ONHCO_2Et} + Et_3N \rightleftharpoons \underset{\mathbf{2}}{ArSO_2\bar{O}NCO_2Et} + Et_3NH^+ \quad (1)$$

$$\downarrow$$

$$\underset{\mathbf{3}}{(Et_3NH)^+(ArSO_3)^-} + \underset{\mathbf{4}}{NCO_2Et}$$

Results and Discussion

When equimolar amounts of *n*-hexyl azide (**5**) and NBSU (**1**) in nitromethane are treated with excess triethylamine at room temperature, products are generated as shown in Scheme I.

Scheme I

$$\underset{\mathbf{5}}{n\text{-}C_6H_{13}N_3} + \underset{\mathbf{1}}{ArSO_2ONHCO_2Et} \xrightarrow{Et_3N}$$

$$\underset{\mathbf{6}}{n\text{-}C_5H_{11}CH{=}NNHCO_2Et} + \underset{\mathbf{3}}{(Et_3NH)^+(ArSO_3)^-}$$

11% 95%

$$+ \underset{\mathbf{7}}{EtO_2CNH_2} + \underset{\mathbf{8}}{EtO_2CNHNHCO_2Et}$$

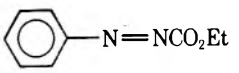
14% 3%

The major azide-derived product is *n*-hexaldehyde ethoxycarbonylhydrazone (**6**); 20% of azide **5** is decomposed, generating hydrazone in 55% yield, based on decomposed azide.[15] As discussed previously,[3] the azide is attacked by ethoxycarbonylnitrene rather than its anionic precursor **2** as shown by studies with added cyclohexene. The most reasonable explanation for the formation of the hydrazone is that the azide–nitrene reaction initially generates ethyl *n*-hexylazocarboxylate (**9**) which rearranges to the isolated hydrazone **6**.

$$\underset{\mathbf{9}}{n\text{-}C_6H_{13}N{=}NCO_2Et} \longrightarrow \underset{\mathbf{6}}{n\text{-}C_5H_{11}CH{=}NNHCO_2Et}$$

Ethyl *n*-hexylazocarboxylate (**9**), prepared by oxidation of *N*-*n*-hexyl-*N'*-ethoxycarbonylhydrazine, does indeed isomerize to *n*-hexaldehyde ethoxycarbonylhydrazone (**6**) at room temperature in ethanol (half-life 3 days), within 5 min in chloroform in the presence of a catalytic amount of triethylamine, or within 1 h in refluxing nitromethane. Unsuccessful attempts were made to isolate **9** from reactions run at 0 °C or to detect this proposed intermediate by monitoring the reaction mixture at 380 nm, where **9** exhibits an ultraviolet maximum.

Azo compounds bearing an α hydrogen to the azo group readily isomerize to the corresponding hydrazone.[16] Generation of ethoxycarbonylnitrene in the presence of an azide not bearing hydrogen α to the azido group should produce an isolable azo compound, thus lending support for the intermediacy of **9** from azide **5**. Indeed, this is the case with phenyl azide. Under conditions similar to standard runs with **5**, phenyl azide is decomposed (18%) and generates ethyl phenylazocarboxylate (**10**), the azo compound expected from the reaction of phenyl azide with ethoxycarbonylnitrene.



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Initially a search was made for a favorable solvent for the reaction of azide **5** and nitrene **4** with the results shown in Table I. A number of solvents (hexafluorobenzene, fluorotrichloromethane, 1,2-difluoro-1,1,2,2-tetrachloroethane, 1,1,2-trifluoro-1,2,2-trichloroethane) were not used because of the insolubility of NBSU. Other common solvents (alcohols, acetonitrile, pyridine, benzene) were not utilized because of their known reactivity with ethoxycarbonylnitrene. The lack of azide decomposition in tetramethylene sulfone and dimethoxyethane may well be accounted for by the reported reactivity of nitrenes with sulfoxides[17] and ethers,[18] respectively.

The reactivity of other organic azides was examined by determining the percent azide decomposition under the same reaction conditions as for **5**. The results, recorded in Table II, show the general trend one might expect when an azide is being attacked by electrophilic ethoxycarbonylnitrene: the nucleophilic alkyl azides are decomposed more efficiently than the electrophilic acyl and sulfonyl azides. Benzoyl azide and trimethylsilyl azide are unstable under the basic standard reaction conditions, an observation in accord with the known reactivity of acyl azides with amines[19] and silyl azides toward various nucleophiles.[20]

The 95% yield of triethylammonium *p*-nitrobenzenesulfonate (**3**) suggests that NBSU is quantitatively converted to ethoxycarbonylnitrene.[21] However, the maximum observed azide decomposition, with wide variations of solvent and azide structures, is only 22%. These results suggest that there are reactions of ethoxycarbonylnitrene in competition with the azide–nitrene reaction. Nitrenes are known to exist in singlet and triplet spin states which differ not only in electronic configurations but also in their reactivities.[24] Thus, it is conceivable that organic azides are more reactive toward one spin state of ethoxycarbonylnitrene than another. With these possibilities in mind, we initiated studies to determine the effect of reaction conditions on the efficiency of the azide–nitrene reaction, investigate possible side reactions, and determine the spin state of ethoxycarbonylnitrene that is reactive toward *n*-hexyl azide.

The first step in the production of ethoxycarbonylnitrene from NBSU is the reversible generation of the anionic precursor **3** of ethoxycarbonylnitrene (eq 1). A large excess of triethylamine should shift this equilibrium to the right,[25] minimizing side reactions involving NBSU, such as insertion of ethoxycarbonylnitrene into the N–H bond.[24] The results in Table III show that neither excess triethylamine (expt 6) and the use of triethylamine as solvent (Table I) nor the inverse addition of NBSU (expt 8, 9) had any appreciable effect upon percent azide decomposition. Another possibility, shown to occur in a similar system,[17] is attack by the nitrene on the anionic precursor **2**. Were this side reaction occurring to an appreciable extent, inverse addition of NBSU should increase azide decomposition, a result not observed (expt 8, 9).

Another side reaction to be considered is insertion of ethoxycarbonylnitrene into the carbon–hydrogen bonds of the *n*-hexyl azide. The extent of this reaction was determined by

Table I. Reaction of *n*-Hexyl Azide and Ethoxycarbonylnitrene in Various Solvents at 35 °C[a]

Solvent	% dec of n-$C_6H_{13}N_3$[b]	Solvent	% dec of n-$C_6H_{13}N_3$[b]
Dimethoxyethane	0	Dichloromethane	11
Tetramethylenesulfone	0	Nitrobenzene	13
Dibromomethane	3	*N,N*-Dimethylacetamide	14
Acetone	8	Nitromethane	20[c]
N,N-Dimethylformamide	9	Triethylamine	22[c,d]

[a] Initial concentration of *n*-hexyl azide and NBSU, 0.35 M; a 10% excess of Et_3N was used. [b] Experimental error ±2%. [c] Average value for several runs. [d] Inverse addition of NBSU.

Table II. Reaction of Various Azides with Ethoxycarbonylnitrene in Nitromethane at 35 °C[a]

Registry no.	Azide	% dec of azide[b]
	n-Hexyl azide	20
2101-87-3	*p*-Methoxyphenyl azide	18
622-37-7	Phenyl azide	18
24886-73-5	1-Azidoadamantane	16
14309-25-2	Trityl azide	15
3296-05-7	*p*-Chlorophenyl azide	11
817-87-8	Ethyl azidoformate	6
938-10-3	Benzenesulfonyl azide	4[c]
98-59-9	Tosyl azide	3[c]
582-61-6	Benzoyl azide	*d*
4648-54-8	Trimethylsilyl azide	*d*

[a] Initial concentration of azides and NBSU, 0.35 M; a 10% excess of Et_3N was used. [b] Experimental error ±2%. [c] CH_2Cl_2 used as solvent owing to instability of azide in nitromethane/triethylamine mixtures. [d] Unstable to reaction conditions.

Table III. Reaction of *n*-Hexyl Azide with Ethoxycarbonylnitrene in Nitromethane at 35 °C under Varied Reaction Conditions

Expt	Initial concn, M: n-$C_6H_{13}N_3$	NBSU	Et_3N	% dec of azide[a]
1	0.17	0.17	0.20	14
2	0.35	0.35	0.38	20[b]
3	0.70	0.70	0.75	25
4	0.70	0.35	0.38	12
5	0.35	0.70	0.75	28
6	0.35	0.35	1.40	19
7	0.35	0.35	0.38	21[c]
8	0.35	0.35	0.38	18[d]
9	0.35	0.70	0.75	28[d]
10	0.63	0.63	0.70	19[e]
11	0.63	0.63	0.70	22[d,f]

[a] Based on initial azide concentration; experimental error ±2.0%. [b] Standard reaction; average of numerous runs. [c] Simultaneous addition of NBSU and base. [d] Inverse addition of NBSU. [e] Average of two runs. [f] Azide decomposition determined by VPC analysis.

comparing azide decomposition as measured by infrared analysis with *n*-hexyl azide decomposition as measured by VPC. Insertion of the nitrene into a carbon–hydrogen bond on the *n*-hexyl group would result in a product, the azido absorption of which would be essentially indistinguishable by infrared analysis from the *n*-hexyl azide absorption. The VPC analysis is, however, quite specific for *n*-hexyl azide. The results from expt 10 and 11 of Table III indicate that insertion into carbon–hydrogen bonds of *n*-hexyl azide is not a major side reaction. An additional insertion process to be considered is the intramolecular reaction of the nitrene with the methyl carbon–hydrogen bond, producing 2-oxazolidone. Using VPC techniques with which a 2% yield could be detected, we found no 2-oxazolidone, in accordance with Lwowski's results.[26] Ethoxycarbonylnitrene may also dimerize to generate diethyl azodicarboxylate. This product was not produced in our system in detectable amounts (VPC analysis), an observation not surprising in light of the reported reactivity of azo compounds with nitrenes[27] and of diethyl azodicarboxylate toward triethylamine.[11]

One possible reaction of ethoxycarbonylnitrene is with the solvent, nitromethane. Conceivably, the nitrene could insert into the C–H bond or react with the nitro group. However, the observation of a greater percent azide decomposition in nitromethane (20%) than in dichloromethane (11%), a solvent known to be unreactive toward ethoxycarbonylnitrene,[28] suggests this not to be the source of any major side reaction. This was confirmed by VPC analysis of product mixtures from the generation of ethoxycarbonylnitrene in nitromethane in the presence and absence of *n*-hexyl azide, revealing one minor solvent-derived product, the structure of which was not determined.[29]

Experiments 1–5 of Table III have a direct bearing on the question of the spin state of ethoxycarbonylnitrene reacting with *n*-hexyl azide. These experiments show the effect of *n*-hexyl azide and NBSU concentrations on percent azide decomposition. Simultaneously increasing the azide and NBSU concentrations while maintaining a constant azide–NBSU ratio (expt 1, 2, 3) enhances the efficiency (amount of azide decomposed/mole of nitrene generated) of the azide–nitrene reaction, as does an increase in the azide–NBSU ratio (expt 2, 4, 5). Similar concentration effects upon absolute yields of products generated from nitrenes in hydrocarbon solvents have been observed by Lwowski[30] and Belloli.[31] Treatment of NBSU with triethylamine generates ethoxycarbonylnitrene exclusively in the singlet state. However, conversion to the triplet ground state competes quite favorably with intermolecular reactions, especially at low substrate concentrations.[28,32] In the reaction of ethoxycarbonylnitrene with *trans*-1,2-dimethylcyclohexane, a substrate–nitrene source ratio of 10:1 was not a sufficiently great excess of substrate to provide maximum yields of insertion products. It was concluded that the decomposition of the singlet nitrene was the side reaction responsible for reducing the insertion yields.[31] Such a possibility also exists within our system as most reactions were run with equimolar amounts of azide and NBSU, the nitrene source.

In our study of solvent effects upon azide decomposition, a noteworthy decrease in azide decomposition from 11% to 3% was observed in changing the solvent from dichloromethane to dibromomethane (Table I). The solvents differ very little in their chemical reactivities; thus, such a difference may be

Table IV. Effects of Additives on the Reaction of *n*-Hexyl Azide with Ethoxycarbonylnitrene in Nitromethane at 35 °C[a]

Expt	Additive	Concn, mol %	% dec of azide[b]	Absolute yield, % 3	7
1	None	0	20	95	14
2	CH_2Br_2	5	11		27
3	CH_2Br_2	10	7		27
4	CH_2Br_2	25	5		38
5	CH_2Br_2	50	0		40
6	CH_2Br_2	95	0		44
7	CH_2Br_2	100	3	88	14
8	CH_2Cl_2	100	11	95	9
9	$Ph(CH_3)C{=}CH_2$	5	13		11
10	$Ph(CH_3)C{=}CH_2$	10	13		11
11	$Cl_2C{=}CCl_2$	10	17		14
12	$Cl_2C{=}CCl_2$	20	18		14
13	N_2	*c*	18		
14	O_2	*d*	18		
15	None	*e*	15		
16	None	*f*	16		

[a] Initial concentration of *n*-hexyl azide and NBSU, 0.35 M; a 10% excess of Et_3N was used. [b] Based on initial azide concentration; experimental error ±2%. [c] Reaction mixture bubbled with N_2. [d] Reaction mixture bubbled with O_2. [e] Degassed, vacuum system apparatus. [f] Not degassed, using vacuum system apparatus.

explained either by assuming that dibromomethane stabilizes ethoxycarbonylnitrene more than dichloromethane and hence alters its reactivity, or that dibromomethane promotes singlet–triplet crossover of ethoxycarbonylnitrene and decreases the amount of singlet nitrene reacting with the azide. The reactivity of singlet nitrenes is solvent dependent. Previous reports have attributed solvent effects to either a stabilization of the singlet nitrene via formation of a solvent–nitrene complex (dichloromethane,[30,33] hexafluorobenzene[31,34]) or promotion of the singlet–triplet crossover rate by collisional deactivation of ethoxycarbonylnitrene (dibromomethane[35]). Anastassiou observed a decrease in the stereospecificity of cyanonitrene in dibromomethane relative to dichloromethane as a result of a "thermochemical heavy atom effect".[36] In the reaction of thermally generated ethoxycarbonylnitrene with 3-methylhexane, an increase in the production of triplet-derived ethyl carbamate and a decrease in singlet-derived insertion products were observed in going from dichloromethane to dibromomethane.[37] Belloli, in examining the reaction of thermally generated ethoxycarbonylnitrene with cyclohexene, also noted a reduction in singlet character upon dilution of cyclohexene with dibromomethane.[35]

In order to examine the multiplicity of the nitrene interacting with *n*-hexyl azide, a study was done on the effect of various additives upon azide decomposition. Also monitored was the production of ethyl carbamate (**7**), a product known to arise from triplet ethoxycarbonylnitrene.[26] The results are displayed in Table IV.

The obvious effect of diluting the nitromethane with dibromomethane is to decrease the observed azide decomposition while increasing the formation of the triplet-derived ethyl carbamate (expt 1–7), produced according to eq 2.

$$\mathrm{EtOCO\dot{N}\cdot} \xrightarrow{\mathrm{RH}} \mathrm{EtOCONH} \xrightarrow{\mathrm{R'H}} \underset{\mathbf{7}}{\mathrm{EtOCONH_2}} \qquad (2)$$

Thus, the effect of the dibromomethane is to promote singlet–triplet crossover of ethoxycarbonylnitrene. Addition of α-methylstyrene, known to be more reactive toward triplet than singlet ethoxycarbonylnitrene,[32] decreases azide decomposition and carbamate formation (expt 9, 10). The percent azide decomposition is not affected by the presence of oxygen (expt 13–16). However, it has been reported that oxygen reacts with triplet ferrocenyl[38] and aryl nitrenes[5,39] and effects triplet ethoxycarbonylnitrene reactions.[26,32,35]

These results are best explained by assuming *n*-hexyl azide to be reactive toward singlet ethoxycarbonylnitrene. No definitive statement concerning the reactivity of *n*-hexyl azide with triplet ethoxycarbonylnitrene can be made beyond the observation that the azide is much more reactive toward singlet than triplet ethoxycarbonylnitrene. The consistently small amount of azide decomposition observed under various reaction conditions suggests that the crossover of singlet to triplet ethoxycarbonylnitrene competes quite favorably with the reaction of the singlet ethoxycarbonylnitrene with *n*-hexyl azide. The use of a specific triplet nitrene trap, shown to be absolutely unreactive toward singlet nitrene, would shed light on this question; no such trap is presently known. Tetrachloroethylene has been used as such a trap for thermally generated ethoxycarbonylnitrene.[34] However, when up to 20 mol % tetrachloroethylene was added to nitromethane, we observed no effect upon either azide decomposition or ethyl carbamate (**7**) production (expt 1, 11, 12). This is in contrast to the effect observed by Breslow in the thermal generation of ethoxycarbonylnitrene from ethyl azidoformate.[34]

These results contrast with work done with alkyl[4] and aryl[5] nitrenes photolytically generated from alkyl and aryl azides. In both cases, the triplet nitrene was shown to react with the azide. Such a difference may be due to the different modes of formation of ethoxycarbonylnitrene and the alkyl and aryl nitrenes or to a larger difference in energy between the singlet and triplet alkyl and aryl[5] nitrenes than between singlet and triplet ethoxycarbonylnitrenes.[40]

Experimental Section

Infrared spectra and quantitative analyses were determined using a Beckman Acculab 3 or IR-8 spectrophotometer; ultraviolet spectra were recorded using a Coleman-Hitachi EPS-3T. Melting points were determined on a Mel-Temp apparatus; melting and boiling points are uncorrected. VPC analyses were determined on a Varian Aerograph Autoprep 700 with helium as carrier gas. Microanalyses were performed by Chemalytics, Tempe, Ariz.

Materials. The azides[41] and *N*-(*p*-nitrobenzenesulfonoxy)urethane (**1**)[14] were prepared by previously described methods. Triethylamine was dried over sodium hydroxide and fractionally distilled from α-naphthyl isocyanate. Reagent grade nitromethane was dried over Drierite before being distilled at 45 °C (97 mm).

***n*-Hexaldehyde Ethoxycarbonylhydrazone (6).** Following the procedure outlined by Rabjohn and Barnstorff,[42] to *n*-hexaldehyde (30 g, 0.30 mol) dissolved in ethanol (105 mL) in a 250-mL round-bottomed flask sufficient water was added to cause turbidity and then ethanol was added to clear the solution. Glacial acetic acid (10 mL) and ethyl carbazate (30 g, 0.29 mol) were added and the mixture was refluxed with stirring for 1 h before removal of the solvent. The residue was recrystallized from 40% ethanol, producing **6** (30 g, 54%): mp 65–66 °C; IR ($CHCl_3$) 3375 (s), 1737 (s), 1710 cm^{-1} (s). Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.06; H, 9.68; N, 15.05. Found: C, 58.42; H, 10.18; N, 15.05.

***N*-*n*-Hexyl-*N'*-ethoxycarbonylhydrazine.**[43] A mixture of **6** (60 g, 0.32 mol), platinum oxide (1.14 g), and glacial acetic acid (150 mL) was added to a Parr pressure reaction bomb, which was sealed and charged with hydrogen at a pressure of 50 psi. The reaction mixture was stirred for 3 h with maintenance of the hydrogen pressure at 50 psi, after which the mixture was filtered. The filtrate was washed with water (140 mL); the aqueous layer was extracted with three 200-mL portions of ethyl ether; the combined organic layers were washed with 10% $NaHCO_3$ until basic and twice with water, dried (Na_2SO_4), filtered, and evaporated on a rotary evaporator. The resulting light yellow oil was fractionally distilled at 98 °C (0.8 mm), producing *N*-*n*-hexyl-*N'*-ethoxycarbonylhydrazine (14.3 g, 26%): IR (CCl_4) 3340 (s), 1718 cm^{-1} (s). Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.45; H, 10.64; N, 14.89. Found: C, 57.61; H, 10.88; N, 14.92.

Ethyl *n*-Hexylazocarboxylate (9).[43] *N*-*n*-Hexyl-*N'*-ethoxycarbonylhydrazine (8.9 g, 0.05 mol) and 45 mL of a saturated sodium chloride solution were added to a three-necked 500-mL round-bottomed flask equipped with a stirrer, an additional funnel, and a drying tube, and cooled by a dry ice–isopropyl alcohol bath to −15 °C. Bromine (7.9 g, 0.05 mol) in 200 mL of water was added over a 4-h period. After stirring for 1.5 h, the mixture was extracted with two 100-mL portions of cold ethyl ether; the combined ether layers were washed with 10% $NaHCO_3$ and water and dried ($MgSO_4$). Removal of solvent produced 3 mL of **9** as a bright red oil: IR ($CHCl_3$) 1755 cm^{-1} (s); UV (EtOH) 380 nm. IR analysis of the oil showed no peaks characteristic of either *N*-*n*-hexyl-*N'*-ethoxycarbonylhydrazine or **6**.

Ethyl Phenylazocarboxylate (10). To a 100-mL round-bottomed flask containing 60 mL of CH_2Cl_2, 4 mL of pyridine, and 3.6 g (20 mmol) of *N*-phenyl-*N'*-ethoxycarbonylhydrazine[44] was added 3.5 g (20 mmol) of NBS at −20 °C over a 25-min period. After stirring at room temperature for 30 min, the solution was washed twice with dilute sodium thiosulfate, water, 2 N HCl, 10% sodium bicarbonate, and water. After drying and removal of solvent, the resulting red mixture was distilled, giving 1.0 g (31%) of **10**, a red oil: bp 90–92 °C (0.9–1.1 mm); IR ($CHCl_3$) 1740 cm^{-1} (s); UV (dioxane) 287, 424 nm. Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.61; N, 15.73; Found: C, 58.42; H, 5.72; N, 15.96.

Reaction of *n*-Hexyl Azide (5) with Ethoxycarbonylnitrene Generated from NBSU (1). To a three-necked flask equipped with a $CaCl_2$ drying tube and charged with *n*-hexyl azide (1.27 g, 0.01 mol), NBSU (2.90 g, 0.01 mol), and 25 mL of nitromethane, was added triethylamine (1.21 g, 0.012 mol) over a period of 45 min. The reaction mixture was then stirred for 3 h in the dark.

For quantitative infrared analyses of azide decomposition, the azido group absorbance at 2095 cm^{-1} was determined using matched sodium chloride cells. Beer's law plots of the azido group absorbance were found to be linear in the concentration range employed. For VPC determination of *n*-hexyl azide, bromobenzene was used as an internal standard under the following conditions: 5 ft × 0.125 in., 10% OV-1 on 60/80 Chromosorb W, 68 °C.

For experiments involving the other organic azides, the reaction was run on a scale such that the total volume of the reaction mixture was 8 mL. Upon completion of the reaction, the reaction mixture was transferred into a 10-mL volumetric flask and the 15-mL round-bottomed reaction flask rinsed with small amounts of nitromethane until the volumetric was filled to the mark. Infrared analyses for azide decomposition on these solutions agreed well with those of larger runs. For the reactions run under a nitrogen atmosphere or when saturated with oxygen, the solvent was saturated with the gas by a bubbling device and a steady stream of the gas was utilized over the 3-h reaction time. In the degassing experiments, a simple device was fabricated by which separate mixtures of **5**, **1**, and nitromethane (solution 1) and triethylamine and nitromethane (solution 2) were degassed through three freeze–thaw cycles before solution 2 was distilled into the compartment containing solution 1. The simultaneous addition of triethylamine and **1** was effected by using two addition funnels charged with solutions of the amine and of **1** and adding these dropwise to azide **5** dissolved in nitromethane. The inverse addition of **1** was effected by the addition of the solid reagent **1** to a mixture of azide **5**, amine, and solvent over a 40-min period. In experiments involving additives, the additive was present in the reaction mixture prior to the addition of the triethylamine.

Isolation and Quantitative Analyses of Products from the Reaction of *n*-Hexyl Azide (5) with Ethoxycarbonylnitrene Generated from NBSU (1). Upon completion of the reaction, most of the nitromethane was removed under vacuum and ether was added to precipitate triethylammonium *p*-nitrobenzenesulfonate (**3**), which was quantified gravimetrically. For isolation of **6**, **7**, and **8**, the reaction mixture was distilled at 33 °C (55 mm), yielding a mixture of **5** and nitromethane. To the residue was added 25 mL of water and 20 mL of pentane. The layers were separated, the aqueous layer washed with pentane, and the combined organic layers dried prior to distillation at 34 °C (17 mm), yielding more azide **5**. Pure *n*-hexaldehyde ethoxycarbonylhydrazone (**6**) was isolated from the residue by preparative VPC (5 ft × 0.25 in., 10% SF-96 on 60/80 Chromosorb W, 173 °C). Similar conditions (6 ft × 0.375 in., 20% SF-96 on 60/80 Chromosorb A, 150 °C) were employed for isolation of ethyl carbamate (**7**) and *N*,*N'*-diethoxycarbonylhydrazine (**8**).

For quantitative VPC analyses of products **6**, **7**, and **8**, the reaction was run as previously described and the mixture diluted to the mark in a volumetric flask. Relative peak areas were determined by weighing of peaks cut from photostatic copies. Owing to the composition of the product mixtures, internal standards could not be used. To determine absolute yields, the peaks from aliquots of the reaction mixture were compared with those of standard solutions. The error was taken to be twice the standard deviation found. The following conditions were used: for **6**, 6 ft × 0.125 in., 10% SF-96 on 60/80 Chromosorb W, 145 °C; for **7**, 5 ft × 0.25 in., 20% XF-1150 on 45/60 Chromosorb W, 132 °C; for **8**, same as for **7** except 190 °C.

Rearrangement of Ethyl *n*-Hexylazocarboxylate (9) to *n*-Hexaldehyde Ethoxycarbonylhydrazone (6). **9** (2 mL) was added to 5 mL of chloroform and 0.5 mL of triethylamine. The disappearance of the azo compound **9**, as indicated by infrared analysis, was complete within 30 min. The solution was concentrated under vacuum and the residue recrystallized three times from 40% ethanol. The solid melted at 62–63 °C; a mixture with pure **6** also melted at 62–63 °C. A dichloromethane solution of azide **5** and **9** was stable at room temperature for 24 h. Upon addition of an equimolar amount of triethylammonium *p*-nitrobenzenesulfonate and stirring for 12 h, infrared analysis indicated almost quantitative rearrangement of **9** to **6**. This same rearrangement is effected by refluxing a nitromethane solution of **9** for 1 h.

Reaction of Phenyl Azide with Ethoxycarbonylnitrene Generated from NBSU (1). Ethoxycarbonylnitrene was generated from **1** in methylene chloride in the presence of phenyl azide in a manner similar to that described for **5**. Addition of water, washes with 2 N HCl, 10% $NaHCO_3$, and water, drying ($MgSO_4$), and removal of solvent produced an oily residue analyzed by preparative TLC (6 × 6 in., 2 mm silica gel). Development twice with benzene produced four distinct bands, the third one of which yielded a compound having the same R_f value on silica gel and identical infrared and ultraviolet spectra as ethyl phenylazocarboxylate (**10**): IR (CH_2Cl_2) 1740 cm^{-1} (s); UV (dioxane) 287 nm.

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Registry No.—**1**, 2955-74-0; **3**, 4113-69-3; **4**, 2655-26-7; **5**, 6926-45-0; **6**, 50785-98-3; **7**, 51-79-6; **8**, 4114-28-7; **9**, 50785-99-4; **10**, 943-76-0; *n*-hexaldehyde, 66-25-1; ethyl carbazate, 4114-31-2; *N*-*n*-hexyl-*N'*-ethoxycarbonylhydrazine, 50786-00-0; *N*-phenyl-*N'*-ethoxycarbonylhydrazine, 6233-02-9.

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Azaindolizines. 4. Synthesis and Formylation of 8-Azaindolizines

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The 8-azaindolizines (**1–10**) were synthesized by a Chichibabin reaction between 2-methylpyrimidines and an α-halo ketone. 2-Methylpyrimidine itself gave in low yield 2-carbethoxy- (**2**), 2-methyl- (**3**), 2,3-dimethyl- (**4**), and 2-phenyl-8-azaindolizine (**5**) when reacted with ethyl bromopyruvate, bromoacetone, 3-bromobutanone, and phenacyl bromide; hydrolysis and decarboxylation of **2** gave the parent system (**1**). 2,4-Dimethylpyrimidine similarly gave **6** and **7** with bromoacetone and 3-bromobutanone. 2-Methyl-4-methoxypyrimidine when reacted with phenacyl bromide and bromoacetone gave the expected 7-methoxy-8-azaindolizine structures **8** and **9** along with the 8-methyl-8-azaindolizinones **22, 23,** and **32.** 2-Methyl-4-hydroxypyrimidine with bromoacetone gave **25** and **34.** The structures of the 8-azaindolizines isolated were deduced from their ^{1}H NMR spectra and the ^{1}H NMR spectra of their formyl derivatives. Formylation has been shown to occur preferentially at C-3, and 1,3-dipolar addition of dimethyl acetylenedicarboxylate with **6** and **23** occurs to give the corresponding 5-azacycl[3.2.2]azines **37** and **38.**

Substituted 8-azaindolizines have been prepared chiefly by reaction of a 1,3-dicarbonyl compound with a 2-aminopyrrole stabilized by electron-withdrawing groups.[1] An alternative direct synthetic route to 8-azaindolizines would be to employ the Chichibabin reaction[2] between a 2-methylpyrimidine and an α-halo ketone. The simplest and first reported 8-azaindolizine, 5,7-dimethyl-2-phenyl-8-azaindolizine (**11**), was claimed[3] to be obtained by this route using 2,4,6-trimethylpyrimidine and phenacyl bromide; recently we showed[4] that the product of this reaction is the isomeric 5,7-dimethyl-2-phenyl-6-azaindolizine (**14**). In this paper we report the synthesis of the parent 8-azaindolizine (**1**) and several simple derivatives by reaction of a 2-methylpyrimidine with a number of α-halo ketones. The structures of the 8-azaindolizines isolated were determined from their ^{1}H NMR spectra, shown in Table I, and the ^{1}H NMR spectra of their formylated derivatives. The assignments of the protons in these structures were made on the basis of their proximity to nitrogen, by the assistance of double irradiation, by deuterium exchange,[5,6] and by a comparative examination of related spectra.

Reaction between 2-methylpyrimidine and ethyl bromopyruvate gave a product whose infrared and ^{1}H NMR spectra indicated it to be 2-carbethoxy-8-azaindolizine (**2**). The ^{1}H NMR spectrum showed a 2 H methylene quartet and a 3 H methyl triplet at δ 4.38 and 1.37 assigned to the carbethoxy ethyl group, two lower field 1 H singlets at δ 7.03 and 7.71 assigned to H-1 and H-3, respectively, a 1 H complex signal approximating to a triplet at δ 6.58 assigned to H-6, and a 2 H doublet at δ 8.14 assigned to H-5 and H-7. Alkaline hydrolysis of the ester (**2**) followed by neutralization and decarboxylation gave the parent 8-azaindolizine (**1**) as a yellow oil, stable in vacuo but which decomposed rapidly on exposure to air; the ^{1}H NMR spectrum of **1** is shown in Figure 1. The 1 H apparent triplet at δ 6.98 is assigned to H-2 since it is coupled with the adjacent H-1 and H-3 protons. The H-1 and H-3 signals are weakly coupled to each other and occurred as differentially exchangeable[7] multiplets at δ 6.64 and 7.19, respectively. The 1 H apparent quartet centered at δ 6.48 is assigned to H-6, its multiplicity arising mainly from coupling with H-5 and H-7. The two lower field overlapping multiplets at δ 8.00–8.24 were assigned to H-5 and H-7. Irradiation at δ 6.48 simplified the multiplet at δ 8.00–8.24 to two broad singlets and to some extent sharpened the H-3 signal at δ 7.19. Support for the above assignments was provided from the ^{1}H NMR spectrum of its formyl derivative (**17**). The spectrum of **17**, when compared to the spectrum of **1**, showed the absence of the H-3 multiplet, the emergence of a 1 H formyl singlet at δ 9.73, and a marked downfield shift (ca. 170 Hz) of the position of one of the lower field signals; such a shift can only be accounted for by the anisotropic deshielding effect of a 3-formyl group via its peri orientation to H-5. 2-Methylpyrimidine reacted with bromoacetone, bromobutanone, and phenacyl bromide to give 2-methyl- (**3**), 2,3-dimethyl- (**4**), and 2-phenyl-8-azaindolizine (**5**).

Reaction between 2,4-dimethylpyrimidine and phenacyl

Table I. Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of the 8-Azaindolizines (1–10) in $CDCl_3$[a]

Structure	R_1	R_2	R_3	H-1	H-5	H-6
1	6.98 dd* J = 3.5, 3.0 Hz	7.19 dd* J = 3.0, 1.5 Hz	8.00–8.24 m	6.64 dd* J = 3.5, 1.5 Hz	8.00–8.24 m	6.40–6.56 m
2	1.37 t, 4.38 q J = 7.0 Hz (COOEt)	7.71 d* J = 1.5 Hz	8.14 d* J = 5.5 Hz	7.03 d* J = 1.5 Hz	8.14 d* J = 5.5 Hz	6.58 dd* J = 5.5, 5.5 Hz
3	2.34 (CH_3)	6.99*	7.91–8.15 m	6.44*	7.91–8.15 m	6.33–6.53 m
4	2.32 (CH_3)	2.36 (CH_3)	7.80–8.04 m	6.47	7.84–8.04 m	6.42–6.60 m
5	7.17–7.77 m (Ph)	7.46*	8.00–8.23 m	6.91*	8.00–8.23 m	6.44–6.58 m
6	2.30 (CH_3)	6.87*	2.43 (CH_3)	6.27*	7.90 d J = 7.0 Hz	6.27 d J = 7.0 Hz
7	2.28 (2.31) (CH_3)	2.31 (2.28) (CH_3)	2.45 (CH_3)	6.27	7.76 d J = 7.5 Hz	6.34 d J = 7.5 Hz
8	7.10–7.70 m (Ph)	7.20*	3.94 (OCH_3)	6.54*	7.90 d J = 7.5 Hz	6.08 d J = 7.5 Hz
9	2.26 (CH_3)	6.75*	3.92 (OCH_3)	6.07*	7.85 d J = 7.5 Hz	6.02 d J = 7.5 Hz
10	1.36 t, 4.34 q J = 7.0 Hz (COOEt)	7.49*	3.94 (OCH_3)	6.61*	7.92 d J = 7.5 Hz	6.18 d J = 7.5 Hz

[a] Unless otherwise stated values given refer to singlet absorption: d = doublet, dd = double doublet, t = triplet, q = quartet, and m = complex multiplet absorption. Coupling constants (hertz) are approximate and measured directly from spectra. Signals marked by an asterisk are broadened and/or further split.

bromide proved unsuccessful.[3] Reaction with bromoacetone and bromobutanone, however, gave in low yields the 7-methyl-8-azaindolizines **6** and **7**, respectively. The isolation of the 7-methyl-8-azaindolizines **6** and **7** rather than the isomeric 5-methyl-8-azaindolizines **12** and **13** or the 6-azaindolizines **15** and **16** would be expected by attack of the halo ketone at the more accessible nitrogen of 2,4-dimethylpyrimidine, followed by cyclization via the 2-methyl group. That the products of reaction were the 7-methyl-8-azaindolizines **6** and **7** was shown by a comparative examination of their ^{1}H NMR spectra with the ^{1}H NMR spectra of their formylation products **18** and **21**. Thus the spectrum of **6** showed two high-field 3 H singlets at δ 2.30 and 2.43 assigned to the 2- and 7-methyl protons, two deuterium exchangeable[7] lower field aromatic singlets at δ 6.27 and 6.87 assigned to H-1 and H-3, and a pair of spin coupled doublets at δ 7.90 and 6.27 assigned to H-5 and H-6, respectively. Vilsmeier formylation of **6** gave the 3-formyl-2,7-dimethyl-8-azaindolizine (**18**), which showed, relative to the spectrum of **6**, the absence of the lower field H-3 singlet and a large deshielding (179 Hz) of the lower field H-5 doublet due to the peri orientated 3-formyl group whose signal occurred at δ 9.79. Reduction of **18** using lithium aluminum hydride and aluminum chloride gave 2,3,7-trimethyl-8-azaindolizine (**7**) whose ^{1}H NMR spectrum was identical with the spectrum of the product obtained from the reaction between 3-bromobutanone and 2,4-dimethylpyrimidine. Formylation of **7** gave a compound whose ^{1}H NMR spectrum when compared to that of **7** showed the absence of the 1 H singlet at δ 6.27 and the emergence of a 1 H singlet at δ 10.43 assigned to the presence of a 1-formyl proton. The absorption positions of the H-5 and H-6 doublets of 1-formyl-2,3,7-trimethyl-8-azaindolizine (**21**) were only marginally lower than their positions in **7**. Had 2,5-dimethyl-8-azaindolizine (**12**) been isolated from the reaction between bromoacetone and 2,4-dimethylpyrimidine its formylation product could in no way show a peri shift by formylation at C-1 or C-3; had the 6-azaindolizine **15** been isolated formylation would be expected to yield a 5-azacycl[3.2.2]azine structure.[4]

The low yields (0.2–5.6%) obtained for simple 8-azaindolizines compared with the yields (6.0–89%) obtained in the

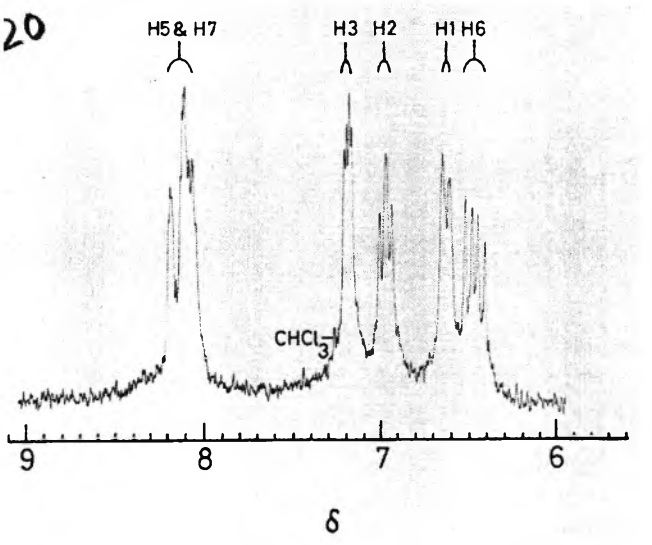


Figure 1. 100 MHz ^{1}H NMR spectrum of 8-azaindolizine in $CDCl_3$.

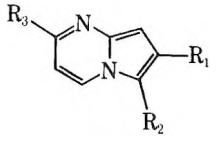
Chichibabin synthesis of 6-azaindolizines from 4-methylpyrimidines[4,8,9] and the preferential formation of 6-azaindolizines from the reaction between 2,4,6-trimethylpyrimidine and bromoacetone or phenacyl bromide[4] suggest that the 2-methyl group is less reactive than the 4-methyl group in methyl substituted pyrimidines.[10] Since a 4-methoxy group would be expected to increase the reactivity of the 2-methyl group, it was hoped that improved yields of 8-azaindolizines would be obtained from the reaction of 4-methoxy-2-methylpyrimidine and an α-halo ketone. Quaternization of 4-methoxy-2-methylpyrimidine with phenacyl bromide at room temperature followed by cyclization gave in fact 7-methoxy-2-phenyl-8-azaindolizine (**8**) in 27% yield. When quaternization was carried out at higher temperatures, however, the main product (58%) was a compound isomeric with **8**, but whose infrared spectrum showed a strong carbonyl band. Further, although the pattern of the ^{1}H NMR spectrum

of this compound was similar to that of the methoxy-2-phenyl-8-azaindolizine (8), the chemical shift of the lower field 3 H methyl signal occurred at higher field (δ 3.48). This suggests that the methyl group is attached to nitrogen rather than oxygen and that the main product of reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide at the higher temperature is 8-methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (**22**). This structure was confirmed by formylation to give **26**. Minor products isolated from this reaction were the *N*-phenacylindolizinones **24** and **31**. The main product (**22**) is possibly formed from an *N*-methylpyrimidone by rearrangement of the methoxypyrimidine,[11,12] and the minor products (**24** and **31**) from 2-methylpyrimidone by demethylation of 4-methoxy-2-methylpyrimidine with hydrogen bromide produced during quaternization.

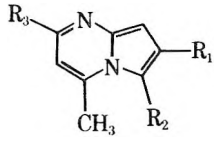
The reaction between 4-methoxy-2-methylpyrimidine and bromoacetone gave the 2,8-dimethyl-8-azaindolizin-7(8*H*)-one (**23**) as the major product (39%) even when quaternization was carried out at room temperature. Only a small amount (1.5%) of the 8-azaindolizine **9** was isolated together with the indolizinones **32** and **34**. Similar products, viz., **10, 28, 29,** and **33,** all in low yields, were obtained when 4-methoxy-2-methylpyrimidine was treated with ethyl bromopyruvate.

Confirmation for the indolizinone structures was obtained by reacting 4-hydroxy 2-methylpyrimidine with bromoacetone. This reaction gave two *N*-acetonylindolizinones presumably resulting from bicarbonate cyclization of the *N,N*-diacetonyl quaternary salt (**36**). One of the products was shown to be 8-acetonyl-2-methyl-8-azaindolizin-7(8*H*)-one (**25**) since on formylation it showed a peri shift (162 Hz) of its lower field doublet signal assigned to H-5. The UV spectrum of this compound closely resembled that of the major product (**23**) of the reaction between 4-methoxy-2-methylpyrimidine and bromoacetone. Formylation studies on the other product from the reaction between 4-hydroxy-2-methylprimidine and bromoacetone indicated it to be 8-acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (**34**), identical with one of the minor products isolated from the reaction between 4-methoxy-2-methylpyrimidine and bromoacetone.

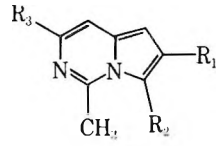
Although formylation was primarily employed to aid in structure elucidation of the products isolated, it also indicates the preferred site of reaction; thus the parent 8-azaindolizine (**1**) formylates at C-3 and 2,7-dimethyl-8-azaindolizine (**6**) preferentially at C-3 and then C-1. Thioformylation of **6** occurs at C-3. These findings correlate well with theoretical MO calculations[13] which predict electrophilic substitution of 8-azaindolizine to occur firstly at C-3 and then C-1. Not sur-



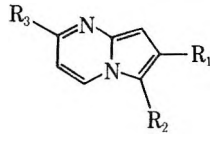
	R_1	R_2	R_3
1	H	H	H
2	COOEt	H	H
3	CH_3	H	H
4	CH_3	CH_3	H
5	Ph	H	H
6	CH_3	H	CH_3
7	CH_3	CH_3	CH_3
8	Ph	H	OCH_3
9	CH_3	H	OCH_3
10	COOEt	H	OCH_3



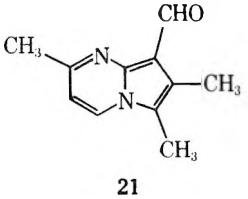
	R_1	R_2	R_3
11	Ph	H	CH_3
12	CH_3	H	H
13	CH_3	CH_3	H



	R_1	R_2	R_3
14	Ph	H	CH_3
15	CH_3	H	H
16	CH_3	CH_3	H



	R_1	R_2	R_3
17	H	CHO	H
18	CH_3	CHO	CH_3
19	Ph	CHO	OCH_3
20	CH_3	CHS	CH_3



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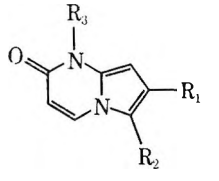
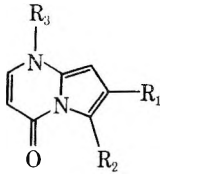
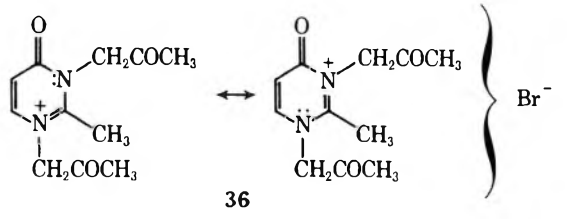


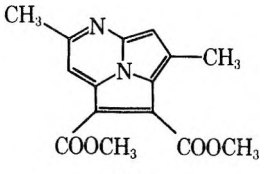
	R_1	R_2	R_3
22	Ph	H	CH_3
23	CH_3	H	CH_3
24	Ph	H	CH_2COPh
25	CH_3	H	CH_2COCH_3
26	Ph	CHO	CH_3
27	CH_3	CHO	CH_3
28	COOEt	H	H
29	COOEt	H	CH_3
30	CH_3	CHO	CH_2COCH_3



	R_1	R_2	R_3
31	Ph	H	CH_2COPh
32	CH_3	H	CH_3
33	COOEt	H	CH_3
34	CH_3	H	CH_2COCH_3
35	CH_3	CHO	CH_2COCH_3



36



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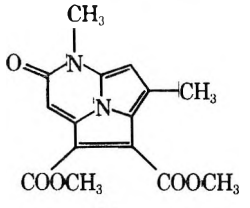

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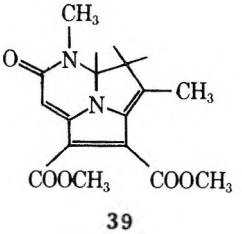

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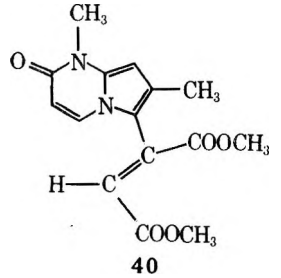

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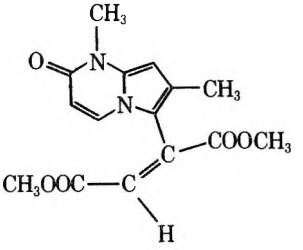

41

prisingly, the 8-azaindolizinones **22, 23, 25,** and **34,** which can be considered to be substituted pyrroles, preferably formylate at C-3.

The 8-azaindolizine **6** and the 8-azaindolizinone **23** underwent dipolar addition with dimethyl acetylenedicarboxylate to give the 5-azacycl[3.2.2]azines **37** and **38,** respectively. In addition **23** gave the dihydrocyclazine **39,** and the cis and trans isomeric 8-azaindolizines **40** and **41.** The configuration of the cis and trans stereoisomers was made tentatively on the basis of a comparison of their ^{1}H NMR spectra. The vinyl proton of one stereoisomer absorbs at δ 5.93 whereas the vinyl proton of the other absorbs at δ 7.13. We suggest that the vinyl proton of the trans isomer absorbs at lower field.[14,15]

The dihydro compound **39** was readily dehydrogenated to **38.** The cis and trans isomers were only partially interconverted on heating in toluene with palladium on charcoal; none of the cyclazine **38** was formed. This suggests that the cis and trans isomers are not intermediates en route to the cyclazine **38.**

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed by the analytical laboratories of Aberdeen University. Infrared spectra were measured for Nujol mulls unless otherwise stated with a Unicam SP200 spectrometer. Ultraviolet spectra were measured on a Unicam SP800 spectrometer. Light absorption data refer to solutions in ethanol unless otherwise stated, principal maxima are italicized, and inflections are given in parentheses. ^{1}H NMR spectra were recorded with a Varian HA-100D spectrometer using tetramethylsilane as an internal standard. Unless otherwise stated values given on the δ scale refer to singlet absorption, approximate coupling constants are in hertz, and integration values and signal assignment are in parentheses. For multiplets d = doublet, dd = double doublet, t = triplet, q = quartet, and m = complex multiplet. Mass spectra (70 eV) were recorded with an AE1 MS30 spectrometer.

Procedures. Solutions were dried over anhydrous magnesium sulfate and solvents evaporated at reduced pressure on a rotary film evaporator. Thin layer chromatography (TLC) was carried out on Merck Kieselgel GF_{254} using benzene–ethyl acetate (3:1) for development and chloroform for band extraction unless otherwise stated. Bands are recorded in the order of their speed of movement, the fastest being given first. Where indicated, spraying with Ehrlich's reagent[16] aided compound identification. Petroleum ether refers to the fraction boiling at 80–100 °C.

The following general procedure was used in the Chichibabin synthesis of the 8-azaindolizines. Deviations are given in individual cases. The α-bromo ketone was added to the pyrimidine and left at room temperature for 1–3 days. Water was added and the aqueous solution extracted with ether or chloroform, then warmed to remove dissolved solvent, before adding an excess of sodium hydrogen carbonate. The resultant was either steam distilled or heated on a boiling water bath for 10–30 min. The steam distillate or the aqueous bicarbonate solution was extracted several times with ether or chloroform, the combined organic extracts dried, and the solvent evaporated to leave a crude residue of the 8-azaindolizine.

2-Methylpyrimidine[17] (5.0 g, 0.053 mol) and ethyl bromopyruvate (10.4 g, 0.053 mol) gave a yellow oil (1 g) which on TLC gave a number of bands. The yellow band, which gave a blue Ehrlich's test on being heated at 100 °C, was extracted and further chromatographed using petroleum ether–ethyl acetate (1:1). The faster moving of the two yellow bands which developed afforded **2-carbethoxy-8-azaindolizine (2),** 94 mg (1.0%), as a yellow oil which gave a waxy, crystalline solid on cooling: mp 48–60 °C; λ_{max} *225,* 235, 242, (249), (258), 282, 292, 303, 370 nm (broad), log ϵ 4.37, 4.35, 4.33, 4.10, 3.95, 3.48, 3.52, 3.37, 3.22; IR (melt) 770, 1198, 1230, 1700 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_{10}H_{10}N_2O_2$: 190.0742. Found: M$^+$ (base peak) 190.0742.

Hydrolysis of the ester **2** (80 mg) with excess ethanolic KOH (3 cm^3) gave the potassium salt of 8-azaindolizine-2-carboxylic acid, 79 mg (94%), as a dark yellow powder which did not melt below 350 °C: λ_{max} (water) *218,* (237), 241, (247), (256), 283, 292, 304, 372 nm (broad), log ϵ 4.33, 4.29, 4.30, 4.02, 3.91, 3.40, 3.47, 3.37, 3.11; IR 770, 1322, 1570 cm^{-1}; ^{1}H NMR (CF_3COOH) δ 7.29 (dd, J = 5.0 and 7.0 Hz, 1 H, H-6), 7.50 (H-1), 8.45 (H-3), 8.75 (d, J = 5.0 Hz, 1 H, H-5 or H-7), 9.17 (d, J = 7.0 Hz, 1 H, H-5 or H-7). Neutralization of a solution of the potassium salt (35 mg, 0.175 mmol in a few drops of water) with 1 M HCl (0.175 cm^3, 0.175 mmol) gave a precipitate of 8-azaindolizine-2-carboxylic acid hydrochloride, 22 mg (63%), as a yellow powder, decomposing >290 °C: λ_{max} *219,* (238), *242,* (247), 282, 292, 303, 374 nm (broad), log ϵ 4.50, 4.45, 4.50, 4.45, 3.61, 3.67, 3.54, 3.37; IR 734, 790, 1250, 1495, 1698, 1880 (broad), 2590 (broad), 2750 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] 6.77 (m, 2 H, H-1 and H-6), 7.96 (d, J = 2.0 Hz, 1 H, H-3), 8.18 (m, 1 H, H-5 or H-7), 8.68 (d, with additional fine splitting, J = 7.5 Hz, 1 H, H-5 or H-7).

Decarboxylation of the hydrochloride (32 mg) by heating with copper powder[18] in a sealed, evacuated tube (0.01 mm, block temperature 260 °C) gave **8-azaindolizine (1),** 15 mg (79%), as a yellow oil: λ_{max} (234), *239,* 244, (285), 291, 302, 374 nm (broad), log ϵ 4.35, 4.43, 4.37, 3.18, 3.26, 3.08, 3.08; IR 771, 1206, 1257, 1307, 1508, 1612 cm^{-1}; ^{1}H NMR (see Figure 1 and Table I). Calcd mass for $C_7H_6N_2$: 118.0530. Found: M$^+$ (base peak) 118.0529.[19]

2-Methylpyrimidine (0.94 g, 0.01 mol) and bromoacetone (1.31 g, 0.01 mol) gave a few milligrams of a yellow oil which on TLC with benzene–ethyl acetate (10:1) and then with ether gave a yellow band. Ether extraction followed by distillation in a sealed evacuated tube (0.01 mm, 90 °C) gave **2-methyl-8-azaindolizine (3),** 7 mg (0.5%), as a yellow oil which crystallized on cooling: mp 43–45.5 °C; λ_{max} (238), *243,* 250, (291), 301, 313, 347 nm (broad), log ϵ 4.28, 4.35, 4.29, 3.12, 3.27, 3.30, 3.07; IR 747, 773, 799, 1254, 1506, 1615 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_8H_8N_2$: 132.0687. Found: M$^+$ (base peak) 132.0683.

2-Methylpyrimidine (0.94 g, 0.01 mol) and 3-bromo-2-butanone (1.51 g, 0.01 mol) gave a few milligrams of a solid which on TLC with ether gave a yellow band. Ether extraction followed by distillation in a sealed evacuated tube (0.01 mm, 100 °C) gave **2,3-dimethyl-8-azaindolizine (4),** 4 mg (0.3%), as yellow prisms: mp 93–94 °C; λ_{max} (228), 232, *249,* 256, (295), 302, 315, 390 nm (broad), log ϵ 4.25, 4.28, 4.44, 4.37, 3.29, 3.37, 3.37, 3.24; IR 771, 1268, 1502, 1614 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_9H_{10}N_2$: 146.0843. Found: M$^+$ (63% base peak) 146.0841.

2-Methylpyrimidine (0.82 g, 8.7 mmol) and phenacyl bromide (1.73 g, 8.7 mmol) gave a red oil (0.1 g) which on TLC gave a number of bands. The yellow band, which slowly gave a blue Ehrlich's test, on extraction gave **2-phenyl-8-azaindolizine (5),** 9 mg (0.5%), as pale yellow crystals: mp 138–141 °C; λ_{max} *253,* 325, 371 nm (broad), log ϵ 4.54, 3.78, 3.37; IR (KBr) 738, 768, 1198, 1267, 1370, 1510, 1600, 1618 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_{13}H_{10}N_2$: 194.0843. Found: M$^+$ (base peak) 194.0846.

2,4-Dimethylpyrimidine[17] (5.40 g, 0.05 mol) and bromoacetone (6.85 g, 0.05 mol) gave an oil (1.1 g) which on TLC with ether gave a fast-moving yellow band. Ether extraction followed by distillation in a sealed, evacuated tube (0.01 mm, 100 °C) gave **2,7-dimethyl-8-azaindolizine (6),** 0.406 g (6%), as a yellow oil which subsequently crystallized: mp 33–49 °C; λ_{max} (239), *245,* 252, (291), 296, (306), 370 nm (broad), log ϵ 4.33, 4.42, 4.40, 3.54, 3.56, 3.39, 3.06; IR (melt) 780, 1143, 1253, 1521, 1622 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_9H_{10}N_2$: 146.0843. Found: M$^+$ (base peak) 146.0842.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89. Found: C, 74.2; H, 7.2.

2,4-Dimethylpyrimidine (5.40 g, 0.05 mol) and 3-bromo-2-butanone (7.60 g, 0.05 mol) were quaternized by heating with a flame for 15 min. Bicarbonate cyclization afforded an oil (0.15 g) which on TLC gave a yellow band. Ether extraction and then distillation in a sealed, evacuated tube (0.01 mm, 100 °C) gave **2,3,7-trimethyl-8-azaindolizine (7),** 18 mg (0.3%), as a yellow oil which subsequently crystallized: mp 65 °C; λ_{max} (237), *250,* (255), 299, 313, 386 nm (broad), log ϵ 4.37, 4.55, 4.50, 3.56, 3.41, 3.26; IR 780, 1268, 1620 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_{10}H_{12}N_2$: 160.1000. Found: M$^+$ (71% base peak) 160.1000.

Reaction between 4-Methoxy-2-methylpyrimidine and Phenacyl Bromide. A. 4-Methoxy-2-methylpyrimidine[20] (0.31 g, 2.5 mmol) and phencyl bromide (0.50 g, 2.5 mmol) gave directly by filtration of the cooled aqueous bicarbonate cyclization solution a buff-colored solid (0.16 g). This was purified by TLC, recrystallized from petroleum ether containing a small amount of benzene, and finally distilled (0.01 mm, 170 °C) to give **7-methoxy-2-phenyl-8-azaindolizine (8),** 150 mg (27%), as pale yellow crystals: mp 147–148 °C; λ_{max} *251,* (255), 301, (310), 347 nm (broad), log ϵ 4.62, 4.61, 3.95, 3.88, 3.31; IR 705, 763, 1015, 1232, 1307, 1627 cm^{-1}; ^{1}H NMR (see Table I); mass spectrum *m/e* 224 (M$^+$, base peak).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.8; H, 5.7; N, 12.2.

B. Quaternization of 4-methoxy-2-methylpyrimidine (0.31 g, 2.5 mmol) with phenacyl bromide (0.50 g, 2.5 mmol) by warming to start the exothermic reaction and then maintaining it at 40 °C for 6 h, gave

directly by filtration of the bicarbonate solution sand-colored crystals (0.36 g). Distillation of these (0.01 mm, 160–170 °C) followed by recrystallization from benzene gave **8-methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (22),** 324 mg (58%), as yellow crystals: mp 158.5–160.5 °C; λ_{max} *243,* (289), 301, (329) nm, log ϵ 4.52, 4.09, 4.12, 3.55; IR 740, 1220, 1548, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) 3.48 (3 H, CH_3N), 5.92 (H-1), 5.95 (d, J = 7.5 Hz, 1 H, H-6), 6.98 (H-3), 7.10–7.66 (m, 5 H, Ph), 7.66 (d, J = 7.5 Hz, 1 H, H-5); mass spectrum m/e 224 (M^+, base peak).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.8; H, 5.6; N, 12.3.

The chloroform washing of the quaternary salt solution gave 50 mg of a yellow solid, which on TLC gave a number of bands. The band which gave a green Ehrlich's test and had the same R_f as **22** yielded after recrystallization from ethanol **8-phenacyl-2-phenyl-8-azaindolizin-5(8*H*)-one (31),** 11 mg (1.3%), as needles: mp 244.5–246.5 °C; λ_{max} *247,* (278), (297), 347 nm, log ϵ 4.64, 4.05, 3.85, 3.76; IR 748, 1218, 1590, 1638, 1658, 1688 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] 5.60 (d, J = 8.0 Hz, 1 H, H-6), 5.78 (2 H, methylene), 6.56 (d, J = 2 Hz, 1 H, H-1), 7.11–8.24 (m, 12 H, H-3, H-7, and Ph). Calcd mass for $C_{21}H_{16}N_2O_2$: 328.1211. Found: M^+ (32% base peak) 328.1213.

C. Quaternization of 4-methoxy-2-methylpyrimidine (0.62 g, 5 mmol) with phenacyl bromide (1.0 g, 5 mmol) by warming for 15 min yielded 0.8 g of a brown oil which on TLC gave a number of bands. The pale yellow band which had an R_f greater than that of **22** and gave a blue-green Ehrlich's test yielded on recrystallization from ethanol **8-phenacyl-2-phenyl-8-azaindolizin-7(8*H*)-one (24),** 19 mg (1.2%), as yellow crystals: mp 209–213 °C; λ_{max} *243,* 300, (331) nm, log ϵ 4.62, 4.12, 3.56; IR 750, 1224, 1554, 1655, 1670 cm^{-1}; ^1H NMR 5.40 (2 H, methylene), 5.74 (d, J = 1.5 Hz, 1 H, H-1), 5.97 (d, J = 8.0 Hz, 1 H, H-6), 6.97 (d, J = 1.5 Hz, 1 H, H-3), 7.19–8.19 (m, 10 H, Ph), 7.73 (d, J = 8.0 Hz, 1 H, H-5). Calcd mass for $C_{21}H_{16}N_2O_2$: 328.1211. Found: M^+ (94% base peak) 328.1210.

The band with the same R_f as **22** on extraction gave 0.32 g of yellow crystals. Fractional crystallization from benzene containing a small percentage of ethanol gave **31,** 21 mg (1.3%), with identical melting point and spectral characteristics as the sample obtained previously. The next fraction gave **22,** 213 mg (19%), with identical melting point and spectral characteristics as the sample obtained above.

Reaction between 4-Methoxy-2-methylpyrimidine and Bromoacetone. A. 4-Methoxy-2-methylpyrimidine (0.31 g, 2.5 mmol) and bromoacetone (0.35 g, 2.5 mmol) when mixed at room temperature yielded an oil which was separated by TLC. The fast moving pale yellow band which gave a blue Ehrlich's test was extracted to give a pale yellow chloroform solution. Evaporation of the extract gave **7-methoxy-2-methyl-8-azaindolizine (9),** 6 mg (1.5%), as an oil which crystallized on cooling to a waxy solid: mp gradual up to 54 °C; λ_{max} *242,* 249, 274, 285, 297, 352 nm (broad), log ϵ 4.36, 4.36, 3.37, 3.34, 3.16, 3.04; IR 785, 1025, 1232, 1315, 1635 cm^{-1}; ^1H NMR (see Table I). Calcd mass for $C_9H_{10}N_2O$: 162.0793. Found: M^+ (base peak) 162.0794.

The next broad yellow band gave on recrystallization from benzene–petroleum ether **2,8-dimethyl-8-azaindolizin-7(8*H*)-one (23),** 159 mg (39%), as yellow needles: mp 122–124 °C; λ_{max} *239,* 287, 335 nm (broad), log ϵ 4.18, 3.85, 3.02; IR 740, 1502, 1558, 1628, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 2.16 (3 H, CH_3-2), 3.40 (3 H, CH_3N), 5.47 (H-1), 5.84 (d, J = 8.0 Hz, 1 H, H-6), 6.47 (H-3), 7.56 (d, J = 8.0 Hz, 1 H, H-5); mass spectrum m/e 162 (M^+, base peak).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.64; H, 6.22; N, 17.27. Found: C, 66.4; H, 6.5; N, 17.0.

The following band with a blue fluorescence under UV light gave a few milligrams of an oil which on distillation (0.01 mm, 110 °C) gave **2,8-dimethyl-8-azaindolizin-5(8*H*)-one (32),** 3 mg (0.7%), as a waxy solid: mp 78–83.5 °C; λ_{max} *226,* (255), 345 nm, log ϵ 4.36, 3.68, 3.63; IR (mulled under dry N_2) 732, 782, 1600, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) 2.24 (3 H, CH_3-2), 3.58 (3 H, CH_3N), 5.54 (d, J = 1.5 Hz, 1 H, H-1), 7.15 (d, J = 7.5 Hz, 1 H, H-7), 7.26 (d, J = 1.5 Hz, 1 H, H-3). Calcd mass for $C_9H_{10}N_2O$: 162.0793. Found: M^+ (base peak) 162.0794.

B. Quaternization of 4-methoxy-2-methylpyrimidine (1.00 g, 8.1 mmol) with bromoacetone (1.11 g, 8.1 mmol) at 40 °C for 2 days gave in addition to **23** (22%) and **32** (0.5%) a slower moving band with a turquoise fluorescence under UV light. This band gave **8-acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (34),** 12 mg (0.7%), as needles: mp 170.5–174.5 °C; λ_{max} *225,* (255), 347 nm (broad), log ϵ 4.39, 3.74, 3.58; IR 782, 1598, 1660, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 2.19 (3 H, CH_3-2 or CH_3 of acetonyl), 2.20 (3 H, CH_3-2 or CH_3 of acetonyl), 4.54 (2 H, methylene), 5.53 (H-1), 5.62 (d, J = 8.0 Hz, 1 H, H-6), 7.09 (d, J = 8.0 Hz, 1 H, H-7), 7.22 (H-3); mass spectrum m/e 204 (M^+, 50% base peak).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.6; H, 6.2.

Reaction between 4-Methoxy-2-methylpyrimidine and Ethyl Bromopyruvate. A. 4-Methoxy-2-methylpyrimidine (0.62 g, 5 mmol) and ethyl bromopyruvate (0.98 g, 5 mmol) when mixed at room temperature yielded an oil which was subjected to TLC. The fast moving band, which gave a blue Ehrlich's test, yielded after recrystallization from petroleum ether **2-carbethoxy-7-methoxy-8-azaindolizine (10),** 19 mg (1.7%), as yellow needles in clusters: mp 117.5–119 °C; λ_{max} *231,* 239, 256, 264, (277), (287), 343 nm (broad), log ϵ 4.58, 4.51, 4.04, 4.02, 3.66, 3.45, 3.11; IR 1020, 1220, 1640, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) 1.36 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 3.94 (3 H, CH_3O), 4.34 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 6.18 (d, J = 7.5 Hz, 1 H, H-6), 6.61 (H-1), 7.49 (d, J = 1.5 Hz, 1 H, H-3), 7.92 (d, J = 7.5 Hz, 1 H, H-6). Calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847. Found: M^+ (base peak) 220.0844.

B. Quaternization of 4-methoxy-2-methylpyrimidine (0.62 g, 5 mmol) and ethyl bromopyruvate (0.98 g, 5 mmol) at 50 °C for 6 h gave only a trace of **10.** However, the ether washing of the quaternary salt solution gave 0.6 g of a brown oil which on TLC gave four bands. The fast moving band, which gave a blue Ehrlich's test, gave **10,** 4 mg (0.4%). The next band, which gave a purple Ehrlich's test, gave after recrystallization from benzene–petroleum ether **2-carbethoxy-8-methyl-8-azaindolizin-7(8*H*)-one (29),** 14 mg (1.3%), as pale yellow crystals: mp 207–207.5 °C; λ_{max} *226,* (232), (271), 275, 286, 328 nm (broad), log ϵ 4.51, 4.42, 4.05, 4.10, 3.98, 3.18; IR 1213, 1658, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 1.36 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 3.45 (3 H, CH_3-N), 4.34 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 6.05 (H-1), 6.06 (d, J = 7.5 Hz, 1 H, H-6), 7.31 (d, J = 2 Hz, 1 H, H-3), 7.68 (d, J = 7.5 Hz, 1 H, H-5). Calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847. Found: M^+ (base peak) 220.0844.

The following band, which gave a turquoise Ehrlich's test, gave after recrystallization from benzene–petroleum ether **2-carbethoxy-8-methyl-8-azaindolizin-5(8*H*)-one (33),** 5 mg (0.5%), as needles: mp 178.5–179.5 °C; λ_{max} *231,* (239), (256), (277), 347 nm, log ϵ 4.48, 4.37, 3.52, 3.12, 3.74; IR 1190, 1208, 1660, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 1.36 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 3.64 (3 H, CH_3N), 4.34 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 5.60 (d, J = 7.5 Hz, 1 H, H-6), 6.30 (d, J = 2.0 Hz, 1 H, H-1), 7.26 (d, J = 7.5 Hz, 1 H, H-7), 8.02 (d, J = 2.0 Hz, 1 H, H-3). Calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847. Found: M^+ (base peak) 220.0844.

The slowest band, which gave a blue Ehrlich's test, gave after recrystallization from benzene–ethanol **2-carbethoxy-8-azaindolizin-7(8*H*)-one (28),** 16 mg (1.6%), as a pale yellow solid: mp 260 °C dec; λ_{max} *226,* (233), (272), 276, 286, 328 nm (broad), log ϵ 4.49, 4.37, 4.08, 4.12, 3.97, 3.09; IR 1228, 1424, 1700, 2740 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] 1.26 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 4.20 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 5.76 (d, J = 1.5 Hz, 1 H, H-1), 5.91 (d, J = 8.0 Hz, 1 H, H-6), 7.54 (d, J = 1.5 Hz, 1 H, H-3), 8.21 (d, J = 8.0 Hz, 1 H, H-5), 11.5 (broad, exchangeable on addition of D_2O, 1 H, HN). Calcd mass for $C_{10}H_{10}N_2O_3$: 206.0691. Found: M^+ (base peak) 206.0688.

Reaction between 4-Hydroxy-2-methylpyrimidine and Bromoacetone. 4-Hydroxy-2-methylpyrimidine[21] (3.0 g, 27 mmol) and bromoacetone were heated in dimethylformamide (30 cm^3) at 60 °C for 8 h. The bulk of the solvent was removed and the dark colored residue extracted into water and worked up in the usual manner to give a small volume of a brown liquid. TLC gave two main bands. The faster band, which gave a violet Ehrlich's test, gave **8-acetonyl-2-methyl-8-azaindolizin-7(8*H*)-one (25),** 84 mg (1.5%), as a yellow oil which subsequently crystallized: mp 100 °C; λ_{max} *238,* 287, 340 nm (broad), log ϵ 4.29, 3.80, 2.84; IR 768, 1169, 1351, 1549, 1641, 1660, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 2.10 (3 H, CH_3-2), 2.17 (3 H, CH_3 of acetonyl), 4.64 (2 H, methylene), 5.30 (H-1), 5.86 (d, J = 8.0 Hz, 1 H, H-6), 6.48 (H-3), 7.62 (d, J = 8.0 Hz, 1 H, H-5); mass spectrum m/e 204 (M^+, 89% base peak).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.09; H, 5.92. Found: C, 64.4; H, 6.0.

The slower band, which gave a blue Ehrlich's test and had a turquoise fluorescence under UV light, gave 8-acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (**34**), 63 mg (1.0%), with identical melting point and spectral characteristics as the sample obtained previously from 4-methoxy-2-methylpyrimidine and bromoacetone.

General Formylation Procedure. To a stirred solution of the azaindolizine in dimethylformamide (DMF) (1 cm^3) was added a 10% molar excess of phosphoryl chloride in DMF (1 cm^3). After 2–4 h the resultant solution was poured into 2 M NaOH (30 cm^3), or 2 M NaSH[22] in the case of thioformylation, and extracted with chloroform or ether. Evaporation of the ether or chloroform extract and any residual DMF gave the crude aldehyde, which was purified by TLC.

8-Azaindolizine (**1**), 15 mg, gave **3-formyl-8-azaindolizine (17),** 8 mg (43%), as pale yellow needles from petroleum ether: mp 121–122

°C; λ_{max} 222, (267), *270*, 343 nm, log ϵ 4.17, 4.43, 4.44, 4.03; IR 786, 1408, 1604, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) 6.75 (d, J = 5.0 Hz, 1 H, H-1), 6.93 (dd, J = 4.0 and 7.0 Hz, 1 H, H-6), 7.63 (d, J = 5.0 Hz, 1 H, H-2), 8.47 (dd, J = 2.0 and 4.0 Hz, 1 H, H-7), 9.73 (CHO), 9.82 (dd, J = 2.0 and 7.0 Hz, 1 H, H-5); mass spectrum *m/e* 146 (M^+, base peak).

Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14. Found: C, 65.7; H, 4.2.

2,7-Dimethyl-8-azaindolizine (**6**), 40 mg, gave **3-formyl-2,7-dimethyl-8-azaindolizine (18),** 22 mg (46%), as pale yellow needles from petroleum ether: mp 110 °C; λ_{max} (227), 230, (266), (276), *282*, 352 nm, log ϵ 4.21, 4.22, 4.22, 4.36, 4.43, 4.11; IR 720, 1438, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) 2.57 (6 H, CH_3-2 and CH_3-7), 6.35 (H-1), 6.73 (d, J = 7.0 Hz, 1 H, H-6), 9.69 (d, J = 7.0 Hz, 1 H, H-5), 9.79 (CHO). Calcd mass for $C_{10}H_{10}N_2O$: 174.0793. Found: M^+ (base peak) 174.0792. Similarly, by pouring the intermediate Vilsmeier salt solution into 2 M aqueous sodium hydrogen sulfide, **6** gave **3-thioformyl-2,7-dimethyl-8-azaindolizine (20),** 26 mg (50%), as red needles in clusters from benzene–petroleum ether: mp 168.5–169 °C; λ_{max} *227*, 275, (310), 317, 418, *429* nm, log ϵ 4.38, 4.01, 3.95, 4.06, 4.47, 4.50; IR 977, 1422, 1500, 1530, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) 2.54 (3 H, CH_3-2), 2.61 (3 H, CH_3-7), 6.48 (H-1), 6.90 (d, J = 7.0 Hz, 1 H, H-6), 10.65 (CHS), 11.26 (d, J = 7.0 Hz, 1 H, H-5). Calcd mass for $C_{10}H_{10}N_2S$: 190.0563. Found: M^+ (67% base peak) 190.0561.

Anal. Calcd for $C_{10}H_{10}N_2S$, C, 63.13; H, 5.30. Found: C, 63.4; H, 5.2.

7-Methoxy-2-phenyl-8-azaindolizine (**8**), 31 mg, gave **3-formyl-7-methoxy-2-phenyl-8-azaindolizine (19),** 22 mg (63%), as needles from petroleum ether: mp 143–143.5 °C; λ_{max} 230, 249, *277*, 350 nm, log ϵ 4.24, 4.10, 4.43, 4.13; IR 810, 1240, 1410, 1625, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) 4.04 (3 H, CH_3O), 6.45 (H-1), 6.45 (d, J = 7.0 Hz, 1 H, H-6), 7.32–7.72 (m, 5 H, Ph), 9.64 (CHO), 9.73 (d, J = 7.0 Hz, 1 H, H-5); mass spectrum *m/e* 252 (M^+, base peak).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.1; H, 5.1; N, 11.1.

2,3,7-Trimethyl-8-azaindolizine (**7**), 12 mg, gave **1-formyl-2,3,7-trimethyl-8-azaindolizine (21),** 4 mg (28%), as pale yellow needles from benzene–petroleum ether: mp 140 °C; λ_{max} *235*, 242, 255, 280, 289, 324, 360 nm, log ϵ 4.14, 4.13, 3.92, 3.80, 3.80, 3.79, 3.24; IR 786, 1278, 1535, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) 2.32 (3 H, CH_3-3), 2.51 (3 H, CH_3-7), 2.58 (3 H, CH_3-2), 6.70 (d, J = 7.0 Hz, 1 H, H-6), 7.91 (d, J = 7.0 Hz, 1 H, H-5), 10.43 (CHO). Calcd mass for $C_{11}H_{12}N_2O$: 188.0949. Found: M^+ (base peak) 188.0946.

8-Methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (**22**), 31 mg, gave **3-formyl-8-methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (26),** 28 mg (80%), as needles from benzene: mp 218.5 °C; λ_{max} 226, 239, *295*, 340 nm, log ϵ 4.21, 4.23, 4.39, 4.05; IR 840, 1542, 1618, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) 3.57 (3 H, CH_3N), 5.95 (H-1), 6.17 (d, J = 7.5 Hz, 1 H, H-6), 7.48 (5 H, Ph), 9.32 (d, J = 7.5 Hz, 1 H, H-5), 9.57 (CHO); mass spectrum *m/e* 252 (M^+, base peak).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.1; H, 4.9; N, 11.2.

2,8-Dimethyl-8-azaindolizin-7(8*H*)-one (**23**), 280 mg, gave **2,8-dimethyl-3-formyl-8-azaindolizin-7(8*H*)-one (27),** 228 mg (69%), as sand-colored prisms from benzene containing a small amount of petroleum ether: mp 212 °C; λ_{max} (220), (229), (226), *283*, (287), 312, 336 nm, log ϵ 3.92, 3.76, 3.95, 4.19, 4.16, 4.09, 4.06; ir 890, 1288, 1501, 1620, 1637, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) 2.45 (3 H, CH_3-2), 3.48 (3 H, CH_3-N), 5.68 (H-1), 6.06 (d, J = 8.0 Hz, 1 H, H-6), 9.15 (d, J = 8.0 Hz, 1 H, H-5), 9.61 (CHO); mass spectrum *m/e* 190 (M^+, base peak).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.2; H, 5.4; N, 14.8.

8-Acetonyl-2-methyl-8-azaindolizin-7(8*H*)-one (**25**), 25 mg, gave **8-acetonyl-3-formyl-2-methyl-8-azaindolizin-7(8*H*)-one (30),** 18 mg (63%), as glassy needles from benzene: mp 196–197 °C; λ_{max} (220), (229), (267), *283*, 288, 311, 335 nm, log ϵ 3.97, 3.76, 3.98, 4.22, 4.20, 4.12, 4.07; IR 818, 1642, 1665, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 2.27 (3 H, CH_3 of acetonyl), 2.42 (3 H, CH_3-2), 4.77 (2 H, methylene), 5.48 (H-1), 6.11 (d, J = 8.0 Hz, 1 H, H-6), 9.24 (d, J = 8.0 Hz, 1 H, H-5), 9.66 (CHO); mass spectrum *m/e* 232 (M^+, 75% base peak).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21. Found: C, 62.2; H, 5.5.

8-Acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (**34**), 15 mg, gave **8-acetonyl-3-formyl-2-methyl-8-azaindolizin-5(8*H*)-one (35),** 11 mg (64%), as needle clusters from benzene–ethanol and then chloroform: mp 201–202 °C; λ_{max} *225*, 247, 337, 343 nm, log ϵ 4.38, 4.05, 4.28, 4.28; IR 803, 1500, 1580, 1632, 1671, 1722 cm^{-1}; ^1H NMR 2.29 (3 H, CH_3 of acetonyl), 2.52 (3 H, CH_3-2), 4.66 (2 H, methylene), 5.64 (H-1), 5.85 (d, J = 8.0 Hz, 1 H, H-6), 7.13 (d, J = 8.0 Hz, 1 H, H-7), 10.95 (CHO). Calcd mass for $C_{12}H_{12}N_2O_3$: 232.0847. Found: M^+ (40% base peak) 232.0846.

1,3-Dipolar Addition. Reactions with dimethyl acetylenedicarboxylate (DAD) were carried out by a procedure similar to that reported by Boekelheide.[8]

2,7-Dimethyl-8-azaindolizine (**6**), 100 mg (0.68 mmol,) and DAD, 150 mg (1.06 mmol), gave after recrystallization from ethanol **1,2-dicarbmethoxy-3,6-dimethyl-5-azacycl[3.2.2]azine (37),** 129 mg (66%), as yellow crystals which had a green fluorescence in solution: mp 137 °C; λ_{max} *250*, (280), (294), (317), 434 nm, log ϵ 4.39, 4.03, 3.93, 3.68, 3.80; IR 1120, 1195, 1310, 1598, 1700, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 2.71 (3 H, CH_3-3), 2.93 (3 H, CH_3-6), 3.99 (3 H, CH_3 of ester), 4.07 (3 H, CH_3 of ester), 7.04 (H-4), 7.99 (H-7); mass spectrum *m/e* 286 (M^+, 84% base peak).

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.2; H, 5.2; N, 9.5.

2,8-Dimethyl-8-azaindolizin-7(8*H*)-one (**23**), 110 mg (0.68 mmol), and DAD, 145 mg (1.02 mmol), gave via TLC four colored bands. The fast-moving, yellow band gave an oil which crystallized to give **4,4a-dihydro-1,2-dicarbmethoxy-3,5-dimethyl-5-azacycl-[3.2.2]azin-6(5*H*)-one (39),** 8 mg (3.9%), as orange crystals: mp 128–131 °C; λ_{max} 240 (broad), 280 (broad), *420* nm, log ϵ 4.00, 3.71, 4.02; IR 805, 1130, 1280, 1680, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) 2.11 (d, J = 1.5 Hz, 3 H, CH_3-3), 2.47 (dd, J = 14.5 and 15.5 Hz, 1 H, H of methylene), 3.12 (dd, J = 5.5 and 15.5 Hz, 1 H, H of methylene), 3.25 (3 H, CH_3-N), 3.75 (3 H, CH_3O), 3.96 (3 H, CH_3O), 4.77–5.03 (m, 1 H, methine), 5.63 (H-7) (irradiation at δ 4.90 causes the signals at 2.47 and 3.12 to become broad doublets, $J \simeq 15$ Hz, and the signal at 2.11 to become a broad singlet); mass spectrum *m/e* 304 (M^+, 63% base peak).

Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.4; H, 5.1; N, 9.2.

The next yellow band gave **3-(*cis*-dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (40),** 28 mg (13.6%), as an oil which crystallized slowly: mp 116–118 °C; λ_{max} *240*, 285, 370 nm, log ϵ 4.13, 3.78, 4.03; IR 1240, 1650, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) 2.20 (3 H, CH_3-2), 3.43 (3 H, CH_3N), 3.78 (3 H, CH_3O), 3.88 (3 H, CH_3O), 5.65 (H-1), 5.93 (vinyl H), 5.96 (d, J = 8.0 Hz, 1 H, H-6), 7.96 (d, J = 8.0 Hz, 1 H, H-5). Calcd mass for $C_{15}H_{16}N_2O_5$: 304.1059. Found: M^+ (71% base peak) 304.1056.

The following orange band gave **3-(*trans*-dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (41),** 37 mg (18%), as an oil which crystallized slowly: mp 106–110 °C; λ_{max} *240*, 284, 420 nm (broad), log ϵ 4.38, 3.83, 3.48; IR 1240, 1660, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) 2.01 (3 H, CH_3-2), 3.44 (3 H, CH_3N), 3.68 (3 H, CH_3O), 3.82 (3 H, CH_3O), 5.63 (H-1), 5.89 (d, J = 8.0 Hz, 1 H, H-6), 7.13 (vinyl H), 7.33 (d, J = 8.0 Hz, 1 H, H-5). Calcd mass for $C_{15}H_{16}N_2O_5$: 304.1059. Found: M^+ (79% base peak) 304.1056.

The slow-moving red band gave after recrystallization from ethyl acetate **1,2-dicarbomethoxy-3,5-dimethyl-5-azacycl[3.2.2]azin-6(5*H*)-one (38),** 121 mg (59%), as dark red needle clusters with a strong fluorescence in solution: mp 179.5–180 °C; λ_{max} *231*, (240), 278, (287), (298), 362, (498), 526, (552) nm, log ϵ 4.32, 4.27, 4.18, 4.13, 3.60, 3.66, 3.81, 3.99, 3.66; IR 1083, 1290, 1658, 1689, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) 2.49 (3 H, CH_3-3), 3.78 (3 H, CH_3N), 3.91 (3 H, CH_3O), 4.04 (3 H, CH_3O), 6.20 (H-4), 7.02 (H-7) (double resonance shows signals at δ 2.49 and 6.20 to be weakly coupled); mass spectrum *m/e* 302 (M^+, base peak).

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.4; H, 4.5; N, 9.5.

Dehydration of 4,4a-Dihydro-1,2-dicarbomethoxy-3,5-dimethyl-5-azacycl[3.2.2]azin-6(5*H*)-one (39). The dihydro derivative (**39**), 30 mg, in toluene (15 cm^3) and 5% Pd on charcoal (25 mg) were refluxed for 20 h under a stream of nitrogen. The solution was filtered, concentrated, and subjected to TLC. The slow-moving red band gave 1,2-dicarbomethoxy-3,5-dimethyl-5-azacycl[3.2.2]azin-6(5*H*)-one (**38**), 13 mg (43%), as dark red crystals, with identical spectral characteristics with the sample obtained previously.

Attempted Cyclization of 3-(*cis*-Dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (40). The cis isomer (**40**), 12 mg, in toluene (15 cm^3) and 5% Pd on charcoal (20 mg) were refluxed under a stream of nitrogen for 4 h. The catalyst was removed and the resulting orange solution was concentrated and subjected to TLC. The first yellow band gave unchanged starting material, 10 mg. The following orange band gave 3-(*trans*-dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (**41**), 2 mg (17%). No red band corresponding to the cyclized derivative (**38**) was observed.

Similarly the trans isomer (**41**), 20 mg, when subjected to the same treatment gave unchanged starting material, 15 mg, and the cis isomer (**40**), 3 mg.

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Registry No.—**1**, 274-66-8; **2**, 61900-67-2; **3**, 61900-68-3; **4**, 61900-69-4; **5**, 61900-70-7; **6**, 61900-71-8; **7**, 61900-72-9; **8**, 61900-73-0; **9**, 61900-74-1; **10**, 61900-75-2; **17**, 61900-76-3; **18**, 61900-77-4; **19**, 61900-78-5; **20**, 61900-79-6; **21**, 61915-57-9; **22**, 61900-80-9; **23**, 61900-81-0; **24**, 61900-82-1; **25**, 61900-83-2; **26**, 61900-84-3; **27**, 61900-85-4; **28**, 61900-86-5; **29**, 61900-87-6; **30**, 61900-88-7; **31**, 61900-89-8; **32**, 61900-90-1; **33**, 61900-57-0; **34**, 61900-58-1; **35**, 61900-59-2; **37**, 61900-60-5; **38**, 61900-61-6; **39**, 61900-62-7; **40**, 61900-63-8; **41**, 61900-64-9; 2-methylpyrimidine, 5053-43-0; ethyl bromopyruvate, 70-23-5; 8-azaindolizine-2-carboxylic acid K, 61900-65-0; 8-azaindolizine-2-carboxylic acid HCl, 61900-66-1; bromoacetone, 598-31-2; 3-bromo-2-butanone, 814-75-5; phenacyl bromide, 70-11-1; 2,4-dimethylpyrimidine, 14331-54-5; 4-methoxy-2-methylpyrimidine, 7314-65-0; 4-hydroxy-2-methylpyrimidine, 19875-04-8; DAD, 762-42-5.

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Reactions of Aryl Diazonium Salts and Arylazo Alkyl Ethers in Basic Alcoholic Solvents.[1] Steric and Mechanistic Studies

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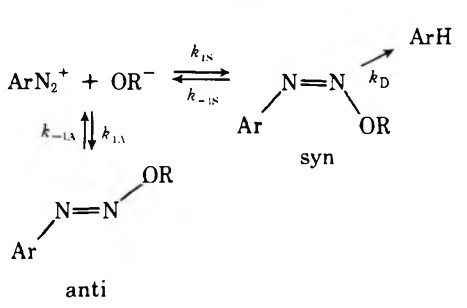
Kinetic studies of the rate of ionization of halo-substituted *anti*-arylazo alkyl ethers show that the enhanced reactivity of the 2-halo substituted compounds is a function of the size of the halogen atom concerned. It is concluded that this effect is a steric effect. Comparison of the effects of *o*- and *p*-nitro groups on the rates of ionization of *syn*- and *anti*-arylazo alkyl ethers leads to the conclusion that the transition state for ionization of the syn ether is later than the transition state for ionization of the anti ether. This interpretation is consistent with the observed solvent and substituent effects on the two processes. Solvent and substituent effects on the initial partitioning of the diazonium salt are also explained on the basis of this interpretation. For carbanionic dediazoniation of the 2-chloro and 3-chloro compounds the species undergoing dediazoniation is shown to be the *syn*-arylazo alkyl ether.

Dediazoniation of aryldiazonium salts in basic methanolic solution can occur by either a free-radical or a carbanionic mechanism.[2] The mechanism depends on the base concentration[2] and on the substituent on the aromatic ring.[2] As the electron-withdrawing power of the substituent on the aromatic ring is increased (4-CH_3O → 2,4-Cl_2) the amount of anionic reaction increases, but a further increase in the electron-withdrawing power of the substituent (4-NO_2) causes a complete reversion to the radical mechanism.[2] In the case of the 4-nitro substituted compound it has been shown[1] that the processes occurring on dissolving the diazonium salt in basic methanol are as in Scheme I.

Scheme I



These reactions occur in three distinct stages. Phase 1 involves partitioning of the diazonium ion between the *syn*- and *anti*-arylazo alkyl ethers. This occurs extremely rapidly and Ritchie[3] has estimated a rate constant for production of the syn ether at 23 °C in methanol ($k_{1S} = 3 \times 10^8\ M^{-1}\ s^{-1}$), and also an equilibrium constant ($K = k_{1S}/k_{-1S} = 5.6 \times 10^7\ M^{-1}$). A small fraction of *anti*-arylazo alkyl ether is also produced[1] and the rate constant, $k_{1A} = 2.5 \times 10^6\ M^{-1}\ s^{-1}$. Thus the ratio $k_{1S}/k_{1A} = 120$.

Phase 2 involves a slower partitioning of the syn ether between decomposition and protection. Protection involves conversion of the syn ether into the anti ether via the free diazonium ion.

$$k_p = (\text{syn} \rightarrow \text{anti})$$

$$k_p = k_{-1S}\frac{k_{1A}}{k_{1A} + k_{1S}} \quad (1)$$

In the case of the *p*-nitro compound, which decomposes via a free-radical mechanism, it is the syn ether that actually undergoes decomposition, not the free diazonium ion[1] (k_D = syn → ArH).

Phase 3 involves the slow dediazoniation of the anti ether via the free diazonium ion and the syn ether. The rate of this process (k_ψ, i.e., anti → ArH) is defined as follows.

Table I. Rate Constants (k_{-1A}) for the Ionization of *anti*-Arylazo Alkyl Ethers in Basic Alcoholic Solvents in the Presence of α-Naphthol[a]

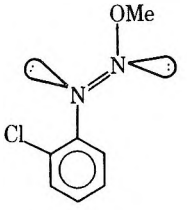
Substrate[b]	10^4k_{-1A}, s^{-1} (temp, °C) Methanol (R = CH_3)	Registry no.	Ethanol (R = C_2H_5)	Registry no.
2-FC_6H_4N=NOR	24.2 (15)	62375-77-3		
3-FC_6H_4N=NOR	16.8 (15)	62375-78-4		
4-FC_6H_4N=NOR	322. (15)	62375-79-5	10.3 (15)	62375-80-8
2-ClC_6H_4N=NOR	36.4 (15) 118 (30)[c]	58692-57-2	1.25 (15) 5.8 (30)	62375-81-9
3-ClC_6H_4N=NOR	14.4 (15)	58692-55-0	0.59 (15)	62375-82-0
4-ClC_6H_4N=NOR	75.5 (15)	58692-56-1	3.18 (15)	62375-83-1
2-BrC_6H_4N=NOR	27.1 (15)	62375-84-2		
3-BrC_6H_4N=NOR	16.5 (15)	62375-85-3		
4-BrC_6H_4N=NOR	64.2 (15)	62375-86-4		
2-IC_6H_4N=NOR	49.7 (15)	62375-87-5		
3-IC_6H_4N=NOR	27.5 (15)	62375-88-6		
4-IC_6H_4N=NOR	86.7 (15)	62375-89-7		
2-$NO_2C_6H_4N$=NOR	2.63 (30)	62375-90-0		
4-$NO_2C_6H_4N$=NOR	2.9[c] (30)	16020-14-7	0.19[c] (30)	58692-48-1

[a] Base concentration 0.1 M. α-Naphthol concentration 0.01–0.02 M. Rate constants were independent of α-naphthol concentration within this range. [b] Substrate concentration 2–3 × 10^{-5} M. [c] Reference 1.

$$k_\psi = k_{-1A}\left(\frac{k_{1S}}{k_{1A} + k_{1S}}\right)\left(\frac{k_D}{k_P + k_D}\right) \quad (2)$$

It is of interest to determine what species undergoes dediazoniation for a reaction proceeding by a carbanionic mechanism. It is also of considerable interest to measure directly k_{-1S} since this in conjunction with k_P would provide an independent method to measure the ratio k_{1S}/k_{1A} using eq 1, and allow us to determine substituent and solvent effects on this ratio.

It has also been observed[1] that the rate of ionization of the anti ether (k_{-1A}) for the 2-chloro compound was faster than expected on purely electronic grounds. This rate acceleration has been attributed to a steric effect in which a nonbonded interaction between the chlorine and the lone pair on either the α nitrogen (structure 1) or β nitrogen (structure 2) provides



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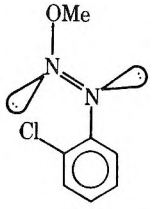

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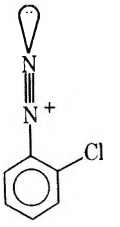
a driving force for the ionization. To confirm the steric nature of this effect, it is of interest to see if the magnitude is dependent on the size of the ortho substituent.

Discussion

Steric Effects of Ortho Substituents on k_{-1A} Values. Rate constants (k_{-1A}) for the ionization of *anti*-arylazo alkyl ethers are in Table I. For all of the halogen derivatives it can be seen that the rate of reaction for the ortho isomer is greater than that of the meta isomer. Since the electron-withdrawing inductive effect of the halogens would be much greater from the ortho position than from the more distant meta position, the rate of reaction for the ortho compounds should be less than that for the meta compounds. Indeed this effect is seen both in the hydrolysis of the corresponding halo-substituted cumyl chlorides[4] and in the basicity of the halo-substituted anilines.[5]

Thus the ortho-substituted arylazo methyl ethers must be experiencing some other effect to produce these results. This has been postulated as being a steric acceleration caused by a nonbonded interaction between the ortho halogen and the lone pair of either the α or β nitrogen.[1] This steric interaction would be less in the transition state for this reaction because of the linear arrangement of the nitrogen atoms in the product diazonium ion (3). If this is a steric acceleration then the



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magnitude should be dependent on the size of the halogen atom at the ortho position.

To enable us to get a quantitative measure of this steric acceleration for each halogen atom it is necessary to isolate the steric acceleration from other steric effects and from electronic effects of the substituents. To do this the ortho/para rate ratios for the ionization of the *anti*-arylazo methyl ethers are compared with the ortho/para rate ratios for the cumyl chloride solvolyses (Table II).

It can be seen that the ortho/para rate ratios for the hydrolyses of the fluoro, chloro, and bromo substituted cumyl chlorides are quite similar. This is the result of a balance[4] between the inductive effects of the ortho halogen groups (F > Cl > Br) and steric inhibition of resonance of the ortho halogen groups (Br > Cl > F).

For the ionization of the *anti*-arylazo methyl ethers, however, the ortho/para rate ratio for the fluoro compounds is much less than for the other halogens. This is because of the enhanced reactivity of the ortho chloro, bromo, and iodo compounds. Thus the steric acceleration for the ortho halogen substituted compounds is reflected in the ratio

$$\frac{\text{ortho/para rate ratio} - \text{anti ethers}}{\text{ortho/para rate ratio} - \text{cumyl chlorides}}$$

It can be seen that as the size of the halogen atom is increased (van der Waals' volumes) (F → Cl) then the steric acceleration becomes apparent. The steric acceleration is, however, lessened in the bromo and iodo compounds compared to the chloro compound possibly because of the in-

Table II. Comparison of Steric Effects in the Ionization of *anti*-Arylazo Methyl Ethers and the S_N1 Solvolyses of Cumyl Chlorides[a]

Halogen	Bond length[b] (C-halogen), Å	van der Waals[c] volume, cm^3/mol	Solvolysis of cumyl chlorides ortho/para ratio	Ionization of *anti*-arylazo methyl ethers ortho/para ratio	Ortho/para anti ethers / ortho/para cumyl chlorides
F	1.41	5.8	0.0234	0.0751	3.2
Cl	1.76	12.0	0.0258	0.482	18.7
Br	1.91	15.1	0.0292	0.422	14.5
I	2.10	19.6	0.0452	0.573	12.7

[a] Reference 4. [b] Reference 6. [c] Reference 7.

creased carbon–halogen bond length, but it is still considerably greater than for the fluoro compound.

In the cumyl chloride solvolysis, the planar intermediate would experience as much steric interaction between the side chain and an ortho substituent as the reactant. Thus there is no relief of steric strain on going from ground state to transition state for that reaction and no steric acceleration is observed.

Steric Effects of Ortho Substituents on k_P/k_D Ratios. From k_{-1A} and k_ψ values it is possible to derive k_P/k_D ratios for phase 2 reactions using eq 2. Since $k_{1S} \gg k_{1A}$ eq 2 can be simplified to give

$$k_\psi = k_{-1A}\left(\frac{k_D}{k_P + k_D}\right) \quad (3)$$

which on rearrangement gives

$$\frac{k_P}{k_D} = \left(\frac{k_{-1A}}{k_\psi} - 1\right) \quad (4)$$

From Table III we can see that k_P/k_D ratios are high for the ortho chloro, bromo, and iodo compounds when compared to the other halo derivatives. This is probably due to a steric acceleration in k_{-1S} values for the ortho compounds similar to the steric effects on the k_{-1A} values. It is obviously of interest to measure the rate of ionization of the *syn*-arylazo alkyl ethers (i.e., k_{-1S}).

Measurement of k_{-1S} Values. Since the rate of ionization of the *syn*-arylazo alkyl ethers (k_{-1S}) is very rapid, it is necessary to use a stopped-flow technique at 0 °C to follow this reaction. In addition it is only currently possible to measure k_{-1S} for compounds containing strong electron-withdrawing substituents (e.g., NO_2, CN, and CF_3) because of the manipulations that are required.

Cold solutions of the aryl diazonium salt and methoxide ion are rapidly mixed and are added to one of the syringes of the stopped-flow machine. The other syringe contains α-naphthol solution. On triggering the stopped-flow machine, the solutions are mixed in the reaction chamber and k_{-1S} is obtained from the rate of production of the azo dye **6**. It is necessary to premix the diazonium salt and methoxide ion solutions to ensure that there is no free diazonium ion present when the α-naphthol is added. As soon as the *syn*-arylazo alkyl ether is ionized, the product, i.e., the diazonium ion, is trapped by the α-naphthoxide ions in solution. The factor limiting measurement of k_{-1S} rates is that for some diazonium salts the phase 2 reactions are so rapid that by the time the solution is mixed with the naphthol solution all the syn ether has been converted either to dediazoniation product or to anti ether.

Comparison of k_{-1S} and k_{-1A} Values. From Table IV it can be seen that k_{-1S} for the *o*-nitro compound is much less than for the *p*-nitro compound. However, k_{-1A} values for the *o*- and *p*-nitro compounds (Table I) are very similar.

It is difficult to explain why k_{-1S} for the ortho compound is less than k_{-1S} for the para compound when k_{-1A} is so similar for these compounds. In fact molecular models show that steric interactions with ortho substituents are more serious in the ground states for the *syn*- than for the *anti*-arylazo alkyl ethers and we would expect k_{-1S} (ortho NO_2) > k_{-1S} (para NO_2) due to steric acceleration. This effect is being overshadowed by some more important effect.

Table III. Rate Constants (k_ψ) for the Dediazoniation of *anti*-Arylazo Alkyl Ethers in Basic[a] Alcoholic Solvents at 15 °C and k_P/k_D Ratios Derived from k_{-1A} and k_ψ

Substrate[b]	$10^4 k_\psi$, s^{-1} (k_P/k_D) Methanol (R = CH_3)	Ethanol (R = C_2H_5)
2-$FC_6H_4N{=}NOR$	2.22 (9.9)	
3-$FC_6H_4N{=}NOR$	1.91 (7.8)	
4-$FC_6H_4N{=}NOR$	14.9 (20.7)	6.84 (0.56)
2-$ClC_6H_4N{=}NOR$	1.15 (30.7)	0.83 (0.5)
	8.04[c] (13.8)	
3-$ClC_6H_4N{=}NOR$	1.60 (8.0)	0.59 (<0.1)
	12.3[c] (3.6)	
4-$ClC_6H_4N{=}NOR$	4.20 (17.0)	
	34.4[c] (4.9)	
2-$BrC_6H_4N{=}NOR$	1.35 (19.0)	
3-$BrC_6H_4N{=}NOR$	2.16 (6.6)	
4-$BrC_6H_4N{=}NOR$	4.54 (13.1)	
2-$IC_6H_4N{=}NOR$	1.25 (38.8)	
3-$IC_6H_4N{=}NOR$	3.58 (6.7)	
4-$IC_6H_4N{=}NOR$	4.31 (19.1)	
2-$NO_2C_6H_4N{=}NOR$	0.526[c] (4.0)	

[a] Base concentration 0.1 M. [b] Substrate concentration 2–3 × 10^{-5} M. [c] Temperature 30.0 °C.

An explanation that we favor is that for ionization of the *syn*-arylazo alkyl ether there is a later transition state with more charge development than for the ionization of the *anti*-arylazo alkyl ether. Thus for the syn ether the strong electron-withdrawing inductive effect of the o-nitro group caused a large reduction in the rate of ionization compared to the *p*-nitro compound. For ionization of the anti ether the early transition state with much less charge development is less sensitive to the inductive effect of the *o*-nitro group.

Some support for this explanation is available from the work of Zollinger.[8] Zollinger states that for reactions of diazonium salts with nucleophiles, if the transition state is reactant-like (early) then nucleophilic attack in the syn configuration is preferred. Similarly if the transition state is product-like (late) then nucleophilic attack in the anti configuration is preferred. By the law of microscopic reversibility therefore, ionization of the syn ether must have a late transition state and ionization of the anti ether must have an early transition state (Scheme II).

Substituent Effects on k_{-1S} and k_{-1A}. The above mechanistic conclusions depend on the relative electronic effects of *p*- and o-nitro groups on k_{-1A} and k_{-1S}. To exclude

Table IV. Rate Constants (k_{-1S}) for the Ionization of *syn*-Arylazo Alkyl Ethers in Basic[a] Alcoholic Solvents in the Presence of α-Naphthol[a] at 0 °C

Substrate[b]	10^4k_{-1S}, s^{-1}			
	Methanol (R = CH_3)	Registry no.	Ethanol (R = C_2H_5)	Registry no.
2-$NO_2C_6H_4N$=NOR	910	62375-91-1	6.20	62375-92-2
4-$NO_2C_6H_4N$=NOR	9800	58909-76-5	120	62375-93-3
4-CNC_6H_4N=NOR	26 000	62375-94-4		
4-$CF_3C_6H_4N$=NOR	107 000	62375-95-5		

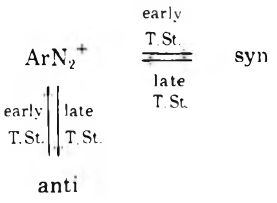
[a] Base concentration 0.1 M. α-Naphthol concentration 0.01 M. [b] Substrate concentration 8×10^{-5} M.

Table V. Rate Constants at 0 °C for the Phase 2 Reactions in Basic Methanol and Ethanol[a]

Substrate	10^4k_P, s^{-1}		10^4k_D, s^{-1}	
	Methanol	Ethanol	Methanol	Ethanol
2-$NO_2C_6H_4$-N=NOR	3.6		3.2	
4-$NO_2C_6H_4$-N=NOR	41.3	2.0	16.7	22.3

[a] Base concentration 0.1 M. Substrate concentration $2–3 \times 10^{-4}$ M.

Scheme II



alternative steric arguments the magnitude of the effects of para substituents on k_{-1A} and k_{-1S} was studied.

From Table IV and Figure 1, it can be seen that k_{-1S} is more sensitive to substituent effects than k_{-1A}.[1] This supports the interpretations based on the results for the nitro compounds.

Because of the problems associated with measurements of k_{-1S} the results for the 4-CN (±20%) and 4-CF_3 (±8%) compounds are not as dependable as those for the 4-NO_2 (±4%) compound.

Solvent Effects on k_{-1S} vs. k_{-1A}. If the transition state for ionization of the *syn*-arylazo alkyl ether is later (i.e., has a greater charge) than that for ionization of the *anti*-arylazo alkyl ether, then this should be reflected by the solvent effects on the two processes.

The effect of increasing the ion solvating power of the solvent by changing the solvent from ethanol (dielectric constant 24.2) to methanol (dielectric constant 31.5) is to increase k_{-1A} 15 times for the 4-nitro compound,[1] whereas the solvent effect on k_{-1S} is 82 (4-nitro) and 147 (2-nitro). These solvent effects are consistent with the transition states postulated above.

Solvent and Substituent Effects on Partitioning of the Diazonium Ion (k_{1S}/k_{1A}). Rate constants (k_P and k_D) for the phase 2 reactions of the *syn*-arylazo alkyl ethers are in Table V. From k_{-1S} and k_P values it is possible to calculate k_{1S}/k_{1A} ratios using eq 1.

For the *p*-nitro compound at 0 °C k_{1S}/k_{1A} = 237 in methanol and k_{1S}/k_{1A} = 54 in ethanol. For the *o*-nitro compound at 0 °C in methanol k_{1S}/k_{1A} = 252. That is, the syn ether is more favored in methanol, the more polar solvent. This is reasonable since the transition state to produce the syn isomer is early (i.e., high charge density) whereas that for the anti ether is later (i.e., lower charge density). Consequently, the more polar solvent favors the transition state with the least

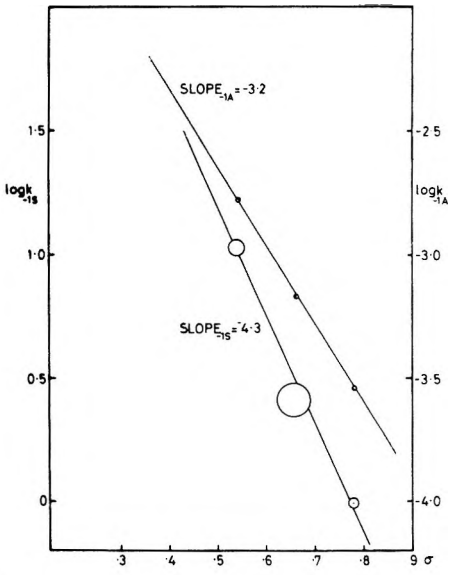


Figure 1.

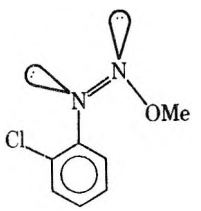
charge dispersal, which is consistent with the Hughes–Ingold solvent theory.[6]

The value of k_{1S}/k_{1A} for the 4-nitro compound (237) compares favorably with the previously obtained value (120), which was calculated using published data for k_P[9] and k_{-1S},[3] when you consider that the accuracy of Ritchie's rate (k_{1S}) and equilibrium ($K = k_{1S}/k_{-1S}$) constants is ca. 50% and that the k_P value was obtained by extrapolation to 23 °C of rate constants obtained between −16.4 and 2.5 °C.

The k_{1S}/k_{1A} ratios for the *p*-nitro compound (237) and the o-nitro compound (252) are very similar. It appears as if there is no substituent effect operating. However, it is quite feasible that the observed results are a composite of two opposing effects, i.e., a steric effect of the o-nitro group which may increase k_{1S}/k_{1A} since steric effects would be more severe in the reaction with the later transition state (production of the anti ether) and an electronic effect of the *o*-nitro group which may decrease k_{1S}/k_{1A} since the more electron-withdrawing *o*-nitro group should favor the reaction with the most charge dispersal (production of the anti ether).

Steric Effects on k_{-1A} vs. k_{-1S}. Since there is a later transition state (more bond breaking) for ionization of the syn ether than for ionization of the anti ether we would expect the steric effect of ortho halogens to be more pronounced for ionization of the syn ethers, because there is greater release of steric interactions on moving from reactant to transition state. In addition molecular models show that steric effects are more serious in the reactant ground state for the syn ethers (structures 4 and 5) than for the anti ethers (structures 1 and 2).

A result of the steric acceleration of k_{-1S} by ortho halogen groups is an increase in k_P which causes an increase in the



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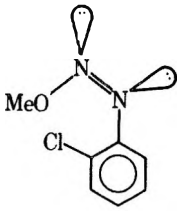

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k_P/k_D rate ratio for the ortho-substituted compounds compared to the corresponding meta- and para-substituted compounds (Table III). Variation of k_D cannot, however, be ruled out as an additional factor in the large k_P/k_D rate ratios for these compounds.

For the halo compounds the ortho/para ratio of k_P/k_D is consistently greater than the ortho/para ratio of k_{-1A}, i.e., the steric effect is more significant in k_{-1S} than k_{-1A}.

What Species Is Undergoing Dediazoniation? For the *p*-nitro compound it was concluded that the syn ether was the species actually undergoing dediazoniation.[1] This decomposition occurs by a free-radical mechanism. An example of a compound for which the mechanism of decomposition is ionic is the 2-chloro compound.[2]

For the *p*-nitro compound it was found that k_P, which involves ionization of the syn ether, was greatly reduced on solvent transfer (MeOH → EtOH), but k_D was slightly increased. The net result of this was a large reduction of the k_P/k_D ratio on transfer from methanol (k_P/k_D = 2.5) to ethanol (k_P/k_D = 0.09) at 0 °C.

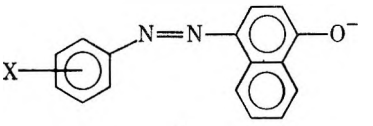
If the free diazonium ion is the species being dediazoniated then we would expect k_D also to be greatly reduced on solvent transfer and thus we would expect the ratio k_P/k_D to be relatively independent of the solvent.

From Table III it is clear that for both the 2-chloro and 3-chloro compounds the k_P/k_D ratio is greatly reduced on solvent transfer. Thus we conclude that in the carbanionic mechanism the species undergoing dediazoniation is also the *syn*-arylazo alkyl ether.

Experimental Section

Diazonium salts were prepared as described previously.[1] Alcoholic solvents (MeOH, EtOH) were dried by distillation from the corresponding magnesium alkoxide.[10]

Kinetic Methods. A. Kinetics in the Presence of α-Naphthol. The technique used to measure the rate of ionization of the anti ethers (k_{-1A}) has been described.[1] To measure the much faster rate of ionization of the syn ethers (k_{-1S}) the above method was adapted for use of the stopped-flow apparatus. Solutions of diazonium salt in acidic solution (0.004 M toluenesulfonic acid), α-naphthol, and sodium alkoxide were all cooled to 0 °C. The α-naphthol solution (0.02 M) was placed into one of the syringes of the stopped-flow apparatus which was also equilibrated to 0 °C. Then the diazonium salt solution (2×10^{-4} M, 4 mL) and sodium methoxide solution (1 M, 1 mL) were rapidly mixed and added to the other syringe of the stopped-flow apparatus. The stopped-flow apparatus was triggered, equal aliquots from each syringe were mixed, and the rate of production of the azo dye **6** was followed spectrophotometrically.



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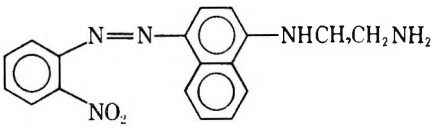
B. Kinetics in the Presence of *N*-1-Naphthylethylenediamine (NED). At 0 °C the kinetics of the phase 2 reactions (i.e., k_P and k_D) were followed as described previously[1] except that the azo dye produced from the o-nitro compound and NED (**7**) was not stable in



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acidic solution. Thus after sampling the reaction mixture and coupling in acidic NED, the mixture was made basic with a fixed amount of sodium methoxide. In basic methanol the azo dye **7** was quite stable.

C. Kinetics Using Direct UV Analysis (k_ψ). The rate of dediazoniation of the anti ether (k_ψ = anti → ArH) was measured by direct UV analysis as described previously.[1]

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References and Notes

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Catalytic Proton Bridge in Acetylimidazolium Ion Hydrolysis Implicated by a Proton Inventory

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The origin of the solvent isotope effect, k_{H_2O}/k_{D_2O} = 2.58, for the water-promoted hydrolysis of acetylimidazolium ion has been probed using the proton inventory technique. The proton inventory suggests that the observed effect is comprised of three transition state contributions. A chemical model is proposed for the hydrolysis transition state which contains a catalytic proton bridge between the reorganizing substrate and a water molecule serving as a general base catalyst.

The importance of acyl transfer and hydrolysis reactions in biochemical systems is well established and these reactions have been the object of considerable study.[2] Special emphasis has been placed on determining the importance and mechanisms of proton transfer in a variety of systems which can serve as models for the myriad biological systems.[3] In order to fully delineate the mechanism of biological acyl transfer reactions it is necessary to understand their nonbiological analogues in extreme detail. As part of a continuing effort to develop sophisticated techniques for the elucidation of such biochemical mechanisms we have applied the proton inventory technique to such a system.

The reactions of acetylimidazole have been studied under a variety of conditions by Jencks and co-workers.[4] We report here a study of the pH-independent water-promoted hydrolysis of acetylimidazolium ion in mixtures of protium oxide and deuterium oxide. Such a study constitutes a proton inventory and allows us to suggest likely roles for the water molecules in the transition state for this hydrolysis reaction.

Experimental Section

Materials. Acetylimidazole was prepared by the method of Boyer[5] and had mp 99–100 °C (lit.[5] mp 101.5–102.5 °C). Acetonitrile (Fisher reagent grade) was stirred over calcium hydride overnight, distilled from calcium hydride through a 30-cm fractionating column packed with glass helices, and stored under a nitrogen atmosphere. Deuterium oxide (99.8 atom % deuterium, Aldrich) was purified by distillation in an all-glass apparatus before use. Water was glass distilled before use. Sodium chloride (Fisher Certified) and concentrated hydrochloric acid (Mallinckrodt analytical reagent) were used as obtained.

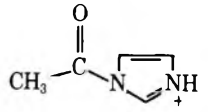
Kinetics. The hydrolysis of acetylimidazolium ion was monitored by following the decrease in absorbance at 245 nm using a Cary 118C UV–vis spectrophotometer equipped with a constant temperature cell compartment and cell holder to control the temperature at 25.00 ± 0.05 °C.

Reactions were initiated by injecting 50 μl of a stock solution which was 6×10^{-3} M acetylimidazole in acetonitrile into 3.00 ml of the appropriate HCl, DCl, or HCl–DCl solution. Stock 0.02 N HCl and DCl solutions in H_2O and D_2O, respectively, were prepared from concentrated hydrochloric acid. The ionic strength was maintained at 0.20 with sodium chloride. The amount of protium introduced into the 0.02 M DCl solution in D_2O in this manner was determined on a sample of the pure DCl–D_2O solution by Mr. Josef Nemeth.[6] This factor has been considered in the data analysis. Reactions in H_2O–D_2O mixtures were done using appropriate volumes of the HCl–H_2O and DCl–D_2O stock solutions.

Reactions were followed to greater than 80% completion and infinity absorbances were taken at 10 half-lives. The pH(D) of the reaction solutions was measured at the completion of each run using a Leeds and Northrup Model 7413 expanded scale pH meter equipped with a combination electrode. First-order rate constants were determined using a nonlinear least-squares computer program which calculates first-order rate constants from given time and absorbance values. These constants were confirmed by plots of log $(A_t - A_\infty)$ vs. time.

Results and Discussion

The hydrolysis of acetylimidazole was studied in 0.02 N HCl (DCl) and 0.02 N HCl–DCl mixtures at 25.00 ± 0.05 °C. Jencks and Carriuolo had previously shown that the hydrolysis of acetylimidazole exhibits a plateau in the pH–rate profile below about pH 3.[4a] This suggested that the reaction observed below pH 3 is the simple water-catalyzed hydrolysis of acetylimidazolium ion (1).



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The presence of this plateau in the pH–rate profile allowed the present study of the hydrolysis of 1 to be conducted in isotopic solvent mixtures in the absence of buffer components in order to characterize the role of the water molecules in this hydrolysis reaction.

Table I and Figure 1 show the dependence of the observed first-order rate constants on the isotopic composition of the solvent. Also included in Table I are calculated values of the observed rate constants based on a chemical model discussed below. The solid line drawn through the data points in Figure 1 is based on this chemical model.

The observed rate constants in the "pure" isotopic solvents are in good agreement with those reported in the literature.[4a] The solvent isotope effect, k_{H_2O}/k_{D_2O}, was determined to be 2.58 in this study, which is also in excellent agreement with the value of 2.5 in the literature.[4a] The nonlinear dependence of the rate constant on the atom fraction of deuterium in the solvent is obvious from Figure 1. The implications of this result will be discussed below.

Proton Inventory Background. A study of the dependence of a reaction rate constant on the atom fraction of deuterium in the solvent has been appropriately termed a proton inventory.[7] The magnitude of a measured solvent isotope effect allows speculation about its origin and the role of proton transfers, general and specific acid–base catalysts, nucleophilic catalysts, and solvent molecules in the reaction mechanism. The proton inventory allows one to suggest chemical models consistent with the observed solvent isotope effect. An analysis of each model allows us to specify the sites expected to contribute to the isotope effect. The magnitude of the contribution of each site to the observed effect can also be specified within reasonable limits for each model considered.

The theory of the proton inventory is well documented in the literature and is presented only in limited detail here.[8] Several recently published inventories serve to further illustrate its potential.[9] The observed reaction rate constant, k_n,

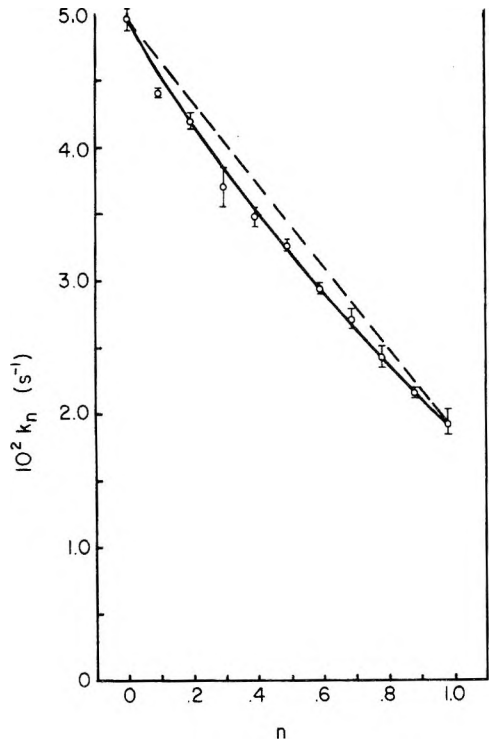


Figure 1. Dependence of the observed first-order rate constants for the hydrolysis of acetylimidazolium ion on the atom fraction of deuterium in the solvent. The data are taken from Table I. The solid line is calculated for the chemical model in (3) using $\phi_a^* = 0.55$ and $\phi_b^* = 0.83$. The dashed line is included to emphasize the nonlinear nature of the data.

in an H_2O–D_2O mixture is related to the rate constant in pure H_2O, k_0, by

$$k_n = k_0 \prod_i^{TS} (1 - n + n\phi_i^*) \Big/ \prod_j^{RS} (1 - n + n\phi_j) \qquad (1)$$

The rate constant in a given H_2O–D_2O mixture, specified by the atom fraction of deuterium n, is seen to depend on the ratio of i transition state (TS) terms to j reactant state (RS) terms. Each exchangeable isotopic transition state site i will be characterized by an isotopic fractionation factor ϕ_i^* and each exchangeable isotopic reactant state site j will be characterized by a similar factor ϕ_j. These isotopic fractionation factors are defined by eq 2. They express the deuterium

$$\phi_k = ([D]/[H])_k/([D]/[H])_{solvent} \qquad (2)$$

preference for the site in question relative to the deuterium preference for an average solvent site. Fractionation factors less than unity imply a greater preference for deuterium in the solvent than in the site in question (i.e., a greater preference for protium in the site in question). Since protium, the lighter isotope, tends to accumulate where the binding is weaker the site in question must contain the isotopic atom in a binding potential weaker than that in the bulk solvent. The inverse of this argument can be used to show that fractionation factors greater than unity are associated with binding potentials tighter than those in the bulk solvent for the isotopic atoms in question.

The curvature exhibited by a plot of k_n vs. n depends upon the magnitude of the observed solvent isotope effect and the number of transition state and reactant state contributors to the measured effect. It can be seen in eq 1 that only sites which change fractionation factor on going from the reactant state to the transition state will be important in determining the solvent isotope effect. A site whose fractionation factor remains the same in the reactant state and transition state will contribute equal terms to the denominator and numerator of eq 1 and they will cancel one another.

Table I. First-Order Rate Constants for the Hydrolysis of Acetylimidazolium Ion in Mixtures of 0.02 N HCl–H_2O and 0.02 N DCl–D_2O at 25.00 ± 0.05 °C [a]

Atom fraction of deuterium (n)	No. of runs[b]	$10^5 k_n$, s^{-1}	$10^5 k_n$ calcd,[c] s^{-1}
0.000	8	4966 ± 81[d]	4966
0.098	3	4413 ± 32	4590
0.196	4	4193 ± 62	4213
0.294	3	3710 ± 149	3889
0.392	3	3497 ± 55	3563
0.490	3	3267 ± 47	3253
0.587	3	2937 ± 42	2961
0.685	3	2707 ± 67	2682
0.783	4	2430 ± 77	2417
0.881	2	2165 ± 35	2167
0.979[e]	5	1926 ± 100	1930

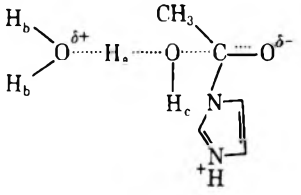
[a] Ionic strength was maintained at 0.20 with NaCl. [b] Combined runs from two independent experiments conducted by different workers. [c] Calculated based on the model in (3) using $\phi_a^* = 0.55$ and $\phi_b^* = 0.83$. [d] Error limits are standard deviations. [e] Atom fraction of deuterium in "100%" 0.02 N DCl–D_2O as determined by Mr. Josef Nemeth.[6]

For a reaction in which all the exchangeable reactant state sites have $\phi = 1.0$ the denominator of eq 1 becomes unity. This is frequently the case when all of the isotopic reactants are solvent molecules whose exchangeable isotopic sites have fractionation factors of unity by the definition of eq 2. In these cases we need only consider the transition state contributions to the solvent isotope effect.

Contributions by more than one proton in the transition state will result in curvature in plots of k_n vs. n except under highly unlikely circumstances involving cancellations of large numbers of transition state and reactant sites.[10] The analysis of a nonlinear proton inventory is illustrated in the discussion of acetylimidazolium ion hydrolysis.

Fitting a Chemical Model to the Observed Proton Inventory for the Hydrolysis of 1. The analysis of the proton inventory for the hydrolysis of 1 is simplified somewhat since the denominator of eq 1 can be neglected. It then becomes necessary to formulate a reasonable chemical model for the transition state and compare the predicted proton inventory for this model with the experimental inventory. Reasonable models, in this case, must involve multiple protons in order to account for the curvature in the plot of k_n vs. n.

A transition state model based on information gleaned from the study of general base catalysis of this reaction[4] and utilizing the concept of a "catalytic proton bridge" of Schowen and co-workers[7,11] is shown in (3).



(3)

The proton bridge (H_a) serves to link a water molecule acting as a general base catalyst to the reorganizing substrate function. This model is consistent with the observation of general base catalysis in the hydrolysis of acetylimidazolium ion and the fact that the "water point" falls on the Brønsted line ($\beta = 0.34$).[4c]

The model in (3) has four isotopically exchangeable protons which could contribute to the observed solvent isotope effect. The proton (H_a) being transferred to the water molecule

acting as the general base should contribute a primary solvent isotope effect to the overall effect. Such protons frequently exhibit fractionation factors of about 0.5 which corresponds to an isotope effect contribution of $k_{H_2O}/k_{D_2O} \sim 2$ for this "in-flight" proton.[8c] The proton H_c should have a fractionation factor near unity and will thus contribute nothing to the observed effect. The two H_b protons will contribute secondary isotope effects and would exhibit fractionation factors of 0.69 each if H_a was fully transferred to generate a fully developed hydronium ion.[8c] If H_a is not transferred to any extent at all in the transition state then the fractionation factors for each H_b would be unity. We have thus established reasonable limits for the fractionation factors associated with the two H_b protons.

A quantitative estimate of the fractionation factors for each H_b can be made using an extension of the Brønsted hypothesis as illustrated in eq 4.[8e]

$$\phi_b^{TS} = (\phi_b^{RS})^{1-\beta}(\phi_b^{PS})^{\beta} \quad (4)$$

The transition state fractionation factor for each H_b is determined by the extent of development of hydronium ion character by the general base water molecule in the transition state. This is correlated with the Brønsted β value. Substituting unity for the reactant state fractionation factor for H_b (ϕ_b^{RS}), 0.69 for the product state (i.e., a full hydronium ion) fractionation factor for H_b (ϕ_b^{PS}) and the observed Brønsted β of 0.34 into eq 4 we calculate a transition state fractionation factor (ϕ_b^{TS}) of 0.88. Substitution of this value for ϕ_b^*, values of the observed rate constant in protium oxide and deuterium oxide, and the value of n which corresponds to "pure" deuterium oxide (0.979 in this case) into eq 5 allows us to calculate a value of ϕ_a^* consistent with the observed effect. This gives $\phi_a^* = 0.53$ and would correspond to a primary isotope effect contribution of $k_{H_2O}/k_{D_2O} = 1.89$ for H_a. Equation 5 is a three-proton version of the generalized form in eq 1 based on a solvent isotope effect attributable to only three transition state contributions as depicted in (3). Substitution of various values of n into eq 5 allows one to calculate a theoretical proton inventory for this model.

$$k_n = k_0(1 - n + n\phi_a^*)(1 - n + n\phi_b^*)^2 \quad (5)$$

It was necessary to slightly alter the values of ϕ_a^* and ϕ_b^* in order to generate a model-based proton inventory consistent with the experimental inventory. The values of k_n calculated using this refined model ($\phi_a^* = 0.55$ and $\phi_b^* = 0.83$) are included in Table I for comparison with the experimental values. The solid line of Figure 1 is based on this model and accurately describes the nonlinear nature of the experimental inventory.

Conclusion

The transition state model in (3) having $\phi_a^* = 0.55$ and $\phi_b^* = 0.83$ describes the observed proton inventory sufficiently well to suggest that the transition state for the water-catalyzed hydrolysis of acetylimidazolium ion does indeed involve a catalytic proton bridge between a water molecule acting as a general base and the reorganizing substrate. This is highly similar to the transition state structure suggested earlier by Wolfenden and Jencks.[4b] Other models consistent with the proton inventory alone could be derived but the model of eq 3 is chemically consistent with the observed general base catalysis and Brønsted β value.

The results of this study show that the proton inventory technique can be used to confirm mechanisms suggested by classical Brønsted data and give a more detailed picture of the transition state structure for the reaction. The implications for mechanistic studies of enzymatic systems are equally important. Such systems do not lend themselves to the buffer catalysis studies required for making a Brønsted plot but are susceptible to study using the proton inventory technique. The excellent agreement illustrated for the two techniques in this system emphasizes the potential of this mechanistic probe in such biological studies.

The observation of a proton bridge serves to illustrate the potential importance of such catalytic mechanisms in enzyme catalysis. Recent proton inventories of several enzymatic systems thought to utilize charge-relay type mechanisms have implicated the involvement of such bridges in some cases. However, one cannot conclude that all simple "water reactions" will employ such proton bridges and exhibit nonlinear proton inventories. A recent inventory of the water-promoted hydrolysis of bis(4-nitrophenyl) carbonate gave a linear dependence of k_n on n at 50 °C.[9d] Clearly more work is needed in this area before general trends and factors controlling the shapes of proton inventories will be obvious.

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Intramolecular Catalysis of Sulfonamide Hydrolysis. 3. Intramolecular Acid-Catalyzed Hydrolysis of (*Z*)-2-Carboxy-*N*-methyl-*N*-phenylethenesulfonamide and *N*-Methyl-*N*-phenylmaleamic Acid under Conditions of Varying Water Ordering Effects

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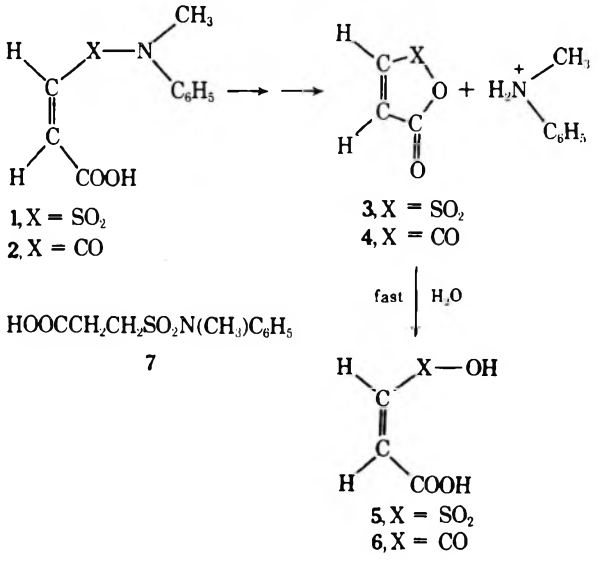
This paper reports rate constants and activation parameters for the intramolecular carboxyl-catalyzed hydrolysis of the title sulfonamide (1) and carbonamide (2) in *t*-BuOH–H_2O as a function of the mole fraction of water (n_{H_2O}). For both processes, reaction rates are retarded with decreasing n_{H_2O} in the range n_{H_2O} = 1.00–0.80. The variation of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ as a function of n_{H_2O} shows mirror image behavior. Both quantities pass through extremes at n_{H_2O} ca. 0.95, the solvent composition for which the formation of hydrophobic hydration spheres reaches a maximum. Sulfonamide 7, the saturated analogue of 1, hydrolyzes 87 times slower than 1 (at 39.8 °C). This rate difference is predominantly determined by the $\Delta H^{\ddagger}$ terms, indicating that contributions from rotational entropy of the reactants are not directly reflected in the activation parameters. A tentative explanation for this result is offered in terms of different solvation requirements of the hydrolyses of 1 and 7.

A variety of chemical and biochemical processes in water show enthalpy–entropy compensation upon perturbation of the aqueous environment.[1] It has been proposed that such behavior is a ubiquitous property of water and it has, inter alia, been employed as a diagnostic test for the participation of water in protein processes. In these studies, *linear* ΔH–ΔS relationships of the type $\Delta H = \alpha + T_c\Delta S$ have often been claimed, and the isokinetic temperatures (T_c) derived from the estimated slopes of the regression lines have been tested for their significance[2] and interpreted.[3] Despite extensive previous work, recent thorough statistical analysis has indicated that detectable extrathermodynamic enthalpy–entropy effects are rare.[4] Nevertheless, analysis of enthalpy and entropy factors in intramolecular and enzymic reactions is of great interest since this may shed light on the effects of geometrical constraints, solvation, and microenvironment which are of crucial importance in determining the efficiency of intramolecular catalysis.[5,6]

In the present study we compare rate constants and thermodynamic quantities of activation for the hydrolysis of (*Z*)-2-carboxy-*N*-methyl-*N*-phenylethenesulfonamide (1)[7] and *N*-methyl-*N*-phenylmaleamic acid (2) in *t*-BuOH–H_2O. In both reactions the neighboring carboxyl group provides effective intramolecular catalysis for hydrolysis of the (sulfon)amide bond (Scheme I). In addition, some data have been obtained for 7, the saturated analogue of 1. The *t*-BuOH–H_2O system has been chosen in order to probe into the effect of varying diffusionally averaged "water structure" on the kinetic parameters of the processes[8] shown in Scheme I. There is abundant evidence[9] that the addition of *t*-BuOH to water leads initially to *increased* water–water hydrogen bonding, until the formation of hydrophobic hydration spheres reaches a maximum at n_{H_2O} ca. 0.95 (n_{H_2O} = mole fraction of water). Further addition of *t*-BuOH then causes a gradual collapse of the solvent structure. Several physical properties[9] and some chemical processes[1a,5,8,10] respond to these water ordering effects.

Scheme I



Results and Discussion

Hydrolysis of 1. The intramolecular carboxyl-catalyzed hydrolysis of 1 [pK_A = 2.01, $k(D_2O)/k(H_2O)$ = 1.36 at pH 1, 40 °C][11] most likely involves rate-determining nucleophilic attack of the carboxylate anion on the sulfur atom of the N-protonated sulfonamide, to yield the cyclic mixed anhydride 3.[7,12] Rate constants (k_{obsd}) and activation parameters as a function of n_{H_2O} in *t*-BuOH–H_2O (n_{H_2O} = 0.80–1.00) are listed in Table I.

Consistent with the proposed mechanism, reaction rates are retarded markedly with increasing concentrations of *t*-BuOH. Figure 1 portrays the approximately linear relationship between $\Delta G^{\ddagger}$ and the dielectric constant (ϵ).[13] There exists no linear correlation between log k_{obsd} and solvatochromism scales like the *Z* or E_T values. For the sake of comparison, we have also determined some rate constants for hydrolysis of 1 in ethanol–H_2O and 2,2,2-trifluoroethanol (TFE)–H_2O (Table I). Again, k_{obsd} values decrease upon lowering the dielectric constant, the effect being less pronounced in TFE–H_2O than in EtOH–H_2O. The latter effect may indicate increased transition state stabilization by hydrogen bonding interactions with TFE.

In contrast to the monotonic increase of $\Delta G^{\ddagger}$ in *t*-BuOH–H_2O, $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ clearly show mirror image behavior

Table I. Rate Constants and Activation Parameters for the Hydrolysis of 1 and 7 in Various Aqueous Mixtures at Various Mole Fractions of Water (n_{H_2O})

Compd	Solvent system	n_{H_2O}	ϵ	$k_{obsd} \times 10^4$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	H_2O	1.00	73.5	11.68[a]	18.6 ± 0.2	−12.4 ± 0.5
1	*t*-BuOH–H_2O	0.96	61.1	8.27[a]	18.1 ± 0.3	−14.8 ± 1.1
1	*t*-BuOH–H_2O	0.95	58.7	6.79[a]	18.1 ± 0.3	−15.1 ± 0.9
1	*t*-BuOH–H_2O	0.94	56.4	5.81[a]	17.7 ± 0.2	−16.8 ± 0.7
1	*t*-BuOH–H_2O	0.90	47.5	3.58[a]	18.6± 0.2	−14.7 ± 0.6
1	*t*-BuOH–H_2O	0.85	38.6	2.43[a]	19.0 ± 0.2	−14.5 ± 0.6
1	*t*-BuOH–H_2O	0.80	31.7	1.82[a]	19.1 ± 0.2	−14.7 ± 0.7
1	EtOH–H_2O	0.95	67.3	9.31[b]		
1	EtOH–H_2O	0.85	56.4	5.23[b]		
1	EtOH–H_2O	0.75	47.5	2.75[b]		
1	TFE–H_2O	0.95	66.1	9.22[b]		
1	TFE–H_2O	0.85	53.2	6.12[b]		
1	TFE–H_2O	0.75	44.5	5.23[b]		
7	H_2O	1.00		0.402[c]	21.9 ± 0.2	−10.8 ± 0.7
7	*t*-BuOH–H_2O	0.95		0.134[c]	20.7 ± 0.2	−16.8 ± 0.7

[a] At 39.8 °C and pH ca. 0.85. [b] At 39.0 °C and pH ca. 0.85. [c] At 49.7 °C and pH ca. 1.50.

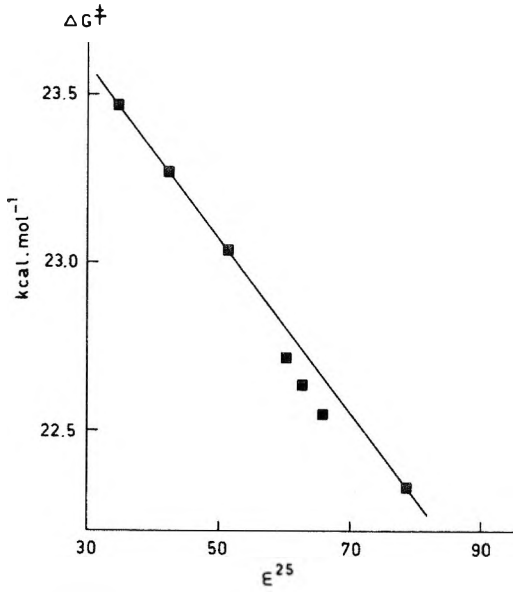


Figure 1. Plot of $\Delta G^{\ddagger}$ vs. ϵ for the intramolecular carboxyl-catalyzed hydrolysis of 1 in *t*-BuOH–H_2O at 25 °C.

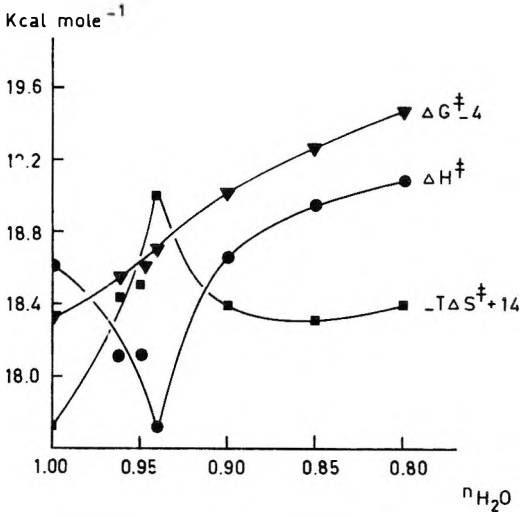


Figure 2. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the intramolecular carboxyl-catalyzed hydrolysis of 1 in *t*-BuOH–H_2O at 25 °C.

(Figure 2). Although the overall changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are well outside experimental error, the variations are too small to justify a rigorous test for linear $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ compensation. However, our results demonstrate for the first time that a simple, intramolecular catalyzed hydrolysis may change from a process in which entropy changes primarily modulate $\Delta G^{\ddagger}$ (n_{H_2O} = 1.00–0.94) to one in which enthalpy changes primarily control changes in $\Delta G^{\ddagger}$ (n_{H_2O} = 0.94–0.80). This change occurs around the "magic mole fraction" of water (n_{H_2O} = 0.95) in the *t*-BuOH–H_2O solvent system. Previously, several chemical phenomena have been found to pass through extremes at high water concentrations in alcohol–water mixtures.[9] This also applies to some protein reactions as illustrated by the enthalpy of denaturation of ribonuclease,[14] which exhibits a maximum at n_{H_2O} ca. 0.85 in EtOH–H_2O at 10 °C. There is considerable evidence in several cases that this type of behavior reflects changes in "water structure" induced by the cosolvent and accompanying changes in the magnitude of hydrophobic interaction between reactants and *t*-BuOH.[8,10]

In view of the absence of thermodynamic data for the initial state of 1 in *t*-BuOH–H_2O, we have not attempted a more detailed interpretation. We only note that the minimum of $\Delta H^{\ddagger}$ at the n_{H_2O} of maximum water–water interaction may be reconciled with maximal hydrogen bond stabilization of the polar transition state when the structural integrity of the solvent reaches a maximum.[10]

It is interesting to compare the kinetic parameters for the intramolecular catalyzed hydrolysis of 1 with those of 7 (pK_A = 3.58). The pH–rate profile for 7 is shown in Figure 3. This sulfonamide hydrolyzes via a similar pathway to 1, as indicated by the solvent deuterium isotope effect $k(D_2O)/k(H_2O)$ = 1.29 (at 38.6 °C, pH 1.53), but the catalytic efficiency of the COOH group is less than in 1 [k_{obsd} (1)/k_{obsd} (7) = 87 at 39.8 °C]. Since an additional mode of rotation is available in 7, one could argue that the rate difference finds its major origin in different entropic contributions[15] to the efficiency of the intramolecular catalyzed process.[16,17] In fact, the difference in $\Delta G^{\ddagger}$ is brought about primarily by different enthalpic contributions at both n_{H_2O} = 1.00 and 0.95 (Table I). A possible explanation involves the consideration of different solvation changes upon hydrolysis of 1 and 7. Thus, we suggest that the

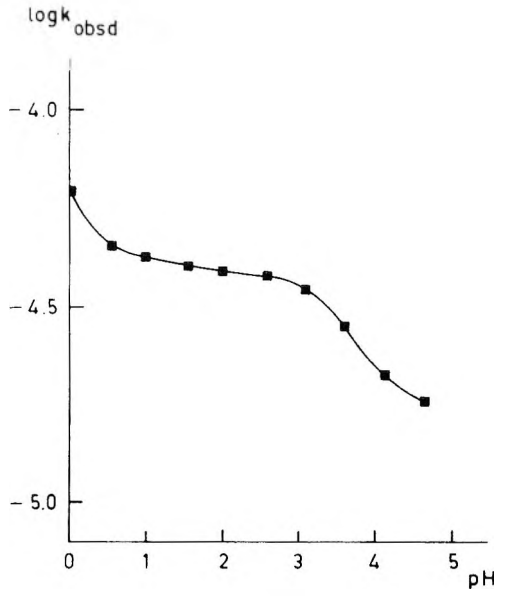


Figure 3. pH–rate profile for the hydrolysis of 7 in water at 49.5 °C.

Table II. Rate Constants (k_{obsd}) and Activation Parameters for the Hydrolysis of 2 in *t*-BuOH–H_2O at 40 °C

	pH 2.85			pH 0.87
n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$k_{obsd} \times 10^4$, s^{-1}
1.00	2.88	19.3 ± 0.2	−13.0 ± 0.7	24.2
0.96	1.43	18.7 ± 0.2	−16.5 ± 0.7	14.6
0.95	1.22	18.2 ± 0.2	−18.2 ± 0.7	12.5
0.94	1.09	18.6 ± 0.3	−17.4 ± 1.0	11.1
0.90	0.681	19.6 ± 0.3	−15.3 ± 1.0	7.28
0.85	0.467	19.6 ± 0.3	−15.9 ± 1.0	5.78
0.80	0.341	19.8 ± 0.2	−15.9 ± 0.7	5.09

entropy loss due to bringing together the sulfonamide and carboxyl groups in 7 will be largely cancelled by the entropy gain from partial desolvation of both groups when they are located in proper proximity necessary for reaction. Since the latter process, which is of course absent in the hydrolysis of 1, will be associated with a net loss of free enthalpy, the rate difference between 1 and 7 will then appear in $\Delta H^{\ddagger}$ rather than in $\Delta S^{\ddagger}$. A similar type of analysis has been advanced by Larsen[18] in his discussion of Jenck's theory[5,6] for the driving force for rate accelerations in intramolecular and enzymic reactions in aqueous media.

Hydrolysis of 2. Carbonamide hydrolysis catalyzed by a neighboring carboxyl group has been studied in detail.[19] Usually, a tetrahedral intermediate is formed upon nucleophilic attack of the carboxylate group on the O-protonated carbonamide function which subsequently breaks down in a rate-determining step.

The log k_{obsd}–pH profile for the acid-catalyzed hydrolysis of 2 is shown in Figure 4 and indicates that the rate of hydrolysis of 2 rapidly increases below pH ca. 2. This is in accord with recent work[20] which showed that the hydrolysis of maleanilic acids is much more susceptible to general acid catalysis than that of maleamic acids.[21] Since we are most interested in the solvent dependence of the activation parameters for the "water reaction" (which most likely involves rate-limiting decomposition of the tetrahedral intermediate), we have measured the pH-independent rate constant (k_{obsd}) as a function of temperature (Table II) at pH ca. 2.8 in *t*-BuOH–H_2O. For comparison, rates are given for the same n_{H_2O} at pH 0.85 (ca. 90% general acid catalysis). At both pH values the rate constants decrease with decreasing n_{H_2O} but show no simple correlation with macroscopic solvent parameters like ϵ and $(\epsilon - 1)/(2\epsilon + 1)$ or with solvatochromism scales like Z or E_T values. As in the case of 1, the monotonic increase of $\Delta G^{\ddagger}$ for the "water reaction" of 2 conceals mutually compensating changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. As shown in Figure 5,

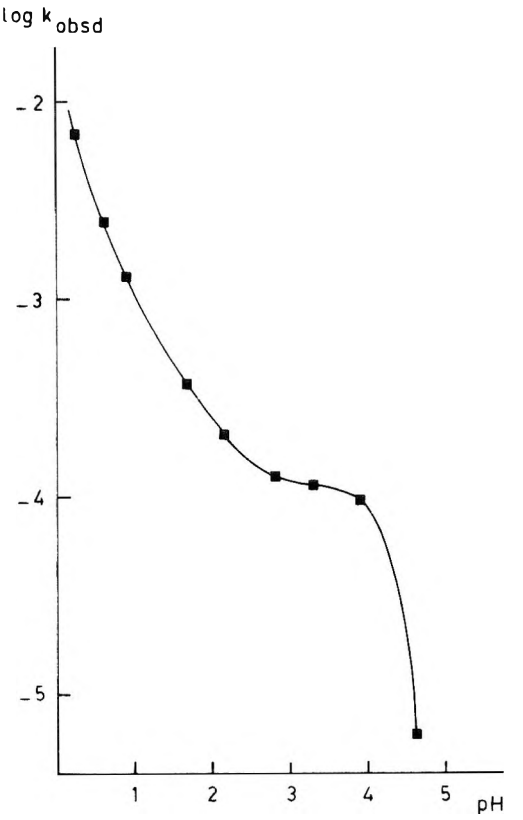


Figure 4. pH–rate profile for the hydrolysis of 2 in *t*-BuOH–H_2O, n_{H_2O} = 0.95 at 40.9 °C.

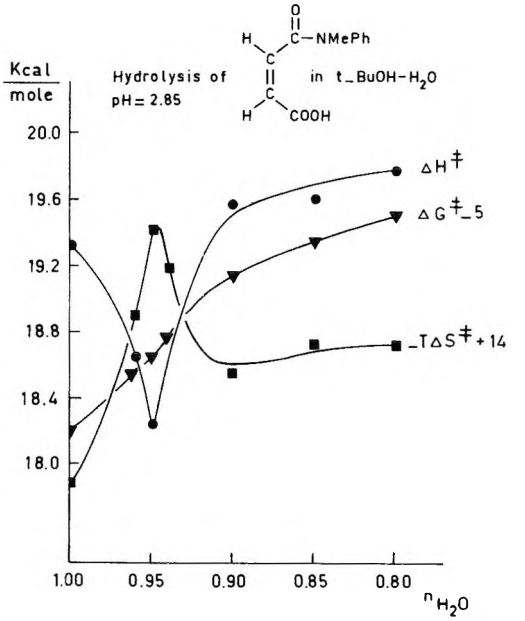


Figure 5. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the intramolecular carboxyl-catalyzed hydrolysis of 2 in *t*-BuOH–H_2O at pH 2.85 (25.0 °C).

$\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ pass through extrema located around n_{H_2O} = 0.95, the solvent composition of maximum structural integrity.

In conclusion, we note that the rates of the intramolecular carboxyl group assisted hydrolysis of **1**, **2**, and **7** are retarded by the addition of organic cosolvents to water. The gradual increase of $\Delta G^{\ddagger}$ is composed of larger, mutually compensating changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

Despite the difference in mechanism, the hydrolysis of both **1** and **2** exhibits extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ at n_{H_2O} = 0.95 in *t*-BuOH–H_2O, which is the solvent composition of maximum water ordering. The extremes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ most likely reflect secondary solvation effects due to the formation of hydrophobic cavity type hydration spheres induced by the addition of the first 5 mol % of *t*-BuOH. In addition, comparison of the activation parameters for **1** and **7** provides further evidence for the notion[5] that contributions from rotational entropy of the reactants generally cannot be determined from the observed entropy of activation as measured in aqueous reaction mixtures.

Experimental Section

Materials. Sulfonamide **1** was synthesized as reported previously.[7] The new compounds **2** and **7** were prepared according to standard procedures and gave the expected acid and amine upon hydrolysis.

***N*-Methyl-*N*-phenylmaleamic acid (2),** mp 111.3–111.8 °C. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.53; N, 6.75.

2-Carboxy-*N*-methyl-*N*-phenylethanesulfonamide (7), mp 144.5–144.7 °C. Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found: C, 49.37; H, 5.36; N, 5.89; S, 13.08.

The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit. D_2O was obtained from Reactor Centrum Nederland (99.94 ± 0.05% D_2O) and was used as such. *t*-BuOH and TFE were obtained from Aldrich and anhydrous EtOH was obtained from Merck and were of the best quality available. The solvent mixtures were all made up by weight.

Kinetic Measurements. The rates of hydrolysis of **1**, **2**, and **7** were determined by following the change of the absorbance at 235, 240, and 224 nm, respectively. The reactions were carried out in 1-cm quartz cells, which were placed in the adequately thermostated (±0.05 °C) cell compartment of a Beckman Model 24 spectrophotometer. About 5 μl of a concentrated solution of the sodium salt of **1** in H_2O, of **2** in *t*-BuOH, and of **7** in EtOH were added to the aqueous reaction media in the cuvette (3 mL) by means of a capillary pipet and under vigorous shaking. Initial substrate concentrations were ca. 5×10^{-5} M for **1** and **2** and ca. 10^{-4} M for **7**. Measurements were taken for at least 3 half-lives. Accurate pseudo-first-order kinetics were observed and k_{obsd} values were reproducible to within 2%. In the mixed solvent systems pH measurements were complicated by the presence of the organic cosolvent. However, this constitutes no serious problem since the k_{obsd} values refer to pH-independent rate constants. In all cases the breakdown of the cyclic anhydride intermediate was too fast to influence the observed rate. Activation parameters were calculated from k_{obsd} values at four different temperatures in the range of 34.5–48.5 °C for **1**, 39.5–52.0 °C for **2** at pH 2.85, and 38.5–54.0 °C for **7**. The errors listed in Tables I and II are statistical errors.

Registry No.—**1**, 59632-54-1; **2**, 62416-03-9; **7**, 62416-04-0.

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(11) The effective concentration of the COOH group in **1** is ca. 10^8 M. For a definition of this quantity see T. H. Fife, J. E. C. Hutchins, and M. S. Wang, *J. Am. Chem. Soc.*, **97**, 5878 (1975).

(12) At present there is no evidence that the reaction proceeds via a pentacoordinated intermediate. For recent discussions on nucleophilic displacement reactions at sulfonyl sulfur, see (a) O. Rogne, *J. Chem. Soc., Perkin Trans. 2*, 1468 (1975); (b) A. R. Haughton, R. M. Laird, and M. J. Spence, *ibid.*, 637 (1975).

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(16) The different rates may also be partly determined by the different geometries of the reactive syn-planar conformations of **1** and **7** which are transferred into the cyclic mixed anhydride. However, we contend that these factors will be primarily reflected in $\Delta H^{\ddagger}$ and will not affect significantly our discussion of the $\Delta S^{\ddagger}$ values.

(17) For the intramolecular COOH-catalyzed hydrolysis of carbonamides the situation is quite different and may reflect the difference in rate-determining step, i.e., breakdown of the cyclic, tetrahedral intermediate. Compare (a) T. Higuchi, L. Eberson, and A. K. Herd, *J. Am. Chem. Soc.*, **88**, 3805 (1966); (b) A. J. Kirby and P. W. Lancaster, *J. Chem. Soc., Perkin Trans. 2*, 1206 (1972).

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N-Alkyl (Aryl) Sulfonylphosphoramidate Monoesters

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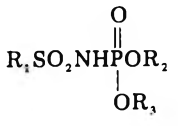
The syntheses and chemical and enzymatic properties of four N-substituted sulfonylphosphoramidate monoesters (I) are presented. These compounds, which were prepared from N-substituted sulfonylphosphoramidate diesters by dealkylation using sodium iodide, are electronic analogues of phosphomonoesters. Their first pKs lie in the range from 1 to 2 and the second in the range from 5.5 to 7. The compounds are not substrates for alkaline phosphatases from two different sources but are weak competitive inhibitors (K_is $\approx 10^{-3}$ M).

In the course of research on the synthesis and properties of analogues of phosphomonoesters, we recently investigated monoesters of N-substituted phosphoramidate (I).



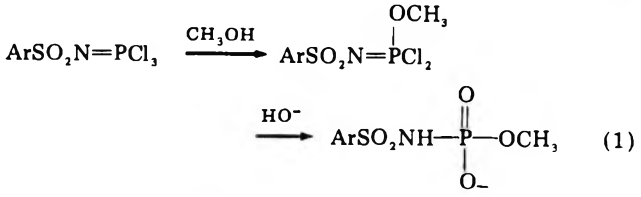
I, R_1 = alkyl or aryl; R_2 = alkyl; R_3 = H
II, R_1 = alkyl or aryl; R_2, R_3 = alkyl
III, R_1 = alkyl or aryl; R_2, R_3 = H

Gilyarov et al.[2] and Izako et al.[3] have shown that the corresponding diesters (II) have pK_a values ranging from 1.49 to 2.36; these pK_a values are in the range of the first pK_a for orthophosphoric acid, 2.12.[4] We expected, on the basis of electrostatic effects, that the removal of one ester group from the diesters would give monoesters with two ionization constants closely resembling those of monoesters of phosphoric acid; they should have pK_a values in the ranges 1–2 and 5.5–7.[4]

Although a variety of methods serve to synthesize N-substituted phosphoramidic acids (III) and their diesters (II),[5] no systematic approach to the series of monoesters (I) had previously been devised. The corresponding diesters are hydrolytically stable in neutral solution and decompose only very slowly in alkaline media.[6] Thus, although phosphoramidate monoesters can be prepared from the corresponding diesters by alkaline cleavage,[7] the N-substituted sulfonylphosphoramidate monoesters cannot be made in the same fashion. Undoubtedly the anionic character of the starting diesters severely inhibits nucleophilic attack by water or hydroxide ion on the phosphorus atom. The same inhibitory effect is observed in the alkaline hydrolysis of simple phosphodiesters.[8]

An alternative possibility for the preparation of N-substituted sulfonylphosphoramidate monoesters, namely, acid-catalyzed hydrolysis of diesters, yields mostly products resulting from P–N cleavage,[6] i.e., sulfonamide derivatives and diesters of phosphoric acid.

Kirsanov et al.[9] have published the only reported synthesis of a monoester of N-substituted sulfonylphosphoramidate. They obtained it from partial alcoholysis of a trichloro *N*-sulfonylphosphorimidate, followed by hydrolysis of the intermediate (eq 1). However, the difficulties inherent in partial



(1)

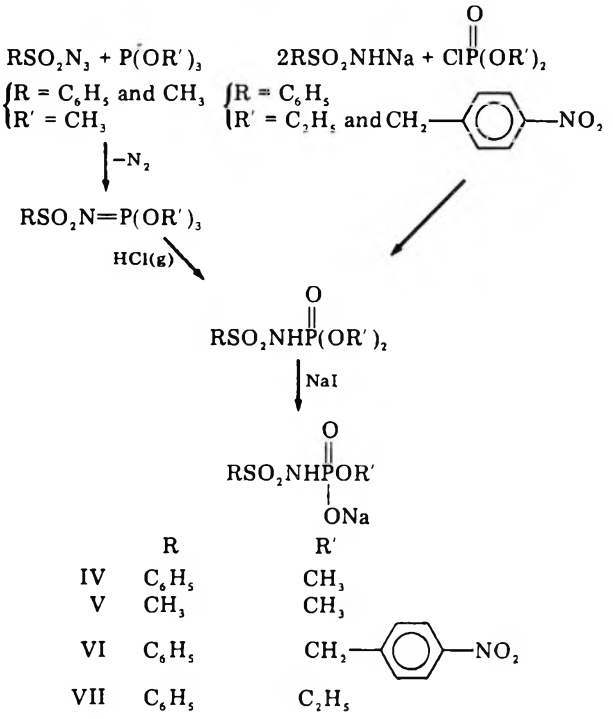
alcoholyses of trihalophosphoryl derivatives and the apparent limited applicability and low yields of Kirsanov's method prompted us to search for a more general and efficient synthetic method; ideally, such a method would use the readily accessible diesters II as intermediates.

This paper reports that dealkylation of four diesters of N-substituted sulfonylphosphoramidate by sodium iodide in acetone gives moderate to high yields of the easily purified monoesters and, in fact, constitutes an efficient method of entry into the monoester series. The new compounds were compared to simple phosphomonoesters with respect to their pK_a values and their effects as inhibitors for alkaline phosphatase were measured.

Results and Discussion

Scheme I presents the method of synthesis used for the preparation of the title compounds. The precursor diesters,

Scheme I



	R	R′
IV	C_6H_5	CH_3
V	CH_3	CH_3
VI	C_6H_5	CH_2–(p-C_6H_4)–NO_2
VII	C_6H_5	C_2H_5

two of which had previously been reported (see Experimental Section), were prepared by two different routes. The first route, used by Gilyarov et al.,[2] involved the reaction of trimethyl phosphite with the appropriate alkyl or arylsulfonyl azide to give the intermediate trimethyl N-substituted sulfonylphosphorimidates which were easily dealkylated by gaseous HCl to the diester; the second route involved the direct condensation of the appropriate diester chlorophosphate with the sodium salt of benzenesulfonamide and is based on the work of Rätz.[10]

The final dealkylation of the diester by sodium iodide was carried out following standard procedures for this reaction;[11]

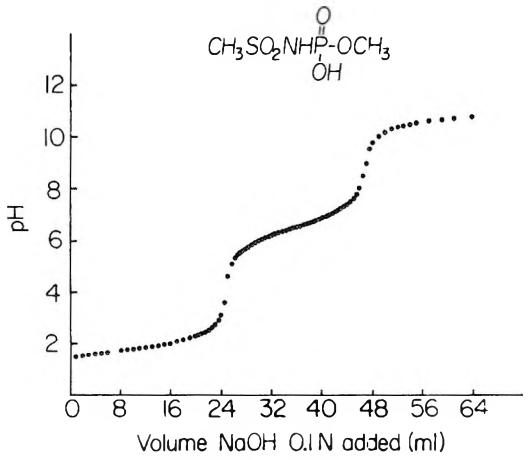


Figure 1. Titration curve for methyl *N*-methanesulfonylphosphoramidate (V). Conditions: 25 °C, aqueous solution.

Table I. Ionization Constants for N-Substituted Sulfonyl Phosphoramidate Monoesters and Selected Model Compounds

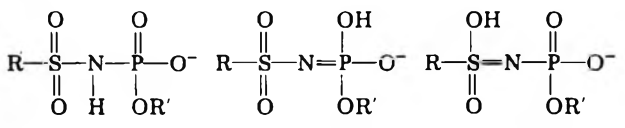
Compd	pK_a(I)	pK_a(II)
IV	1.05 ± 0.3	6.25 ± 0.2
V	1.16 ± 0.2	6.55 ± 0.2
VI	1.62 ± 0.1	5.90 ± 0.1
VII	1.80 ± 0.4	6.50 ± 0.4
Inorganic phosphate[4]	2.12	7.21
Methyl phosphate[4]	1.54	6.31
Ethyl phosphate[4]	1.60	6.62

the solvent of choice was acetone since both starting materials were soluble in it but the product monoester was not and conveniently precipitated in the course of the reaction. The success of this reaction depended critically on fully protonating the starting diester, since attempts to dealkylate the sodium salt of di-*p*-nitrobenzyl-*N*-benzenesulfonyl phosphoramidate met with failure. The inhibitory effect of a negative charge on the attack by iodide ion has been observed before[12] and can be explained on the basis of electrostatic repulsion.

Details of the synthetic procedures for new compounds are given in the Experimental Section.

The results in Table I and Figure 1 show that the newly prepared monoesters of *N*-alkyl (or aryl) sulfonylphosphoramidate behave as dibasic acids in aqueous solution. The pK_as for all four compounds are similar to the first two pK_as of inorganic phosphate and of phosphomonoesters. Thus, although a dialkyl phosphate group lowers the pK_a of methanesulfonamide (pK_a = 10.8[13]) by about 9 pK_a units,[2,3] a monoalkyl monoanion phosphate group lowers it only 4.3 units. This difference in acidity of about 5 powers of ten is consistent with the difference in acidity between the first ionization constant of phosphoric acid and the second one, or the first and second ionization constants of phosphate monoesters. It reflects the effect of a full negative charge on the loss of a second proton from the same molecule.

The microscopic site of protonation (or deprotonation) of the monoesters, however, is not defined by these data and will depend on the relative populations of three different tautomers:



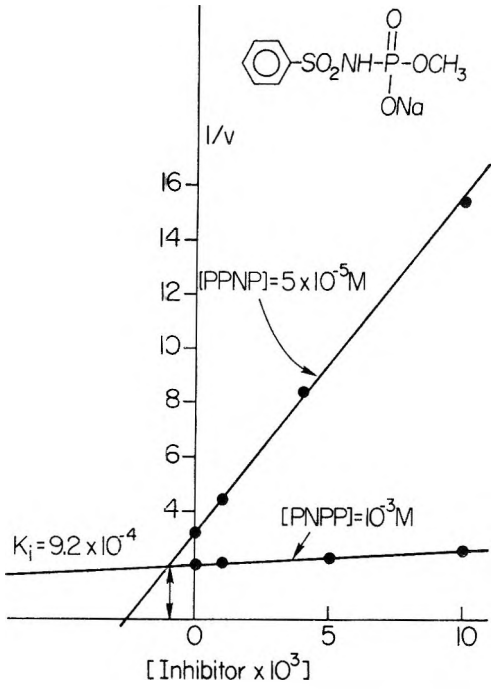


Figure 2. Dixon plot for the inhibition of alkaline phosphatase from *E. coli* by methyl *N*-benzenesulfonylphosphoramidate (IV). PNPP: *p*-nitrophenyl phosphate. Assays were run under standard conditions for the enzyme[21] in 1 M Tris HCl buffer, pH 8.0, at 25 °C.

Kabachnik et al.[14] and Matrosov et al.[15] have discussed the tautomeric distribution in N-substituted sulfonylphosphoramidate diesters and concluded, on the basis of infrared evidence, that the amide form [–NHP(=O)$(OR)_2$] predominates over the imidol form [–N=P(OH)$(OR)_2$] in these compounds. An analogous conclusion might be drawn for the monoester series, based on Kabachnik and Matrosov's assignment of infrared bands and our available spectroscopic data. However, since these authors failed to take into account possible effects on the frequencies of the sulfonyl group, and since their assignments depend on subtle differences in absorption in the region of 1200–1400 cm^{-1}, where the monoesters show two to three broad bands, we refrain here from reaching a definite conclusion on this subject.

We took advantage of the observation that the synthetic *N*-alkyl (or aryl) sulfonylphosphoramidate monoesters exist as dianions at pH 8 and tested their action as inhibitors for alkaline phosphatase from two different sources. These enzymes are phosphomonoesterases with a strict requirement that their substrates and competitive inhibitors[16] be dianions. Dixon plots[17] were used to discriminate between competitive and other forms of inhibition and to measure the inhibition constants. The results are presented in Table II and Figures 2 and 3.

The compounds are indeed recognized by the active sites as indicated by their behavior as competitive inhibitors. In addition, compounds IV, V, and VI were tested as pseudosubstrates for alkaline phosphatase from *E. coli*, by incubating them in the presence of enzyme and assaying for the release of alcohol in each case (VPC was used to detect the product from IV and V; UV was used for VI). The results were disappointingly negative since no alcohol could be detected in any of the experiments. Although the newly synthesized dianionic compounds bind at the active site, they do not fulfill the requirements for successful enzymatic P–O cleavage, and are thus not hydrolyzed.

Finally it should be pointed out that our method of preparation of N-substituted sulfonylphosphoramidate monoesters from the corresponding diesters will not be successful for ar-

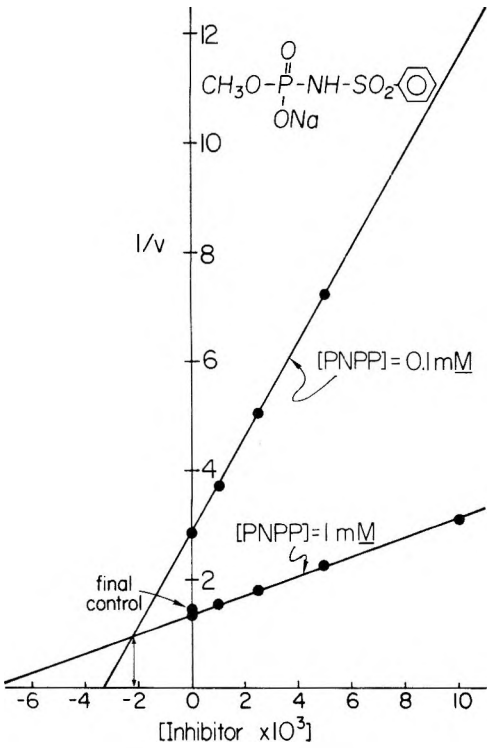


Figure 3. Dixon plot for the inhibition of alkaline phosphatase from chicken intestine by methyl *N*-benzenesulfonylphosphoramidate (IV). PNPP:*p*-nitrophenyl phosphate. Assays were run under analogous conditions as for the *E. coli* enzyme (see Figure 2).

Table II. Competitive Inhibition Constants for N-Substituted Sulfonylphosphoramidate Monoesters with Alkaline Phosphatases

Compd	K_i, M
IV[a]	9.2×10^{-4}
V[a]	2.4×10^{-2}
VI[a]	3.5×10^{-3}
VII[a]	4.8×10^{-3}
IV[b]	2.2×10^{-3}

[a] Enzyme from *E. coli*; $K_m = 2.65 \times 10^{-5}$ M. [b] Enzyme from chicken intestine; $K_m = 1.1 \times 10^{-4}$ M.

omatic residues, since the dealkylation reaction by iodide ion limits the method to aliphatic groups. This limitation, however, does not necessarily rule out the preparation of N-substituted sulfonylphosphoramidate aromatic monoesters. If the appropriate sulfonylphosphoramidate mixed aromatic–aliphatic diesters can be prepared, it should be possible, in principle, to apply our dealkylation reaction to them. The synthesis of asymmetric phosphate diesters by an improved method recently presented by Ramirez,[18] followed by standard chlorination procedures[19] to give the mixed chlorophosphate diesters, might yield the needed precursors.

Experimental Section

Melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are uncorrected unless otherwise specified. pH was measured with a Radiometer pH meter Type TTT1C. Ultraviolet-visible spectra were taken on a Gilford 240 or a Cary 15 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 137 sodium chloride spectrophotometer; spectra of aqueous samples were taken in Silanor (Merck). Vapor phase chromatography (VPC) was performed on an F & M Scientific, Hewlett-Packard 5750 research instrument. Elemental analyses were performed by Spang Microanalytical Laboratory and Dornis und Kolbe (West Germany).

Alkaline phosphatase from *E. coli* was obtained from Worthington and assayed by standard procedures.[20] Alkaline phosphatase from chicken intestine was Boehringer's. All commercial reagents and solvents were of the best available purity and were further purified in most cases by standard methods.[21]

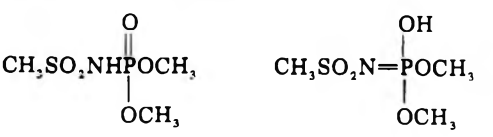
Trimethyl *N*-Benzenesulfonylphosphorimidate. Benzenesulfonyl azide in 50-g batches was prepared by the method of Boyer et al.,[22] using dry acetonitrile as solvent, instead of methanol. Freshly distilled trimethyl phosphite (1 equiv) was added drop by drop to a well-stirred solution of benzenesulfonyl azide in diethyl ether at room temperature. Gas evolution was strong during the first few minutes, but subsided upon addition of the last few drops of phosphite. The two phases which formed were separated and the lower one was crystallized by scratching it with a glass rod. The water-insoluble, wet-looking white solid was purified by pumping on it at 0.1 mmHg for 1 h: ^{1}H NMR (deuterioacetone) δ 3.83 (d, J = 12 Hz, 9 H), 7.95 ppm (m, 5 H); yield 60%.

Dimethyl *N*-Benzenesulfonylphosphoramidate. Dry HCl was bubbled into a solution of trimethyl *N*-benzenesulfonylphosphorimidate (30 g) in acetonitrile, in a three-necked round-bottom flask, equipped with a stirring bar, a gas bubbler, and a thermometer. The reaction, which was easily followed by noticing a rise and eventual fall in the temperature of the solution, was stopped after 45 min; the solvent was removed by rotoevaporation and the remaining oily residue was crystallized by scratching it for a few minutes with a glass rod. After pumping on it overnight at 0.1 mmHg, the resulting white solid was pure as judged by NMR spectroscopy: ^{1}H NMR (deuterioacetone) δ 3.70 (d, J = 12 Hz, 6 H), 7.71 and 8.13 ppm (m, 5 H); yield 90%.

Methyl *N*-Benzenesulfonylphosphoramidate Sodium Salt. Sodium iodide (11.32 g, Mallinckrodt), dissolved in a minimum amount of acetone, was added to a solution of 1 equiv of dimethyl *N*-benzenesulfonylphosphoramidate in acetone. The homogeneous solution was brought to reflux and after 10 min a white solid precipitated. Reflux was continued for another 30 min; the solution was then brought to room temperature and filtered. The white solid was thoroughly washed with fresh acetone and purified by dissolving it in hot water, decolorizing the aqueous solution with Norit, and precipitating the solid with 8 volumes of cold acetone. After filtration and drying, the solid melted at 220–223 °C: yield 76%; IR 1200 (P=O), 2700 (P-O-H or P-N-H), 3000 cm^{-1} (C-H); ^{1}H NMR (Silanor) δ 3.41 (d, J = 12 Hz, 3 H), 7.70 and 8.00 ppm (m, 5 H). Anal. Calcd for $C_7H_9NSPO_5Na$: C, 30.77; H, 3.32; N, 5.13; S, 11.74; P, 11.34; Na, 8.42. Found: C, 30.75; H, 3.70; N, 5.10; S, 11.71; P, 11.33; Na, 8.35.

Trimethyl *N*-Methanesulfonylphosphorimidate. Methanesulfonyl azide was prepared in 100-g batches by the method of Boyer et al.[22] using dry acetonitrile as solvent instead of methanol. The title compound was prepared following the method used for the *N*-benzenesulfonyl derivative (vide supra) and is essentially identical with that of Gilyarov et al.:[2] yield 84%; ^{1}H NMR (neat) δ 2.9 (d, J = 1.8 Hz, 3 H), 3.95 ppm (d, J = 12 Hz, 9 H).

Dimethyl *N*-Methanesulfonylphosphoramidate. The title compound was prepared following the method used for the *N*-benzenesulfonyl derivative (vide supra) and is essentially that of Gilyarov et al.[2] However, since the starting material is a liquid, gaseous hydrogen chloride was bubbled into it directly, without the need to carry out the reaction in solution. After 30 min of bubbling, the passage of gas was interrupted and the flask was put on ice. The wet, white solid which appeared was dissolved in a minimum of hot ethanol and crystallized by allowing the solution to cool slowly to room temperature. After filtration and drying under vacuum, the small needles melted at 111–112 °C (lit.[2] 111–112 °C): ^{1}H NMR (Silanor) δ 3.26 (s, 3 H), 3.86 (d, J = 12 Hz, 6 H), 4.8 ppm (s, HDO). The IR shows a characteristic doublet at 2710 and 2760 cm^{-1}. This band has been extensively discussed in the literature[14,15] and can be assigned either to the P–N–H stretch of the phosphoramidate or to the P–O–H stretch of the tautomeric phosphimidol:



Methyl *N*-Methanesulfonylphosphoramidate Sodium Salt. Sodium iodide (3.65 g) was dissolved in a minimum of acetone and added to a solution of dimethyl *N*-methanesulfonylphosphoramidate (5.2 g, 1 equiv) in 50 mL of dry acetone. The homogeneous solution was refluxed for 15 min; the white solid that precipitated at room temperature was filtered and washed thoroughly with fresh

acetone. The solid was then recrystallized from boiling methanol to yield 4 g of a dry, white, crystalline solid, which melted at 214–216 °C: yield 80%; ^{1}H NMR (Silanor) δ 3.20 (s, 3 H), 3.61 (d, J = 12 Hz, 3 H), 4.66 ppm (s, HDO). Anal. Calcd for $C_2H_7NPSO_5Na$: C, 11.38; H, 3.33; N, 6.64; S, 15.19; P, 14.67; Na, 10.89. Found: C, 11.50; H, 3.33; N, 6.60; S, 15.26; P, 14.83; Na, 10.84.

Di-*p*-nitrobenzyl *N*-Benzenesulfonylphosphoramidate. Di-*p*-nitrobenzyl chlorophosphate was prepared by the method of Zervas and Dilaris.[11] The sodium salt of benzenesulfonamide was prepared by titrating a suspension of benzenesulfonamide with 1 equiv of aqueous sodium hydroxide, until a homogeneous solution was obtained. This solution was then extracted several times with diethyl ether and lyophilized to yield sodium benzenesulfonamidate in 92% yield. The title compound was prepared by suspending sodium benzenesulfonamidate (1.85 g, 0.01 mol) in freshly distilled refluxing chloroform. To this suspension di-*p*-nitrobenzyl chlorophosphate (2.0 g, 0.005 mol[23]) was added. Reflux was continued for 28 h; the suspension was then allowed to come to room temperature and filtered. The solid obtained was washed thoroughly with fresh chloroform and dried under vacuum; its melting point was higher than 300 °C. The salt dissolved in 40 mL of hot water; on addition of an excess of 1 M HCl, the acid separated as an oil. After standing for 12 h at 4 °C it yielded a white solid, which was filtered, washed with water, and dried: yield 88%; mp 165–166 °C; IR 2700 cm^{-1} (P–N–H or P–O–H, vide supra for the IR spectrum of dimethyl *N*-methanesulfonylphosphoramidate); ^{1}H NMR (dimethyl sulfoxide-d_6) δ 4.86 (d, J = 9 Hz, 4 H), 7.20–8.06 ppm (m, 12 H).

***p*-Nitrobenzyl *N*-Benzenesulfonylphosphoramidate Disodium Salt.** Di-*p*-nitrobenzyl *N*-benzenesulfonylphosphoramidate (2.0 g, 0.004 mol) and sodium iodide (0.6 g, 0.004 mol) were dissolved in 50 mL of dry acetone. The homogeneous solution was refluxed for 45 min and then kept overnight at 4 °C. The resulting white precipitate was filtered, washed with acetone, and dried. The product was dissolved in 1 M NaOH; an insoluble impurity was removed by extraction with diethyl ether and methylene chloride. The clear, alkaline phase was cooled to 0–4 °C and titrated with concentrated HCl until no more white solid precipitated. The solid was collected by filtration and washed with water. It was then stirred overnight with 2 equiv of NaOH in water at 25 °C, after which the solution was extracted with diethyl ether and lyophilized to dryness. The resulting solid was twice crystallized from aqueous acetone, filtered, and dried under vacuum. Its melting point was higher than 300 °C: yield 52%; ^{1}H NMR (Silanor) δ 4.92 (d, J = 7–8 Hz, 2 H), 7.5–8.4 ppm (m, 9 H). Anal. Calcd for $C_{13}H_{11}N_2PSO_7Na_2$: C, 37.15; H, 3.60; N, 6.67; P, 7.37; S, 7.63; Na, 10.94. Found: C, 37.26; H, 3.60; N, 6.58; P, 7.37; S, 7.60; Na, 10.98.

Ethyl *N*-Benzenesulfonylphosphoramidate Sodium Salt. Diethyl *N*-benzenesulfonylphosphoramidate was prepared according to Rätz.[10] The title compound was prepared by dissolving diethyl *N*-benzenesulfonylphosphoramidate (0.6 g, 2.1 mmol) in 15 mL of dry acetone and adding solid sodium iodide (0.34 g, 2.1 mmol) to the solution. The homogeneous solution was refluxed for 13 h; the white solid that precipitated at room temperature was filtered and thoroughly washed with acetone. The solid was then dissolved in a minimum of water, precipitated with acetone, filtered through a Hirsch funnel, and dried under vacuum. This process yielded 0.41 g of a white, shiny, crystalline solid which melted at 235 °C: ^{1}H NMR (Silanor) δ 1.00 (t, J = 5 Hz, 3 H), 3.68 (q, J = 7 Hz, 2 H), 7.63 and 7.9 ppm (m, 5 H). Anal. Calcd for $C_8H_{11}NPO_5SNa$: C, 33.45; H, 3.86; N, 4.88; S, 11.16; P, 10.78; Found: C, 33.49; H, 3.96; N, 4.90; S, 11.29; P, 10.67.

Determination of pK_as. The compounds (mono- or disodium salts) were dissolved in deionized water to yield concentrations in the range 0.02–0.07 M and an equivalent amount of concentrated hydrochloric acid was added to prepare the diacid forms. These solutions were then titrated with 0.1 N sodium hydroxide at 25 °C. An example of a titration curve is shown in Figure 1; from such curves the two acid dissociation constants, pK_a(I) and pK_a(II), were calculated as follows.

pK_a(I). Since the values of K_a(I) are large, the ionization of the acid contributes importantly to the concentration of the monoanion, HA$^-$. For each acid, 5–12 values of K_a(I) were calculated, one for each increment of alkali, from the observed pH and the law of mass action. The concentration of the monoanion, HA$^-$, was set equal to the sum of that produced by neutralization of H_2A with sodium hydroxide and that produced by the self-ionization of the diacid; the latter, of course, is the same as the hydrogen ion concentration. The pK_a(I) values presented in Table I are calculated for each acid from the average of the K_as found as above. Although these low pK values necessarily are somewhat uncertain, the qualitative similarity of these pK_as to the first ionization constant of phosphates is unmistakable.

pK_a(II). This constant was set equal to the value of the pH at half-ionization for the second proton of the diacids. The pK_a values are not ionic strength corrected.

Acknowledgments. The author would like to thank Professor Frank Westheimer for suggesting this topic and for constant encouragement and fruitful discussions during the completion of the project. The work was supported by the National Science Foundation under Grant MPS74-17595 A01.

Registry No.—IV, 62461-21-6; V, 62461-22-7; VI, 62461-23-8; VII, 62461-24-9; trimethyl *N*-benzenesulfonylphosphorimidate, 62461-25-0; benzenesulfonyl azide, 938-10-3; trimethyl phosphite, 121-45-9; dimethyl *N*-benzenesulfonylphosphoramidate, 4140-56-1; trimethyl *N*-methanesulfonylphosphorimidate, 7109-06-0; methanesulfonyl azide, 1516-70-7; dimethyl *N*-methanesulfonylphosphoramidate, 7109-15-1; di-*p*-nitrobenzyl *N*-benzenesulfonylphosphoramidate, 62461-26-1; sodium benzenesulfonamidate, 18522-93-5; di-*p*-nitrobenzyl chlorophosphate, 57188-46-2; *p*-nitrobenzyl *N*-benzenesulfonylphosphoramidate disodium salt, 62461-27-2; diethyl *N*-benzenesulfonylphosphoramidate, 1467-28-3.

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(23) Since the product has an acidic hydrogen (pK_a 1–2) it will readily protonate sulfonamidate anion. This exchange reaction causes 2 equiv of sulfonamidate to be consumed for each equivalent of product formed. Thus, the use of a twofold excess of sulfonamidate over chlorophosphate is critical in this reaction.

6-Sulfinyl Derivatives of Xanthines

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6-Thiopurines are oxidized by hydrogen peroxide or by perbenzoic acid to 6-sulfinylpurines. In general, these compounds are unstable and only a number of theophylline derivatives have been obtained in pure form. In this series only the isomers in which the 6-sulfinyl group is directed toward 7-NH are formed, since they are stabilized by an intramolecular hydrogen bridge. Their structure has been derived from dipole moments and from the chemical shift of the 1-methyl substituent. The 2-thiocarbonyl group in 2-thiotheophyllines is not attacked by the oxidants used. The latter convert 6-selenoxanthines directly into the corresponding xanthines.

In 1966, Walter et al. described the 6-sulfinyl derivative **2c** (Table I) of theophylline, obtained by oxidation of 6-thiotheophylline **2b** with hydrogen peroxide.[1] We have observed that **2c** can be prepared more conveniently by treating a suspension of **2b** in chloroform with perbenzoic acid. The reaction takes place instantaneously and produces a clear solution of **2c**, the color changing from slightly yellowish to intense green-yellow.

We have studied the generality of this reaction both with aqueous hydrogen peroxide and with solutions of perbenzoic acid in organic solvents. Most of the 6-thiopurines tested were attacked, since their solutions changed color to intense yellow, orange, or green (see footnote to Table I), but the sulfinyl derivatives formed were rather unstable. Isolation of pure 6-sulfinyl derivatives succeeded only in a few cases, notably the theophylline derivatives **2c–5c** (Table I). Heating solutions of the latter in protic organic solvents was sufficient to convert them back to the 6-thiopurines **2b–5b.** Likewise, aqueous hydrogen sulfide or sodium bisulfite reduced the sulfinyl group instantaneously to 6-thiocarbonyl.

Certain 6-SMe purines undergo thiohydrolysis, i.e., the 6-SMe substituent is replaced by SH.[2] However, such a reaction is possible only for univalent SR groups.[3] Therefore it appears improbable that an SH group could substitute directly for SOH, especially in view of the easy reduction of the sulfinylpurines by bisulfite or protic solvents.

The facile reduction of the sulfines by chemical means finds its counterpart in the formation of $[M - 16]^+$ under electron impact. In the mass spectrum of **2c** and **3c,** this ion shows the highest peak, followed by $[M - 48]^+ = [M - SO]^+$. Loss of oxygen from sulfoxides under electron impact is well known.[4] However, splitting off of SO appears to be specific for the sulfinyl derivatives studied here.

It should be noted that the oxidants used did not attack a 2-C=S group (see **3c** and **5c** in Table I).

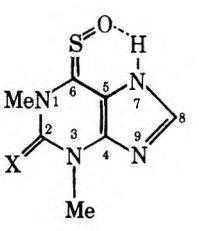
All sulfinylpurines formed complexes with ferric chloride, with characteristic colors (Table IV). Formation of complexes with Cu^{II}, Ni^{II}, and Hg^{II} was recognized by changes in the UV spectrum.

We have also tried to prepare 6-selenoxides by oxidation of 6-selenoxanthines. However, the latter lost elementary selenium and were rapidly converted to the corresponding xanthines.

The relevant physical properties of xanthines, 6-thioxanthines, and their 6-sulfinyl derivatives are compared in Tables I and II. The following statements are pertinent.

1. In the neutral forms of the xanthines **1a–5a** thiation at position 6 causes a bathochromic shift of λ_{max} of 55–75 nm, while introduction of a 2-C=S group has a much weaker influence.[5] The 6-C=S=O substituent further displaces λ_{max} to longer wavelengths by 28–35 nm. Therefore the total shift for the transformation 6-C=O → 6-C=S=O is 80–100 nm.

2. Anion formation in the 6-sulfinyl derivatives **2c–5c** takes place at a higher pK than in the corresponding thioxanthines **2b–5b.** Presumably the 7-NH group is stabilized by hydrogen bonding to 6-S=O (see structure I). The opposite effect is observed for the theobromine derivative **1c** (see structure III). In the latter, the pK for dissociation of the 1-NH group is 1.7



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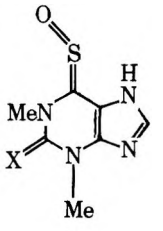
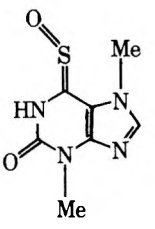


II



III

units *lower* than for 6-thiotheobromine **1b,** i.e., the sulfinyl group—by virtue of its electron-attracting character—enhances the acidity of the neighboring NH. In **2c–5c,** this effect is overshadowed by the stabilizing influence of the hydrogen bridge, shown in I.

3. The NMR signals of the 8 substituents are only little influenced by changes at position 6. For example, the 8-H band in series **1–3** shifts slightly downfield when one proceeds from 6-C=O to 6-C=S=O. Likewise the 8-phenyl signals are practically identical in the three derivatives **a–c** of series **4** and **5** (see Table II).

The 3-methyl band is displaced to lower field by 0.3–0.45 ppm, when 2-C=O is exchanged by 2-C=S,[6] but the different substitutions at C-6 alter its position only little.

Replacement of either 2- or 6-C=O by thiocarbonyl shifts the 1-methyl signal downfield by 0.4–0.5 ppm. These shifts are additive,[6] i.e., simultaneous thiation at positions 2 and 6 displaces the 1-methyl band by 0.87 ppm (compare the pairs **2a, 3b** and **4a, 5b** in Table II).

In contrast, introduction of a 6-sulfinyl group causes a marked upfield shift of the 1-methyl signal; the latter is now shielded even relative to the corresponding signal in the xanthines **2a–5a** [$\Delta\delta_{1\text{-Me}}$ (**a–c**) 0.12–0.17 ppm].

Although two geometrical isomers of 6-sulfinylpurines (I and II) are possible,[7] only a single compound was isolated in

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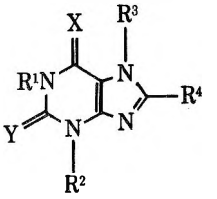
Table I. pK Values and UV Absorption Spectra of Xanthines, 6-Thioxanthines, and the Corresponding 6-Sulfinyl Derivatives[a,c]



Series no.		(a) Xanthines (X = O) pK	(a) λ_{max}, nm N	A	C	(b) 6-Thioxanthines (X = S) pK	(b) λ_{max}, nm N	A	C	(c) 6-Sulfinyl derivatives (X = S=O) pK	(c) λ_{max}, nm N	A	C
1	$R^2 = R^3$ = Me $R^1 = R^4$ = H Y = O	+0.3 11.0	273	275	265	+0.3 8.8	347	325	333	+0.4[b] 7.1	376	367	346
2	$R^1 = R^2$ = Me $R^3 = R^4$ = H Y = O	+0.7 8.5	272	275	266	+0.4 8.2	343	340	329	+1.0 8.9	377	373	343
3	$R^1 = R^2$ = Me $R^3 = R^4$ = H Y = S	−0.3 8.6	284	290	284	−1.0 7.8	348	349	352	0 8.1	383	378	366
4	$R^1 = R^2$ = Me R^3 = H; $R^4 = C_6H_5$ Y = O	+0.1 7.4	306	313	307	+0.9 8.9	364	381	354	−0.3 10.8	392	398	363
5	$R^1 = R^2$ = Me R^3 = H; $R^4 = C_6H_5$ Y = S	−0.5 7.3	320	328	323	−0.5 7.9	375	388	371	−1.5 10.6	403	407	391

[a] In the following cases, formation of the 6-sulfinyl derivatives was established by the color change of the solution and eventually by the bathochromic shift of λ_{max} (values in brackets), but the oxidation products could not be isolated because of their instability: 3,7-dimethyl-6-thiopurine (color change from yellow to green); 3-methyl-8-phenyl-6-thiopurine (from yellowish to intense yellow); 3-methyl-6-thioxanthine (372 nm at pH 8); 6-thiocaffeine (375 nm in ethanol); and 6-thioisocaffeine (375 nm in ethanol). [b] This compound was not obtained in analytically pure form, but was sufficiently stable to permit spectral measurements. [c] N, neutral form; A, anion; C, cation.

Table II. NMR Spectra and R_f Values of Xanthines, 6-Thioxanthines, and the Corresponding 6-Sulfinyl Derivatives

No.	Substituent	δ_{ppm}[a] (a)	(b)	(c)	Solvent	R_f values[b] and fluorescence[c] (a)	(b)	(c)
1	(3-Me)	3.52	3.52	3.56	(1)	0.51 violet	0.73 yellow	0.44 violet
	(7-Me)	4.00	4.15	3.82	(2)	0.66	0.71	0.14
	(8-H)	8.00	8.00	8.10	(3)	0.63	0.68	0.51
2	(1-Me)	3.42	3.83	3.30	(1)	0.68 violet	0.81 yellow	0.67 sky-blue
	(3-Me)	3.62	3.66	3.66	(2)	0.68	0.72	0.58
	(8-H)	8.16	8.20	8.28	(3)	0.68	0.71	0.63
3	(1-Me)	3.85	4.29	3.68	(1)	0.76 violet	0.82 yellow	0.70 black
	(3-Me)	4.02	3.99	4.00	(2)	0.72	0.76	0.69
	(8-H)	8.21	8.23	8.26	(3)	0.71	0.74	0.64
4	(1-Me)	3.46	3.84	3.33	(1)	0.95 radiant	0.98 rose	0.92 violet
	(3-Me)	3.68	3.79	3.74	(2)	0.79 violet	0.82	0.80
	(8-C_6H_5)	7.58[d]	7.56	7.57	(3)	0.76	0.77	0.77
		8.19	8.23	8.24				
5	(1-Me)	3.91	4.33	3.75	(1)	0.93 light blue	0.82 orange	0.82 dark blue
	(3-Me)	4.13	4.08	4.12	(2)	0.81	0.86	0.86
	(8-C_6H_5)	7.60[d]	7.58	7.58	(3)	0.73	0.79	0.82
		8.30	8.27	8.27				

[a] All measurements in CD_3COOD at 30 °C. For the symbols (a), (b), (c), see Table I. [b] (1), (2), and (3) indicate the solvents used for paper chromatography (see Experimental Section). [c] Under a Mineralight UV lamp, λ ~254 or 366 nm. [d] The values of δ 7.5–7.6 integrate for 3 protons and represent the multiplet for meta, parahydrogens of the phenyl ring. The signals at δ 8.20–8.30 ppm integrate for two protons and represent the orthohydrogens.

all cases. **3c** and **5c** gave single spots on chromatograms in a variety of solvents (Table II). With **2c** and **4c** a second spot was observed, but was identified as **2b** and **4b**, respectively, resulting from reduction of the sulfinyl group by the paper. Thus the question arises: Does structure I or II represent the single isomer found?

Dipole Moments. We first computed the dipole moments by the CNDO/2 method.[8] The theoretical values for **2a, 3a,** and **2b** were in reasonable agreement with the experimental results.[5] However, unexpected difficulties arose in the calculation of the dipole moments of **3b, 2c,** and **3c**. After a few converging iterations, the energies either oscillated between two slowly-changing limits or they diverged. The results were not improved by small modifications of the geometry of the C=S or C=S=O groups. Similar difficulties have been reported by Cignitti and Paolini.[9] Therefore the moments of structures I and II were calculated by vector addition, assuming the 6-C=S=O group to lie in the plane of the imid-

Table III. Dipole Moments[a]

No.	α'	β'	P_{200}	MR[b]	μ, D	μ, calcd for I[c]	μ, calcd for II[c]
2b	20.06	−1.80	321.4	49.2	3.7		
2c	11.78	−0.83	211.1	60.4	2.7	2.6	5.2
3b	32.28	−0.98	506.1	57.0	4.7		
3c	17.38	−0.57	304.0	68.1	3.4	3.5	6.1
4b	30.67	−0.65	509.9	72.5	4.6		
4c	11.91	−0.75	234.9	83.6	2.7		
5b	45.64	−1.08	721.5	80.1	5.6		
5c	18.20	−0.64	333.5	91.2	3.5		

[a] In dioxane (AR, dried over sodium metal) at 30 °C. [b] Calculated from bond electronic polarizations.[19] [c] See structural formulas.

azole ring. The vector of the 6-carbonyl group was subtracted from the known dipole moments of the xanthines **2a** and **3a**.[5] Then the moment of the sulfinyl group[10] was added in two opposite directions, as indicated by structures I and II. Since all possible mesomeric effects were neglected, the calculations are necessarily crude. Nevertheless, the differences predicted for the moments of I and II are large enough to permit unequivocal assignment of structure I to **2c** and **3c**, by comparison of calculated and experimental values (see Table III).

Introduction of an 8-phenyl substituent does not alter the dipole moment of **2c** and **3c**, respectively, suggesting that **4c** and **5c** are also represented by structures like I.

It should be noted that the dipole moments of the 6-sulfinyl derivatives are considerably smaller than those of the corresponding 6-thioxanthines (see Table III).

Shielding of the 1-Methyl Group by the 6-Sulfinyl Substituent. The most important effect of the 6-sulfinyl group consists in the upfield shift of the 1-methyl signal (Table II). Calculations show that this peculiar shift supports further the assignment of structure I to the sulfines **2c–5c**. The direct electrostatic contribution of a dipolar substituent like C=S=O to the shielding of the protons of the adjacent 1-methyl group can be obtained with the aid of the equation of Schweizer et al.[11] This equation evaluates the effect of a dipolar group by assigning partial charges, equivalent to the group dipole moment, on both sides of a given bond. The figures so obtained differ considerably for $\delta_{1\text{-Me}}$ in I and II. For I, we calculate that the 6-sulfinyl group shields the protons of the 1-Me substituent, while in II it causes a marked shift to lower field, relative to the corresponding signals in the **b** derivatives.

Although the sulfine **1c** could not be isolated in pure form, its NMR spectrum was clearly separated from that of the accompanying **1b**. In **1c** we observe a marked upfield shift of the 7-Me signal, relative to its position in **1b**. By analogy to the structure, assigned to **2c–5c** on the basis of $\delta_{1\text{-Me}}$, this observation suggests that **1c** possesses structure III, in which the sulfinyl group is directed away from position 7. Here again we have calculated the influence of the C=S=O dipole[10] on the two possible isomers of **1c**. In structure III, this dipole causes marked shielding of the 7-Me signal, while in the isomer corresponding to I this signal would be shifted strongly to *lower* field.

It should be noted that the stable H-bonded structure in I is six membered. In III, a hydrogen bridge between the sulfinyl oxygen and the 1-NH group would create a five-membered ring. Therefore the tendency to hydrogen bonding in III—if present at all—is much weaker than in I.

Stability of the 6-Sulfinyl Derivatives to pH Changes. The hydrogen bond in I is broken by anion formation. Therefore alkalinization and reacidification of an aqueous solution of I may yield some of the isomer II. However, from such cycles only the pure isomers I were recovered.

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Microanalyses were performed by M. Goldstein, Jerusalem. UV spectra were measured on a Varian Techtron Model 635 or a Cary 14 spectrophotometer, and NMR spectra on a JEOL MH-100 instrument, using tetramethylsilane as internal standard. pK values were derived from plots of λ_{max} or of optical density as function of pH.

For paper chromatography by the descending method, Whatman paper No. 1 was used with the following solvents: (1) 1-butanol–acetic acid–water (12:3:5 v/v), (2) 2-propanol–dimethylformamide–ammonia (d 0.88) (13:5:2 v/v), (3) ethanol–dimethylformamide–water (3:1:1 v/v). Theophylline (R_f 0.68 in all solvents) served as standard for evaluation of R_f values. Spots were located by their fluorescence under a Desaga MinUvis ultraviolet lamp (λ ~254 and 366 nm).

Known Compounds. The following purines were synthesized by known methods: **3a**,[12] **4a**,[13] **1b**,[12] **2b**,[12] **3b**,[14] **1c**.[1] The following pyrimidines are known: 5,6-diamino-1,3-dimethyluracil[15] and its 2-thio derivative.[12]

General Synthetic Procedures. 1. Thiation of Xanthines 4a and 5a. A suspension of a xanthine (1 g) and phosphorus pentasulfide (4 g) in β-picoline (20 mL) was refluxed for 3 h. The solvent was removed in vacuo and the residue treated with boiling water for 15 min. After cooling, the 6-thioxanthine was filtered off and dissolved in hot sodium hydroxide, and the solution was decolorized with charcoal and filtered. The 6-thioxanthines were then precipitated by acidification with acetic acid. For further purification see Table IV.

2. Oxidation of 6-Thioxanthines with Perbenzoic Acid. The 6-thioxanthine was suspended in chloroform or dissolved in methanol; at 0 °C a solution of 1.1 equiv of perbenzoic acid in chloroform was added under continuous stirring. If the product crystallized directly, it was filtered off and purified (Table IV, procedure 2a). If the product remained in solution, the latter was extracted with aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and the solvent removed in vacuo (procedure 2b).

3. Oxidation of 6-Thioxanthines with H_2O_2. The 6-thioxanthine was dissolved in a mixture of ethanol–chloroform (1:1), containing 1% triethylamine. The solution was stirred and warmed to 50 °C. Hydrogen peroxide (30%, 1.1 equiv) was added dropwise. The mixture was brought to dryness in vacuo and the residue was purified (Table IV).

8-Phenyl-2-thiotheophylline (5a). An intimate mixture of 5,6-diamino-1,3-dimethyl-2-thiouracil sulfate (6.3 g), benzamidine hydrochloride (8.1 g), and anhydrous sodium acetate (3.6 g) was heated to 185 °C for 10 min. The cake was treated with 75 mL of hot water and the mixture filtered. The insoluble product **5a** (yield quantitative) was purified as described in Table IV.

6-Selenotheophylline. A. 1,3-Dimethyl-6-methylthio-2-oxopurine.[2] S-Methylation of **2b** was carried out by a modification of the procedure of Neiman et al.[2] A mixture of methyl iodide and of the sodium salt of **2b** was stirred at 4 °C for 48 h. The precipitate formed was recrystallized repeatedly from benzene, mp 189–191 °C, yield 60%.

B. 6-Selenotheophylline. A solution of the foregoing thioether in ethanol was stirred at room temperature, while hydrogen selenide was bubbled through for 30 min.[16] The precipitate formed was recrystallized from ethanol. From concentrated solutions, the product crystallized in square yellow plates, from dilute solutions in yellow needles: yield 76%; mp >300 °C dec; pK −0.5, 7.4; λ_{max} (N) 290, 368 nm; (A) 363 nm; (C) 364 nm; R_f (solvent 1) 0.77; (2) 0.70; (3) 0.69; fluorescence, yellow-gray at 254 nm, orange at 366 nm; $\delta_{1\text{-Me}}$ 3.94; $\delta_{3\text{-Me}}$

Table IV. Preparation and Analysis of New Purines

No.	Mp or dec p, °C	Solvent for crystn	Crystal form and color	Procedure used[a]	Yield, %	Color of complex with $FeCl_3$
			I. Xanthines			
5a	>300	Dioxane	Colorless prisms	*a*	Quant	
			II. 6-Thioxanthines			
4b	257–258	Acetic acid	Yellow, hairlike needles	(1)	95	
5b	284–285	Benzene	Fluffy yellow needles	(1)	Quant	
			III. 6-Sulfinyl Derivatives			
1c	287–290	Ethanol[b]	Stars of yellow needles	(2a)	36	Green
2c	241–244	2-Propanol	Stars of greenish needles	(2b, 3)	50	Dark blue
3c	244–245	1-Butanol	Intense yellow needles	(2a)	93	Green
4c	218–219	Ethanol	Hairlike orange needles	(3)	Quant	Orange
5c	>300	Ethanol	Hairlike orange needles	(3)	Quant	Brown

[a] For procedures used, see Experimental Section. [b] This compound was not obtained in analytically pure form. Satisfactory C, H, N, and S values were obtained for all other compounds.

3.58; $\delta_{8\text{-H}}$ 8.32 ppm (acetic acid). Anal. Calcd for $C_7H_8N_4OSe$: C, 34.6; H, 3.3. Found: C, 35.0; H, 3.3.

6-Selenotheobromine. Through a refluxing solution of 3,7-dimethyl-6-methylthio-2-oxopurine[17] in ethanol, hydrogen selenide was passed for 15 min. The precipitate (yield quantitative) crystallized from ethanol in long, yellow needles: mp 269–272 °C; pK <−2, 8.8; λ_{max} (N) 372 nm; (A) 348 nm; (C) 360 nm; R_f (solvent 1) 0.68; (2) 0.70; (3) 0.68; fluorescence at 366 nm orange; $\delta_{3\text{-Me}}$ 3.47; $\delta_{7\text{-Me}}$ 4.21; $\delta_{8\text{-H}}$ 8.25 ppm (acetic acid). Anal. Calcd for $C_7H_8N_4OSe$: C, 34.6; H, 3.3. Found: C, 34.85; H, 3.1.

Oxidation of 6-Selenoxanthines. When a solution of a 6-selenoxanthine in chloroform was treated at room temperature with perbenzoic acid in chloroform, a red precipitate appeared immediately. After evaporation of the solvent, the organic residue was identified as the corresponding xanthine. With aqueous hydrogen peroxide, the precipitation of selenium was much slower, but again the xanthines were the end products.

Measurement of Dipole Moments. The compounds studied are practically insoluble in nonpolar solvents. Therefore we have used dioxane, although dipole moments in this solvent are somewhat higher than those measured in truly nonpolar solvents.[18] Even in dioxane the maximal concentration of all sulfinyl derivatives amounted to less than 10^{-3} molar fraction. Therefore the moments bear a relatively large error of 0.1–0.2 D. Because of limited solubility, we did not attempt to obtain the molar refractions from the refractive indices of the dioxane solutions, but calculated them from the bond electronic polarizations.[19]

Details of the experimental procedure have been given previously;[5] calculations were performed by the method of Halverstadt and Kumler.[20]

Registry No.—**1a,** 83-67-0; **1b,** 38759-03-4; **1c,** 62006-24-0; **2a,** 58-55-9; **2b,** 2398-70-1; **2c,** 62006-25-1; **3a,** 6603-63-0; **3b,** 6501-94-6; **3c,** 62006-26-2; **4a,** 961-45-5; **4b,** 62006-27-3; **4c,** 62029-53-2; **5a,** 62029-54-3; **5b,** 62006-28-4; **5c,** 62006-29-5; 5,6-diamino-1,3-dimethyl-2-thiouracil sulfate, 62006-30-8; benzamidine hydrochloride, 1670-14-0; 6-selenotheophylline, 62006-31-9; 1,3-dimethyl-6-methylthio-2-oxopurine, 62006-32-0; 6-selenotheobromine, 62006-33-1.

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Annelation of Pyridinium Rings onto Nitrogen Heterocycles

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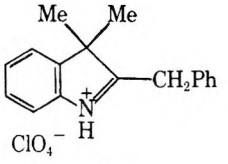
Numerous new fused pyridinium salts were synthesized by the interaction of protonated heterocycles with α,β-unsaturated ketones. The mode of addition was shown to depend on the heterocycle used and sometimes on the reaction conditions. Dihydropyridinium intermediates could be isolated in many cases.

In a preliminary communication[1] we described a simple method for the synthesis of fused pyridinium salts by the reaction of protonated heterocycles with methyl vinyl ketone. In this paper we report the extension of this method to other heterocycles and unsaturated ketones.

The first example of this synthesis[1] was the preparation of 3-methyl-4-phenylpyrido[2,1-*b*]benzothiazolium bromide (**4**) according to Scheme I. The formal Michael addition of 2-benzylbenzothiazolium bromide (**1**) to methyl vinyl ketone (MVK) in acetonitrile gave the adduct **2**. Additions of this type to salts of other nitrogen heterocyclic bases have been reported previously.[2,3] Product **2** was characterized by its IR, NMR spectra, and elemental analysis.

Heating **2** in a variety of solvents caused ring closure of the active methylene and the carbonyl group to give the dihydropyridobenzothiazolium salt **3**. The NMR spectrum (Me_2SO-d_6) of this compound showed a methyl group at δ 2.03 and two methylene triplets centered at δ 3.18 and 4.85. The aromatization of **3** to **4** could be carried out in a variety of ways, e.g., prolonged heating in DMA or Me_2SO, but most easily by heating with Pd/C in DMA. Characteristic peaks in the NMR spectrum (Me_2SO-d_6) of **4** were a methyl group at δ 2.53 and a single proton doublet at δ 10.24 assigned to the hydrogen at position 1.

The extension of this reaction sequence to the other nitrogen heterocyclic salts shown (**5**–**8**) gave varying results. Under



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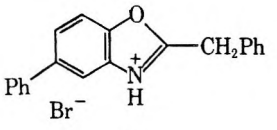

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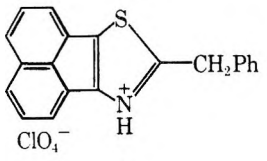

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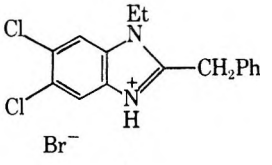

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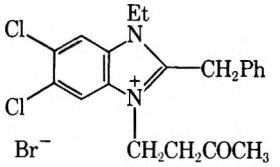
appropriate conditions salts **6** and **7** gave in turn Michael adducts (**9** and **12**), ring-closed dihydropyridinium salts (**10** and **13**), and the fully aromatic fused pyridinium salts (**11** and **14**) (Scheme II). Although **8** successfully formed the Michael adduct **15** with MVK, it failed to give an appreciable amount



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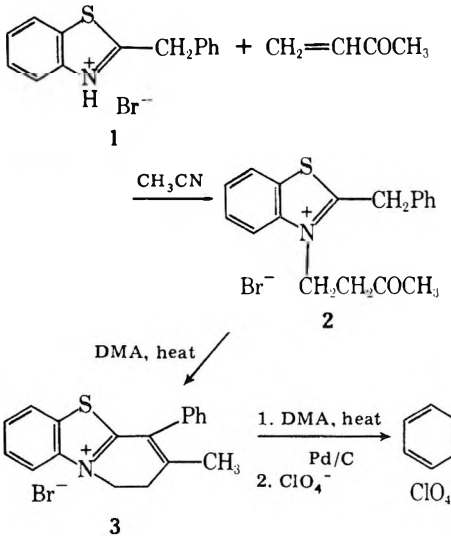
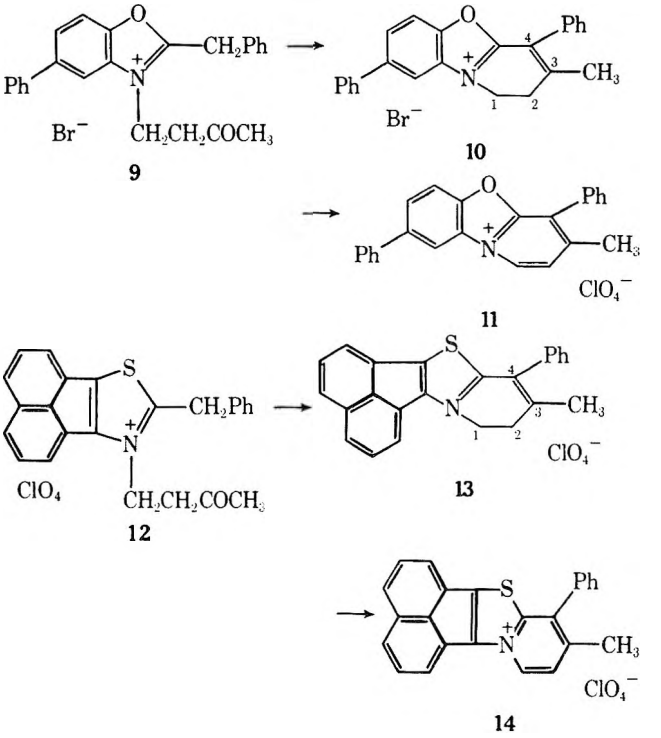
of ring-closed dihydropyridinium salt. This behavior was attributed to the low acidity of the benzylic methylene causing

Scheme I

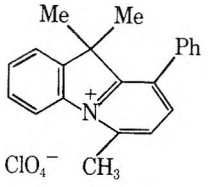


Scheme II



the reverse Michael reaction to compete favorably with ring closure. When the Michael addition was carried out with **5**, the vinyl group of the MVK became attached to the benzylic carbon as opposed to the nitrogen, and cyclization and aromatization occurred to give **16** instead of the expected **17**.

The structure of **16** was established by its NMR spectrum, which showed a methyl peak at δ 3.32 which is at least 0.5 ppm toward lower field than that expected from structure **17**. The



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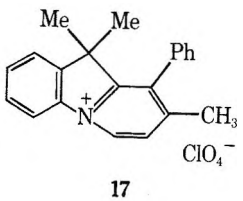

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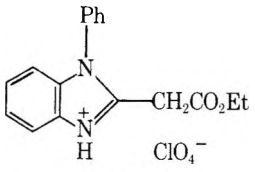
spectrum also lacked the doublet at δ 10.0 which is characteristic of a proton α to a positively charged pyridine nitrogen. This reversal of the mode of addition of MVK will be discussed later with reference to 2,3,3-trimethyl-3*H*-indolium salts and other unsaturated ketones.

In order to facilitate ring closure of the Michael adducts from various benzimidazolium salts and MVK, the acidities of the hydrogens involved in the condensations were increased by activating with ethoxycarbonyl groups. When 18 was treated with MVK in acetonitrile, the Michael adduct was not



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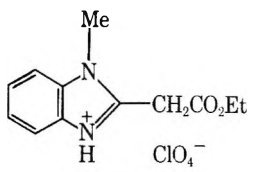

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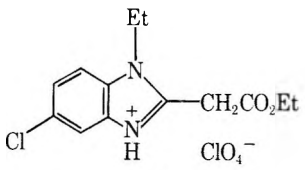

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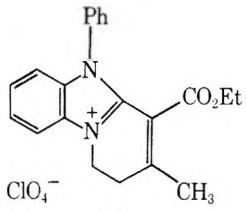
isolated in crystalline form. The resulting syrup was boiled in 2,6-lutidine and subsequently treated with ethanol to give the dihydropyridinium salt **21**. Aromatization to **22** was achieved by heating in DMA with Pd/C as before. When **19**



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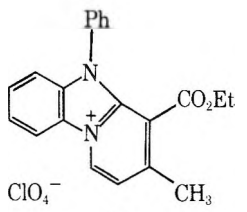
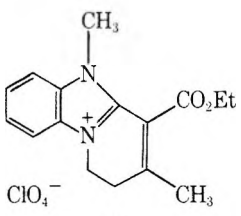
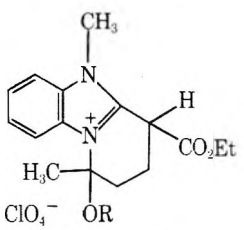


22

was reacted with MVK in acetonitrile, again a crystalline adduct was not isolated. Ring closure presumably occurred when the resulting syrup was subsequently boiled in pyridine. In addition to the expected product, **23**, **24**, or **25** was also



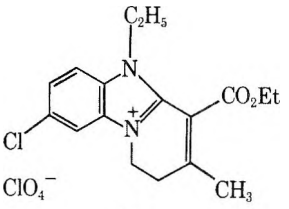
23



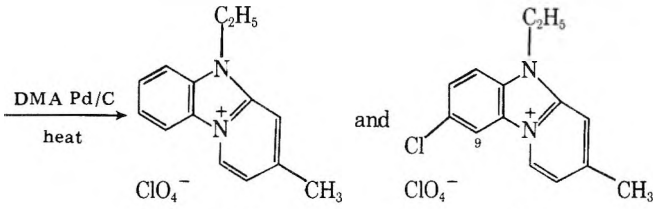
24, R = Et
25, R = H

isolated depending upon whether the workup involved ethanol (to give **24**) or acetic acid (to give **25**). Evidently, the vinyl group of the MVK reacted partially at nitrogen and partially at the activated methylene. The structures of **24** and **25** were assigned from the NMR spectra (90 MHz; 100 atom % Me_2SO-d_6) using decoupling techniques.

The dihydropyridinium ester **26** was prepared from **20** via the procedure used to prepare **23** from **19**. Upon aromatization, loss of the ethoxycarbonyl group and substantial hydrogenolysis of the chlorine–carbon bond also occurred giving an inseparable mixture of **27** and **28**. The mole percentages of the two salts present were estimated from the elemental analyses as both the perchlorate and fluoroborate salts. The NMR (Me_2SO-d_6) of mixed **27** and **28** showed a broadened



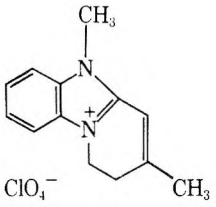
26



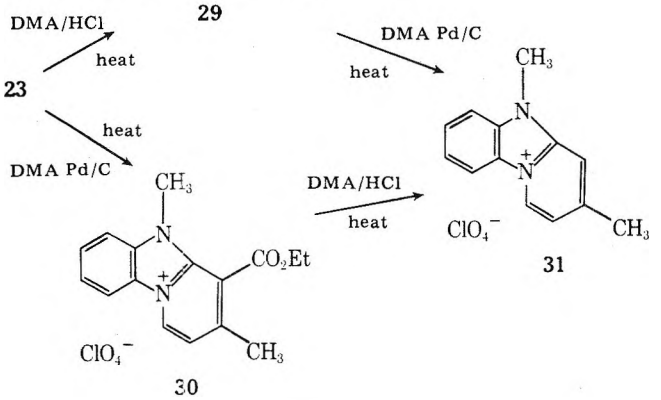
27 (~80%) 28 (~20%)

doublet at δ 8.53 (J = 8 Hz) assigned to the proton at position 9 in **27**; a small doublet at δ 8.76 (J = 2 Hz) was assigned to the proton at position 9 in **28**. The unexpected loss of the ester group during this reaction suggested that hot DMA containing HCl might be an effective medium for carrying out the ester hydrolysis of compounds of this type.

In support of this suggestion it was found that the dihydropyridinium ester **23** could be selectively aromatized or hydrolyzed and decarboxylated. The resulting quaternary salts **29** and **30** were then converted to **31**. Boiling DMA con-



29

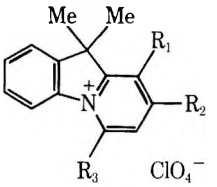


30 31

taining 5% of concentrated hydrochloric acid was very effective at hydrolyzing and decarboxylating the esters if part of the solvent was allowed to boil off. The use of a reflux condenser resulted in substantially lower yields.

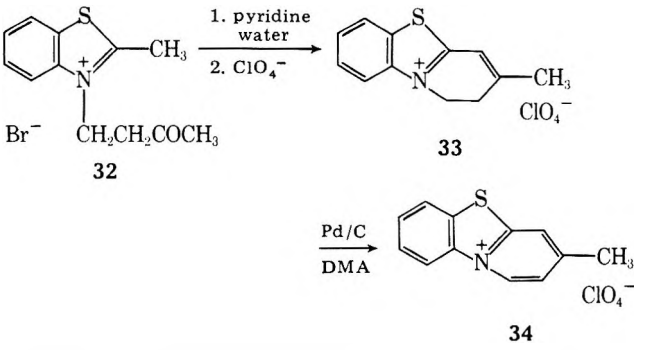
With Michael adducts containing a 2-methyl group of sufficient acidity, e.g., the 2-methylbenzothiazolium adduct **32**, the ring closure reaction to form **33** does occur but only to the

Table I[a]



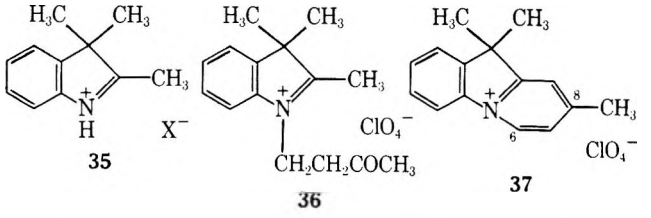
Registry no.	R_1	R_2	R_3	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mp, °C	Yield, %	CH_3, ppm
55867-79-3	CH_3	H	CH_3	59.3	5.0	4.3	59.6	5.3	4.6	217	27	3.20
55868-11-6	H	CH_3O-Ph	CH_3	63.5	5.2	3.4	63.7	5.2	3.6	298–300	50	3.22
62476-17-9	H	Ph	Ph	69.8	5.0	3.1	69.4	5.1	3.1	>310	30	
55953-69-0	H	CH_3O-Ph	Ph	67.8	5.1	2.9	67.8	5.3	2.9	258	26	
55953-76-9	H	Ph	CH_3O-Ph	67.8	5.1	2.9	67.5	5.3	2.9	245	43	
62476-19-1	CH_3	CH_3O-Ph	CH_3	67.3	5.9	3.4	67.1	5.9	3.3	290	25	3.32

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table.



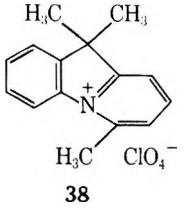
extent of a 17% yield owing to the competition with the reverse Michael reaction. Aromatization to **34** was carried out in the normal manner.

In the case of the reaction of 2,3,3-trimethyl-3*H*-indolium perchlorate (**35**) with MVK either neat or in acetonitrile the product was the open-chain adduct **36** which when heated in



pyridine formed the aromatic compound **37**. No dihydro intermediate was observed.

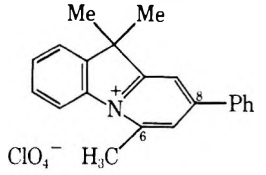
If, however, the initial reaction of **35** with MVK was run in DMA at room temperature no **36** was obtained and the only



product was **38** analogous to **16** in which carbon alkylation predominated.

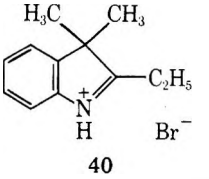
The two products **37** and **38** could readily be distinguished by the methyl resonances in their NMR spectra: **37** at δ 2.79 and **38** at δ 3.33.

2,3,3-Trimethylindolium perchlorate (**35**) also proved to be the most reactive of all the salts studied in terms of its reaction with other unsaturated ketones. When it was heated



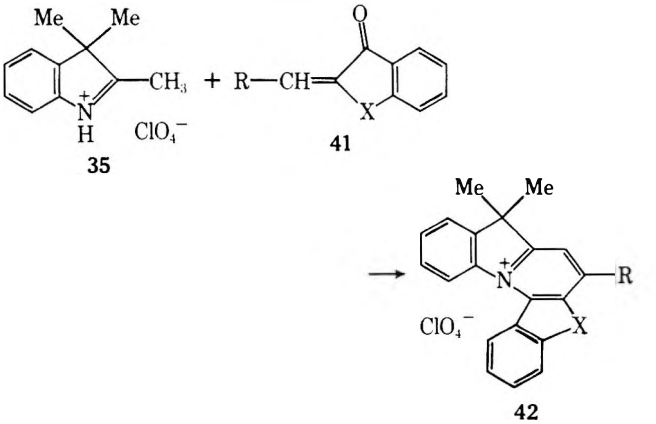
with benzylideneacetone at 100 °C, addition and cyclization occurred to form **39**, the 8-phenyl analogue of **38**.

Some other pyridoindolium salts formed by the carbon alkylation of both the 2-methylindolium salt **35** and the 2-



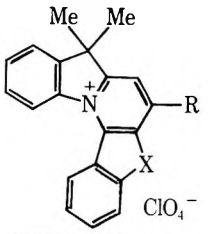
ethylindolium salt **40** with unsaturated ketones are shown in Table I.

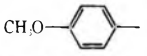
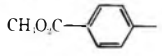
The 3*H*-indolium salt **35** will also react with unsaturated ketones where the ketone function is contained in a ring; for



example, 2-benzylidene-1-indanone **41** (R = Ph; X = CH_2) gives the indenopyridoindolium salt **42** (R = Ph; X = CH_2).

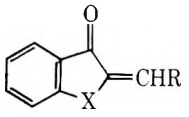
Table II[a]

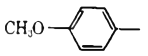
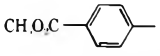


Registry no.	R	X	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mp, °C	Yield, %
55953-71-4	Ph	CH_2	70.5	4.8	3.1	70.5	5.1	2.8	259–261	48
62476-21-5		CH_2	68.6	4.9	2.9	68.5	4.9	2.8	229–230	29
61049-39-6		CH_2	66.8	4.5	3.1	66.5	4.8	3.0	229–230	18
61049-41-0		O	64.8	4.2	2.7	64.8	4.1	2.6	300	26
62476-23-7	Ph	C=O	68.4	4.2	3.0	68.4	4.5	2.8	300	11

[a] Satisfactory analytical data (± 0.4% for C, H, N) were reported for all new compounds listed in the table.

Table III



R	X	Mp, °C	Lit. mp, °C
Ph	CH_2	111	111[a]
	CH_2	141	141[a]
	CH_2	119	119[a]
Ph	C=O	152	152[b]
	O	204[d]	[c]

[a] Y. Poirier and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1062 (1966). [b] L. Geita and G. Vanags, *Zh. Ohshch. Khim.*, 27, 3107 (1957). [c] Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.9; H, 4.3. Found: C, 73.1; H, 4.1. [d] Registry no., 61049-42-1.

Other examples of this type of product where X and R are varied are shown in Table II. The necessary intermediates for the synthesis of the compounds listed in Table II are given in Table III.

From the variety of examples discussed, it can be seen that this new annelation method provides a means for the synthesis of novel heterocycles by a simple one-step or two-step process. Although the yields seldom exceed 50%, the simplicity of the process more than compensates for this.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. The IR spectra were measured as potassium bromide pressings on a Perkin-Elmer 257 grating spectrophotometer. TheNMR spectra were recorded with a Varian A-60 or Brüker 90-MHz instrument, and absorption values are given in parts per million downfield from tetramethylsilane added as an internal standard. Gas chromatography was run on an FM 650 chromatograph using a 6-ft column of 10% OV-17 packing.

Most of the salts used were prepared by addition of the appropriate acid to a solution of the heterocyclic base in ether. After filtration they were generally used without further purification.

2-Benzylbenzothiazole was prepared as described by Hofmann[4] and converted to the hydrobromide.

2-Benzyl-3-(3-oxo-1-butyl)benzothiazolium Bromide (2). 2-Benzylbenzothiazolium bromide (1, 24.5 g) in acetonitrile (100 mL) was treated with methyl vinyl ketone (6 g) and stirred overnight at room temperature. The starting material dissolved and the product precipitated: yield 19.9 g (66%); mp 144 °C; IR 1710 cm^{-1}; NMR (MeOD) δ 5.05 (s, 2 H, CH_2Ph), 2.2 (s, 3 H, CH_3CO), 3.4 (t, 2 H, $-CH_2CO$), 5.07 (t, 2 H, N^+CH_2).

Anal. Calcd for $C_{18}H_{18}BrNOS$: C, 57.4; H, 4.8; N, 3.7. Found: C, 57.3; H, 5.1; N, 3.8.

1,2-Dihydro-3-methyl-4-phenylpyrido[2,1-*b*]benzothiazolium Bromide (3). The adduct 2 (10 g) was heated to reflux in dimethylacetamide (50 mL). The solution was then cooled and the product collected, yield 8 g. Recrystallization from ethanol gave mp 208–210 °C: NMR (Me_2SO-d_6) δ 2.03 (s, 3 H, CH_3), 3.18 (t, 2 H, $-CH_2C=$), 4.85 (t, 2 H, $-CH_2N^+$), 7.4–8.4 (m, 9 H, aryl).

Anal. Calcd for $C_{18}H_{16}BrNS$: C, 60.3; H, 4.5; N, 3.9; S, 8.9. Found: C, 60.0; H, 4.6; N, 3.9; S, 8.9.

3-Methyl-4-phenylpyrido[2,1-*b*]benzothiazolium Perchlorate (4). The dihydro compound 3 (1 g) was refluxed in dimethylacetamide (20 mL) in the presence of 10% palladium on charcoal (0.1 g) for 2 h. The product was isolated by filtration and converted to the perchlorate: yield 0.6 g after recrystallization from ethanol; mp 218–219 °C; NMR (Me_2SO-d_6) δ 2.53 (s, 3 H, CH_3), 7.7 (s, 5 H, Ph), 7.81–9.23 (m, 5 H, aryl), 10.24 (d, 1 H, J = 7 Hz, H_1).

Anal. Calcd for $C_{18}H_{14}ClNO_4S$: C, 57.5; H, 3.8; N, 3.7; S, 8.5. Found: C, 57.6; H, 3.9; N, 3.5; S, 8.6.

2-Benzyl-5-phenylbenzoxazole (Free Base of 6). 2-Amino-4-phenylphenol (89 g) and phenylacetic acid (65 g) were heated together at 200–220 °C for 3 h. The product was treated with aqueous sodium hydroxide and the mixture extracted with chloroform. Removal of the chloroform gave an oil which was crystallized from hexane (Norit carbon) to give white needles (67 g, 49%), mp 52–54 °C.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.2; H, 5.3; N, 4.9. Found: C, 84.2; H, 5.5; N, 4.9.

2-Benzyl-3-(3-oxo-1-butyl)-5-phenylbenzoxazolium Bromide (9). 2-Benzyl-5-phenylbenzoxazolium bromide (6, 1.7 g) was suspended in acetonitrile (25 mL) and methyl vinyl ketone (0.7 g) added with rapid stirring. The solid dissolved and after 40 min the solution was poured into ether (150 mL). The product (0.8 g, 40%) was collected and had mp 106–108 °C, IR 1710 cm^{-1}. Attempts to recrystallize this material led to decomposition.

1,2-Dihydro-4,8-diphenyl-3-methylpyrido[2,1-*b*]benzoxazolium Bromide (10). 2-Benzyl-5-phenylbenzoxazolium bromide (6, 6.7 g) and methyl vinyl ketone (2.8 g) in dry acetonitrile (100 mL) were stirred at room temperature for 104 h. The product (4 g, 55%) was isolated by filtration and after recrystallization from chloroform–hexane had mp 300–313 °C dec; NMR (MeOD) δ 2.12 (s, 3 H, CH_3), 3.25 (m, 2 H, CH_2), 4.75 (m, 2 H, CH_2N^+).

Anal. Calcd for $C_{24}H_{20}BrNO$: C, 69.0; H, 4.8; N, 3.4; Br, 19.1. Found: C, 68.6; H, 4.9; N, 3.3; Br, 19.0.

4,8-Diphenyl-3-methylpyrido[2,1-*b*]benzoxazolium Perchlorate (11). 1,2-Dihydro-4,8-diphenyl-3-methylpyrido[2,1-

b]benzoxazolium bromide (**10**, 2.0 g) was dissolved in dimethyl sulfoxide and heated. The clear solution turned deep blue and after a few minutes of heating went yellow. Sodium perchlorate (0.6 g) in isopropyl alcohol (20 mL) was added to the cooled solution followed by an excess of ether. The product was separated by decantation and recrystallized from ethanol: yield 1.1 g; mp 252–254 °C; NMR (Me_2SO) δ 2.6 (s, 3 H, CH_3), 9.72 (d, J = 7 Hz, 1 H, N^+=CH–).

Anal. Calcd for $C_{24}H_{13}ClNO_5$: C, 66.1; H, 4.2; N, 3.2. Found: C, 65.8; H, 4.3; N, 3.3.

8-Benzylacenaphtho[1,2-*d*]thiazole (Free Base of 7). 2-Bromoacenaphthenone[5] (8.65 g, 0.035 mol) and phenylthioacetamide (5.3 g, 0.035 mol) in toluene (400 mL) were heated at 70–80 °C for 2 h with stirring. The tan solid was filtered and dried to give 9.73 g. This solid was heated in concentrated sulfuric acid (20 mL) at 60–80 °C for 5 min, and the dark solution was added to water (50 mL) and stirred for 30 min. The resulting solid was stirred in warm sodium carbonate solution and, after cooling, the crude product was extracted into ether. The ether layer was evaporated and the residue was recrystallized from methanol, yield 5.1 g (49%), mp 98–104 °C. A second recrystallization from ligroin gave mp 103–105 °C.

Anal. Calcd for $C_{20}H_{13}NS$: C, 80.2; H, 4.4; N, 4.7; S, 10.7. Found: C, 79.9; H, 4.1; N, 4.4; S, 10.5.

9-(3-Oxo-1-butyl)-8-benzylacenaphtho[1,2-*d*]thiazolium Perchlorate (12). To 8-benzylacenaphtho[1,2-*d*]thiazole (4.8 g, 0.016 mol) in cold ether (300 mL) was added dropwise with stirring 70% perchloric acid until no more salt separated. The salt was filtered, washed with ether, and dissolved in dry acetonitrile (180 mL). Methyl vinyl ketone (10 mL) was added, and the mixture was stirred at room temperature for 3 days. The solution was evaporated and the syrup was warmed in methanol, then cooled to give crystalline product, yield 5.85 g (78%), mp 167–170 °C dec. A second recrystallization from methanol gave mp 172–173 °C dec: NMR (CD_3CN) δ 2.2 (s, 3 H, $-COCH_3$), 3.4 (t, 2 H, J = 6.5 Hz, $-CH_2CO-$), 4.9 (s, 2 H, $-CH_2Ph$), 5.0 (t, 2 H, J = 6.5 Hz, N^+CH_2); IR 1714 cm^{-1}.

Anal. Calcd for $C_{24}H_{20}ClNO_5S$: C, 61.3; H, 4.3; N, 3.0; S, 6.8. Found: C, 61.6; H, 4.2; N, 2.7; S, 6.6.

1,2-Dihydro-3-methyl-4-phenylpyrido[2′,1′:8,9]acenaphtho-[1,2-*d*]thiazolium Perchlorate (13). 9-(3-Oxo-1-butyl)-8-benzylacenaphtho[1,2-*d*]thiazolium perchlorate (12 4.7 g, 0.01 mol) was boiled in pyridine (125 mL) until the blue solution turned yellow-brown. The pyridine was evaporated, and the syrup was heated in methanol until crystalline: yield 3.75 g (83%); mp 243–245 °C dec; NMR (CD_3CN) δ 2.05 (s, 3 H, CH_3), 3.17 (t, 2 H, J = 8.5 Hz, $-CH_2C=$), 4.87 (t, 2 H, J = 8.5 Hz, N^+CH_2); IR 1590, 1610 cm^{-1}.

Anal. Calcd for $C_{24}H_{18}ClNO_4S$: C, 6.37; H, 4.0; N, 3.1; S, 7.1. Found: C, 63.2; H, 3.9; N, 3.0; S, 6.9.

3-Methyl-4-phenylpyrido[2′,1′:8,9]acenaphthothiazolium Perchlorate (14). 1,2-Dihydro-3-methyl-4-phenylpyrido[2′,1′:8,9]-acenaphtho[1,2-*d*]thiazolium perchlorate (13, 1.36 g, 0.003 mol) was refluxed with stirring for 30 min in dimethylacetamide (20 mL) containing 10% palladium on charcoal (0.25 g). The solution was cooled, filtered, and poured into stirring ether (1 L). After 1 h the product was filtered and recrystallized from water: yield 0.62 g (46%); mp 151 °C (becomes glassy); NMR (CD_3CN) δ 2.53 (s, 3 H, CH_3); IR 1600 cm^{-1}.

Anal. Calcd for $C_{24}H_{16}ClNO_4S \cdot \frac{1}{2}H_2O$: C, 62.8; H, 3.7; N, 3.0; S, 7.0. Found: C, 62.5; H, 3.9; N, 2.7; S, 7.2.

2-Benzyl-5,6-dichloro-1-ethylbenzimidazolium Bromide (8). 4,5-Dichloro-*N*-ethyl-*o*-phenylenediamine dihydrochloride[6] (14 g) and phenylacetyl chloride (8 g) were dissolved in pyridine (35 mL) and heated under reflux for 1.5 h. The mixture was cooled, poured into water, and extracted with ether. The dried ether solution was distilled and the fraction 210–240 °C (0.5 mm) collected. It was recrystallized from isopropyl alcohol, mp 107–110 °C, yield 7.9 g (53%).

The free base was dissolved in ether and treated with an excess of hydrogen bromide in acetic acid. The precipitate was filtered, washed with ether followed by cold acetone, and dried, mp 182–205 °C.

Anal. Calcd for $C_{16}H_{15}BrCl_2N_2$: C, 49.8; H, 3.9; N, 7.3. Found: C, 49.4; H, 3.9; N, 7.1.

2-Benzyl-5,6-dichloro-1-ethyl-3-(3-oxo-1-butyl)benzimidazolium Bromide (15). 2-Benzyl-5,6-dichloro-1-ethylbenzimidazolium bromide (8, 6 g, 0.0155 mol) and methyl vinyl ketone (20 mL, excess) were stirred in *N*,*N*-dimethylacetamide (100 mL) for 5 days. The resulting mixture was stirred in ether (1.5 L) for 2 h and then filtered. The product was washed with ether and dried to give 6.8 g (96.3%): mp 172–173 °C; NMR ($CDCl_3$) δ 1.37 (t, 3 H, J = 7 Hz, CH_3C-), 2.16 (s, 3 H, CH_3CO), 3.55 (t, 2 H, J = 6 Hz, $-CH_2CO$), 4.63 (q, 2 H, J = 7 Hz, $-CH_2Me$), 4.89 (t, 2 H, J = 6 Hz, $-CH_2N^+$), 5.15 (s, 2 H, $-CH_2Ph$), 7.1–7.5 (m, 5 H, Ph), 8.1 (s, 1 H), and 8.46 (s, 1 H).

Anal. Calcd for $C_{20}H_{21}BrCl_2N_2O \cdot \frac{1}{2}H_2O$: C, 51.6; H, 4.8; N, 6.0. Found: C, 51.4; H, 4.7; N, 5.8.

All attempts to cyclize this compound by heating in a variety of solvents with or without the presence of base were unsuccessful. Either starting material was recovered or the 3-oxo-1-butyl group was lost.

2-Benzyl-3,3-dimethyl-3*H*-indolium Perchlorate (5). 3-Methyl-1-phenylbutan-2-one[7] (4 g) and phenylhydrazine (2.7 g) in acetic acid (20 mL) were refluxed for 1 h. The reaction mixture was then evaporated to dryness and dissolved in ether. The ether solution was extracted with 2 N HCl (3 × 60 mL). The product was recovered by basification and extraction with methylene chloride. Removal of the solvent gave a semisolid product which was converted first to the hydrobromide and then to the perchlorate salt, yield 3 g. After recrystallization from ethanol, the product melted at 173–175 °C.

Anal. Calcd for $C_{17}H_{18}ClNO_4$: C, 60.8; H, 5.4; N, 4.2. Found: C, 60.5; H, 5.4; N, 4.2.

If the crude indole was not converted to the salt immediately, it underwent a rapid aerial oxidation[8,9] to the 2-benzoyl derivative. Some of the indole (ca. 1 g) was dissolved in isopropyl alcohol and left at room temperature. The oxidation was monitored by gas chromatography on 10% OV-17 packing. Workup by recrystallization from ethanol gave 2-benzoyl-3,3-dimethyl-3*H*-indole: mp 80–81 °C; 0.4 g; mass spectrum *m*/*e* 249.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.9; H, 6.1; N, 5.6. Found: C, 81.9; H, 6.2; N, 5.5.

6,10,10-Trimethyl-9-phenyl-10*H*-pyrido[1,2-*a*]indolium Perchlorate (16). 2-Benzyl-3,3-dimethyl-3*H*-indolium perchlorate (5, 1.7 g) and methyl vinyl ketone (1 g) were stirred at room temperature in acetonitrile (10 mL) overnight. The product was isolated by dilution with ether and recrystallized from methanol: yield 0.8 g; mp 260 °C; NMR (Me_2SO-d_6) δ 1.7 [s, 6 H, $C(CH_3)_2$], 3.32 (s, 3 H, CH_3), 7.3–8.4 (m, 11 H, aryl).

Anal. Calcd for $C_{21}H_{20}ClNO_4$: C, 65.4; H, 5.2; N, 3.6. Found: C, 65.3; H, 5.3; N, 3.9.

4-Ethoxycarbonyl-1,2-dihydro-3-methyl-5-phenyl-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (21). To ethyl *N*-phenyl-2-benzimidazolylacetate[10] (14.02 g, 0.05 mol) in ether (1 L) 70% perchloric acid was added dropwise with stirring until no more reddish syrup separated. The ether was decanted, and the syrup was stirred with fresh ether for 15 min and again decanted. The syrup was dissolved in dry acetonitrile (300 mL), methyl vinyl ketone (25 g) was added, and the solution was stirred for 10 days at room temperature. The acetonitrile and excess methyl vinyl ketone were evaporated giving a syrup which would not crystallize. This syrup was boiled for 1 min in 2,6-lutidine (25 mL) and the solution was evaporated to dryness. The residue was warmed in ethanol to induce crystallization. The solid was recrystallized from ethanol to give 8.0 g (37%): mp 213–214 °C; NMR (Me_2SO-d_6) δ 2.37 (s, 3 H, CH_3), 3.15 (t, 2 H, J = 7.5 Hz, $-CH_2C=$), 4.7 (t, 2 H, J = 7.5 Hz, $-N^+CH_2$); IR 1740 cm^{-1}.

Anal. Calcd for $C_{21}H_{21}ClN_2O_6$: C, 58.3; H, 4.9; Cl, 8.2; N, 6.5. Found: C, 58.6; H, 4.9; Cl, 8.2; N, 6.5.

4-Ethoxycarbonyl-3-methyl-5-phenyl-5*H*-pyrido[2,1-*b*]-benzimidazolium Perchlorate (22). Compound 21 (4.33 g, 0.01 mol) was refluxed for 1 h with stirring in dimethylacetamide (50 mL) containing 10% palladium on charcoal (0.5 g). The mixture was cooled and filtered, and the filtrate was stirred with ether (1 L) for 15 min. The product was filtered and recrystallized from ethanol: yield 2.14 g (49.7%); mp 230–232 °C dec; NMR (Me_2SO-d_6) δ 2.63 (s, 3 H, CH_3), 9.9 (d, 1 H, J = 7 Hz, N^+CH); IR 1738 cm^{-1}.

Anal. Calcd for $C_{21}H_{19}ClN_2O_6$: C, 58.5; H, 4.4; N, 6.5. Found: C, 58.3; H, 4.5; N, 6.4.

Ethyl *N*-Methyl-2-benzimidazolylacetate (Free Base of 19). *N*-Methyl-*o*-phenylenediamine (48.9 g, 0.4 mol) and ethyl carboethoxyacetimidate hydrochloride[11] (78.3 g, 0.4 mol) were refluxed in ethanol (250 mL) for 3 h. The hot mixture was filtered to remove ammonium chloride, and the filtrate was evaporated to a syrup. The syrup in chloroform was washed twice with water, dried ($MgSO_4$), and evaporated. The residue was recrystallized twice from ether with dry ice cooling: yield 61 g (70%); mp 66–67 °C; NMR ($CDCl_3$) δ 1.1 (t, 3 H, J = 7 Hz, CH_3 of ethyl), 3.4 (s, 3 H, CH_3), 3.7 (s, 2 H, $-CH_2CO$), 3.9 (q, 2 H, J = 7 Hz, $-CH_2-$ of ethyl).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5; N, 12.8. Found: C, 65.6; H, 6.5; N, 12.9.

4-Ethoxycarbonyl-1,2-dihydro-3,5-dimethyl-5*H*-pyrido-[2,1-*b*]benzimidazolium Perchlorate (23) and 1-Ethoxy-4-ethoxycarbonyl-1,5-dimethyl-1,2,3,4-tetrahydro-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (24). To ethyl *N*-methyl-2-benzimidazolylacetate (6.55 g, 0.03 mol) in ether (1 L) 70% perchloric acid was added dropwise with stirring until no more syrup separated. The ether layer was decanted, and the syrup was stirred for 15 min with fresh ether and decanted again. The syrup was dissolved in acetonitrile (100 mL) and methyl vinyl ketone (10 g) was added. This mixture

was stirred for 4 weeks at room temperature. The acetonitrile and excess methyl vinyl ketone were evaporated, and the residual syrup was stirred for 1 day under ether. The ether was decanted, and the syrup was taken up and boiled for 1 min in pyridine (50 mL). The pyridine was evaporated and the syrup was dissolved in hot ethanol (500 mL). This solution was concentrated and cooled to give the dihydro product (**23**). Recrystallization from ethanol gave 2.0 g (18%): mp 202 °C dec; NMR (Me_2SO-d_6) δ 2.44 (s, 3 H, $\geq CH_3$), 3.0 (t, 2 H, J = 7.5 Hz, $-CH_2\leq$), 3.9 (s, 3 H, NCH_3), 4.6 (t, 2 H, J = 7.5 Hz,2 $^+NCH_2-$); IR 1735 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}ClN_2O_6$: C, 51.9; H, 5.2; Cl, 9.6; N, 7.6. Found: C, 51.9; H, 5.2; Cl, 9.8; N, 7.2.

The ethanol filtrate from above was evaporated to a syrup which was dissolved in a minimum of chloroform and chromatographed on a 3 ft silica gel column (chloroform). Elution of the column was carried out with chloroform, mixture of chloroform and acetonitrile, and finally pure acetonitrile. Two of the middle fractions slowly gave a crystalline material after evaporation. The solid was washed with ether, filtered, and recrystallized from ethanol to give 2.0 g (16%), mp 166–168 °C, of the tetrahydro product: NMR (100 atom % Me_2SO-d_6) δ 1.07 (t, 3 H, J = 7 Hz, CH_3 of ethoxy), 1.19 (t, 3 H, J = 7 Hz, CH_3 of ethoxycarbonyl), 1.87 (s, 3 H, CH_3CN), 2.0–2.7 (m, 4 H, $-CH_2CH_2-$), 2.89 (q, q, 1 H, J = 7, 9 Hz, one of the $-CH_2-$ hydrogens of the ethoxy), 3.68 (q, q, 1 H, J = 7, 9 Hz, the other $-CH_2-$ hydrogen of the ethoxy), 4.03 (s, 3 H, CH_3N), 4.25 (q, 2 H, J = 7 Hz, $-CH_2-$ of ethoxycarbonyl), 4.85 (broad s, 1 H, EtOOCCH slightly coupled to $-CH_2CH_2-$), 7.5–8.2 (m, 4 H, aromatics); IR 1737 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}ClN_2O_7$: C, 51.9; H, 6.05; Cl, 8.5; N, 6.7. Found: C, 51.6; H, 5.9; Cl, 8.6; N, 6.8.

4-Ethoxycarbonyl-1,2-dihydro-3,5-dimethyl-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (23) and 4-Ethoxycarbonyl-1,5-dimethyl-1-hydroxy-1,2,3,4-tetrahydro-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (25). The hydroperchlorate salt from ethyl *N*-methyl-2-benzimidazolylacetate (**19**, 32.8 g, 0.15 mol) was reacted for 1 week in acetonitrile (250 mL) containing methyl vinyl ketone (100 mL) as described in the preparation of **23** and **24**. However, the residue obtained after having been boiled with pyridine and evaporation was treated with pure, dry tetrahydrofuran in place of ethanol. The insoluble solid was the dihydro product **23**, yield 19.2 g (34.5%).

The tetrahydrofuran filtrate was evaporated to a syrup which became crystalline on treatment with hot acetic acid followed by cooling. Recrystallization from acetic acid gave 12.3 g (21.1%), mp 119–121 °C, of the tetrahydro product (**25**): NMR (CD_3CN) δ 1.23 (t, 3 H, J = 7 Hz, CH_3- of ethoxycarbonyl), 1.8 (s, 3 H, CH_3CN), 2.2–2.8 (m, 4 H, $-CH_2CH_2-$), 3.95 (s, 3 H, CH_3N), 4.2 (q, 2 H, J = 7 Hz, $-CH_2-$ of ethoxycarbonyl), 4.5 (m, 1 H, EtOOCCH), 5.4 (broad, 1 H, -OH), 7.5–8.3 (m, 4 H, aromatics); IR 1730 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}ClN_2O_7 \cdot \frac{1}{2}H_2O$: C, 48.3; H, 5.5; N, 7.04. Found: C, 48.3; H, 5.4; N, 7.1.

Ethyl 5-Chloro-1-ethyl-2-benzimidazolylacetate (Free Base of 20). 2-Amino-4-chloro-*N*-ethylaniline[12] (34.1 g, 0.2 mol) and ethyl carboethoxyacetimidate hydrochloride (39.1 g, 0.2 mol) were reacted in ethanol (150 mL) in the manner described for the preparation of ethyl *N*-methyl-2-benzimidazolylacetate. The product was recrystallized from ether with dry ice cooling and then from petroleum ether: yield 35.2 g (66%); mp 44–45 °C; NMR ($CDCl_3$) δ 1.1 (t, 3 H, J = 7 Hz, CH_3C), 1.2 (t, 3 H, J = 7 Hz, other CH_3C), 3.7 (s, 2 H, $-CH_2CO$), 3.9 (q, q, 4 H, J = 7, 7 Hz, $-CH_2-$ of the two ethyls).

Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.5; H, 5.7; N, 10.5; Cl, 13.3. Found: C, 58.3; H, 5.8; N, 10.4; Cl, 13.7.

8-Chloro-4-ethoxycarbonyl-5-ethyl-1,2-dihydro-3-methyl-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (26). The hydroperchlorate salt from ethyl 5-chloro-1-ethyl-2-benzimidazolylacetate (**20**, 32 g, 0.12 mol) was reacted for 2 weeks in acetonitrile (250 mL) containing methyl vinyl ketone (70 mL) as described in the preparation of **23**. The residue obtained after having been boiled with pyridine and evaporated was treated with isopropyl alcohol (800 mL) and the somewhat sticky solid was filtered. This solid became more crystalline on stirring in aqueous sodium perchlorate solution. The product was filtered and recrystallized from ethanol/acetonitrile (2/1): yield 12.8 g (25.5%); mp 232–233 °C dec; NMR (Me_2SO-d_6) δ 2.36 (s, 3 H, CH_3), 3.02 (t, 2 H, J = 7.5 Hz, $-CH_2CMe$), 4.26 (t, 2 H, J = 7.5 Hz, N^+CH_2-), 7.7 (d, d, 1 H, J = 9, 2 Hz, H_7), 8.1 (d, 1 H, J = 9 Hz, H_6), 8.2 (d, 1 H, J = 2 Hz, H_9); IR 1725 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}Cl_2N_2O_6$: C, 48.8; H, 4.8; Cl, 16.9; N, 6.7. Found: C, 48.4; H, 4.8; Cl, 16.6; N, 6.7.

Attempted Dehydrogenation of 8-Chloro-4-ethoxycarbonyl-5-ethyl-1,2-dihydro-3-methyl-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate. Compound **26** (6.29 g, 0.015 mol) was refluxed for 1 h with stirring in dimethylacetamide (100 mL) containing 10% palladium on charcoal (2 g). The mixture was cooled and filtered, and the filtrate was stirred with ether (1.5 L) for 1 h. The product was filtered, washed with ether, and dried. Surprisingly, the infrared spectrum showed only a trace of carbonyl. Recrystallizations from ethanol and then from water gave 2.35 g of carbonyl-free material of mp 262–264 °C dec. The product consisted of an inseparable mixture of 5-ethyl-3-methyl-5*H*-pyrido[2,1-*b*]benzimidazolium perchlorate (78% by weight or 80% mole fraction) and 8-chloro-5-ethyl-3-methyl-5*H*-pyrido[2,1-*b*]benzimidazolium perchlorate (22% by weight or 20% mole fraction) via elemental analysis. The product mixture was converted to the mixed chloride salts with Amberlite IRA-400 chloride anion exchange resin, and then to the mixed fluoroborate salts by adding fluoroboric acid to an aqueous solution of the chloride salts. Elemental analysis of the mixed fluoroborate salts fit for 74% weight or 76% mole fraction of the chlorine free salt and 26% by weight or 24% mole fraction of the 8-chloro salt. The reaction was repeated with nearly identical results. NMR (Me_2SO-d_6): δ 1.4 (t, 3 H, J = 7 Hz, CH_3 of ethyl), 2.63 (s, 3 H, $ArCH_3$), 4.64 (q, 2 H, J = 7 Hz, $-CH_2-$ of ethyl), 8.53 (d, 1 H, J = 8 Hz, H_9), 9.42 (d, 1 H, J = 7 Hz, H_1). A small band at δ 8.76 (d, J = 2 Hz) is probably due to H_9 in the 8-chloro component.

Anal. Calcd for $(C_{14}H_{15}ClN_2O_4)$ (0.80) + $(C_{14}H_{14}Cl_2N_2O_4)$ (0.20): C, 52.9; H, 4.7; N, 8.8; Cl, 13.4. Found: C, 52.5; H, 5.0; N, 8.5; Cl, 13.1.

Anal. Calcd for $(C_{14}H_{15}BF_4N_2)$ (0.76) + $(C_{14}H_{14}BClF_4N_2)$ (0.24): C, 54.9; H, 4.9; N, 9.1; Cl, 2.8. Found: C, 54.5; H, 5.3; N, 8.8; Cl, 2.5.

4-Ethoxycarbonyl-3,5-dimethyl-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (30). Compound **23** (2.22 g, 0.006 mol) was refluxed for 1 h with stirring in dimethylacetamide (30 mL) containing 10% palladium on charcoal (0.4 g). The mixture was cooled and filtered, and the filtrate was stirred with ether (600 mL) for 1 h. The product was filtered and recrystallized from ethanol: yield 1.18 g (53.5%); mp 242–245 °C dec; NMR (Me_2SO-d_6) δ 2.67 (s, 3 H, CH_3Ar), 4.03 (s, 3 H, CH_3N), 7.82 (d, 1 H, J = 7 Hz, $^+NC{=}CH-$), 9.7 (d, 1 H, J = 7 Hz, $^+NCH{=}$); IR 1740 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}ClN_2O_6$: C, 52.1; H, 4.6; N, 7.6. Found: C, 52.0; H, 4.9; N, 8.0.

1,2-Dihydro-3,5-dimethyl-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (29). Compound **23** (7.92 g, 0.0213 mol) was boiled for 40 min with stirring in dimethylacetamide (50 mL) containing concentrated hydrochloric acid (3 mL) as approximately half of the solvent was permitted to boil off. The mixture was cooled and stirred with ether (1 L) overnight. The ether was decanted and the crude solid was dissolved in hot water (300 mL), treated with Norit carbon (2 g), and filtered. On cooling, some gum separated upon the sides of the flask. The clear liquid was decanted into a beaker, treated with sodium perchlorate (20 g), and cooled with ice. The crude product which separated was filtered and recrystallized from ethanol/acetonitrile (5/1): yield 3.28 g (51.6%); mp 206–210 °C dec; NMR (CD_3CN) δ 2.2 (s, 3 H, $=CCH_3$), 2.85 (broad t, 2 H, J = 8.0 Hz, $-CH_2CMe$), 3.86 (s, 3 H, NCH_3), 4.4 (t, 2 H, J = 8.0 Hz, $-N^+CH_2-$), 6.7 (m, 1 H, H_4); IR 1640 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}ClN_2O_4$: C, 52.3; H, 5.1; N, 9.4. Found: C, 52.3; H, 5.1; N, 9.4.

3,5-Dimethyl-5*H*-pyrido[2,1-*b*]benzimidazolium Perchlorate (31). Compound **29** (2.0 g, 0.0067 mol) was refluxed for 1 h with stirring in dimethylacetamide (40 mL) containing 10% palladium on charcoal (0.5 g). The reaction mixture was worked up as described in the preparation of **29**, and the crude product was recrystallized twice from ethanol, yield 1.15 g (58%), mp 240–245 °C.

The identical material was also prepared by boiling compound **30** for 1 h with stirring in dimethylacetamide containing concentrated hydrochloric acid as previously described in the preparation of **29**: yield 1.09 g (55%); NMR (Me_2SO-d_6) δ 2.6 (s, 3 H, $ArCH_3$), 4.04 (s, 3 H, NCH_3), 8.54 (d, 1 H, J = 8 Hz, H_9), 9.42 (d, 1 H, J = 7 Hz, H_1); IR 1657 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}ClN_2O_4$: C, 52.6; H, 4.4; N, 9.4. Found: C, 52.4; H, 4.5; N, 9.4.

3-(3-Oxo-1-butyl)-2-methylbenzothiazolium Bromide (32). 2-Methylbenzothiazolium bromide (37 g, 0.16 mol) and methyl vinyl ketone (34.5 g, 0.49 mol) in dimethylacetamide (75 mL) were stirred at room temperature overnight. The solid was filtered and washed in turn with acetone and ether, yield 35 g (73%). After two recrystallizations from ethanol, the yield was 31 g (65%): mp 152–153 °C dec; IR 1704 cm^{-1}; NMR (Me_2SO-d_6) δ 2.19 (s, 3 H, CH_3CO), 3.55 (s + t, 5 H, $CH_3C{=}N^+$ and CH_2CO), 4.93 (2 H, J = 6 Hz, $^+NCH_2-$), 7.9 (m, 2 H, aryl), 8.55 (m, 2 H, aryl).

Anal. Calcd for $C_{12}H_{14}BrNOS{\cdot}H_2O$ (prolonged drying leads to decomposition): C, 45.3; H, 5.1; N, 4.4; S, 10.1. Found: C, 45.6; H, 5.1; N, 4.6; S, 10.5.

1,2-Dihydro-3-methylpyrido[2,1-*b*]benzothiazolium Per-

chlorate (33). Compound **32** (2.0 g, 0.0067 mol) was boiled for 30 min in a mixture of water (150 mL) and pyridine (5 mL). The solution was evaporated to dryness, and the residue was washed with ether. The crude product was dissolved in water (15 mL), sodium perchlorate (3 g) was added, and product separated upon cooling: yield 0.35 g (17.5%); mp ~195 °C; NMR (CD_3CN) δ 2.23 (broad s, 3 H, CH_3), 3.0 (t, 2 H, J = 8.5 Hz, $-CH_2CMe$), 4.68 (t, 2 H, J = 8.5 Hz, N^+CH_2), 6.95 (q, 1 H, J = 1.5 Hz, HC=CMe); IR 1580, 1628 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}ClNO_4S$: C, 47.8; H, 4.0; Cl, 11.8. Found: C, 48.0; H, 3.9; Cl, 11.5.

3-Methylpyrido[2,1-*b*]benzothiazolium Perchlorate (34). 1,2-Dihydro-3-methylpyrido[2,1-*b*]benzothiazolium perchlorate (**33**, 5.22 g, 0.0173 mol) was refluxed with stirring for 3 h in dimethylacetamide (50 mL) containing 10% palladium on charcoal (1.7 g). The mixture was cooled and filtered, and the filtrate was stirred for 15 min in ether (2 L). The crude brown product was scraped from the sides of the beaker, and the mixture was filtered. The solid was dissolved in water, treated with Norit carbon, and filtered. Sodium perchlorate (15 g) was dissolved in the chilled filtrate whereupon the product crystallized: yield 3.42 g (66%); mp 202–204 °C dec; NMR (CD_3CN) δ 2.75 (s, 3 H, CH_3), 9.7 (d, 1 H, J = 7 Hz, N^+CH); IR 1625 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}ClNO_4S{\cdot}H_2O$: C, 45.4; H, 3.8; N, 4.4. Found: C, 45.7; H, 4.2; N, 4.4.

2,3,3-Trimethyl-1-(3-oxo-1-butyl)-3*H*-indolium Perchlorate (36) and 8,10,10-Trimethyl-10*H*-pyrido[1,2-*a*]indolium Perchlorate (37). 2,3,3-Trimethyl-3*H*-indolium perchlorate (**35**, X = ClO_4^-) (20 g) and methyl vinyl ketone (40 mL) were heated together on the steam bath for 15 min. The reaction mixture was chilled until solid and then filtered to yield 20 g of crude adduct **36**. A sample was recrystallized for analysis from isopropyl alcohol: mp 168–170 °C; IR 1720 cm^{-1}; NMR (Me_2SO-d_6) δ 1.52 [s, 6 H, $C(CH_3)_2$], 2.15 (s, 3 H, CH_3CO), 2.86 (s, 3 H, $CH_3C{=}N^+$), 3.25 (t, 2 H, J = 6 Hz, CH_2CO), 4.59 (t, 2 H, J = 6 Hz, CH_2N^+), 7.72 (m, 4 H, aromatic).

Anal. Calcd for $C_{15}H_{20}ClNO_5$: C, 54.6; H, 6.1; N, 4.3. Found: C, 54.9; H, 6.0; N, 4.6.

The same product was also obtained by reaction in acetonitrile at room temperature for 12 h.

The open-chain adduct **36** was dissolved in pyridine (100 mL) and the solution refluxed for 1 h. The pyridine solution was reduced to half volume and diluted with ether. The product **37** was isolated by filtration and purified by recrystallization from ethanol: yield 9 g, 36%; mp 206 °C; NMR (Me_2SO) δ 1.73 [s, 6 H, $C(CH_3)_2$], 2.79 (s, 3 H, CH_3), 7.62–8.60 (m, 6 H, aryl), 9.6 (d, 1 H, J = 6 Hz, $^+NCH{=}$).

Anal. Calcd for $C_{15}H_{16}ClNO_4$: C, 58.2; H, 5.2; N, 4.5. Found: C, 58.5; H, 5.1; N, 4.6.

6,10,10-Trimethyl-10*H*-pyrido[1,2-*a*]indolium Perchlorate (38). 2,3,3-Trimethyl-3*H*-indolium bromide (**35**, X = Br^-) (10 g) and methyl vinyl ketone (5.6 g) were dissolved in dry dimethylacetamide and stirred for 3 days at room temperature. The reaction mixture was poured into ether (500 mL), and the liquid was decanted from the gummy product. After conversion to the perchlorate, the product was purified by recrystallization from methanol: yield 3.2 g, 26%; mp 215–218 °C; NMR (Me_2SO) δ 1.72 [s, 6 H, $C(CH_3)_2$], 3.33 (s, 3 H, CH_3), 7.58–8.71 (m, 7 H, aryl).

Anal. Calcd for $C_{15}H_{16}ClNO_4$: C, 58.2; H, 5.2; N, 4.5. Found: C, 57.8; H, 5.4; N, 4.3.

6,10,10-Trimethyl-8-phenyl-10*H*-pyrido[1,2-*a*]indolium Perchlorate (39). 2,3,3-Trimethyl-3*H*-indolium perchlorate (1 g) and 4-phenylbut-3-en-2-one (3 g) were heated together on the steam bath for 10 h. The cooled reaction mixture was diluted with ether and the precipitated material recrystallized from methanol: yield 0.35 g, 22%; mp 288–289 °C; NMR (Me_2SO) δ 3.15 (s, 3 H, CH_3).

Anal. Calcd for $C_{21}H_{20}ClNO_4$: C, 65.4; H, 5.2; N, 3.6. Found: C, 65.5; H, 5.1; N, 3.6.

2-Ethyl-3,3-dimethyl-3*H*-indolium Bromide (40). 2-Methylpentan-3-one[13,14] (10 g) and phenylhydrazine (10.8 g) were dissolved in acetic acid (50 mL) and refluxed for 2 h. The remainder of the workup was identical with that described above for the 2-benzyl derivative **5**, yield of crude indole 11 g. Gas chromatography at 170 °C on a 6 ft column of OV-17 packing gave only one peak.

The product was dissolved in ether and treated with excess 40% HBr in acetic acid. The hydrobromide salt was filtered off and recrystallized from isopropyl alcohol: mp 205 °C; NMR (Me_2SO) δ 3.1 (q, 2 H, CH_2), 1.4 (t, 3 H, CH_3), 1.5 [s, 6 H, $C(CH_3)_2$].

The salts listed in Table I were synthesized by heating the appropriate starting materials either neat or in DMF solution above 100 °C for several hours.

5,8-Dihydro-8,8-dimethyl-6-phenylindeno[1′,2′-6,5]pyrido[1,2-*a*]indolium Perchlorate (42, X = CH_2). 2,3,3-Trimethyl-3*H*-indolium perchlorate (**35**, X = ClO_4^-) (1 g) and 2-benzylideneindan-1-one (**41**, 2 g) were heated together at 140–150 °C for 24 h. The product was isolated by dissolving the melt in methanol and chilling in the refrigerator, yield 0.9 g.

The compounds listed in Table II were synthesized similarly to the above.

Acknowledgments. The authors wish to thank Dr. T. H. Regan and Mr. R. L. Young for the NMR spectra, Mr. D. P. Maier for the mass spectra, and Mr. G. W. Thompson and Ms. L. Pepper for expert technical assistance.

Registry No.—**1**, 54507-57-2; **2**, 38494-40-5; **3**, 37937-74-9; **4**, 62476-25-9; **5**, 54507-77-6; **6**, 54507-59-4; **6** free base, 62476-26-0; **7** free base, 55868-14-9; **8**, 62476-27-1; 8 free base, 62476-28-2; **9**, 38494-46-1; **10**, 37937-75-0; **11**, 55867-38-4; **12**, 55868-16-1; **13**, 55868-18-3; **14**, 55868-22-9; **15**, 62476-29-3; **16**, 54507-79-8; **18** free base, 7767-16-0; **19**, 54507-69-6; **19** free base, 2735-61-7; **20**, 62476-30-6; **20** free base, 55868-51-4; **21**, 62476-32-8; **22**, 55868-28-5; **23**, 62476-33-9; **24**, 62476-35-1; **25**, 62476-36-2; **26**, 55868-50-3; **27**, 62476-02-2; **27** fluoroborate, 62476-03-3; **28**, 55868-41-2; **28** fluoroborate, 62476-04-4; **29**, 55868-39-8; **30**, 62476-05-5; **31**, 62476-07-7; **32**, 51588-76-2; **33**, 55868-13-8; **34**, 62476-09-9; **35** (X = ClO_4^-), 53057-95-7; **35** (X = Br^-), 53642-08-3; **36**, 62476-11-3; **37**, 55867-89-5; **38**, 55867-61-3; **39**, 55868-00-3; **40**, 62476-12-4; **40** free base, 18781-53-8; **41** (R = Ph; X = CH_2), 5706-12-7; **41** (R = $MeOC_6H_4$-*p*; X = CH_2), 5706-14-9; **41** (R = 2-methylfuranyl; X = CH_2), 6072-59-1; **41** (R = Ph; X = C=O), 5381-33-9; $R_3COCH{=}CHR_2$ (R_2 = H; R_3 = CH_3), 78-94-4; $R_3CO{-}CH{=}CHR_2$ (R_2 = $MeOC_6H_4$-*p*; R_3 = CH_3), 943-88-4; $R_3CO{-}CH{=}CHR_2$ (R_2, R_3 = Ph), 94-41-7; $R_3COCH{=}CHR_2$ (R_2 = $MeOC_6H_4$-*p*; R_3 = Ph), 959-33-1; $R_3COCH{=}CHR_2$ (R_2 = Ph; R_3 = $MeOC_6H_4$-*p*), 959-23-9; 2-amino-4-phenylphenol, 1134-36-7; phenylacetic acid, 103-82-2; 2-bromoacenaphthenone, 16269-27-5; phenylthioacetamide, 645-54-5; 4,5-dichloro-*N*-ethyl-*o*-phenylenediamine dihydrochloride, 62476-13-5; phenylacetyl chloride, 103-80-0; 3-methyl-1-phenylbutan-2-one, 2893-05-2; phenylhydrazine, 100-63-0; 2-benzoyl-3,3-dimethyl-3*H*-indole, 62476-14-6; *N*-methyl-*o*-phenylenediamine, 4760-34-3; ethylcarboethoxyacetimidate HCl, 2318-25-4; 2-amino-4-chloro-*N*-ethylaniline, 62476-15-7; 2-methylbenzothiazolium bromide, 874-45-3; 4-phenylbut-3-en-2-one, 122-57-6; 2-methylpentan-3-one, 565-69-5.

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The $S_{RN}1$ Mechanism in Heteroaromatic Nucleophilic Substitution. Photostimulated Reactions of Halopyridines with Ketone Enolates[1]

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2-Bromopyridine undergoes photostimulated $S_{RN}1$ reactions in liquid ammonia with the potassium enolates of acetone, 2,4-dimethyl-3-pentanone, cyclohexanone, and pinacolone. 2-Pyridyl radicals formed in these reactions show a preference for combination with tertiary enolates over primary enolates in competitive experiments. The reactivity of a series of haloaromatics toward potassioacetone was found to be 2-chloroquinoline > 2-bromopyridine > bromobenzene. In the 2-halopyridine series the order of reactivity with potassioacetone is 2-bromopyridine > 2-chloropyridine > 2-fluoropyridine; while the isomeric bromopyridines exhibit the order 2-bromopyridine > 3-bromopyridine > 4-bromopyridine. The reactivity of alkali salts of acetone toward 2-bromopyridine was found to be K > Na > Li. 2,6-Dibromo- and 2,6-dichloropyridine react with the potassium enolate of pinacolone to form the 2,6-disubstituted product without accumulation of a monosubstituted intermediate. The synthetic value of the present reactions is demonstrated by a large scale preparation of 2-acetonylpyridine.

Recently,[2,3] we have found that various ketone enolates react with 2-chloroquinoline in liquid ammonia under near-ultraviolet irradiation to afford α-(2-quinolyl) ketones via the radical chain process illustrated in Scheme I.

Scheme I

$$\text{Het–X} + \text{RCO}\bar{\text{C}}\text{H}_2 \xrightarrow{h\nu} \text{Het–X}^{-}\cdot + \text{RCOCH}_2\cdot \quad (1)$$

$$\text{Het–X}^{-}\cdot \longrightarrow \text{Het}\cdot + \text{X}^{-} \quad (2)$$

$$\text{Het}\cdot + \text{RCO}\bar{\text{C}}\text{H}_2 \longrightarrow \text{HetCH}_2\text{COR}^{-}\cdot \quad (3)$$

$$\text{HetCH}_2\text{COR}^{-}\cdot + \text{Het–X} \longrightarrow \text{HetCH}_2\text{COR} + \text{Het–X}^{-}\cdot \quad (4)$$

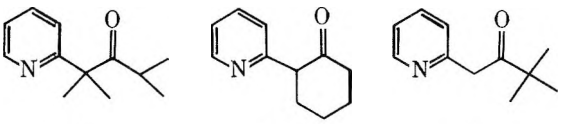
Initiation (step 1) is provided by photostimulated electron transfer, presumably from the enolate ion, to form the radical anion of the halogenated heterocycle. Expulsion of halide ion to form the heterocyclic radical (step 2), combination of the enolate with this radical (step 3), and transfer of an electron from the resulting radical anion to a substrate molecule constitute the propagating steps of the mechanism. Similar mechanisms have been verified for reactions of various nucleophiles with aliphatic[4] and carboaromatic[5] substrates containing appropriate leaving groups. These reactions have been designated by Bunnett as $S_{RN}1$ processes.[6]

In spite of the documented occurrence of $S_{RN}1$ reactions with the aforementioned classes of substrates, there are still relatively few verified examples implicating this mechanism in the area of heteroaromatic nucleophilic substitution.[2,3,7-9] Because of this, we have continued our investigations of the scope of the heteroaromatic $S_{RN}1$ mechanism by studying the reactions of halopyridines with ketone enolates. The present paper describes the results of such a study, in which it has been found that $S_{RN}1$ reactions do indeed occur under conditions of photostimulation. This is the first reported instance of participation of enolate ions in light-induced $S_{RN}1$ reactions on the pyridine nucleus.

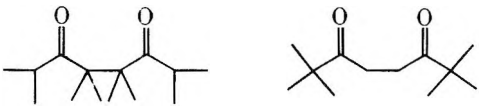
Results and Discussion

Treatment of 2-bromopyridine (**1**) with 3.75 molar equiv of potassioacetone (**2**) in liquid ammonia at −33 °C in a reaction flask protected from light resulted in nearly quantitative recovery of **1** after a reaction time of 60 min (expt 1, Table I). Photostimulation was demonstrated in a similar experiment conducted under full illumination (four 12.5-W output lamps) in a Rayonet photochemical reactor at 350 nm for 15 min. In this reaction 2-acetonylpyridine (**3**) was obtained in 95% yield (expt 2). Low intensity irradiation with a single lamp for 10 min or less (expt 3) led to incomplete reaction, whereas irradiation with one lamp for 15 min gave **3** in quantitative yield (expt 4). The radical-chain character of the substitution process was clearly indicated by a 15-min irradiation (one lamp) in the presence of 10 mol % of the radical scavenger, di-*tert*-butyl nitroxide.[10] Under these conditions less than 5% of **1** was consumed and no **3** was detected (expt 5). Evidently the nitroxide breaks chains involving propagating steps 2–4 (Scheme I) either by combining with 2-pyridyl radicals or by oxidizing radical anion intermediates. In connection with the inhibition studies utilizing di-*tert*-butyl nitroxide, we observed that reactions conducted under full illumination were also inhibited, but the inhibition period was usually less than 15 min with 5 mol % of inhibitor.

Photostimulated reactions of **1** with the potassium salts of 2,4-dimethyl-3-pentanone, cyclohexanone, and pinacolone proceeded smoothly to afford **4**, **5**, and **6**, respectively (expt 6, 7, and 8). In addition to ketone **4**, a small amount of

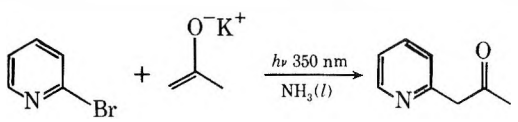


4 **5** **6**



7 **8**

2,4,4,5,5,7-hexamethyloctane-3,6-dione (**7**) was produced in expt 6. Recently, Bunnett and co-workers reported that the photostimulated reaction of iodobenzene with the potassium enolate of 2,4-dimethyl-3-pentanone gave **7** and benzene in equimolar quantities along with the normal $S_{RN}1$ product.[11] The mechanism proposed[11] for formation of **7** involves electron transfer from the enolate ion to an aryl radical yielding an aryl anion, which abstracts a proton from the solvent, and a β-keto alkyl radical, which either dimerizes or combines with another enolate ion with subsequent electron transfer. The present results, along with those of an earlier study,[2] demonstrate that 2-pyridyl and 2-quinolyl radicals are less susceptible to reduction by the enolate of 2,4-dimethyl-3-pentanone than are phenyl radicals. This might be attributed to



1 **2** **3**

Table I. Photostimulated $S_{RN}1$ Reactions of Ketone Enolates with Halopyridines[a]

Expt. no.	Substrate	Enolate derived from	Irradiation time, min	Product distribution[b] Pyridyl no.	Ketone yield, %	Unreacted substrate, %
1	2-BrPy	Acetone	c	3	0	98
2	2-BrPy	Acetone	15	3	95	0
3	2-BrPy	Acetone	10[d]	3	85	10
4	2-BrPy	Acetone	15[d]	3	100	0
5	2-BrPy	Acetone	15[d,e]	3	0	95
6	2-BrPy	2,4-Dimethyl-3-pentanone	60	4	97	0[f]
7	2-BrPy	Cyclohexanone	60	5	47	Present
8	2-BrPy	Pinacolone	90	6	94[g]	0
9	2-BrPy	Acetone	15	3	21	0[f]
		2,4-Dimethyl-3-pentanone		4	77	
10	2-BrPy	2,4-Dimethyl-3-pentanone	15	4	61	36
11	2-BrPy	Acetone[h]	15	3	74	0
12	2-BrPy	Acetone[i]	15	3	6	58
13	2-ClPy	Acetone	60	3	85	0
14	2-FPy	Acetone	120	3	40	20
15	3-BrPy	Acetone	15	14	65	0
16	3-BrPy	Acetone	15[c,e]	14	0	Mostly
17	4-BrPy	Acetone	15	15	28	Present

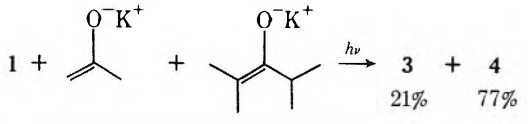
[a] In expt 8 the ratio of 2-BrPy to enolate was 1:2.5 and in expt 9, the ratio of 2-BrPy to the two enolates was 1:1.9:1.9. In all other cases the ratio of halopyridine to enolate was 1:3.75. [b] In all reactions employing acetone, appreciable quantities of 4-hydroxy-4-methyl-2-pentanone were formed along with small amounts of 2,6-dihydroxy-2,6-dimethyl-4-heptanone. [c] This experiment was conducted in the dark (foil-wrapped vessel). [d] This reaction was irradiated with single 12.5-W output 350-nm lamp. [e] Di-*tert*-butyl nitroxide (10 mol % based on 1) was present. [f] Dimer 7 was produced in 5% yield in expt 6 and 2% yield in expt 9. [g] Isolated yield. [h] The sodium enolate was used. [i] The lithium enolate was used.

the greater electrophilicity of the heterocyclic radicals, which favors their combination with the enolate ion, while the less electrophilic phenyl radicals suffer appreciable reduction via electron transfer from the enolate.[8]

Another 1,4-diketone, 8, was found in prolonged irradiations of pinacolone enolate with halopyridines. In these cases, however, the diketone arises from a photostimulated reaction independent of the $S_{RN}1$ reaction, since 8 accumulated only slowly, even though the $S_{RN}1$ reactions were rapid. Irradiation of pinacolone potassium enolate alone in liquid ammonia for 120 min gave 8, but a similar experiment conducted in the dark did not produce 8.

2-Bromopyridine failed to react under irradiation with the monoanion of benzoylacetone (120 min) or the potassium enolates of acetophenone and propiophenone (both 60 min). Previous attempts to react β-dicarbonyl monoenolates with 2-chloroquinoline[2] or halobenzenes[11] have all met with failure. Potassioacetophenone is totally unreactive toward bromo- and iodobenzene under photostimulation,[11] whereas with 2-chloroquinoline, a very slow substitution occurs.[2]

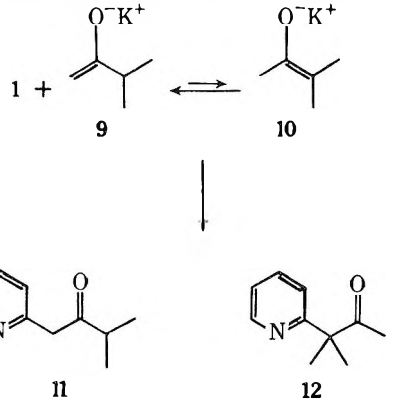
Competitive Reactions. In an earlier study, we observed that 2-quinolyl radicals, generated during photostimulated $S_{RN}1$ reactions, exhibited a significant degree of selectivity in competitive reactions involving mixtures of primary and tertiary potassium enolates. In order to ascertain if 2-pyridyl radicals might show similar selectivity, 1 was allowed to react with an equimolar mixture of the potassio salts of acetone and



2,4-dimethyl-3-pentanone for 15 min under full illumination (expt 9). Pyridyl ketones **4** and **3** were produced in yields of 77 and 21%, respectively. This product ratio (3.7:1) is nearly the same as that (3.2:1) observed when an identical mixture of enolates was allowed to react with 2-chloroquinoline under the same reaction conditions.[2] The present results indicate that 2-pyridyl radicals exhibit a degree of selectivity similar to 2-quinolyl radicals in reactions with enolates.

A comparison of expt 1, 9, and 10 revealed an additional feature of this competitive reaction. When 2,4-dimethyl-3-pentanone enolate was irradiated with 1 for 15 min, **4** was obtained in only 61% yield (expt 10), while acetone enolate gave **3** in 95% yield (expt 1) after the same irradiation time. The 77% yield of **4** obtained in expt 9 demonstrates entrainment[2,4] of 2,4-dimethyl-3-pentanone enolate by acetone enolate. In the entrainment process, acetone enolate functions as the better electron-donating species (step 1, Scheme I) thus initiating more chains than 2,4-dimethyl-3-pentanone enolate, while 2,4-dimethyl-3-pentanone enolate is the better nucleophile for combination with the pyridyl radicals (step 3, Scheme I).

A further competitive experiment was performed using 3-methyl-2-butanone, which can form isomeric enolates **9** and **10**. Irradiation of 1 with the equilibrium mixture of **9** and **10** for 15 min produced pyridyl ketones **11** and **12** in a 7:1 ratio.



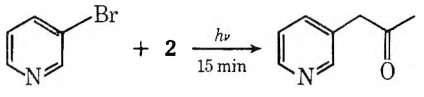
Comparison of these results with those from a previous study[12] concerning photostimulated phenylation of enolates **9** and **10** indicates that the ratio of pyridyl ketones **11** and **12** is determined mainly by the equilibrium composition of this enolate mixture in liquid ammonia.

In order to determine the relative $S_{RN}1$ reactivity of **1** compared to other haloaromatic compounds, two competitive reactions were conducted employing bromobenzene and 2-chloroquinoline. Irradiation of an equimolar mixture of **1** and bromobenzene in the presence of acetone enolate for 7 min (one lamp) resulted in complete consumption of **1** and production of phenylacetone and **3** in a ratio of 0.27:1.00. Thus **1** is seen to be more reactive than bromobenzene toward $S_{RN}1$ substitution. Irradiation of an equimolar mixture of **1** and 2-chloroquinoline with acetone enolate for 1.5 min (one lamp) returned **1** unchanged and converted 66% of the 2-chloroquinoline to 2-acetonylquinoline. Presumably, 2-bromoquinoline would show even greater reactivity than 2-chloroquinoline in a competitive reaction with **1**. Previously,[2] we had determined that 2-chloroquinoline was more reactive than iodobenzene toward $S_{RN}1$ substitution by acetone enolate. This comparison may now be expanded to give the following reactivity sequence: 2-haloquinoline > 2-halopyridine > halobenzene, provided similar halogen substituents are compared. This selectivity may be linked to the ease with which the haloaromatic substrate is reduced to its radical anion as in steps 1 and 4 of Scheme I.

Metallic Cation Effects. In order to assess the influence of the gegenion, a series of experiments using **1** with the sodio and lithio salts of acetone were conducted under illumination for 15 min. As may be seen from Table I (expt 11 and 12), potassioacetone (**2**) was superior to either the sodium or lithium enolate, although for preparative scale reactions, sodioacetone may be a satisfactory substitute for the potassio analogue.

Influence of Halogen. Whereas potassioacetone reacted with **1** to form **3** in quantitative yield after 15 min of illumination, the reaction of 2-chloropyridine with potassioacetone was somewhat slower, affording 85% of **3** after 60 min of irradiation (expt 13). A further decrease in reactivity was observed when 2-fluoropyridine was irradiated for 120 min with potassioacetone. In this experiment, 20% of 2-fluoropyridine was recovered and **3** was formed in only 40% yield (expt 14). It has been shown that 2-fluoropyridine forms a relatively stable radical anion upon reduction with sodium in liquid ammonia, whereas the radical anions of 2-bromo- and 2-chloropyridine quickly expel their respective halide ions.[13] In view of this, it appears that the comparatively low reactivity of 2-fluoropyridine may be traced to step 2 of Scheme I, where expulsion of halide ion is necessary for maintenance of the propagating sequence.

Effect of Halogen Position. To date, photostimulated $S_{RN}1$ reactions of enolates with haloquinolines and halopyridines have involved displacement of halide exclusively from the 2 position of the heterocycle. We have now found that 3-bromopyridine (**13**) readily participates in the reaction with potassioacetone (**2**). Thus, exposure of **13** to 3.75 molar equiv of the enolate with illumination for 15 min afforded ketone



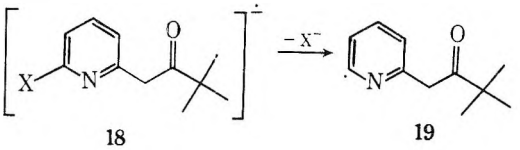
13 14

14 in 65% yield. The $S_{RN}1$ character of this reaction was confirmed by an experiment in which a mixture of **13**, 2, and 10 mol % of di-*tert*-butyl nitroxide was maintained in the dark for 15 min (expt 16). No starting material was consumed. Substitution at the 4 position of 4-bromopyridine by **2** proceeded poorly. Irradiation of the reaction mixture for 15 min gave only 28% of 4-acetonylpyridine (**15**) along with an appreciable amount of recovered 4-bromopyridine (expt 17).

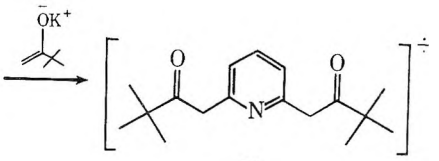
2,6-Dihalopyridines. Photostimulated reaction of the potassium enolate of pinacolone with 2,6-dibromopyridine gave 89% of the 2,6-disubstituted derivative **16**, along with a trace of **6** after 60 min of irradiation. 2,6-Dichloropyridine reacted similarly to give a 86% yield of **16**. Formation of disubstituted product **16** appears to arise directly from 2,6-dichloropyridine without buildup of the monosubstituted

16 17

compound **17**. Evidence for direct formation of **16** was obtained from an experiment in which a reaction of 2,6-dichloropyridine and pinacolone enolate was irradiated for only 45 s. Under these conditions, none of the monosubstituted pyridine **17** (X = Cl) was detected, but rather starting material and **16** were found in a ratio of 1:3. Similar results have been observed recently in the $S_{RN}1$ reactions of dihalobenzenes with thiophenoxide in liquid ammonia.[14] By analogy with these studies, disubstitution without accumulation of monosubstituted product is attributed to preferential expulsion of halide from an intermediate radical anion such as **18** to form



18 19



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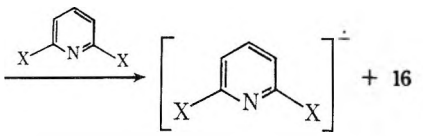


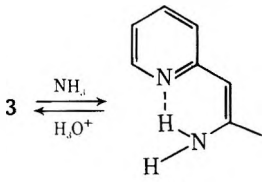
radical **19** rather than electron transfer from **18** to 2,6-dihalopyridine as in step 4 of Scheme I. Combination of radical **19** with pinacolone enolate yields radical anion **20**, which then initiates a new cycle by transferring an electron to another molecule of 2,6-dihalopyridine. In our experiments, the small amount of **6** formed may result from either reduction of radical **19** or reduction of the initial 6-chloro-2-pyridyl radical followed by $S_{RN}1$ reaction of the resulting 2-chloropyridine with pinacolone enolate.

Metal-Promoted Reaction. Solvated electrons, furnished by alkali metals, have been shown to promote $S_{RN}1$ reactions between enolate nucleophiles and halobenzenes in liquid ammonia.[15] The solvated electrons initiate the chain sequence by a one-electron reduction of the substrate to its radical anion.

Addition of 1 molar equiv of potassium metal to a liquid ammonia solution of **1** and **2**, maintained in a flask protected from light, failed to effect significant catalysis of the substitution reaction. Instead, 38% of **1** was recovered, an appreciable quantity of pyridine was generated, and ketone **3** was produced in only 4% yield. Formation of pyridine indicates that reduction of 2-pyridyl radicals to 2-pyridyl anions by solvated electrons and subsequent protonation by ammonia competes strongly with the desired combination of 2-pyridyl radicals with enolate **2**. To date, metal-promoted $S_{RN}1$ reac-

tions of heteroaromatics have been found to be less satisfactory than those involving carboaromatic substrates.[2,3]

Preparative Scale Reactions. The synthetic utility of the present photostimulated reactions was verified by a preparative scale reaction involving 0.4 mol of **1** and 1.2 mol of **2**, which afforded **3** in 84% isolated yield after 90 min of irradiation. It should be noted that reactions which produce **3** may be accompanied by formation of enamine **21** if evaporation



21

of the ammonia subsequent to quenching is not carried out rapidly. However, this minor inconvenience can be circumvented easily by hydrolyzing **21** with dilute hydrochloric acid (see Experimental Section). A reaction similar to the preceding one, conducted in a 5-L flask illuminated from 15 cm by a 150-W flood light, required 9 h to achieve completion. For more economical use of the ketone, the ketone enolate to halopyridine ratio may be reduced to a small excess over the theoretical ratio of 2:1.[16] A ratio of 2.5:1 of pinacolone enolate to **1** gave **6** in 94% isolated yield after 90 min of irradiation (expt 8).

Experimental Section

General. All reactions were conducted under an atmosphere of nitrogen. The photostimulated reactions were carried out using a Rayonet RPR-204 photochemical reactor equipped with four 12.5-W output 350-nm lamps. Photolysis vessels were of cylindrical Pyrex 4.4 cm i.d. or 10.6 cm i.d. for preparative runs and were occasionally rinsed with ethanol to remove the frost buildup. Product yields were determined by vapor phase chromatography (VPC) on Varian Associates 90-P or 1200 instruments using columns of 10% SE-30 or 1.5% SE-52 on Chromosorb W AW/DMCS or 5% Carbowax 20M on Chromosorb G employing methyl benzoate, dimethyl phthalate, or benzyl benzoate as internal standard. ^{1}H NMR spectra were obtained on a JEOL JMN-PS-100 instrument with internal tetramethylsilane as reference. Mass spectra (70 eV) were recorded on Varian MAT CH-7 or 112 instruments. Microanalyses were performed in this laboratory by C. D. Anderson employing a Perkin-Elmer 240 elemental analyzer or by Galbraith Laboratories, Knoxville, Tenn. Unless otherwise noted, analytical samples were obtained by preparative VPC using the columns described above.

Liquid ammonia (Matheson) was used directly from the tank since essentially no difference was observed in product composition and yield compared to ammonia distilled from benzophenone potassium ketyl. 2-Bromopyridine (**1**) and acetone were dried and fractionated, 2,6-dichloropyridine was vacuum sublimed; other reagents were used as received. Anhydrous magnesium sulfate was routinely used as a drying agent. Di-*tert*-butyl nitroxide[17] was prepared from 2-methyl-2-nitropropane.[18] Inhibited reactions were carried out by mixing the di-*tert*-butyl nitroxide (10 mol %, based on halopyridine) with the halopyridine before it was added to the enolate solution. Dark reactions were run in a darkened room using a foil-wrapped 500-mL three-necked flask equipped with a mechanical stirrer, air-cooled condenser, addition funnel, and nitrogen inlet. The molar ratio of halopyridine to ketone enolate was 1:3.75 unless otherwise indicated. Starting material was often consumed before the end of the irradiation period given in Table I.

Reaction Workup. After an appropriate period (Table I), reaction mixtures were poured onto excess solid ammonium chloride contained in a 1.5-L beaker. Ether (300 mL) was added to the resulting suspension while the ammonia was evaporated with the aid of a warm water bath. The ether was then allowed to boil briefly to ensure removal of the residual ammonia. At this point either workup procedure A or B was followed.

Procedure A. Water (150 mL) was added, followed by enough dilute hydrochloric acid to make the aqueous layer distinctly acidic (pH <1). Sodium bicarbonate was then added to neutralize the acid, and the ethereal layer was separated. The aqueous layer was extracted twice with chloroform (75 mL). The combined organic extracts were dried, concentrated, mixed with an internal standard, and analyzed by VPC.

Procedure B. The ethereal suspension remaining after evaporation of the ammonia was decanted through a filter and the residual salts were triturated with warm ether (4 × 75 mL). The combined ethereal extracts were concentrated, mixed with an internal standard, and analyzed by VPC.

2-Acetonylpyridine (3). Potassium metal (2.93 g, 75 mg-atoms) was added to 300 mL of liquid ammonia along with a small amount of powdered ferric nitrate nonahydrate. After the potassium amide had formed, acetone (4.36 g, 75 mmol) was added dropwise and rinsed into the vessel with a small amount of anhydrous ether. Irradiation was begun after the enolate had been stirred for 10 min, and 2-bromopyridine (**1**, 3.16 g, 20 mmol) was added along with 50 mL of anhydrous ether. After 15 min of illumination, the reaction was processed according to procedure A. Analytical and spectral properties of **3** are given in the description of the large scale preparation of **3** (vide infra).

Enamine 21. Enamine **21** was isolated as a light yellow oil by preparative VPC of the crude product mixture obtained by employing workup procedure B in an experiment otherwise identical with the one described above. Highly air sensitive **21** showed ^{1}H NMR (CCl_4) δ 1.91 (s, 3 H, CH_3), 4.86 (s, 1 H, CH), 6.46 (broad s, 2 H, disappeared on shaking with D_2O, NH_2) 6.62–6.82 (m, 2 H, PyH-3,5), 7.26–7.47 (m, 1 H, PyH-4), and 8.29–8.39 (m, 1 H, PyH-6); mass spectrum *m/e* (rel intensity) 134 (40), 133 (100), 117 (13), 93 (61), 92 (43), 90 (19), 79 (11), 78 (16), 66 (19), 65 (31), 63 (10), 52 (10), 43 (17), 42 (13), 41 (11), and 39 (23).

Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.94; H, 7.26; N, 20.94.

2,4-Dimethyl-2-(2-pyridyl)-3-pentanone (4). 2-Bromopyridine (**1**, 3.16 g, 20 mmol) was added to an enolate solution prepared from 8.56 g (75 mmol) of 2,4-dimethyl-3-pentanone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 60 min, it was processed by procedure B. This reaction afforded 5% of **7** and 97% of **4**, the latter of which was isolated as a colorless oil by preparative VPC and showed ^{1}H NMR (CCl_4) δ 0.85 (d, J = 6.6 Hz, 6 H, isopropyl methyls), 1.45 [s, 6 H, $C(CH_3)_2$], 2.61 (septet, J = 6.6 Hz, 1 H, CH), 6.97–7.22 (m, 2 H, PyH-3,5), 7.44–7.64 (m, 1 H, PyH-4), and 8.38–8.48 (m, 1 H, PyH-6) (no enol).[19]

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.47; H, 9.08; N, 7.39.

A similar reaction mixture irradiated for 15 min gave unchanged **1** (36%) and 61% of **4**.

Diketone **7**, obtained as a colorless oil by preparative VPC, was spectroscopically identical with an authentic sample of **7** prepared by irradiation of iodobenzene with the potassium enolate of 2,4-dimethyl-3-pentanone in liquid ammonia according to the procedure of Bunnett and Sundberg.[11]

2-(2-Pyridyl)cyclohexanone (5). 2-Bromopyridine (**1**, 3.16 g, 20 mmol) was added to the white enolate suspension (all other potassium enolates were soluble) prepared from 7.36 g (75 mmol) of cyclohexanone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 90 min, it was worked up by procedure B. VPC analysis showed unreacted **1** along with 47% of **5**. A sample of **5** was collected for analysis. This light yellow oil had ^{1}H NMR (CCl_4) δ 1.5–2.4 (m, cyclohexyl protons), 6.82–7.10 (m, 2 H, PyH-3,5), 7.45–7.65 (m, 1 H, PyH-4), 8.21–8.31 (m, PyH-6 of enol), 8.35–8.45 (m, PyH-6 of keto), and 14.62 (broadened s, enol OH) (enol content ca. 84%).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.58; H, 7.44.

3,3-Dimethyl-1-(2-pyridyl)-2-butanone (6). 2-Bromopyridine (**1**, 15.8 g, 100 mmol) was added to the enolate solution prepared from 25.0 g (250 mmol) of pinacolone and potassium amide [prepared from 9.78 g (250 mg-atoms) of potassium in 1500 mL of liquid ammonia]. After the mixture had been irradiated for 90 min, it was poured onto excess ammonium chloride and the ammonia was evaporated while 300 mL of ether was added. The ethereal extract was filtered and the residual salts were washed twice with 100 mL of ether. The salts were dissolved in water and extracted further with chloroform (2 × 100 mL). The combined organic extracts were dried, concentrated, and distilled to give 16.6 g (94%) of **6**: bp 51–53 °C (0.15 mm); ^{1}H NMR (CCl_4) δ 1.16 (s, keto methyls), 1.19 (s, enol methyls), 3.87 (s, CH_2), 5.24 (s, enol CH), 6.70–7.16 (m, 2 H, PyH-3,5), 7.31–7.55 (m, 1 H, PyH-4), 8.10–8.20 (m, PyH-6 of enol), 8.27–8.37 (m, PyH-6 of keto), and 14.35 (broad s, enol OH) (enol content ca. 50%).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.40; H, 8.49.

2,2,7,7-Tetramethyloctane-3,6-dione (8). To a potassium amide

solution prepared from 2.93 g (75 mg-atoms) of potassium and 300 mL of liquid ammonia was added 7.51 g (75 mmol) of pinacolone followed by a rinse of anhydrous ether (25 mL). The enolate solution was irradiated for 120 min, quenched with excess solid ammonium chloride, and evaporated. The residual salts were triturated repeatedly with anhydrous ether to extract the organic components. The combined ether extracts were concentrated and examined by VPC showing, in addition to unreacted pinacolone, an appreciable amount of 8. A sample of 8 was collected as a viscous oil: ^{1}H NMR (CCl_4) δ 1.12 (s, 18 H, CH_3) and 2.62 (s, 4 H, CH_2).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19. Found: C, 72.56; H, 11.07.

An experiment similar to the one above was conducted in a foil-wrapped flask in a darkened room for 120 min. After the mixture had been quenched in the dark, an identical workup was followed. VPC analysis showed unreacted pinacolone with no trace of diketone 8.

Reaction of 1 with Acetone and 2,4-Dimethyl-3-pentanone Enolates. 2-Bromopyridine (1, 3.16 g, 20 mmol) was added under irradiation to the enolate solution prepared from 2.18 g (37.5 mmol) of acetone, 4.28 g (37.5 mmol) of 2,4-dimethyl-3-pentanone, and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 15 min, it was quenched and worked up by procedure **A**. VPC analysis showed 2% of **7**, 21% of **3**, and 77% of **4**.

Reaction of 1 with 3-Methyl-2-butanone Enolate. 2-Bromopyridine (1, 3.16 g, 20 mmol) was added under irradiation to the enolate solution prepared from 6.46 g (75 mmol) of 3-methyl-2-butanone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After a 15-min irradiation period, the mixture was quenched and worked up by procedure B. VPC analysis showed a moderate amount of 5-hydroxy-2,5,6-trimethyl-3-heptanone along with 3-methyl-1-(2-pyridyl)-2-butanone (**11**) and 3-methyl-3-(2-pyridyl)-2-butanone (**12**) in a ratio of 7:1. Isomeric ketones **11** and **12** were isolated as colorless oils by preparative VPC. Compound **11** showed ^{1}H NMR (CCl_4) δ 1.07 (d, J = 6.6 Hz, keto methyls), 1.16 (d, J = 6.6 Hz, enol methyls), 2.39 (septet, J = 6.6 Hz, isopropyl methine of enol), 2.71 (septet, J = 6.6 Hz, isopropyl methine of keto), 3.80 (s, keto CH_2), 5.17 (s, enol vinyl H), 6.70–7.14 (m, 2 H, PyH-3,5), 7.31–7.56 (m, 1 H, PyH-4), 8.10–8.20 (m, PyH-6 of enol), and 8.30–8.40 (m, PyH-6 of keto) (enol content ca. 37%).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.44; H, 7.92.

Compound **12** showed ^{1}H NMR (CCl_4) δ 1.44 [s, 6 H, $C(CH_3)_2$], 1.84 (s, 3 H, CH_3), 6.94–7.19 (m, 2 H, PyH-3,5), 7.43–7.63 (m, 1 H, PyH-4), and 8.39–8.49 (m, 1 H, PyH-6) (no enol).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.33; H, 7.98.

Reaction of Acetone Enolate with 1 and Bromobenzene. A mixture of bromobenzene (1.57 g, 10 mmol) and **1** (1.58 g, 10 mmol) was added in the dark to 75 mmol of potassioacetone in 300 mL of liquid ammonia. The mixture was irradiated with one 12.5-W output lamp for 7 min, quenched, and worked up by procedure A. VPC analysis showed complete reaction of **1** and partial consumption of the bromobenzene to give phenylacetone and **3** in a ratio of 0.27:1.00.

Reaction of Acetone Enolate with 1 and 2-Chloroquinoline. A mixture of 1 (1.58 g, 10 mmol) and 2-chloroquinoline (1.64 g, 10 mmol) was added in the dark to 75 mmol of potassioacetone in 300 mL of liquid ammonia. After the mixture had been irradiated for 1.5 min with one lamp (12.5-W output), it was quenched and worked up by procedure A. VPC analysis showed complete recovery of 1 and, along with some 2-chloroquinoline, 66% of 2-acetonylquinoline.[2]

3-Acetonylpyridine (14). 3-Bromopyridine (3.16 g, 20 mmol) was added to 75 mmol of acetone enolate prepared from 4.36 g (75 mmol) of acetone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 15 min, it was quenched and worked up by procedure B. VPC analysis showed no 3-bromopyridine and 65% of **14**, which was collected as a colorless oil: ^{1}H NMR (CCl_4) δ 2.10 (s, 3 H, CH_3), 3.60 (s, 2 H, CH_2), 7.04–7.19 (m, 1 H, PyH-5), 7.32–7.46 (m, 1 H, PyH-4), and 8.23–8.37 (m, 2 H, PyH-2,6) (no enol).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 70.94; H, 6.64.

4-Acetonylpyridine (15). 4-Bromopyridine hydrochloride (3.89 g, 20 mmol) was dissolved in ice water, neutralized with sodium bicarbonate, and extracted four times with cold ether (25 mL). The combined ethereal extracts were dried, filtered, and added to an acetone enolate solution prepared from 4.36 g (75 mmol) of acetone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 15 min, it was quenched and worked up by procedure B. VPC analysis showed an appreciable amount of unreacted 4-bromopyridine along with 28% of liquid keto6e **15**: ^{1}H NMR (CCl_4)$_4$ δ 2.10 (s, 3 H, CH_3), 3.61 (s, 2 H, CH_2), 6.94–7.03 (m, 2 H, PyH-3,5), and 8.30–8.40 (m, 2 H, PyH-2,6) (no enol).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 70.90; H, 6.78.

2,6-Bis(pivaloylmethyl)pyridine (16). A solution of 2.37 g (10 mmol) of 2,6-dibromopyridine in 25 mL of ether was added to the enolate solution prepared from 7.51 g (75 mmol) of pinacolone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 60 min, it was quenched and worked up by procedure B. VPC analysis showed a trace of **6** and 89% of **16**.

A similar reaction with 1.48 g (10 mmol) of 2,6-dichloropyridine in place of the 2,6-dibromopyridine produced **16** in 86% yield.

A preparative experiment conducted with 25 mmol of 2,6-dichloropyridine and 150 mmol of the potassium enolate of pinacolone afforded a 44% isolated yield of **16**:[20] bp 155–162 °C (0.5 mm); mp 47.5–49 °C; ^{1}H NMR (CCl_4) δ 1.17, 1.19, and 1.20 (singlets, 18 H, *tert*-butyl methyls of keto and enol), 3.81 and 3.82 (singlets, CH_2 of keto and enol), 5.22 (s, CH of enol), 6.62–7.05 (m, 2 H, PyH-3,5), 7.31–7.52 (m, 1 H, PyH-4), and 14.15 (broad s, enol OH) (enol content ca. 53%).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.18; H, 9.17.

Short Irradiation of 2,6-Dichloropyridine with Pinacolone Enolate. An ethereal solution of 2,6-dichloropyridine (1.48 g, 10 mmol) was added in the dark to 75 mmol of pinacolone potassium enolate in 300 mL of liquid ammonia. After the mixture had been irradiated for 0.75 min, it was quenched and worked up by procedure B. VPC analysis showed 2,6-dichloropyridine and **16** in a 1:3 ratio. Although a trace of **6** was seen, no **17** was detected.

Preparative Scale Synthesis of 2-Acetonylpyridine (3). A potassium amide solution was prepared in a cylindrical Pyrex vessel from 47 g (1.2 g-atoms) of potassium, 2.5 L of liquid ammonia, and a small amount of ferric nitrate nonahydrate. Acetone (69.7 g, 1.2 mol) was added over a period of 10 min and rinsed into the vessel with 50 mL of anhydrous ether. After the enolate solution had been stirred for 15 min, irradiation was begun and 63.2 g (0.40 mol) of **1** was added during a 10-min period and rinsed into the vessel with 50 mL of ether. After the mixture had been irradiated for 90 min, the orange-yellow solution was poured into a 4-L beaker and quenched with excess solid ammonium chloride. Ether (500 mL) was added while the ammonia was evaporated with the aid of a warm water bath. After 500 mL of water had been added, dilute HCl was added to pH <1 and the mixture was shaken. Excess solid sodium bicarbonate was added in portions to neutralize the acid, and the ethereal layer was separated. The aqueous layer was extracted with chloroform (3 × 250 mL). The combined organic extracts were dried, concentrated, and vacuum fractioned to yield, after a forerun of 4-hydroxy-4-methyl-2-pentanone (18.8 g), 45.3 g (83.8%) of 2-acetonylpyridine (**3**) as a yellow liquid: bp 49 °C (0.1 mm) [lit.[21] bp 92 °C (1.5 mm)]; IR (neat) ν 1710 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.93 (s, CH_3 of enol), 2.09 (s, CH_3 of keto), 3.78 (s, CH_2), 5.20 (s, CH of enol), 6.70–7.16 (m, 2 H, PyH-3,5), 7.37–7.62 (m, 1 H, PyH-4), 8.13–8.23 (m, PyH-6 of enol), 8.37–8.47 (m, PyH-6 of keto), and 14.17 (broad s, enol OH) (enol content ca. 28%); mass spectrum m/e (rel intensity) 135 (5), 120 (5), 94 (6), 93 (100), 92 (18), 66 (12), 65 (13), 43 (32), and 39 (12).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.87; H, 7.00; N, 10.46.

The 4-hydroxy-4-methyl-2-pentanone forerun was identical with an authentic sample:[22] ^{1}H NMR (CCl_4) δ 1.18 [s, 6 H, $C(CH_3)_2$], 2.11 (s, 3 H, CH_3), 2.52 (s, 2 H, CH_2) and 3.74 (broad s, 1 H, disappeared on shaking with D_2O, OH).

Small amounts of 2,5-dihydroxy-2,6-dimethyl-4-heptanone were obtained by preparative VPC on the crude reaction mixture: mp 57–57.5 °C [lit.[23] mp 56.4 °C; lit.[24] mp 57–58 °C]; ^{1}H NMR (CCl_4) δ 1.21 [s, 12 H, $C(CH_3)_2$], 2.53 (s, 4 H, CH_2), and 3.38 (broad s, 2 H, disappeared on shaking with D_2O, OH).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.21; H, 10.20.

Registry No.—**1**, 109-04-6; **2**, 25088-58-8; **3**, 6302-02-9; **4**, 62415-76-3; **5**, 3311-57-7; **6**, 34552-04-0; **8**, 27610-88-4; **9**, 62415-77-4; **10**, 62415-80-9; **11**, 10330-59-3; **12**, 62415-78-5; **13**, 626-55-1; **14**, 6302-03-0; **15**, 6304-16-1; **16**, 62415-79-6; **21**, 62415-85-4; 2-chloropyridine, 109-09-1; 2-fluoropyridine, 372-48-5; 4-bromopyridine HCl, 19524-06-2; potassio-2,4-dimethyl-3-pentanone, 62415-81-0; potassiocyclohexanone, 62415-82-1; sodioacetone, 62415-83-2; lithioacetone, 62415-84-3; 2-chloroquinolone, 612-62-4; 2,6-dibromopyridine,

626-05-1; 2,6-dichloropyridine, 2402-78-0; 2,6-dihydroxy-2,6-dimethyl-4-heptanone, 3682-91-5.

References and Notes

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Heterodienophiles. 8.[1] Acid-Catalyzed Reactions of Benzal- and Methylenebisurethanes with α-Phellandrene. Structural and Stereochemical Studies

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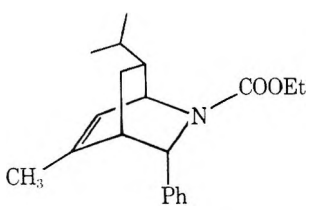
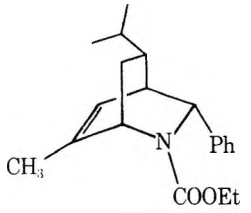
The boron trifluoride/copper bromide catalyzed reactions of benzal- and methylenebisurethane with α-phellandrene (**3**) have been investigated. Benzalbisurethane (**4**) affords a 37/63 mixture of 3-*endo*- and -*exo*-phenyl-5-methyl-7-isopropylisoquinuclidines (**1** and **6**), the products of regiospecific 1,4-cycloaddition of benzaliminourethane (**5**) to α-phellandrene (**3**). Methylenebisurethane **17** and α-phellandrene (**3**), however, afford *N*-carbethoxy-1-methyl-4-isopropenyl-6-azabicyclo[3.2.1]octane (**19**) and *N*-carbethoxy-3,7,7-trimethyl-9-azabicyclo-[4.3.0]non-2-ene (**20**), products derived by formal 1,3-cycloaddition of iminourethane to *p*-menthadiene isomers of α-phellandrene (**4**); thus, methylenebisurethane **17** and α-terpinene also afforded **19** and **20**. Ozonolysis of **19** completed a two-step synthesis of *N*-carbethoxy-1-methyl-6-azabicyclo[3.2.1]oct-4-one (**21**). Camphene (**29**) and **17** afforded amidoalkylation product **31**.

The Diels–Alder cycloaddition of imines with conjugated dienes offers a convenient synthetic route to diverse azacyclic and azabicyclic molecules.[1–4] Surprisingly, however, questions of regiochemistry and stereochemistry in these additions have been little explored.[3] In one study by Harter and Liisberg[3g] a regioisomeric mixture of *anti*-isopropyl, *endo*-phenylisoquinuclidines **1** and **2** of unspecified relative amounts has been



1



2

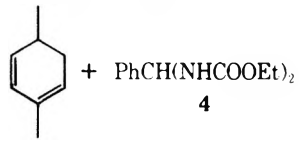
reported from the reaction of α-phellandrene (**3**) with benzalbisurethane (**4**), a precursor of the iminourethane **5**.

We decided to continue the study of alkylidenebisurethane reactions with cyclic terpenes for several reasons. We doubted the regiochemical and stereochemical assignments given to the mixture of **1** and **2**. Cycloaddition reactions of iminourethane **5** with cyclohexa-1,3-diene do not afford 3-*endo*-phenylisoquinuclidine (**7**) only; they afford a 3-*endo*/*exo*-phenylisoquinuclidine **7**/**8** mixture with the 3-*exo*-phenyl isomer **8** predominating.[1g] Also, considerations of relative carbonium ion stabilities in a stepwise addition of an immonium ion[1b,f,g] to α-phellandrene might favor regioisomer **1** to the exclusion of **2**. Cyclic terpenes are readily available and facile synthetic access to the ring skeletons of several alkaloid[5,6] systems is available by direct cycloaddition[2i] or rearrangement[4] of initially formed adducts. We hoped to extend the scope of these syntheses.

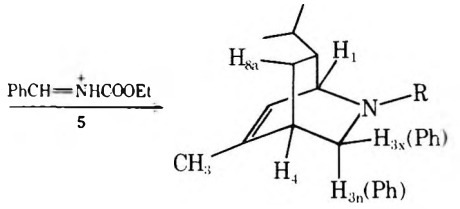
Results and Discussion

Reactions of α-Phellandrene and Benzalbisurethane. Reaction of α-phellandrene (**3**) with benzalbisurethane (**4**) in

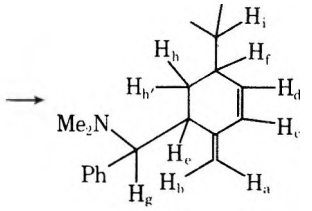
refluxing benzene or chloroform containing boron trifluoride etherate and copper bromide as catalyst[3c] gave what was shown by NMR analysis to be a mixture of 3-*endo*-phenyl adduct **1** (37%) and 3-*exo*-phenyl adduct **6** (63%). For the



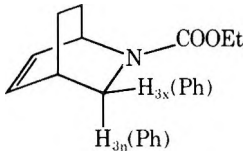
3 4



1, Ph-*endo*, H_{3x}, R = COOEt
6, Ph-*exo*, H_{3n}, R = COOEt
9, Ph-*endo*, H_{3x}, R = CH_3
10, Ph-*exo*, H_{3n}, R = CH_3
11, Ph-*exo*, H_{3n}, NR = NMe_2^+



12



7, Ph-*endo*, H_{3x}
8, Ph-*exo*, H_{3n}

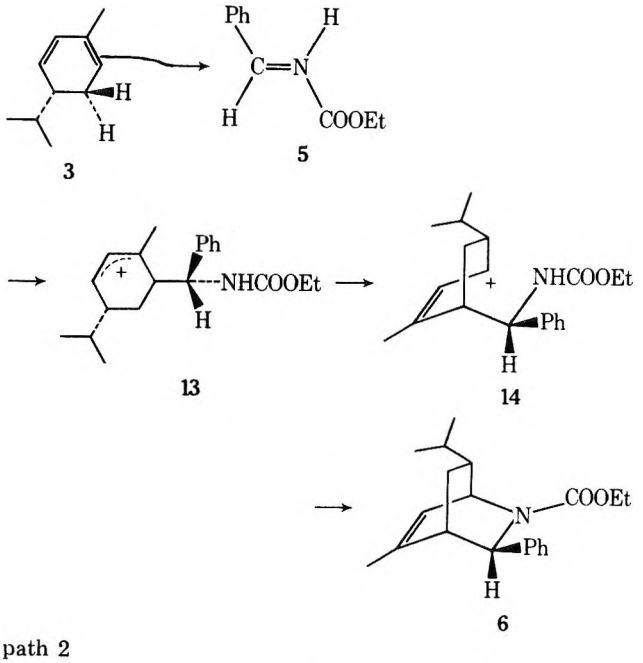
minor *endo*-phenyl isomer **1** proton H_{3x} at δ 4.60 (d, $J_{3x,4}$ = 4 Hz) coupled only with H_4 at δ 2.50. With the major *exo*-phenyl isomer **6** proton H_{3n} at δ 4.36 (m, $J_{3n,4}$ = 4.75, $J_{3n,8a}$ = 2 Hz) showed long-range W-plan coupling to H_{8a} characteristic of the 3-endo proton in isoquinuclidines.[1e,g] Absorption for allylic methyls of **1** and **6** appeared as singlets at δ 1.86 and 1.88. The downfield shift of H_{3x} (δ 4.60) of **1** relative to H_{3n} (δ 4.36) of **6** compares favorably with the chemical shifts (acetone-d_6) of *N*-carbethoxy-*endo*- and *exo*-3-phenylisoquinuclidines (**7** and **8**) for H_{3x} (δ 4.70) and H_{3n} (δ 4.38).[1g] Stereochemical ratios of **1** and **6** were determined by the relative NMR integrated areas for protons H_{3x} and H_{3n}. A somewhat lower *exo*-phenyl preference is observed with α-phellandrene (**3**) as diene (63% 3-*exo*-phenyl isomer **6**) than with cyclohexa-1,3-diene (80% 3-*exo*-phenyl isomer **8**).[1g]

The mixture of **1** and **6** was reduced with lithium aluminum hydride in ether to afford a mixture of the 3-*endo*-phenylamine **9** and the 3-*exo*-phenylamine **10**. Column chromatography gave amines **9** (42%) and **10** (58%) in a ratio comparing favorably with the ratio of **1** to **6** (37/63) obtained by NMR integration. Reaction of the mixture of **9** and **10** as reported by Harter and Liisberg[3g] with methyl iodide in acetone at room temperature afforded a crystalline methiodide **11** from the major 3-*exo*-phenyl isomer **10** and a residue of the minor 3-*endo*-phenyl isomer **9** which had not been methylated. The gross structural features of the cycloadduct **6** were confirmed by pyrolyzing the hydroxide salt of quaternary ammonium salt **11** to form amine **12**. The structure of **12** was determined from its NMR spectrum; the spectral analysis did not enable a determination of the relative stereochemistry of the alkyl substituents of **12**.

Mechanistic Discussion. Several reaction sequences for formation of cycloaddition products from diene and immonium ions have been proposed.[1g] These are shown in Scheme

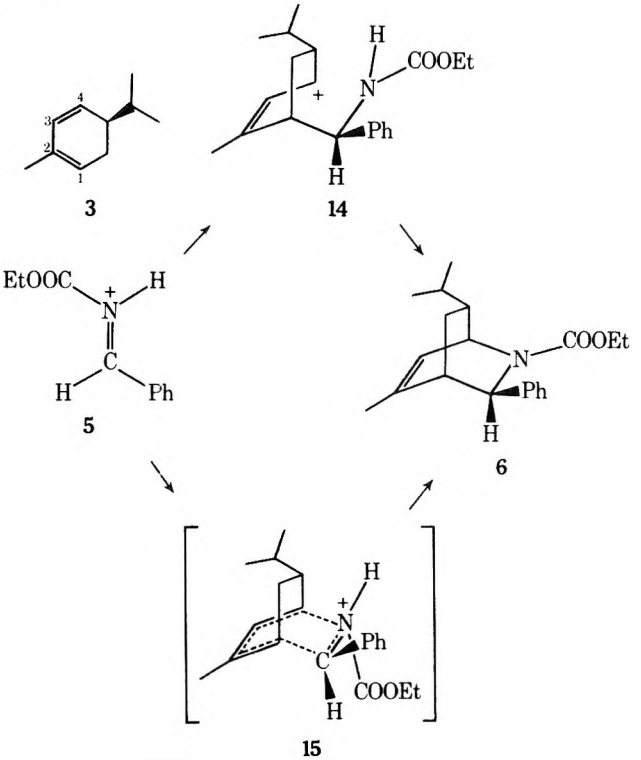
Scheme I. Mechanistic Alternatives for Formation of Isoquinuclidine 6

path 1



3 5 13 14 6

path 2



3 14 5 6 15

I for isoquinuclidine **6**; the mechanistic scheme for the stereoisomer **1** is the same in principle.

Path 1. A stepwise addition of the diene **3** to the carbon of the immonium ion **5** leads to the terminally methyl-substituted allylic cation **13**; intramolecular trapping of **13** leads to isoquinuclidine **6**. An anti orientation for isopropyl would result from attack of **5** at the less hindered face of the diene, but the distance of the isopropyl group from the reaction site makes it difficult to account for facial selectivity via this mechanistic pathway. The preferential 3-*exo*-phenyl stereochemistry favoring **6** over **1** results if the immonium ion **5** approaches the diene **3** with the larger phenyl substituent

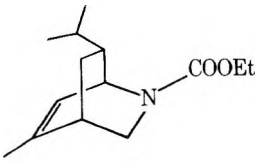
oriented predominantly over the diene and away from the hydrogens of the diene bridge to give **13**. Subsequent bond rotation to **14** and intramolecular ring closure leads to 3-*exo*-phenylisoquinuclidine (**6**).[7] Since Dreiding molecular models suggest intolerable steric interaction between phenyl and the allylic proton in a path 1 transition state going to **13** but affording the stereoisomeric 3-*endo*-phenylisoquinuclidine (**1**), we do not favor the path 1 mechanism.

Path 2. Cyclic stepwise or concerted [$_\pi$4 + $_\pi$2] transition states might be involved. The observed regiochemistry in forming **6** from intermediate **14** or transition state **15** is that expected from consideration of allylic carbonium ion stabilities. A concerted cycloaddition of a charged immonium ion **5** to diene **3** via **15** might be expected to have a transition state polarization paralleling in stability the ground state allylic cation **14**. An anti orientation for the isopropyl group can be suggested on the basis of the rule of steric approach control[8] in cycloaddition reactions as has been done for other α-phellandrene cycloadducts.[9] The preferential formation of 3-*exo*-phenylisoquinuclidine (**6**) in a kinetically controlled cycloaddition[10] would result if carbethoxyl has a greater endo preference than phenyl and if the immonium ion **5** has the more stable[1b] *E* configuration.[11] Substituent preferences determined in the Diels–Alder reaction of cyclopentadiene with *trans*-cinnamic acid methyl ester show 44% *exo*-phenyl isomer and 2-phenylmethylacrylic acid affords 60% *exo*-phenyl isomer.[8] These results indicate that phenyl and carbethoxyl have similar endo substituent preferences in the Diels–Alder reaction and they are consistent with the observed 63/37 ratio of **6**/**1** in a cyclic transition state. It is nevertheless possible that the *exo*-phenyl preference may be due to other factors associated with a longer lived carbonium ion species formed by a stepwise, but cyclic, reaction. Selectivity in trapping of intermediate **14** by external urethane nucleophile may affect the observed stereochemical preference.[1g]

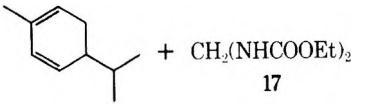
Reaction of α-Phellandrene with Methylenebisurethane. In an attempt to synthesize the isoquinuclidine ring system **16** by a [4 + 2] cycloaddition α-phellandrene (**3**) and methylenebisurethane **17** were reacted in benzene or chloroform using boron trifluoride etherate and copper bromide catalysts. Two major products were isolated; neither adduct corresponds to the expected cycloaddition product **16**! The major products, assigned structures **19** and **20**, arise not by 1,4-cycloaddition, but by novel 1,3-cycloadditions of iminourethane to *p*-menthadiene isomers of α-phellandrene.

The structures of **19** and **20** were assigned with the aid of NMR spectral parameters. Of special interest to the present study was the NMR ($CDCl_3$) resonance for the major product *N*-carbethoxy-1-methyl-4-isopropenyl-6-azabicyclo[3.2.1]-octane (**19**) at δ 1.60 (s) for the two isopropylidene methyl groups and the absence of peaks in the vinyl region. Proton H_5 at δ 4.84 (d, $J_{5,8s}$ = 6 Hz) is allylic and next to nitrogen. The proton H_{7x} at δ 3.26 (d, J = 10 Hz) is coupled only to H_{7n} at δ 3.02 (d)[12] confirming the bridgehead position for the singlet methyl at δ 1.05. One of the allylic protons H_3 appears at δ 2.48 (dd, J = 15.5, 5.7 Hz); the other H_3 proton is part of a broad envelope from δ 0.8 to 2.0. Ozonolysis of **19** afforded 1-methyl-6-azabicyclo[3.2.1]oct-4-one (**21**). The NMR spectrum of **21** showed a single methyl peak at δ 0.78 (s) confirming cleavage of the isopropylidene double bond and loss of the allylic methyl groups.

The NMR spectrum of the minor product *N*-carbethoxy-3,7,7-trimethyl-9-azabicyclo[4.3.0]non-2-ene (**20**) showed peaks for the protons H_{8x} and H_{8n} next to nitrogen at δ 3.32 and 3.10 only mutually coupled with J = 11 Hz; geminal methyls appear as singlets at δ 1.02 and 0.98. Olefinic proton H_2 at δ 5.94 is broad, but narrows to a broadened doublet, J = 3 Hz (long-range coupling), upon irradiation of H_1 at δ 4.20 (broad). The allylic methyl appears as a singlet at δ 1.72. The

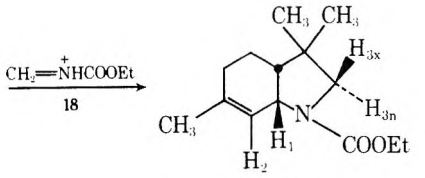


16

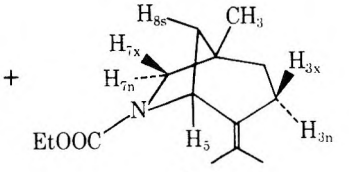


17

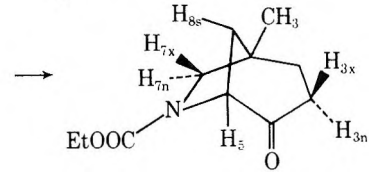
3



20



19

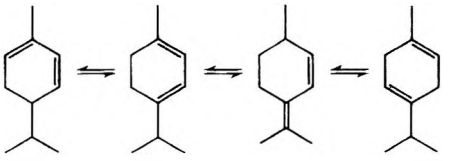


21

difficulty in resolving H_1 precluded determination of the stereochemistry of ring fusion using spin decoupling techniques;[13c] however, the broadening of H_1 suggests the more flexible cis configuration for **20** in agreement with mechanistic considerations (vide infra).

Mechanism. Equilibration studies[14] of *p*-menthadienes in sulfuric acid (Scheme II) show that α-phellandrene (**3**), the

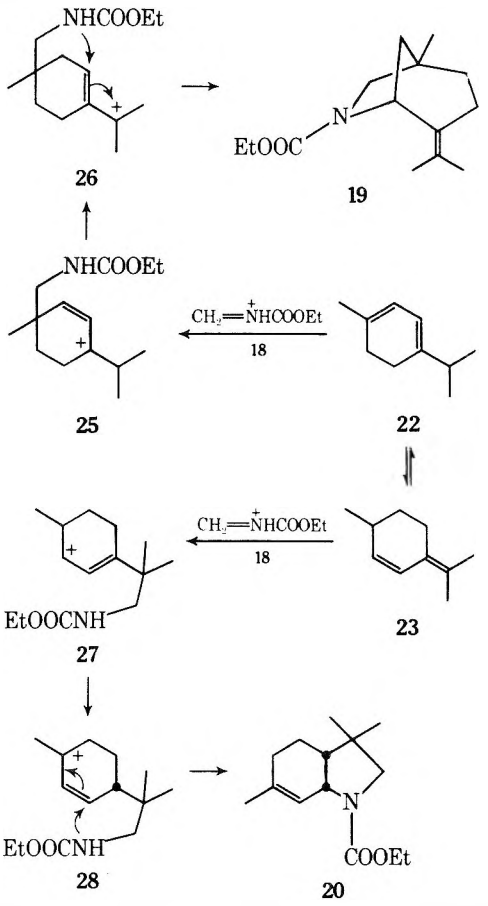
Scheme II. Equilibrium Concentrations of *p*-Menthadienes in Acid[14]



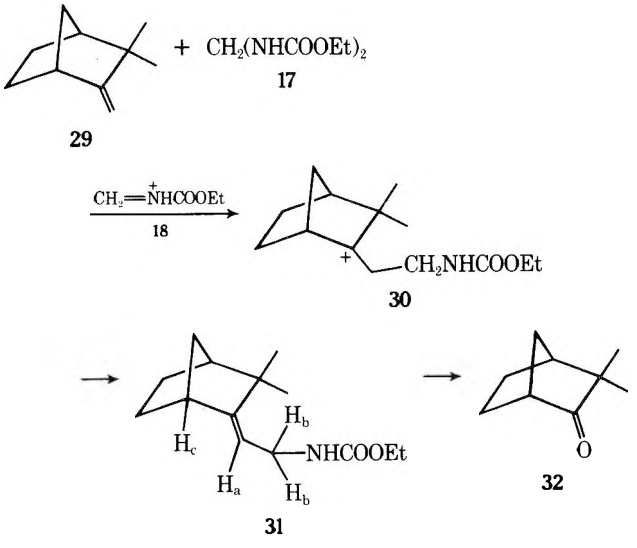
3 (0%) 22 (53%) 23 (30%) 24 (14%)

starting material in the formation of **19** and **20**, is nearly totally converted to a mixture of α-terpinene (**22**), isoterpinolene (**23**), γ-terpinene (**24**), and other minor components. Upon consideration of the data of Scheme II a postulated mechanism for formation of **19** and **20** from *p*-menthadienes in acidic medium can be shown in Scheme III. Addition of an acid complexed iminourethane **18** to the less hindered end of the major conjugated diene **22** in an equilibrating mixture of *p*-menthadienes will afford cation **25**. Proton loss and reprotonation will give a new allylic cation **26**, which upon internal trapping by the proximate nucleophilic urethane nitrogen gives **19**. Similarly, addition of protonated iminourethane **18** to the exocyclic terminus of **23** will afford allylic cation **27**. Deprotonation of **27** and reprotonation to give **28** will lead to **20** upon intramolecular cyclization by urethane nitrogen. Consideration of models of a planar allylic cation **28** indicates that ring closure will lead to a cis ring fusion in **20**[13] because of conformational rigidity of the intermediate.

Scheme III. Proposed Mechanisms for Formation of 19 and 20



Consistent with the proposed mechanism of Scheme III was the reaction of α-terpinene (**22**) with methylenebisurethane **17** to give **19** and **20** in a 60/40 ratio. The greater percentage of **20** in this reaction possibly indicates a greater percentage of **23** in a preequilibrium mixture of *p*-menthadienes than found during the reaction with α-phellandrene (**3**). Although the *p*-menthadiene equilibrium has been reached from α-pinene,[15] attempted reactions with α- and β-pinene, Δ-carene, or limonene did not lead to a clean formation of **19** and **20**, but to mixtures of numerous components. This is reasonable, since during acid-catalyzed terpene equilibration the numerous olefinic species can be trapped by protonated iminourethanes or by protons and urethane before the equilibrium mixture of *p*-menthadienes rich in **22** and **23** can be reached. Camphene (**29**) did not equilibrate to *p*-menthadienes during reaction with methylenebisurethane **17**, but afforded cleanly



the amidoalkylation product **31**. The structural assignment to **31** was based upon ruthenium tetroxide cleavage of **31** to camphenilone (**32**) and the NMR spectrum ($CDCl_3$) of **31**, δ 4.95 (t, J = 7 Hz, H_a), 3.73 (t, J = 7 Hz, H_b), 4.74 (NH). Adduct **31** can be formed by attack of **29** on immonium ion **18** to afford carbonium ion **30**; loss of a proton from **30** yields **31**.

Conclusion

The reaction of benzalbisurethane **4** with α-terpinene (**22**) afforded a mixture of numerous components; however, TLC comparison showed no evidence for formation of **1** and **2**. Thus, primary formation of **1** and **2** in the reaction of benzalbisurethane **4** with α-phellandrene (**3**) rather than with later formed isomeric *p*-menthadienes (Scheme II) is consistent with a greater reactivity of benzaliminourethane **5** than methyleneurethane **18** with α-phellandrene under conditions of boron trifluoride etherate catalysis. This contrasts with a reported much lower reactivity of **4** than **18** with norbornadiene;[2c] it is possible that steric effects in the transition state for reaction of the phenyl substituted imine **5** with norbornadiene present too high a barrier to reaction.

The present conversion of α-phellandrene to **19** represents one of the simplest synthetic routes to this azabicyclic ring system.[16] The indication that product formation can be dependent on the timing of introduction of the alkylidenebisurethane to a dienic system capable of acid-catalyzed isomerization is under further investigation in order to extend the synthetic utility of these reactions.

Experimental Section

NMR spectra were determined on a Varian Associates XL-100-15 spectrometer using Me_4Si as internal standard. Solutions of 5–10% solute in $CDCl_3$, acetone-d_6, or benzene-d_6 were used for NMR measurements. Chemical shifts were where necessary obtained with the aid of decoupling experiments. NMR spectra were simplified by observation at elevated temperatures (77–88 °C) in order to rapidly average urethane conformations. At ambient temperatures superimposed spectra of conformers often complicate the observed patterns for the protons directly adjacent to nitrogen.

General Procedure for Reaction of Terpenes. A solution of diene (13.6 g, 0.1 mol) in 100 mL of dry benzene or chloroform was added dropwise over 30 min to a stirred refluxing solution of alkylidenebisurethane (0.1 mol) and 5 mL of boron trifluoride etherate in 200 mL of dry benzene or chloroform. In some cases copper bromide (1–2 g) was initially added. After refluxing for 3–15 h the reaction mixture was cooled, washed with water, aqueous sodium carbonate, 10% hydrochloric acid, and water, and then dried over magnesium sulfate. Solvent was removed in vacuo and the residue was extracted with petroleum ether. After evaporation of solvent the product was isolated by distillation, column chromatography, or VPC. The α-phellandrene (**3**) (MCB) was 83% pure by VPC; 17% had aromatized.[24] Wallach's[25] procedure was used to convert terpineol to α-terpinene (**22**), which was purified by spinning band distillation. Camphene (**29**) was obtained from MCB.

3-*endo*- and -*exo*-Phenyl-5-methyl-7-isopropylisoquinuclidines (1 and 6). Reaction of α-phellandrene (**3**) with benzalbisurethane **4** in benzene with boron trifluoride catalysis according to the Harter procedure[3g] afforded a liquid mixture of the previously reported, inadequately characterized, and incorrectly identified **1** and **6**: bp 141–153 °C (0.125 mm) [lit.[3g] bp 170 °C (2 mm)]; NMR (acetone-d_6, 70 °C) of the mixture of **1** and **6**, δ 0.78 (3 H, t, J = 6 Hz), 0.86–1.86 (10 H, m), 1.86, 1.88 (3 H, two s), 2.50 (H_4, m), 3.95 (2 H, q), 4.36 (H_{3n}, m, $J_{3n,4}$ = 4.75, $J_{3n,8a}$ = 2 Hz, 63% of a proton integral), 4.60 (H_{3x}, d, $J_{3x,4}$ = 4 Hz, 37% of a proton integral), 4.90 (H_1, m), 6.00 (H_6, m), 7.20 (5 H, m). The 63/37 ratio of 6/1 was determined from the relative integrals for H_{3n} and H_{3x} of **6** and **1**.

***N*-Methyl-3-*endo*- and -*exo*-phenyl-5-methyl-7-isopropylisoquinuclidines (9 and 10).** Reduction of 1.1 g of the mixture of **1** and **6** with lithium aluminum hydride according to the procedure of Harter[3g] afforded an endo/exo mixture of amines **9** and **10**, bp 101–110 °C (0.15 mm) [lit.[3g] bp 110 °C (0.5 mm)]. The amines could be separated by dry column chromatography (Analtech, silica gel GF, 1000 μm, 10 hexane:1 ethyl acetate) to give **9**, 410 mg (42%), and **10**, 570 mg (58%). NMR ($CDCl_3$) of **9** showed δ 0.64–1.84 (10 H, m), 1.94 (3 , s), 2.20 (3 H, s), 2.24 (1 H, m), 2.94 (H_{3x}, broad s), 3.34 (H_1, dd, J = 2, 5

Hz), 5.88 (1 H, d, J = 5 Hz, some small coupling), 7.30 (5 H, m). NMR ($CDCl_3$) of **10** showed δ 0.80–1.90 (10 H, m), 1.48 (3 H, s), 2.26 (H_4, m), 2.34 (3 H, s), 3.06 (H_{3n}, broad singlet), 3.30 (H_1, dd, J = 5, 1 Hz), 6.14 (H_6, m, $J_{1,6}$ = 5 Hz), 7.20 (5 H, m).

Hofmann Degradation of Amine 10. Treatment of the amine mixture **9** and **10** according to Harter[3g] with methyl iodide in acetone at room temperature afforded the crystalline methiodide **11** of the major 3-*exo*-phenyl isomer **10**: mp 194–195 °C (acetone) (lit.[3g] mp 193–194 °C); NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 6 Hz), 1.04 (3 H, d, J = 6 Hz), 0.90–1.30 (3 H, br), 2.20 (3 H, s), 2.64 (3 H, s), 2.86–2.70 (2 H, br), 3.66 (3 H, s), 4.86 (H_1, d, J = 6 Hz), 5.16 (H_{3n}, br), 6.26 (H_6, d), 7.42 (5 H, s). The minor 3-*endo*-phenyl isomer **9** failed to quaternize and remained in the mother liquor.

The methiodide **11** (375 mg) was placed with silver oxide (226 mg) in 1:1 methanol–water (5 mL) and stirred for 2 h at 25 °C. The mixture was filtered, the residue was washed with methanol–water (5 mL), and the filtrate was concentrated in vacuo at 100 °C. The residue (248 mg) was distilled at 140–145 °C (0.3 mm) to afford amine **12** (77 mg): NMR ($CDCl_3$) δ 2.20 (s, NMe_2), 5.00, 5.06 (H_a, H_b, s, s), 5.74 (H_c, d, $J_{c,d}$ = 10 Hz), 6.28 (H_d, dd, $J_{d,f}$ = 3 Hz), 3.12 (H_e, td, $J_{e,g}$ = 11.5, $J_{e,hh'}$ = 4 Hz), 1.90 (H_f, m), 3.66 (H_g, d), 1.28–1.64, (H_h, $H_{h'}$, H_i, m, $J_{f,hh'}$ = 8 Hz), 0.76 (CH_3, d, J = 6 Hz), 7.10–7.50 (Ph, m).

Anal. Calcd for $C_{19}H_{27}N$: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.59; H, 9.80; N, 5.09.

***N*-Carbethoxy-1-methyl-4-isopropenyl-6-azabicyclo[3.2.1]-octane (19) and *N*-Carbethoxy-3,7,7-trimethyl-9-azabicyclo[4.3.0]non-2-ene (20).** Reaction of α-phellandrene (**3**, 8.2 g, 0.06 mol) in $CHCl_3$ with methylenebisurethane **17** (11.6 g, 0.06 mol) according to the general procedure afforded upon distillation (0.16 mm) mainly **19**, 3.1 g (22%), bp 100–110 °C, and a 60/40 mixture of **19** and **20**, 1.5 g (11%), bp 110–120 °C; the mixture was separated by VPC (6 ft × 0.25 in. SF-96 on Chromosorb W, 140 °C). Further distillation afforded a mixture of minor components. Use of benzene as solvent resulted in slightly lower yields (20–25%) but the **19**/**20** ratio of 84/16 changed little. Longer reflux times (20 h) resulted in disappearance of **19** and **20** as shown by GC monitoring of the reaction. At 30 °C adducts **19** and **20** were not formed. The NMR spectrum of **19** ($CDCl_3$, 80 °C) showed δ 0.8–2.0 (broad envelope), 4.84 (H_5, d, $J_{5,8s}$ = 6 Hz), 3.26 (H_{7x}, d, J = 10 Hz), 3.02 (H_{7n}, d), 2.48 ($H_{3x(3n)}$, dd, J = 15, 6 Hz), 1.76 (H_{8s}), 1.05 (CH_3), 1.60 (CH_3C=), 1.61, 1.71 (in acetone-d_6).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.89; H, 9.70; N, 5.91. Found: C, 70.78; H, 9.85; N, 5.72.

The NMR spectrum ($CDCl_3$, 80 °C) of **20** showed δ 1.1–2.0 (broad), 4.20 (H_1, buried under CH_2 of ethyl ester), 5.94 (H_2, broad, narrows to a broadened doublet, J = 3 Hz, upon irradiation of H_1), 3.32, 3.10 ($H_{8x,8n}$, d, J = 11 Hz), 1.02, 0.98 (CH_3, singlets), 1.72 (CH_3C=, s).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.89; H, 9.70; N, 5.91. Found: C, 70.82; H, 9.41; N, 5.84.

***N*-Carbethoxy-1-methyl-6-azabicyclo[3.2.1]octan-4-one (21).** Ozone[26] was bubbled through a methylene chloride (5 mL) solution of **19** (234 mg, 1 mmol) at −78 °C for 2 h. The blue color was discharged by bubbling nitrogen through the solution and dimethyl sulfide (2 mL) in methylene chloride (2 mL) was added dropwise. Methylene chloride (10 mL) was added, the solution was extracted with water (6 × 5 mL) and dried over magnesium sulfate, and solvent was removed in vacuo to afford 190 mg (91%) of oil, bp 100–110 °C (0.05 mm) (molecular distillation). VPC (5 ft × 0.25 in. 6% XF 1150 Chromosorb W, 180 °C, t_R 20 min) gave pure **21**: NMR (benzene-d_6, 80–85 °C) δ 1.0–1.8 (complex), 1.1 (3 H, t, J = 7 Hz), 4.02 (2 H, q, J = 7 Hz), 4.14 (H_5, d, $J_{5,8s}$ = 5.8 Hz), 3.36 (H_{7x}, d, J = 10.3 Hz), 3.08 (H_{7n}, dd, J = 10.3, 1.5 Hz), 1.8–2.50 ($H_{3x(3n)}$, broad multiplet), 0.78 (CH_3, s).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.56; H, 8.06; N, 6.64. Found: C, 62.80; H, 8.26; N, 6.64.

Reaction of Methylenebisurethane 18 with α-Terpinene (22). Reaction of α-terpinene (**22**, 2.05 g, 0.015 mol) in chloroform for 5 h according to the general procedure afforded **19** and **20** in a 60/40 ratio by VPC, 1.04 g (25%).

Reaction of Methylenebisurethane 18 with Camphene (29). Reaction of camphene (**29**, 2.75 g, 0.02 mol) according to the general procedure afforded upon distillation at 120–130 °C (0.01 mm) 3.3 g (69%) of **31**: IR (neat) 3350, 1710 cm^{-1}; NMR ($CDCl_3$) δ 4.95 (H_a, t, J = 7 Hz), 4.74 (NH), 4.08 (OCH_2, q), 3.73 (H_b, t, J = 7 Hz), 2.95 (H_c, m), 0.98 (s, 3 H), 1.0–1.9 (m, 10 H).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.76; N, 5.90. Found: C, 70.64; H, 9.67; N, 5.96.

Oxidation of 31 to Camphenilone (32). A solution of ruthenium tetroxide in carbon tetrachloride (25 mL) was prepared from ruthenium dioxide tetrahydrate (200 mg, soluble form).[27] Adduct **31** (200 mg) in carbon tetrachloride (5 mL) was added to the solution and stirred at 25 °C for 24 h. Filtration, removal of solvent, and molecular distillation (80 °C, 0.2 mm) afforded an oil which was further purified by GC to give camphenilone (**32**); IR, NMR, and VPC retention time were identical with those of a known purified sample (Chemical Samples). Ozonolysis of **31** was less effective in cleaving the olefinic bond; only trace amounts of camphenilone (**32**) were formed.

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Registry No.—**1**, 62227-97-8; **3**, 99-83-2; **4**, 3693-54-7; **6**, 62278-86-8; **9**, 62278-87-9; **10**, 62278-88-0; **11**, 62227-99-0; **12**, 62228-00-6; **17**, 3693-53-6; **18**, 62227-98-9; **19**, 61654-90-8; **20**, 61654-91-9; **21**, 61654-92-0; **22**, 99-86-5; **29**, 79-92-5; **31**, 62228-01-7.

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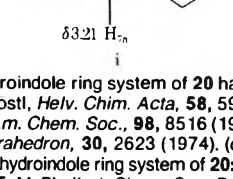
(10) Although the **1**/**6** ratio is essentially unchanged over reaction times from 5 to 15 h, there may be reversible steps before product formation and stereochemical preferences may be affected.

(11) Cyclopentadiene and cyclohexa-1,3-diene react with *Z* immonium ions to afford 3-endo-substituted adducts.[1c]

(12) Proton H_{7x} is assigned the downfield resonance on the basis of the shifts in *N*-carbethoxy-7-azabicyclo[3.2.1]oct-2-ene (i).[4]



i

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Thermal Decomposition of Bis(diphenylmethyl) Diselenide

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The thermal decomposition of bis(diphenylmethyl) diselenide (**1**) has been investigated in the melt and in chlorobenzene solution. In the melt, **1** decomposes readily at 210 °C under reduced pressure with quantitative formation of 1,1,2,2-tetraphenylethane (**3**) and elemental selenium. The decomposition products at 140 °C are **3** (87%), Se (86.4%), bis(diphenylmethyl) selenide (6.5%), and 6.5% of starting material. In chlorobenzene solution, the decomposition follows first-order kinetics over the temperature range 100–120 °C and polyselenides are produced as additional products. The results are consistent with a radical mechanism involving C–Se and Se–Se bond scissions.

The thermal instability of organic diselenides has often been cited in the literature, but little is known about the kinetics and mechanisms of these thermal decomposition reactions. Morgan and Burstall[1-3] reported that cyclic diselenides, e.g., 1,2-diselenacyclohexane, 1,2-diselenacycloheptane, and 1,2-diselenacyclooctane, lose one selenium atom with concomitant ring contraction when they were heated. Similarly, bis(chloromethyl) diselenide thermally decomposed to give elemental selenium and bis(chloromethyl) selenide.[4] Recently, Lardon[5] has shown that benzyl diselenide undergoes rapid thermal decomposition in the melt or in solution at 150–170 °C to produce a complex mixture of products, including dibenzyl selenide, selenium, and several dibenzyl polyselenides. Substantial quantities of toluene and some 1,2-diphenylethane were formed after heating the melt to 225 °C for about 1 h.

Apart from these studies little else has appeared in the literature. Previously, the thermal instability of bis(diphenylmethyl) diselenide (**1**) was noted,[6] but its thermal chemistry has not been reported. As part of our continuing studies on the chemistry of organochalcogens,[7-9] we initiated a detailed study of thermal chemistry of this diselenide **1**. In the present work, we have investigated the thermal decomposition of **1** in the melt and in solution over the temperature range 100–210 °C. The decomposition products were identified. The kinetics of decomposition were determined and the reaction mechanism is discussed.

Results and Discussion

Diselenide **1** was conveniently prepared in 78% yield by the reaction of sodium diselenide[10] with benzhydryl chloride in ethanol. Bis(diphenylmethyl) selenide (**2**) was synthesized by treating benzhydryl chloride with an ethanolic solution of sodium hydrogen selenide[9] and sodium ethoxide.

Thermolysis of **1** neat under reduced pressure at 210 °C was completed within 20 min and yielded 1,1,2,2-tetraphenylethane (**3**) and elemental selenium as the only products (eq 1). In contrast to benzyl diselenide,[5] formation of monoselenide and polyselenides was not observed. It appears that **1** is much less stable than benzyl diselenide and the former has weaker C–Se bonds. At 140 °C, heating **1** for 23 h resulted in a decreased yield of **3** (87%) and selenium (86.4%) with formation now of monoselenide **2** (6.5%) and recovery of **1** in 6.5% yield. Monoselenide **2**, when heated at 140 °C for 23 h, converted to diselenide **1** (15.8%), selenium (16%), **3** (55.2%), and polyselenides **4** (13.8%), with some **2** (15.2%) remaining. This suggests that **2** is one of the major initial products in the thermolysis of **1** at lower temperatures (140 °C) and that it further decomposes under prolonged conditions.

$$\underset{\mathbf{1}}{Ph_2CHSeSeCHPh_2} \xrightarrow{\Delta} \underset{\mathbf{3}\ (99.4\%)}{Ph_2CHCHPh_2} + \underset{(99.8\%)}{Se} \qquad (1)$$

The kinetics of decomposition of **1** were studied in purified and degassed chlorobenzene at temperatures of 100–120 °C. The rate of disappearance of **1** was determined spectrometrically by following the decrease in peak area of the methine proton with a chemical shift of δ 4.95 in the NMR spectrum. In all cases, the decomposition reactions obeyed a first-order rate law. Figure 1 shows typical first-order plots. The rate constants determined from the slopes of the first-order plots for the thermal decomposition of **1** in chlorobenzene in the temperature range 100–120 °C are listed in Table I. The lack of rate constant change with variation in initial concentration of **1** listed in Table I further supports a first-order kinetic scheme for this decomposition reaction. Nonlinear first-order plots were obtained at reaction temperatures exceeding 120 °C. The control reactions showed that monoselenide **2**, one of the initial decomposition products, is not stable at temperatures above 120 °C and further decomposed to re-form diselenide **1** along with other products. The deviation from the first-order kinetics is apparently due to the secondary

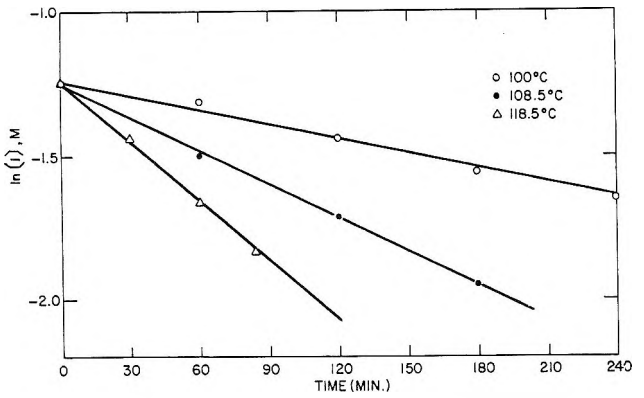

Figure 1. First-order plots for the decomposition of bis(diphenylmethyl) diselenide (1) in chlorobenzene.

Table I. Rate Constants for the Thermal Decomposition of Bis(diphenylmethyl) Diselenide in Chlorobenzene

Temp, °C	M[a]	10^4k, s^{-1}
100	0.286	0.294 ± 0.023[b]
108.5	0.286	0.637 ± 0.017
118.5	0.286	1.117 ± 0.040
118.5	0.285	1.119 ± 0.036
118.5	0.199	1.108 ± 0.184
118.5	0.119	1.120 ± 0.062

[a] Initial diselenide concentration. [b] Standard deviation.

thermolysis of **2**. An Arrhenius plot of the rate constants given in Table I yielded a straight line from which the energy of activation for the decomposition of **1** in chlorobenzene was calculated to be 20.9 kcal mol^{-1}.

Table II gives the products formed and their yields as determined by NMR analyses for the thermal decomposition of **1** in chlorobenzene at various temperatures. The ratios of the products were judged on the basis of the integration of the various methine proton peaks observed in the NMR spectrum. It is noteworthy that at the temperature range 100–120 °C, precipitation of elemental selenium was not observed and the formation of polyselenides **4** was detected by NMR analysis.[5] Attempts at isolating polyselenides failed, since they slowly decomposed in chlorobenzene at room temperature and upon prolonged heating. They were also unstable under TLC conditions in a variety of solvents. The reduction in the concentration of polyselenides is accompanied by the precipitation of elemental selenium. Krafft and Lyons[11] reported that aromatic polyselenides split off selenium under a variety of conditions, such as dissolving in any solvent or mild heating. Diphenyl triselenide readily decomposed to selenium and the diselenide upon treatment with solvents.[12] The precipitation of elemental selenium and the absence of polyselenides **4** in the product mixture at higher reaction temperature or by prolonged heating (Table II) confirm the instability of the polyselenides.

The kinetic information makes it reasonably certain that the thermal decomposition of **1** in chlorobenzene is a unimolecular process at temperatures of 100–120 °C. It has been shown that both Se–Se bond and C–Se bond cleavages are the important processes for photolysis of benzyl diselenide.[7] Based on the luminescence bands of diphenylmethyl radical, the scission of the C–S bond by UV radiation of bis(diphenylmethyl) disulfide has been confirmed.[13] If a similar reaction mechanism is assumed for the thermal decomposition of **1**, then the primary processes are undoubtedly the homolysis of the Se–Se bond (eq 2) and the cleavage of C–Se bond (eq 3).

$$\mathrm{RSeSeR} \xrightarrow{k_2} 2\mathrm{RSe}\cdot\ (\mathrm{R} = \mathrm{Ph_2CH}) \qquad (2)$$

$$\mathrm{RSeSeR} \xrightarrow{k_3} \mathrm{RSeSe}\cdot + \mathrm{R}\cdot \qquad (3)$$

The control experiments showed that monoselenide **2** is stable at 100–120 °C and decomposes to diselenide **1** and other products at 140 °C. Therefore, it is reasonable to assume that diphenylmethylselenyl radicals (RSe·) do not decompose to elemental selenium and diphenylmethyl radicals. Initially formed diphenylmethylselenyl radicals (eq 2) could either recombine or attack the weak Se–Se linkage leading to radical displacement and re-formation of **1**. These reactions, of course, give no decomposition products to be observed. The following reactions are proposed to account for the experimental observations:

$$\mathrm{RSeSe}\cdot \xrightarrow{k_4} \mathrm{RSe}\cdot + \mathrm{Se} \qquad (4)$$

$$\mathrm{R}\cdot + \mathrm{RSeSeR} \xrightarrow{k_5} \mathrm{RSeR} + \mathrm{RSe}\cdot \qquad (5)$$

$$\mathrm{R}\cdot + \mathrm{RSe}\cdot \xrightarrow{k_6} \mathrm{RSeR} \qquad (6)$$

$$\mathrm{RSe}\cdot + \mathrm{RSe}\cdot \xrightarrow{k_7} \mathrm{RSeSeR} \qquad (7)$$

$$\mathrm{RSeSeR} \xrightarrow{k_8} \mathrm{R-R} + 2\mathrm{Se} \qquad (8)$$

$$\mathrm{RSe}\cdot + n\mathrm{Se} \xrightarrow{k_9} \mathrm{RSe}\cdot_{n+1} \qquad (9)$$

$$\mathrm{RSe}\cdot_{n+1} + \mathrm{RSe}\cdot \xrightarrow{k_{10}} \mathrm{RSe}_{n+2}\mathrm{R} \qquad (10)$$

The thermally produced diphenylmethyl radicals (eq 3) may diffuse away from the formation cage, undergoing secondary reaction with **1** to yield monoselenide **2** (eq 5). Recombination of R· and RSe· radicals would also produce **2** (eq 6). Since the concentration of R· is very low during the thermal decomposition and the radical coupling reaction (i.e., R· + R· → R–R) is a second-order radical reaction, we may simplify the reaction kinetics by assuming that all the R· diffused out of the solvent "cage" are consumed in either eq 5 or 6. The formation of **3** may be rationalized by the recombination of diphenylmethyl radicals within a solvent cage, or possibly by a molecular mechanism (eq 8).

Table II. Reaction Products from the Thermal Decomposition of Bis(diphenylmethyl) Diselenide in Chlorobenzene[a]

Temp, °C	Time, h	Product composition, %[b]				
		1[c]	2	3	4	Se[d]
100	4	67.4	9.8	6.5	16.3	e
108.5	4	41.7	12.9	6.9	38.5	
118.5	2	51.6	20.3	19.6	8.5	
118.5	20	29.7	16.7	53.6		57.6
150	2	9.7	8.0	82.3		83.1

[a] Reactions were carried out in sealed tubes (<10^{-4} Torr). [b] Determined by NMR analysis of the reaction mixture. [c] Unreacted diselenide. [d] Isolated yield. [e] Not observed.

The presence of polyselenides **4** may be attributed to recombination reactions such as 9 and 10. This would be consistent with the results of Lardon,[5] who reported that dibenzyl polyselenides are the thermal reaction products of benzyl diselenide. Assuming steady-state conditions for all reaction intermediates, the following rate expression may be derived.

$$-d[RSeSeR]/dt = (k_3 + k_8)[RSeSeR]$$

The result is in agreement with the first-order dependence for **1** found experimentally.

The decomposition mechanism proposed (eq 2–10) adequately accounts for all the products and kinetic results. The present study shows, therefore, that the thermal decomposition of bis(diphenylmethyl) diselenide (**1**) in chlorobenzene proceeds by a radical mechanism and follows first-order kinetics over the temperature range 100–120 °C.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are not corrected. NMR spectra were determined on a JEOL C60H instrument with $CDCl_3$ or C_6H_5Cl as solvent and tetramethylsilane as internal standard. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Chlorobenzene. Baker reagent grade chlorobenzene was vigorously stirred with three portions of reagent sulfuric acid and washed successively with distilled water, sodium bicarbonate solution, and distilled water. After successive 24-h periods of drying with calcium chloride and phosphorus pentoxide, the chlorobenzene was distilled from phosphorus pentoxide. A middle fraction, bp 131.8–132.5 °C, was collected.

Bis(diphenylmethyl) Diselenide (1). Ethanolic sodium diselenide solution was prepared by reaction of 6.0 g (76 mmol) of selenium powder and 2.0 g (54 mmol) of sodium borohydride in absolute ethanol according to the procedure of Klayman and Griffin.[10] To ethanolic sodium diselenide solution was added 10.54 g (52 mmol) of benzhydryl chloride with stirring, and the solution was heated at reflux under nitrogen for 30 min. The yellow reaction mixture was cooled to room temperature and stirred overnight. The resulting mixture was acidified with glacial acetic acid and purged with N_2 to remove hydrogen selenide by trapping it into an aqueous lead acetate solution. The ethanol was then removed on a rotatory evaporator and the residue was extracted with hot chloroform. The crude product, obtained by removal of chloroform from the extracts, was recrystallized from ethanol to yield 9.98 g (78%) of **1** as pale yellow needles: mp 123–124 °C (lit.[6] 120–123 °C); NMR ($CDCl_3$) δ 4.95 (2 H, s), 7.17 (20 H, s).

Anal. Calcd for $C_{26}H_{22}Se_2$: C, 63.42; H, 4.50; Se, 32.07. Found: C, 63.52; H, 4.37; Se, 31.89.

Bis(diphenylmethyl) Selenide (2). Benzhydryl chloride (30.96 g, 152 mmol) and sodium ethoxide (5.2 g, 76 mmol) were added with stirring to an ethanolic solution of sodium hydrogen selenide (76 mmol) prepared by adapting the method of Klayman and Griffin,[10] and the mixture was stirred under nitrogen at room temperature for 18 h. After purging with nitrogen to remove H_2Se, the reaction mixture was filtered. The filtrate was concentrated in vacuo and the residue was extracted with hot petroleum ether to give 12.82 g (41%) of **2**. Recrystallization from petroleum ether (bp 20–40 °C) yielded the analytical sample: mp 65–66 °C; NMR ($CDCl_3$) δ 4.84 (2 H, s), 7.16 (20 H, s).

Anal. Calcd for $C_{26}H_{22}Se$: C, 75.54; H, 5.36; Se, 19.09. Found: C, 75.70; H, 5.27; Se, 18.94.

Thermolysis of 1. Thermolysis was conducted in a bulb-to-bulb distillation apparatus. **1** (0.545 g) was placed in a reaction bulb at one end of the apparatus and the system was evacuated with a vacuum pump. After the pressure was about 2 mmHg, the reaction bulb was heated at 210 °C for 20 min in a microdistillation oven; the receiving bulb was cooled in liquid nitrogen. The black solid residue in the reaction bulb was washed with organic solvents and dried to yield 0.169 g of elemental selenium. The slightly pink-colored solids in the receiving bulb were dissolved in chloroform and the resulting mixture was filtered to remove selenium (0.005 g). The filtrate was concentrated in vacuo to give 0.365 g (99.4%) of 1,1,2,2-tetraphenylethane: mp 208–209 °C; NMR ($CDCl_3$) δ 4.63 (2 H, s), 7.04 (20 H, s). The total yield of elemental selenium was 0.174 g (99.8%).

General Procedure for Thermal Decomposition Study. Solid samples or solutions of organic selenides in chlorobenzene were placed inside Pyrex ampules which were sealed under high vacuum ($<1 \times 10^{-4}$ Torr) after being degassed at liquid nitrogen temperature. In the case of the solutions, a four degassing cycle "freeze–degas–thaw" procedure was used. The ampules were placed in a thermostat-bath (Thermocal Model TH-050 Fluidized solids constant temperature bath) at the desired temperature, withdrawn at various times, and rapidly quenched in ice water. The bath temperature did not vary by more than 0.5 °C during an experiment. The ampules were cleaned and cracked open with a hot glass rod. The content of each ampule was analyzed by NMR. In the case of the solid samples, the decomposition products were extracted with chloroform. The solid selenium was dried and weighed, and the extracts were concentrated and analyzed by NMR.

Kinetic Measurements. The decomposition of organic diselenide (**1**) was followed by the disappearance of its methine protons chemical shift (δ 4.95) in the NMR spectrum. The chemical shifts of the methine protons for bis(diphenylmethyl) selenide (δ 4.84), diselenide (δ 4.95), and 1,1,2,2-tetraphenylethane (δ 4.63) are sufficiently different to allow spectral peak areas to be compared. The NMR data at each time interval for each complete run were then used to construct a first-order plot. The first-order rate constant was calculated from the slope of the plot. The activation energy was calculated from the slope of a plot of $\ln k$ vs. $1/T$. Least-squares treatments were used to calculate the slopes.

Acknowledgment. We are deeply indebted to Professor J. A. Kampmeier for stimulating discussions, to Dr. T. Davidson for making available to us the thermostat-bath, and to Dr. W. H. H. Gunther, without whose help and encouragement this work could not have been performed.

Registry No.—**1**, 1482-82-2; **2**, 1842-38-2; **3**, 632-50-8; chlorobenzene, 108-90-7; sodium diselenide, 39775-49-0; benzhydryl chloride, 90-99-3; sodium hydrogen selenide, 12195-50-5.

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The pK_a of Acetophenone in Aqueous Solution

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A method is reported for the determination of the pK_a of acetophenone based on the aqueous reference state. The basis of the method is the measurement of the rates of aminolysis of α-acetoxystyrenes. The correlation of the rates of the uncatalyzed aminolysis with pK_a of the leaving group, established for aryl acetates, defines the pK_a of the respective acetophenone enols. Detailed arguments concerning the microscopic steps in the aminolysis reaction are presented to show that steric effects on the aminolysis reaction should be minimal for the *uncatalyzed* aminolysis, and that aryl acetates and α-acetoxystyrenes should thus fall on the same correlation of rate vs. leaving group pK_a. The rates of aminolysis of phenyl acetate in the same solvent system are reported, and were determined to ensure the comparison of the aminolysis of the two classes of compounds under identical conditions. The enolization constant of acetophenone was determined using a potentiometric procedure, and was found to be $(1.92 \pm 0.03) \times 10^{-5}$ in 40 vol % *tert*-butyl alcohol–water. This value, together with the pK_a of acetophenone enol estimated by the kinetic procedure to be 11.0 ± 1.0, defines the carbon pK_a of acetophenone to be 15.8 ± 1.0. This number is compared with values obtained from previous determinations and with the absolute pK_a determined in dimethyl sulfoxide.

The proton acidity and basicity of organic substances is one of the most important foundations for reasoning by analogy in organic chemistry. There exists a continuing interest in the acidity of weak acids, and in the relationship of ionization constants of acids whose pK_a values are too weak to measure to the dilute aqueous reference state, where pK_a measurements for relatively stronger acids are common. Absolute acidity scales have been developed in solvents such as dimethyl sulfoxide (Me_2SO) because, in this solvent in particular, ionization constants can be determined over a wide range of acidity.[2,3] A similar determination of a wide range of pK_a values is not possible in aqueous solution, of course, because of the protic nature of the solvent. However, the facts that water is the solvent for biochemical process, and that water as a solvent is of interest for mechanistic investigations of a number of organic reactions, require the use of pK_a values truly based on the aqueous (or largely aqueous) reference state. Since the pK_a values of weak acids cannot be measured directly in water, it is of interest to have methods for estimating them indirectly. The H_- acidity function has been used in an attempt to relate the pK_a values of weak acids determined in water/Me_2SO mixtures to pK_a values determined in pure water.[4] The basis of this method is the use of a series of indicator overlaps which establish pK_a values in mixtures of continuously variable solvent composition. Since relative acidities determined by this procedure can be substantially different from relative acidities in water, this procedure does not really provide access to the dilute aqueous reference state for weak acids. Furthermore, the approximations underlying the H_- acidity function itself have in some cases been shown to fail badly.[5] In this paper, we report a novel method for estimating carbon pK_a values of substituted acetophenones which should be applicable to other ketones as well. In this method, the pK_a of acetophenone enols is estimated kinetically, and the enolization constant of acetophenone, redetermined by a method more reliable than that used previously, is used to complete a thermodynamic cycle to the pK_a of acetophenone. The number obtained is considerably lower than previous values determined in other solvent systems.

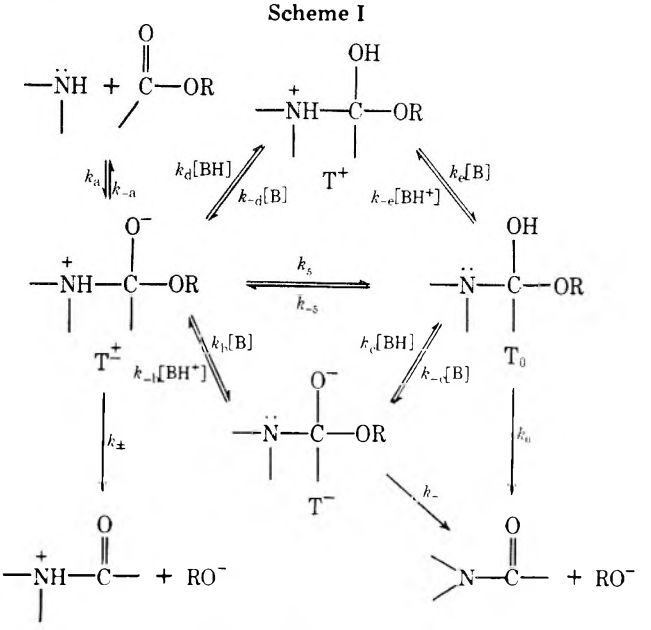
Results and Discussion

The pK_a of Acetophenone Enol. We recently found that the aminolysis of substituted α-acetoxystyrenes (**1a–f**) according to eq 1 follows the same general rate law observed for the similar reaction of other acetate esters, and is given by

$$k_{obsd} - k_0 = k_1[Am] + k_2[Am]^2 + k_3[Am][OH^-] + k_4[Am][Am \cdot H^+] \quad (1)$$

in which k_{obsd} = observed first-order rate constant for appearance of acetophenone and k_0 = rate constant for hydrolysis. Our investigations of the mechanism of this reaction have been previously reported,[6,7] and may be summarized by the statement that the mechanism of aminolysis of α-acetoxystyrenes is identical with the mechanism of aminolysis of aryl acetates. This mechanism is summarized in Scheme I.[8] The

Scheme I



Definitions: $K_\pm = k_a/k_{-a}$

interpretation of the k_1 and the k_3 terms of eq 1, on which we shall focus in this paper, in terms of the mechanism of Scheme I are presented in eq 2 and 3.

$$k_1 = (k_a/k_{-a})k_\pm = K_\pm k_\pm \quad (2)$$

$$k_3 = (k_a/k_{-a})k_b = K_\pm k_b \quad (3)$$

In previous work,[6] detailed linear free energy relationships were developed for the effect of both leaving group and amine on the k_1 term of eq 1, and it was found that the sensitivity of the reaction rate of the pK of the nucleophile, β_{nuc}, and the sensitivity of the reaction rate to the substituent effect on the leaving group enol, β_{lg}, are essentially identical with the values of these quantities found for aryl acetates.

It has been found that plots of log k_1 vs. pK_a of the leaving group define excellent straight lines when leaving groups of related structure are considered. Thus, we were able to esti-

Table I. Values of Some Observed and Elementary Rate Constants for Aminolysis of Phenyl Acetate and *m*-Chloro-α-acetoxystyrene

Registry no.	Amine	pK_a[b]	k_1,[a] M^{-1} min^{-1}	k_3,[a] M^{-2} min^{-1}	$K_\pm$, M^{-1}	$k_\pm$, min^{-1}
			Phenyl Acetate			
110-89-4	Piperidine[c]	11.22	4.3	400	2.9×10^{-10}	15.0×10^9
107-10-8	Propylamine[d]	10.84	4.9	3480	2.5×10^{-9}	2.0×10^9
124-40-3	Dimethylamine[c]	10.64	4.5	2430	1.7×10^{-9}	2.6×10^9
109-76-2	1,3-Diaminopropane[d]	10.62	19.9	11 300	8.1×10^{-9}	2.5×10^9
74-89-5	Methylamine[e]	10.62	17.0	7000	5.0×10^{-9}	3.4×10^9
109-73-9	n-$C_4H_9NH_2$[c]	10.59	4.5	1900	1.4×10^{-9}	3.2×10^9
	n-$C_4H_9NH_2$[f]	10.57	4.1	1500	1.1×10^{-9}	3.7×10^9
107-15-3	$H_2NCH_2CH_2NH_2$[d]	10.18	1.7	1000	7.1×10^{-10}	2.4×10^9
141-43-5	$HOCH_2CH_2NH_2$[f]	9.57	0.326	146	1.05×10^{-10}	3.1×10^9
			m-Chloro-α-acetoxystyrene (1e)			
123-75-1	Pyrrolidine[f]	11.32	19.6	4300	3.1×10^{-9}	6.3×10^9
	n-$C_4H_9NH_2$[f]	10.57	2.76	600	4.3×10^{-10}	6.4×10^9
	$HOCH_2CH_2NH_2$[f]	9.57	0.204	37	2.6×10^{-11}	7.8×10^9

[a] Equation 1. [b] The pK_a reported under conditions of the experiment. [c] Source: ref 30. Conditions: water, μ = 1.0 M (KCl), 25 °C. [d] Source: ref 33. Conditions: water, μ = 1.0 M (KCl), 25 °C. [e] Source: ref 32. Conditions: water, μ = 1.0 M (KCl), 25 °C. [f] This work. Conditions: 5% ethanol water, μ = 0.5 M (KCl), 30 °C.

mate the relative pK_as of acetophenone enols (using the reasonable assumption that ρ for ionization of these compounds in water is about unity) from their ability to act as leaving groups in the reaction characterized by the k_1 term of eq 1. The slope of this line, β_{lg}, was essentially the same as the slope found for the aminolysis of aryl acetates. However, the question of the *absolute* pK_a values for acetophenone enols remains. In order to estimate the absolute pK_a values of acetophenone enols, one can assume that the log k_1 vs. leaving group pK_a correlation for α-acetoxystyrenes is not only parallel to the correlation for aryl acetates, but also coincident with that correlation. The grounds for this assumption, however, have not been carefully examined. One could reasonably object that, although the lines might be parallel, they would not be expected to be coincident because of the differential steric effects in the aminolysis of the two classes of compounds. For example, the k_2 term of eq 1 shows parallel but separate lines for phenol and alcohols in the aminolysis of phenyl acetates and alkyl acetates.[8,9] Similarly, it has been found that the aminolysis of a gluconolactone derivative is much faster than would be predicted on the basis of the pK_a of the leaving group because of the constraint of the lactone into the presumably more reactive cis ester conformation, and because of this increase in rotational freedom of the compound which attends ring opening.[10] On the other hand, the *n*-butylaminolysis of α-naphthyl acetate, which could roughly be considered to be an isostere of α-acetoxystyrene (and which is, if anything, more bulky in its leaving group than α-acetoxystyrene), has a rate which is only 2.5 times slower than one would predict from the pK_a of α-naphthol and the β_{lg} of unity for the aminolysis reaction.[11] This last result suggests that the k_1 term in eq 1 is only minimally sensitive to steric effects, and that the determination of pK_a values by the correlation of k_1 terms in the aminolysis rates of various esters is justifiable.

The experimental data for the aminolysis of phenyl acetates and the relationships of eq 2 and 3 allow us to determine the values for $k_\pm$ and $K_\pm$ for α-acetoxystyrenes and aryl acetates (Scheme I). In order to ensure the greatest degree of accuracy, the data for the aminolysis of phenyl acetate were redetermined for several amines in our solvent system [5% ethanol, μ = 0.5 M (KCl), 30 °C]. The raw data from these determinations are reported in Table III (supplementary material). The k_b in eq 3 is identified with a diffusion-controlled proton transfer from the amine in the tetrahedral intermediate $T_\pm$ to hydroxide ion. This number should be essentially independent of the nature of the leaving group. It is this independence, rather than the exact value of this number, on which subsequent calculations depend, but the number can nevertheless be estimated to be close to that observed for the known average rate of proton transfer from several ammonium ions to OH^-, determined by Eigen and his co-workers[12] to be $(1.4 \pm 0.4) \times 10^{12}$ M^{-1} min^{-1} at 25 °C. Assuming the constancy of this value for all acylated phenols and enols studies, one may then calculate $K_\pm$ from the k_3 term in the rate law of eq 1 and the relationship in eq 3. Knowing $K_\pm$ from this calculation, one may then revert to eq 2 and, using the observed k_1 values for phenyl acetate and α-acetoxystyrenes, one may calculate the $k_\pm$ value for these compounds. The values for k_1, k_3, $k_\pm$, and $K_\pm$ for phenyl acetate and *m*-chloro-α-acetoxystyrene are presented in Table I. A number of points should be noted about the values in this table. Inspection shows that the dependence of $K_\pm$ on the pK_a of the attacking amine gives a β value of about unity, as suggested by Satterthwait and Jencks.[8] On the other hand, $k_\pm$ is essentially independent of the identity of the amine, as suggested by Ritchie,[13] and is thus approximately constant for a particular leaving group. It has been found that, for hydrazinolysis of acetate esters, log $K_\pm$ correlates with the pK_a of the leaving group with a β_{lg} of −0.6.[8] Likewise, log $k_\pm$ also correlates with the pK_a of the leaving group with a β_{lg} of −0.4.[8] Since we now know the values of $K_\pm$ and $k_\pm$ for *m*-chloro-α-acetoxystyrene, it is of interest to use these β_{lg} values and assumed correlations of log $K_\pm$ and log $k_\pm$ with leaving group pK_a to calculate an apparent pK_a of *m*-chloroacetophenone enol. The average $k_\pm$ for phenyl acetate (ignoring the apparently anomalous value for piperidine) is $(2.9 \pm 0.6) \times 10^9$ min^{-1}, whereas the average value for this quantity for *m*-chloro-α-acetoxystyrene is $(6.8 \pm 0.8) \times 10^9$ min^{-1}. With a β_{lg} of −0.4 for this quantity, one can calculate an apparent pK_a for *m*-chloroacetophenone enol which is 0.9 units lower than that of phenol. Since the pK_a of phenol in a solvent system closely related to that used in the kinetic studies[31] is 10.24, the apparent pK_a for *m*-chloro-α-acetoxystyrene is set in this way at 9.3. A comparison of $K_\pm$ for the reactions of both phenyl acetate and α-acetoxystyrene gives a $K_\pm$ for phenyl acetate which is (3.5 ± 0.5) times larger than the corresponding value of *m*-chloro-α-acetoxystyrene. The correlation of log $K_\pm$ with pK_a of the leaving group defines the apparent pK_a of *m*-chloroacetophenone enol to be 11.2.

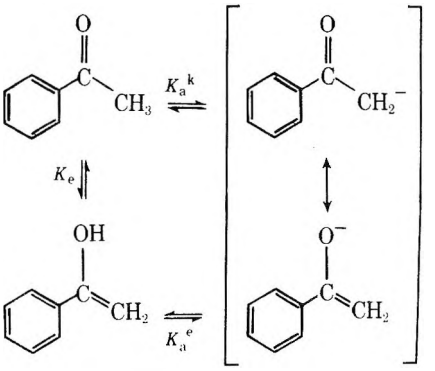
One can see that the apparent pK_a values for *m*-chloroacetophenone enol calculated from these two correlations are

rather disparate. However, the disagreement between these two estimates is exactly what one would expect if steric effects in each of the microscopic steps of the aminolysis of phenyl acetates and α-acetoxystyrenes are different. Since correlations of log $K_{\pm}$ vs. leaving group pK_a have been observed,[8] two compounds with leaving groups of similar pK_a should have similar $K_{\pm}$ values for a given amine unless the tetrahedral intermediate, $T_{\pm}$, is more sterically crowded for one type of compound than the other. If this is so, then $K_{\pm}$ for the more encumbered intermediate will be smaller than expected for the pK_a of the leaving group. In fact, this effect apparently occurs in the hydrazinolysis of various acetates. The $K_{\pm}$ values for the hydrazinolysis of primary alkyl and aryl acetates define two separate but parallel log $K_{\pm}$ vs. pK_a linear free energy relationships.[8] The line for phenyl acetates lies about an order of magnitude below the line of aliphatic acetates, presumably because of increased steric crowding in the tetrahedral intermediates derived from the aryl acetates. The lack of an observed reaction between tertiary amines and α-acetoxystyrenes[6,7] is evidence that these esters form more sterically crowded tetrahedral intermediates than do aryl acetates. The disparity between the two pK_a estimates above based on $K_{\pm}$ and $k_{\pm}$ is further evidence of the steric effect. If the tetrahedral intermediate formed from a given amine in **1e** is more sterically crowded than the corresponding intermediate in aryl acetate aminolysis, estimates of the pK_a of the leaving group in **1e** based on the comparison of $K_{\pm}$ values of phenyl acetate *will be too high,* because $K_{\pm}$ will be lowered by steric hindrance in the intermediate formed from **1e.** Thus, the leaving group from **1e** will appear to be more basic than it is in reality. One would expect that the value of $k_{\pm}$ will also be affected by steric hindrance in $T_{\pm}$. The decomposition of a sterically crowded intermediate will be accelerated by the relief of steric compression; that is, $k_{\pm}$ will be larger for **1e** than expected for the corresponding value derived for aryl acetates. Thus, values of the leaving group pK_a in **1e** based on the correlation of log $k_{\pm}$ vs. the leaving group pK_a in aryl acetates *will be too low.* Since k_1 of eq 1 is a composite of $K_{\pm}$ and $k_{\pm}$ (eq 2) in which the former is sterically depressed and the latter is sterically accelerated, the value of k_1 will tend to reflect a cancellation of these opposing steric effects and therefore estimates of pK_a based on log k_1 will be relatively free from steric effects. The close correspondence of the log k_1 for the *n*-butylaminolysis of α-naphthyl acetate[11] to that calculated on the basis of the pK_a of α-naphthol (see above) shows that these conclusions are reasonable. On the other hand, the abnormally high value of k_1 for the aminolysis of 3,4,6-*O*-trimethyl-2-deoxy-δ-gluconolactone[10] relative to the value predicted from the pK_a of the leaving group is expected from an abnormally large value of $K_{\pm}$ attributable to the cis ester effect, and from an abnormally large value of $k_{\pm}$, attributable to the increase of rotational freedom which accompanies ring opening. In the latter case, both factors contributing to k are changed in the same direction. It has been shown by Gerstein and Jencks[14] that equilibrium constants for ester aminolysis show an excellent correlation between the logarithm of the equilibrium constant for the aminolysis reaction vs. pK_a of the ester leaving group for all types of leaving groups; that is, separate lines are not required to correlate the behavior of alkyl groups and aryl groups. Of course, equilibrium constants for aminolysis are expected to be more devoid of steric effects than the rate constants under consideration. Equilibrium constants for the aminolysis of α-acetoxystyrenes are inaccessible, however, and we must rely on kinetics for the estimate of the pK_a of the leaving group. The kinetic constant in eq 1 which is expected to resemble most closely the equilibrium constant in its relative insensitivity to steric effects is k_1, because in the mechanism to which this constant is assigned (Scheme I, eq 2) bond formation to the amine is essentially complete, and bond breaking to the leaving group is substantial.

It is clear that the two estimates of the pK_a for *m*-chloroacetophenone enol based respectively on $K_{\pm}$ and $k_{\pm}$ apparently bracket the real pK_a of this substance. Thus, the pK_a of *m*-chloroacetophenone enol may be estimated to be 10.5 ± 1.0 with a good deal of confidence; the error limits reflect the maximum uncertainty in this quantity. Since the steric effects inherent in $K_{\pm}$ and $k_{\pm}$ which lead to this uncertainty tend to cancel, the uncertainty is probably smaller. From the correlation of log k_1 for aminolysis of α-acetoxystyrenes against pK_a of the leaving group (β_{lg} = 1.0). the assumed value of ρ of 1.0 for ionization of various substituted acetophenone enols justified previously,[6] and the relative values of k_1 for *n*-butylaminolysis of substituted α-acetoxystyrene,[6] the pK_a of acetophenone enol itself may be estimated to be 11.0 ± 1.0.

The Enolization Constant of Acetophenone. The pK_a of acetophenone is related to the pK_a of acetophenone enol by the thermodynamic cycle shown in Scheme II. It is clear

Scheme II



from this thermodynamic cycle that the carbon pK_a of acetophenone may be calculated from our enol pK_a as derived above provided that an accurate value for the fraction enol in acetophenone is known.

A value for the enolization constant, K_e, of acetophenone was determined by Gero[15] to be $K_e = 3.5 \times 10^{-4}$. This value was determined by titration of the enol present in acetophenone by iodine monochloride. The fraction enol in a number of other ketones was also determined by this method, and subsequent, more accurate determinations[16] have shown that the numbers determined by Gero are consistently too high. Sources of error in this type of determination include the rather rapid formation of enol compared with the rate of enol titration, titration of impurities in the solvent, and titration of impurities in the ketone, which was claimed to be 95% pure (minimum). Therefore, we believed that it was important to determine accurately the value for the enolization constant of acetophenone by a more reliable method. The method of choice is an electrochemical technique which was described in detail by Bell and Smith.[16] The essence of this technique is the ability to determine accurately and almost instantly the concentration of small quantities of Br_2. Such determinations can be made repeatedly on the same ketone solution after allowing more enol to form. The values obtained for a number of ketones in such repetitive determinations were found to be self-consistent.[16] Impurities in the solvent may thus be titrated initially before the enol determination takes place. Applying the method of Bell and Smith[16] to the enolization of acetophenone, we obtained the value $K_e = (1.92 \pm 0.03) \times 10^{-5}$ in 40% *tert*-butyl alcohol–water.

Since the concentration of bromine is extremely low in these experiments relative to the concentration of acetophenone, the small amount of α-bromoacetophenone produced should have negligible effect on the values of K_e determined by this method. Furthermore, repetitive determinations of K_e on the

Table II. Some Values of the pK_a of Acetophenone

Value	Solvent	Ref	Method
19.2	Water	17	Rates of iodination
19	Ether	19	Colorimetric, spectroscopic; based on aqueous pK_a of methanol (= 16)[21]
19.1	Polyethers	21	Equilibration with acids whose pK_a is based on 15.9 for 4-nitrodiphenylamine (established by H_- techniques)[24]
20	Ether	22	Acetophenone taken as arbitrary standard
21.5	Me_2SO/H_2O[a]	24	Rates of detritiation compared with standard compound of known pK_a
24.7	Me_2SO	3, 18	Determined directly using indicators (as 22.5) and corrected because of known (constant) difference of values provided by indicator and electrochemical techniques
15.8	5 vol % ethanol–water	This work	

[a] 0.011 M Me_4N^+ OH^-. [b] μ = 0.5 M (KCl).

same solution gave the same result; were α-bromoacetophenone contributing to the observed value of K_e, a systematic drift in the results would be observed as more of this material is formed. The nonaqueous cosolvent was necessary for solubilization of the acetophenone, but was not expected to have a major effect on the value of K_e. An attempt was made to determine K_e in an ethanol–water mixture, but the potentials were found to drift, apparently because of a slow oxidation of the ethanol by Br_2. Such a drift was not observed in the 40% *tert*-butyl alcohol–water system. As a check of the method in this solvent system, the enol content of cyclopentanone was determined in this solvent system. The value of $(3.32 \pm 0.07) \times 10^{-5}$ determined in this solvent system is in good agreement with the value $(1.3 \pm 0.1) \times 10^{-5}$ determined by Bell and Smith[16] for the enolization in water.

Although the values of enolization constants are expected to be solvent dependent, the comparison of the value determined by us for cyclopentanone in 40% *tert*-butyl alcohol with that determined in water[16] shows that the *tert*-butyl alcohol cosolvent has a relatively minor effect.

The pK_a of Acetophenone. The value of K_e for acetophenone combined with the estimate of the pK_a of acetophenone enol calculated in the previous discussion yields a value for the carbon pK_a of acetophenone itself of 15.8 ± 1.0. It is interesting to compare this value with other values for the pK_a of acetophenone, some of which are tabulated in Table II. The only value in this table determined in aqueous solution is the determination of Bell,[17] which employed rates of deprotonation of various ketones as a method for pK_a estimation. In this study the validity of the Brønsted correlation between the rates of exchange and the difference in basicity of the ketone and the catalyzing base was assumed. Furthermore, the pK_a scale was anchored on a value of 10.7 for ethyl acetoacetate, and the extrapolation to the pK_a of acetophenone was rather lengthy.

The assumptions used in the present study are fundamentally different. It could be argued that we have not taken adequate account of the steric effect on the aminolysis reaction on which the pK_a correlation is based. However, it should be pointed out that the assumption of a greater steric retardation than that which we have analyzed above only serves to reduce the value of the pK_a of acetophenone which emerges from the correlation.

It is interesting to compare the value which we calculate for the pK_a of acetophenone and the corresponding values for cyclohexanone and cyclopentanone. Bell and Smith[16] considered the bromination of these two ketones as a function of pH (a technique which could not be used with acetophenone because of the more rapid self-condensation). Knowing the fraction enol, these authors were able to calculate the carbon pK_a of these ketones and found a pK_a value of 16.7 for both compounds. This number is rather close to the value which we have calculated for the pK_a of acetophenone; the somewhat lower value for the latter compound, if it is real and not due to accumulated errors, is consistent with the greater electron-withdrawing character of the aromatic ring.

The other values for the pK_a of acetophenone cited in Table II were determined in either nonaqueous or partially aqueous solvents using various methods, and all depend on arbitrary standards of reference, with the exception of the value in Me_2SO, which was determined as part of a study of absolute acidities in that solvent.[3,18] These acidities are ultimately referred to standard results of a potentiometric method for the determination of the acidities of weak acids in Me_2SO.[2a,b] As pointed out by Bordwell and co-workers, the apparent agreement of the remaining values in this table is fortuitous, and occurs largely because of the use of different standards of reference in the different studies.

It was noted by Rappoport[25] that rates of addition of amines to electrophilic olefins CH_2=CHX in methanol correlate with the pK_a of the carbon acid CH_3X; the point X = $-COC_6H_5$ was assigned a pK_a value of 19 and fit the correlation well. Such a correlation, however, requires only correct *relative* pK_a values, rather than absolute pK_a values. Furthermore, most of the pK_a values used in this correlation were obtained from kinetic measurements of the rate of ionization (e.g., rates of bromination or deuterium exchange).[17,26-28]

Although the concept of the inherent strength of an acid or base in solution has no meaning,[29] measurements of acidity of weak acids in various solvents when compared with gas phase acidity measurements can provide important information on solvation phenomena. Thus, there is no "correct" number for *the* pK_a of acetophenone. The physical organic chemist interested in aqueous solution mechanisms or the biochemist interested in the pK_a of a proton adjacent to a carbonyl group in a molecule of intermediary metabolism will find the pK_a values implied by this study and others[16] to be appropriate. The synthetic organic chemist interested in the relative base strengths of anions in polar aprotic solvents such as Me_2SO, tetrahydrofuran, or other such solvents which are commonly used in organic synthesis would be more interested in the absolute scale of acidities in Me_2SO. The connection between the two kinds of pK_a values of a weak acid is provided by the relative standard free energies of transfer of the components of the acid–base equilibrium between water and Me_2SO. The comparison between absolute acidities in the two types of solvents—polar aprotic vs. water—has been nicely summarized by Bordwell and co-workers.[3] Compounds whose conjugate bases have negative charge largely localized on a heteroatom (carboxylates, enolates) will have a higher absolute acidity in water than they do in Me_2SO, whereas compounds whose conjugate bases are highly delocalized anions will be relatively more acidic in Me_2SO. These conclusions follow from the relative importance of hydrogen bonding in anion stabilization in the former cases compared with the relative importance of other types of forces in the latter. In fact, the aqueous acidity of acetophenone estimated here compared with that in Me_2SO is in exactly the order predicted by these conclusions, so that no conflict in these data exists.

Values of pK_a determined by the H_- scale incorporate effects of mixed solvents, and cannot be considered to be pK_as which are based on the dilute aqueous reference state except in the limit of the rather strong bases whose pK_a values are determined in essentially aqueous solution, as Bordwell et al. have pointed out.[3]

It may be that the method used here to determine the pK_a of substituted acetophenones may be applicable to pK_a determinations of other carbonyl compounds as well.

Experimental Section

Kinetics. Phenyl acetate was obtained commercially and purified by preparative gas–liquid partition chromatography on a 0.25 in. × 8 ft SE-30 column at 130 °C. The method of performing the kinetics and the treatment of data has been described previously.[6] Concentrations of phenyl acetate used and the wavelength at which the reaction was monitored are from Jencks and Carriuolo.[30]

K_e Determination of Acetophenone and Cyclopentanone. The procedure used for this determination is very similar to that described by Bell and Smith.[16] The solvent system chosen was 40 vol % *tert*-butyl alcohol–water so that the acetophenone would have adequate solubility. All measurements were performed at 25.0 ± 0.1 °C. The measuring buffer was 0.05 M in total acetic acid + acetate concentration (1:1 HOAc–KOAc) and 0.075 M in KBr. All water used in the measurement was distilled twice from $KMnO_4$, and *tert*-butyl alcohol was distilled under argon. The uncorrected pH of the measuring buffer was 5.36 ± 0.02. Solutions of the ketones were 0.5 M in ketone, and were otherwise identical with the measuring buffer.

Measurements were performed with a basket-type Pt electrode and a Radiometer G202C glass electrode. A Radiometer PHM 26 pH meter with expanded scale millivolt capability was used to monitor potentials. The concentration of Br_2 could be determined from the observed potential by the use of

$$E = E_0 + 29.58 \log [Br_2] \quad (4)$$

in which E is the observed potential, and E_0 is a standard potential which depends on the electrode system, pH, ionic strength, etc. E_0 could be determined by measuring the potential of known concentrations of Br_2 in the measuring buffer; the value of E_0 was found to be 784.2 ± 0.1 mV.

Ketone solutions were pretreated with Br_2 ($\approx 10^{-3}$ M) to remove any impurities and were then incubated for about 1 h after the Br_2 had disappeared from the solution. Aliquots (5 mL) of the pretreated ketone solution were removed and injected into 50 mL of the rapidly stirred measuring buffer containing enough Br_2 ($\approx 2 \times 10^{-6}$ M) so that a 5–10 mV initial decrease in potential occurred. The potential stabilized at the new reading within 15 s of the injection and remained constant for 30–60 s before slowly decreasing further. The value of K_e was determined from the potentials before and after injection (eq 4), the known concentration of ketone, and the known volumes of solutions by methods previously described.[16]

Control experiments in which the ketone was injected into a measuring buffer containing a high concentration of Br_2 ($3–7 \times 10^{-4}$ M) or in which a solution containing no ketone was injected into the measuring buffer at a Br_2 concentration of ca. 3×10^{-6} M gave the potential drop expected for a simple dilution effect.

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Registry No.—1e, 22391-00-0; phenyl acetate, 122-79-2; acetophenone, 98-86-2.

Supplementary Material Available. Table III (rates of aminolysis of phenyl acetate in 5 vol % ethanol–water) (2 pages). Ordering information is given on any current masthead page.

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Hydrolysis of α-Acetoxystyrenes. Kinetics and Investigations of ^{18}O Exchange

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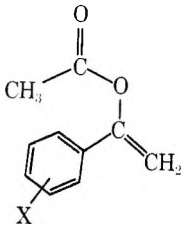
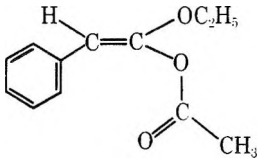
The alkaline hydrolyses of α-acetoxystyrenes **1a–f** and 1-acetoxy-1-ethoxy-2-phenylethylene (**2**) have been shown to proceed by the same mechanism which has been demonstrated for the hydrolysis of alkyl and aryl acetates. Among the pieces of experimental evidence leading to this conclusion are the inverse solvent deuterium isotope effects (0.74 + 0.07 for **1c**, 0.80 ± 0.09 for **2**), the kinetics of hydrolysis, which are first order in hydroxide ion, and the absence of general base catalysis of hydrolysis. In mildly acidic solution, however, the hydrolysis of **2** proceeds exclusively by a mechanism involving a rate-determining proton transfer to the leaving group double bond, a mechanism which was previously demonstrated for α-acetoxystyrenes in strongly acidic solution. Carbonyl labeled α-acetoxystyrene-^{18}O was synthesized, and ^{18}O exchange from the carbonyl position during alkaline hydrolysis was investigated; no ^{18}O exchange was observed. This behavior is similar to that observed for aryl esters, and contrasts with that observed for hydrolysis of esters with less acidic leaving groups. These observations support our contention that acetophenone enols are about as acidic as phenols, a conclusion which, along with the fraction enol in acetophenone, leads to a carbon pK_a for acetophenone of 15.8 ± 1.0.

Recently, we reported[2] that results from a kinetic investigation of the aminolysis of the α-acetoxystyrenes **1a–f** indicate that these compounds aminolyze by a mechanism identical



1a, X = *p*-OCH_3 **d**, X = *p*-Cl
b, X = *p*-CH_3 **e**, X = *m*-Cl
c, X = H **f**, X = *p*-NO_2



2

with that observed for aminolysis of aryl acetates.[3,4] In addition, our results indicated that acetophenone enols are about as acidic as phenol, with an estimated pK_a for acetophenone enol itself of 11.0 ± 1.0.[2,5] If phenols and enols are indeed as similar in their acid–base behavior as our previous studies suggest, then the hydrolysis of enol acetates should resemble hydrolysis of aryl acetates in any mechanism in which leaving group basicity and rate of reaction are correlated, in the absence of a strongly overriding steric effect.

We have completed a study of the alkaline hydrolysis of compounds **1a–f** and **2**. Correlations of kinetic data, solvent deuterium isotope effects, and ^{18}O exchange data (for **1c**) have been gathered, and these results, which we now report, suggest that α-acetoxystyrenes and aryl acetates hydrolyze in base by the same mechanism. Furthermore, the hydrolysis of **2** in acid proceeds by a mechanism, previously observed for α-acetoxystyrenes,[6] which involves a rate-determining protonation of the carbon–carbon double bond.

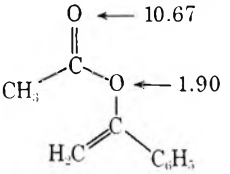
Experimental Section

Materials. Deuterium oxide (99.8%) was obtained from the Stuart Oxygen Co., and was flushed with argon before use. Solutions of 20% DCl in D_2O (Ventron) and 40% KOD in D_2O (Aldrich) were used to prepare standardized 1.0 M DCl and KOD solutions.

All water used in the experiments was deionized, double distilled, flushed with argon, and stored under argon in glass containers. Absolute ethanol and reagent grade KCl were used without further purification. Phenyl acetate was obtained commercially (Aldrich).

Acetic acid-^{18}O was prepared from acetyl chloride and 22.5 atom % ^{18}O enriched water (Yeda Research and Development Co.). A slight excess of the acetyl chloride was slowly added to the isotopically enriched water, which was stirred at 0 °C under argon. After addition, the solution was refluxed to help remove dissolved HCl. The extent of the reaction was monitored by the position of the hydroxyl proton resonance of acetic acid in the NMR, and more acetyl chloride was added if necessary. The acetic acid-^{18}O was distilled under argon when the reaction was complete.

Isopropenyl acetate-^{18}O was prepared by a modification of a procedure due to Hennion and Nieuwland.[7] Methylacetylene was condensed into a 40-mL, thick-walled hydrolysis tube to an approximate volume of 30 mL. Then 0.5 mL of boron trifluoride etherate, 0.5 g of HgO, and 4.0 g of acetic acid-^{18}O were added, the tube was sealed under vacuum, and the mixture was incubated at 30 °C for 10 h. After incubation was complete, the tube was cooled in liquid N_2 and opened. The contents were dissolved in 100 mL of ether and the methylacetylene was allowed to evaporate. The ethereal solution was then washed twice with 50 mL of 5% $NaHCO_3$ and once with 50 mL of distilled water. The ethereal solution was then rapidly dried over $MgSO_4$. The solution was not allowed to remain in contact with $MgSO_4$ for more than 2 min since it has been reported that carbonyl-^{18}O-enriched esters lose their isotopic oxygen in the presence of this salt.[8d] The ether was then removed under argon, and the remaining volatiles were collected in a cold trap under vacuum. The isopropenyl acetate-^{18}O was then distilled from the volatiles. The yield of the ester never exceeded 20% in any specific preparation. The α-acetoxystyrene-^{18}O was then prepared from the isopropenyl acetate-^{18}O by the method previously described for normal α-acetoxystyrene.[2] The analysis of these materials for isotopic content is described below, and indicates the following isotopic distribution for α-acetoxystyrene (numbers are atom % excess ^{18}O):



1-Acetoxy-1-ethoxy-2-phenylethylene was prepared by acetoxymercuration of 1-ethoxy-2-phenylacetylene, the synthesis of which has been previously described.[9] Approximately 2.9 g (20 mmol) of 1-ethoxy-2-phenylacetylene and 0.10 g of $Hg(OAc)_2$ were dissolved in 20 mL of methylene chloride and stirred at 0 °C as a solution of 1.00 g (16.7 mmol) of acetic acid in 30 mL of methylene chloride was added dropwise. The mixture was allowed to reach room temperature and was then stirred for 23 h. The mixture was then partitioned between 100 mL of water and 150 mL of ether, and the ether layer was washed a second time with water. Drying and concentration of the ether solution left a yellow oil which was distilled to give starting material and the desired compound (78% yield based on unrecovered starting

material): bp 76–78 °C (0.01 Torr); NMR ($CDCD_3$, downfield from internal Me_4Si) δ 1.32 (t, 3 H), 2.17 (s, 3 H), 3.95 (q, 2 H), 5.32 (s, 1 H), 7.0–7.6 (m, 5 H); IR (liquid film) 3050, 2970, 1780, 1680, 1205, 755, 695 cm^{-1}; mass spectrum (electron impact, 70 eV) *m/e* 206, 164, 91, 77, 43, 29.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.64; H, 6.80.

All spectral and physical evidence (including reaction kinetics) indicated that this material is one geometrical isomer, although there is no conclusive evidence available which would indicate which isomer is in hand. The usual trans mode of addition in acetoxymercuration suggests that the compound is the *Z* isomer shown in structure **2**. Product studies from the kinetics and a nuclear Overhauser experiment (NOE)[10] established without doubt that the vinyl proton and the phenyl group are bonded to the same carbon; however, the NOE experiment was inconclusive in identifying the geometrical isomer present.

Products of Hydrolysis. The products of basic hydrolysis of a acetoxystyrene, **1c**, were shown to be acetophenone and presumably acetic acid. The former product could be isolated from hyrolysis reaction mixtures in nearly quantitative yield by extraction with ether and comparison with authentic material. Likewise, UV spectra of hydrolysis mixtures at the completion of reaction were identical with those of acetophenone. Acetic acid was not specifically identified, although in *n*-butylaminolysis reactions of α-acetoxystyrene, *N*-*n*-butylacetamide and acetophenone were isolated.[2,5]

The products of acidic and basic hydrolysis of **2** were ethyl phenylacetate, isolated by ether extraction and identified by comparison with authentic material, and presumably acetic acid, which was not specifically identified. Aminolysis of **2** with glycinamide, however, yielded *N*-acetylglycinamide and ethyl phenylacetate.

Kinetic Methods. The solvent system employed in the kinetic studies was 5 vol % ethanol–water, ionic strength μ = 0.5 M (KCl), at 29.9 ± 0.1 °C. In deuterated solvent it was established that the pH meter reading was related to pD by

$$\text{pD} = \text{meter reading} + 0.30 \quad (1)$$

A value for the pK_a of D_2O in this solvent system was established as 14.50 ± 0.02 at 30 °C. The pseudo-first-order reactions of **2** were followed by the disappearance of the 272-nm UV absorption of this compound. The reactions of **1c** were observed by the appearance of the 279-nm absorption of acetophenone. The alkaline hydrolysis of phenyl acetate in nondeuterated solutions was also followed spectrophotometrically. Wavelengths and concentrations used for these experiments are from Jencks and Carriuolo.[3a] Preparation of solutions for kinetics and calculations of the rate constants have been previously described for the rate constants determined under pseudo-first-order conditions.[2]

The alkaline hydrolysis of α-acetoxystyrene under second-order conditions, $[OH^-] = [1c]$, was followed to verify that we could reproduce the rate constant observed under first-order conditions, and to provide a method for following the progress of the hydrolysis reaction during the ^{18}O exchange experiments which were themselves performed under second-order conditions. Kinetic solutions were prepared in a manner identical with that used in the first-order cases, and solutions of KOH and **1c** were made so that injection of 25 μL of an ethanolic solution of **1c** into 3 mL of the KOH solution would give an initial concentration of each reagent equal to 1.08×10^{-3} M. The progress of the reaction was followed at 29.9 ± 0.1 °C by the change in UV absorbance at 302 nm. The respective extinction coefficients for acetophenone (=S) and **1c**, ϵ_S and ϵ_α, could be determined from A_∞, A_0, and the initial concentration of **1c** by

$$\epsilon_S = A_\infty/(1.08 \times 10^{-3}) \quad (2)$$

$$\epsilon_\alpha = A_0/(1.08 \times 10^{-3}) \quad (3)$$

The concentration of the starting material as a function of time could then be calculated by

$$[1c]_t = 0.00108 \text{ M} - \frac{A_t - A_0}{\epsilon_S - \epsilon_\alpha} \quad (4)$$

Plots of $1/[1c]$ vs. time were linear to at least 70% completion, and rate constants determined from the slopes of these plots for both the ^{18}O-enriched and normal ester were in excellent agreement with the value of 63 ± 2 M^{-1} min^{-1} which was previously determined under first-order conditions.

General Methods and Sample Handling in ^{18}O Experiments. The synthesis of the ^{18}O-enriched α-acetoxystyrene has been described above. During all experiments concerning this ester, great care was taken to avoid contact of the ester with atmospheric moisture in order to avoid possible exchange reactions. When possible, the ester was protected with a blanket of argon, and stored in a desiccator. Contact with drying agents such as $MgSO_4$ was kept to a minimum because of the reported exchange of the carbonyl oxygen of esters in the presence of such drying agents.[8d]

Methylene chloride and pentane used in the experiments with the ^{18}O-enriched ester were distilled prior to use. The pentane was distilled under argon from CaH_2 since it was the solvent used in the analysis of the ester by gas chromatography–mass spectroscopy.

Mercuric chloride, used in the pyrolysis of ester samples of CO_2, was sublimed under a dry vacuum and stored in a desiccator. The amine 7,8-benzoquinoline, which was used as an HCl trap in the pyrolysis experiments, was recrystallized to a constant melting point from ethanol, thoroughly dried under vacuum, and stored in a desiccator. Water used in the experiments was deionized, and distilled under argon. After distillation, it was flushed with argon and stored in an all-glass bottle under an argon blanket until used. The Finnigan 3300 mass spectrometer was used for all ^{18}O analyses.

Methods of ^{18}O Analysis. The ^{18}O-enriched samples of α-acetoxystyrene were analyzed for ^{18}O content by mass spectrometric analysis of samples of the intact compound. Samples were prepared for analysis by dissolving 1 μL of the ester in 1 mL of dry pentane. Two GLC columns were used for gas chromatographic separation of the ester from solvent on the mass spectrometer: a 6 ft × 0.125 in. 5% DEGS column used at 130 °C, and a 6 ft × 0.125 in. 3% OV 101 column used at 90–100 °C. Both columns gave comparable results.

The ^{18}O content of the **1c** was determined by monitoring the relative abundance of ^{18}O- and ^{16}O-containing fragments of this compound. Three sets of ions with the following *m/e* ratios were monitored: 43 and 45; 120 and 122; 162 and 164. The ions with *m/e* of 43 and 45 contained oxygen from only the carbonyl position (see below), the ions with *m/e* of 120 and 122 contained oxygen from the acetophenone enol portion of the molecule, and the ions of *m/e* 162 and 164 are the molecular ions for molecules of **1c** containing no ^{18}O atoms and one ^{18}O atom, respectively. Depending on the conditions, either the peak at *m/e* 43 or 120 was the base peak. The molecular ion peak was about 12% as large as the base peak.

The abundance data for these peaks were collected from intact **1c** by one of two methods. Method A involved taking the average value of the ratio $(p + 2)/p$ for the three sets of ions from a total of four to six mass spectral scans in the region near the peak of the reconstructed gas chromatogram of this compound. Method B involved the use of a program which summed the relative abundances of the six peaks for all the mass spectral scans within the gas chromatographic peak of the ester. Three injections of each sample were made to establish an average value and a standard deviation for the ratios $(p + 2)/p$. In method A, the normal procedure of substracting a background spectrum from the spectrum of **1c** was employed. It was shown that for method B, substracting a background collected by summing over an equal number of scans containing no solvents or other compounds resulted in no appreciable change of the $(p + 2)/p$ ratios. This background substraction method was therefore, not used.

In both cases, the excess fraction of ^{18}O in the enriched compound was obtained by correcting for the normal isotope level of ^{18}O and other isotopes by the use of abundance data collected in an identical manner for a sample of the unlabeled compound. The excess fraction of ^{18}O, calculated from a given set of peaks $(p + 2)$ and p, X_p, could be determined for each of the three sets of peaks from

$$X_p = \left(\frac{(p+2)}{p} \Big/ \left(1 + \frac{(p+2)}{p}\right)\right)_e - \left(\frac{(p+2)}{p} \Big/ \left(1 + \frac{(p+2)}{p}\right)\right)_u \quad (5)$$

where $(p + 2)/p$ is the average ratio of the abundance of the ^{18}O-containing ion to the abundance of the unlabeled ion as determined by one of the two methods previously described. The subscripts e and u refer to the enriched and unenriched samples, respectively. Table I gives the values of X_p for the ^{18}O-enriched α-acetoxystyrene as determined by the two methods.

If the peaks at *m/e* 43 and 45 contain only oxygen from the carbonyl position, and the peaks at *m/e* 120 and 122 contain only oxygen from the enol position of the molecule, then X_{162}, the observed excess fraction of ^{18}O for the molecular ion, is given by

$$X_{162} = X_{43} + X_{120} - 2X_{43}X_{120} \quad (6)$$

This is due to the fact that X_{43} and X_{120} do not represent mutually exclusive events, and X_{162} is the excess fraction of molecules containing one and only one ^{18}O atom. Contributions from a peak at *m/e* 166, which is too small to measure, would need to be included to represent the excess fraction of molecules containing either one or two ^{18}O atoms.

Table I. Excess Fractions of ^{18}O, X_p, as Determined for p = 43, 120, and 162 for α-Acetoxystyrene by Methods A and B

	X_p[a]	
	Method A	Method B
X_{43}	0.1068 ± 0.0031	0.1066 ± 0.0011
X_{120}	0.0195 ± 0.0005	0.0186 ± 0.0002
X_{162}	0.1214 ± 0.0042	0.1214 ± 0.0008

[a] X_p is defined by eq 5. The values are given with their standard deviations.

The calculated value of X_{162} given by the results of X_{43} and X_{120} for the two methods is 0.1221 ± 0.0038 from method A, and 0.1212 ± 0.0014 from the results of method B. In both cases, the agreement between observed and calculated values of X_{162} is excellent. The results are consistent with the idea that the peaks of *m/e* 43 and 120 arise from portions of the molecule which contain the two different oxygens.

Inspection of Table I also shows that the standard deviations of the excess fractions as determined by method B are less than those determined by method A. This was a general phenomenon also observed during analysis of the samples of **1c** recovered from partial hydrolysis experiments, and probably reflects the very much larger sample size used in the determination of the excess fractions by method B.

A sample of this ester was also analyzed for ^{18}O content by conversion to CO_2 by the method of Rittenburg and Ponticorvo.[11] The ester (5 μL) and 0.5 g of mercuric chloride were sealed in a 12-cm pyrolysis tube, with a break-seal at the closed end, under a vacuum of approximately 5×10^{-4} Torr. The tube was immersed in a 2-propanol–dry ice bath to prevent loss of the α-acetoxystyrene during the evacuation and sealing process. This tube was then heated at 400 °C in a glass pyrolysis oven for 4.5 h to convert the ester to CO_2. The tube was then placed in a larger glass tube (about 30 cm long) with a standard taper joint which would allow easy connection to a vacuum line. Since HCl is a by-product of the pyrolysis, 0.25 g of 7,8-benzoquinoline was used as an HCl trap. The amine had been applied to the inner walls of the large tube before the pyrolysis tube was inserted by melting the amine in the tube with a heat gun. A stainless steel weight was also included to provide a means to break the break-seal of the pyrolysis tube. The contents of the large tube were evacuated to a vacuum of 10^{-4} Torr. The tube was immersed in a 2-propanol–dry ice bath during this time to prevent sublimation of the benzoquinoline. After approximately 0.5 h of evacuation, the tube was isolated from the vacuum line, the break-seal of the pyrolysis tube was broken, and the HCl was allowed to react with the benzoquinoline for about 5 min. The tube was then immersed in a liquid nitrogen bath, and was again subjected to evacuation at about 10^{-4} Torr to remove noncondensable gases. After about 10 min, the vacuum line was isolated from the pump and the liquid nitrogen cold traps, the liquid nitrogen bath was removed from the tube and replaced by a 2-propanol–dry ice bath, and the CO_2 was allowed to sublime into a 2 × 7 cm tube, with an adjustable high vacuum Teflon valve, that was cooled in a liquid nitrogen bath. The valve was then closed, and the contents of the tube were analyzed by mass spectrometry. The ratio of the abundance of the *m/e* 46 peak to the *m/e* 44 peak could be converted into the excess fraction of ^{18}O, X_{CO_2}, by use of

$$X_{CO_2} = \frac{(r) + \frac{1}{2}(r)^2}{2 + 2(r) + \frac{1}{2}(r)^2} - Q \qquad (7)$$

where Q is the fraction of ^{18}O in a sample of unenriched **1c** and r is equal to the ratio of the abundance of the peak at *m/e* 46 to the abundance of the peak at *m/e* 44. The equations used by others[8,12] are approximations to this equation in which the terms in $(r)^2$ are ignored. This approximation is only valid in the limit of low levels of ^{18}O and amounts to an error of several percent in the case of a compound with the amount of label used in this study. The value of Q was determined to be 0.0021 ± 0.0001 from the pyrolysis of a sample of the unenriched ester. This is in excellent agreement with the accepted value of 0.00204.[8c]

Analysis of the excess fraction of ^{18}O in the α-acetoxystyrene by this method gave a value of X_{CO_2} of 0.0637 ± 0.0009. This is in excellent agreement with the value of $(X_{43} + X_{120})/2$ of 0.0626 ± 0.0007 as determined by the analysis of the intact ester via method B. This is further evidence that the original assumptions concerning the origin of the oxygen atoms in the *m/e* 43 and 120 fragments are valid.

In the analysis of the ^{18}O exchange experiments, it was therefore assumed that X_{43} represented the excess fraction of ^{18}O in the carbonyl position, and that X_{120} represented the excess fraction of ^{18}O in the enol position of the compound **1c**.

The CO_2 method of ^{18}O determination was not used in the analysis of the samples subjected to partial hydrolysis because we had considerable difficulty in obtaining reproducible results by that method. The source of this problem could not be determined. Further disadvantages of this method compared to direct analysis of **1c** were the necessity for larger sample sizes (5 μL, compared to 1 μL for direct analysis), and the inability to monitor the ^{18}O content of the carbonyl and enol positions independently.

^{18}O Exchange Experiments. The concentrations of the ^{18}O-enriched α-acetoxystyrene and KOH used in the exchange experiment were identical with those used in the second-order hydrolysis experiments described above. Before each exchange experiment, the ester was preparatively gas chromatographed at 140 °C on an 8 ft × 0.25 in. 10% SE-30 column to ensure purity.

A volume of 500 or 1000 mL of the KOH solution (1.09×10^{-3} M KOH) was stirred under argon in a three-necked, 2-L, round-bottomed flask immersed in a water bath at 30.0 ± 0.5 °C. When the KOH solution has reached the temperature of the bath (30–40 min), a quantity of a freshly prepared 0.1309 M solution of the ^{18}O-enriched α-acetoxystyrene in ethanol was added so that the concentration of the α-acetoxystyrene was equal to that of KOH. The progress of the reaction was followed by monitoring the change in absorbance at 302 nm of 3 mL of the hydrolysis reaction mixture. Aliquots, which were adjusted in size in order to contain about 10–15 mg of the unreacted **1c**, were withdrawn at intervals and quickly neutralized with 0.1 M HCl. The pH of the aliquots after neutralization was between 6.5 and 7.0. These solutions were then extracted five times with 0.25 volumes of methylene chloride after 10 g of NaCl per 100 mL of aqueous solution was added to aid in the extraction. The methylene chloride extracts were combined and quickly dried with $MgSO_4$ on a fritted filter. Contact with $MgSO_4$ was kept to less than 1 min to avoid loss of the carbonyl enrichment. The methylene chloride solutions were then distilled through a 12-in. Hempel column until no further material would distill at a pot temperature of 55 °C. The remaining material was transferred to a 25-mL pear-shaped flask, and the methylene chloride which remained was removed under a dry vacuum on a rotary evaporator. Argon was bled into the system upon completion of the evaporation to protect the samples from atmospheric moisture. The α-acetoxystyrene was then separated from the hydrolysis product, acetophenone, by preparative gas chromatography on an 8 ft × 0.25 in. SE-30 comumn at 140 °C. Control experiments with unlabeled **1c** showed that approximately 90% recovery of the ester could be achieved by this method. The purified samples of the ester were stored in sealed glass ampules until ^{18}O analysis could be performed by the methods described above. A control experiment in which the recovery procedure was followed for an ^{18}O-enriched sample of the α-acetoxystyrene dissolved in the 5% ethanol solvent system containing no KOH showed that no diminution in the excess fraction of ^{18}O had occurred.

The data from the exchange experiments were evaluated according to the methods of Bender[8a] and Shain and Kirsch[8c] by plotting log $(100X_{43}/X_{0,43})$ vs. log $(100\ E/E_0)$, where $X_{0,43}$ is the initial value of X_{43} before hydrolysis, and E/E_0 is the fraction unreacted ester as *observed* from a plot of absorbance at 302 nm vs. time. The experiment was repeated three times to establish the reproducibility of the results.

Results and Discussion

Products of Hydrolysis. The products of alkaline hydrolysis of **1** were identified as acetophenone and (presumably) acetic acid. The hydrolysis of **2** under both acidic and alkaline conditions was found to yield ethyl phenylacetate and acetic acid.

Kinetics of Alkaline Hydrolysis of 1a–f and 2. The hydrolytic pseudo-first-order rate constants, k_{obsd}, in alkaline solution [5 vol % ethanol, μ = 0.5 M (KCl), 29.9 °C] for compounds **1a–f** and **2** were determined to have a first-order dependence on $[OH^-]$:

$$k_{obsd} = k_2[OH^-] \qquad (8)$$

Values of k_2 for **1a–f** and **2** are given in Table II. A correlation of log k_2 for **1a–f** against σ for the substituent on the leaving group is excellent and has a slope, ρ, equal to 0.47 ± 0.03. For

Table II. Rate Constants for Alkaline Hydrolysis of 1a–f and 2

Compd	k_2,[a] M^{-1} min^{-1}	Compd	k_2,[a] M^{-1} min^{-1}
1a	54 ± 1	1e	102 ± 3
1b	55 ± 1	1f	158 ± 4
1c	63 ± 2	2	410 ± 30
1c (D_2O)[b]	85 ± 6	2 (D_2O)[b]	510 ± 20
1d	94 ± 3		

[a] Second-order rate constants for hydrolysis by OH^- at 29.9 °C, reported with their standard deviations (eq 8). The range of hydroxide ion concentration used to establish the second-order rate law was 0.008–0.08 M. [b] The solvent system is identical with that used in the other hydrolysis experiments, except that C_2H_5OH, H_2O, and KOH are replaced by C_2H_5OD, D_2O, and KOD, respectively.

Table III. Rate Constants for the Acid Hydolysis of 1-Acetoxy-1-ethoxy-2-phenylethylene (2) in HCl, DCl, and Formic Acid Buffers[a]

Catalyzing species HA	k_{HA}, M^{-1} min^{-1}	k_{DA}, M^{-1} min^{-1}
$H_3O^+(D_3O^+)$	7.19 ± 0.07[b]	2.30 ± 0.05[c]
Formic acid[e]	0.0564 ± 0.0002[d]	

[a] Rate constants reported with their standard deviations. [b] Determined in HCl solutions from pH ca. 1.00 to 2.70 and from the intercepts of formic acid buffer plots, pH 2.56 to 3.12. [c] Determined in two DCl solutions, pD 1.51 and 2.24, made from standardized ca. 1.0 M DCl. [d] Determined from the intercept of a plot of buffer slopes vs. fraction of formate. This plot gave no evidence for a term in formate ion. [e] $pK_a = 3.50 \pm 0.02$ under the conditions of our experiment.

Table IV. Results of ^{18}O Exchange Experiments for the Partial Hydrolysis of ^{18}O-Enriched α-Acetoxystyrene[a]

Expt no.	E/E_0[b]	X_{43}[c]
1	1.00	0.1086 ± 0.0045
	0.73 ± 0.02	0.1092 ± 0.0018
	0.54 ± 0.01	0.1081 ± 0.0016
	0.38 ± 0.01	0.1069 ± 0.0021
	0.23 ± 0.01	0.1089 ± 0.0069
2	1.00	0.1028 ± 0.0027
	0.70 ± 0.02	0.1042 ± 0.0022
	0.37 ± 0.01	0.1024 ± 0.0023
	0.19 ± 0.01	0.1043 ± 0.0025
3	1.00	0.1083 ± 0.0004
	10.71 ± 0.02	0.1083 ± 0.0004
	0.37 ± 0.01	0.1084 ± 0.0011
	0.28 ± 0.01	0.1089 ± 0.0004

[a] Conditions: 5% ethanol-water, μ = 0.5 M (KCl), [ester] = $[OH^-] = 1.08 \pm 0.01 \times 10^{-3}$ M, 30.0 ± 0.5 °C. [b] Fraction ester unreacted as observed from a plot of absorbance vs. time of an aliquot of the reaction mixture at 302 nm. [c] Excess ^{18}O fraction in carbonyl as determined in the Experimental Section. Experiments 1 and 2 were determined by method A and experiment 3 by method B. Errors are standard deviations.

comparison purposes, the value of k_2 for phenyl acetate, determined in the same solvent system, was found to be 138 ± 3 M^{-1} min^{-1}.

Solvent Deuterium Isotope Effects. Buffer Catalysis. It was previously shown[2] that the amine-containing terms in the rate law for aminolysis of **1a–f** corresponded to true aminolysis rather than amine-catalzyed hydrolysis; thus, the hydrolysis of **1a–f** in alkaline solution does not show detectable buffer catalysis with the amine buffers examined. A comparison of the hydrolytic rate constants of **1c** in deuterated and nondeuterated solvent (Table II) yields the solvent isotope effect, $k_{2,OH}/k_{2,OD}$, equal to 0.74 ± 0.07, which is identical with that observed during alkaline hydrolysis of phenyl acetate under similar conditions.[3a] The relative rate constants for hydrolysis of **2** in OH^- and OD^- (Table II) yield a solvent isotope effect for the hydrolysis of this compound equal to 0.80 ± 0.09, similar to that observed for the hydrolysis of **1c** as well as that observed for other esters.[3a,13]

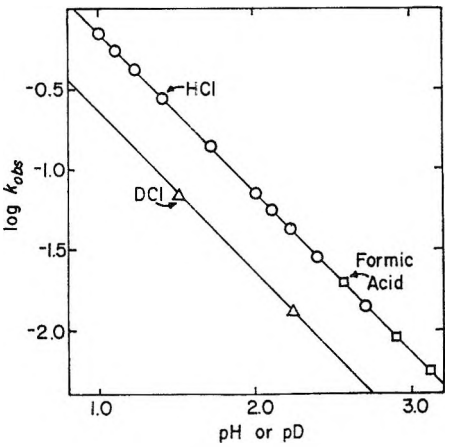


Figure 1. The dependence of the observed, pseudo-first-order rate constant for the hydrolysis of **2** on pH and pD in the acidic pH region. The circles are directly measured, and the squares are extrapolated to zero buffer concentration in the plots shown in Figure 2.

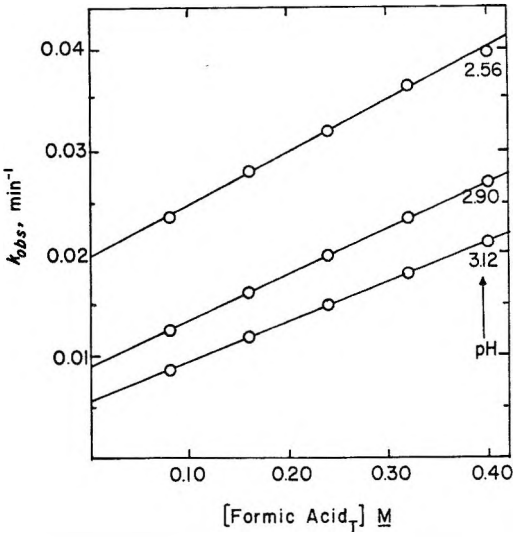


Figure 2. The dependence of the observed, pseudo-first-order rate constant for the hydrolysis of **2** on total buffer concentration.

However, in mildly acid solution the hydrolysis of **2** does not appear to conform to the normal behavior observed for alkyl and aryl esters.[14,15] Table III summarizes the rate constants for hydrolysis of **2** in HCl and DCl solutions and in formate buffers. Figure 1 shows the pH (and pD) rate profile for acid-catalyzed hydrolysis of **2**, and Figure 2 shows the dependence of the rate constant for hydrolysis on the concentration of formic acid in formate buffers. The solvent deuterium isotope effect for hydrolysis, $k_{H_3O^+}/k_{D_3O^+}$, 3.1 ± 0.1, and general acid catalysis of hydrolysis by the acidic components of formate buffers is observed.

^{18}O Exchange Experiments. α-Acetoxystyrene, ^{18}O enriched largely in the carbonyl oxygen, was synthesized by an acid-catalyzed acetate exchange between acetophenone and isopropenyl acetate-^{18}O, as described in the Experimental

Table V. ^{18}O Exchange Data for the Alkaline Hydrolysis of Various Esters

Ester	pK_a of the alcohol	Conditions	k_2/k_{ex}	Ref
tert-Butyl benzoate	17.3[a]	62.5 °C, 33% dioxane–water	7.6	8a
Isopropyl benzoate	16.6[a]	25.1 °C, 33% dioxane–water	3.7	8a
Ethyl benzoate	16.0[b]	25.1 °C, water	4.8	8a
Ethyl benzoate	16.0[b]	25.1 °C, water, μ = 0.003 M	12.6	8c
Methyl benzoate	15.5[b]	25 °C, water, μ = 0.003 M	27.7	8c
Methyl benzoate	15.5[b]	25 °C, 33% dioxane–water, μ = 0.01 M	89	8c
Methyl formate	15.5[b]	25 °C, water, μ = 0.1 M	18.3	8d
p-Chlorobenzyl benzoate	*c*	25 °C, 66.7% dioxane–water	>100	8e
p-Chlorobenzyl benzoate	*c*	25 °C, 50% dioxane–water	60	8e
p-Methoxybenzyl benzoate	*c*	25 °C, 66.7% dioxane–water	>100	8e
Phenyl benzoate	10.0[d]	50% dioxane–water	>100	8f
α-Acetoxystyrene	11.0[e]	5 vol % ethanol–water, μ = 0.5 M	>100	This work

[a] These values estimated from a correlation of pK_a vs. σ^* ($\rho = -1.42$) for a series of substituted methanols from ref 17, and σ^* values from ref 18. [b] Source: ref 17. [c] The pK_a of benzyl alcohol in water can be estimated to be 15.0 based on a correlation of pK_a values of substituted methyl alcohols vs. σ^* from ref 17 and a value of σ^* for C_6H_5 of 0.60 from ref 18. The *p*-chloro and *p*-methoxy substituted alcohols would be expected to have slightly lower and slightly higher pK_a values, respectively. [d] Source: ref 4a. [e] Source: ref 2 and 5.

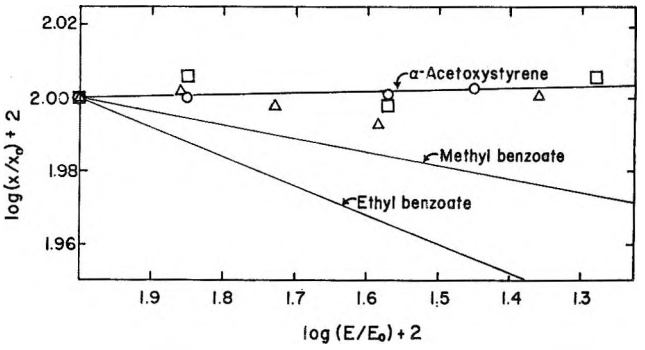


Figure 3. A plot of the logarithm of the percent ^{18}O exchange vs. logarithm of the percent observed reaction for the hydrolysis of **1c** with an ^{18}O-enriched carbonyl group. The different symbols represent different experiments (see text). The similar plots (from ref 8c) for methyl and ethyl benzoate, k_{obsd}/k_{ex} = 27.7 and 12.6, respectively, are presented for comparison purposes.

Section. The labeled isopropenyl acetate was in turn prepared from the addition of acetic acid-^{18}O to methylacetylene. Table IV gives the results of three experiments in which the ^{18}O content of the labeled α-acetoxystyrene was monitored as a function of the extent of alkaline hydrolysis by mass spectral analysis of unreacted compound recovered at appropriate times during alkaline hydrolysis under conditions in which $[OH^-] = [\mathbf{1c}]$. The results indicate that X_{43}, the excess fraction of ^{18}O in the carbonyl position of **1c**, does not decrease as the hydrolysis proceeds. This fact indicates that there is no ^{18}O exchange with solvent during the hydrolysis. The results were fit by means of a weighted linear least-squares calculation to

$$\log (100X/X_0) = (k_{ex}/k_2) \log (100E/E_0) + 2.0 - 2.0(k_{ex}/k_2) \quad (9)$$

in which E/E_0 is the ratio of unreacted α-acetoxystyrene at time t to the initial concentration of this compound, X/X_0 is the ratio of the excess fraction ^{18}O in the carbonyl position of **1c** at time t to the initial excess fraction, k_2 is the rate constant for alkaline hydrolysis (eq 8), and k_{ex} is the rate constant for ^{18}O exchange. This equation, or one similar to it, has been used previously to calculate the ratio k_2/k_{ex} from ^{18}O exchange data.[8a,c]

The correlation line which resulted from the calculation had a negative slope (-0.0048 ± 0.0021), a fact which indicates that the ^{18}O content of the carbonyl position of labeled **1c** increases as the hydrolysis proceeds. This kind of phenomenon has been observed previously in the concurrent ^{18}O exchange and alkaline hydrolysis of esters which very large k_2/k_{ex} ratios, and has been attributed to the kinetic isotope effect, k_{16O}/k_{18O}, for the hydrolysis reaction.[8c]

Figure 3 is a plot of log $(100X/X_0)$ vs. log $(100E/E_0)$ for the data derived for hydrolysis of **1c**. The correlation lines for the ^{18}O exchange data in alkaline solution determined for ethyl and methyl benzoate in water[8c] are included for comparison purposes. The values of k_2/k_{ex} for the two latter esters at 25 °C are 12.6 and 27.7, respectively.[8c] The behavior of α-acetoxystyrene much more closely resembles that of phenyl benzoate, which also shows no ^{18}O exchange upon alkaline hydrolysis.[8f] A lower limit for k_2/k_{ex} for **1c** of approximately 10^2 can be estimated from the limits of detection of very small changes in ^{18}O levels and the carbonyl oxygen isotope effect, which can lead to an overall increase in the excess fraction of ^{18}O as a function of the extent of reaction if k_2/k_{ex} is very large.[8c]

The fact that no ^{18}O exchange could be detected during the partial hydrolysis of carbonyl-^{18}O enriched **1c** is further evidence that acetophenone enols are quite acidic. Ester of weakly acidic alcohols such as methyl and ethyl benzoate[8a,c] or methyl formate[8d] show considerable ^{18}O exchange, as Table V indicates. This table shows that the ratio of hydrolysis to exchange, k_2/k_{ex}, generally increases as the pK_a of the alcohol corresponding to the leaving group decreases. The results for *p*-chlorobenzyl and *p*-methoxybenzyl benzoates[8e] appear to be anomalous, but may be due to the large fraction of dioxane cosolvent used in these experiments.[8c] It has been shown that the ratio k_2/k_{ex} increases as the fraction of dioxane in the solvent is increased. The behavior of α-acetoxystyrene resembles that of phenyl benzoate with regard to a lack of observed ^{18}O exchange during alkaline hydrolysis.

The acid-catalyzed hydrolyses of compounds **1a–f** and **2** do not correspond in their mechanistic behavior to that observed for the corresponding hydrolyses of alkyl and aryl esters. Solvent deuterium isotope effects, $k_{H_3O^+}/k_{D_3O^+}$, for the hydrolysis of esters by the $A_{AC}2$ mechanism are inverse,[19a] and no general acid catalysis of hydrolysis in aqueous solution is observed.[19b] These and other pieces of evidence[8a,d,15,20] indicate that the acid-catalyzed hydrolysis of esters by the $A_{AC}2$ mechanism proceeds by a rate-limiting attack of water on a protonated ester which is formed in a rapid preequilibrium.

The hydrolysis of α-acetoxystyrenes in strongly acidic media ($H_0 < -1.0$) has been shown to proceed by a different mechanism, however.[6] A primary solvent deuterium isotope

effect of 3.1 for the hydrolysis of **1a** in strongly acidic media indicates that the rate-limiting step of the hydrolysis of this ester under these conditions is proton transfer from solvent to the double bond to form a carbonium ion which is subsequently rapidly attacked by water. Under mildly acidic conditions the α-acetoxystyrenes apparently hydrolyze via the normal $A_{AC}2$ mechanism of acid-catalyzed ester hydrolysis.[6] However, our studies with the acylenol **2** indicate that this compound hydrolyzes via rate-determining proton transfer to the double bond even in the mildly acidic pH region. The solvent deuterium isotope effect, 3.1 ± 0.1, for the hydrolysis of **2**, determined in the acidic pH region is similar to solvent deuterium isotope effects of 2.5–3.0 observed for the hydrolysis of ketene acetals[21] and vinyl ethers,[22] both of which hydrolyze by rate-determining protonation of the double bond. This isotope effect is also identical with that observed for hydrolysis of **1a** (see above) in the strong acid region of acidity.

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Registry No.—**1a**, 22390-98-3; **1b**, 22390-99-4; **1c**, 2206-94-2; **1d**, 22479-32-9; **1e**, 22391-00-0; **1f**, 22391-01-1; **2**, 62415-90-1; acetyl chloride, 75-36-5; $H_2{}^{18}O$, 14314-42-2; isopropenyl acetate-^{18}O, 62415-91-2; acetic acid-^{18}O, 60321-43-9; methylacetylene, 74-99-7; 1-ethoxy-2-phenylacetylene, 32569-84-9; $Hg(OAc)_2$, 1600-27-7; α-acetoxystyrene-^{18}O, 62415-92-3.

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Notes

Quinoxaline Studies. 24.[1a] 3-(α-Cyano)benzyl-2(1*H*)-quinoxalinone *vs.* 2,3-Di(α-cyano)benzylquinoxaline. A Reinvestigation

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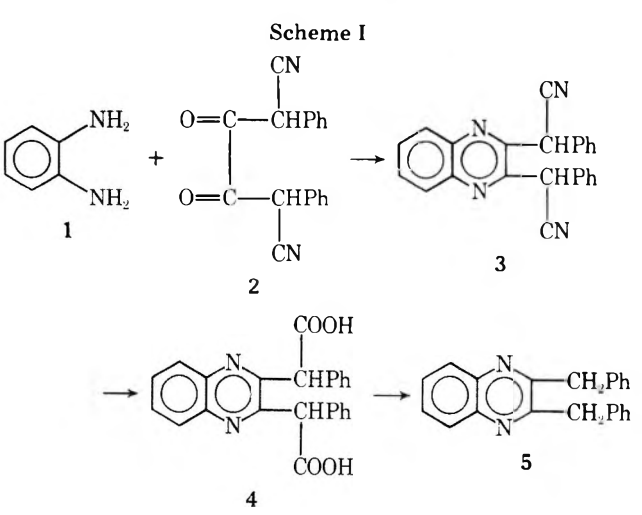
Dutt and Sen[2] reported the preparation of quinoxalines of structure **3** by condensation of *o*-phenylenediamine (**1**) with the diketone **2** prepared by condensation of diethyl oxalate with 2 mol of benzyl cyanide. In an effort to repeat this work for the purpose of preparing **4** and **5** (Scheme I) we found that the starting carbonyl compound used by Dutt and Sen was actually the 1:1 condensation product **6**, and their final condensation product was 3-(α-cyanobenzyl)-2(1*H*)-quinoxalinone (**7**). Our experiments also indicated that **2** would not condense with **1** to give **3**, but fortuitously synthesis of type **5** compounds has been recently reported.[3]

Interestingly, Dutt and Sen[2] claimed to have prepared 1,4-dicyano-1,4-diphenyl-2,3-butanedione (**2**) by a variation of the method of Volhard,[4] wherein diethyl oxalate was condensed with 2 equiv of benzyl cyanide with sodium in ethanol.

Scheme I



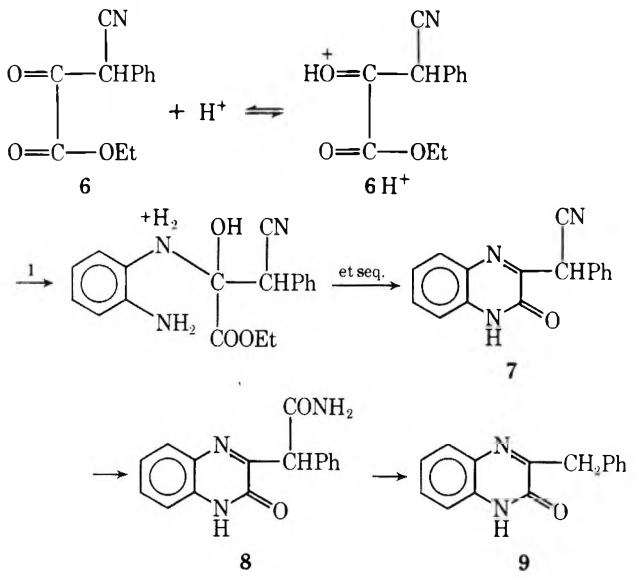
But in contrast to Volhard's procedure, Dutt and Sen omitted the ethanol. Repetition of both procedures showed that Volhard prepared **2**, but that Dutt and Sen had prepared ethyl phenylcyanopyruvate (**6**). Formation of **6** in the absence of EtOH and an excess of benzyl cyanide is probably the consequence of precipitating the sodium salt of **6** formed by interaction of 1 equiv each of diethyl oxalate and benzyl cyanide,

thus interdicting further alkylation of **6**. Compound **6** is better prepared by the method of Adams and Calvery.[5]

Condensation of **6** with **1** by the reported procedure in either cold HOAc or hot EtOH gave **7** monohydrate. In hot HOAc the hydrolysis product, 3-(α-carboxamido)benzyl-2(1*H*)-quinoxalinone (**8**) was, however, obtained. Complete hydrolysis with spontaneous decarboxylation of either cyanide **7** or amide **8** gave the known 3-benzyl-2(1*H*)-quinoxalinone (**9**).[6]

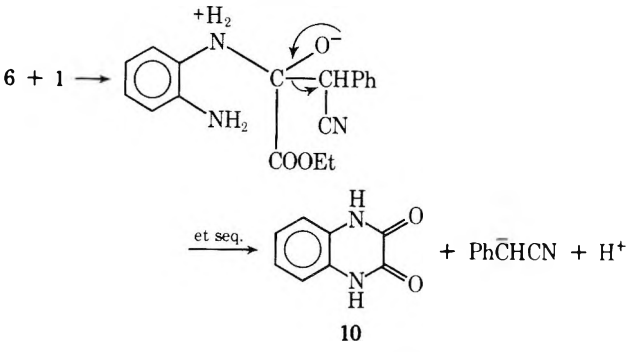
Obviously, condensations of **1** with **6** in HOAc and EtOH proceed via the classical "addition–elimination" (A–E) sequence (Scheme II) about the keto group of **6**, wherein water is eliminated in the second (E) step of the reaction.

Scheme II



Surprisingly, in the aprotic solvent THF, the second step of the A–E sequence referred to above results in elimination of the relatively stable cyanobenzyl carbanion (instead of water), with formation of 2,3(1*H*,4*H*)-quinoxalinedione (**10**)! This reaction is outlined in Scheme III.

Scheme III



Experimental Section[7]

α,α'-Dicyanodibenzyl diketone (2) was prepared by the Volhard[4] procedure. Yellow material (29%) was obtained: mp 285–287 °C from HOAc–H_2O (1:1, 100 mL/g) (lit.[2] mp 132 °C); green powder, mp 279 °C from amyl alcohol (150 mL/g) (lit.[4] mp 270 °C); IR (KBr) 3300 (OH), 2300 (CN), 1530 cm^{-1} (C=C); NMR (Me_2SO) δ 7.29–8.15 (m, 10, aromatic), 9.35 (s, 2, OH).

Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.98; H, 4.19; N, 9.72. Found: C, 74.63; H, 4.38; N, 9.43 (lit.[2] N, 9.4; lit.[4] C, 75.11; H, 4.27; N, 9.89).

Ethyl Phenylcyanopyruvate (6). The Dutt and Sen[2] "modified" procedure for **2** was used, wherein the above procedure for the preparation of **2** was altered by omitting EtOH solvent, Na being added directly to a solution of diethyl oxalate and benzyl cyanide: mp 126–128 °C from EtOH–H_2O (1:1, 10 mL/g) (lit.[2] mp 132 °C, lit.[5] mp 130 °C); lit.[5] preparation mmp 125–127 °C.

Anal. Calcd for $C_{12}H_{11}O_3N$: N, 6.45 (lit.[2] N, 9.4).

3-(α-Cyano)benzyl-2(1*H*)-quinoxalinone (7). A solution of 2.8 g (0.014 mol) of **6**, 1.2 g (0.011 mol) of **1**, and 20 mL of HOAc was stirred for 0.5 h at 25 °C, diluted with water, and filtered to give 2.6 g (85%) of yellow solid: mp 222–223 °C; mp 215–217 °C from HOAc–H_2O (1:1, 150 mL/g), mp 217–218 °C from EtOH–H_2O (1:1, 100 mL/g) (lit.[2] mp 227 °C for alleged **3**); IR (KBr) 4000–2700 (NH, OH), 2170 (CN), 1650 (CO), 1600 cm^{-1} (NH bend).

Anal. Calcd for $C_{16}H_{11}N_3O\cdot H_2O$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.82; H, 4.57; N, 15.15.

The same weights of **1** and **6** in 20 mL of boiling EtOH for 0.5 h gave the same results as above.

Anal. Found: C, 68.36; H, 4.15; N, 15.30.

After drying at 78 °C (1 mm), the samples had mp 219–220 °C; analysis then showed the substance to be a hemihydrate which regained its original weight upon standing in air; IR (KBr) 3400 (NH, OH), 2180 (CN), 1650 (CO), 1600 cm^{-1} (NH bend); UV max 372 nm (ε 11 111), 356 (infl), 290 (infl), 226 (21 111), 200 (end absorption).

Anal. Calcd for $C_{16}H_{11}N_3O\cdot\frac{1}{2}H_2O$: C, 71.10; H, 4.47; N, 15.54. Found: C, 70.95; H, 4.22; N, 15.61.

3-(α-Carboxamido)benzyl-2(1*H*)-quinoxalinone (8). Method A. Refluxing **7** in HOAc (20 mL/g) for 3 h gave 44% of yellow **8**: mp 297–299 °C; mp 301–303 °C from HOAc–H_2O (1:1, 60 mL/g); IR (KBr) 3360–3180 (NH), 1650 cm^{-1} (CO); UV max 340 nm (ε 5571), 282 (5352), 254 (infl), 229 (16 571), 200 (end absorption); NMR (Me_2SO) δ 5.51 (s, 1, CH), 7.25–7.90 (m, 12, aromatics, NH_2).

Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.55; H, 4.75; N, 15.13.

Method B. Refluxing a solution of 2.4 g of **1** and 5.6 g of **6** in 40 mL of HOAc for 3 h gave 29% of **8**, melting point and mixture melting point as above.

3-Benzyl-2(1*H*)-quinoxalinone (9). Method A. A suspension of **8** in 6 N HCl (66 mL/g) was refluxed for 6 h to give 78% of yellow **9**, mp 199–202 °C. The crude product was treated with Darco and Filteraid in 4.5 N NH_4OH solution, filtered, and reprecipitated with 6 N HCl to give white **9**: mp 199–202 °C; mp 200–201 °C (lit.[6] mp 196 °C) from Me_2CO (50 mL/g); IR (KBr) 1650 cm^{-1} (CO); UV max 344 nm (ε 7176), 334 (infl), 282 (6588), 254 (infl), 229 (21 647), 200 (end absorption); NMR (Me_2SO) δ 4.2 (s, 2, CH_2), 7.0–8.0 (m, 10, aromatics, OH).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.26; H, 5.14; N, 11.52.

Method B. Hydrolysis of **8** in boiling 2 N KOH for 6 h gave 44% yield of white **9**: mp 196–200 °C; mp 201–202 °C from EtOH–H_2O (1:1, 100 mL/g); same mixture melting point, IR, UV, and NMR as cited above.

Anal. Found: C, 76.05; H, 5.09; N, 11.74.

2,3(1*H*,4*H*)-Quinoxalinedione (10). Method A. A solution of 5.6 g (0.028 mol) of **6** and 2.4 g (0.022mol) of **1** in 40 mL of boiling THF for 1 h gave 2.0 g (56%) of yellow solid: mp <360 °C; mp <360 °C from EtOH (200 mL/g) (lit.[8] mp <360 °C); IR (KBr) 3050–2800 (NH), 1660 cm^{-1} (CO); UV (0.1 N NaOH) max 342 nm (ε 11 000), 327 (16 800), 315 (13 440), 264 (infl), 200 (end absorption) [lit.[8] 340 (11 000), 326 (14 500), 315 (12 000)]; NMR (Me_2SO) δ 7.3 (s, 4, aromatics) 12.0 (s, 2, NH).

Method B. Preparation of **10** by the method of Newbold and Spring[8] gave **10** of the same melting point, mixture melting point, IR, UV, and NMR as cited above.

Registry No.—**1**, 95-54-5; **2**, 10471-29-1; **3**, 62212-27-5; **6**, 6362-63-6; **7**, 38036-61-2; **8**, 62212-21-9; **9**, 24949-43-7; **10**, 15804-19-0.

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(6) A. H. Cook and C. A. Perry, *J. Chem. Soc.*, 394 (1943).

(7) Melting points, uncorrected, were determined on a Thomas-Hoover apparatus. Spectra were recorded as follows: UV, Jasco ORD/UV in 95% EtOH at concentrations of ~5 mg/L in 1-cm quartz cells; ^1H NMR, Hitachi Perkin-Elmer R-20, 60 MHz, 34 °C, δ in parts per million from internal Me_4Si; IR, Beckman IR-10. Elemental analyses were performed by PCR, Inc., Gainesville, Fla.

(8) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 519 (1948), and references cited therein.

Reaction of Unsymmetrical Benzils with Cyanide Ion in Dimethyl Sulfoxide[1]

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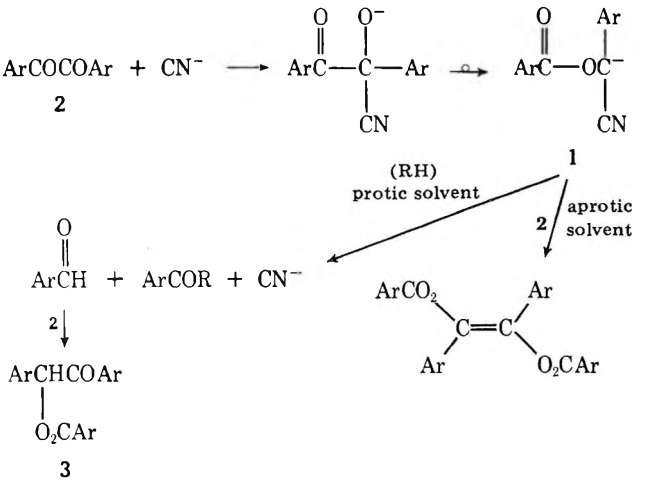
It was reported by others[2-5,7] that the reaction of benzils, **2**, with cyanide ion gives a variety of products depending on the reaction conditions. The reported mechanism assumes cleavage of the central C–C bond after addition of CN^- to form a resonance stabilized carbanion, **1**, which was proposed[3] as the common intermediate that leads to the formation of the observed diversity of products as indicated in part by Scheme I.

Scheme I



Evidence that **1** may indeed be the common intermediate for the products isolated was obtained by Trisler,[5] who reported that 4-nitromandelonitrile benzoate (**10**), the protonated form of **1**, is isolated in good yield when 4-nitrobenzil (**2c**) is made to react with 1 equiv of CN^- in Me_2SO or DMF.

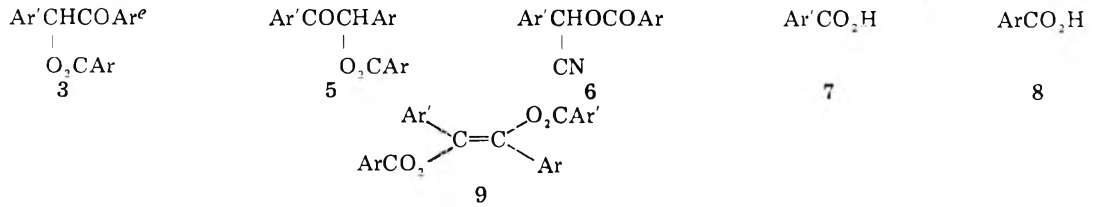
We observed,[6] however, that conversion of mandelonitrile benzoate to products under the same experimental conditions is considerably slower than the rate of conversion of benzil to products, which is inconsistent with the accepted mechanism. Moreover, we noted[6] that the kinetics of the CN^--catalyzed ammonolysis of benzil to afford benzaldehyde and benzamide is also not consistent with this mechanism as discussed previously.[6] It was decided, therefore, to investigate this reaction further using unsymmetrical benzils in the hope of resolving the somewhat ambiguous results thus far reported.

Accordingly, we repeated the reactions of CN^- in Me_2SO with 4-dimethylaminobenzil (**2a**), 4-dimethylamino-4′-chlorobenzil (**2b**), and 4-nitrobenzil[5] (**2c**), using somewhat different experimental conditions to determine the effect on product distribution. The data are collected in Table I. The materials balance ranges from 98 to 25%. The data show that the benzoin esters **3a** and **3b** were isolated as the major products of reaction with **2a** and **2b** in relatively good yields, whereas the alternative esters, **5a** and **5b**, were isolated as minor products in relatively poor yields. Reaction with **2c**, however, gave a product mixture from which the 4′-nitrobenzoate of *trans*-4-nitrostilbenediol (**9c**) was the only product isolated in 25% yield.

The isolation of **9c** as the major product instead of 4-nitromandelonitrile benzoate (**10**) as reported by Trisler,[5] who used an equimolar amount of 4-nitrobenzil and CN^-, is attributable to the difference in reactant ratios. We used a fourfold excess of 4-nitrobenzil so that the intermediate, **1c**, or any other adduct produced by very rapid and complete reaction with available CN^-, had a threefold excess of residual benzil with which to react further to give the stilbene **9c**. Trisler's conditions, on the other hand, produced rapid and complete conversion to **1c** leaving no available benzil for further reaction. The stable carbanion was isolated in good yield, therefore, as **10** when the reaction mixture was quenched with water.[5]

Our isolation of 4-dimethylaminomandelonitrile benzoate (**6a**) in small amount from the reaction mixture obtained with 4-dimethylaminobenzil (**2a**) is an evidence that **1a** may be an intermediate in this reaction, but the isolation of **3a**, **3b**, and **9c** as the major products of reaction with **2a**, **2b**, and **2c**, respectively, suggests that these products may be formed by an alternate pathway. The formation of these products via the accepted mechanism requires that the CN^- and the corresponding carbanions, **1**, add preferentially to the less electrophilic carbonyl center (ArCO), which is contrary to theory.

Table I. Reaction of Unsymmetrical Benzils with NaCN at Room Temperature in Me_2SO under N_2

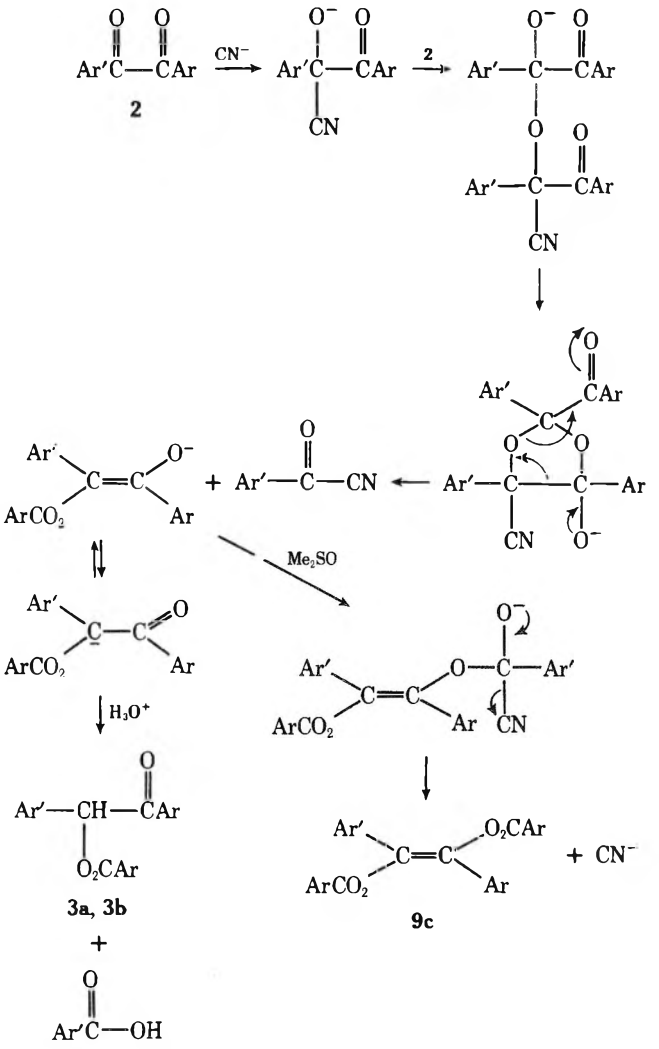


Reactant No.[a]	mmol	NaCN, mmol	Solvent, mL	Reaction time, h	Product, % yield 3	4[d]	5	6	7	8	9	% benzil units recovery as product
2a	4.0	6.6	25	6	34	5[b]	0		10	9		59
2a	5.0	4.0	30	40	48	8[b]	0	21[c]	11	10		98
2a	5.0	9.0	30	8	29	0	4.4		18	15		66
2b	3.5	4.0	20	15	31		2.6		16			50
2b	2.3	2.0	15	10	28		3.5		12	Trace		44
2c	2.6	0.6	15	1							25	25

[a] 2a, *p*-dimethylaminobenzil; 2b, *p*-chloro-*p*′-dimethylaminobenzil. [b] % by weight. [c] Yield of reddish tough mass from which a small amount of 6a was obtained. [d] Unidentified product. [e] Here, Ar′ is the more electron-withdrawing aromatic group of 2.

Because of this discrepancy, we postulate an alternative pathway, which is consistent with product distributions obtained, and involves addition of the anion to the more electrophilic carbonyl (Ar'CO) as shown in Scheme II, where Ar' is the more electron-withdrawing aromatic group.

Scheme II



a, Ar' = Ph; Ar = 4-$Me_2NC_6H_4$
b, Ar' = 4-ClC_6H_4; Ar = 4-$Me_2NC_6H_4$
c, Ar' = 4-$NO_2C_6H_4$; Ar = Ph

To test the possibility that the enolate ion of the nitrobenzoin benzoate can indeed add to benzoyl cyanide as shown in Scheme II, benzoin benzoate itself was converted to the corresponding enolate ion by reaction with NaH dispersed in mineral oil. Benzoyl cyanide was then added to give a highly colored solution, which was quenched soon thereafter with ice-cold aqueous sulfuric acid. As expected, stilbenediol dibenzoate was isolated in good yield from the product mixture.

More work is needed, of course, to prove or disprove the validity of this postulated alternative pathway, which thus far appears to be more consistent with the product distributions actually obtained than the pathways proposed earlier.

Experimental Section

Infrared, UV, and NMR spectra were recorded on a Perkin-Elmer 337 IR spectrophotometer, a Hitachi 124 spectrophotometer, and a JEOL C-60 HL spectrometer, respectively. Melting points were uncorrected.

Materials. Substituted benzils were prepared according to procedures described previously.[6,9-11] 4-Nitrobenzil (**2c**) had mp 138–139 °C (lit.[11] 136–137 °C). Benzoin benzoate[6] and benzoyl cyanide[12] were also prepared using procedures reported earlier. Me_2SO was dried over CaH_2 and distilled in vacuo.

Reaction of 4-Dimethylaminobenzil with NaCN. The reaction procedure was similar to that reported by Trisler.[2] To a partly dissolved solution of NaCN (0.2 g, 4 mmol) in Me_2SO (30 mL) was added **2a** (1.27 g, 5 mmol) under N_2. The solution became dark green in color. After 40 h at room temperature, the mixture was separated by filtration. The product was isolated as fine yellow crystals (0.48 g, 48%), mp 240–248 °C dec. The product was purified further by one recrystallization from pyridine as indicated by its melting point (258–262 °C dec). This product was identified as 4'-dimethylaminobenzoin 4-dimethylaminobenzoate (**3a**) by its melting point, IR and NMR spectra, and elemental analysis.

The Me_2SO filtrate from which **3a** was removed by filtration was poured into acidic ice–water. The mixture was extracted with benzene. The benzene extract was washed with aqueous $NaHCO_3$, and then evaporated to dryness to give a reddish, tough mass (ca. 0.7 g) as residue, which on recrystallization from EtOH and treatment with active carbon gave 0.1 g of crystalline material (mp 139–144 °C). This product was purified further by one recrystallization from ethanol to give crystals that melted at 159–161 °C. This material, **4a**, is not yet identified. Evaporation of ethanolic filtrate left a dark brown material as residue (0.29 g, 21% by wt). The IR spectrum of this material was consistent with that of mandelonitrile 4-dimethylaminobenzoate (**6a**). This material was purified further by repeated crystallizations from petroleum ether to give a small amount of **6a** in the form of colorless crystals, mp 70–73 °C. The residue obtained by evaporation of the combined filtrate was dark brown, tarry material, from which no definite product could be isolated further. The aqueous $NaHCO_3$ extract of the benzene solution from which **6a** was isolated was acidified to pH 5 and extracted with CCl_4. The CCl_4 extract was evaporated to dryness. The residue (0.07 g, 10%), mp 215–230 °C, was identified as *p*-dimethylaminobenzoic acid (**8a**) by its melting point and IR spectrum. Acidification of a residual aqueous solution to pH 1 and extraction with CCl_4 gave **7a** (0.07 g, 11%), mp 118–120 °C, which was identified as benzoic acid by its melting point and IR spectra. The unidentified product **4a**, which was isolated in low yield, might be a benzoin benzoate having at least one *p*-dimethylamino group in view of the NMR [τ, 7.03, 6 H for $(CH_3)_2N$–; 1.9–2.9, 15 H aromatic], MS (*m/e* 359, 4.6%), and elemental analysis. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 75.60; H, 5.88; N, 4.04. The mass spectrum showed a base peak of p-$Me_2NC_6H_4CO^+$ (*m/e* 148, 100%) and peaks of $PhCO^+$ (105, 17%) and Ph^+ (77, 12%), but the IR spectrum (ν C=O 1705, 1685, 1665 cm^{-1}) is inconsistent with those of any authentic sample of benzoin 4-dimethylaminobenzoate, 4'-dimethylaminobenzoin benzoate, and **3a** or of their mixtures. Repeated recrystallizations did not change the IR spectrum, and it might be a mixture, since the UV spectrum showed the existence of both p-$Me_2NC_6H_4CO$ (346 nm) and p-$Me_2NC_6H_4COO$ (318 nm) groups. **4a** is neither symmetrical benzoin nor stilbene derivative in view of spectral data.

3a: IR (KBr) 1680, 1660 cm^{-1}; NMR (Me_2SO-d_6) τ 2.0–3.5 (m, 14 H of aromatic and methine), 7.07 (s, 12 H of NMe); MS *m/e* 402, 148, 120, 77; UV ($CHCl_3$) 323 nm (ϵ 40 000), 348 (38 000). Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 73.35; H, 6.40; N, 7.81. The sample agreed with the authentic specimen of 4'-dimethylaminobenzoin 4-dimethylaminobenzoate (**3a**) prepared from 4'-dimethylaminobenzoin and 4-dimethylaminobenzoyl chloride.

6a: IR (KBr) 1710 cm^{-1}; NMR (Me_2SO-d_6) τ 2.25 (d, aromatic 2 H, J = 10 Hz), 2.50 (m, 5 H of Ph), 3.23 (s, 1 H of methine), 3.32 (d, aromatic 2 H, J = 10 Hz), 7.01 (s, 6 H of NMe); UV (MeOH) 318 nm ($\epsilon \geq 10^4$). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.21; H, 5.97; N, 9.64. Treatment of the sample with NaOMe in dioxane gave benzaldehyde (79%) and methyl 4-dimethylaminobenzoate (74%) on GLC analysis. Alkaline hydrolysis of the sample followed by acidification gave a positive test (cupric acetate–benzidine) for HCN, which indicates the existence of the CN group in **6a** in spite of no band of CN in its IR spectrum.

Reaction of 4-Chloro-4'-dimethylaminobenzil (2b) with NaCN. The analogous reaction of **2b** (1.44 g) with NaCN (0.45 g) for 8 h gave light green crystals of 4-chloro-4'-dimethylaminobenzoin 4-dimethylaminobenzoate (**3b**, 0.31 g, 29%), mp 252–265 °C dec. The analogous workup of the filtrate gave 4'-dimethylamino-4-chlorobenzoin 4-dimethylaminobenzoate (**5b**, 0.047 g, 4%), mp 254–262 °C, crude 4-dimethylaminobenzoic acid (**8b**, 0.12 g, 15%), and 4-chlorobenzoic acid (**7b**, 0.14 g, 18%).

3b: IR (KBr) 1690, 1660 cm^{-1}; NMR (Me_2SO-d_6) τ 2.2–3.5 (m, 13 H of aromatic and methine), 7.07 (s, 12 H of NMe); MS *m/e* 436, 315, 148, 120, 77; UV ($CHCl_3$) 323 nm (ϵ 34 000), 350 (31 000). Anal. Calcd

for $C_{25}H_{25}ClN_2O_3$: C, 68.76; H, 5.77; N, 6.42. Found: C, 66.49; H, 5.56; N, 5.79. This was same material as the authentic specimen.

5b: IR (KBr) 1715, 1705 cm^{-1}; NMR (Me_2SO-d_6) τ 2.1–3.5 (m, 13 H of aromatic and methine), 7.00 and 7.02 (s, 12 H of NMe); UV ($CHCl_3$) 323 nm (ϵ 54 000). Anal. Calcd for $C_{25}H_{25}N_2O_3Cl$: C, 68.76; H, 5.77; N, 6.42. Found: C, 67.83; H, 5.22; N, 6.64.

Reaction of 4-Nitrobenzil (2c) with NaCN. 4-Nitrobenzil (**2c**, 0.64 g) was added to a solution of NaCN (0.03 g) in Me_2SO (15 mL). Reaction was allowed to occur at room temperature for 1 h and then the mixture was poured into acidic ice–water to produce a light green precipitate. This precipitate was washed with ethanol and recrystallized from benzene–ethanol to give 4-nitrostilbenediol 4′-nitrodibenzoate (**9c**) in the form of light yellow crystals (0.16 g, 25%), mp 212–216 °C, which were identified by IR and NMR spectra and elemental analysis. Only a small amount of yellow solid (0.01 g), mp 175–180 °C, was recovered from the combined ethanol washings and mother liquor.

9c: IR (KBr) 1740, 1520, 1340 cm^{-1}; NMR ($CDCl_3$) τ 1.69 (s, 4 H of 4-nitrobenzoyloxy), 1.7–2.3 (m, 2 H meta to NO_2 and 4 H ortho to C=O; 1.82 d and 2.22 d, J = 9 Hz), 2.3–2.7 (m, 5 H of Ph and 3 H meta and para to C=O); MS m/e 510, 255, 240, 239, 150, 135, 122, 105. Anal. Calcd for $C_{28}H_{18}N_2O_8$: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.75; H, 3.82; N, 5.69. Treatment of the sample with methanolic MeONa gave an equimolar mixture of methyl benzoate and methyl 4-nitrobenzoate (1:0.84) as determined by GLC analysis.

Reaction of Benzoin Benzoate with Benzoyl Cyanide in the Presence of NaH. Benzoin benzoate (1.58 g, 5 mmol) was converted into the enolate ion by treatment with NaH dispersed in mineral oil (0.50 g, 5 mmol) in Me_2SO (30 mL) under N_2 to give a deep green colored solution. Addition of benzoyl cyanide (0.68, g, 5 mmol) at room temperature caused the solution to become very dark. After 20 min the mixture was poured into ice-cold aqueous H_2SO_4, giving a precipitate (1.84 g). This precipitate was recrystallized from benzene–petroleum to give stilbenediol dibenzoate (SDD) (0.53 g, 25%), in the form of crystals, mp 191–193 °C. An additional SDD (0.13 g, total 31%) was isolated as a second crop (mp 179–193 °C). Evaporation of the filtrate to dryness and crystallization of the residue from EtOH gave benzoin benzoate (0.59 g, 37%) in the form of crystals, mp 124–126 °C.

Acknowledgments. We wish to thank Shionogi Research Laboratory for the elemental analysis and National Chemical Laboratory for Industry, Tokyo, for the mass spectra.

Registry No.—**2a**, 22711-20-2; **2b**, 60955-65-9; **2c**, 22711-24-6; **3a**, 62139-42-8; **3b**, 62139-43-9; **5b**, 62139-44-0; **6a**, 62139-45-1; **7a**, 65-85-0; **7b**, 74-11-3; **8a**, 619-84-1; **9c**, 62139-46-2; NaCN, 143-33-9; benzaldehyde, 100-52-7; methyl 4-dimethylaminobenzoate, 1202-25-1; benzoin benzoate, 1459-20-7; benzoyl cyanide, 613-90-1; stilbenediol dibenzoate, 1924-29-4; dimethyl sulfoxide, 67-68-5.

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(8) However, if the assumption is made that the hydrolysis of Ar $\bar{C}$(CN)OCOAr′ affording ArCHO is preferred exclusively to that of Ar′C(CN)OCOAr (**1a,b**) affording Ar′CHO with a trace amount of water which might exist in the system, then the preferred condensation of **1a,b** with ArCHO should give the benzoate **3** via **5** (Ar = 4-$Me_2NC_6H_4$). The assumption is consistent with the previous observations that the rate of basic hydrolysis with ethyl benzoate is higher by a factor of 40 than with ethyl 4-aminobenzoate: D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1439 (1938); E. Tommila and C. N. Hinshelwood, *ibid.*, 862 (1938). It is not unreasonable.
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Disproportionation and Pyrolysis of *p*-Toluenesulfonylhydrazine

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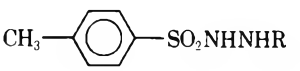
p-Toluenesulfonylhydrazine (**1**) is a standard reagent, widely used in the synthesis of organic compounds.[1] Its chemistry, particularly deviations from the normal behavior of hydrazine derivatives, is thus of interest. In 1965, Chang[2] found that an anomalous reaction between **1** and 12-oxocholane produced 12-oxocholane azine in addition to the expected tosylhydrazone. The azine presumably arose via a disproportionation of **1** into hydrazine and di(*p*-toluenesulfonyl)-hydrazine (**2**), but the disubstituted hydrazine was not isolated. We found that a similar disproportionation occurred when 1,3-dioxolen-2-one was heated with **1** in the presence of sulfuric acid; and **2**, shown below to be the 1,2 isomer, was formed in low yield.



1, R = H
2, R = *p*-$CH_3C_6H_4SO_2$

A better synthesis of **2** involved deprotonation of **1** with bases such as *n*-butyllithium or triethylamine followed by reaction with *p*-toluenesulfonyl chloride. Recrystallization from acetonitrile yielded 1,2-di(*p*-toluenesulfonyl)hydrazine as white needles, mp 194–195 °C dec. The compound underwent extensive fragmentation on electron impact and no parent ion was observed in the mass spectrum. Instead, a cluster of peaks due to $C_7H_7SO_2^+$, $C_7H_7SO_2H^+$, and $C_7H_7SO_2H_2^+$, respectively, was observed. The methane chemical ionization mass spectrum showed the m/e 157 ($C_7H_7SO_2H_2^+$) ion as the base peak. In contrast, the mass spectrum of **1** showed a readily identifiable M^+ peak at m/e 186.

The infrared spectrum of **2** in acetonitrile exhibited strong bands at 1165 and 1345 cm^{-1} due to the sulfonyl groups. An additional band at 3180 cm^{-1}, which shifted to 2350 cm^{-1} on crystallization of **2** from tetrahydrofuran–D_2O, was assigned to ν_{NH}. The presence of only one N–H stretching band implies that only secondary amine groups are present, for otherwise, two bands, symmetric and asymmetric stretch, would be observed.[3] Further evidence that **2** is the 1,2 isomer was obtained from the ^1H NMR spectrum in which the NH protons appeared as a broad singlet at 3.4_2 ppm (Me_2SO-d_6). The shifts of the NH protons are 3.4_2 (2 H) and 4.1_1 ppm (1 H) for **1** and 3.4 ppm for *p*-toluenesulfonamide. This indicates that NH protons adjacent to a *p*-toluenesulfonyl group resonate at ~3.4 ppm, as observed in **2**.

It is probable that **2** is formed by nucleophilic attack by the conjugate base on **1** on toluenesulfonyl chloride. In this case, it is interesting to note that proton abstraction from N-2 takes place rather than from N-1, adjacent to the electron-withdrawing tosyl group.

The melt pyrolysis of *p*-toluenesulfonylhydrazine was studied to determine whether thermal disproportionation would occur. Upon heating at 140 °C under vacuum, the hydrazine derivative decomposed to give nitrogen, ammonium *p*-toluenesulfonate (**3**), *p*-toluenesulfonamide, and *p*-ditolyl disulfide dioxide (**4**). Identification of **3** followed from its elemental analysis and behavior as a 1:1 electrolyte in nitromethane. The electron impact and methane chemical ion-

ization showed only peaks due to ions derived from *p*-toluenesulfonic acid.

$$1 \xrightarrow{\Delta} \underset{3}{NH_4^+ p\text{-}CH_3C_6H_4SO_3^-} + N_2 + p\text{-}CH_3C_6H_4SO_2SC_6H_4CH_3\text{-}p + \underset{4}{p\text{-}CH_3C_6H_4SO_2NH_2}$$

The unsymmetrical structure of **4** deduced from the ^1H NMR spectrum[4] is confirmed by the observation of two nonequivalent methyl resonances at 21.5 and 21.3 ppm in the ^{13}C NMR spectrum and by the infrared spectrum, which reveals symmetrical and asymmetrical S–O stretching modes.[5,6]

Melt pyrolysis of **1** presumably generates N_2H_2 and *p*-toluenesulfinic acid (**5**) by 1,2-elimination as suggested by Dewey and Van Tamelen.[7] Reduction of added olefins is good evidence for the generation of N_2H_2 as an intermediate. Subsequent disproportionation of the sulfinic acid to *p*-toluenethiol and *p*-toluenesulfonic acid (**6**), followed by loss of water, would form **4**. Condensation of ammonia, derived from N_2H_2, and **6** would produce both **3** and *p*-toluenesulfonic acid. Di-*p*-tolyl disulfide, observed as a pyrolysis product by Meier and Menzel,[8] was not isolated. Our reactions were carried out under vacuum and it is possible that the disulfide is produced by air oxidation of *p*-toluenethiol. These workers did not analyze the benzene-insoluble reaction products and did not report the formation of **3**. *p*-Toluenesulfinic acid was not observed among the pyrolysis products[7] and it is probably unstable under the conditions required for its formation from **1**. This is in agreement with Otto and Von Gruber[9] with the work of Yoshida et al.,[10] who reported facile disproportionations of benzenesulfinic acid.

We conclude that solid **1** decomposes by 1,2-elimination to form toluenesulfinic acid and diimide as the primary products and does not generate the symmetrical ditosylhydrazine **2**. Formation of this derivative in solution requires the presence of acid and may arise by attack at sulfur in the conjugate acid of **1** by additional **1**. An analogous mechanism has been previously proposed to account for the acid-catalyzed conversion of tosylhydrazones to azines.[11]

Experimental Section[12]

Commercial *p*-toluenesulfonylhydrazine was crystallized from tetrahydrofuran–hexane. Infrared spectra were recorded on a grating spectrometer. ^1H and ^{13}C NMR spectra were obtained at 60 and 22.6 MHz, respectively, and chemical shifts are reported with respect to internal $(CH_3)_4Si$; positive shifts arbitrarily refer to lower field. Elemental analyses were performed by Schwarzkopf Laboratories. Melting points are uncorrected. Mass spectra were obtained by using a direct insertion probe and a quadrupole spectrometer. Electron impact spectra were obtained at 70 eV. Methane was used as the reagent gas in chemical ionization experiments.

1,2-Di(*p*-toluenesulfonyl)hydrazine (2). A solution of 0.65 g (3.5 mmol) of **1** in 10 mL of tetrahydrofuran was cooled to −78 °C and 2.2 mL of 1.6 M *n*-butyllithium in hexane added dropwise with rapid stirring. *p*-Toluenesulfonyl chloride (0.67 g, 3.5 mmol) in 10 mL of tetrahydrofuran was then added. The cold bath was removed, and the reaction mixture stirred overnight, then filtered. The filtrate was evaporated to 10 mL and treated with 80 mL of petroleum ether to give, after chilling, a gummy product. This was dissolved in methanol and slowly added to cold water. The white precipitate was recrystallized from acetonitrile to give 0.2 g (17%) of product as white needles, mp 194–195 °C dec. Anal. Calcd for $C_{14}H_{16}N_2O_4S_2$: C, 49.41; H, 4.70; N, 8.24; S, 18.82. Found: C, 49.29; H, 4.88; N, 8.50; S, 19.36. IR (CH_3CN) 3180 (br), 1600 (w), 1345 (m), 1190 (w), 1185 (s), 1165 (s), 1090 (m), 815 (m), 710 (m, br), 750 cm^{-1} (m). Electronic spectrum [ethanol, λ_{max} (log ϵ)] 228 (4.24). ^1H NMR (Me_2SO-d_6) 7.6 (m, 4 H), 3.4 (br, s 1 H), 2.42 (s, 3 H). Mass spectrum [*m/e* (assignment, rel abundance)] 185 ($C_7H_7SO_2N_2H_2$, 0.8), 157 ($C_7H_7SO_2H_2^+$, 15), 156 ($C_7H_7SO_2H^+$, 44), 155 ($C_7H_7SO^+$, 20), 91 ($C_7H_7^+$, 100).

Reaction of Vinylene Carbonate and *p*-Toluenesulfonylhydrazine. A solution of 1.86 g (10 mmol) of *p*-toluenesulfonylhydrazine, 0.86 g (10 mmol) of vinylene carbonate, and 2 drops of concentrated sulfuric acid in 30 mL of 1:1 ethanol–chloroform was refluxed for 10 h. The reaction mixture was filtered and evaporated to give an oily residue which was extracted with petroleum ether. Evaporation of the petroleum ether yielded a solid which was recrystallized from acetonitrile to give 0.08 g of **2** (4%), identified by its infrared and mass spectra and melting point. This product was not isolated when the acid was omitted.

Melt Pyrolysis of *p*-Toluenesulfonylhydrazine. A 1.05-g sample of **1** was placed in a small flask which was evacuated and heated with an oil bath whose temperature was gradually raised to 140 °C. Heating was continued for 15 min after gas evolution ceased.

The material remaining in the flask was extracted with 5 mL of dichloromethane. Insoluble ammonium *p*-toluenesulfonate (**3**) was collected on a filter and recrystallized by slow evaporation of methanol–acetonitrile solution to give 0.06 g of thin, colorless plates, mp 330–333 °C (lit. 340,[13] 325–330 °C[14]). Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.44; H, 5.82; N, 7.40; S, 16.93. Found: C, 45.07; N, 5.87; N, 7.74; S, 17.20. IR (Nujol) 3125 (br, s), 1160 (br, s), 1030 (m), 1010 (m), 810 (s), 680 (s). The mass spectrum matched that of *p*-toluenesulfonic acid. Λ_M (CH_3NO_2, 8.8×10^{-4} M) 70.8 mol^{-1} ohm^{-1} cm^2.

The dichloromethane solution was chromatographed on a 12 × 1 in. silica gel column. Elution with dichloromethane afforded 0.41 g of di-*p*-tolyl disulfide dioxide (**4**) which was recrystallized from methylcyclohexane to give colorless needles: mp 72–73.5 °C (lit.[15] 76 °C); IR ($CHCl_3$) 3030 (w), 2980 (w), 1595 (m), 1490 (m), 1330 (s), 1305 (m), 1290 (w), 1140 (s), 1080 (m), 1015 (w), 810 (s), 650 (s), 580 (s), 525 (m), 510 cm^{-1} (m); electronic spectrum (C_2H_5OH) λ_{max} 234 (3.96), 212 (sh); (^1H) ^{13}C NMR (acetone-d_6) 145.5, 142.7, 141.3, 136.9, 130.8, 130.2, 128.1, 125.4, 21.5, 21.3 ppm; mass spectrum *m/e* 280 ($C_{14}H_{14}O_2{}^{32}S^{34}S^+$, 10), 279 ($^{13}C^{12}C_{13}H_{14}O_2S_2^+$, 17), 278 ($M^+$, 100), 155 ($C_7H_7SO_2^+$, 15), 139 ($C_7H_7SO^+$, 58), 123 ($C_7H_7S^+$, 18), 91 ($C_7H_7^+$, 26).

Continued elution of the column with acetone yielded 0.12 g of *p*-toluenesulfonamide which was identified by comparison of its infrared and mass spectra with those of an authentic sample.

Acknowledgments. The referees are thanked for numerous helpful suggestions.

Registry No.—**1**, 1576-35-8; **2**, 14062-05-6; **3**, 4124-42-9; **4**, 2943-42-2; *p*-toluenesulfonyl chloride, 98-59-9; vinylene carbonate, 872-36-6.

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A New and Simple Synthesis of Alkyl, Cycloalkyl, and Aralkyl Diselenides from Aliphatic and Aromatic Aldehydes. Aliphatic Ketones and Cyclo Ketones

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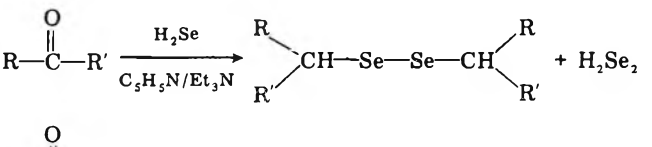
We recently described the preparation of symmetrical disulfides by the reaction of carbonyl compounds and H_2S.[1] The parallel formation of diselenides from ketones with H_2Se was reported by Margolis and Pittman,[2] but this reaction has apparently not had further application. Since diselenides are versatile intermediates for other organoselenium compounds we have extended this chemistry and have found that the reaction of H_2Se with aldehydes and ketones in the presence of triethylamine and pyridine provides a general method for preparing alkyl, cycloalkyl, and aralkyl diselenides.

The experiments showed (Table I) that the best contact time for obtaining diselenides from aldehydes and ketones and hydrogen selenide in the presence of triethylamine and pyridine at room temperature is 10 days.

Table I. Effects of Temperature and Time in Diselenide Formation

Compd	Time of passage of H_2Se and temp	Time of contact,, days	Respective diselenide yield, %
Benzaldehyde	1 h/room temp	2	12
Benzaldehyde	1 h/room temp	4	13
Benzaldehyde	1 h/room temp	6	60
Benzaldehyde	1 h/room temp	8	70
Benzaldehyde	1 h/room temp	10	76
Benzaldehyde	2 h/reflux	4 h	36
Benzaldehyde	2 h/reflux	1	50
Benzaldehyde	2 h/reflux	3	72
Cyclohexanone	1 h/room temp	2	
Cyclohexanone	1 h/room temp	5	
Cyclohexanone	1 h/room temp	8	29
Cyclohexanone	1 h/room temp	10	38
Cyclohexanone	2 h/reflux		
Cyclohexanone	2 h/reflux	3	34



R—C—R′ = aliphatic and aromatic aldehydes, aliphatic ketones, cyclo ketones

R = alkyl, aryl
R′ = H, alkyl

Previous preparations have involved the oxidation of selenoles,[3,4] or from other suitable compounds such as selenocyanates,[5] halides with sodium diselenide,[6-8] Grignard reagent with selenium bromide,[9,10] alkyl halides with $NaBH_4$ and Se,[11] and arylselenyl bromides with PPh_3.[12]

Of these methods, the best one for preparing diselenides is from selenols. In the first step of this procedure, selenols can be synthesized in a number of ways. Treatment of selenols with a mild oxidizing agent, such as air, provides diselenides. However, the present method is a simplified, one-step procedure, giving alkyl, cycloalkyl, and aralkyl diselenides in good yields.

The NMR spectrum of the diselenides shows a CH_2Se proton signal at δ 2.80–4.12 and a CHSe proton signal at δ 2.7–3.40.

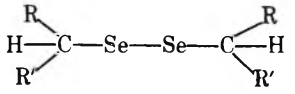
Experimental Section

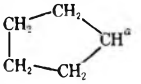
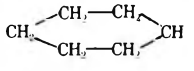
General. Proton magnetic resonance spectra were determined with a Varian T-60 spectrometer using tetramethylsilane as internal standard. Melting points were measured on a Kofler hot-bench apparatus. Elemental analyses were performed by CNRS (Service Central de Microanalyses, 2 rue Henry-Dunant, 94-Thiais, France).

All of the aliphatic and aromatic aldehydes, aliphatic ketones, and cyclo ketones were purchased from commercial sources.

General Procedure for Synthesis of Alkyl, Cycloalkyl, and Aralkyl Diselenides. Method A. Solid Diselenides. The following preparation of dibenzyl diselenide (Table II, expt 1) will serve as an example of the procedure used to prepare the solid diselenides listed in Table II. In this case, a solution of 10.6 g (0.1 mol) of benzaldehyde and 25 mL of dry pyridine and 10 mL of triethylamine in a 100-mL

Table II. Diselenides



No.	RR′CH	Mp, °C	Bp, °C	Yield, %	Registry no.
1	$C_6H_5CH_2$	92		76	1482-82-2
2	p-$ClC_6H_4CH_2$	76		85	56344-11-7
3	p-$CH_3OC_6H_4CH_2$	72		78	62212-22-0
4	p-$C_2H_5OC_6H_4CH_2$	78		68	62212-23-1
5	α-$C_{10}H_7CH_2$	102		72	53391-04-1
6	$CH_3(CH_2)_2$		92[10]	48	7361-89-9
7	$(CH_3)_2CH$		58[5]	25	37826-18-9
8	$CH_3(CH_2)_3$		108[8]	80	20333-40-8
9	$CH_3(CH_2)_4$[a]		126[10]	85	52056-07-2
10	$(C_2H_5)_2CH$[a]		100[12]	30	62212-24-2
11	$CH_3(CH_2)_5$		148[11]	70	52056-08-3
12	$(C_2H_5)_2CHCH_2$[a]		119[4]	28	62212-25-3
13			138[5]	43	62212-26-4
14			158[3]	38	56592-97-3

[a] New compound.

round-bottom flask was chilled in an ice bath. About 20 g (0.25 mol) of dry hydrogen selenide (hydrogen selenide was generated from aluminum selenide by addition of water and passed through the calcium chloride tube) was passed through the solution. In the course of time the elemental selenium precipitated at the bottom of the flask. After 10 days at room temperature, the elemental selenium was removed by filtration. The filtrate was poured into cold water and diselenide was collected by filtration, treated with dilute hydrochloric acid, and washed with water. Recrystallization from ethanol provided 1 (76%), mp 92 °C. The solid diselenides listed in Table II were recrystallized from absolute alcohol to afford analytically pure products.

Method B. Liquid Diselenides. The following synthesis of dipropyl diselenide (Table II, expt 6) will serve as general procedure for the preparation of liquid diselenides. Following the general procedure described above (method A) with the slight modification, a mixture of 5.8 g (0.1 mol) of propionaldehyde, 25 mL of anhydrous pyridine, and 10 mL of triethylamine in a 100-mL flask was chilled in an ice bath. About 20 g (0.25 mol) of dry hydrogen selenide was passed through the solution. After 10 days at room temperature, and elimination of elemental selenium as described in method A, the solution was poured into cold water and extracted with three 50-mL portions of diethyl ether. The extracts were combined, treated with dilute hydrochloric acid, and washed with water. The ether solution was dried over anhydrous sodium sulfate. Evaporation of the solvent left a liquid which on distillation gave 5.8 g (48%) of **6**, bp 92 °C (10 mm).

Registry No.—Benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1; 4-methoxybenzaldehyde, 123-11-5; 4-ethoxybenzaldehyde, 10031-82-0; 1-naphthalenecarboxaldehyde, 66-77-3; propanal, 123-38-6; 2-propanone, 67-64-1; butanal, 123-72-8; pentanal, 110-62-3; 3-pentanone, 96-22-0; hexanal, 66-25-1; 2-ethylbutanal, 97-96-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; hydrogen selenide, 7783-07-5.

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A Reinvestigation of Nitration in Aqueous Sulfuric Acid of Benzene and Halogenobenzenes

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The nitration of benzene in aqueous sulfuric acid is a matter of interest because its reaction mechanism appears to be affected by an encounter rate-determining step.[1,2] Evidence for this circumstance comes from the estimated rate coefficient at 68% H_2SO_4. The value appears to be close to the rate coefficient for encounter between two species, under the same conditions.[1,2] Also a limiting rate of nitration, reached with sufficiently reactive aromatics, has been regarded as an important source of information, in connection with the influence of encounter upon the benzene.[1,2]

Concerning the acidity dependence of the rate profile, two different slope values have been observed in the range 63–82% H_2SO_4 on the plot log $k_{2(obsd)}$ vs. $(H_R + \log a_w)$.[1,2] The behavior of the rate profile prompted us to extend previous kinetic data for benzene.[2,3] This was during the attempt to determine whether the observed deviation from linearity is significant evidence of the interference of different rate-determining steps upon the benzene. For comparative purposes, the nitration of some deactivated compounds, such as halogenobenzenes, has been reinvestigated.[3,4]

Table I. Second-Order Rate Coefficients for Nitration in Aqueous Sulfuric Acid at 25 °C

H_2SO_4, %[a]	$[HNO_3]$, mol/L	[AcOH], mol/L	Log $k_{2(obsd)}$, L mol^{-1} s^{-1}[c]
	Benzene[b]		
71.77	4.24×10^{-3}		0.24
70.97	3.72×10^{-3}		−0.328
70.97	3.26×10^{-3}		−0.328
69.87	3.47×10^{-3}		−0.775
69.87	3.76×10^{-3}		−0.787
69.87	3.98×10^{-3}		−0.779
69.87	4.15×10^{-3}		−0.791
69.87	4.39×10^{-3}	3.80×10^{-4}	−0.810
69.20	4.12×10^{-3}		−0.997
68.22	5.74×10^{-3}		−1.335
68.18	2.37×10^{-3}		−1.369
67.71	4.06×10^{-3}		−1.577
66.95	4.57×10^{-3}		−1.775
66.95	3.53×10^{-3}	1.69×10^{-3}	−1.793
66.78	2.37×10^{-2}		−1.849
66.08	4.25×10^{-3}		−2.096
66.04	2.37×10^{-2}		−2.173
65.41	1.02×10^{-2}		−2.364
64.79	3.33×10^{-3}		−2.587
64.68	1.69×10^{-2}		−2.534
64.68	1.69×10^{-2}	5.12×10^{-4}	−2.553
63.91	3.07×10^{-3}		−2.848
62.37	9.43×10^{-3}	6.01×10^{-4}	−3.422
	Fluorobenzene[b]		
69.91	1.08×10^{-2}		−1.613
69.43	4.27×10^{-2}	3.99×10^{-3}	−1.801
67.69	1.31×10^{-2}		−2.409
67.11	1.94×10^{-2}		−2.609
65.76	1.27×10^{-1}		−3.049
	Chlorobenzene[b]		
73.37	7.71×10^{-3}		−0.497
71.42	6.73×10^{-3}		−1.259
69.43	1.39×10^{-2}		−2.060
69.43	8.86×10^{-2}	3.52×10^{-3}	−2.064
67.11	8.93×10^{-2}		−2.902
65.76	1.099×10^{-1}		−3.378
	Bromobenzene[b]		
73.37	5.201×10^{-3}		−0.576
71.42	1.67×10^{-2}		−1.296
69.43	1.13×10^{-1}		−2.087
69.43	1.07×10^{-1}	3.99×10^{-3}	−2.105
67.11	7.66×10^{-2}		−2.981
65.76	1.62×10^{-1}		−3.567
	Iodobenzene[b]		
73.37	4.586×10^{-3}	1.998×10^{-3}	−0.097
71.21	1.691×10^{-3}	1.998×10^{-3}	−0.970
70.57	4.722×10^{-3}	1.998×10^{-3}	−1.150
67.65	1.173×10^{-1}	1.998×10^{-3}	−2.153
67.11	7.687×10^{-2}		−2.343
65.81	2.873×10^{-1}	1.998×10^{-3}	−2.698

[a] ±0.1%. [b] [Aromatic] = $10^{-4}/10^{-5}$ mol L^{-1}. [c] Estimated percentage of standard error of the mean ±2.5%.

Results and Discussion

Rate coefficients for the nitration of benzene and halogenobenzenes in the range 62–74% sulfuric acid are in Table I.

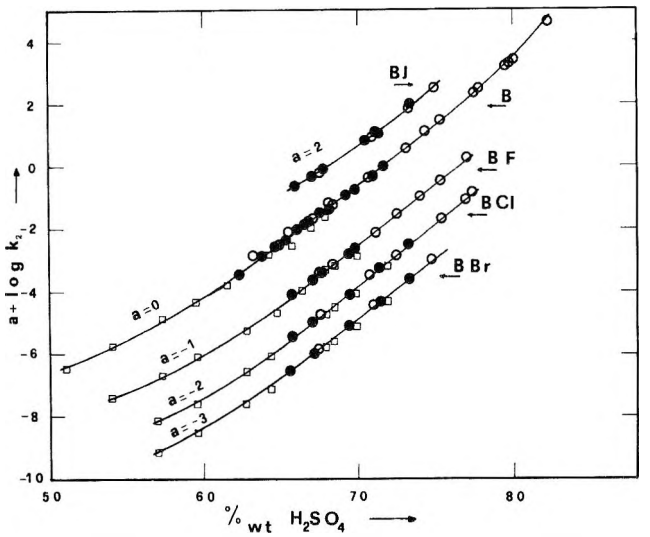

Figure 1. Plots of $[a + \log k_{2(obsd)}]$ vs. percentage of nitration at 25 °C in aqueous sulfuric acid: (B) benzene; (BF) fluorobenzene; (BCl) chlorobenzene; (BBr) bromobenzene; (BJ) iodobenzene (○, data of ref 2, 11; □, data of ref 8; ●, present work).

Because of the limited solubilities of aromatic compounds in aqueous acids, the influence of acetic acid added to acid solutions has been also investigated (Table I). Kinetic runs with and without AcOH, performed under conditions otherwise the same, show that addition of ca. 10^{-3} M AcOH increases appreciably the solubility of aromatic substrates, without affecting the rate values. Although this feature cannot be generalized, it assures, in this case, the satisfactory utilization of the results which come from the work of Deno,[3] obtained in the presence of a small amount of AcOH.

The kinetic data reported in this paper, combined with extant data of the literature, permit us to obtain the rate profiles given in Figure 1. It can be seen that the results of each data set show good agreement among them; the spread of experimental points is not greater than expected from experimental errors. The figure, then, provides evidence of the influence of medium acidity upon the nitration, when a wide range of acid concentration is investigated (51–82% H_2SO_4).

The significant feature observed on the plots log $k_{2(obsd)}$ vs. percentage acid concentration is the curvature of rate profiles of halogenobenzenes, compared to the known curvature of benzene.[1,2] The analysis of the plots of log $k_{2(obsd)}$ vs. $(H_R + \log a_w)$ gives the same results[5] (Figure 2) using either the H_R values of Cook et al.[6] or those of Deno.[7] It follows that the previous observed linearity of rate profiles is only apparent, arising from the shortness of the acidity range examined.

Concerning the halogenobenzenes, independent evidences[4,8] show that concentrations of reagents, nitration products, and isomeric compositions are not significantly affected by side reactions in the whole acidity range examined. Their curved lines then, do not appear a result of specific interactions or variations of mechanism, since the encounter rate should not affect these deactivated compounds.[4]

These reasons make it impossible to relate the curvature of the plots for benzene to some changeover of mechanism even if its influence were important. Such a behavior also suggests that the curved lines are a consequence of the specific criteria of analysis already discussed and usually applied to nitration. Evidence for this suggestion in sulfuric acid comes from the plots[9a] of log $k_{2(obsd)}$ vs. H_0 acidity function, since linear rate profiles are now observed for benzene and halogenobenzenes in the whole acidity range (51–82% H_2SO_4).[9b] The results of nitrations carried out in perchloric acid[10] also support the above conclusions.

In the range 59–68% $HClO_4$, isomeric compositions and relative reactivities of halogenobenzenes are as observed in sulfuric acid. It follows from this analysis that the rate profiles which have been examined are of little value for understanding mechanistic problems and appear in some cases not related to chemical behavior of compounds.

Experimental Section

Materials. Benzene and halogenobenzenes (R. P. Carlo Erba) were each distilled several times and their purity was checked by gas–liquid chromatography. The purified halogenobenzenes were stored in the dark. Nitric acid purified by vacuum distillation from concentrated sulfuric acid (1:2 v/v) was used and stored at −40 °C. Sulfuric acid was Analar grade and percentage composition of solutions was determined

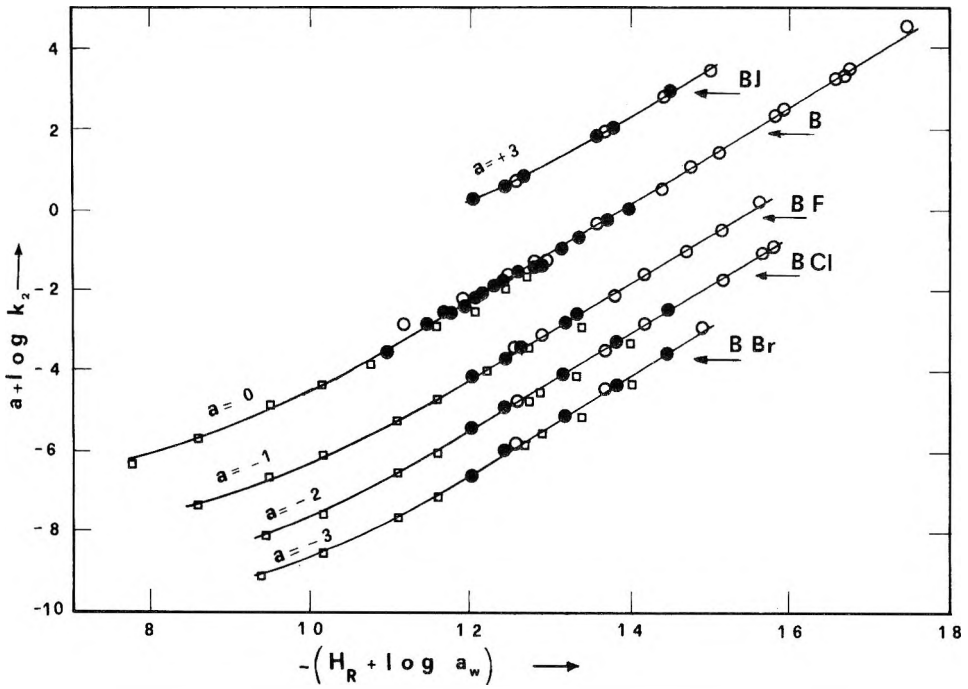

Figure 2. Plots of $[a + \log k_{2(obsd)}]$ vs. $(H_R + \log a_w)$ for nitration at 25 °C in aqueous sulfuric acid: (B) benzene; (BF) fluorobenzene; (BCl) chlorobenzene; (BBr) bromobenzene; (BJ) iodobenzene (○, data of ref 2, 11; □, data of ref 8; ●, present work; H_R values of ref 7).

by automatic potentiometric titrations of weighted samples against standard solutions of sodium hydroxide. Titrations were performed on an Amel 235 instrument, using a motorized buret (Model 232–233). Each percentage value is the average of at least ten titrations and the estimated error is ±0.1%. Two different normal solutions of HCl were used for the standardization of normal solutions of NaOH.

Kinetic Measurements. Separate solutions of aromatic compounds (with and without added AcOH) and nitric acid in the appropriate concentration of sulfuric acid were prepared and thermostated at 25 °C. Equal volumes of solutions of both reagents were rapidly mixed by syringes in a thermostated silica cell and the changes of absorbance with time, at selected wavelengths, were obtained on Perkin-Elmer EPS-3T and CGA PM5 spectrophotometers. Because of the limited solubilities of aromatic compounds in sulfuric acid, preliminary experiments were carried out using aromatic solutions in acid solutions kept for different times before use. The rates were independent of time. By using nitric acid concentrations at least ten times those of the substrates, good linear pseudo-first-order kinetic plots were obtained and $k_{2(obsd)}$ values were calculated from the stoichiometric concentration of nitric acid. Guggenheim's method was used in a few cases. Second-order rate constants for the nitration at 25 °C of the substrates are given in Table I.

Acknowledgments. We are grateful to Professor J. H. Ridd and Professor K. Schofield for helpful discussions. We thank the Consiglio Nazionale delle Ricerche (Roma) for financial support.

Registry No.—Benzene, 71-43-2; fluorobenzene, 462-06-6; chlorobenzene, 108-90-7; bromobenzene, 108-86-1; iodobenzene, 591-50-4; nitric acid, 7697-37-2; sulfuric acid, 7664-93-9.

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m-Nitrophenyl D-Glucose and D-Galactose Ethers via Alkoxide Displacement of a *m*-Nitro Group

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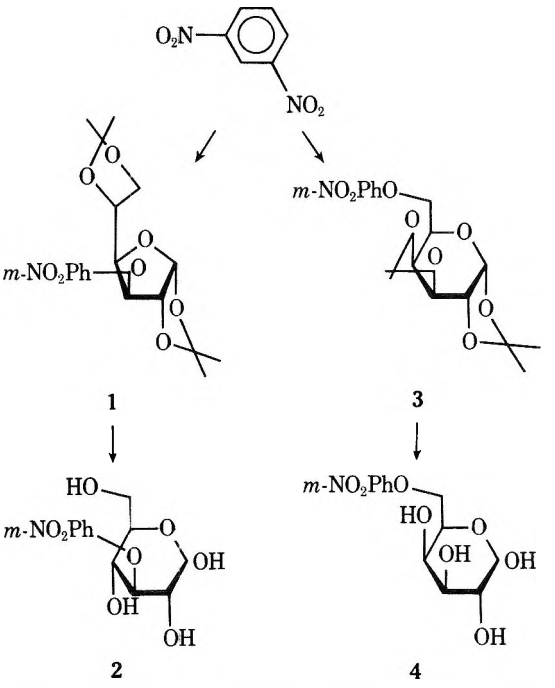
Our interest in the design and synthesis of carbohydrate derivatives[2a,b] as compounds with possible application as radiocontrast agents[3] brought our attention to the feasibility of *m*-nitrophenyl sugar ether synthesis. The unusual hydrolytic stability of benzyl sugar ethers,[4] e.g., relative to glucosides, suggests high relative stability for phenyl sugar ethers.

For design reasons, precursors to benzene based radiocontrast agents must have a meta orientation of substituents.[3] Yet only *p*-nitrophenyl[5] and 2,4-dinitrophenyl[6] sugar ethers were heretofore reported. However, a recent report of the synthesis of *m*-nitroanisole by methoxide displacement of a nitro group from *m*-dinitrobenzene[7] suggested the parallel reaction with a sugar alkoxide. We wish to report the synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*m*-nitrophenyl)-D-glucofuranose (**1**) and 1,2:3,4-di-*O*-iospropylidene-6-*O*-(*m*-nitrophenyl)-D-galactopyranose (**3**) by this route. The corresponding nonsubstituted compounds **2** and **4** were also prepared (Scheme I).

Scheme I



Since benzylation of carbohydrates using a strong base in dry, aprotic media (e.g., benzylbromide/DMF/NaH[8]) proceeds with isomeric integrity, and since the use of diisopropylidene sugars precludes any isomeric products based upon the position of phenylation, it was anticipated that *m*-nitro phenylation (*m*-dinitrobenzene/HMPA/NaH) would not involve significant amounts of isomerization. This contention was borne out by the relatively high yields of isomerically pure products **1** (82%) and **3** (62%). Both crude products **1** and **3**, after decolorization on alumina columns, were readily crystallizable from cyclohexane/petroleum ether to give sharp melting points, 119–121 and 109–111 °C, respectively. Removal of the isopropylidene groups from **1** and **3** (H_2O/*p*-dioxane/H_2SO_4) was accomplished in high yields as monitored by TLC, but isolated yields were 50 and 26%, respectively, suggesting anomeric mixtures.[9]

We anticipate that this work may engender interest in pharmacophysiological investigation of meta-substituted sugar ethers as relatively stable sugar derivatives, since product **2** exhibited no apparent hydrolysis[10] (monitored by TLC) at pH 7.4 after 48 h at 75 °C in a 1% aqueous solution. Compound **4** was not sufficiently H_2O soluble to test for hydrolytic stability.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus in open capillaries and are uncorrected. Infrared spectra (KBr) were recorded on a Beckman Acculab 4 instrument. NMR spectra were recorded on a Varian EM 360 instrument using tetramethylsilane as internal reference. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin layer chromatograms (TLC) were performed on silica gel 60F-254 (E. Merck, Darmstadt, Germany) precoated glass plates, developed with THF (93 mL)/C_6H_{12} (7 mL)/H_2O (5 mL), and visualized with UV and/or 40% aqueous H_2SO_4 at 110 °C. Column (30 mm o.d. × 35 cm) chromatography was accomplished on aluminum oxide, activated, basic, CAMAG (Ventron, Beverly, Mass.). Reagents were obtained from the following sources: 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose from Pfanstiehl Labo-

ratories, Inc., Waukegan, Ill.; 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose from Aldrich Chemical Co., Inc., Milwaukee, Wis.; *m*-dinitrobenzene from Fisher Scientific Co., Fair Lawn, N.J. Hexamethylphosphoramide (HMPA) was a product of Aldrich Chemical Co. and was stored before use over molecular sieves, 8–12 mesh, activated, type 4A.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(*m*-nitrophenyl)-D-Glucofuranose (1). Into a three-necked, 250-mL round-bottom flask equipped with N_2 inlet and outlet and magnetic bar stirring were charged HMPA (75 mL) and 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (28.6 g, 110 mmol). Next NaH (50% in oil), 5.5 g (115 mmol), was added over a 1-h period in 1.0–1.5-g portions. When the evolution of H_2 was nearly complete, *m*-dinitrobenzene (16.8 g, 100 mmol) was added at once. An exothermic reaction ensued but soon subsided and the reaction mixture was allowed to cool and stir at room temperature overnight. Next, the reaction mixture was slowly poured into 1.5 L of vigorously stirred water. Subsequently, most of the water layer was decanted and then the crude product collected by filtration. The solid was dissolved in CCl_4 (250 mL), then washed well with H_2O. The CCl_4 layer was evaporated to residue, then eluted from an alumina column with initially CCl_4 and finally $CHCl_3$. Those fractions resulting in a light yellow oil were crystallized by dissolution in cyclohexane, then addition of 30–60 °C petroleum ether (PE) with scratching. The light yellow solid was filtered, washed with PE, and dried in a forced air oven at 100 °C to obtain the title compound, **1**, 31.1 g (82%): mp 119–122 °C; α^{23}_D −38° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.3–1.6 [m, 12 H, $(CH_3)_2C$], 4.0–4.9 [m, 6 H, H-(2–6)], 5.97 (d, 1 H, H-1, $J_{1,2}$ = 4 Hz), 7.2–8.0 (m, 4 H, aromatic); IR 1520, 1370, 1340 cm^{-1} ($-NO_2$).

Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.89; H, 6.41; N, 3.44.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*m*-nitrophenyl)-D-galactopyranose (3). Using the same procedure as for **1**, HMPA (70 mL), 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (25.0 g, 96 mmol), NaH (50% in oil, 4.8 g, 100 mmol), and *m*-dinitrobenzene (14.5 g, 86 mmol) were combined to react, with stirring under N_2. The initial evolution of heat soon subsided and the reaction mixture was stirred for 44 h at room temperature before workup. The reaction mixture was partitioned between 1 L of H_2O and 300 mL of CCl_4. The CCl_4 layer was then washed well with H_2O before concentrating for elution from an alumina column with CCl_4 and then $CHCl_3$. Those fractions which gave a light yellow oil were crystallized from cyclohexane/PE at room temperature with scratching to obtain the title compound **3**, 20.3 g (62%): mp 109–111 °C; α^{23}_D −106° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.4–1.6 [m, 12 H, $(CH_3)_2C$], 4.2–4.9 [m, 6 H, H-(2–6)], 5.63 (d, 1 H, H-1, $J_{1,2}$ = 5 Hz), 7.3–8.0 (m, 4 H, aromatic); IR 1540, 1370, 1340 cm^{-1} ($-NO_2$).

Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 57.07; H, 6.14; N, 3.67.

3-*O*-(*m*-Nitrophenyl)-D-glucopyranose (2). The following ingredients were combined and heated at reflux overnight: *p*-dioxane (20 mL), H_2O (15 mL), concentrated H_2SO_4 (4 drops), compound **1** (7.6 g, 20 mmol). TLC showed the absence of protected sugar derivative **1**. The reaction mixture was evaporated to residue, dissolved in minimum hot H_2O, and cooled with stirring overnight to crystallize. The off-white solid was collected by filtration, then recrystallized from MeOH/Et_2O/PE. The nearly white solid was filtered, washed with PE, and dried in a forced air oven at 100 °C to obtain pure title compound **2**, 3.0 g (50%): mp 142–144 °C; α^{23}_D 40° (c 1.0, MeOH); ^{1}H NMR (Me_2SO) showed the absence of isopropylidene groups.

Anal. Calcd for $C_{12}H_{15}NO_8$: C, 47.91; H, 5.01; N, 4.64. Found: C, 48.37; H, 5.40; N, 4.67.

6-*O*-(*m*-Nitrophenyl)-D-galactopyranose (4). Using precisely the same procedure as for **2**, compound **3** (7.6 g, 20 mmol) was deprotected to give a crude product which was dissolved in boiling MeOH by the addition of minimum H_2O. The addition of Et_2O and cooling overnight at ice temperature gave nearly white, crystalline title compound **4**, 1.6 g (26%): mp 203–206 °C; α^{23}_D 33° [c 1.0, THF/H_2O (1:1 v/v)]; ^{1}H NMR (Me_2SO) showed the absence of isopropylidene groups.

Anal. Calcd for $C_{12}H_{15}NO_8$: C, 47.91; H, 5.01; N, 4.64. Found: C, 47.91; H, 5.17; N, 4.57.

Acknowledgment. This work was supported by USPHS Grant GM 22911.

Registry No.—**1**, 62263-57-4; **2**, 62263-58-5; **3**, 62263-59-6; **4**, 62263-60-9; 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose, 582-52-5; *m*-dinitrobenzene, 99-65-0; 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose, 4064-06-6.

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Synthesis of 2*H*-Pyrido[1,2-*b*]-*as*-triazines Using Azirines Generated by Modified Neber Reactions

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In earlier studies[1,2] we have shown that pyridinium *N*-imines reacted smoothly with 2-phenylazirine to afford the corresponding 3-phenyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives and that this reaction has a high synthetic value in virtue of the wide variability of pyridinium *N*-imines. So far as isolated azirines are used, however, further extension of this reaction must be limited to a large extent by the problems in an azirine synthesis. For example, Hassner's procedure[3,4] is one of the most convenient methods for the preparation of azirine derivatives at present, but not applicable to the cases in which appropriate olefins are not available. On the other hand, if azirines without isolation can be used in the reactions with pyridinium *N*-imines, many routes to azirine may serve for the preparation of dihydropyridotriazines. Among these types of azirine formations, Neber[5,6] and related reactions[7–9] are especially important because of the ready availability of the ketonic precursors. This paper deals with the reactions of pyridinium *N*-imines with various azirines generated in situ by modified Neber reactions and the extended syntheses of the corresponding 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazines.

We examined at first the possibility for the preparation of dihydropyridotriazines by the reactions involving oxime *O*-tosylates as an azirine precursor, but found that these reactions have only a low synthetic value for lack of reproducibility and for the instability and the low yields of oxime *O*-tosylates. These problems were, however, solved by replacing oxime *O*-tosylates with dimethylhydrazone methiodides.

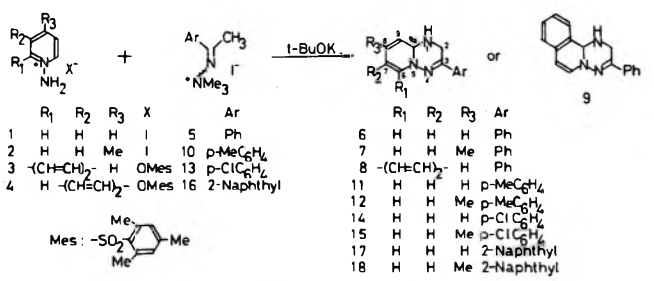
The reactions of 1-aminopyridinium salts or quinolinium *N*-imine dimer with dimethylhydrazone methiodides of several aryl alkyl ketones were carried out in tetrahydrofuran in the presence of potassium *tert*-butoxide with stirring at room temperature or on heating at the reflux temperature. For example, the reactions of the salts **1–4** with acetophenone, *p*-methyl-, *p*-chloroacetophenone, and 2-acetonaphthone dimethylhydrazone methiodides, **5**, **10**, **13**, and **16**, proceeded smoothly at room temperature to give the corresponding 3-aryldihydropyridotriazines **6–9**, **11**, **12**, **14**, **15**, **17**, and **18** in

Table I. ^{1}H NMR Spectral Data of 2*H*-Pyridotriazines

Registry no.	Compd	C_6	C_7	C_8	C_9	C_{9a}	NH	C_2H	C_2R'	Ar	
62154-45-4	11	6.60 (d)	4.71 (br t)	5.97 (m)	5.22 (br d)	5.41 (br s)	1.97 (br s)	3.76 (d)	4.08 (d)	7.08[a] (d)	7.46[a,b] (d)
				$J_{6,7}$ = 7.5, $J_{7,8}$ = 7.5, $J_{8,9}$ = 11.0, $J_{2,2}$ = 17.5 Hz							
62154-46-5	12	6.61 (d)	4.64 (dd)	1.77 (d)	5.00 (br s)	5.33 (br s)	1.90 (br s)	3.73 (d)	4.06 (d)	7.13[a] (d)	7.50[a,c] (d)
				$J_{6,7}$ = 7.5, $J_{7,9}$ = 1.5, $J_{8,9}$ = 1.0, $J_{2,2}$ = 18.0 Hz							
62154-47-6	14	6.56 (d)	4.73 (br t)	5.95 (m)	5.20 (br d)	5.37 (br s)	2.35 (br s)	3.67 (d)	4.01 (d)	7.23[a] (d)	7.47[a] (d)
				$J_{6,7}$ = 7.5, $J_{7,8}$ = 7.5, $J_{8,9}$ = 10.0, $J_{2,2}$ = 17.5 Hz							
62154-48-7	15	6.56 (d)	4.66 (dd)	1.75 (d)	5.00 (br s)	5.32 (br s)	2.00 (br s)	3.73 (d)	4.06 (d)	7.27[a] (d)	7.52[a] (d)
				$J_{6,7}$ = 7.5, $J_{7,9}$ = 1.5, $J_{8,9}$ = 0.5, $J_{2,2}$ = 17.5 Hz							
62154-49-8	17	6.70 (d)	4.80 (br t)	6.02 (m)	5.30 (br d)	5.52 (br s)	2.30 (br s)	3.92 1)d)	4.24 (d)	7.3–8.1 (m)	
				$J_{6,7}$ = 7.5, $J_{7,8}$ = 7.5, $J_{8,9}$ = 10.0, $J_{2,2}$ = 18.5 Hz							
62154-50-1	18	6.66 (d)	4.68 (dd)	1.79 (d)	5.05 (br s)	5.41 (br s)	1.95 (br s)	3.91 (d)	4.22 (d)	7.3–8.1 (m)	
				$J_{6,7}$ = 7.5, $J_{7,9}$ = 1.5, $J_{8,9}$ = 1.0, $J_{2,2}$ = 18.5 Hz							
62154-51-2	20	6.60 (dd)	4.71 (br t)	5.95 (m)	5.17 (br d)	5.42 (br s)	2.10 (br s)	3.87 (q)	1.25 (d)	7.1–7.6 (m)	
				$J_{6,7}$ = 7.5, $J_{7,8}$ = 7.5, $J_{8,9}$ = 10.0, $J_{6,8}$ = 0.5, $J_{2,2}$ = 7.5 Hz							
62154-52-3	22	6.63 (d)	4.66 (dd)	1.76 (d)	5.00 (br s)	5.40 (br s)	1.98 (br s)	3.96 (q)	1.31 (d)	7.2–7.7 (m)	
				$J_{6,7}$ = 7.5, $J_{7,9}$ = 1.5, $J_{8,9}$ = 1.0, $J_{2,2}$ = 7.5 Hz							
62154-53-4	24	6.63 (d)	4.75 (br t)	5.98 (m)	5.23 (br d)	5.42 (br s)	2.07 (br s)	3.60 (br d)	1.75[d] (m)	7.1–7.6 (m)	
				$J_{6,7}$ = 7.5, $J_{7,8}$ = 7.5, $J_{8,9}$ = 10.0, $J_{2,2}$ = 8.5 Hz							
62154-54-5	25	6.60 (d)	4.65 (dd)	1.75 (s)	5.00 (br s)	5.32 (br s)	1.93 (br s)	3.61 (br d)	1.75[e] (m)	7.1–7.6 (m)	
				$J_{6,7}$ = 7.5, $J_{7,9}$ = 1.5, $J_{2,2}$ = 8.5 Hz							
62154-55-6	27	6.74 (d)	4.78 (br t)	5.97 (m)	5.10 (br d)	5.40 (br s)	2.30 (br s)	4.91 (s)	*f*	7.1–7.7 (m)	
				$J_{6,7}$ = 7.5, $J_{7,8}$ = 7.5, $J_{8,9}$ = 10.0 Hz							
62154-56-7	28	6.71 (d)	4.67 (dd)	1.73 (d)	4.87 (br s)	5.30 (br s)	2.20 (br s)	4.90 (s)	*f*	7.1–7.7 (m)	
				$J_{6,7}$ = 7.5, $J_{7,9}$ = 2.0, $J_{8,9}$ = 1.0 Hz							
62154-57-8	21	7.23 (d)	5.68 (dt)	6.66 (br t)	6.40 (dd)			4.81 (q)	1.26 (d)	7.2–7.4 (m)	7.7–7.9 (m)
				$J_{6,7}$ = 7.5, $J_{7,8}$ = 7.5, $J_{8,9}$ = 10.0, $J_{7,9}$ = 1.5, $J_{6,8}$ = 1.5 Hz							

[a] Appeared as A_2B_2 patterns (J = 7.5–8.0 Hz). [b] Plus δ 2.31 (3 H, s). [c] Plus δ 2.33 (3 H, s). [d] Plus δ 0.98 (3 H, t, J = 7.5 Hz). [e] Plus δ 0.98 (3 H, t, J = 7.5 Hz). [f] Overlapped with signals at δ 7.1–7.7.

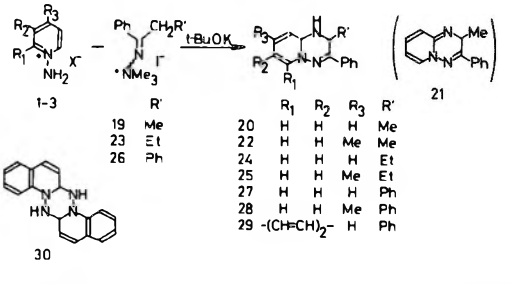
Scheme I



	R_1	R_2	R_3	X		Ar
1	H	H	H	I	5	Ph
2	H	H	Me	I	10	p-MeC_6H_4
3	-(CH=CH)-		H	OMes	13	p-ClC_6H_4
4	H	-(CH=CH)-		OMes	16	2-Naphthyl

	R_1	R_2	R_3	Ar
6	H	H	H	Ph
7	H	H	Me	Ph
8	-(CH=CH)-		H	Ph
11	H	H	H	p-MeC_6H_4
12	H	H	Me	p-MeC_6H_4
14	H	H	H	p-ClC_6H_4
15	H	H	Me	p-ClC_6H_4
17	H	H	H	2-Naphthyl
18	H	H	Me	2-Naphthyl

Scheme II



	R'
19	Me
23	Et
26	Ph

	R_1	R_2	R_3	R'
20	H	H	H	Me
22	H	H	Me	Me
24	H	H	H	Et
25	H	H	Me	Et
27	H	H	H	Ph
28	H	H	Me	Ph
29	-(CH=CH)-		H	Ph

10–53% yields (Scheme I). On the other hand, reactions with dimethylhydrazone methiodides of propiophenone, *n*-butyrophenone, and benzyl phenyl ketone, **19, 23,** and **26,** in which disubstituted azirines must be formed, did not take place at room temperature, but, by heating the reaction mixtures, the corresponding 2,3-disubstituted dihydropyridotriazines **20, 22, 24, 25,** and **27–29** were obtained in 12–57% yields (Scheme II). The compound **29** was also formed in 38% yield by the reaction of quinolinium *N*-imine dimer **30** with the methiodide **26.** Strange to say, dehydro compound **21** was obtained in 30% yield for only one time during our several runs of the reaction of the salt **1** with the methiodide **19,** but our attempts to reproduce this phenomenon were unsuccessful.

The structures of products **6–9, 11, 12, 14, 15, 17, 18, 20, 22, 24, 25,** and **27–29** were determined by physical and spectral means and by comparisons with those of known dihydropyridotriazines synthesized earlier by us.[1,2] In particular, the large similarity of the chemical shifts (Table I) of the products **11, 12, 14, 15, 17, 18, 20, 22, 24, 25, 27,** and **28** with those of known dihydropyridotriazines supported strongly our proposed structures. All new compounds gave satisfactory analyses, and all melting points and IR and NMR spectral patterns of compounds **6–9** and **29** were in good accord with those of pyridotriazines prepared by the reactions of pyridinium *N*-imines with 2-phenylazirine or 2,3-diphenylazirine.[2]

The NMR spectrum of compound **21** exhibited signals at

Table II. Results and Some Properties of Pyridotriazines

Compd[a,d]	Reactant: N-Imine[e]	Reactant: Methiodide[f]	Yield, %	Mp, °C	IR (KBr), cm^{-1}: NH	IR (KBr), cm^{-1}: C=C or C=N
6[b]	1	5	29	98–100		
7[b]	2	5	23	114–117		
8[b]	3	5	53	127–129		
9[b]	4	5	10	158–160		
11	1	10	29	124–126	3272	1635
12	2	10	25	131–133	3200	1653
14	1	13	38	116–118	3258	1636
15	2	13	23	130–132	3222	1652
17	1	16	26	168–170	3208	1633
18	2	16	31	142–143	3216	1655
20	1	19	35	65–68	3225	1637
21	1	19	30	Oil		1644[c]
22	2	19	42	79–81	3278	1661
24	1	23	57	68–70	3278	1637
25	2	23	57	105–107	3268	1656
27	1	26	15	132–134	3255	1637
28	2	26	12	113–115	3273	1655
29[b]	3	26	24	184–186		
29[b]	30	26	38	184–186		

[a] **11.** Anal. Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.34; H, 6.90; N, 18.66. **12.** Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.09; H, 7.25; N, 17.63. **14.** Calcd for $C_{13}H_{12}N_3Cl$: C, 63.54; H, 4.92; N, 17.10. Found: C, 63.32; H, 4.91; N, 17.24. **15.** Calcd for $C_{14}H_{14}N_3Cl$: C, 64.73; H, 5.43; N, 16.18. Found: C, 64.76; H, 5.41; N, 16.16. **17.** Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.32; H, 5.78; N, 15.86. **18.** Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.56; H, 6.31; N, 15.14. **20.** Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.45; H, 6.87; N, 18.38. **21** (its picrate, mp 178–181 °C). Calcd for $C_{20}H_{16}N_6O_7$: C, 53.10; H, 3.57; N, 18.58. Found: C, 53.08; H, 3.60; N, 18.67. **22.** Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.01; H, 7.19; N, 17.40. **24.** Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.01; H, 7.19; N, 17.41. **25.** Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.87; H, 7.62; N, 16.54. **27.** Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.13; H, 6.03; N, 14.46. **28.** Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.43; H, 6.25; N, 13.80. [b] See ref 2. [c] Neat. [d] Registry no.: **6,** 54855-55-9; **7,** 54855-56-0; **8,** 59065-86-0; **9,** 59247-65-3; **29,** 59247-66-4. [e] Registry no.: **1,** 6295-87-0; **2,** 7583-92-8; **3,** 39996-55-9; **4,** 39996-57-1; **30,** 7184-52-3. [f] Registry no.: **5,** 33785-82-9; **10,** 33785-84-1; **13,** 33777-73-0; **16,** 33777-77-4; **19,** 19679-61-9; **23,** 33777-79-6; **26,** 33777-82-1.

δ 1.26 (3 H, d, J = 7.5 Hz, C_2CH_3), 4.81 (1 H, q, J = 7.5 Hz, C_2 H), 5.68 (1 H, dt, J = 7.5, 7.5, and 1.5 Hz, C_7 H), 6.40 (1 H, dd, J = 10.0 and 1.5 Hz, C_9 H), 6.66 (1 H, bt, J = 10.0 and 7.5 Hz, C_8 H), 7.23 (1 H, dd, J = 7.5 and 1.0 Hz, C_6 H), 7.2–7.4 (3 H, m, meta, meta′, and para protons of C_3 phenyl), and 7.7–7.9 (2 H, m, ortho and ortho′ protons of C_3 phenyl). Compared with the dihydro isomer **20,** the largely shifted signals to lower region and the disappearances of both a 9a and an amino proton signal were observed in the NMR spectrum of compound **21,** which corresponds clearly to the change from 1,9a-dihydro-2*H*-pyridotriazine to its dehydro 2*H* isomer as seen in our earlier work.[10] This structural assignment was also supported by the dehydrogenation of compound **20,** in which 2*H*-pyridotriazine **21** was obtained in 15% yield.

$$\mathbf{20} \xrightarrow[\text{in benzene}]{\text{palladium on carbon (5\%)}} \mathbf{21}$$

This reaction, though yields are generally lower than those of the reactions using isolated 2-phenylazirine, has a high utility because the possibility of its extension from stable to fleeting or nonisolable azirines is realized.

Experimental Section[11]

Materials. 1-Aminopyridinium salts **1–4** were prepared by Gösl's[12] and Tamura's methods[13] and quinolinium *N*-imine dimer **30** was obtained by alkaline treatment of salt **3.**[14] Dimethylhydrazone methiodides **5, 10, 13, 16, 19, 23,** and **26** were prepared by the reactions of acetophenone, *p*-methyl-, *p*-chloroacetophenone, 2-acenaphthone, propio-, *n*-butyrophenone, and benzyl phenyl ketone with *N,N*-dimethylhydrazine, followed by the quaternizations of the resulting dimethylhydrazones with methyl iodide.[9]

Preparations of 2*H*-Pyridotriazine Derivatives. Method A. An equimolar mixture (2 mmol) of 1-aminopyridinium salt and dimethylhydrazone methiodide was treated with potassium *tert*-butoxide (4 mmol) in tetrahydrofuran (50 mL) at room temperature for 1 day and then the reaction mixture was filtered to remove the insoluble substances. The filtrate was concentrated under reduced pressure and the residual oil was separated by column chromatography (alumina) using *n*-hexane at first and then ether as an eluent. Recrystallizations of crude products from *n*-hexane or ether–*n*-hexane gave pale yellow to yellow needles of 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazines **6–9, 11, 12, 14, 15, 17,** and **18.**

Method B. A similar reaction mixture was allowed to react in tetrahydrofuran at the reflux temperature for 10–20 min in the reactions of salts **1** and **2** with methiodides **19, 23,** and **26,** or for 60 min in that of salt **3** with methiodides **26.** Usual workup gave the corresponding dihydropyridotriazines **20, 22, 24, 25,** and **27–29.** Dehydro compound **21** was also obtained in 30% yield for only one time during our several runs of the reaction of salt **1** with methiodide **19.** When the reactions of salts **1** and **2** with methiodides **19, 23,** and **26** were carried out for a prolonged reflux time (50–60 min), decreased yields of dihydropyridotriazines **20, 22, 24, 25, 27,** and **28** were observed.

These results and some properties of these pyridotriazine derivatives are summarized in Table II.

Reaction of Quinolinium *N*-Imine Dimer with Methiodide 26. A mixture of quinolinium *N*-imine dimer **30** (1 mmol) and methiodide **26** (2 mmol) was heated under reflux in tetrahydrofuran (50 mL) for 60 min in the presence of potassium *tert*-butoxide (2 mmol). Similar separation of the reaction mixture gave dihydropyridotriazine **29** in 38% yield.

Dehydrogenation of Dihydropyridotriazine 20. A benzene solution (50 mL) of dihydropyridotriazine **20** (170 mg) was stirred with palladium on carbon (5%, 1.0 g) at room temperature until the material disappeared (by TLC). The resulting mixture was then filtered and the filtrate was concentrated under reduced pressure. Usual separation of the residual oil gave 2-methyl-3-phenyl-2*H*-pyrido[1,2-*b*]-*as*-triazine (**21,** 25 mg, 15%) as a yellow oil. The IR spectrum and the melting point (its picrate, 179–181 °C) of this product were in good accord with those of compound **21** obtained above.

Registry No.—**21** picrate, 62154-58-9.

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Andalusol, a New Diterpenoid from a *Sideritis arborescens* Salzm. Subspecie. Chemical and X-Ray Structure Determination[1]

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Continuing our studies[2] on diterpenoids from a subspecie of *Sideritis arborescens* Salzm. (family Labiatae) we have now isolated a new compound, andalusol (**1**, $C_{20}H_{34}O_3$), the UV spectrum of which showed characteristic absorption (λ_{max} 224 nm, ϵ 11 000) for a monosubstituted conjugated diene grouping.[3] Treatment of compound **1** with acetic anhydride in pyridine solution gave the diacetate **2** plus a minor triacetyl derivative (**3**), thus establishing the hydroxylic nature of the three oxygen atoms of the molecule of andalusol. The ^{1}H NMR spectrum of **3** showed signals for an exocyclic methylene (δ 4.98, 2 H, broad singlet) and a vinyl group (δ_X 6.34, 1 H, quartet, and δ_A, δ_B 5.00–5.54, 2 H, multiplet), responsible for the UV diene absorption.

Hydroxylation of the diacetate **2** with osmium tetroxide gave a product which without further characterization was treated with HIO_4 to yield the lactone **4**.

With the preceding information a single-crystal x-ray determination of the structure of **4** was undertaken in order to establish the structure and relative stereochemistry of andalusol. A computer-generated drawing of the final x-ray model is shown in Figure 1. This model shows that the hydroxyl groups in andalusol are at C-6 (eq), C-8 (eq), and C-18 on a labdane skeleton. The lactone ring presents approximately an envelope conformation, being C-8, C-11, and C-9 at −0.12, 0.08, and 0.70 Å, respectively, out of the plane defined by C-12, C-13, O-25, and O-26. This envelope conformation is related to the special geometry displayed by the planar group: C-11–C-12 = 1.50, C-12–C-13 = 1.49, C-13–O-26 = 1.19, C-13–O-25 = 1.33, O-25–C-8 = 1.48 Å, C-11–C-12–C-13 = 119.8, C-12–C-13–O-26 = 121.7, C-12–C-13–O-25 = 119.7, O-25–C-13–O-26 = 118.6, C-13–O-25–C-8 = 122.2°. Both acetyl groups are coplanar with the carbon atoms at which they are bonded (C-6, C-18), the carbonyl oxygen atoms being at the cis positions. Electronic repulsion between all three methyl groups causes a bending effect on the main plane of the molecule. Distances between these groups follow: C-19–C-20 = 3.33 and C-17–C-20 = 3.24 Å. (For most details on x-ray structure determination see Experimental Section.)

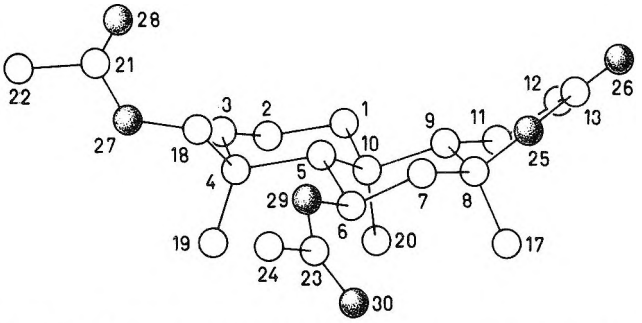
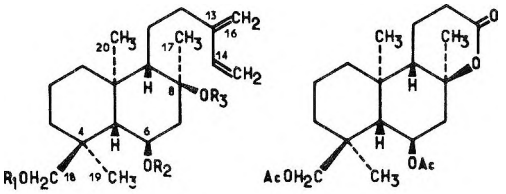


Figure 1. Computer-generated perspective drawing of *ent*-6 α,18-diacetoxy-14,15,16-trinorlabdan-13,8α-olide (**4**).

The absolute stereochemistry of the diterpenoid was established as follows. Treatment of compound **1** with benzoyl chloride in pyridine solution under controlled conditions yielded the monobenzoate **5**. Horeau's method[4] of partial resolution applied to product **5** afforded (+)-α-phenylbutyric acid, defining as 6*R* the absolute configuration of this center. On the other hand, application of Brewster's "benzoate rule"[5] to compounds **5** and **6** confirmed the above assignation.

Therefore andalusol is *ent*-13(16),14-labdadiene-6α,8α,18-triol (**1**).



1, $R_1 = R_2 = R_3 = H$
2, $R_1 = R_2 = Ac$; $R_3 = H$
3, $R_1 = R_2 = R_3 = Ac$
5, $R_1 = COPh$; $R_2 = R_3 = H$
6, $R_1 = R_2 = COPh$; $R_3 = H$

4

Experimental Section

All melting points were determined in a Kofler apparatus and are uncorrected. The optical rotations were measured with a Perkin-Elmer 141 polarimeter with 1-dm cells; the UV spectra were recorded on a Perkin-Elmer 402 spectrophotometer and the IR spectra on a Perkin-Elmer 257 spectrometer. The ^{1}H NMR spectra were obtained on a 60-MHz Perkin-Elmer R-12 or a 100-MHz Varian XL-100 apparatus with Me_4Si as an internal standard. The mass spectra were determined on an Hitachi Perkin-Elmer RMU 6MG apparatus. Elemental analyses were carried out in this laboratory with the help of an automatic analyzer.

Isolation of Andalusol (1). Dried and finely powdered *S. arborescens* Salzm. subspecie plants (5 kg), collected near Barbate (Cádiz), were extracted with light petroleum (16 L) in a Soxhlet apparatus during 120 h. The extract was concentrated under vacuum to 2 L and repeatedly extracted with 90% aqueous methanol (6 × 200 mL). The methanolic extracts were concentrated to 0.5 L, diluted with water (3 L), and extracted with chloroform (6 × 200 mL). The chloroform extracts were dried, filtered, and concentrated under vacuum to leave a residue (52 g) which was chromatographed on an Al_2O_3 (1.5 kg) (grade III) column with C_6H_6–EtOAc (19:1) as eluent, yielding the following compounds in order of elution: siderol[6] (320 mg), barbatol[2] (136 mg), and andalusol **1** (7.3 g) [mp 167–170 °C (acetone–*n*-hexane); $[\alpha]^{20}_D$ −38.2° (c 0.69, EtOH); UV (EtOH) λ_{max} 224 nm (ϵ 11 000); IR (KBr) 3270, 3200, 3090, 3020, 1640, 1600, 1047, 920, 895 cm^{-1}; mass spectrum M$^+$ *m/e* 322]. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.17; H, 10.51.

Acetylation of 1. Compounds 2 and 3. Acetic anhydride (5 mL) was added to a solution of **1** (300 mg) in pyridine (2.5 mL) and the mixture placed for 24 h at room temperature, poured into ice–water, and extracted with chloroform. Vacuum distillation of the solvent left

a residue (308 mg) which was separated by PLC on SiO_2 plates (C_6H_6–EtOAc, 9:1, as eluent) into two components, **2** (most polar, 270 mg) and 3 (35 mg).

Compound **2** is a syrup: IR (film) 3550, 3100, 1735, 1600, 1250, 940, 895 cm^{-1}; NMR)100 MHz, $CDCl_3$) δ 6.34 (1 H, q, J_{XA} = 18, J_{XB} = 10 Hz, H-14), 5.36–4.88 (3 H, m, H-6 and H-15 protons), 4.99 (2 H, s, H-16), 3.86 (2 H, AB system, J = 11 Hz, H-18), 2.06 and 2.01 (3 H each, s, two –OAc), 1.26 (3 H, s, H-17), 0.92 and 0.85 (3 H each, s, H-20 and H-19 protons, respectively); mass spectrum M^+ m/e 406.

Compound **3**: mp 118–120 °C (aqueous EtOH); $[\alpha]^{20}_D$ −31° (c 0.18, $CHCl_3$); IR (KBr) no –OH absorption, 3100, 1745, 1600, 1255, 920, 900 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 6.34 (1 H, q, J_{XA} = 18, J_{XB} = 10 Hz, H-14), 5.54–4.90 (3 H, m, H-6 and H-15 protons), 4.99 (2 H, s, H-16), 3.83 (2 H, AB system, J = 11 Hz, H-18), 2.13, 2.07, and 2.00 (3 H each, s, three –OAc), 1.58 (3 H, s, H-17), 0.96 and 0.85 (3 H each, s, H-20 and H-19 protons, respectively); mass spectrum $[M - 60]^+$ m/e 388. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.73; H, 8.89.

Lactone 4. The diacetate **2** (250 mg) was treated with an excess of osmium tetroxide in Et_2O–dioxane (1:1) solution yielding quantitatively a product which without further characterization was treated with HIO_4 in aqueous ethanol solution affording 210 mg of **4**: mp 145–147 °C (aqueous EtOH); $[\alpha]^{20}_D$ −88.7° (c 0.40, $CHCl_3$); IR (KBr) 1740, 1720, 1235 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 5.07 (1 H, sextet, $J_{aa'} = J_{aa''}$ = 11, $J_{ae'}$ = 4 Hz, H-6), 3.86 (2 H, AB system, J = 11 Hz, H-18), 2.60 (2 H, m, H-12), 2.26 (1 H, q, J_{gem} = 12, $J_{ea'}$ = 4 Hz, equatorial H-7), 2.06 and 2.03 (3 H each, s, two –OAc), 1.49 (3 H, s, H-17), 0.98 and 0.87 (3 H each, s, H-20 and H-19 protons, respectively); mass spectrum $[M - 60]^+$ m/e 320. Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.42; H, 8.57.

X-Ray Structure Determination of 4. $C_{21}H_{32}O_6$ (**4**) crystallizes in the space group $P2_1$ with two molecules in a cell of dimensions a = 10.790 (1), b = 10.055 (1), c = 9.458 (1) Å, and β = 93.95 (1)°. The molecular weight is 380 g mol^{-1} and the calculated density is 1.23 g cm^{-3}. The intensity of 3144 independent reflections with $\theta \leq 30°$ were measured on a computer-controlled diffractometer using graphite-monochromated Mo Kα radiation (0.7107 Å). No crystal decomposition was observed during the data collection. After correction for Lorentz and polarization effects, 1707 reflections were considered observed with the criterion $I > 2\sigma(I)$. The structure was solved by using the multisolution tangent formula.[7] It was necessary to take into account the amplitude error[8] to obtain a substantial fragment of the molecule among several E-map solutions. The rest of the molecule was found on a difference map after a "hard" least-squares correction ($\sin\theta/\lambda < 0.4$) of the first fragment. The hydrogen atoms, found on a difference map, were included in the last weighted anisotropic least-squares refinements (isotropic for H atoms). Final unweighted and weighted disagreement indices are R = 0.051 and Rw = 0.066, respectively.[9]

Monobenzoate 5. Benzoyl chloride (200 mg) was added to a solution of **1** (300 mg) in dry pyridine (5 mL) and the mixture kept for 2 h at 0 °C, poured into water, and extracted with chloroform. Vacuum distillation of the solvent left a residue from which the compound **5** (280 mg) was chromatographically isolated [PLC on SiO_2, C_6H_6–EtOAc (9:1)]: mp 139–143 °C (aqueous EtOH); $[\alpha]^{20}_D$ −16.6° (c 0.58, $CHCl_3$); IR (KBr) 3540, 3500, 3300, 3100, 3080, 1700, 1600, 1285, 915, 890, 715 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 8.40–7.30 (5 H, m, phenyl protons), 4.20 (2 H, AB system, J = 11 Hz, H-18), 3.85 (1 H, m, H-6). Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 75.90; H, 8.89.

Application of Horeau's Method[4] to 5. A mixture of (±)-α-phenylbutyric anhydride (0.37 mmol) and **5** (36 mg) in pyridine solution (2 mL) was kept at room temperature during 20 h: α_1 = −0.106, α_2 = −0.201; $\alpha_1 - (1.1\alpha_2)$ = +0.115. Configuration: 6R.

Dibenzoate 6. Reaction of a pyridine solution of compound **1** with a large excess of benzoyl chloride for 24 h at room temperature yielded **6**: mp 62–65 °C (EtOH); $[\alpha]^{20}_D$ −13.8° (c 0.53, $CHCl_3$); IR (KBr) 3520, 3100, 3080, 1720, 1600, 1275, 940, 890, 710 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 8.40–7.20 (10 H, m, phenyl protons), 4.20 (2 H, s, H-18), no signal at 4.00–3.00. Anal. Calcd for $C_{34}H_{42}O_5$: C, 76.95; H, 7.98. Found: C, 77.01; H, 7.94.

Application of the "Benzoate Rule":[5] **6**, $[M]_D$ −73.6° **5**, $[M]_D$ −70.7°; Δ $[M]_D$ = −2.9. Absolute stereochemistry: 6R.

Acknowledgments. The authors thank Dr. J. Borja, Botany Department, Faculty of Pharmacy, Madrid, for the collection and botanical classification of the plant material, and Professor S. García-Blanco for the facilities given for the use of the automatic diffractometer. We also thank the Centro de Proceso de Datos del Ministerio de Educación y Ciencia for the use of the 1108 UNIVAC computer.

Registry No.—**1**, 62279-93-0; **2**, 62264-72-6; **3**, 62264-73-7; **4**, 62264-74-8; **5**, 62264-75-9; **6**, 62264-76-0; benzoyl chloride, 98-88-4.

Supplementary Material Available. A list of atomic parameters, bond distances, and angles (3 pages). Ordering information is given on any current masthead page.

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Structure, Chemistry, and Absolute Configuration of 1(*S*)-Bromo-4(*R*)-hydroxy-(−)-selin-7-ene from a Marine Red Alga *Laurencia* Sp.

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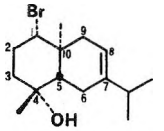
As part of a program aimed at assessing the diversity of halogen-based terpene synthesis in the red seaweed *Laurencia* (Rhodomelaceae), we have investigated the metabolites from a number of unrecorded species from this genus indigenous to the Gulf of California.[1-3] One collection of an apparently unrecorded *Laurencia*[4] has now yielded a bromine-containing derivative of the selinane type (**1**), which is a previously unknown ring system from this source.

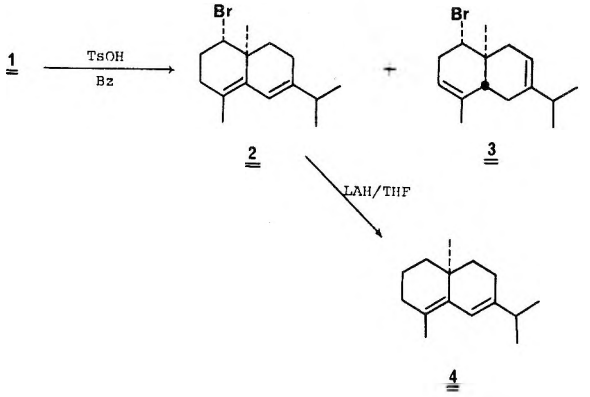


1

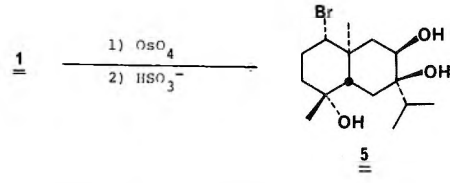
1(*S*)-Bromo-4(*R*)-hydroxy-(−)-selin-7-ene (**1**), an oil, $[\alpha]^{22}_D$ +52.6° (c 4.62, $CHCl_3$), was obtained in high yield (10% extract) from silica gel chromatography of the chloroform–methanol extract of the fresh alga. High-resolution mass spectral analysis of **1** established a molecular formula of $C_{15}H_{25}OBr$ and illustrated a facile loss of water. Intense infrared absorption at 3450 cm^{-1} further confirmed that **1** was an alcohol. The lack of acetylation upon treatment with acetic anhydride in pyridine (25 °C), the presence of a quaternary carbon resonance at 70.4 ppm in the ^{13}C NMR (relative to Me_4Si = 0), and a singlet at δ 1.16 in the ^1H NMR spectrum indicated the hydroxyl to be tertiary and located at a methyl-bearing carbon. The ^{13}C NMR spectrum of **1** further indicated a secondary bromine-containing carbon (doublet at 68.5 ppm) and a single trisubstituted olefin (singlet at 142.0 and doublet at 116.4 ppm) to be present in the molecule, which indicated that **1** is bicyclic. The ^1H NMR spectrum gave considerable insight into the structure of **1**. A symmetrical one-proton heptet at δ 2.16 and a six-proton doublet at δ 1.0 indicated that **1** contained an isopropyl group. Also, a complex signal at δ 2.43, appearing as a double quartet (actually a dddd

with J = 13, 13, 13, 4 Hz), was assignable to the axial methylene proton at C-2 based upon analogous bands rigorously defined for iriediol,[2] oppositol,[5] and bromosphaerol.[6] This ring proton suffers deshielding, presumably from both the adjacent equatorial bromine at C-1 and the axial hydroxyl at C-4. This proton appears to be recognizable in rigid *cis*-1,4-cyclohexane bromohydrin systems and moves to usually obscured high field when either bromine or hydroxyl are eliminated.

Consideration of gross spectral characteristics allowed the preliminary conclusion that this metabolite possessed the selinane ring system; however, unambiguous assignments could not be made based upon spectral analysis. Treatment of **1** with *p*-toluenesulfonic acid in benzene gave the isomeric bromodienes **2** and **3** in good yield. Diene **2** was isolated by thick layer chromatography and was converted by $LiAlH_4$ dehalogenation to the diene **4** which had spectral characteristics (NMR, IR, UV, and $[\alpha]_D$) identical with those published for (−)-(δ)-selinene.[7] These conversions allowed an unequivocal assignment of **1** to the selinane group and also defined the absolute stereochemistry at the angular methyl carbon, C-10, as α.

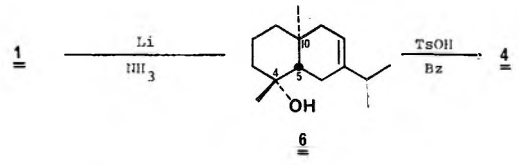


To fix the position of the double bond in **1**, the C-7, C-8 cis diol was prepared by treatment with OsO_4 in diethyl ether. The NMR spectrum of **5** clearly shows the existence of the C-8



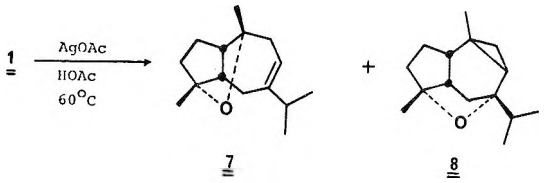
alcohol methine proton at δ 4.02, appearing as a double doublet, J = 12, 4 Hz. These data indicate an axial proton coupled to an adjacent methylene pair. These criteria can be met only by an equatorial hydroxyl specifically at C-8, proving that **1** contains a Δ^7 olefin rather than Δ^6.

Lithium in ammonia reduction of **1** gave the debromo alcohol **6**, which was spectrally identical but of opposite rotation, $[\alpha]_D$ +57.1°, with the corresponding compound, $[\alpha]_D$ −62.1 ± 3°, derived from oplodiol.[8] Hence the chiral centers at C-4, -5, and -10 have the same relative configuration as in oplodiol, but are of opposite absolute configuration. To confirm these conclusions, **6** was also converted to (−)-δ-selinene (**4**) by

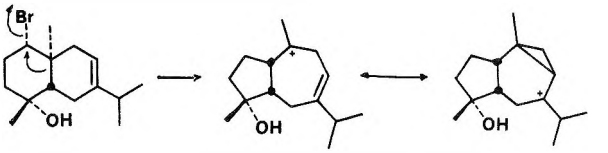


treatment with *p*-toluenesulfonic acid in benzene. These data indicate that **1** contains the trans ring juncture as drawn. NMR evidence to fix the stereochemistry at C-5 can also be obtained from the triol **5**. In this compound, the C-5 proton is resolved at δ 1.93 as a doublet of doublets with J = 12, 5 Hz. These coupling constants and multiplicities confirm that the C-5 proton is axial and is flanked by a methylene pair.

The remaining stereochemistry of **1**, not rigorously defined by the chemistry outlined above, is at the bromine-bearing carbon, C-1. The axial coupling constants for the methine proton at C-1 (dd, J = 12, 4 Hz) and the analogy to similar *Laurencia* metabolites allow a reasonable assignment of the bromine to an equatorial position. In further support of this assignment and also of the gross structure of **1** are the products obtained from the reaction of **1** with AgOAc in HOAc at 60 °C for 2 h. Under these conditions a high yield of two rearranged ethers, **7** and **8**, is obtained.



The structures of **7** and **8** are assigned based upon interpretation of ^{13}C and ^1H NMR, MS, and infrared data, as well as the conversion of **7** to guaiazulene with Pd/C.[9] A bridged ether analogous to **7** has recently been described which is formed from treatment of the perhydroazulene lactone eremanthine with NBS in aqueous dioxane.[10] Molecular models reveal that ether formation between the carbon atoms indicated in **7** requires a cis ring fusion. The formation of these products is consistent with a concerted elimination of an equatorial bromine, migration of the anti bridgehead bond, and subsequent trapping of the carbonium ion by a proximate hydroxyl before and after participation of the Δ^7 olefinic bond.



Natural compounds containing the bicyclic cyclohexane-1,4-bromohydrin system, now exemplified by compound **1**, the irieols,[2] oppositol,[5] and bromosphaerol,[6] appear to be common in some red seaweeds.[11] Based upon the biomimetic studies of Sutherland et al.,[12] the bromohydrin system in **1** is probably produced by a bromonium ion induced transannular cyclization of a germacrene intermediate, and the related structures from other medium-size ring intermediates.

Experimental Section

NMR spectra were recorded on Varian HR-220 or EM-360 spectrometers; chemical shifts are expressed as δ values in parts per million relative to tetramethylsilane = 0. Infrared spectra were obtained on a Perkin-Elmer 137 sodium chloride spectrophotometer and UV spectra were recorded on a Perkin-Elmer 124 double beam spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 1410 polarimeter.

Mass spectra were obtained on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were measured by Dr. Kai Fang, Department of Chemistry, UCLA.

Isolation of 1(*S*)-Bromo-4(*R*)-hydroxy-(−)-selin-7-ene (1). Crude extract (20.0 g) obtained from the chloroform–methanol (1:1) extraction of the fresh alga (~2.5 kg) was applied to a column containing 250 g of silica gel (Grace Chemical). This was eluted with a solvent gradient system from petroleum ether to benzene to ethyl ether. The majority of **1** was found in five fractions which were eluted with 100% benzene. These fractions were combined (2 g) and rechromatographed to give on benzene–petroleum ether (9:1) elution a pure sample of **1** (1.25 g): high-resolution mass spectrum M^+ *m/e* 300.1085 for $C_{15}H_{25}O^{79}Br$ (calcd, 300.1089); ^{13}C NMR (20 MHz,

benzene-d_6, relative to Me_4Si) 142.0 (s), 116.4 (d), 70.4 (s), 68.5 (d), 48.1 (d), 43.1 (t), 42.5 (t), 38.6 (s), 34.9 (d), 30.5 (t), 29.6 (q), 24.6 (t), 21.9 (q), 21.3 (q), and 14.2 ppm (q); ^{1}H NMR (220 MHz, $CDCl_3$, relative to Me_4Si) δ 5.32 (1 H, bd, J = 6 Hz), 4.00 (1 H, dd, J = 12, 4 Hz), 2.43 (1 H, dddd, J = 13, 13, 13, 4 Hz), 2.16 (1 H, heptet, J = 7 Hz), 1.64 (1 H, m), 1.16 (3 H, s), 1.09 (3 H, s), and 1.00 ppm (6 H, d, J = 7 Hz).

Dehydration of 1. Compound **1** (70 mg) was dissolved in benzene (10 mL) and a catalytic amount of *p*-toluenesulfonic acid monohydrate was added (~5 mg). The mixture was refluxed for 30 min, after which time diethyl ether (75 mL) was added and the organic phase neutralized with $NaHCO_3$. The ether phase was separated and dried with anhydrous $MgSO_4$, and the ether was removed in vacuo to yield a light, mobile oil (50 mg). Silica gel TLC showed the production of two relatively nonpolar products, one UV active at R_f 0.7 (petroleum ether) and one non-UV-active at R_f 0.8. Preparative layer chromatography (petroleum ether) gave pure samples of **2** and **3** in a 3:2 ratio. For compound **2**: NMR (60 MHz, CCl_4) δ 6.00 (1 H, s), 4.03 (1 H, dd, J = 12, 5 Hz), 1.67 (3 H, s), 1.05 (6 H, d, J = 7 Hz), 1.03 (3 H, s); UV λ_{max} (CH_2Cl_2) 240, 247, 257 nm; mass spectrum m/e 282/284 (M^+), $C_{15}H_{23}Br$. For compound **3**: NMR (220 MHz, CCl_4) δ 5.39 (1 H, bs), 5.27 (1 H, bs), 4.23 (1 H, dd, J = 11, 5 Hz), 1.66 (3 H, s), 1.02 (6 H, d, J = 8 Hz), 0.86 (3 H, s); mass spectrum M^+ m/e 282/284 (1:1) for $C_{15}H_{23}Br$.

(−)-δ-Selinene (4) from 2. A solution of 20 mg of **2** in 5 mL of anhydrous THF containing excess $LiAlH_4$ was refluxed in a nitrogen atmosphere for 4 h. Standard hydrolytic workup gave 5 mg of (−)-δ-selinene (**4**): NMR (60 MHz, CCl_4) δ 6.02 (1 H, s), 1.67 (3 H, s), 1.05 (6 H, d, J = 7 Hz), 0.92 (3 H, s); UV λ_{max} (CH_3OH) 237, 244, 255 nm; IR (film) ν 2900, 1645, 1620, 1385, 1375, 1295, 1270, 1215, 1175, 1065, 1030, 995, 955, 876, and 805 cm^{-1}; $[\alpha]^{22}_D$ −188° (*c* 0.08, $CHCl_3$); mass spectrum M^+ m/e 204 for $C_{15}H_{24}$.

1(*S*)-Bromo-4(*R*),7(*R*),8(*R*)-trihydroxy-(−)-selinane (5). A solution of 57 mg of **1** and 50 mg of OsO_4 in 5 mL of anhydrous ether containing 5 drops of pyridine was stirred for 48 h at 25 °C. The reaction was quenched by adding 15 mL of pyridine followed by 20 mL of a 5% solution of $NaHSO_3$. After stirring for 2 h, the reaction mixture was extracted with ether. The ether solution was washed five times with 5% HCl solution and once with saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Filtration and evaporation gave a single product (50 mg), an oil (**5**): NMR (220 MHz, $CDCl_3$) δ 4.02 (1 H, dd, J = 12, 4 Hz), 3.92 (1 H, dd, J = 12, 5 Hz), 2.39 (1 H, dddd, J = 13, 13, 13, 4 Hz), 1.93 (1 H, dd, J = 12, 5 Hz), 1.23 (3 H, s), 1.18 (3 H, s), 1.04 (3 H, d, J = 8 Hz), 0.99 (3 H, d, J = 8 Hz); mass spectrum m/e 291/293 (M^+ − 43), 273/275 M^+ − (43 + H_2O), 255/257 M^+ − (43 + $2H_2O$), 237 M^+ − (43 + Br).

4(*R*)-Hydroxy-(−)-selin-7-ene (6). To a solution of excess Li in liquid ammonia (dry ice–acetone bath) and diethyl ether, 30 mg of **1** in 2 mL of ether was added with stirring. After 2 h, NH_4Cl was added slowly and the reaction mixture was allowed to warm to room temperature. When the ammonia had evaporated, the reaction mixture was washed with 5% HCl followed by saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated to give, after thick layer chromatography, 20 mg of **6** as a colorless oil: $[\alpha]^{21}_D$ +57.1° (*c* 1.37, dioxane); NMR (220 MHz, $CDCl_3$) δ 5.32 (1 H, bs), 2.22 (1 H, hep, J = 7 Hz), 1.17 (3 H, s), 1.02 (6 H, d, J = 7 Hz), 0.96 (3 H, s); IR (film) ν 3350, 2900, 1625, 1140 cm^{-1}; mass spectrum m/e 204 (M^+ − H_2O) $C_{15}H_{24}$, 189 (M^+ − H_2O − CH_3) $C_{14}H_{21}$.

Conversion of 6 to (−)-δ-Selinene. A solution of 20 mg of **6** in 5 mL of benzene containing a catalytic amount of *p*-toluenesulfonic acid monohydrate was refluxed for 1 h. Workup yielded two olefins as judged by NMR, one of which was **4**. The mixture was dissolved in 2 mL of acetic acid containing 2 drops of H_2SO_4 and stirred for 30 min. Workup gave 15 mg of a single olefin, **4**, which was identical with that produced from **2**.

Silver Acetate Rearrangement of 1. A solution of 100 mg of **1** in glacial acetic acid was added slowly with stirring to a suspension of excess AgOAc in glacial acetic acid. The reaction mixture was stirred at 60 °C for 2 h and filtered, and the filtrate was washed with ether. The ether–acetic acid was washed with water, followed by $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to give a yellow oil. TLC of the reaction mixture indicated two major products which were less polar than **1**. TLC (ether–petroleum ether, 1:1 v/v), R_f 0.4 (**7**) and R_f 0.5 (**8**). Thick layer chromatography gave pure samples of **7** (30 mg) and **8** (20 mg). For compound **7**: ^{13}C NMR (20 MHz, $CDCl_3$) 143.0 (s), 117.7 (d), 86.1 (s), 80.0 (s), 50.3 (d), 49.1 (d), 42.8, 37.2, 36.3, 27.5, 27.1, 24.2, 21.9, 21.7, 17.2 ppm; ^{1}H NMR (220 MHz, $CDCl_3$) δ 5.23 (1 H, dd, J = 5, 5 Hz), 1.26 (3 H, s), 1.23 (3 H, s), 1.02 (6 H, d, J = 8 Hz); mass spectrum m/e 220 (M^+) $C_{15}H_{24}O$. For compound **8**: ^{13}C NMR (20 MHz, $CDCl_3$) 92.0, 86.1, 53.0, 42.1, 35.7, 31.2, 30.7, 31.0, 27.3, 27.1, 26.2, 25.0, 24.5, 24.2, 17.4 ppm; ^{1}H NMR (220 MHz, $CDCl_3$) δ 1.20 (3 H, s), 0.95 (3 H, s), 0.94 (3 H, d, J = 7 Hz), 0.92 (3 H, d, J = 7 Hz), 0.45 (1 H, bs), 0.43 (1 H, dd, J = 7, 3 Hz); mass spectrum m/e 220 (M^+) $C_{15}H_{24}O$.

Guaiazulene. A solution of 20 mg of **7** in xylene was refluxed in the presence of 10% Pd on charcoal for 48 h. Filtration and evaporation left a blue residue. TLC (petroleum ether) purification of this mixture gave approximately 1 mg of a blue hydrocarbon which was determined to be identical with guaiazulene by TLC and visible spectra.

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Registry No.—**1**, 62264-66-8; **2**, 62264-67-9; **3**, 62264-68-0; **4**, 28624-23-9; **5**, 62288-63-5; **6**, 62264-69-1; **7**, 62264-70-4; **8**, 62264-71-5.

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Carbonyl Homologation with α-Substitution. A New Synthesis of 4,4-Disubstituted 2-Cyclopentenones

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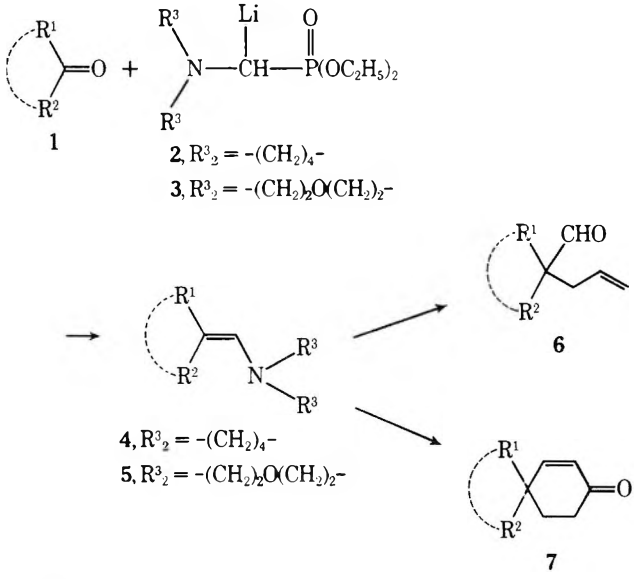
One of the most difficult tasks in organic synthesis is the creation of a quaternary carbon center. Since ketones are among the most accessible compounds in organic chemistry, a procedure for the geminal alkylation at a carbonyl carbon with functionally dissimilar substituents would be very attractive. We have recently described a new approach to this problem which involved the conversion of ketone carbonyl groups into either the pyrrolidine enamines **4** or the morpholine enamines **5** of the homologous aldehydes, and the necessary reagents for effecting these conversions were diethyl lithiopyrrolidinomethylphosphonate (**2**) or diethyl lithiomorpholinomethylphosphonate (**3**), respectively.[1,2] The inherent advantage of these procedures for carbonyl homologation is that the enamines **4** and **5**, which are useful functional derivatives of the corresponding aldehydes, are obtained

directly. Furthermore, these enamines may be employed in subsequent reactions with electrophilic reagents without purification. For example, treatment of the pyrrolidine enamines **4** with allyl bromide gave the α-allyl dialkylaldehydes **6** in good overall yields,[1] and the reaction of the morpholine enamines **5** with methyl vinyl ketone, followed by aldol cyclodehydration, gave the 4,4-disubstituted 2-cyclohexenones **7** in moderate overall yields.[2] This latter procedure constitutes a facile method for the spiroannelation of six-membered rings.



We have, in the course of our synthetic investigations of the acorane sesquiterpenes, developed a need for a method which allows the spiroannelation of a functionalized five-membered ring. Although the geminal allyl–formyl moiety of **6** could be modified for the eventual conversion to a substituted cyclopentane, a number of steps would obviously be required. Consequently, a procedure for the geminal alkylation with substituents which could be directly converted to the cyclopentane ring system would have obvious advantages. We now wish to report a useful modification of our original procedures whereby ketones may be readily converted to 4,4-disubstituted 2-cyclopentenones. The application of this reaction sequence to cyclic ketones constitutes a new method for the spiroannelation of five-membered rings which are suitably functionalized for further synthetic transformations.

The base-catalyzed cyclization of 1,4-dicarbonyl compounds is a useful method for the construction of cyclopentenones.[3] We envisioned, therefore, that the reaction of the enamines **4** with an electrophilic, 2-oxopropyl synthon would afford the requisite γ-ketoaldehydes which could then be cyclized to the desired 2-cyclopentenones. Since the reaction of the enamines of α,α-disubstituted aldehydes with α-bromo ketones is plagued by side reactions such as N-alkylation and polymerization,[4-6] we decided that the introduction of the necessary 2-oxopropyl group would be better achieved by the alkylation of the enamines **4** with 2,3-dibromopropene.[7] Although the latent γ-ketoaldehyde could be unmasked by acid-catalyzed hydrolysis, we anticipated that the 2-(2-bromo-2-propenyl) aldehydes **8** would undergo *direct* acid-catalyzed cyclization to give, after aqueous workup, the desired 4,4-disubstituted 2-cyclopentenones **9**.[8]

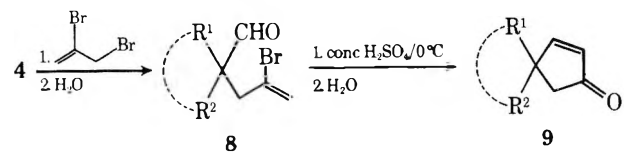


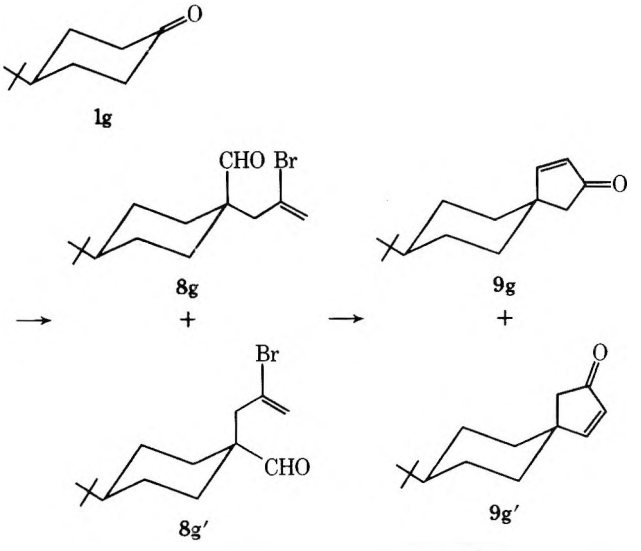
Table I

Starting ketone	% yield of **8**[a]	% yield of **9**[a]
3-Heptanone (**1a**)	40	72
4-Heptanone (**1b**)	43	85
4-Methyl-2-pentanone (**1c**)	33	77
Cyclohexanone (**1d**)	24	78
2-Methylcyclohexanone (**1e**)	32[b]	63[c]
4-Methylcyclohexanone (**1f**)	29[d]	75[e]
4-*tert*-Butylcyclohexanone (**1g**)	28[f]	54[g]

[a] Yields are of isolated product but are not optimized. [b] Obtained as a 83:17 mixture of diastereomers. [c] Obtained as a 82:18 mixture of diastereomers. [d] Obtained as a 83:17 mixture of diastereomers. [e] Obtained as a 78:22 mixture of diastereomers. [f] Obtained as a 82:18 mixture of diastereomers. [g] Obtained as a 78:22 mixture of diastereomers.

In the event, a solution of the enamines **4**, generated in situ from the ketones **1**, and an excess of 2,3-dibromopropene in tetrahydrofuran were heated at reflux for 48 h, and the resultant mixture was hydrolyzed with water at room temperature to give the 2-(2-bromo-2-propenyl) aldehydes **8**. When the aldehydes **8** were treated with concentrated sulfuric acid at 0 °C for 2 h, the 2-cyclopentenones **9** were obtained in acceptable overall yields (Table I).

Preliminary results have also indicated that this new synthetic procedure for geminal alkylation and spiroannelation proceeds with a reasonable degree of stereoselectivity. For example, 4-*tert*-butylcyclohexanone (**1g**) was smoothly converted to a diastereomeric mixture of the 2-(2-bromo-2-propenyl) aldehydes **8g** and **8g′** in about a 4:1 ratio. The assignment of the relative stereochemistry at the newly created chiral center is based upon the observed chemical shifts of the formyl proton (**8g**, δ_{CHO} = 9.67 and **8g′**, δ_{CHO} = 9.63). It is well known in similar systems that the axial formyl proton is deshielded relative to the equatorial one by steric crowding.[9] Furthermore, the methylene of the axial 2-bromo-2-propenyl group in **8g′** (δ_{CH_2} 2.90) is deshielded relative to the methylene of the equatorial 2-bromo-2-propenyl group in the major diastereomer **8g** (δ_{CH_2} 2.64). Sulfuric acid promoted cyclization gave the spiro[4.5]decenones **9g** and **9g′** in approximately a 4:1 ratio. The relative stereochemistry in **9g** and **9g′** may again



be easily confirmed from an analysis of the ^1H and ^{13}C NMR spectra of the mixture. The β-vinyl proton of the major isomer **9g** (δ_{CH} = 8.00, J = 5.5 Hz) is deshielded relative to the β-vinyl proton of the minor isomer **9g′** (δ_{CH} 7.42, J = 5.5 Hz). Owing

to steric compression, the β-vinyl carbon of **9g** (δ 169.5) appears upfield from the β-vinyl carbon of **9g'** (δ 174.3).[10]

We are presently investigating the scope and limitations of this new synthetic sequence as well as its application to the total synthesis of spirosesquiterpene natural products.

Experimental Section

General Procedure for the Conversion of Ketones 1a–g into 2-(2-Bromo-2-propenyl) Aldehydes 8a–g. To a well-stirred solution of diethyl pyrrolidinomethylphosphonate (4.0 g, 18.0 mmol) in anhydrous THF (60 mL) under dry nitrogen at −78 °C was slowly added *n*-butyllithium (7.5 mL of a 2.40 N solution in hexane, 18.0 mmol), and the stirring was continued at −78 °C for 1 h. A solution of the appropriate ketone **1a–g** (15 mmol) in anhydrous THF (5 mL) was then added, and the stirring was continued at −78 °C for 4 h and at room temperature overnight to give a solution of the enamine **4a–g**. 2,3-Dibromopropene (15.0 g, 75 mmol) was added, and the mixture was heated at reflux for 48 h. Upon cooling to room temperature, water (30 mL) was added, and the resulting mixture was stirred vigorously at room temperature for 4 h. The reaction mixture was diluted with saturated brine (50 mL), the layers were separated, and the aqueous layer was extracted with ether (3 × 75 mL). The combined organic layers were washed with 1 N HCl (2 × 50 mL) and saturated sodium bicarbonate (2 × 50 mL). After drying ($MgSO_4$), the excess solvent was removed under reduced pressure to give the crude 2-(2-bromo-2-propenyl) aldehyde **8a–g** which was distilled and used in the next step without further purification.

4-Bromo-2-ethyl-2-*n*-butyl-4-pentenal (8a): 40%, bp 85–87 °C (1.0 mm); IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.60 (s, 1 H), 5.60 (m, 2 H), 2.78 (s, 2 H), 0.65–1.95 (m, 14 H); mass spectrum *m/e* 248, 246, 167 (base), 85, 57, 55, 41. 2,4-Dinitrophenylhydrazone: mp 124.5–126 °C (from ethanol).

Anal. Calcd for $C_{17}H_{23}O_4N_4Br$: C, 47.78; H, 5.42. Found: C, 48.10; H, 5.17.

4-Bromo-2,2-di-*n*-propyl-4-pentenal (8b). 43%, bp 110–112 °C (3.3 mm); IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.57 (s, 1 H), 5.60 (m, 2 H), 2.82 (m, 2 H), 0.70–2.00 (m, 14 H); mass spectrum *m/e* 248, 246, 167 (base). 95, 55, 43, 41.

4-Bromo-2-methyl-2-isobutyl-4-pentenal (8c): 33%, bp 140–142 °C (4.2 mm); IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.73 (s, 1 H), 5.63 (m, 2 H). 2.78 (d, 2 H, *J* = 6 Hz), 0.63–2.00 (m, 12 H); mass spectrum *m/e* 234, 232, 153 (base), 112, 97, 83, 69, 43, 41.

1-(2-Bromo-2-propenyl)cyclohexanecarboxaldehyde (8d): 24%, bp 145–147 °C (6.0 mm); IR ($CHCl_3$) 1725 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.65 (s, 1 H), 5.58 (m, 2 H), 2.73 (s, 2 H), 1.20–2.10 (m, 10 H); mass spectrum *m/e* 232, 230, 151 (base), 110, 81, 79, 41.

1-(2-Bromo-2-propenyl)-2-methylcyclohexanecarboxaldehyde (8e): 32% as an 83:17 mixture of diastereomers, bp 146–148 °C (6.0 mm); IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) (major diastereomer) δ 9.83 (s, 0.83 H), 5.62 (m, 2 H), 2.90 (d, 2 H, *J* = 10 Hz), 0.78–2.15 (m, 12 H), (minor diastereomer) δ 9.70 (s, 0.17 H); mass spectrum *m/e* 246, 244, 165 (base), 124, 95, 81, 79, 67, 55, 41.

1-(2-Bromo-2-propenyl)-4-methylcyclohexanecarboxaldehyde (8f): 29% as an 83:17 mixture of diastereomers, bp 148–150 °C (6.0 mm); IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) (major diastereomer) δ 9.75 (s, 0.83 H), 5.55 (m, 2 H), 2.65 (s, 1.66 H), 0.75–2.40 (m, 12 H), (minor diastereomer) δ 9.73 (s, 0.17 H), 2.90 (s, 0.34 H); mass spectrum *m/e* 246, 244, 165 (base), 124, 95, 81, 79, 67, 55, 41.

1-(2-Bromo-2-propenyl)-4-*tert*-butylcyclohexanecarboxaldehyde (8g): 28% as an 82:18 mixture of diastereomer, bp 137–140 °C (1.5 mm); IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) (major diastereomer) δ 9.67 (s, 0.82 H), 5.53 (m, 2 H), 2.64 (s, 1.64 H), 0.72–2.36 (m, 18 H), (minor diastereomer) δ 9.63 (s, 0.18 H), 2.90 (s, 0.36 H); mass spectrum *m/e* 288, 286, 207 (base), 166, 81, 79, 67, 57, 41. 2,4-Dinitrophenylhydrazone: mp 168–170 °C (from ethanol).

Anal. Calcd for $C_{20}H_{27}O_4N_4Br$: C, 51.39; H, 5.82. Found: C, 51.26; H, 5.52.

General Procedure for the Cyclization of 2-(2-Bromo-2-propenyl) Aldehydes 8a–g to 4,4-Disubstituted 2-Cyclopentenones 9a–g. While a rapid stream of dry nitrogen was bubbled through concentrated sulfuric acid (4 mL) cooled to 0 °C, the 2-(2-bromo-2-propenyl) aldehyde (**8a–g** 1.0 g) was added dropwise. After completion of the addition, the dark mixture was stirred under dry nitrogen at 0 °C for 2 h, whereupon it was poured slowly onto crushed ice. The aqueous mixture was extracted with methylene chloride (3 × 100 mL), and the combined extracts were washed with saturated sodium bicarbonate (2 × 50 mL) and then dried (Na_2SO_4). Evaporation of the excess solvents under reduced pressure afforded the crude 4,4-disubstituted 2-cyclopentenone **9a–g** which was purified by vacuum distillation.

4-*n*-Butyl-4-ethyl-2-cyclopentenone (9a): 72%, bp 77–80 °C (0.7 mm); IR ($CHCl_3$) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.45 (d, 1 H, *J* = 5.5 Hz), 6.05 (d, 1 H, *J* = 5.5 Hz), 2.16 (s, 2 H), 0.66–1.85 (m, 14 H); mass spectrum *m/e* 166, 110 (base), 109, 96, 95, 81. Exact mass: calcd for $C_{11}H_{18}O$, 166.1358; found, 166.1350. 2,4-Dinitrophenylhydrazone: mp 134–135 °C (from ethanol).

4,4-Di-*n*-propyl-2-cyclopentenone (9b): 85%, bp 114–116 °C (6.0 mm); IR ($CHCl_3$) 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.43 (d, 1 H, *J* = 5.5 Hz), 6.07 (d, 1 H, *J* = 5.5 Hz), 2.18 (s, 2 H), 0.84–1.60 (m, 14 H); mass spectrum *m/e* 166, 124, 96, 95 (base), 81. Exact mass: calcd for $C_{11}H_{18}O$, 166.1358; found, 166.1355. 2,4-Dinitrophenylhydrazone: mp 114.5–116 °C (from ethanol).

Anal. Calcd for $C_{17}H_{22}O_4N_4$: C, 58.94; H, 6.40. Found: C, 59.21; H, 6.13.

4-Isobutyl-4-methyl-2-cyclopentenone (9c): 77%, bp 84–86 °C (2.4 mm); IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.55 (d, 1 H, *J* = 5.5 Hz), 6.08 (d, 1 H, *J* = 5.5 Hz), 2.27 (d, 2 H, *J* = 4 Hz), 0.70–1.85 (m. 12 H); mass spectrum *m/e* 152, 96 (base), 95, 67, 41. Exact mass: calcd for $C_{10}H_{16}C$, 152.1201; found, 152.1196. 2,4-Dinitrophenylhydrazone: mp 98–99.5 °C (from ethanol).

Spiro[4.5]dec-3-en-2-one (9d): 78%, bp 115–117 °C (6.0 mm); IR ($CHCl_3$) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.57 (d, 1 H, *J* = 5.5 Hz), 6.05 (d, 1 H, *J* = 5.5 Hz), 2.22 (s, 2 H), 1.15–1.81 (m, 10 H); mass spectrum *m/e* 150 (base), 107, 95, 82, 79. Exact mass: calcd for $C_{10}H_{14}O$, 150.1045; found, 150.1046. Semicarbazone: mp 198–200 °C (from aqueous ethanol) which was identical (IR, mp, mmp) with an authentic sample.[11]

6-Methylspiro[4.5]dec-3-en-2-one (9e): 63% as an 82:18 mixture of diastereomer, bp 90–92 °C (0.5 mm); IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) (major diastereomer) δ 7.80 (d, 0.82 H, *J* = 5.5 Hz), 6.17 (d, 0.82 H, *J* = 5.5 Hz), 2.15 (d, 1.64 H, *J* = 7.0 Hz), 0.63–2.00 (m, 12 H), (minor diastereomer) δ 7.37 (d, 0.18 H, *J* = 5.5 Hz), 6.07 (d, 0.18 H, *J* = 5.5 Hz), 2.22 (d, 0.36 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 209.0 (C_2), 168.5 (C_4), 133.9 (C_3), (minor diastereomer) δ 209.9 (C_2), 173.7 (C_4), 131.8 (C_3); mass spectrum *m/e* 164, 122, 95, 94 (base), 66. Exact mass: calcd for $C_{11}H_{16}O$, 164.1201; found, 164.1196. 2,4-Dinitrophenylhydrazone: mp 147–148 °C (from ethanol).

Anal. Calcd for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85. Found: C, 59.19; H, 5.91.

8-Methylspiro[4.5]dec-3-en-2-one (9f): 75% as a 78:22 mixture of diastereomers, bp 86–88 °C (0.6 mm); IR ($CHCl_3$) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) (major diastereomer) δ 7.92 (d, 0.78 H, *J* = 5.5 Hz), 6.08 (d, 0.78 H, *J* = 5.5 Hz), 2.19 (s, 2 H), 0.82–1.88 (m, 12 H), (minor diastereomer) δ 7.43 (d, 0.22 H, *J* = 5.5 Hz), 6.03 (d, 0.22 H, *J* = 5.5 Hz); mass spectrum *m/e* 164 (base), 136, 107, 95, 82. Exact mass: calcd for $C_{11}H_{16}O$, 164.1201; found, 164.1194. 2,4-Dinitrophenylhydrazone: mp 183–184 °C (from ethanol).

8-*tert*-Butylspiro[4.5]dec-3-en-2-one (9g): 54% as a 78:22 mixture of diastereomers, bp 129–131 °C (0.4 mm); IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) (major diastereomer) δ 8.00 (d, 0.78 H, *J* = 5.5 Hz), 6.12 (d, 0.78 H, *J* = 5.5 Hz), 2.19 (s, 2 H), 0.81–2.07 (m, 18 H), (minor diastereomer) δ 7.42 (d, 0.22 H, *J* = 5.5 Hz), 6.02 (d, 0.22 H, *J* = 5.5 Hz); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 209.0 (C_2), 169.5 (C_4), 132.5 (C_3), (minor diastereomer) δ 209.7 (C_2), 174.3 (C_4), 131.5 (C_3); mass spectrum *m/e* 206, 151, 150, 107, 95, 57 (base). Exact mass: calcd for $C_{14}H_{22}O$, 206.1671; found, 206.1669. 2,4-Dinitrophenylhydrazone: mp 197–199 °C (from ethanol).

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Registry No.—**1a**, 106-35-4; **1b**, 123-19-3; **1c**, 108-10-1; **1d**, 108-94-1; **1e**, 583-60-8; **1f**, 589-92-4; **1g**, 98-53-3; **4a**, 58712-03-1; **4b**, 62167-26-4; **4c**, 62167-27-5; **4d**, 6815-55-0; **4e**, 62167-28-6; **4f**, 62167-29-7; **4g**, 62167-30-0; **8a**, 62167-31-1; **8a** DNP, 62167-32-2; **8b**, 62167-33-3; **8c**, 62167-34-4; **8d**, 62167-35-5; *cis*-**8e**, 62167-36-6; *trans*-**8e**, 62167-37-7; *cis*-**8f**, 62167-38-8; *trans*-**8f**, 62167-39-9; *cis*-**8g**, 62167-40-2; *trans*-**8g**, 62167-41-3; *cis*-**8g** DNP, 62167-42-4; *trans*-**8g** DNP, 62167-43-5; **9a**, 62167-44-6; **9a** DNP, 62167-45-7; **9b**, 62167-46-8; **9b** DNP, 62167-47-9; **9c**, 59346-67-7; **9c** DNP, 62167-48-0; **9d**, 62167-49-1; **9e** α-methyl, 62167-50-4; **9e** DNP α-methyl, 62167-51-5;

9f α-methyl, 62167-52-6; **9f** DNP α-methyl, 62167-53-7; **9g** α-methyl, 62167-54-8; **9g** DNP α-methyl, 62197-67-5; diethyl pyrrolidinomethylphosphonate 51868-96-3; 2,3-dibromopropene, 513-31-5; **9e** β-methyl, 62167-55-9; **9e** DNP β-methyl, 62167-56-0; **9f** β-methyl, 62167-57-1; **9f** DNP β-methyl, 62167-58-2; **9g** β-methyl, 62167-59-3; **9g** DNP β-methyl, 62197-69-7.

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(11) We thank Professor Ernest Wenkert, Rice University, for providing us with a sample of the authentic material for comparison.

Photocycloaddition of Bicyclic Cyclopentenones with Cyclohexene

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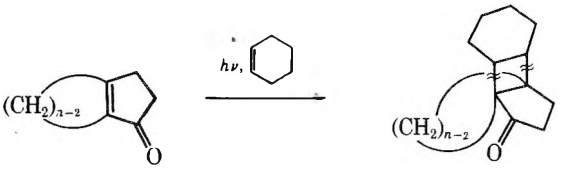
While one of the most important problems in the field of photocycloaddition of cyclic enones to an alicyclic olefin is the stereochemistry of photoannelation adducts, very few studies have been made.[1] We wish to report here the remarkable effect of the fused ring size on the photocycloaddition of a series of bicyclic cyclopentenones **1–4** with cyclohexene.

On irradiation of the enones **1**, **3**, and **4** with 10 molar excess of cyclohexene, the respective cycloadducts **5**,[2] **7**, and **8** were obtained as major products in good yields, but these cycloadducts consisted of three or four stereoisomers.[3] On the other hand, the photoreaction of the enone **2** under a similar condition gave the sole cycloadduct **6** in an 84% yield, along with small amounts of three kinds of other products (Chart I). Concerning the structure of **6**, the absolute configuration

Chart I



1, n = 5	5a, 21%; b, 35%; c, 12%; d, 5%
2, n = 6	6, 84%
3, n = 7	7a, 7%; b, 82%; c, 5%
4, n = 8	8a, 3%; b, 79%, c, 5%

about the cyclobutane ring was established to be cis-anti-trans by means of x-ray analysis[4] (Figure 1).

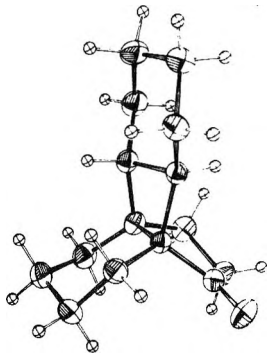


Figure 1. Molecular structure of **6**.

Table I. Phosphorescence Spectra and Lifetimes of the Enones 1–4[a]

Enone	Phosphorescence, cm^{-1} Origin	Max	10%	τ, ms
1[b]	26 000	21 200	24 800	760
2[b]	25 800	20 900	25 100	28
3	26 100	22 200	25 500	64
4	26 200	22 300	25 500	150

[a] Measured at 77 K in EPA matrix. [b] Measured by Cargill et al.[1b,6]

The quantum yield for the formation of **6** was determined to be 0.69. The stereoselective cycloaddition of **2** as well as the high quantum efficiency, compared with 0.25 for **5a–d**[1b] and 0.48 for tricyclo[6.3.0.$0^{2,7}$]undecan-9-ones,[5] suggests that **6** may be formed in a concerted manner via a singlet excited state of **2**. But the formation of **6** was quenched by added piperylene, and, therefore, the participation of triplet species was concluded.

It is obvious, however, from the spectroscopic data listed in Table I that there is no significant difference in the nature of each triplet excited state of **1–4**.

Consequently, it is reasonable that the observed distinction in reactivity among these enones is considered in terms of the steric effect of fused alicyclic rings on the cycloaddition via triplet 1,4-diradical intermediates derived from the enones and cyclohexene. Namely, it may be assumed that nonbonded interaction of hydrogens between ring methylenes plays a key role in the determination of the stereoisomer distribution. In the case of either **1**, having planar cyclopentene ring, or **3** and **4**, having flexible cycloheptene and cyclooctene ones, four or three isomers are formed. It is probably due to little difference in the nonbonded interaction among the four possible stereoisomers. On the other hand, in the case of **2**, having a less flexible cyclohexene ring, the nonbonded interaction may be much severer than in other cases and, as a result, only the cis-anti-trans isomer, having the least interaction, may be produced selectively.

Experimental Section[7]

Materials. The enones **1–3** were prepared according to the procedures reported by Kulkarni and Dev,[8] by Dev,[9] and by Plattner and Büchi,[10] respectively, and **4** was prepared by a method similar to that of **3**.

General Irradiation Procedure. The enones **1–4** were irradiated with 10 molar excess of cyclohexene using a 500-W high-pressure mercury lamp through a Pyrex filter under nitrogen at room temperature, and the irradiation was continued until the enones were almost consumed (>95%). After removal of cyclohexene, the residue was distilled under reduced pressure. The products were analyzed by GLC (6 ft × 0.125 in. columns: A, 10% PEG-20M; B, 5% SE-30; C, 10% FFAP; D, 10% DEGS), and isolated by preparative GLC. Yields were

estimated based on the enones reacted. [Yields and retention times on column D (temperature) are given for each adduct below.]

All the cycloadducts showed only aliphatic protons in the NMR spectra, and gave weak parent peaks with base peaks of molecular ions corresponding to the respective enone plus hydrogen in the mass spectra. The carbonyl absorptions in the IR spectra of **5a–d**, **6**, and **7a–c** were at 1715 cm^{-1} and of **8a–c** at 1710 cm^{-1}. 6-(3-Cyclohexenyl)bicyclo[4.3.0]nonan-7-one (**9**) was identified with the authentic sample prepared from **2** and 3-bromocyclohexene using the method of Stork et al.[11] The other products were identified with the authentic materials.

Irradiation of 1. Four isomeric cycloadducts **5a–d** were obtained: **5a** [21%, 10.6 min (140 °C)]; **5b** [35%, 13.7 min (140 °C)], mp 59–61 °C; **5c** [12%, 15.6 min (140 °C)]; **5d** [5%, 18.4 min (140 °C)].

Irradiation of 2. Cis-anti-trans cycloadduct **6**, adduct **9**, bicyclo[4.3.0]nonan-7-one (1%), and 3,3′-bicyclohexenyl were obtained. **6** [84%, 12.3 min (150 °C)], mp 70–71 °C. 2,4-Dinitrophenylhydrazone mp 184–185 °C. Anal. Calcd for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.25; H, 6.47; N, 14.02. **9** [3%, 17.7 min (150 °C)]: IR 1725, 720 cm^{-1}; NMR δ 0.90–2.60 (m, 20 H), 5.25–5.80 (m, 2 H); mass spectrum *m/e* 218 (M^+), 138, semicarbazone mp 238–240 °C. Anal. Calcd for $C_{16}H_{25}ON_3$: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.62; H, 9.29; N, 15.05.

Irradiation of 3. Three isomeric cycloadducts **7a–c**, bicyclo[5.3.0]-decan-8-one (3%), and 3,3′-bicyclohexenyl were obtained. **7a** [7%, 11.0 min (160 °C)]. **7b** [82%, 14.7 min (160 °C)], mp 47–48 °C. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.48; H, 10.60. **7c** [5%, 20.1 min (160 °C)].

Irradiation of 4. Three isomeric cycloadducts **8a–c**, bicyclo[6.3.0]-undecan-9-one (1%), and 3,3′-bicyclohexenyl were obtained. **8a** [3%, 12.4 min (170 °C)]. **8b** [79%, 17.0 min (170 °C)], mp 91–92 °C. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.63; H, 10.79. **8c** [5%, 23.0 min (170 °C)].

Quantum Yield Measurement. A 0.13 M solution of **2** in cyclohexene was irradiated to about 3% conversion. After irradiation the calibrating compound was added and the amount of **6** determined by GLC (column C). Actinometry was by the ferrioxalate method.

Quenching of Photocycloaddition of 2 with Cyclohexene. A 0.05 M solution of **2** in cyclohexene was used with added piperylene (0.01–0.5 M).

Registry No.—**1**, 10515-92-1; **2**, 22118-00-9; **3**, 769-32-4; **4**, 38262-50-9; **5a**, 62264-61-3; **5b**, 62319-07-7; **5c**, 62319-08-8; **5d**, 62319-09-9; **6**, 58595-14-5; **6** 2,4-DNPH, 62264-62-4; **9** semicarbazone, 62264-63-5; **7a**, 62264-64-6; **7b**, 62319-10-2; **7c**, 62356-50-7; **8a**, 62264-65-7; **8b**, 62319-11-3; **8c**, 62319-12-4; cyclohexene, 110-83-8.

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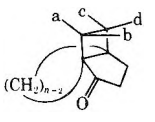
(2) Cargill et al. reported that four isomeric cycloadducts were obtained on irradiation of **1** with cyclohexene in methylene chloride,[1b] which is in agreement with our result.

(3) Generally, photocycloaddition of the cyclic enone to an alicyclic olefin gives a number of stereoisomers.[1] In the present case, the formation of four stereoisomers is possible, and the nomenclature is as follows:



cis-anti-trans, bridging a to d
cis-syn-trans, bridging b to c
cis-anti-cis, bridging a to c
cis-syn-cis, bridging b to d

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(7) Melting points are uncorrected. Infrared spectra were recorded using a JASCO IR-G spectrometer. NMR spectra were obtained in a JEOL JNM-PS-100 spectrometer using CCl_4 as a solvent and Me_4Si as an internal standard. Mass spectra were measured with a Hitachi RMU-6E spectrometer. Analytical GLC was carried out on a Hitachi 163 gas chromatograph, and preparative GLC separation was conducted on a Varian Aerograph 90-P gas chromatograph. Phosphorescence spectra were recorded on a Hitachi MPF-3 spectrometer.

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Oxidation of L-Cystine by Dimethyl Sulfoxide. Cysteic Acid–Sulfoxide Compounds

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The oxidation of disulfides to sulfonic acids by dimethyl sulfoxide (Me_2SO) has been described;[1] however, L-cystine is insoluble in Me_2SO and satisfactory oxidation is not accomplished without modification of the procedure. The needed changes are an increase in the amount of halogen or hydrogen halide catalyst to about twice the number of moles of L-cystine and a significantly lower reaction temperature. With an appropriately high concentration of mixed I_2–HCl catalyst, oxidation occurs smoothly at room temperature, the water necessary for stoichiometry (eq 1) and reaction moderation being supplied through the use of concentrated hydrochloric acid.

$$(SCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH)_2 + 5CH_3\overset{\displaystyle O}{\overset{\|}{S}}CH_3 + H_2O \xrightarrow{\text{cat}} 2HO_3SCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH + 5CH_3SCH_3 \quad (1)$$

Addition of acetone to the reaction mixture gave abundant precipitate, but this was not the expected L-cysteic acid (CysA). Accumulated evidence—high weight of product, acidic and oxidizing properties, elemental analysis, conversion to CysA by solvent extraction or vacuum drying, and ready formation by direct combination of CysA and Me_2SO—established that this was a 1:1 compound of CysA and Me_2SO.

My obtaining this molecular complex led to investigation of related compounds. It was found that CysA also dissolves in tetramethylene sulfoxide (TMSO) and, on addition of acetone, the corresponding TMSO compound precipitates. CysA has quite limited solubility in methyl phenyl sulfoxide, so, in this instance, no complex is obtained. The combinations DL-cysteic acid–Me_2SO and DL-homocysteic acid with both Me_2SO and TMSO were also checked. The corresponding molecular complexes were obtained; though, with DL-homocysteic acid, these were syrups from which it appeared that the compounds slowly crystallized.

The explanation for formation of these compounds would appear to lie in the ability of the oxygen of sulfoxides such as Me_2SO and TMSO to serve as a proton acceptor.[2] Such salts of strong acids have been reported[3] though the mole ratio is not always 1:1. CysA and, most likely, the other cysteic acids exist as the ammonium sulfonate zwitterion,[4] the carboxyl group being un-ionized. This leads to the interpretation of the subject compounds as carboxylic acid salts or associates of sulfoxides. These have also been investigated and isolated.[5] Those that I have obtained differ in being significantly more stable and amenable to characterization.

Experimental Section

General. The Me_2SO, iodine, hydrochloric and hydrobromic acids, and solvents were reagent grade. Other materials were a quality,

commercial grade and used directly except TMSO, which was dried over molecular sieves and distilled.

Melting points are by the capillary method and uncorrected. Those of CysA were obtained by inserting the capillary into the heating bath about 10 °C below the expected decomposition temperature. Elemental analysis are by Elek Microanalytical Laboratories, Torrance, Calif., and C. F. Geiger, Ontario, Calif.

Oxidation of L-Cystine. Iodine (1.5 g, 11.8 mg-atoms) was dissolved with stirring in a mixture of 24 g (99.9 mmol) of L-cystine and 150 mL of Me_2SO. Gradually, 18 mL (216 mmol) of concentrated hydrochloric acid was added. Stirring at room temperature was continued for 24 h by which time all L-cystine had dissolved and some dimethyl sulfide appeared as a second phase.[6]

The oxidation was also conducted by using 18 mL (160.2 mmol) of concentrated hydrobromic acid in place of the iodine and hydrochloric acid and heating for 6.75 h at 75 °C with distillation of dimethyl sulfide.

CysA–Me_2SO Compound. Acetone (375 mL) was gradually stirred into the mixture obtained by I_2–HCl catalyzed oxidation. After cooling in an ice bath for 2 h, the precipitate was filtered off, reslurried with an 8% solution of Me_2SO in acetone, again collected, and rinsed with acetone. Obtained was 46.5 g (94% yield) of CysA–Me_2SO compound. This sintered at 160 °C, then decomposed at about 180 °C. Recrystallization was accomplished by dissolving in Me_2SO and adding acetone but without change in the decomposition temperature, $[\alpha]^{25}_D$ +5.92° (11%, water). Other solvents such as ethyl acetate or chloroform could be used in place of acetone.

Anal. Calcd for $C_5H_{13}NO_6S_2$: C, 24.28; H, 5.30; N, 5.37; S, 25.93. Found: C, 24.64; H, 5.40; N, 5.45; S, 26.03. Calcd neut equiv, 247.3. Found, 248.3. Calcd % Me_2SO for $C_3H_7NO_5S{\cdot}C_2H_6OS$, 31.59. Found by reduction with 57% hydriodic acid,[7] 31.65.

Conversion of CysA–Me_2SO Compound to CysA. A. By Solvent Extraction. CysA–Me_2SO compound (10 g, 40.5 mmol) was mixed with 40 mL of methanol and repeatedly triturated over a 1.5-h period. CysA was filtered off and rinsed with fresh methanol. Obtained was 6.45 g (94% yield), mp 273–274 °C dec (lit.[8] mp 274 °C dec). Recrystallization from water gave CysA monohydrate, mp 272–274 °C dec (lit.[9] mp 278 °C dec), $[\alpha]^{25}_D$ +8.45° (7.4%, anhydrous basis, water) (lit.[10] +8.66°). Identification was confirmed by comparing the IR spectrum with that of authentic material.

Acetonitrile or ethanol could be used in place of methanol in this extraction.

B. By Vacuum Drying. CysA–Me_2SO compound (0.8838 g, 3.58 mmol) was heated for 9 h at 120 °C (10 mm). The residual CysA weighed 0.6022 g, mp 260–263 °C dec (lit.[8] mp 274 °C dec). Calcd wt loss for $C_3H_7NO_5S{\cdot}C_2H_6OS$, 31.59. Found, 31.86.

Direct Formation of CysA–Me_2SO Compound. On treating 1.10 g (5.90 mmol) of CysA monohydrate with 4 mL of Me_2SO, it dissolved slowly, and stirring and some heating were used to complete solution. Acetone (5 mL) was added to start precipitation. Later 2 mL more was added. After cooling in an ice bath, CysA–Me_2SO compound was filtered off and given a final rinse with acetone. Obtained was 1.37 g (94% yield) identical with that described above.

Other Cysteic Acid–Sulfoxide Compounds. About 2.9 mmol of the cysteic acid was treated with 2 mL of Me_2SO or 6–8 mL of TMSO. Solution occurred gradually and was usually completed with gentle heating. Precipitation was by addition of acetone. Yields were about 90%. Where possible, recrystallization was by dissolving in the same sulfoxide followed by addition of acetone. The appropriate cysteic acid was recovered by treating with methanol.

CysA–TMSO Compound. This darkened, then decomposed at 215–216 °C. Anal. Calcd for $C_7H_{15}NO_6S_2$: N, 5.13; S, 23.46. Found: N, 4.87; S, 23.61.

DL-Cysteic Acid–Me_2SO Compound. This showed partial melting at 161–165 °C followed by gradual decomposition. Anal. Calcd for $C_5H_{13}NO_6S_2$: N, 5.67; S, 25.93. Found: N, 5.82; S, 26.08.

DL-Homocysteic Acid–Me_2SO Compound. Addition of acetone resulted in formation of a syrup. This was extracted with fresh acetone until the extract would no longer rapidly decolorize added aqueous $KMnO_4$ solution. This syrup gradually crystallized. Its aqueous solution decolorized aqueous $KMnO_4$. Anal. Calcd for $C_6H_{15}NO_6S_2$: N, 5.36; S, 24.54. Found: N, 4.31; S, 20.75. Ratio: S to N, 2.1.

DL-Homocysteic Acid–TMSO Compound. A syrup was obtained as with Me_2SO. After exhaustive extraction with acetone, its aqueous solution continued to rapidly decolorize $KMnO_4$ solution.

Registry No.—L-Cysteic acid, 498-40-8; L-cystine, 56-89-3; Me_2SO, 67-68-5; cysA–Me_2SO compound, 60643-99-4; TMSO, 1600-44-8; cysA–TMSO compound, 60644-00-0; DL-cysteic acid, 3024-83-7; DL-cysteic acid–Me_2SO compound, 62337-55-7; DL-homocysteic acid, 504-33-6; DL-homocysteic acid–Me_2SO compound, 60644-01-1; DL-homocysteic acid–TMSO compound, 62337-56-8.

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anhydro-2-Mercaptothiazolo[3,2-*f*]phenanthridinium Hydroxide, a Mesoionic Thiazole Ring System Containing Exocyclic Sulfur

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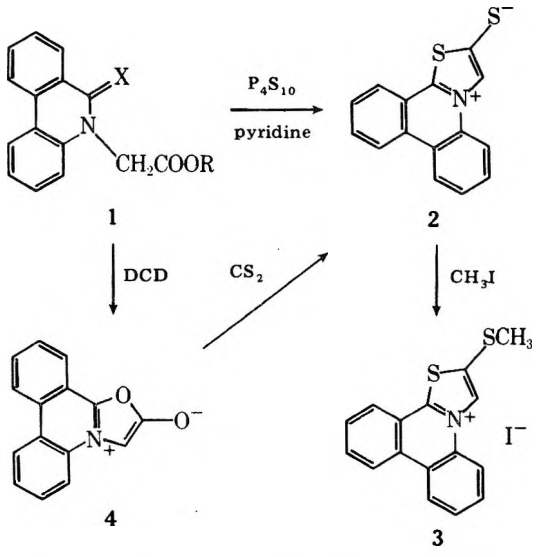
The synthesis of mesoionic ring systems with exocyclic sulfur atoms by a direct ring closure sequence is usually effective only in those systems with a nitrogen atom adjacent to the carbon bearing the sulfur, as in the 1,3,4-oxadiazole,[1] 1,3,4-thiadiazole,[1,2] and 1,2,4-triazole[3] ring systems. In these cases an isothiocyanate is presumed to be the reactive intermediate. Interconversion of mesoionic systems by the use of a reactive dipolarophile, such as the reaction of *anhydro*-2,4-diphenyl-5-hydroxy-3-methyloxazolium hydroxide with carbon disulfide to give *anhydro*-2,4-diphenyl-5-mercapto-3-methylthiazolium hydroxide,[4] requires an exceptionally reactive substrate and has only been successful in the above example, although the hydrolytic rearrangement of the *anhydro*-5-hydroxy-1,3,4-thiadiazolium hydroxide system to the corresponding *anhydro*-5-mercapto-1,3,4-oxadiazolium hydroxide system is well documented.[1] We now describe a direct approach that has been successful in the synthesis of the title ring system.

6-Oxo-5(6*H*)-phenanthridineacetic acid (**1**, R = H; X = O) when refluxed in pyridine for 1 h with an equimolar quantity of P_4S_{10} gave *anhydro*-2-mercaptothiazolo[3,2-*f*]phenanthridinium hydroxide (**2**), characterized further by the ready formation of 2-methylthiothiazolo[3,2-*f*]phenanthridinium iodide (**3**) on reaction with methyl iodide. Use of the methyl ester of **1** (R = CH_3; X = O) in toluene required 21.5 h of reflux for the formation of **2** whereas, if the reaction were run for shorter periods (45 min), no **2** was formed, the product isolated being the corresponding thioester **1** (R = CH_3; X = S). Confirmation of the structure of **2** was obtained by an alternative synthesis. Cyclization of **1** (R = H; X = O) with dicyclohex-

ylcarbodiimide gave the oxazolone 4 which was reacted in situ[5] with carbon disulfide to form **2**. This mesoionic system did not undergo cycloaddition with dimethyl acetylenedicarboxylate.

Thionation of the amide carbonyl group is undoubtedly the initial step in the reaction. A longer reaction period converts the acid group into a thio acid which then undergoes a cyclodehydrative ring closure. This is an extremely attractive route



to mesoionic systems of this type but attempts to develop it as a general reaction sequence were unsuccessful under analogous conditions. *N*-Benzoyl-*N*-phenylglycine and its ethyl ester, as well as 2-oxo-1(2*H*)-pyridineacetic acid, gave multicomponent reaction mixtures.

Experimental Section[6]

***anhydro*-2-Mercaptothiazolo[3,2-*f*]phenanthridinium Hydroxide (2). A. By Ring Closure of 1 (R = H; X = O).** 6-Oxo-5(6*H*)-phenanthridineacetic acid[7] (0.5 g, 0.002 mol), P_4S_{10} (0.44 g, 0.002 mol), and pyridine (15 mL) were refluxed for 1 h, the initial light yellow reaction solution turning a deep red after 15 min. After the reaction mixture was poured onto ice, the orange precipitate obtained (0.3 g, 56%) crystallized from DMF or $CHCl_3$–CH_3OH as red plates: mp 298–300 °C dec; UV λ_{max} (C_2H_5OH) 232 nm sh (log ϵ 4.46), 237 (4.48), 252 sh (4.44), 257 (4.46), 263 (4.44), 303 sh (3.93), 310 (3.94), 321 (3.91), 334 sh (3.84), 349 (3.73), 361 (3.71), 392 sh (3.27); IR (Nujol) $\nu_{C=C/C=N}$ 1605, 1555, 1510 cm^{-1}; NMR (TFA) aromatic protons; M^+· *m/e* 267 (100).

Anal. Calcd for $C_{15}H_9NS_2$: C, 67.38; H, 3.39; N, 5.24; S, 23.99. Found: C, 67.16; H, 3.48; N, 5.34; S, 23.44.

B. By Ring Closure of 1 (R = CH_3; X = O). Methyl 6-oxo-5(6*H*)-phenanthridineacetate[7,8] (2.67 g, 0.01 mol), P_4S_{10} (2.45 g, 0.011 mol), and toluene (50 mL) when refluxed for 21.5 h resulted in the formation of a suspension which, after treatment with a solution of $CHCl_3$ (50 mL) and 5% NaOH (50 mL), gave an orange product (2.7 g). Recrystallization gave a product identical[9] with that obtained above.

C. From 1 (R = H; X = O) and DCD/CS_2. The acid 1 (R = H; X = O) (0.64 g, 0.025 mol) and *N,N'*-dicyclohexylcarbodiimide (0.60 g, 0.029 mol) were refluxed in CS_2 (30 mL) for 24 h. After cooling, the suspended red product was collected and this product triturated with hot EtOH to remove *N,N*-dicyclohexylurea. The orange-red prisms remaining, 0.27 g (40%), mp ca. 300 °C dec, were identical[9] with the product obtained above.

2-Methylthiothiazolo[3,2-*f*]phenanthridinium Iodide[10] (3). A suspension of **2** (0.13 g) in CH_3OH (20 mL) and excess methyl iodide was heated under reflux until a clear yellow solution resulted. The solvent was evaporated and the residue triturated with anhydrous ether resulting in an orange-yellow product (0.18 g) which crystallized from ethanol (Norit) as yellow needles: mp 250–255 °C dec; UV λ_{max} (CH_3OH) 230 nm (log ϵ 4.47), 250 (4.44), 267 (4.62), 293 sh (4.08), 370 (4.14); NMR (Me_2SO-d_6) δ 2.92 (s, 3, SCH_3), 7.67–9.12 (m, 8, aromatic), 9.55 (s, 1, C_5H).

Anal. Calcd for $C_{16}H_{12}NIS_2$: C, 46.95; H, 2.96; N, 3.42. Found: C, 46.90; H, 2.92; N, 3.64.

Methyl 6-Thio-5(6*H*)-phenanthridineacetate (1, R = CH_3; X = S). A mixture of 1 (R = CH_3; X = O), P_4S_{10} (0.566 g, 0.026 mol), and toluene (15 mL) was refluxed for 45 min. After cooling, 5% NaOH (10 mL) and $CHCl_3$ (20 mL) were added and the mixture was stirred for 1.5 h and then filtered. The filtrate was washed with H_2O and saturated NaCl solution, dried ($MgSO_4$), and evaporated. The residue (0.495 g) was chromatographed on silica gel (150 g) using 15% EtOAc–cyclohexane, the product (80 mg, 11%) being collected in 300 mL after a small forerun of eluate. It crystallized from ether as colorless needles: mp 184–185 °C; UV λ_{max} (C_2H_5OH) 245.5 nm (log ϵ 4.61), 250 (4.59), 266 (4.21), 291 (3.92), 308 (3.71), 321 (3.70), 355 sh (3.99), 369 (4.12), 387 (3.99); IR (Nujol) ν_{CO} 1740 cm^{-1}; M^+· *m/e* 283 (100).

Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94; S, 11.31. Found: C, 67.99; H, 4.88; N, 4.96; S, 11.22.

Registry No.—1 (R = H; X = O), 37046-34-7; 1 (R = Me; X = O), 62416-28-8; 1 (R = Me; X = S), 62416-29-9; **2**, 62416-30-2; **3**, 62416-31-3; methyl iodide, 74-88-4.

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(9) Criteria used were superimposable IR spectra and nondepression of mixture melting point.
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A Regiospecific Synthesis of Haematommic Acid

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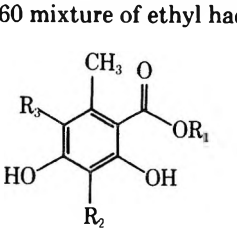
Haematommic acid (**1a**), a common fragment of many depsidones and depsides,[1] has previously been synthesized by two different routes both of which suffer from either experimental difficulties or hazards. St. Pfau[2] first reported the synthesis of **1a** by the reaction of ethyl orsellinate (**1b**) with zinc cyanide and hydrogen chloride in diethyl ether. This reaction yielded a 40/60 mixture of ethyl haematommate (**1c**)

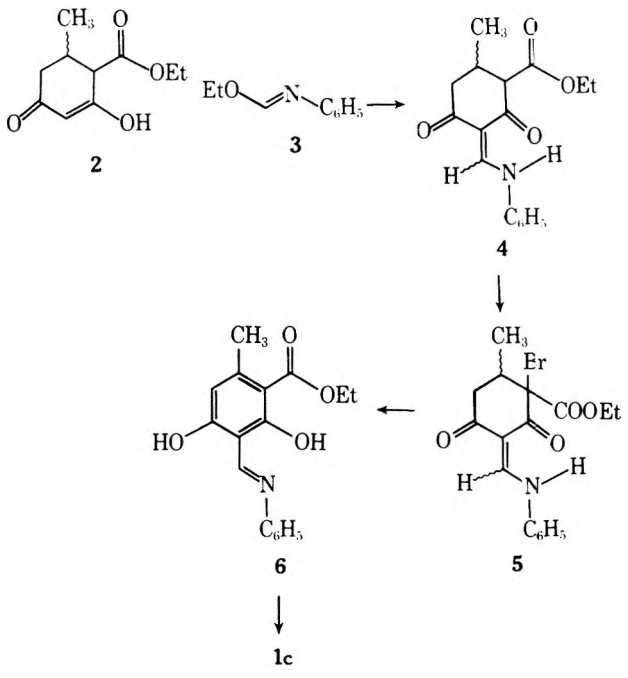


	R_1	R_2	R_3
1a	H	CHO	H
b	Et	H	H
c	Et	CHO	H
d	Et	H	CHO
e	$C_6H_5CH_2$	H	H
f	$C_6H_5CH_2$	CHO	H

and ethyl isohaematommate (**1d**), respectively, which were difficult to separate. Elix[3] has overcome the isomer problem by the reaction of benzyl orsellinate (**1e**) with dichloromethyl methyl ether and titanium tetrachloride. Although this reaction gives specifically benzyl haematommate (**1f**) in 30% yield, the known carcinogenicity of chloromethyl ethers makes this procedure undesirable.

As part of a project directed toward the synthesis of two new depsidones it was necessary to have a convenient synthesis of haematommic acid. Rogers and Smith[4] have shown that cyclohexane-1,3-dione reacts with ethyl *N*-phenylformamidate to yield an anil which can be hydrolized to 2-formylcyclohexane-1,3-dione. Capitalizing upon this reaction we condensed ethyl dihydroorsellinate[5] with ethyl *N*-phenylformamidate[6] (**3**) to yield **4** in 90% yield (Scheme 1). The product

Scheme I



4 was obviously a mixture of two isomers judging from the ^{1}H NMR, which showed two superimposed quartets (J = 7 Hz) centered at δ 4.34 (OCH_2CH_3), two superimposed triplets (J = 7 Hz) centered at δ 1.30 (OCH_2CH_3), and two superimposed doublets (J = 14 Hz) centered at δ 8.72 (C=CHN). The NH hydrogen at δ 13.05 appeared as a broad peak which disappeared upon exchange with D_2O with a corresponding collapse of the two doublets centered at δ 8.72 into two singlets at δ 8.73 and 8.70. Irradiation at δ 13.05 also resulted in the same collapse of the superimposed doublets at δ 8.72. The other features of the ^{1}H NMR were consistent with the proposed structure. It was not determined whether the two isomers were due to the relative stereochemistry of the methyl and carboethoxy groups or to the *E* and *Z* stereochemistry of the enamine double bond since the stereochemistry of both of these positions would be lost upon aromatization of the ring.

A CCl_4 solution of **4** was brominated with *N*-bromosuccinimide in the presence of ultraviolet light to yield **5**. The position of the bromine in **5** was indicated by the absence of the methine (C-1) hydrogen at δ 3.32 in the ^{1}H NMR. As with **4**, the ^{1}H NMR clearly showed a mixture of two isomers. The yield of **5** ranged from 50 to 90% with average in the mid-80%. In the few low-yield cases there was a considerable amount of intractable material produced; however, when the reaction went cleanly the yields were very high.

The dehydrohalogenation of **5** was best accomplished with DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) in Me_2SO/benzene to yield the anil **6** in 51% yield after recrystallization from ethanol. Hydrolysis of **6** to ethyl haematommate (**1c**) in 74% yield was accomplished by stirring an ether solution of **6** with acidic 40% aqueous glyoxal. The physical properties[2] and ^{1}H NMR of the product were consistent with those of ethyl haematommate.

The ester hydrolysis of **1c** by the method of St. Pfau[2] successfully completed the synthesis of haematommic acid.

Experimental Section

Infrared spectra were run on a Beckman Acculab I spectrometer. ^{1}H NMR spectra were run on a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were run on an AEI MS-9 spectrometer at 70 EV. Microanalyses were determined by either Ilse Beetz Microanalytical Laboratory, West Germany, or Galbraith Laboratory, Knoxville, Tenn. Melting points were determined on a Thomas-Kofler micro hot stage and are uncorrected.

Ethyl 6-Methyl-2,4-dioxo-3-[(phenylamino)methylene]-cyclohexanecarboxylate (4). A mixture of 25.5 g (0.131 mol) of ethyl dihydroorsellinate (**2**) and 20.4 g (0.131 mol) of ethyl *N*-phenylformamidate (**3**) was gently heated on a steam bath whereupon an exothermic reaction ensued. Upon cooling the mixture solidified and the crude material was crystallized from 70 mL of boiling ethyl acetate to yield 31.0 g (82%, 0.107 mol) of **4**: mp 121–123 °C; IR 1730 (ester C=O), 1670 (conjugated C=O), 1600 cm^{-1} (conjugated C=C); ^{1}H NMR δ 13.05 (1 H, broad multiplet, NH), 8.72 (1 H, two superimposed doublets, J = 14 Hz, C=CH), 7.4 (5 H, broad multiplet, C_6H_5), 4.34 (2 H, two superimposed quartets, J = 14 Hz, OCH_2CH_3), 3.32 (1 H, two superimposed doublets, J = 5 Hz, CHCOOEt), 3.0–2.0 (3 H, broad multiplet), 1.30 (3 H, triplet, J = 14 Hz, OCH_2CH_3), and 1.10 (3 H, doublet, J = 5 Hz, CH_3); mass spectrum, $C_{17}H_{19}NO_4$, calcd 301.13414, found 301.130537.

Anal. Calcd: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.68; H, 6.32; N, 4.64.

Ethyl 1-Bromo-6-methyl-2,4-dioxo-3-[(phenylamino)methylene]cyclohexanecarboxylate (5). A mixture of 3.01 g (10 mmol) of **4** and 1.85 g (10 mmol) of recrystallized *N*-bromosuccinimide in 150 mL of CCl_4 was stirred at reflux in the presence of UV light for 45 min, during which time the light orange solution turned light yellow and the insoluble material turned to a fine precipitate. The precipitate was filtered and the solvent was removed on a rotary evaporator to yield a crude oil which upon recrystallization from chloroform/cyclohexane yielded 3.10 g (82%, 8.2 mmol) of **5**: mp 150–152 °C; IR 1745 (ester C=O), 1670 (conjugated C=O), 1600 cm^{-1} (conjugated C=C); ^{1}H NMR δ 13.05 (1 H, multiplet, NH), 8.83 (1 H, two superimposed doublets, J = 14 Hz, C=CH), 7.4 (5 H, multiplet, C_6H_5), 4.40 (2 H, two superimposed quartets, J = 8 Hz, OCH_2CH_3), 2.4–3.0 (3 H, broad multiplet), 1.38 (3 H, two superimposed triplets, J = 8 Hz, OCH_2CH_3), and 1.16 (2 H, doublet, J = 5 Hz); mass spectrum $C_{17}H_{18}BrNO_4$, calcd 379.041912, found 379.040515.

Anal. Calcd: C, 53.70; H, 4.77; Br, 21.015; N, 3.684. Found: C, 53.60; H, 4.70; Br, 21.15; N, 3.95.

Ethyl Haematommate Anil (6). A mixture of 3.00 g (7.9 mmol) of **5**, 4 mL (48 mmol) of DBU, and 2 mL of Me_2SO in 25 mL of benzene was gently refluxed for 2 h. The dark solution was cooled and poured into 200 mL of water. The aqueous solution was extracted once with a 200-mL portion of ether and twice with 50-mL portions of ether. The combined organic solution was dried over $CaSO_4$ and filtered, and the solvent was removed on a rotary evaporator to yield a crude brown oil. Recrystallization of the oil from 95% ethanol yielded 1.20 g (51%, 4 mmol) of yellow crystals: mp 125–130 °C, IR 3640 (phenolic OH), 1620 (ester C=O), 1590 cm^{-1} (C=N); ^{1}H NMR δ 15.4 (1 H, broad multiplet, phenolic OH), 13.13 (1 H, singlet, phenolic OH), 9.13 (1 H, singlet, N=CH), 7.43 (5 H, singlet, C_6H_5), 6.40 (1 H, singlet, aromatic H), 4.50 (2 H, quartet, J = 8 Hz, OCH_2CH_3), 2.57 (3 H, singlet, aromatic CH_3), and 1.43 (3 H, triplet, J = 8 Hz, OCH_2CH_3); mass spectrum $C_{17}H_{17}NO_4$, calcd 299.1157, found 299.1163.

Anal. Calcd: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.08; H, 5.80; N, 4.44.

Ethyl Haematommate (1c). A mixture of 129.6 mg (0.43 mmol) of **6** was combined with 15 mL of 40% glyoxal, 15 mL of ether, and 4 drops of concentrated H_2SO_4. The mixture was refluxed for 10 h and the layers were separated. The aqueous layer was extracted with six 25-mL portions of ether. The combined ether layer was dried over $CaSO_4$, filtered, and evaporated to yield a crude product which was recrystallized from absolute ethanol to yield 62.2 mg (74%, 0.29 mmol) of **1c**, mp 112–113 °C. The IR and ^{1}H NMR were identical with those

of a sample of ethyl haematommate prepared by the method of St. Pfau.

Acknowledgments. The authors are grateful to Dr. Jon Clardy of Iowa State University and to the Committee for Research and Curriculum Development at the University of Northern Iowa for partial support for this work.

Registry No.—**1a**, 479-25-4; **1b**, 2524-37-0; **2**, 21855-43-6; **3**, 6780-49-0; **4**, 62392-80-7; **5**, 62392-81-8; **6**, 62392-82-9; *N*-bromosuccinimide, 128-08-5.

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Steric Effects. 8. Racemization of Chiral Biphenyls

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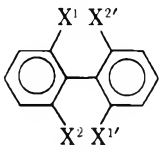
Adams[1] has suggested as a method of predicting the resolvability of chiral biphenyls that when the sum of certain group radii of the groups X^1 and X^2 in I is considerably greater than



I

2.90 Å, the biphenyl will be resolvable; when the sum is considerably less than 2.90 Å, the biphenyl will not be resolvable. We have examined the relationship between the υ steric parameters[2,3] and the Adams group radii. The υ parameters are a function of the van der Waals radii. They are defined by the relationship

$$\upsilon_X = r_{VX} - r_{VH} = r_{VX} - 1.20 \quad (1)$$

where r_{VX} and r_{VH} are the van der Waals radii of the X and H group, respectively. Values of υ were taken from our previous work.[2,3] The group radii used are given in Table I. Correlation was carried out with the equation

$$r_{GX} = m\upsilon_X + c \quad (2)$$

where r_{GX} is the group radius of the X group. Results of the correlation are reported in Table II. The results (set 1) are significant at the 99.9% confidence level (CL). Exclusion of the values for CO_2H and NO_2 (set 1A) results in very much improved correlation as is shown by the value of the F test for significance of the results. Thus, eq 2 has been verified. The deviation of CO_2H and NO_2 is not surprising as the υ values of these groups will be strongly dependent on the transition state of the reaction being studied.

New values of υ were calculated for the NO_2 and CO_2H groups from the appropriate r_{GX} values using set 1A of Table II. They are 0.59 and 0.37, respectively. The value for NO_2 seems reasonable, but the value for CO_2H appears to be too low.

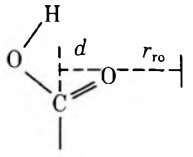
Table I. Data Used in Correlations[a]

1. Adams group radii
H, 0.94; F, 1.39; OH, 1.45; CO_2H, 1.56; NH_2, 1.56; Me, 1.73; Cl, 1.89; NO_2, 1.92, Br, 2.11; I, 2.20
2. Half-lives of 3′-substituted 2-NO_2-6CO_2H-2′-MeO-biphenyls in EtOH at 25 °C
H, 9.4; MeO, 98.1; Me, 332; C, 711; Br, 827; NO_2, 1905
3. Half-lives of 4′-substituted 2-NO_2-6-CO_2H-2′-MeO-biphenyls in MeAc at 25 °C
MeO, 2.6; Me, 3.6; Cl, 12; Br, 25; NO_2, 115
4. Half-lives of 5′-substituted 2-NO_2-CO_2H-2′-MeO-biphenyls in EtOH at 25 °C
H, 9.4; OMe, 10.8; Me, 11.5; Cl, 31; Br, 32; NO_2, 35.4

[a] All data from ref 1 and 6.

These conclusions are based on the point that a planar π-bonded substituent can exist in two extreme conformations with respect to a benzene ring, coplanar or perpendicular. In the perpendicular case, the half-thickness of the substituent determined its υ value, which is minimal and will be referred to as υ_{min}. In the coplanar case the υ value can be calculated as shown in Chart I. It represents a maximal value of υ and is

Chart I



designated υ_{max}. Thus,

$$\upsilon_{max} = d + r_{VO} - 1.20 \quad (3)$$

where r_{VO} is the van der Waals radius of oxygen. Values of υ_{max} and υ_{min} for NO_2 and CO_2H are 1.30, 0.35, and 1.48, 0.50, respectively.

Our results make possible the calculation of Adams group radii from the large number of υ values available, and therefore permit the estimation of optical stability in biphenyls of type I for a wide range of substituents.

We now turn our attention to rates of racemization of substituted biphenyls. Adams and co-workers[1] have measured half-lives for the racemization of 2-NO_2-6-CO_2H-2′-MeO-biphenyls substituted in either the 3′, the 4′, or the 5′ position. These data are reported in Table I. The half-life is related to the rate constants for racemization. The effect of the substituent in the 3′ position has been ascribed to the "buttressing effect". According to Eliel[4] and Ferguson[5] the effect of the substituents in the 4′ position is not well understood. The effect of substituents in the 5′ position is also said to be due to buttressing.[4,5] To investigate these various effects we have examined the correlation of the half-lives by means of the equation

$$\log t_{1/2,X} = \alpha\sigma_{IX} + \beta\sigma_{RX} + \psi\upsilon_X + h \quad (4)$$

in which the σ_I constants[6] and the σ_R constants[6] are measures of the localized (field and/or inductive) and delocalized (resonance) electrical effects. The results of the correlations with eq 4 are given in Table III. The σ_I constants are from our previous work,[6] the σ_R constants were obtained from

$$\sigma_R = \sigma_p - \sigma_I \quad (5)$$

The necessary σ_p constants are from the compilation of McDaniel and Brown.[8] The υ values, as before, are from our collection[2] with the exception of the NO_2 group, for which the

Table II. Results of Correlations with Equations 2 and 9

Set	Slope	Intercept	r^a	F^b	$s_{est}{}^c$	$s_{slope}{}^c$	$s_{intercept}{}^c$	n^d
1	1.56	1.00	0.913	39.97[e]	0.163	0.247[e]	0.118[e]	10
1A	1.67	0.940	0.992	394.3[e]	0.0547	0.0841[e]	0.0410[e]	8
4B	0.859	1.01	0.906	18.23[f]	0.129	0.201[g]	0.0801[e]	6

[a] Correlation coefficient. [b] F test for significance of correlation. [c] Standard errors of the estimate, slope, and intercept. [d] Number of points in set. [e] 99.9% confidence level (CL). [f] 97.5% CL. [g] 98.0% CL.

Table III. Results of Correlations with Equations 5, 7, and 8

Set	α	β	ψ	h	R^a	F^b	$r_{12}{}^c$	$r_{13}{}^c$
2	0.630	0.360	2.87	1.03	0.992	40.07[f]	0.104	0.626
2A	0.684		2.83	0.978	0.987	58.67[j]		0.626
3	1.55	1.27	0.761	0.398	0.990	15.76[m]	0.374	0.432
3A	1.61	1.55		0.831	0.985	32.59[i]	0.374	
4	0.615	0.226	0.429	0.934	0.964	8.646[m]	0.104	0.626
4A	0.648		0.399	0.899	0.947	13.04[i]		0.626

Set	$r_{23}{}^c$	$s_{est}{}^d$	$s_\alpha{}^d$	$s_\beta{}^d$	$s_\psi{}^d$	$s_h{}^d$	n^e
2	0.025	0.168	0.341[g]	0.352[g]	0.401[h]	0.162[i]	6
2A		0.170	0.339[k]		0.402[l]	0.154[l]	6
3	0.725	0.192	0.388[k]	0.624[g]	1.15[n]	0.687[n]	5
3A		0.163	0.319[i]	0.391[o]		0.177[i]	5
4	0.025	0.155	0.233[k]	0.241[g]	0.274[g]	0.111[h]	6
4A		0.113	0.226[o]		0.267[g]	0.102[l]	6

[a] Multiple correlation coefficient. [b] F test for significance of correlation. Superscripts indicate CL. [c] Partial correlation coefficients of σ_I on σ_R, σ_I on υ, σ_R on υ. Confidence level <90.0% unless otherwise indicated by superscripts. [d] Standard errors of the estimate, α, β, ψ, and h. Superscripts indicate CL of Student's t test. [e] Number of points in set. [f] 97.5% CL. [g] 50.0% CL. [h] 98.0% CL. [i] 95.0% CL. [j] 99.5% CL. [k] 80.0% CL. [l] 99.0% CL. [m] <90.0% CL. [n] 20.0% CL. [o] 90.0% CL.

value of 0.59, calculated above, was used. The half-lives of the 3′-substituted 2-NO_2-6-CO_2H-2′-MeO-biphenyls show a good correlation with eq 4 (set 2). The Student's t tests show that α and β are not significant while ψ is significant. The value of β is small as is expected for a substituent in the meta position. Correlation was therefore examined with the equation

$$\log t_{1/2,X} = \alpha\sigma_{IX} + \psi\upsilon_X + h \quad (6)$$

The result was an excellent correlation (set 2A). Although α still was not significant, it was more meaningful than it had been in the correlation with eq 5. It is quite possible that had there been more points in the set, α would have been significant. The ψ value is highly significant. Furthermore, the magnitude of ψ is considerably greater than that of α. This is in accord with a buttressing effect of the 3′ substituent as the predominant factor in its behavior. There may also be an electrical effect of the 3′ substituent upon the electron density in the C^1–C^1 bond which affects the ease of rotation.

The half-lives of the 4′-substituted compounds show no significant correlation with eq 5, undoubtedly due to the small size of the set, which contains only five points (set 3). As the Student's t test showed the least significance for ψ, correlation was carried out with the equation

$$\log t_{1.2,X} = \alpha\sigma_{IX} + \beta\sigma_{RX} + h \quad (7)$$

giving fair results (set 3A). Both α and β were significant as determined by the Student's t test. Undoubtedly, better results would have been obtained had more data been available. We interpret the successful correlation with eq 7 to mean that the 4′ substituent exerts an electrical effect upon the C^1–$C^{1'}$ bond which affects the ease of rotation, and does not produce any steric effect whatsoever. This result is in agreement with the reports by a number of authors of correlations of energy barriers to internal rotation with the Hammett equation.[9] Thus, the hitherto obscure effect of the 4′ substituents can now be well understood.

The half-lives of the 5′-substituted compounds show no significant correlation with eq 4 (set 4). Again, the value of β is small. The Student's t test shows that ψ is more significant than β. Therefore, correlation was carried out with eq 7. The result was a fair correlation, with α being significant and ψ not significant (set 4A). Correlation was then carried out with the equation

$$\log t_{1/2X} = \alpha\sigma_{IX} + h \quad (9)$$

Results of this correlation are given in Table II (set 4B). A good result was obtained. Thus, 5′ substituents appear to exert only an electrical effect upon the rate of racemization. The difference between the 3′ and 5′ substituents is that the former are adjacent to a MeO group whereas the latter are adjacent to a very much smaller hydrogen atom and therefore do not show a buttressing effect.

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Heterocycles from *N*-Ethoxycarbonylthioamides and Dinucleophilic Reagents. 3. Six- and Seven-Membered Rings with Two or Three Heteroatoms

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Reactions of *N*-ethoxycarbonylthioamides (1) with dinucleophilic reagents have allowed convenient preparation of a variety of heterocyclic compounds.[1] Depending upon the relative positions of the two nucleophilic sites in the reagent, these reactions have been observed to proceed in either of two manners. When the nucleophilic groups are adjacent, reaction occurs at both thiocarbonyl and carbonyl of 1 with elimination of H_2S and EtOH and formation of a five-membered, carbonyl-containing heterocycle. Thus, reactions with hydrazines and hydroxylamines yield triazolones and oxadiazolones, respectively.[1a] However, only the thiocarbonyl of 1 participates in reactions with 1,2-dinucleophilic reagents $H_2NCH_2CH_2YH$ and o-$H_2NC_6H_4YH$ (Y = NH, O, S), which take place with elimination of H_2S and ethyl carbamate and lead to dihydroimidazoles, -oxazoles, -thiazoles and benzimidazoles, -oxazoles, -thiazoles, respectively.[1b]

We have now found that reactions of 1 with 1,1-dinucleophilic reagents follow the former, whereas those with 1,3 or 1,4 such reagents the latter course. These and our earlier[1] results indicate that initial interaction between the thiocarbonyl of 1 and an amino group of the reagent results in elimination of H_2S and formation of C=N. The second nucleo-

Scheme I. Reactions of ArC(=S)NHCOOEt with 1,1-, 1,3-, and 1,4-Dinucleophilic Reagents

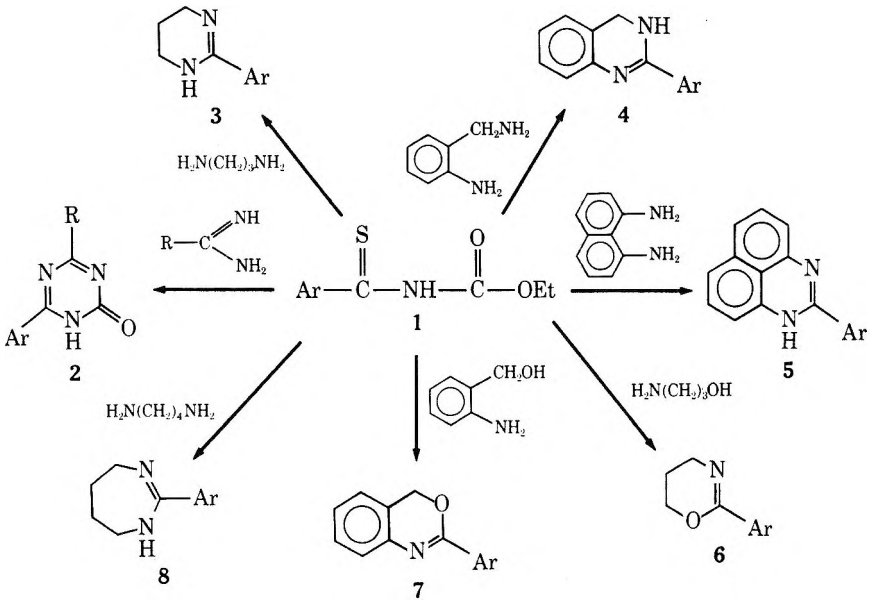
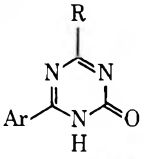


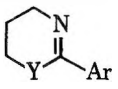
Table I.[a] **1,3,5-Triazin-2(1*H*)-ones (2)**



Registry no.	R	Ar	Yield,[b] %	Mp, °C	IR (C=O), cm^{-1}	NMR, ppm
1917-36-8	Ph	4-MeC_6H_4[c]	50[d]	282.5–283.5[e,f]	1690	2.5 (s, 3), 7.3–7.7 (m, 5), 8.2–8.5 (m, 4), 12.0 (s, 1)[g]
1917-38-0	Ph	4-ClC_6H_4[c]	57[d]	286–288[e,h]	1695	7.5–7.8 (m, 5), 8.3–8.5 (m, 4), 11.3 (s, 1)[g]
62460-53-1	Ph	2-Pyrrolyl[c]	71[d]	312–313 dec[i]	1670	6.2 (m, 1), 7.1 (m, 1), 7.3–7.5 (m, 4), 8.3–8.5 (m, 2), 11.8 (br s, 1)
1917-40-4	Ph	Et[c]	55[d]	231–233[i,j]	1690	1.3 (t, 3), 2.6 (q, 2), 7.3–7.5 (m, 3), 8.0–8.2 (m, 2), 12.4 (br s, 1)
62460-54-2	$PhCH_2S$	4-MeC_6H_4[k]	87[l]	231–232.5[i]	1670	2.6 (s, 3), 4.9 (s, 2), 7.4 (s, 5), 7.5 (m, 2), 8.3 (m, 2), 11.6 (s, 1)[g]
62460-55-3	$PhCH_2S$	4-ClC_6H_4[k]	85[l]	217.5–218.5[i]	1660	4.9 (s, 2), 7.4 (s, 5), 7.7 (m, 2), 8.3 (m, 2), 11.6 (s, 1)[g]
62460-56-4	$PhCH_2S$	4-$EtOC_6H_4$[k]	76[l]	241.5–243[e]	1660	1.5 (t, 3), 4.3 (q, 2), 4.8 (s, 2), 7.2 (m, 2), 7.4 (s, 5), 8.4 (m, 2), 11.5 (s, 1)[g]

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or recrystallized product with melting point lower than that of the pure compound by not more than 10 °C. [c] Reaction run in EtOH with EtONa used to liberate $PhC(=NH)NH_2$ from its HCl salt. [d] The reaction mixture was evaporated to one-half its volume, chilled, and filtered. [e] Recrystallized from *n*-BuOH. [f] Lit. mp 284 °C: E. Degener, H.-G. Schmelzer, and H. Holtschmidt, *Angew. Chem., Int. Ed. Engl.*, 5, 960 (1966). [g] In CF_3COOD. [h] Lit. mp 287–288 °C: ref in *f*. [i] Recrystallized from EtOH. [j] Lit. mp 230 °C: ref in *f*. [k] Reaction run in MeOH with MeONa used to liberate $PhCH_2SC(=NH)NH_2$ from its HCl salt. [l] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed with cold H_2O.

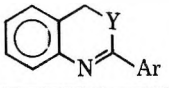
Table II.[a] 1,4,5,6-Tetrahydropyrimidines (3) and 5,6-Dihydro-4*H*-1,3-oxazines (6)



Registry no.	Y	Ar	Yield,[b] %	Mp (bp), °C	NMR, ppm
62460-57-5	NH	4-MeC_6H_4[c]	77[d]	116.5–118.5[e]	1.7 (m, 2), 2.3 (s, 3), 3.3 (m, 4), 5.8 (s, 1), 7.1 (m, 2), 7.6 (m, 2)
46313-35-3	NH	4-$MeOC_6H_4$[c]	63[d]	131.5–133[f]	1.6 (m, 2), 3.3 (m, 4), 3.7 (s, 3), 5.9 (s, 1), 6.7 (m, 2), 7.5 (m, 2)
26131-42-0	NH	2-Thienyl[c]	94[g]	184–186[h,i]	1.7 (m, 2), 3.4 (m, 4), 7.2 (m, 1), 7.6 (m, 2)
62460-58-6	NH	2-Pyrrolyl[j]	94[d]	163–164.5[e]	1.7 (m, 2), 3.3 (m, 4), 5.9 (m, 1), 6.4 (m, 1), 6.6 (m, 1), 7.9 (s, 2)
10431-91-1	O	Et[c]	60[k]	(70–71 (43 Torr))[l]	1.0 (t, 3), 1.5–2.2 (m, 4), 3.2 (m, 2), 3.9 (m, 2)
43221-69-8	O	4-MeC_6H_4[j]	50[k]	(121–123 (2 Torr))[m,n]	1.8 (m, 2), 2.3 (s, 3), 3.4 (m, 2), 4.2 (m, 2), 7.0 (m, 2), 7.5 (m, 2)
62460-59-7	O	4-BrC_6H_4[c]	63[o]	73.5–75[p,q]	1.9 (m, 2), 3.5 (m, 2), 4.3 (m, 2), 7.7 (m, 4)
62460-60-0	O	2-Pyrrolyl[j]	60[d]	139–141[r]	1.8 (m, 2), 3.4 (m, 2), 4.2 (m, 2), 5.9 (m, 1), 6.3 (m, 1), 6.7 (m, 1), 9.8–11.7 (br s, 1)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or recrystallized material with melting point lower than that of the pure compound by not more than 10 °C. [c] Reaction run in THF. [d] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed with cold water. [e] Recrystallized from benzene–petroleum ether (bp 60–75 °C). [f] Recrystallized from EtOAc–petroleum ether (bp 60–75 °C). [g] The residue obtained as in *d* was first washed with aqueous NaOH and then with H_2O. [h] Recrystallized from EtOAc. [i] Lit. mp 183–185 °C: J. W. McFarland, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, D. R. Chisholm, W. C. Austin, R. N. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan, *J. Med. Chem.*, 12, 1065 (1969). [j] Reaction run in EtOH. [k] After the solvent had been distilled under reduced pressure, the liquid residue was extracted with five 20-mL portions of petroleum ether (bp 35–60 °C) and the product was isolated from the extract by removal of the solvent and distillation of the new residue under reduced pressure. [l] Lit. bp 70 °C (43 Torr): A. Levy and M. Pitt, *Polym. Lett.*, 5, 881 (1967). [m] Lit. bp 122–124 °C (2 Torr): Z. Eckstein, K. Majewski, and P. Gluzinski, *Rocz. Chem.*, 36, 73 (1962). [n] Picrate (recrystallized from EtOH): mp 137–138 °C. Lit. mp 134–135 °C: ref in *m*. [o] The residue obtained as in *g* was extracted repeatedly with boiling petroleum ether (bp 60–75 °C) and the decanted extracts were chilled to yield the product. [p] Recrystallized from petroleum ether (bp 60–75 °C). [q] Lit. bp 130 °C (2.5 Torr): ref in *m*. [r] Recrystallized from aqueous EtOH.

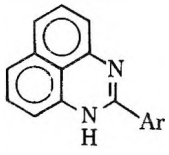
Table III.[a] 3,4-Dihydroquinazolines (4) and 4*H*-1,3-Benzoxazines (7)



Registry no.	Y	Ar	Yield,[b,c] %	Mp, °C	NMR, ppm
62460-61-1	NH	4-MeC_6H_4[d]	50	153–155[e]	2.3 (s, 3), 4.6 (s, 2), 7.0 (m, 4), 7.3 (m, 2), 7.9 (m, 2)
39696-30-5	NH	4-$MeOC_6H_4$[d]	38	177–179[e,f]	3.8 (s, 3), 4.6 (s, 2), 7.0 (m, 6), 7.9 (m, 2)
62460-62-2	O	4-MeC_6H_4[g]	64	104–105.5[h]	2.3 (s, 3), 5.4 (s, 2), 7.2 (m, 4), 7.3 (m, 2), 7.9 (m, 2)
62460-63-3	O	4-$MeOC_6H_4$[g]	67	142–143[h,i]	3.8 (s, 3), 5.4 (s, 2), 7.3 (m, 4), 7.1 (m, 2), 8.1 (m, 2)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed successively with cold 10% aqueous NaOH and cold H_2O. [c] Crude or recrystallized material with melting point lower than that of the pure compound by not more than 7 °C. [d] Reaction run in MeOH with MeONa used to liberate o-$H_2NC_6H_4CH_2NH_2$ from its dihydrochloride salt. [e] Recrystallized from aqueous EtOH. [f] Lit. mp 178–179 °C: M. Lora-Tamayo, R. Madroñero, and G. Garcia Muñoz, *Chem. Ber.*, 94, 208 (1961). [g] Reaction run in THF. [h] Recrystallized from petroleum ether (bp 60–75 °C). [i] Lit. mp 138–142 °C: B. Witkop, J. B. Patrick, and H. M. Kissmary, *Chem. Ber.*, 85, 949 (1952).

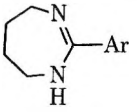
Table IV.[a] Perimidines (5)



Registry no.	Ar	Yield,[b,c] %	Mp, °C	NMR, ppm
15666-84-9	Ph[d]	95	186–188[e,f]	6.6 (m, 2), 7.1 (m, 4), 7.5 (m, 3), 8.0 (m, 2), 10.6 (s, 1)
62460-64-4	4-*i*-PrC_6H_4[g]	83	191.5–193.5 dec[h,i]	1.2 (d, 6), 2.9 (m, 1), 6.5 (m, 1), 6.6 (m, 1), 7.1 (m, 4), 7.3 (m, 2), 7.9 (m, 2), 10.5 (s, 1)
25110-46-7	4-$MeOC_6H_4$[g]	86	205–207 dec[h,i,j]	3.8 (s, 3), 6.6 (m, 1), 6.7 (m, 1), 7.1 (m, 6), 8.0 (m, 2), 10.6 (s, 1)
62460-65-5	2-Thienyl[d]	88	166–168[e]	6.6 (m, 2), 7.1 (m, 5), 7.7 (m, 1), 7.9 (m, 1), 10.8 (s, 1)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or recrystallized material with melting point lower than that of the pure compound by not more than 10 °C. [c] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed with water. [d] Reaction run in benzene. [e] Recrystallized from cyclohexane. [f] Lit. mp 188 °C: W. A. Mosher and T. E. Banks, *J. Org. Chem.*, 36, 1477 (1971). [g] Reaction run in THF. [h] Recrystallized from benzene. [i] Formation of black tar upon melting hinders exact determination of melting point. [j] Lit. mp 205 °C [F. Sachs and M. Steiner, *Chem. Ber.*, 42, 3674 (1909)]; 210–211 °C dec [ref in *f*]; 212 °C [N. P. Buu-Hoi, P. Jacquignon, and M. Marty, *Bull. Soc. Chim. Fr.*, 461 (1960)].

Table V.[a] 4,5,6,7-Tetrahydro-1*H*-1,3-diazepines (8)



Registry no.	Ar[b]	Yield,[c,d] %	Mp,[e] °C	NMR,[f] ppm
62460-50-8	4-MeC_6H_4	40	115–116.5	1.8 (m, 4), 2.3 (s, 3), 3.5 (m, 4), 4.8 (s, 1), 7.1 (m, 2), 7.6 (m, 2)
62460-51-9	4-BrC_6H_4	52	137.5–139	1.8 (m, 4), 3.5 (m, 4), 4.7 (s, 1), 7.5 (s, 4)
62460-52-0	4-ClC_6H_4	57	132.5–134	1.8 (m, 4), 3.5 (m, 4), 4.8 (s, 1), 7.3 (m, 2), 7.5 (m, 2)
62505-86-6	2-Pyrrolyl	25	141.5–142.5	1.7 (m, 4), 3.4 (m, 4), 6.2 (m, 1), 6.4 (m, 1), 6.9 (m, 1), 7.2 (s, 2)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds listed in this table. [b] Reactions run in THF. [c] The reaction mixture was evaporated to dryness under reduced pressure and the residue was boiled repeatedly with petroleum ether (bp 60–75 °C). Chilling of the decanted extracts yielded the product. [d] Recrystallized material with melting point lower than that of the pure compound by not more than 5 °C. [e] Recrystallization from petroleum ether (bp 60–75 °C). [f] In $CDCl_3$.

philic group attacks the ester carbonyl of the intermediate[1a] only if the possibility exists for a five- or six-membered, carbonyl-containing ring to be formed. When this ring would be seven-membered or larger, the second nucleophilic group reacts instead with the C=N of the intermediate to cause elimination of ethyl carbamate and formation of a ring incorporating only the thiocarbonyl carbon atom of **1**.

Thus, *N*-ethoxycarbonylthioamides (**1**) react with benzamidine or 2-benzyl-2-thiopseudothiourea following the first route to yield 1,3,5-triazin-2(1*H*)-ones (**2**, Table I). On the other hand, the second pathway is followed in reactions of **1** with 1,3-diaminopropane, *o*-aminobenzylamine, or 1,8-diaminonaphthalene and the products are 1,4,5,6-tetrahydropyrimidines (**3**, Table II), 3,4-dihydroquinazolines (**4**, Table III), or perimidines (**5**, Table IV), respectively. Use of 3-amino-1-propanol or *o*-aminobenzyl alcohol leads correspondingly to 5,6-dihydro-4*H*-1,3-oxazines (**6**, Table II), or 4*H*-1,3-benzoxazines (**7**, Table III). Finally, treatment of **1** with 1,4-diaminobutane results in convenient formation of 4,5,6,7-tetrahydro-1*H*-1,3-diazepines (**8**, Table V) (Scheme I).

The structures of these products were established by preparation of known members of the various series, as well as by spectroscopic (IR, NMR) and microanalytical data. As before,[1] the reactions were generally run in tetrahydrofuran, ethanol, or methanol, at reflux, and their progress was followed by monitoring the H_2S evolution. Because in some cases (especially those involving use of 1,4-diaminobutane), the NMR spectrum of the crude product indicated incomplete ring closure by the time H_2S had ceased to be evolved, refluxing of the reaction mixture was usually allowed to proceed for an additional 2–3 h or simply overnight.

The reactions described in this paper, characterized by simplicity of operation, ease of product isolation and, in most cases, good yield, further establish the usefulness of *N*-ethoxycarbonylthioamides as starting materials for the synthesis of heterocyclic compounds.

Experimental Section[2]

***N*-Ethoxycarbonylthioamides (1)** were prepared as reported earlier.[1,3]

General Procedure for Preparation of Compounds 2–8. A solution of 0.010 mol of **1** and 0.012 mol of the dinucleophilic reagent in 10 mL of solvent (0.020 mol of reagent and 50 mL of solvent for compounds **8**) was refluxed until evolution of H_2S had ceased (PbOAc paper) and for an additional 2–3 h (or overnight). The reaction mixture was then treated as indicated in Tables I–V.

Acknowledgments. Financial support by the Research Corporation, the Research Allocations Committee of The University of New Mexico, and the Department of Chemistry of The University of New Mexico is gratefully acknowledged.

Registry No.—**1** (Ar = 4-MeC_6H_4), 57774-66-0; **1** (Ar = 4-ClC_6H_4), 57774-74-0; **1** (Ar = 2-pyrrolyl), 37488-43-0; **1** (Ar = Et), 59812-12-3; **1** (Ar = 4-$EtOC_6H_4$), 57774-73-9; **1** (Ar = 4-$MeOC_6H_4$), 57774-72-8; **1** (Ar = 2-thienyl), 51774-59-5; **1** (Ar = 4-BrC_6H_4), 57774-75-1; **1** (Ar = Ph), 5499-31-0; **1** (Ar = 4-*i*-PrC_6H_4), 57774-68-2; benzenecarboximidamide, 618-39-3; benzyl carbamimidothioate, 621-85-2; 1,3-propanediamine, 109-76-2; 2-aminobenzenemethanamine, 4403-69-4; 1,8-naphthalenediamine, 479-27-6; 3-amino-1-propanol, 156-87-6; 2-aminobenzenemethanol, 5344-90-1; 1,4-butanediamine, 110-60-1.

References and Notes

(1) (a) B. George and E. P. Papadopoulos, *J. Org. Chem.*, **41**, 3233 (1976); (b) *ibid.*, **42**, 441 (1977).
(2) Melting points were determined in capillaries by use of a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer using mineral oil mulls. NMR spectra were obtained on a Varian EM360 spectrometer using solutions in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) with tetramethylsilane as internal standard.
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Monochloroborane–Methyl Sulfide, $H_2BCl{\cdot}S(CH_3)_2$, and Dichloroborane–Methyl Sulfide, $HBCl_2{\cdot}S(CH_3)_2$, as New Stable Hydroborating Agents with High Regiospecificity

Summary: Monochloroborane-methyl sulfide, $H_2BCl{\cdot}SMe_2$, and dichloroborane–methyl sulfide, $HBCl_2{\cdot}SMe_2$, are new highly stable hydroborating agents with major advantages over the corresponding unstable etherates.

Sir: Monochloroborane–methyl sulfide, $H_2BCl{\cdot}SMe_2$, and dichloroborane–methyl sulfide, $HBCl_2{\cdot}SMe_2$, are readily synthesized by redistribution of $H_3B{\cdot}SMe_2$ with $Cl_3B{\cdot}SMe_2$ in the appropriate ratios (eq 1, 2). The products are stable indefinitely at room temperature. Yet they hydroborate olefins readily with high regiospecificity and provide a valuable advantageous route to the corresponding dialkylboron chlorides, R_2BCl, and monoalkylboron dichlorides, $RBCl_2$, and to the many derivatives into which these may be transformed.

$$2H_3B{\cdot}SMe_2 + Cl_3B{\cdot}SMe_2 \xrightarrow{25\ ^\circ C} 3H_2BCl{\cdot}SMe_2 \quad (1)$$

$$H_3B{\cdot}SMe_2 + 2Cl_3B{\cdot}SMe_2 \xrightarrow{25\ ^\circ C} 3HBCl_2{\cdot}SMe_2 \quad (2)$$

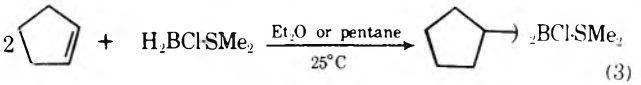
The chloroborane etherates, $H_2BCl{\cdot}OEt_2$ and $HBCl_2{\cdot}OEt_2$, are valuable hydroborating agents, achieving hydroboration with exceptionally high regiospecificity and providing important new routes to the alkylboron chlorides, $RBCl_2$ and R_2BCl.[1,2] The latter derivatives are revealing valuable versatility as intermediates for synthetic applications.[3-8]

Unfortunately, the synthesis of the chloroborane etherates proceeds from lithium borohydride,[1,2] a relatively expensive intermediate. Moreover, the chloroborane etherates must be handled as dilute solutions in ethyl ether. They possess limited stability. They must be freshly prepared and used shortly after their synthesis.

The discovery that borane–methyl sulfide and boron trichloride–methyl sulfide undergo redistribution rapidly at 25 °C[9] led us to undertake the synthesis, characterization, and examination as hydroborating reagents of the products, $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$ (eq 1, 2). The synthesis proved exceptionally simple—it was necessary only to mix borane–methyl sulfide[10] with boron trichloride–methyl sulfide.[9,11] The neat products appeared to be stable indefinitely, as indicated by NMR observations over long periods of time. Accordingly, we examined their hydroborating characteristics. These proved excellent, achieving all of the valuable transformations previously achieved by the chloroborane etherates.

Thus, $H_2BCl{\cdot}SMe_2$ reacts with olefins rapidly at 25 °C in ether or pentane to give the corresponding dialkylboron chlorides. The reaction is general, as indicated by the quantitative reaction of the representative olefins, 1-hexene, 1-octene, *cis*-3-octene, styrene, 2-methyl-1-butene, 2-methyl-2-butene, 1-methylcyclopentene, and norbornene, in <2 h at 25 °C. The regiospecificity achieved in hydroboration with $H_2BCl{\cdot}SMe_2$ is comparable with that with $H_2BCl{\cdot}OEt_2$, as shown in Table I, where the relative yields of the isomeric alcohols produced in the hydroboration–oxidation of the representative olefins with the two reagents are summarized.

The product of the reaction of olefins with $H_2BCl{\cdot}SMe_2$ is the corresponding dialkylchloroborane–methyl sulfide addition compound, $R_2BCl{\cdot}SMe_2$ (eq 3). Pure R_2BCl is obtained



(3)

free of Me_2S by removal of the reaction solvent followed by distillation under low pressure.[12] The corresponding *B*-alkoxy derivatives are obtained by alcoholysis of the hydroboration

Table I. Isomeric Alcohols from the Hydroboration–Oxidation of Representative Olefins with $H_2BCl{\cdot}SMe_2$ at 25 °C and $H_2BCl{\cdot}OEt_2$ at 0 °C

Olefin	Solvent for $H_2BCl{\cdot}SMe_2$	Isomeric alcohols	Isomeric products, %	
			$H_2BCl{\cdot}SMe_2$[a]	$H_2BCl{\cdot}OEt_2$[b]
1-Hexene	Ether	1-Hexanol	99.2	>99.5
		2-Hexanol	0.8	<0.5
1-Hexene	Pentane	1-Hexanol	99.2	
		2-Hexanol	0.8	
Styrene	Ether	2-Phenylethanol	93	96
		1-Phenylethanol	7	4
Styrene	Pentane	2-Phenylethanol	93	
		1-Phenylethanol	7	
2-Methyl-1-butene	Pentane	2-Methyl-1-butanol	>99.9	>99.9
		2-Methyl-2-butanol	<0.1	<0.1
Norbornene	Pentane	*exo*-2-Norbornanol	>99.5	>99.8
		endo-2-Norbornanol	<0.5	<0.2
2-Methyl-2-butene	Pentane	3-Methyl-2-butanol	>99.5	99.7
		2-Methyl-2-butanol	<0.5	0.3
1-Methylcyclopentene	Pentane	*trans*-2-Methylcyclopentanol	99.5	>99.8
		1-Methylcyclopentanol	0.5	<0.2
		cis-2-Methylcyclopentanol	0	0
α-Methylstyrene	Pentane	2-Phenyl-1-propanol	>99.9	100
		2-Phenyl-2-propanol	<0.1	0

[a] Total yields were 95 ± 4%. [b] Reference 1.

Table II. Syntheses of Alkylboron Derivatives by the Hydroboration of Olefins with $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$

Dialkylboron derivative	Solvent	Yield, %	Bp, °C (mm)
Methyl di-*n*-butylborinate	Pentane	93[a]	
Methyl di-*sec*-butylborinate	Pentane	89[a]	
Methyl diisobutylborinate	Pentane	93[a]	
Methyl dicyclopentylborinate	Ether	89[b]	
Diisobutylchloroborane	Ether	84[c]	78–80 (62)
Dicyclopentylchloroborane	Pentane	79[c]	69–70 (1.2)
Dicyclopentylchloroborane	Ether	81[c]	69–70 (1.2)
Di-*n*-butylchloroborane	Ether	85[c]	68–70 (19)
n-Octyldichloroborane	Pentane	85[c]	92–94 (19)

[a] GLC yield. [b] Yield determined by ^1H NMR using benzene as the internal standard. [c] Yields by isolation of the product.

mixture followed by distillation (eq 4). The results of the syntheses of the representative dialkylboron derivatives are given in Table II.

$$R_2BCl{\cdot}SMe_2 + R'OH \rightarrow R_2BOR' + Me_2S + HCl \quad (4)$$

The reaction of $HBCl_2{\cdot}SMe_2$ with olefins is slow and incomplete in pentane or ether, similar to the slow reaction of the etherate $HBCl_2{\cdot}OEt_2$.[2] Again, as in the case of the etherate,[2] $HBCl_2{\cdot}SMe_2$ reacts with olefins cleanly and quantitatively at 25 °C in pentane in the presence of 1 mol equiv of BCl_3 to give the corresponding alkyldichloroborane, $RBCl_2$. The $Cl_3B{\cdot}SMe_2$ precipitates from the reaction medium during the reaction (eq 5). The $RBCl_2$ is readily isolated from the reaction mixture by distillation following removal of the solid $Cl_3B{\cdot}SMe_2$ by filtration under nitrogen. *n*-Octyldichloroborane was isolated in 85% yield by this method.

$$\text{olefin} + HBCl_2{\cdot}SMe_2 \xrightarrow[BCl_3]{\text{pentane}} RBCl_2 + Cl_3B{\cdot}SMe_2\downarrow \quad (5)$$

The following experimental procedure is typical. The addition compound, $Cl_3B{\cdot}SMe_2$, mp 86–87 °C, was prepared by adding boron trichloride to an equimolar amount of methyl sulfide. The $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$ were then prepared by mixing the two reagents, $Cl_3B{\cdot}SMe_2$ and $H_3B{\cdot}SMe_2$,[10] in the stoichiometric ratios (eq 1, 2). Cyclopentene (210 mmol) was dissolved in 90 mL of pentane or ether at 0 °C under nitrogen. While stirring at 0 °C, 100 mmol of $H_2BCl{\cdot}SMe_2$ was slowly added and the stirring continued for 2 h at 25 °C. The solvent was then removed using a water aspirator and pure dicyclopentylchloroborane[12] was obtained by distillation at 69–70 °C (1.2 mm) in 79–81% yield. The methyl dicyclopentylborinate was synthesized in 89% yield by methanolyzing the reaction mixture of cyclopentene and $H_2BCl{\cdot}SMe_2$[13] with 100% excess methanol, followed by removal of the solvent, the excess methanol, and the hydrogen chloride with a water aspirator. The regiospecificity in the hydroboration with $H_2BCl{\cdot}SMe_2$ was established as described earlier for $H_2BCl{\cdot}OEt_2$.[1]

For the synthesis of *n*-octyldichloroborane, 50 mmol of 1-octene was dissolved in 61 mL of pentane and cooled to 0 °C; 25 mL of a 2 M solution of BCl_3 in pentane was added. While the mixture stirred at 0 °C, 50 mmol of $HBCl_2{\cdot}SMe_2$ was slowly added. The mixture was stirred for 2 h at 25 °C. The procedure then follows that previously described for the isolation of the $RBCl_2$ using $HBCl_2{\cdot}OEt_2$. *n*-Octyldichloroborane was isolated in 85% yield.

Although the reactivity and usefulness of $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$ are comparable with those of the corresponding chloroborane etherates reported previously, these new reagents are far more advantageous and convenient to use, as a consequence of their indefinite stability at room temperature and their availability as neat reagents.

Because of the thermal stability of $H_2BCl{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$, these reagents will surely find their major place in the laboratory along with other valuable hydride reagents. This would greatly facilitate application of the recently discovered many synthetically useful reactions of R_2BCl and $RBCl_2$ and their derivatives.[3-8]

References and Notes

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(2) H. C. Brown and N. Ravindran, *J. Am. Chem. Soc.*, **98**, 1798 (1976).
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(8) B. A. Carlson and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 6876 (1973).
(9) H. C. Brown and N. Ravindran, *Inorg. Chem.*, in press.
(10) Available from Aldrich-Borane, a subsidiary of the Aldrich Chemical Co., Milwaukee, Wis.
(11) M. Schmidt and H. D. Block, *Chem. Ber.*, **103**, 3705 (1970).
(12) In the case of unhindered R_2BCl, like *n*-Bu_2BCl, the methyl sulfide addition compound breaks up completely upon vacuum distillation only, whereas in hindered cases like *sec*-Bu_2BCl, the Me_2S addition compounds breaks up completely at 25 °C under aspirator vacuum (10–20 mm).
(13) NMR examination of $H_2BCl{\cdot}SMe_2$ reveals the presence of small amounts of $H_3B{\cdot}SMe_2$ and $HBCl_2{\cdot}SMe_2$. Consequently, the maximum yields of ~93% for R_2BCl (Table II) probably correspond to the actual amount of $H_2BCl{\cdot}SMe_2$ present in the reagent. Distillation readily removes the minor components, R_3B and $RBCl_2$.
(14) Postdoctoral research associate on grants provided by G. D. Searle & Co. and the National Science Foundation (GP 6942X and 41169X).

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Lithium *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonyl Hydride. A New Reagent for the Asymmetric Reduction of Ketones with Remarkable Consistency

Summary: Lithium *B*-isopinocampheyl-9-borabicyclo-[3.3.1]nonyl hydride [Li(HB-IPC-9-BBN)], a highly hindered trialkylborohydride containing an asymmetric alkyl group, reduces rapidly and quantitatively a variety of ketones to the corresponding optically active alcohols, consistently enriched in the *R* enantiomer.

Sir: The asymmetric reduction of ketones has been examined with a number of chiral metal hydride complexes.[1] In particular, lithium aluminum hydride complexes with chiral alkaloids (ephedrine, quinine, cinchonine, etc.), chiral amino alcohols [(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol], and monosaccharides (3-*O*-benzyl-1,2-cyclohexylidene-α-D-glucofuranose) have been recently explored in detail. Unfortunately, such reagents appear not reliable for stereochemical correlations. In the majority of cases, the precise structures of the reducing species are not well defined. Further, both enantiomeric forms of the complexing agent may not be available, thereby limiting the choice of the enantiomer to be synthesized.

Table I. Asymmetric Reduction of Representative Ketones with Lithium *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonyl Hydride in Tetrahydrofuran at −78 °C [a,b]

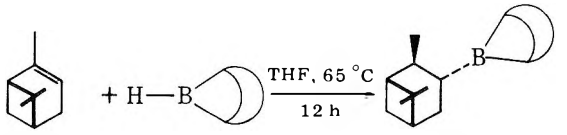
Ketone	Workup procedure[c]	Alcohol[d] (lit.[e] 100% e.e.)	$[\alpha]^{25}_D$, deg, measd	Optical purity, %	Confign
2-Butanone	A	2-Butanol (13.5)	−3.85	29	*R*
2-Hexanone	A	2-Hexanol (11.6)	−3.46	30	*R*
3-Methyl-2-butanone	A	3-Methyl-2-butanol (5.3)	−1.91	36	*R*
3,3-Dimethyl-2-butanone	A	3,3-Dimethyl-2-butanol (8.1)	−0.23	3	*R*
4-Methyl-2-pentanone	A	4-Methyl-2-pentanol (20.5)	−3.38	16	*R*
Acetophenone	B	1-Phenylethanol (42.9)	+6.95	17	*R*
2-Methyl-3-pentanone	A	2-Methyl-3-pentanol (9.8)	+3.61	37	*R*
Propiophenone	B	1-Phenylpropanol (27.7)	+3.6	13	*R*
2-Methylcyclohexanone[f]	B	*cis*-2-Methylcyclohexanol (21.2)	−3.05	14	1*R*,2*S*

[a] Reactions were carried out essentially in stoichiometric ratio of reagent and ketone (10% excess hydride); concentrations were 0.3 M. [b] Precooled hydride solution (−78 °C) was added to the ketone solution of THF maintained at −78 °C; reductions were essentially over in 1 h. [c] A, oxidative workup; B, hydrolysis and direct distillation. [d] Alcohols were isolated in 70–80% range and purified by preparative GLC. [e] W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Oxford University Press, New York, N.Y., 1974. The values listed are the maximum values for $[\alpha]_D$, degree, reported, presumably 100% e.e. or close to that quality. [f] One mole equivalent of hydride was added to 2 mol equiv of the ketone.

Very recently conditions were developed for the synthesis from (+)-α-pinene of (−)-diisopinocampheylborane (IPC_2BH) in high optical purity.[2] The hydroboration of *cis*-2-butene with this high purity reagent followed by oxidation provided (*R*)-(−)-2-butanol in 98.4% e.e. (enantiomeric excess), indicating essentially complete asymmetric induction. It has also been examined in considerable depth for the asymmetric reduction of ketones.[3] Unfortunately, the rate of reduction with hindered ketones is quite sluggish and side reactions, such as the displacement of α-pinene, occurs with possible changes in the stereochemical results.

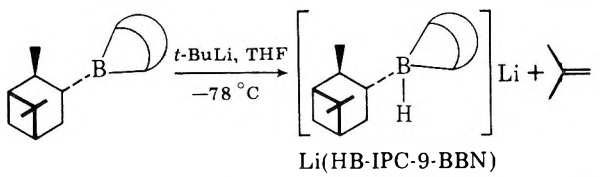
Moreover, lithium trialkylborohydrides have recently emerged as highly attractive reducing agents.[4] One of the major applications of hindered trialkylborohydrides is their ability to introduce steric control in the reduction of cyclic ketones. Thus, the discovery of lithium tri-*sec*-butylborohydride and lithium trisiamylborohydride have revolutionized procedures for the stereoselective reduction of cyclic ketones.[5,6]

In the course of our extensive study of highly hindered trialkylborohydrides, we examined a number of borohydride anions derived from *B*-alkyl-9-borabicyclo[3.3.1]nonane (B-alkyl-9-BBN) derivatives. Hydroboration of (+)-α-pinene ($[\alpha]^{23}_D$ +49.3°, 96% optically pure) with 9-BBN gives *B*-isopinocampheyl-9-BBN (B-IPC-9-BBN) in quantitative yield[7] (eq 1). This can be readily converted into the corresponding



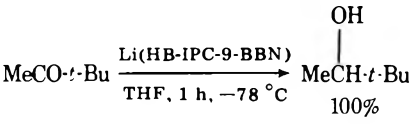
(1*R*,5*R*)-(+)-α-pinene — 100% (1)

trialkylborohydride in quantitative yield[8] (eq 2). ^{11}B NMR



Li(HB-IPC-9-BBN) (2)

of the reagent in tetrahydrofuran (THF) solution exhibits a clean doublet at δ +6.45 (relative to $Et_2O{\cdot}BF_3$), J = 78 Hz. It is an active reducing agent and reduces completely even relatively hindered ketones such as 3,3-dimethyl-2-butanone in <1 h at −78 °C; it is also quite effective in introducing steric control in the reduction of cyclic ketones (eq 3 and 4).



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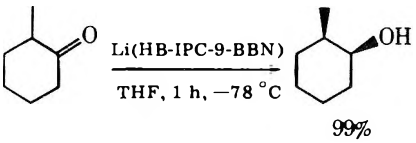
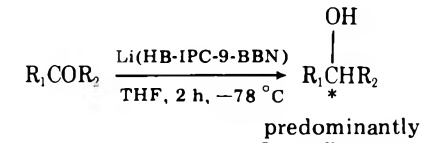


(4)

Consequently, it appeared desirable to explore the applicability of this reagent for the asymmetric reduction of ketones. Accordingly, we undertook to reduce a series of ketones of representative structural features and to examine the resulting alcohols for the magnitude of the optical induction. The general procedure adopted was to add slowly an essentially stoichiometric quantity of the reagent (precooled to −78 °C) to a THF solution of the ketone (cooled to −78 °C). The resulting mixture was stirred for 2 h at −78 °C (eq 5).



predominantly *R* configuration (5)

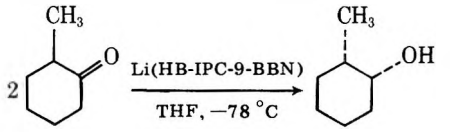
Two procedures can be used to isolate the product. The reaction mixture can be treated with alkaline hydrogen peroxide to oxidize the trialkylborane and the alcohol separated by distillation from 1,5-cyclooctanediol and isopinocampheol. Alternatively, the reaction mixture is hydrolyzed with aqueous potassium carbonate and dried and the alcohol distilled from the trialkylborane. Finally, in both procedures, the alcohol is purified by preparative GLC to remove any optically active components. The results are summarized in Table I.

Thus, 2-butanone is reduced to (*R*)-(−)-2-butanol in 29% e.e. Increasing the chain length has little effect [(*R*)-(−)-2-hexanol obtained in 30% e.e.].

The introduction of a single alkyl substituent in the α position increases the optical induction [(*R*)-(−)-3-methyl-2-butanol, 36% e.e.]. However, introduction of two alkyl substituents decreases the asymmetric induction [(*R*)-(−)-3,3-dimethyl-2-butanol, 3% e.e.]. Going from a particular alkyl

methyl ketone to the corresponding alkyl ethyl ketone does not influence the selectivity significantly [(*R*)-(+)-2-methyl-3-pentanol, 37% e.e.]. Phenyl alkyl ketones also yield alcohols enriched in the *R* enantiomer.

Reduction of 2-methylcyclohexanone represents an interesting case. The ketone already has an asymmetric center. Fortunately, the product is *cis*-2-methylcyclohexanol in 99% isomeric purity. Consequently, the product will contain only two of the four possible diastereomers.[9] Indeed, the product is enriched in (1*R*,2*S*)-(−)-*cis*-2-methylcyclohexanol (eq 6).



(6)

racemic (1*R*,2*S*)-(−)

It is clearly evident from the above discussion that all of the alcohols obtained from the reduction of nine different ketones with this new reagent [from (+)-α-pinene] are consistently enriched in the enantiomer with the *R* configuration.

The following procedure for the asymmetric reduction of 2-hexanone to (*R*)-(−)-2-hexanol is representative. An oven-dried 500-mL flask with a side arm, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was flame dried and cooled under a dry stream of nitrogen. Tetrahydrofuran, 45 mL, was introduced into the reaction flask followed by 8 mL (65 mmol) of 2-hexanone and the contents of the flask were cooled to −78 °C (dry ice–acetone). Then 164 mL (72 mmol) of a 0.44 M solution of Li(HB-IPC-9-BBN) in THF (cooled to −78 °C) was introduced slowly (~15–20 min). The resulting mixture was stirred at −78 °C for 2 h. Then it was brought to 0 °C, excess hydride was destroyed, and the organoborane was oxidized (NaOH, H_2O_2, 60 °C, 2 h). The aqueous phase was saturated with anhydrous K_2CO_3. The THF layer was separated. The aqueous phase was extracted with four 25-mL portions of ether. The combined organic extracts were dried ($MgSO_4$). The volatile solvents were largely removed by distillation through a Widmer column. The pot residue was then transferred to a smaller flask and distilled under reduced pressure, the main fraction being collected at 68–72 °C (40 mm) in a yield of 75–80%.

The 2-hexanol product was purified by preparative GLC, 10% Carbowax 20M, 6 ft × 0.5 in., and appeared to be devoid of any impurities: n^{20}_D 1.4160, $[\alpha]^{23}_D$ −3.46° (neat), 30% e.e. in *R*.

In conclusion, it should be pointed out that the new asymmetric reducing agent reduces even relatively hindered ketones rapidly and quantitatively in <2 h at −78 °C; THF solutions of this reagent appear to be quite stable. The reagent is consistent and highly promising for configurational assignments and stereochemical correlations (no exceptions observed to date). Further, the ready availability of both (+)- and (−)-α-pinene in high optical purities provides a convenient route to both enantiomers. We are actively exploring other applications of this reagent in asymmetric organic synthesis.

References and Notes

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(10) Postdoctoral research associate on a Grant DAAG-29-76-G-0218 from the U.S. Army Research Office.
(11) Postdoctoral research associate on a NATO Fellowship.

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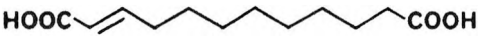
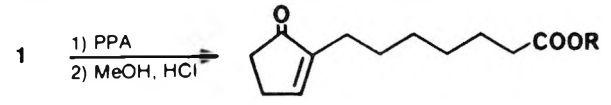
Traumatic Acid

Traumatic acid (*trans*-2-dodecenedioic acid, **1**), first isolated from green bean pods (*Phaseolus vulgaris*) by English *et al.* in 1939,[1] was shown to be capable of promoting renewed growth activity in mature, uninjured cells and tissues. Therefore, it was classed as a plant "wound hormone." Later that year, the same authors reported the structure determination and total synthesis of **traumatic acid**.[2]



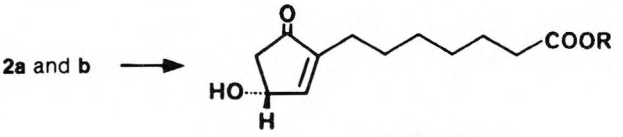
1
Traumatic acid

An important synthetic application of **traumatic acid** is its conversion to keto ester **2a**, a useful prostaglandin intermediate for a variety of 11-deoxyprostanoids such as PGB_1, 11-deoxy-PGE_1, 11,15-bis-deoxy-PGE_1 (also -PGE_2 and -PGF_1), 11-deoxy-13,14-dihydro-PGE_1, 11-deoxy-13,14-dihydro-$PGF_{1\alpha}$ (also -$PGF_{1\beta}$) and 11-deoxy-$PGF_{1\beta}$.[3-6] The transformation of **traumatic acid** to the keto ester **2a** is achieved by treatment with polyphosphoric acid, followed by esterification with methanolic HCl.[7]



2a, R = Me
2b, R = H

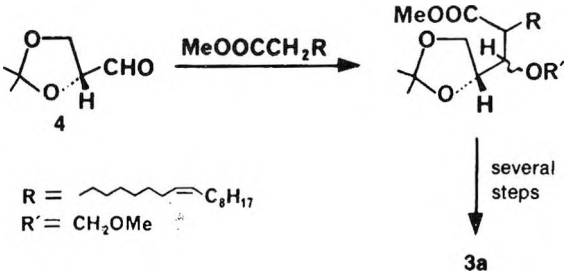
Keto ester **2a**, has been converted to the hydroxy-keto ester **3a**, which has been successfully transformed into 15-deoxy-PGE_1[8] and PGE_1.[4,9]



3a, R = Me
3b, R = H

Methods used to perform this transformation include: microbial hydroxylation of **2b** (using *Aspergillus niger*), which proceeds with partial asymmetric induction giving **3b**;[10] and allylic bromination of **2a**, followed by replacement with acetate and hydrolysis, producing *racemic* **3a**.[11]

Synthesis of optically active **3a** as an intermediate to PGE_1 was recently reported by Stork.[12] Protected **D-glyceraldehyde 4** was used as the starting material to produce intermediate **3a** with the correct absolute configuration. The



stereochemistry of the remainder of the PGE_1 molecule was controlled by the chiral center of the **D-glyceraldehyde** moiety.

Traumatic acid has also been used as a detergent additive to reduce skin irritation,[13] as an antiviral agent, [14] and as a vulnerary (wound-healing) agent.[14] These and other uses for **traumatic acid** are currently under investigation.

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