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THE JOURNAL OF Organic Chemistry

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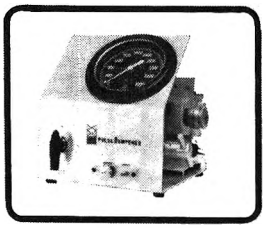

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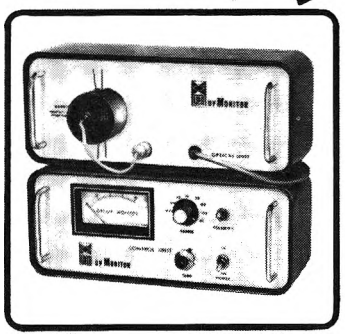

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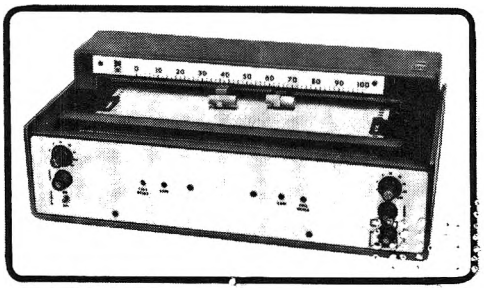

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Editorial Processing Department, American Chemical Society, 20th and Northampton Sts., Easton, Pa. 18042: Head, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, ANDREW J. D'AMELIO.

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JOCEAH 38(13) 2425-2576 (1973)

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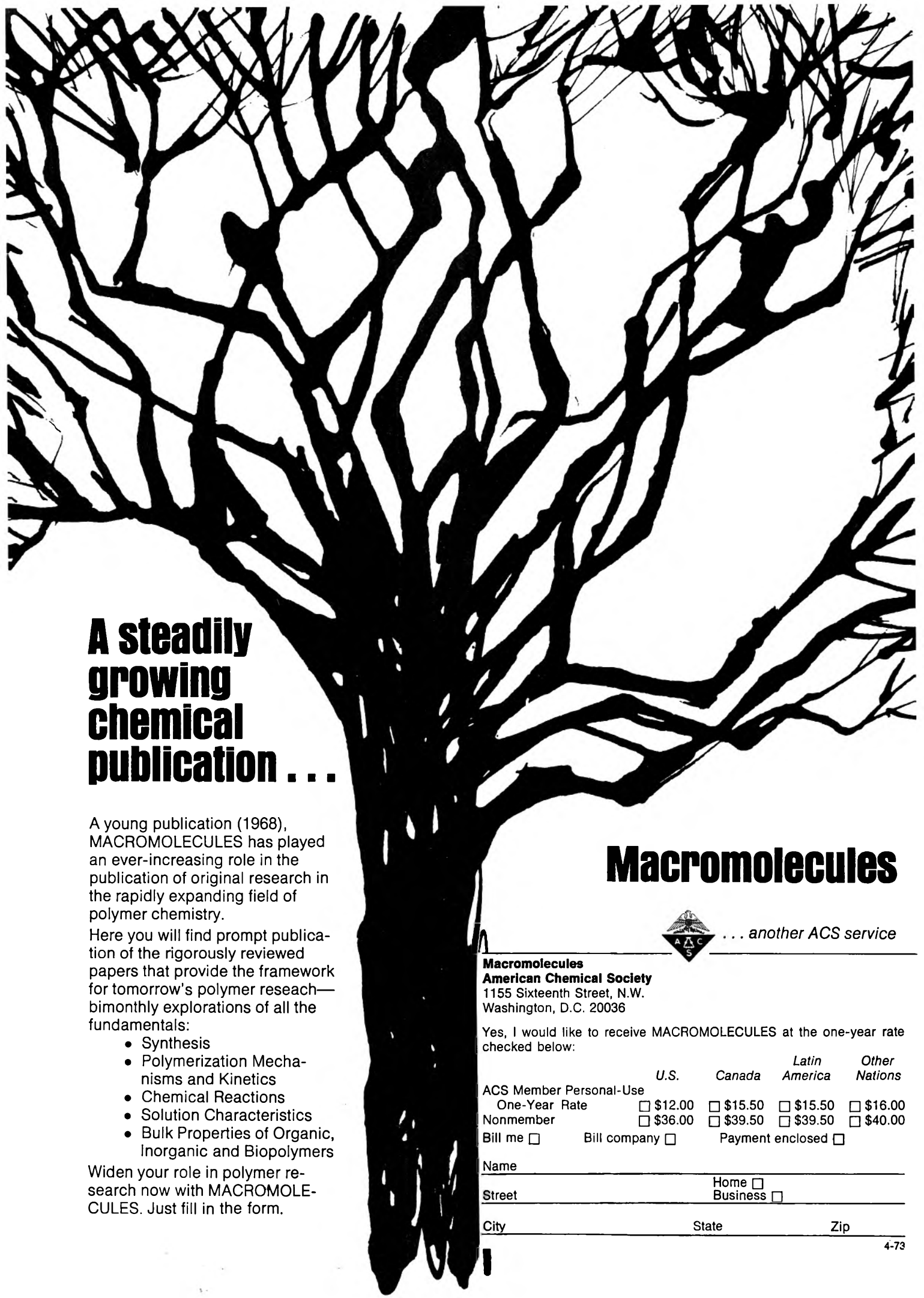

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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 14

JULY 13, 1973

Dyes Containing the Phenalene Ring System. I. Synthesis of Benzothiazole-Containing Dyes

JAMES K. ELWOOD

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received December 7, 1972

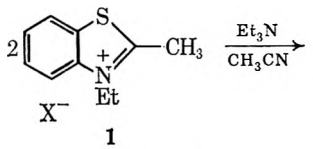
The reactions of 1,3-diethoxy-, 1,4-diethoxy-, 1,6-diethoxy-, 1,4,7-triethoxy-, and 1-ethoxy-6-methoxy-3-methylphenalenium fluoroborates with the methylene base of 3-ethyl-2-methylbenzothiazolium salts and with 3-methyl-2-iminobenzothiazoline gave a variety of dyes of potential photographic interest. The methylene base was found to attack the phenalenium rings at reactive positions bearing hydrogen as well as ethoxy, and to give dyes in the former case by a redox reaction. Some of the dyes absorbed strongly in the near-infrared with very little absorption in the visible. Some unusual chemistry was discovered involving reactions of certain of the alkoxyphenalenium fluoroborates with organic bases.

Although the phenalene ring system has been known for nearly a century, most of the interesting chemistry has appeared during the past 20 years.[1] Compounds containing the phenalene ring may be thought of as "dyes" in the sense that they are generally colored; however, dyes with the phenalene ring in direct conjugation with heterocyclic nuclei are less well known.[2-5]

Results and Discussion

In some recent publications by Hünig and Wolff[2-4] 1,3-diethoxyphenalenium fluoroborate (**3**) was treated with 3-ethyl-2-methylbenzothiazolium fluoroborate (**1**, $X^- = BF_4^-$) under basic conditions to give dyes **4** or **5** depending upon the ratio of reactants.

This reaction was also being explored in these laboratories; however, the methylene base dimer **2b** was



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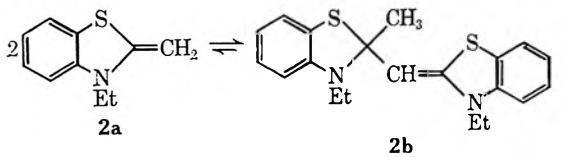
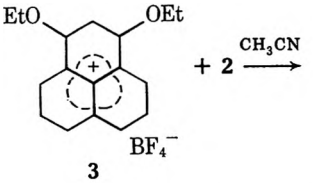


2a **2b**

generally employed to avoid the need for an auxiliary base. In solution, dimer **2b** is known to be in equilibrium with monomer **2a**, which is presumably the reactive species.[6] When a large excess of **2** was employed in the reaction with **3**, dye **6** and small amounts of dye **7** were obtained in addition to dyes **4** and **5**. However, by the dropwise addition of an acetonitrile solution of **2** to a solution of **3** in large excess, the main product was the new dye **8** with **4** as a minor constituent.



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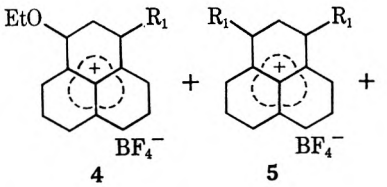
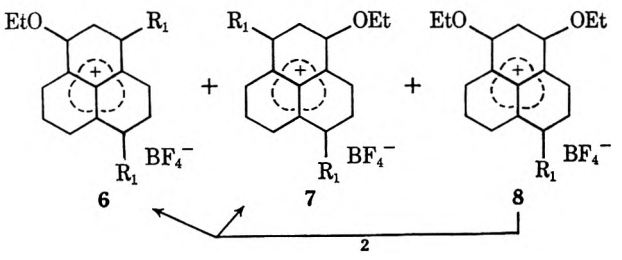
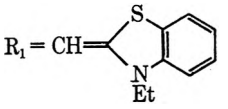


4 **5**



6 **7** **8**



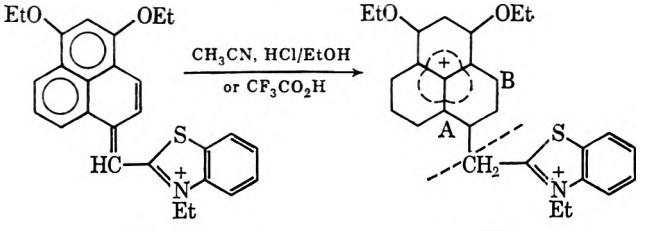
(1) D. H. Reid, *Quart. Rev., Chem. Soc.*, **19**, 274 (1965).
(2) S. Hünig and E. Wolff, *Chimia*, **22**, 33 (1968).
(3) S. Hünig and E. Wolff, *Justus Liebigs Ann. Chem.*, **732**, 7 (1970).
(4) S. Hünig and E. Wolff, *Justus Liebigs Ann. Chem.*, **732**, 26 (1970).
(5) E. Herrmann, A. Treibs, and E. Meissner, *Justus Liebigs Ann. Chem.*, **612**, 229 (1958).
(6) J. R. Owen, *Tetrahedron Lett.*, 2709 (1969).

Clearly, nucleophilic attack can occur at positions of the phenalenium ring carrying hydrogen as well as ethoxy. In the former case, an oxidation–reduction reaction must occur, and the excess **3** presumably functions as a hydride acceptor. Hünig and Wolff have observed similar redox reactions in the reaction of 1-ethoxyphenalenium ions with nitromethane.[4]

It is interesting that in the electronic spectrum of **4** prepared by Hünig and Wolff[4] the absorption band maxima occurred in acetonitrile at 723 nm (ε 2620) as well as at 578 nm (ε 31,800), whereas in the present sample only the absorption at 577 nm (ε 35,200) was observed. It is likely that the former sample contained **8** as an impurity since **8** possesses a maximum at 712 nm (ε 59,400) in acetonitrile.

The products obtained in the two separate reactions of **2** with **3** may be explained as follows: (1) with an excess of the phenalenium ion **3**, methylene base **2** attacked either a ring carbon bearing an ethoxy to give **4** or a ring carbon bearing a hydrogen to give **8** *via* a redox reaction; (2) with an excess of **2**, dyes **4** and **5** were readily formed; however, **4** was not the main intermediate in the formation of **5**, since dye **4** was rather unreactive toward **2** and gave only very small amounts of **5** after several days. The other two dyes **6** and **7** were undoubtedly formed from the reaction of **2** with **8**, which was known to be fast. The transient formation of **8** might be expected: although dimer **2b** was in excess relative to **3**, the reactive monomer **2a** probably was not in excess, at least at the point of addition of **3** to the solution.

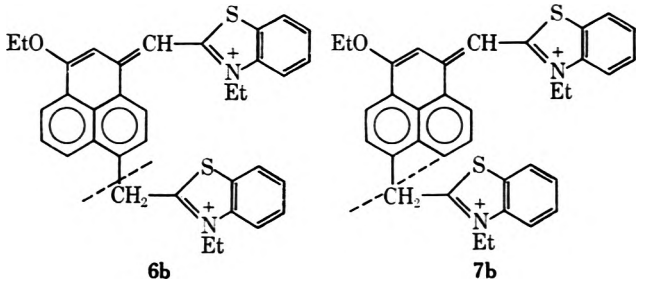
The electronic spectrum of the protonated species **8b** resembled that of **3** and **1** superimposed and lent support to the structure assigned to **8a**. The nmr in CF_3CO_2H of **8b** in comparison with **3** showed a loss of



8a **8b**

one of the resonances at δ 8.9, suggesting attachment at position A in **8b**, since attachment at position B would have resulted in loss of a low-field resonance at δ 9.17, attributed to the hydrogen peri to the ethoxy groups.

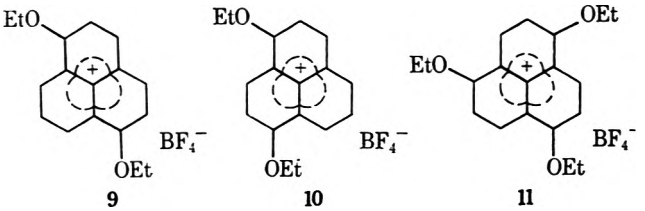
The electronic spectra of acidic solutions of **6** and **7** were nearly identical and resembled remarkably the



6b **7b**

superimposed spectra of dyes **4** and **1**. However, a distinction could not be made without further evidence.

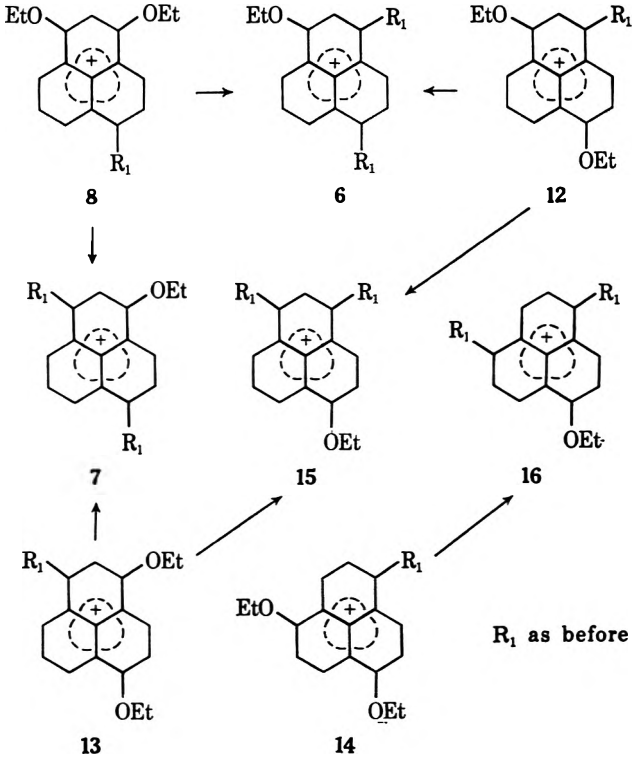
The work was extended by preparing the ethoxyphenalenium salts **9–11** and treating them with meth-



9 **10** **11**

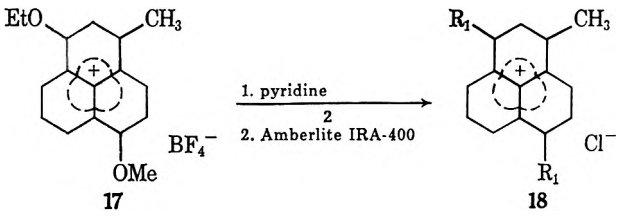
ylene base **2** to give, respectively, the three isomeric blue dyes **12–14** (Scheme I). These dyes were sep-

SCHEME I



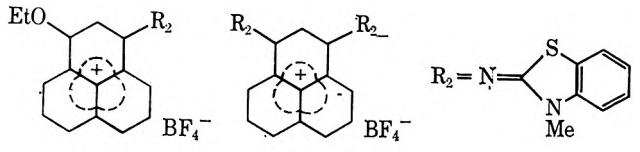
arated from others by column chromatography and recrystallization. The three isomeric dyes (**12–14**), together with a fourth isomer, **8**, provided the necessary intermediates for establishing the structures of the dyes *via* the interrelationships outlined in Scheme I. Each of the four isomers was treated with **2** to give different pairs of isomeric dyes containing two heterocyclic moieties per molecule. Only **14** gave a single secondary dye, since attack at either carbon bearing an ethoxy group led to the same dye. These results, coupled with the analytical and spectral data, were sufficient to allow confidence in the structural assignments.

Since **3** reacted with methylene base **2** to give **5**, it was of interest to look for the isomers of **5** derived from **9** and **10**. Strong evidence for the presence of these compounds in the reaction mixtures of **9** and **10** with **2** was obtained, but the quantities of these isomers obtained were insufficient for characterization. By treating the blocked phenalenium ion **17** with **2** the secondary dye **18** was readily produced which had λ_{max} (MeOH) 905 nm (ε 125,000).



17 18

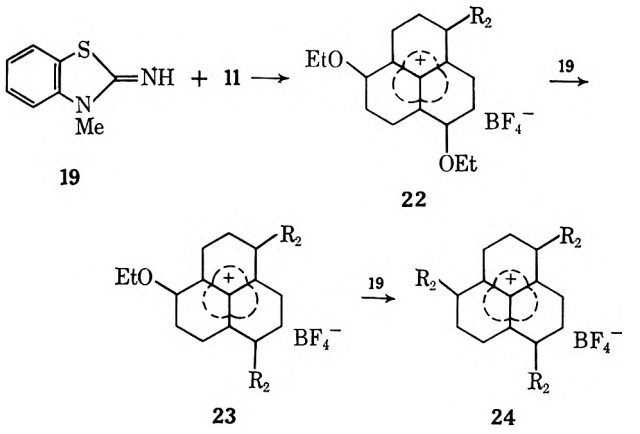
The reactions of the ethoxyphenalenium ions with 3-methyl-2-iminobenzothiazoline (**19**) differed considerably from their reactions with **2**. Compound **3** proceeded to react cleanly in a stepwise fashion with **19** to give **20** and **21** in agreement with the work of



20 21

Hünig and Wolff,[3] who prepared the methoxy analog of **20**.

No products were obtained from attack at ring carbons bearing hydrogen, even when a large excess of **3** was present. This agreed with the findings that strong nitrogen nucleophiles gave no redox products.[4] Likewise, 1,4,7-triethoxyphenalenium fluoroborate (**11**) underwent stepwise attack at the ethoxy carbons, leading to **22**–**24**. In reactions with methylene base **2**,

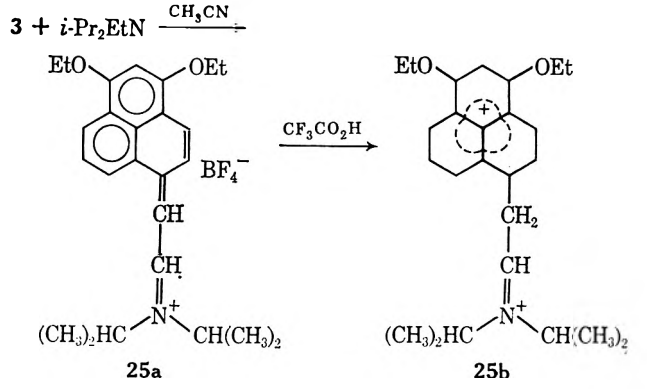


19 22 23 24

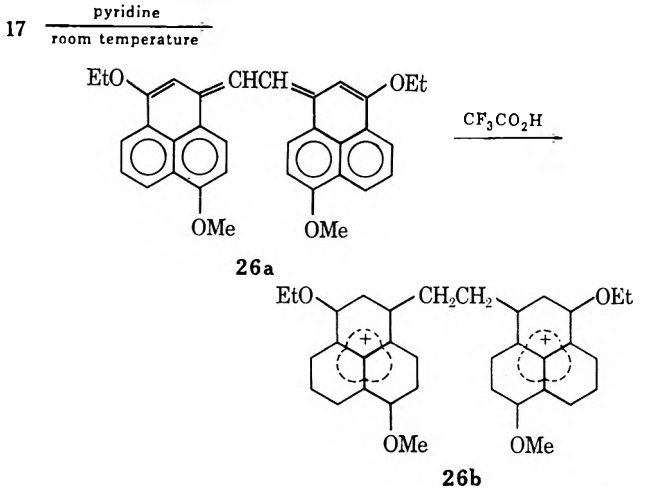
the reactivity of the phenalenium rings toward **2** dropped off rapidly with increasing numbers of R_1 groups in the dye molecules. This was in marked contrast with the reactivity of the phenalenium rings toward **19**. Dye **24** was easily formed from **11** and excess **19** in essentially quantitative yields at room temperature.

As mentioned previously, one of the reasons for using the methylene base **2** instead of **1** was to avoid auxiliary bases which sometimes gave unexpected products. At room temperature, **3** reacted with diisopropylethylamine to give **25a**. Both **25a** and its protonated form **25b** were characterized *via* nmr and their electronic spectra. Other tertiary aliphatic amines with at least one ethyl group reacted similarly.

The methyl group of the blocked phenalenium salt **17** underwent an oxidative coupling reaction in pyridine to give **26a**. The spectra of the doubly protonated form **26b** were in complete agreement with the structure when compared with **17**.



25a 25b



26a 26b

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. The nmr spectra were recorded with a Varian A-60, Varian T-60, or Brüker 90-MHz instrument, and absorption values are given in parts per million downfield from tetramethylsilane added as the internal standard. The electronic spectra were run on a Perkin-Elmer 350 or 450 UV-VIS-NIR spectrophotometer.

1,3-Diethoxyphenalenium Fluoroborate[7] (**3**).—To 3-hydroxyphenalenone[8] (98.1 g, 0.50 mol) in methylene chloride (600 ml) was added diisopropylethylamine (67.9 g, 0.525 mol). After all the material was in solution, triethyloxonium fluoroborate (200 g, 1.05 mol) was added in several portions with swirling. The resulting warm solution was refrigerated for several hours, and the crude **3** was filtered, washed with cold CH_2Cl_2 and then cold water, and dried. Recrystallization of **3** from ethanol–acetonitrile (2:1) gave 55.3 g (32.5%): mp 228° dec (lit.[3] mp 226–228° dec); nmr (TFA)[9] δ 1.9 (t, 6 H, J = 7 Hz),[10] 4.95 (q, 4 H, J = 7 Hz), 7.1 (s, 1 H, H_2),[11] 9.16 (d, 2 H, J = 8 Hz, H_4, H_9), 8.17 (t, 2 H, J = 8 Hz, H_5, H_8), 8.83 (d, 2 H, J = 8 Hz, H_6, H_7); electronic (CH_2Cl_2) λ_{max} 390, 353, 249 nm.

2-[3-Ethoxy-7-(3-ethyl-2-benzothiazolinylidenemethyl)-1-phenalenylidenemethyl]-3-ethylbenzothiazolium Fluoroborate (**6**).—A solution of **3** (1.02 g, 0.003 mol) in 20 ml of anhydrous CH_3CN was added dropwise over several hours to a stirring room-temperature solution of **2** (1.2 g, 0.007 mol) in anhydrous CH_3CN.

(7) In view of some discrepancies with the spectral data as described in ref 3, the current results are reported.

(8) B. Iestert, W. Eifler, and H. Göth, *Chem. Ber.*, **101**, 2162 (1968).

(9) TFA is trifluoroacetic acid.

(10) The nmr values in parentheses are for multiplicities, abundancies, coupling constants, and assignments, respectively. Where assignments are not given the values are for the methyl or methylene of an ethyl group.

(11) Assignment of the absorption to the hydrogen at position 2 of the phenalenium ring is denoted by H_2, etc.

The next day the solution was evaporated and the residue was extracted in a Soxhlet apparatus for a day with ether. The ether was discarded and extraction was continued for another day with methanol. Crude **6** was filtered from the cooled methanol solution and some additional crude **6** was removed from the thimble of the Soxhlet extractor. Recrystallization from CH_3CN gave 160 mg (8.3%): mp 260–263°; ir (KBr)[12] 1617 (m), 1565 cm^{-1} (m); nmr (TFA)[9] δ 1.83 (t, 9 H, J = 7 Hz),[10] 4.7–5.4 (m, 6 H), 5.85 (s, 4 H, 2 $-CH_2-$),[13] 7.7–8.6 (m, 11 H, B,[14] H_2, H_5, H_8), 9.17–9.55 (m, 2 H, H_6, H_9), 9.7 (d, 1 H, J = 8 Hz, H_4); electronic (CH_3CN, neutral) λ_{max} 812 nm (ϵ 97,600), 558 (18,100), 398 (21,000); (CH_3CN, acidic)[15] λ_{max} 577, 404, 332, 280 nm.

Anal. Calcd for $C_{35}H_{31}BF_4N_2OS_2$: C, 65.1; H, 4.84; N, 4.3; S, 9.9; F, 11.7. Found: C, 65.1; H, 5.2; N, 4.1; S, 10.1; F, 11.3.

The methanolic filtrate, consisting of a mixture of **4** and **5** with traces of **6** and **7**, was evaporated, and the residue in CH_3CN was chromatographed on a 3-ft column of Fischer neutral alumina partially deactivated by the addition of 20 ml of water/lb. Elution with CH_3CN gave blue dye **4**, magenta dye **5**, and traces of grayish **6** and **7**, in that order. Recrystallization of **4** from EtOH gave 250 mg (17.7%): mp 315°; ir[12] (KBr) 1625 (m), 1565 cm^{-1} (s); nmr (TFA)[9] δ 1.6–2.2 (m, 6 H),[10] 4.9–5.5 (m, 4 H), 5.93 (s, 2 H, $-CH_2-$),[13] 7.9–8.5 (m, 5 H, H_2, B),[14] 9.77 (d, 1 H, J = 7.5 Hz, H_4), 8.6 (t, 2 H, J = 7 Hz, H_5, H_8), 9.0–9.5 (m, 3 H, H_6, H_7, H_9); electronic[7] (CH_3CN, neutral) λ_{max} 577 nm (ϵ 35,200), 402, 332, 282.

Anal. Calcd for $C_{25}H_{22}BF_4NOS$: C, 63.7; H, 4.7; N, 3.0; S, 6.8; F, 16.1; B, 2.3. Found: C, 63.7; H, 4.9; N, 3.3; S, 7.1; F, 16.0; B, 2.4.

Recrystallization of **5** from EtOH gave 50 mg (3%): mp 278–280°; ir (KBr) 1617 (vw), 1585 cm^{-1} (vw).

For specific preparations of **4** and **5** see ref **3**.

2-[3-Ethoxy-6-(3-ethyl-2-benzothiazolinylidenemethyl)-1-phenalenylidenemethyl]-3-ethylbenzothiazolium Fluoroborate (7).—To dye **8** (0.52 g, 0.001 mol) in pyridine (200 ml) and ether (100 ml) at −60° was added all at once **2** (0.5 g, 0.003 mol) in a little pyridine. The Dry Ice bath was removed, and the stirring reaction mixture was allowed to come to room temperature (3 hr). The mixture of **7**, **6**, and **8** was filtered and recrystallized from CH_3CN to give a gelatinous suspension to which an equal volume of $CHCl_3$ was added. After this suspension was stirred in the $CHCl_3$–CH_3CN mixture for 10 min, the solid was filtered. A second recrystallization and $CHCl_3$ treatment gave, after filtering, 50 mg of **7** (15% based upon unrecovered **8**): mp 320°; ir (KBr) 1610 (mw), 1565 cm^{-1} (w); nmr (TFA)[9] δ 1.6–2.2 (m, 9 H),[10] 4.9–5.4 (m, 6 H), 5.93 (s, 4 H, 2 $-CH_2-$);[13] electronic (CH_3CN, neutral) λ_{max} 840 nm (ϵ 106,500), 400 (7700), 340 (40,000); (CH_3CN, acidic)[15] λ_{max} 577, 405, 332 nm.

Anal. Calcd for $C_{35}H_{31}BF_4N_2OS_2$: C, 65.1; H, 4.8; S, 9.9; N, 4.3. Found: C, 64.1; H, 4.9; S, 10.2; N, 4.7.

Isomer **7** was almost completely insoluble in $CHCl_3$, whereas **6** had appreciable solubility. Tlc (Eastman cellulose–$CHCl_3$) moved **6**, but **7** remained at the origin.

2-(4,6-Diethoxy-1-phenalenylidenemethyl)-3-ethylbenzothiazolium Fluoroborate (8).—To **3** (7.48 g, 0.022 mol) in stirring, room-temperature CH_3CN (250 ml) was added dropwise over 1 hr **2** (1.77 g, 0.01 mol) in CH_3CN (75 ml). The solution was stirred for an additional 1 hr, concentrated to 50 ml, and added to 1 l. of stirring ether. The solid was filtered, washed with ether, and dissolved in CH_3CN (200 ml). The solution was filtered, and treated while stirring with diisopropylethylamine (10 ml). Soon **8** began separating and after being refrigerated for several hours was filtered, washed with ethanol, and recrystallized from CH_3CN to give 3.1 g (60%) of **8** free of **4**, **5**, **6**, and **7**: mp 290°; ir (KBr) 1619 (m), 1560 (m), 1573 (m), 1587 cm^{-1} (m); nmr (TFA)[9] δ 1.6–2.1 (m, 9 H),[10] 4.6–5.4 (m, 6 H), 5.67 (s, 2 H, $-CH_2-$),[13] 7.8–8.3 (m, 6 H, B,[14] H_2, H_8), 9.17 (d, 2 H, J = 7.5 Hz, H_3, H_7), 7.07 (s, 1 H, H_5), 8.9 (d, 1 H, J = 8 Hz, H_9); electronic (EtOH, neutral) λ_{max} 712 nm (ϵ 59,400), 657 vibrational (51,000), 415 (4750), 362 (16,000), 316 (16,000); (EtOH, acidic)[15] λ_{max} 420, 405, 360 nm.

Anal. Calcd for $C_{27}H_{26}BF_4NO_2S$: C, 62.9; H, 5.1; N, 2.7; B, 2.1; F, 14.75. Found: C, 62.9; H, 5.0; N, 2.5; B, 2.1; F, 14.6.

6-Hydroxyphenalenone[16] was prepared by a modification of the procedure of Cooke, Johnson, and Segal[17] in which 1,3,3-trimethoxypropene was substituted for glycerol and sodium nitrobenzenesulfonate. Yields varied up to 50%; mp >230°.

6-Ethoxyphenalenone.—6-Hydroxyphenalenone (4.9 g, 0.025 mol), ethyl iodide (40 g), and K_2CO_3 (20 g) were refluxed in 500 ml of acetone for 24 hr. After the residue was evaporated, 500 ml each of water and ether were added to dissolve all materials. After the ethereal layer was separated, the aqueous layer was washed twice with ether, and the combined ethereal layers were washed twice with water and dried ($MgSO_4$). Slow evaporation of the ether caused the 6-ethoxyphenalenone to crystallize, giving 4.35 g (77.6%), mp 117–121°.

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.3; H, 5.4. Found: C, 79.9; H, 5.5.

4-Ethoxyphenalenone and 7-Ethoxyphenalenone.—4-Hydroxyphenalenone was prepared by the synthesis of Cooke and Segal[18] on a 0.2-mol scale and gave 18.2 g (46.4%), mp 267° (lit.[18] mp 260°).

The alkylation of 4-hydroxyphenalenone (5.9 g, 0.03 mol) gave a mixture of the 4- and 7-ethoxy isomers, which were not separated. Recrystallization from ether gave 6.3 g (93.6%).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.3; H, 5.4. Found: C, 80.6; H, 5.7.

4,7-Diethoxyphenalenone.—4,7-Dihydroxyphenalenone was prepared by the synthesis of Jarcho[19] and alkylation (21.2 g, 0.1 mol) with ethyl sulfate and 2 N NaOH gave 25.5 g (97%) on the alkylation step. Recrystallization from ethanol gave 23.4 g (89%), mp 155–156°.

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0. Found: C, 76.4 H, 6.3.

1,4,7-Triethoxyphenalenium Fluoroborate (11).—4,7-Diethoxyphenalenone (13.17 g, 0.05 mol) was dissolved in a minimum of warm CH_2Cl_2. To this solution was added triethyloxonium fluoroborate (11.4 g, 0.06 mol) with swirling to dissolve. The flask was stoppered and refrigerated overnight; the solution was filtered and gave yellow-orange **11**. The crystals were washed with CH_2Cl_2 and dried to give 13.12 g (69.3%): mp >270° dec; nmr (CD_3CN) δ 1.64 (t, 9 H, J = 7 Hz),[10] 4.62 (q, 6 H, J = 7 Hz), 7.4 (d, 3 H, J = 9 Hz, H_2, H_5, H_8), 8.86 (d, 3 H, J = 9 Hz, H_3, H_6, H_9); electronic (CH_2Cl_2) λ_{max} 450, 246 nm.

Anal. Calcd for $C_{19}H_{21}BF_4O_3$: C, 59.4; H, 5.5. Found: C, 59.8; H, 5.2.

1,6-Diethoxyphenalenium fluoroborate (9) and 1,4-diethoxyphenalenium fluoroborate (10) were prepared by the same procedure as for **11**; however, dilution with ether was required to separate the products, which were hygroscopic.

9 had nmr (CD_3CN) δ 1.67 (t, 6 H, J = 7 Hz), 4.66 (q, 4 H, J = 7 Hz),[10] 7.4 (d, 2 H, J = 9 Hz, H_2, H_5), 8.65 (d, 2 H, J = 9 Hz, H_3, H_4), 9.0 (d, 2 H, J = 8 Hz, H_7, H_9), 8.0 (t, 1 H, J = 8 Hz, H_8); electronic (CH_2Cl_2) λ_{max} 505, 395, 345, 270 nm.

10 had nmr (CD_3CN) δ 1.7 (t, 6 H, J = 7 Hz), 4.7 (q, 4 H, J = 7 Hz),[10] 7.44 (d, 1 H, J = 9 Hz, H_2 or H_5), 7.57 (d, 1 H, J = 9 Hz, H_2 or H_5), 8.9 (d, 1 H, J = 9 Hz, H_3), 8.66 (d, 1 H, J = 9 Hz, H_6), 8.6 (m, 1 H, H_7), 7.9 (t, 1 H, J = 7.5 Hz, H_8), 8.8 (m, 1 H, H_9); electronic (CH_2Cl_2) λ_{max} 460, 360, 256 nm.

2-(3,7-Diethoxy-1-phenalenylidenemethyl)-3-ethylbenzothiazolium Fluoroborate (12).—To **9** (0.68 g, 0.002 mol) in 50 ml of stirring CH_3CN was added dropwise over 1 hr **2** (0.18 g, 0.001 mol) in 40 ml of CH_3CN. The next day the solution was evaporated to dryness, treated with EtOH, and filtered. Recrystallization from 2:1 EtOH–CH_3CN gave 0.16 g (31%) of **12**: mp 322°; ir (KBr) 1623 (ms), 1565 cm^{-1} (s); nmr (TFA)[9] δ 1.6–2.1 (m, 9 H),[10] 4.6–5.4 (m, 6 H), 5.7 (s, 2 H, $-CH_2-$),[13] 7.8–8.3 (m, 4 H, B),[14] 7.8 (s, 1 H, H_2), 9.63 (d, 2 H, J = 8 Hz, H_4, H_6), 8.4 (t, 1 H, J = 8 Hz, H_5), 7.63 (d, 1 H, J = 9 Hz, H_8), 9.1 (d, 1 H, J = 9 Hz, H_9); electronic (CH_3CN, neutral) λ_{max} 635 nm (ϵ

(12) Ir bands are reported only for the 1560–1630-cm^{-1} region. Dyes containing ethoxy groups generally gave bands of moderate intensity in the 1600–1630-cm^{-1} and in the 1560–1600-cm^{-1} regions. In the absence of ethoxy groups only weak bands were found in these regions. s = strong, m = medium, w = weak, v = very.

(13) Nmr spectra run in TFA are for protonated dyes. The $-CH_2-$ links the phenalenium ring with the benzothiazolium ring.

(14) B denotes the aromatic hydrogens of the benzothiazolium ring.

(15) Anhydrous solvents were always used. For the acidic spectra in CH_3CN a drop or two of absolute ethanol saturated with HCl was added.

(16) For a more recent preparation see A. L. Das Gupta and R. M. Chatterje, *J. Chem. Soc.*, 1619 (1971).

(17) R. G. Cooke, B. L. Johnson, and W. Segal, *Aust. J. Chem.*, **11**, 233 (1958).

(18) R. G. Cooke and W. Segal, *Aust. J. Chem.*, **8**, 420 (1955).

(19) M. Jarcho, *J. Amer. Chem. Soc.*, **90**, 4645 (1968).

37,400), 590 (46,400), 425 (13,000), 367 (13,400), 344 (13,700), 337 (13,700); (CH_3CN, acidic)[15] λ_{max} 510, 402, 355 nm.

Anal. Calcd for $C_{27}H_{26}BF_4NO_2S$: C, 62.9; H, 5.1; S, 6.2; F, 14.75. Found: C, 63.3; H, 5.1; S, 6.3; F, 14.6.

The procedure used for **8** would probably be superior.

2-(3,6-Diethoxy-1-phenalenylidenemethyl)-3-ethylbenzothiazolium Fluoroborate (13).—Using the procedure for **12**, compound **10** (0.68 g, 0.002 mol) and **2** (0.18 g, 0.001 mol) gave 0.12 g (23%) of **13** after chromatography (neutral alumina–CH_3CN): mp 300°; ir (KBr) 1621 (ms), 1560 (ms), and 1575 cm^{-1} (ms); electronic (CH_3CN, neutral) λ_{max} 646 nm (ϵ 40,200), 604 (43,800), 412 (7200), 343 (11,000); (CH_3CN, acidic)[15] λ_{max} 460, 358 nm.

Anal. Calcd for $C_{27}H_{26}BF_4NO_2S$: C, 62.9; H, 5.1; N, 2.7; F, 14.75. Found: C, 63.4; H, 5.5; N, 3.1; F, 14.6.

2-(4,7-Diethoxy-1-phenalenylidenemethyl)-3-ethylbenzothiazolium Fluoroborate (14).—Compounds **11** (1.9 g, 0.005 mol) and **1** ($X^- = BF_4^-$) (1.46 g, 0.0055 mol) were refluxed for 10 min in 30 ml of acetic acid containing diisopropylethylamine (2 ml), cooled, poured into ether, and filtered. Recrystallization twice from CH_3CN gave 1.6 g (62.2%) of **14**: mp 310°; ir (KBr) 1613 (ms), 1564 (m), 1588 cm^{-1} (m); nmr (TFA)[9] δ 1.5–2.1 (m, 9 H),[10] 4.6–5.4 (m, 6 H), 5.7 (s, 2 H, $-CH_2-$),[13] 7.9–8.4 (m, 5 H, B, H_2),[14] 9.38 (d, 1 H, J = 8.5 Hz, H_3), 7.8 (d, 1 H, J = 9.5 Hz, H_5 or H_8), 7.7 (d, 1 H, J = 9.5 Hz, H_5 or H_8), 9.52 (d, 1 H, J = 9 Hz, H_6), 9.09 (d, 1 H, J = 9.5 Hz, H_9); electronic (CH_3CN, neutral) λ_{max} 700 nm (ϵ 42,300), 642 (48,500), 410 (14,500), 385 (13,700), 341 (11,300), 312 (13,300); (CH_3CN, acidic)[15] λ_{max} 480, 370, 261 nm.

Anal. Calcd for $C_{27}H_{26}BF_4NO_2S$: C, 62.9; H, 5.1; N, 2.7; S, 6.2. Found: C, 62.5; H, 5.0; N, 2.9; S, 6.5.

2-[6-Ethoxy-3-(3-ethyl-2-benzothiazolinylidenemethyl)-1-phenalenylidenemethyl]-3-ethylbenzothiazolium Fluoroborate (15).—A mixture of **9** (0.68 g, 0.002 mol) and **2** (1.77 g, 0.01 mol) was stirred at room temperature for 4 days in CH_3CN (90 ml). Filtration removed **6** (0.05 g, 7.7%); the filtrate was concentrated and chromatographed (alumina–CH_3CN) with a 3-ft column as described under the preparation for **6**. After the yellow materials and blue dyes were eluted, the magenta dye **15** was obtained and recrystallized from EtOH–CH_3CN to give 0.12 g (18.6%): mp 313–315°; ir (KBr) 1615 (w), 1580 cm^{-1} (m); nmr (TFA)[9] δ 1.93 (t, 9 H, J = 7 Hz),[10] 4.9–5.4 (m, 6 H), 5.9 (s, 4 H, 2 $-CH_2-$),[13] 8.68 (s, 1 H, H_2), 9.2–9.9 (m, 3 H, H_4, H_7, H_9), 7.8–8.6 (m, 10 H, H_5, H_8, B);[14] electronic (CH_3CN, neutral) λ_{max} 757 nm (ϵ 40,000), 573 (52,700), 362 (23,000), 291 (21,000); (CH_3CN, acidic)[15] λ_{max} 590, 350, 287 nm.

Anal. Calcd for $C_{35}H_{31}BF_4N_2OS_2$: C, 65.1; H, 4.8; S, 9.9. Found: C, 64.8; H, 4.8; S, 9.6.

2-[7-Ethoxy-4-(3-ethyl-2-benzothiazolinylidenemethyl)-1-phenalenylidenemethyl]-3-ethylbenzothiazolium Fluoroborate (16).—Compounds **11** (0.76 g, 0.002 mol) and **1** ($X^- = BF_4^-$) (1.33 g, 0.005 mol) were refluxed for 3 hr in pyridine, cooled, and poured into ether. The dye was filtered and chromatographed as described previously, and the bluish-magenta fraction was retained. Recrystallization from EtOH gave 0.06 g (4.6%): mp 170–175°; ir (KBr) 1605 (mw), 1584 cm^{-1} (mw); electronic (CH_3CN, neutral) λ_{max} 845 nm (ϵ 93,800), 572 (22,600), 417 (26,000), 335 (20,000); (CH_3CN, acidic)[15] λ_{max} 580, 296, 255 nm.

Anal. Calcd for $C_{35}H_{31}BF_4N_2OS_2$: C, 65.1; H, 4.8. Found: C, 65.4; H, 5.2.

Ethyl 1-(4-Methoxy-1-naphthyl)ethylidenecyanoacetate.—1-Acetyl-4-methoxynaphthalene[20] (100.12 g, 0.5 mol), ethyl cyanoacetate (56.6 g, 0.5 mol), acetic acid (30 g, 0.5 mol), ammonium acetate (9.2 g), and benzene (150 ml) were refluxed with stirring for 24 hr; 20–21 ml of water and acetic acid were collected in a Dean–Stark trap. The mixture was evaporated and distilled at 187–205° (2 mm) to give 124 g (84%) of golden syrup as a *ca.* 40:60 mixture of geometric isomers as indicated by nmr.

3-(4-Methoxy-1-naphthyl)butanoic Acid.—The isomer mixture from above (118 g, 0.4 mol) was dissolved in EtOH to give 350 ml. The solution was reduced in a Paar bottle with palladium on charcoal (5 g of 20%) for 14 hr at 35° and 20–40 psi, warmed, and catalyst filtered, and the filtrate was evaporated.

The residue was hydrolyzed by refluxing for 2 days in water (400 ml), $CH_3OCH_2CH_2OH$ (150 ml), and KOH (100 g). The solution was diluted with water (100 ml) and filtered; the filtrate was acidified (HCl). The gummy product was treated several times with fresh water (scratching) and finally with warm petroleum ether (bp 30–60°) to crystallize it.

The crystalline product was melted in a porcelain dish until CO_2 evolution ceased, it was then cooled, and the residue was recrystallized from high-boiling ligroin to give 64 g (65.5%), mp 126–128°.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.6. Found: C, 73.9; H, 6.5.

6-Methoxy-3-methylphenalenone.—To 3-(4-methoxy-1-naphthyl)butanoic acid (24.4 g, 0.1 mol) in a polyethylene bottle was added cautiously liquid HF (150 ml). After 3 hr at room temperature the solution was slowly poured with stirring onto crushed ice in a large beaker. The dark gummy material became crystalline in an hour or so. Lumps were broken up and the material was finally filtered, washed with water, and dried to give 21.9 g (96.7%) of mixed, ring-closed products (*ca.* 84:16 ratio of six- to five-membered ring components as indicated by nmr). A repeat using 0.15 mol gave 32.9 g (97%).

The isomeric mixture (49.8 g, 0.22 mol) in warm benzene was filtered to remove a little solid, and to the filtrate was added dichlorodicyanoquinone (50 g, 0.22 mol) in a minimum of benzene. The mixture was refrigerated overnight and filtered to give 87.7 g of solids[21] which were stirred for 30 min with aqueous NaOH to dissolve out dichlorodicyanohydroquinone. Filtration gave 33.4 g of crude product, which was recrystallized from methanol to give 31.3 g (75.5%) based upon correct isomer present, mp 166–168°.

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.3; H, 5.4. Found: C, 79.9; H, 5.8.

1-Ethoxy-6-methoxy-3-methylphenalenium Fluoroborate (17).—6-Methoxy-3-methylphenalenone (29.15 g, 0.13 mol) was alkylated by the procedure for **11** to give 40.2 g (91%) of **17** as a somewhat hygroscopic red-orange powder: mp 225–7° dec; nmr (CD_3CN) δ 1.58 (t, 3 H, J = 7 Hz),[10] 4.38 (q, 2 H, J = 7 Hz), 2.7 (s, 3 H, Me), 4.17 (s, 3 H, MeO), 6.87 (s, 1 H, H_2), 8.34 (d, 1 H, J = 8.7 Hz, H_4), 7.0 (d, 1 H, J = 8.7 Hz, H_5), 8.3 (d, 2 H, J = 7.5 Hz, H_7, H_9), 7.45 (t, 1 H, J = 7.5 Hz, H_8); electronic (CH_3CN) λ_{max} 500, 405, 353, 271 nm.

3-Ethyl-2-[6-(3-ethyl-2-benzothiazolinylidenemethyl)-3-methyl-1-phenalenylidenemethyl]benzothiazolium Chloride (18).—Compounds **17** (3.4 g, 0.01 mol) and **2** (5.3 g, 0.03 mol) were stirred for 3 days at room temperature in pyridine (100 ml). The solid (1.8 g) was filtered and stirred in MeOH (400 ml) with Amberlite IRA-400 resin for 3 hr. The resin and some **26a** were filtered from the cool methanol and the filtrate was evaporated. Recrystallization of the residue from MeCN–H_2O (9:1) gave 1.3 g (22.6%) of **18**: mp 218–220°; ir (KBr) 1606 (w), 1570 cm^{-1} (w); electronic (CH_3CN, neutral) λ_{max} 905 nm (ϵ 125,000), 510 (6800), 430 (4300), 348 (31,700), 327 (33,400); (CH_3CN, acidic)[15] λ_{max} 535, 277 nm.

Anal. Calcd for $C_{34}H_{29}ClN_2S_2 \cdot 6H_2O$: C, 70.9; H, 5.28; Cl, 6.1; S, 11.1; N, 4.86. Found: C, 70.9; H, 5.0; Cl, 5.9; S, 10.9; N, 4.5.

2-(3-Ethoxy-1-phenalenylideneamino)-3-methylbenzothiazolium Fluoroborate (20).—Compounds **3** (1.02 g, 0.003 mol) and **19** (0.49 g, 0.003 mol) were stirred for 1 day at room temperature in 1,2-dichloroethane (20 ml). Crude **20** was filtered, washed with ether, and dried to give 0.9 g (65.5%). Recrystallization from CH_3CN gave 0.6 g (43.6%): mp 275°; electronic (CH_3CN) λ_{max} 517 nm (ϵ 24,500), 395 (12,200), 356 (13,200), 304 (11,100).

Anal. Calcd for $C_{23}H_{19}BF_4N_2OS$: C, 60.3; H, 4.2; N, 6.1; S, 7.0. Found: C, 60.1; H, 4.4; N, 6.3; S, 7.0.

2-(4,7-Diethoxy-1-phenalenylideneamino)-3-methylbenzothiazolium Fluoroborate (22).—Compound **19** (0.08 g, 0.0005 mol) in 1,2-dichloroethane was added dropwise to a stirring solution of **11** (0.3 g, 0.00075 mol). After a few hours the solution was poured into ether and filtered. Crude **22** was recrystallized twice from EtOH to give 0.16 g (64%): mp 280–282° dec; electronic (CH_3CN) λ_{max} 567 nm (ϵ 34,900), 436 (23,100), 327 (13,000).

Anal. Calcd for $C_{25}H_{23}BF_4N_2O_2S$: C, 59.8; H, 4.6; N, 5.6; S, 6.4. Found: C, 60.2; H, 4.7; N, 5.2; S, 6.0.

2-[7-Ethoxy-4-(3-methyl-2-benzothiazolinylideneamino)-1-phenalenylideneamino]-3-methylbenzothiazolium Fluoroborate (23).—Compounds **19** (0.16 g, 0.001 mol) and **11** (0.21 g, 0.00055

(20) M. E. Chapiro and M. M. Delepine, *C. R. Acad. Sci., Ser. C*, **234**, 2081 (1952).

(21) Some of the 5-methoxy-1-methylbenz[*e*]indanone may be recovered from the benzene filtrate, mp 119–121°.

mol) were obtained by the procedure for **22**. Recrystallization from CH_3CN–EtOH gave 0.14 g (45%) of **23**: mp 181–184°; electronic (CH_3CN) λ_{max} 625 nm (ϵ 60,800), 520 (25,300), 420 (7500), 327 (26,000), 302 (26,000).

Anal. Calcd for $C_{31}H_{25}BF_4N_4OS_2$: C, 60.0; H, 4.06; N, 9.0; S, 10.3. Found: C, 59.8; H, 4.1; N, 8.9; S, 10.1.

3-Methyl-2-[4,7-bis(3-methyl-2-benzothiazolinylideneamino)-1-phenalenylideneamino]benzothiazolium Fluoroborate (24).—Compounds **19** (0.32 g, 0.002 mol) and **11** (0.19 g, 0.0005 mol) in $ClCH_2CH_2Cl$ for 2 days, recrystallized from CH_3CN, gave 0.3 g (81.4%) of **24** as fine bronze crystals: mp 310°; electronic (CH_3CN) λ_{max} 635 nm (ϵ 40,700), 332 (20,000).

Anal. Calcd for $C_{37}H_{27}BF_4N_6S_3$: C, 60.2; H, 3.7; N, 11.4; S, 13.0. Found: C, 60.2; H, 4.0; N, 11.6; S, 13.1.

1,3-Diethoxy-6-(2-diisopropylamino)vinylphenalenium Fluoroborate (25a).—Compound **3** (1.7 g, 0.005 mol) in CH_3CN (30 ml) was treated with diisopropylethylamine (3–4 ml) at room temperature for 1 day. The solution was concentrated to 10 ml and poured into ether. The dye was filtered and recrystallized from EtOH to give 0.24 g (20%) of **25a**: mp 220–223°; ir (KBr) 1623 (m), 1605 (m), 1540–1580 cm^{-1} (s); nmr (CD_3CN) δ *ca.* 1.5 (m, 18 H, all methyls), *ca.* 4.34 (m, 6 H, 2 $-OCH_2-$, 2 $=NHC<$), 6.84 (d, 1 H, J = 12 Hz, $=CH-$), 8.2 (d, 1 H, J = 12 Hz, other $=CH-$), 6.56 (s, 1 H, H_2), 7.9 (d, 1 H, J = 10 Hz, H_4), 7.6 (m, 2 H, H_5, H_8), 8.45 (d, 1 H, J = 8 Hz, H_7), 8.7 (d, 1 H, J = 8 Hz, H_9); electronic (CH_3CN, neutral) λ_{max} 667 nm (ϵ 43,000), 613 vibrational (40,000), 400 (3900), 347 (14,200), 310 (24,000).

25b had nmr (TFA)[9] δ 1.3–2.0 (m, 18 H, all methyls), 4.2–5.4 (m, 6 H, 2 $-OCH_2-$, 2 $=NC<$), 5.11 (d, 2 H, J = 4 Hz, $-CH_2-$), 8.75 (t, 1 H, J = 4 Hz, $-CH=N<)^+$, 7.0 (s, 1 H, H_2), 9.04 (d, 2 H, J = 7.7 Hz, H_4 or H_9), 9.11 (d, 2 H, J = 7.7 Hz, H_4 or H_9), 7.95 (d, 1 H, J = 7.7 Hz, H_5), 8.75 (d, 1 H, J = 7.7 Hz, H_7), 8.13 (t, 1 H, J = 7.7 Hz, H_8); electronic (CH_3CN, acidic)[15] λ_{max} 418, 400, 355, 253 nm.

Anal. Calcd for $C_{25}H_{32}BF_4NO_2$: C, 64.5; H, 6.9; N, 3.0. Found: C, 65.0; H, 6.7; N, 2.5.

1-Ethoxy-3-[2-(1-ethoxy-6-methoxy-3-phenalenylidene)ethylidene]-6-methoxy-3*H*-phenalene (26a).—Compound **17** (3.4 g, 0.01 mol) in 50 ml of dry, room-temperature pyridine was allowed to stand for 1 day. Crude **26a** was filtered, washed with pyridine, acetone, and ether, and dried. It was recrystallized twice from toluene to remove small amounts of another material: yield 0.3 g (19%); mp 277° dec; ir (KBr) 1610 (m), 1572 (s), 1578 cm^{-1} (s); nmr (TFA)[9] δ 1.74 (t, 6 H, J = 7 Hz),[10] 4.72 (q, 4 H, J = 7 Hz),[10] 4.47 (s, 6 H, 2 MeO), 4.05 (s, 4 H, $-CH_2CH_2-$), 7.53 (s, 2 H, 2 H_2), 9.06 (d, 2 H, J = 9 Hz, 2 H_4), 7.52 (d, 2 H, J = 9 Hz, 2 H_5), 9.36 (d, 4 H, J = 8 Hz, 2 H_7, 2 H_9), 8.22 (t, 2 H, J = 8 Hz, 2 H_8); electronic ($CHCl_3$) λ_{max} 626 nm (ϵ 60,200), 573 vibrational (30,600), 535 vibrational (14,000); (CH_3CN, acidic)[15] λ_{max} 495, 403, 355 nm.

Anal. Calcd for $C_{34}H_{30}O_4$: C, 81.4; H, 6.0. Found: C, 81.0; H, 6.0.

Registry No.—**1** (X = BF_4), 21800-42-0; **2**, 25082-84-2; **3**, 40082-98-2; **4**, 28275-93-6; **5**, 27906-68-9; **6**, 40084-75-1; **7**, 40084-76-2; **8**, 40084-77-3; **9**, 40082-99-3; **10**, 40083-00-9; **11**, 40083-01-0; **12**, 40084-78-4; **13**, 40084-79-5; **14**, 40084-80-8; **15**, 40084-81-9; **16**, 40084-82-0; **17**, 40083-02-1; **18**, 39981-66-3; **19**, 14779-16-9; **20**, 40084-83-1; **22**, 40084-84-2; **23**, 40084-85-3; **24**, 40084-86-4; **25a**, 40084-87-5; **26a**, 39981-68-5; 3-hydroxyphenalenone, 5472-84-4; triethyloxonium fluoroborate, 368-39-8; 6-hydroxyphenalenone, 3352-82-7; 1,3,3-trimethoxypropene, 17576-35-1; 6-ethoxyphenalenone, 39981-69-6; ethyl iodide, 75-03-6; 4-ethoxyphenalenone, 39981-70-9; 7-ethoxyphenalenone, 39981-71-0; 4-hydroxyphenalenone, 39981-72-1; 4,7-diethoxyphenalenone, 39981-73-2; 4,7-dihydroxyphenalenone, 19996-99-7; ethyl 1-(4-methoxy-1-naphthyl)ethylidenecyanoacetate (*E*), 39990-75-5; ethyl 1-(4-methoxy-1-naphthyl)ethylidenecyanoacetate (*Z*), 39990-76-6; acetyl-4-methoxynaphthalene, 24764-66-7; ethyl cyanoacetate, 105-56-6; 3-(4-methoxy-1-naphthyl)butanoic acid, 39981-76-5; 6-methoxy-3-methylphenalenone, 39981-77-6.

Acknowledgment.—The author is indebted to Dr. T. Regan and Mr. R. Young for providing the nmr spectra.

Dyes Containing the Phenalene Ring System. II. Electronic Spectra and Their Correlations with Hückel Molecular Orbital Theory[1]

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Received December 7, 1972

The electronic spectra of 21 closely related cationic compounds containing phenalene rings in conjugation with benzothiazole rings are discussed. Two transitions were observed in the 500–1000-nm region for all dyes containing two benzothiazole groups, and the relative intensities of these transitions were closely related to the substitution patterns on the phenalene rings. A good correlation was obtained between observed transition energies and those calculated by the Hückel molecular orbital method using optimized heteroatom parameters. Polarizations of the allowed transitions were determined from the molecular orbitals for selected cases.

Results

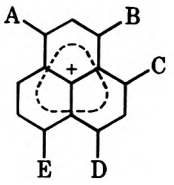
In paper I[1] syntheses were described for a number of dyes in which phenalene rings were in conjugation with benzothiazole rings. The availability of a number of closely related dyes provided a unique opportunity to examine their electronic spectral characteristics in relation to the patterns of substitution on the phenalene rings. Of particular interest were the energies of the transitions and their relative intensities. The compounds studied are summarized in Table I along with their longer wavelength absorption maxima. The transition energies for the transitions of lowest energy or two lowest energies in electron volts are included for comparison with calculated Hückel molecular orbital, (HMO) transition energies in units of β, the resonance integral.

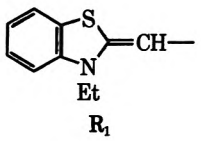
In Figure 1 a plot of observed transition energies (eV) *vs.* those calculated by the HMO method shows, in general, a very good correlation considering the gross approximations inherent in the simple method. The success of the treatment may be attributed largely to two factors: (1) the similarities of the dyes, and (2) the use of optimized heteroatom parameters (see Experimental Section). The line in Figure 1 was that established previously for a large number of cyanine dyes.[2]

(1) Paper I: J. K. Elwood, *J. Org. Chem.*, **38**, 2425 (1973).

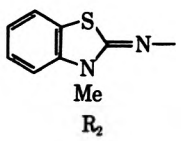
(2) D. M. Sturmer, personal communication.

TABLE I.—ELECTRONIC SPECTRA OF THE PHENALENE COMPOUNDS





R_1



R_2

Compd	A	B	C	D	E	Electronic spectra,[a] λ_{max}, nm (ϵ[b])	E_{max}, eV[c]	Calcd[d] transition energies β	eV
3[e]	EtO	EtO	H	H	H	390 (s)	~3.06[f]	0.828	2.75
						353 (s)			
4	EtO	R_1	H	H	H	577 (35,200)	~2.00[f]	0.508	1.69
						402 (m)	3.08	0.908	3.02
5	R_1	R_1	H	H	H	780 (46,600)	1.59	0.428	1.42
						539 (51,600)	2.30	0.647	2.15
						380 (s)			
6	EtO	R_1	H	R_1	H	812 (97,600)	1.525	0.447	1.49
						558 (18,100)	2.22	0.641	2.13
						398 (21,000)			
7	R_1	EtO	H	R_1	H	840 (106,500)	1.475	0.437	1.45
						540 (vw)	2.29	0.673	2.24
						400 (7700)			
						340 (40,000)			
8[g]	EtO	EtO	H	R_1	H	712 (59,400)	1.74	0.508	1.69
						415 (4750)	2.99	0.921	3.06
9[e]	EtO	H	H	EtO	H	505 (s)	2.46	0.735	2.44
						395 (m)			
10[e]	EtO	H	EtO	H	H	460 (s)	2.69	0.778	2.58
						360 (m)			
11[e]	EtO	H	EtO	H	EtO	450 (s)	2.75	0.826[h]	2.73
						246 (m)			
12	EtO	R_1	H	EtO	H	635 (37,400)	1.95	0.523	1.74
						590 v (46,400)	2.10		
						425 (13,000)	2.92	0.825	2.74
13	R_1	EtO	H	EtO	H	646 (40,200)	1.915	0.514	1.71
						604 v (43,800)	2.05		
						412 (7200)	3.01	0.878	2.92
14	R_1	H	EtO	H	EtO	700 (42,300)	1.77	0.516	1.73
						642 v (48,500)	1.93		
						410 (14,500)	3.02	0.868	2.88
15	R_1	R_1	H	EtO	H	757 (40,000)	1.635	0.459	1.52
						573 (52,700)	2.16	0.615	2.04
						363 (23,000)			
16	R_1	H	R_1	H	EtO	845 (93,800)	1.465	0.447	1.48
						572 (22,600)	2.17	0.641	2.13
						417 (26,000)			
17	EtO	Me	H	MeO	H	495 (s)	2.50	0.749	2.49
						405 (m)			
18	R_1	Me	H	R_1	H	905 (125,000)	1.37	0.418	1.39
						510 (6800)	2.43	0.698	2.32
						430 (4300)			
20	EtO	R_2	H	H	H	517 (24,500)	2.40	0.631	2.10
						395 (12,200)	3.14	0.868	2.88
21	R_2	R_2	H	H	H	592 (23,100)	2.09	0.586	1.95
						499 (33,500)	2.48	0.706	2.35
						358 (9000)			
22	R_2	H	EtO	H	EtO	567 (34,900)	2.185	0.644	2.14
						436 (23,100)	2.84	0.834	2.77
						327 (13,000)			
23	R_2	H	R_2	H	EtO	625 (60,800)	1.98	0.600	1.99
						520 (25,300)	2.38	0.710	2.36
						420 (7500)			
24	R_2	H	R_2	H	R_2	635 (40,700)	1.95	0.605[h]	2.01
						332 (20,000)			

[a] Electronic spectra were run in CH_3CN, unless otherwise specified, on a Perkin-Elmer 350 or 450 UV-VIS-NIR spectrophotometer. At the suggestion of a referee, compounds **4**, **5**, **8**, and **16** were examined in methanol and 2,6-lutidine. The very unsymmetrical dyes **4** and **8** did not show any greater solvent sensitivity than did the relatively symmetrical dyes **5** and **16**. These compounds were shifted bathochromically by *ca.* 10 nm in going from methanol to 2,6-lutidine. [b] Extinction coefficient or letters denoting s = strong, m = moderate, w = weak, v = very. [c] Transition energy in electron volts. [d] Calculated transition energies in units of β, the HMO resonance integral, and in electron volts using the conversion 3.32 eV/β. [e] Spectra run in methylene chloride. [f] The transition was a long-wavelength shoulder on the main absorption. [g] Spectrum run in ethanol. [h] Degenerate highest filled orbitals.

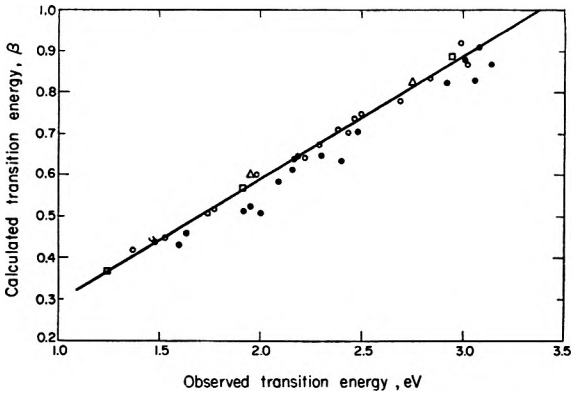
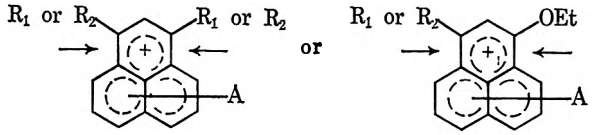


Figure 1.—Plot of observed first or first two transition energies against values calculated by the HMO method. Open squares are for 3,3′-diethylthiacyanine, 3,3′-diethylthiadicarbocyanine, and 3,3′-diethylthiapentacarbocyanine, and serve as reference points. Open circles are for the bulk of the phenalene compounds. Solid circles and open triangles are for the compounds which show deviations for the reasons discussed in the text. Heteroatom parameters used in the calculations are discussed in the Experimental Section.

Discussion

The points for a number of dyes fell somewhat below the line. Examination revealed that these dyes possessed either two R groups or one R group and one ethoxy group joined to the same ring of the phenalene ring system with no other R groups present, as illustrated below (see Table I for definition of R_1 and R_2). These dyes are represented by solid circles in Figure 1.

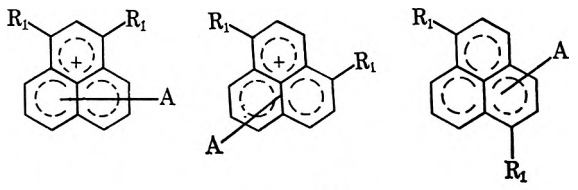


A = H or EtO

A reasonable explanation for this consistent deviation is that the bonds indicated by the arrows have considerably reduced bond order. The bond-order calculations clearly show this; however, the HMO treatment underestimates the reduction. Hünig and Wolff[3] have concluded similarly from nmr and electronic spectral studies on 1,3-disubstituted phenalenium compounds that these bonds are of reduced order and that the compounds should be considered as something intermediate between a completely delocalized system and one in which a naphthalene moiety is fused onto the chromophore chain. When the resonance integrals for these bonds were reduced by 20%, the points were made to move near the line for the cases tried.

Two of the points which fell somewhat above the line for their lowest energy transition are represented by open triangles in Figure 1. These dyes had degenerate highest filled levels of appropriate symmetry to be split by configuration interaction. The spectra appeared as rather broad absorptions consisting of two overlapping bands; however, whether these were due to transitions from different orbitals or from one orbital to different vibrational levels of the excited state is not known.

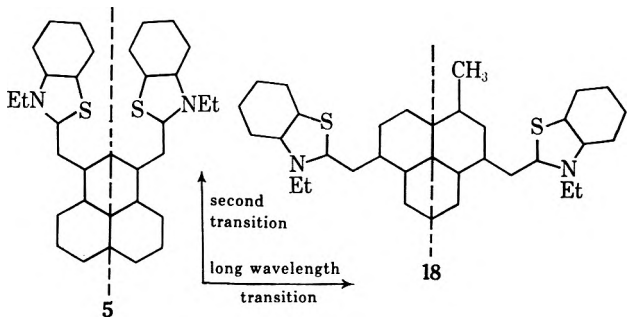
The intensities of the two longest wavelength transitions for the dyes containing two R_1 groups were of particular interest. A comparison of molecular extinction coefficients at λ_{max} revealed that, for the dyes with R_1 groups substituted in 1,3 positions, the intensities of the two transitions were comparable. For dyes with a 1,4-substitution pattern, the long-wavelength transition was much stronger, while those with 1,6 substitution showed only a very weak second transition.



A = H or EtO

longer wavelength	ϵ	$4.0\text{–}4.7 \times 10^4$	$9.3\text{–}9.8 \times 10^4$ $10.5\text{–}12.5 \times 10^4$
shorter wavelength	ϵ	$5.1\text{–}5.3 \times 10^4$	$1.8\text{–}2.3 \times 10^4$ *ca.* 0.6×10^4

An examination of the orbitals for dyes **5** and **18**, which have C_{2v} symmetry (neglecting the small effect of the methyl in **18**), showed that the polarizations of the allowed transitions are as drawn below.[4] Models



suggested that the molecules can achieve planarity only by assuming the geometry indicated. In dye **5** the horizontal and vertical dimensions of the molecule are comparable and, hence, the transition moment vectors for the two transitions can have appreciable components along the allowed polarizations.[5] Dye **18** has a long horizontal dimension, and so the long-wavelength transition should be intense; however, the second transition is only allowed with vertical polarization and this component of its transition moment vector must be small. Dyes possessing a 1,4-substitution pattern might be expected to fall in between these two extremes. In fact, an examination of the absorption spectra of all the dyes containing two R groups revealed a clear-cut correlation of relative band intensities to substitution pattern, thus supporting the structural assignments in paper I.[1]

Kiprianov and coworkers[6,7] have studied extensively the spectra of biscyanines containing two conjugated chromophores and have found that the relative intensities of the two longest wavelength absorption bands depended upon the angle formed between the

(3) S. Hünig and E. Wolff, *Chimia*, **22**, 33 (1968).

(4) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 204–207.

(5) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, pp 169–176.

(6) V. I. Permagarov, G. G. Dyadyusha, F. A. Mikhailenko, and A. I. Kiprianov, *Dokl. Akad. Nauk SSSR*, **188**, 1098 (1969).

(7) A. I. Kiprianov, *Ind. Chim. Belg.*, **32**, special number 100-2 (1967).

two interacting chromophores. They interpreted these results as being due to the reciprocal influence of two oscillators. This is another way of looking at the phenomenon, and it leads to the same conclusions as derived from the molecular orbital approach.

Experimental Section

The molecular orbital calculations were carried out on an IBM 360-65 computer for molecules requiring over a 41 × 41 matrix or when vectors were required; otherwise, a program written by the author for the IBM-1130 was used. The standard convention was adopted for heteroatoms (x) in which h_x and k_{cx} were related, respectively, to the Coulomb integral (α_x) and the resonance integral (β_{cx}) by the relationships $\alpha_x = \alpha_o + h_x\beta_o$ and $\beta_{cx} = k_{cx}\beta_o$.[8] An auxiliary inductive parameter, AIP = $0.1\ \Sigma_x\ h_x$, was used for all carbon atoms adjacent to heteroatoms.

Heteroatom Parameter Optimization.—Dr. D. M. Sturmer, of the Kodak Research Laboratories, supplied the heteroatom parameters used in this work, which he optimized as follows. A special program was used to calculate transition energies (in units of β_o) for a large number of compounds using an initial set of values (h_x and k_{cx}) for the heteroatom. The calculations for all the compounds were then repeated with another set of values for h_x and k_{cx}. The procedure was repeated continuously while varying h_x and k_{cx} systematically. After each set of calculations a linear correlation was made between the observed transition energies and those calculated with that particular set of values. A contour surface was generated when both h_x and k_{cx} were plotted against the standard deviations of the linear correlations. This produced the best set of values for the heteroatom in those compounds.

The values for sulfur were optimized for a large number of cyanine dyes using for ring nitrogen $h_x = 1.5$ and $k_{cx} = 1.0$. The values used for the chain nitrogen in the R_2 groups were optimized for a limited number of 8-azacarbocyanines and 8-azadicarbocyanines. The oxygen parameters were chosen to correlate with the spectra of the 1,6-diethoxy-, 1,4-diethoxy-, and 1,4,7-triethoxyphenalenium ions. The values are summarized below in the order $h_x(k_{cx})$.

S	= 0.75 (0.6)
ring alkyl N	= 1.5 (1.0)
O	= 1.0 (0.7)
chain N	= 0.7 (1.0)
CH_3C	= −0.1 (inductive model)

(8) A. Streitwieser, Jr., *Ind. Chim. Belg.*, 117 (1967).

Registry No.—**3**, 40083-03-2; **4**, 40083-04-3; **5**, 40083-05-4; **6**, 40083-06-5; **7**, 40036-99-5; **8**, 40083-07-6; **9**, 40083-08-7; **10**, 40083-09-8; **11**, 40083-10-1; **12**, 40083-11-2; **13**, 40083-12-3; **14**, 40083-13-4; **15**, 40083-14-5; **16**, 40083-15-6; **17**, 40083-16-7; **18**, 40083-17-8; **20**, 40037-00-1; **21**, 40083-18-9; **22**, 40083-19-0; **23**, 40083-20-3; **24**, 40083-21-4.

Acknowledgment.—The author is greatly indebted to Dr. D. M. Sturmer for supplying the optimized parameters and for those calculations requiring the use of the IBM 360-65 computer.

Transmission of Substituent Effects in Heterocyclic Systems. Evidence for Coplanarity in 2-Phenylthiazole, and a Determination of σ_p^+ for the Coplanar Phenyl Substituent[1]

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Received March 26, 1973

The rate of solvolysis of 1-(2-phenyl-5-thiazolyl)ethyl chloride has been studied and compared with other solvolysis data in the thiazole system. The rate of solvolysis is 20 times that expected for a substituent having a σ_p^+ value of −0.179. This rate is, however, consistent with a σ_p^+ value of −0.34. These results are explained in terms of a coplanar thiazole–phenyl system.

In conjunction with studies from these laboratories of the transmission of substituent effects in heterocyclic systems[2-4] we have had occasion to observe the same substituent in several different electronic and geometric environments. Data on the phenyl substituent in the thiazole system are unique and can be used to understand more fully this versatile substituent. In earlier studies of electrophilic substitution reactions it has been observed that the effect of the *p*-phenyl substituent is variable and inconsistent.[5-7] Stock and Brown have pointed out that the σ^+ substituent constant for phenyl is variable[7,8] and shows much more scatter as evaluated from a variety of reactions than do most electrophilic substituent constants, and that this is probably the result of noncoplanarity.

Berliner and Shieh[9] studied the constrained system 1-(2-fluorenyl)ethyl chloride and found its rate of solvolysis to be 700 times that of 1-phenylethyl chloride. In evaluating the large rate acceleration in this system and in 2-(2-fluorenyl)-2-chloropropane, Brown and Inukai[10] pointed out that a phenyl moiety constrained to coplanarity is much more effective in electron release than a typical biphenyl system. They calculated a replacement constant, σ_{Ar}^+, for the fluorenyl moiety of −0.49. It may be concluded that a *p*-phenyl substituent held to a planar geometry should result in a σ_p^+ value of approximately −0.37 (correcting for *m*-CH_2 and *o'*-CH_2).

In our studies of the transmission of substituent effects in thiazoles, we have analyzed the 1-(2-x-5-thiazolyl)ethanol system where x = H, CH_3, Cl, SCH_3, and OCH_3. These data gave excellent correla-

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

(3) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306, 4311 (1972).

(4) D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, **37**, 2615 (1972).

(5) P. B. D. de la Mare, *J. Chem. Soc.*, 4450 (1954); P. B. D. de la Mare and M. Hassan, *ibid.*, 3004 (1957).

(6) F. B. Deans, C. Eaborn and D. E. Webster, *J. Chem. Soc.*, 3031 (1959).

(7) L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, **84**, 1242 (1962).

(8) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(9) E. Berliner and Shieh, *J. Amer. Chem. Soc.*, **79**, 3849 (1957).

(10) H. C. Brown and T. Inukai, *J. Amer. Chem. Soc.*, **83**, 4825 (1961).

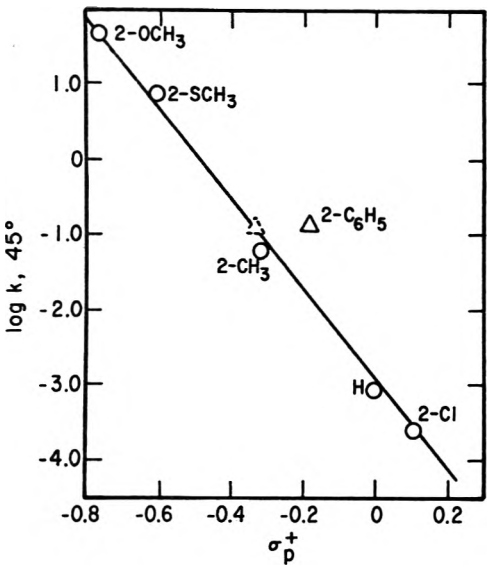

Figure 1.—Correlation of solvolysis rates of substituted 1-(5-thiazolyl)ethyl chlorides in 80% ethanol with σ_p^+.

tion with σ_p^+.[11] However, the additional data shown in Table I for the phenyl substituent do not fit

TABLE I

RATE CONSTANTS FOR THE SOLVOLYSIS OF 1-(2-PHENYL-5-THIAZOLYL)ETHANOL DERIVATIVES IN 80% ETHANOL

Compound solvolyzed	T, °C	Method[a]	k_1, sec^{-1}
1-(2-Phenyl-5-thiazolyl)-ethyl *p*-nitrobenzoate	25.0		1.73×10^{-8} [b]
	75.0	A	1.17×10^{-5}
	110.0	A	4.06×10^{-4}
1-(2-Phenyl-5-thiazolyl)-ethyl chloride	25.0	B	8.24×10^{-3}
1-(5-Thiazolyl)ethyl chloride[c]	25.0	B	8.55×10^{-5}

[a] A, using sealed ampoules; B, at constant pH. [b] Extrapolated from data at higher temperatures. [c] From ref 11.

the same correlation as is apparent from Figure 1. Although the original σ_p^+ constant for phenyl, −0.179,[12] is substantially less negative than the σ_p^+ constant for methyl, −0.311, in the present instance phenyl is more activating than methyl.

Recent molecular orbital calculations of Bodor, Farkas, and Trinajstic[13] agree with these data. Their studies suggest that the planar configuration of 2-phenylthiazole is the most stable form. In contrast, their calculations for the 2-phenylthiazolium cation suggest that it is not planar and that there is an appreciable angle of twist between the two rings. Thus the complete absence of ortho hydrogens apparently allows coplanarity, but the presence of one ortho hydrogen apparently leads to a system with an appreciable angle of twist between the two rings. Concordant with this suggestion is our previous observation[4] that the solvolysis rate of 1-(5-phenyl-2-thienyl)ethyl *p*-nitrobenzoate is in line with the usual constant for phenyl.

Our rate data may therefore be used as an independent basis for calculating an electrophilic substituent constant σ_p^+, for a coplanar phenyl moiety. Using a reaction constant, ρ, of −6.14,[11a] the σ_p^+ constant is −0.34, which is in very satisfying agreement with that calculated above from the fluorenyl moiety.

Experimental Section[14]

2-Phenylthiazole (1).—The procedure of Hantzsch[15] for the synthesis of 2-methylthiazole was modified for the preparation of **1**. A solution of oxalic acid (13.5 g, 0.15 mol) in chloroacetaldehyde dimethyl acetal (18.7 g, 0.15 mol) was heated to reflux for 0.5 hr producing a clear, light tan solution. The oil bath was removed for 10 min and thiobenzamide (20.5 g, 0.15 mol) was added as a solid. The solution was slowly heated and maintained at reflux for 2 hr. After cooling, 70 ml of 30% hydrochloric acid was added with stirring. After refluxing for 5 min, the solution was filtered and extracted with 3 × 50 ml of ether. The combined ether layers were dried ($MgSO_4$) and concentrated to give a light yellow oil which was distilled to yield 14.25 g (59%) of pure 2-phenylthiazole: bp 144–146° (38 mm) [lit.[16] 135–138° (18 mm)]; ir (neat) 3110, 1675, 1475, 1440, 1415, 1310 cm^{-1}; nmr ($CDCl_3$) δ 7.87 (m, 3, 4-H and *o*-phenyl H) and 7.33 (m, 4, 5-H and *m*- and *p*-phenyl H).

Anal. Calcd for C_9H_7NS: C, 67.05; H, 4.38; N, 8.69; S, 19.88. Found: C, 67.31; H, 4.61; N, 8.56; S, 19.65.

1-(2-Phenyl-5-thiazolyl)ethanol (2).—Ether (500 ml) was stirred at −80° under a nitrogen atmosphere while 2-phenylthiazole (10.0 g, 0.062 mol) in 50 ml of ether was added dropwise from a dropping funnel. Simultaneously, *n*-butyllithium (0.07 mol, 43.4 ml in hexane) was added from a second dropping funnel. The thiazole was kept in slight excess during the 30-min addition period. After the addition was complete, the solution was stirred for 75 min before rapidly adding acetaldehyde (11.7 ml, 0.2 mol). After stirring for 1 hr, the colorless solution was quenched with 100 ml of water. The layers were separated and the aqueous layer was extracted with 2 × 100 ml of ether. The combined organic layers were dried ($MgSO_4$) and concentrated, and impurities were distilled away to give the crystalline alcohol **2** in 76% yield: mp 84.5–85° (lit.[17] mp 87–88°); nmr ($CDCl_3$) δ 7.80 (m, 2, o-phenyl H), 7.50 (s, 1, 4-H), 7.33 (m, 3, *m*- and *p*-phenyl H), 5.10 (q, 1, J_{CH,CH_3} = 6.2 Hz, $CHCH_3$), 3.17 (s, 1, OH), 1.58 (d, 3, J_{CH-CH_3} = 6.2 Hz, $CHCH_3$).

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.32; H, 5.41; N, 6.84; S, 15.63. Found: C, 64.11; H, 5.24; N, 6.62; S, 15.49.

1-(2-Phenyl-5-thiazolyl)ethyl Chloride (3).—Alcohol **2** was converted into the chloride **3** in 75% yield using phosphorus pentachloride. Crystallization from hexane afforded a pure sample of **3**: mp 35.5–37.0°; nmr ($CDCl_3$) δ 1.87 (d, 3, J = 6.7 Hz, $CHCH_3$), 5.31 (q, 1, J = 6.7 Hz, $CHCH_3$), 7.37 (m, 3, *m*- and *p*-phenyl H), 7.68 (s, 1, 4-H), 7.87 (m, 2, *o*-phenyl H).

Anal. Calcd for $C_{11}H_{10}ClNS$: C, 59.06; H, 4.51; Cl, 15.84; N, 6.26. Found: C, 59.20; H, 4.38; Cl, 15.72; N, 6.44.

1-(2-Phenyl-5-thiazolyl)ethyl *p*-Nitrobenzoate (4).—The alcohol **2** was converted into the lithium salt using butyllithium and treated with *p*-nitrobenzoyl chloride. Work-up in the usual manner afforded the ester **4** in 85% yield. Crystallization from hexane gave the pure ester **4**: mp 89.5–90.5°; nmr ($CDCl_3$) δ 1.85 (d, 3, J = 6.1 Hz, $CHCH_3$), 6.52 (q, 1, J = 6.1 Hz, $CHCH_3$), 7.43 (m, 3, *m*- and *p*-phenyl H), 7.50 (s, 1, 4-H), 7.90 (m, 2, *o*-phenyl H), 8.30 (s, 4, *p*-nitrophenyl H).

Anal. Calcd for $C_{18}H_{14}N_2O_4S$: C, 61.01; H, 3.98; N, 7.90; S, 9.05. Found: C, 61.17; H, 4.14; N, 8.09; S, 9.13.

Kinetic Procedures. Kinetic procedures have been reported previously.[3]

(11) (a) D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972); (b) D. S. Noyce and S. A. Fike, manuscript in preparation.

(12) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(13) N. Bodor, M. Farkas, and N. Trinajstic, *Croat. Chem. Acta*, **43**, 107 (1971).

(14) Melting points and boiling points are uncorrected. Routine infrared spectra were recorded using a Perkin-Elmer Infracord Model 137. Nmr spectra were obtained using a Varian Associates Model T-60 spectrometer. Elemental analyses were determined by the Chemical Analytical Services Laboratory, College of Chemistry, Berkeley, Calif. 94720.

(15) A. Hantzsch, *Justus Liebigs Ann. Chem.*, **250**, 270 (1889).

(16) H. Erlenmeyer, C. Becker, E. Sorkin, H. Bloch and E. Suter, *Helv. Chim. Acta*, **30**, 2058 (1947).

(17) E. Haruki, S. Izumita, and E. Imoto, *Nippon Kagaku Zasshi*, **86**, 942 (1965).

Registry No.—**1**, 1826-11-5; **2**, 10045-48-4; **3**, 40187-13-1; **4**, 40187-14-2; oxalic acid, 144-62-7; chloroacetaldehyde dimethyl acetal, 97-97-2; thiobenzamide, 2227-79-4; acetaldehyde, 75-07-0; phosphorus pentachloride, 10026-13-8; *p*-nitrobenzoyl chloride, 122-04-3.

The Formation of Allenes on Alkaline Treatment of 3-Nitroso-4,5,5-trialkyl-2-oxazolidones[1]

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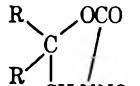
Received February 8, 1973

On treatment of 3-nitroso-4-methyl-5,5-pentamethylene-2-oxazolidone (**3**) with sodium 2-methoxyethoxide in 2-methoxyethanol, or with sodium methoxide in methanol, ~15–20% yields of 1,1-pentamethyleneallene (**4**) are obtained, together with several other compounds. Similarly, 3-nitroso-4,5,5-trimethyl-2-oxazolidone (**11**) yields 6–7% 1,1-dimethylallene (**13**), and 3-nitroso-4,5-dimethyl-5-*tert*-butyl-2-oxazolidone (**12**) yields 1-methyl-1-*tert*-butylallene (**14**) in 15% yield. The reaction of pinacolone with zinc and methyl α-bromopropionate yields the expected mixture of diastereoisomers of methyl 3-hydroxy-2,3,4,4-tetramethylpentanoate (**15**), if carried out under mild conditions. Long refluxing, however, results in the formation of α,β,β,γ-tetramethylvalerolactone (**16**).

Studies of the reactions which occur when 3-nitroso-5,5-dialkyl-2-oxazolidones (**1**) are treated with bases



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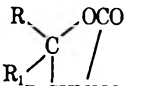

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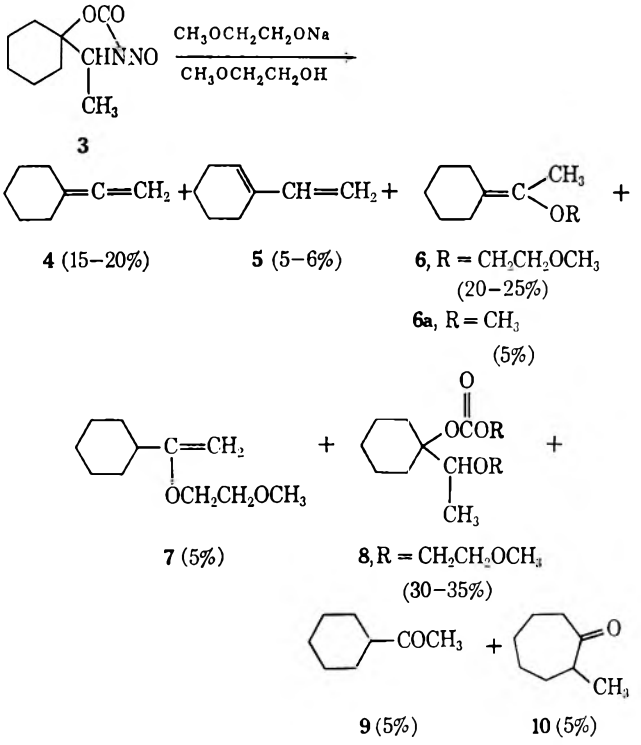
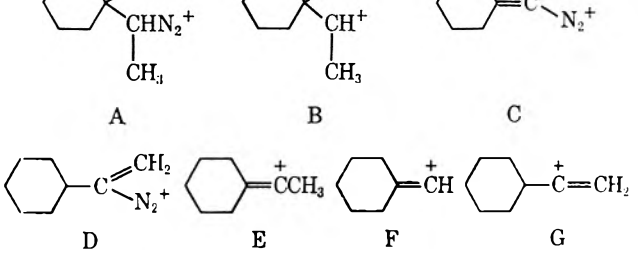
have proved of interest not only because of the wide variety of products produced but also because of the multiplicity of mechanistic interpretations used to account for the results.[3] The present study on the reactions of 3-nitroso-4,5,5-trialkyl-2-oxazolidones (**2**) was undertaken for three main reasons: (1) to find out the synthetic utility of such reactions, (2) to learn more about the behavior of unsaturated cations, and (3) to compare the products formed from diastereoisomers of type **2**.

The most detailed study of reaction products was carried out with 3-nitroso-4-methyl-5,5-pentamethylene-2-oxazolidone (**3**) when treated with sodium 2-methoxyethoxide in 2-methoxyethanol. The main products were 1,1-pentamethyleneallene[4] (**4**), 1-(2-methoxyethoxy)ethylidenecyclohexane (**6**), and 1-[1-(2-methoxyethoxy)ethyl]cyclohexyl 2-methoxyethyl carbonate (**8**). Smaller amounts of 1-vinylcyclohexene[5] (**5**), 1-methoxyethylidenecyclohexane (**6a**), 1-(2-methoxyethoxy)vinylcyclohexane (**7**), methyl cyclohexyl ketone (**9**), and 2-methylcycloheptanone (**10**) were present. Because of the large number of products formed and the fact that none is formed in a large yield, the utility of such reactions will probably be minimal. Probably the most interesting result is that a new allene synthesis has been discovered.

The formation of these compounds may be explained



by assuming attack of the alkoxide ion at the carbonyl group of **3** followed by changes outlined previously[3c,d] to yield the intermediate (A). Loss of nitrogen from



A yields cation B, which can react with solvent to produce **8**.[6] Base-catalyzedel imination of alkylcar-

(1) This work was supported in part by Grant 12445X of the National Science Foundation.

(2) This work was done in an undergraduate research program by Mr. Ving Lee during 1970–1971.

(3) (a) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951); (b) M. S. Newman and S. J. Gromelski, *J. Org. Chem.*, **37**, 3220 (1972); (c) M. S. Newman and C. D. Beard, *J. Amer. Chem. Soc.*, **92**, 4309 (1970); (d) *J. Org. Chem.*, **35**, 2412 (1970); (e) M. S. Newman and T. B. Patrick, *J. Amer. Chem. Soc.*, **91**, 6461 (1969); (f) *ibid.*, **92**, 4312 (1970), and references cited therein.

(4) W. J. Bailey and C. R. Pfeifer, *J. Org. Chem.*, **20**, 95 (1955).

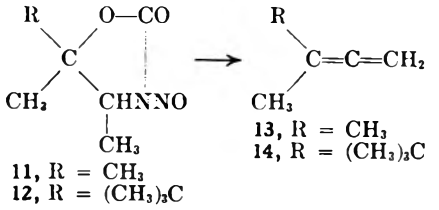
(5) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 58 (1938).

(6) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).

bonic acid yields C, which can undergo a hydride shift to yield D. Loss of a proton and nitrogen from C or D yields the allene **4**. The small amount of diene **5** may arise from a precursor to **4** during the reaction. Loss of nitrogen from C yields the unsaturated cation E, which can react with methoxyethanol to yield **6** as in analogous cases,[6] or can cleave the solvent to yield **6a** as described for the case of an unsymmetrically disubstituted unsaturated cation,[3c] F. Loss of nitrogen from D can lead *via* **6** to **7** in the same way that **6a** is formed from B. The ketone **9** can arise from reaction of E or G with water, and the formation of the ring-expanded ketone **10** can be explained by rearrangement of E followed by hydration.

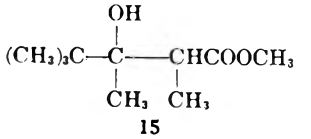
On treatment of **3** with sodium methoxide in methanol, the yield of allene **4** was about the same as when sodium 2-methoxyethoxide was used. In addition, about 25–30% of 1-vinylcyclohexanol and 20–25% of **6a** were formed in addition to smaller amounts of 2-methylcyclopheptanone (**10**), cyclohexyl methyl ketone, and other products.

In order to test the generality of the new allene synthesis observed, 3-nitroso-4,5,5-trimethyl-2-oxazolidone (**11**) and 3-nitroso-4,5-dimethyl-5-*tert*-butyl-2-oxazolidone (**12**) were prepared and treated with base. From **11** a 6–7% yield of 1,1-dimethylallene (**13**) and from **12** a 15% yield of 1-methyl-1-*tert*-butylallene (**14**) were obtained in addition to a number of other products similar to those obtained from **3**.



11, R = CH_3
12, R = $(CH_3)_3C$
13, R = CH_3
14, R = $(CH_3)_3C$

The compound **12** was studied because we wished to see if the diastereoisomers would give different results. However, since it was not feasible to separate the diastereoisomeric methyl 3-hydroxy-2,3,4,4-tetramethylpentanoates (**15**) obtained on treatment of methyl *tert*-butyl ketone with methyl α-bromopropionate and zinc, this objective was not attained. Only one crystalline pure hydrazide was obtained from **15**. Interestingly, in the Reformatsky reaction appreciable amounts of α,β,β,γ-tetramethyl-γ-valerolactone (**16**) were obtained. The formation of this compound could be largely avoided if only slight (*ca.* 5%) excesses of zinc and bromo ester were used and if the ratio of ether to benzene was greater than one. Treatment of **15** with zinc and bromo ester, or with hot dilute sulfuric acid, resulted in rearrangement to **16**.[7] If the Reformatsky reaction was carried out with excesses of zinc and bromo ester and refluxing was continued for long periods, **16** was the major product.



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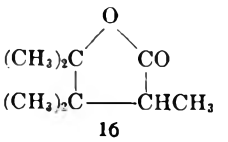

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(7) See A. W. Burgstahler and D. E. Wetmore, *J. Org. Chem.*, **26**, 3516 (1961), for a similar rearrangement.

Experimental Section[8]

Methyl 3-Hydroxy-2-methyl-3,3-pentamethylenepropanoate*.—To a solution of 98.8 g of freshly distilled cyclohexanone in 200 ml of dry ether and 150 ml of benzene containing 66 g of activated[9] zinc was added 186 g of methyl 2-bromopropanoate as rapidly as the rate of reflux of solvent would permit. By 30 min after addition the zinc had all disappeared. After a conventional work-up, 150 g (80%) of redistilled hydroxy ester was obtained, bp 116–117° (10 mm) (98% pure by glpc).

Anal. Calcd for $C_{10}H_{18}O$: C, 64.5; H, 9.8. Found: C, 64.4; H, 9.8.

The corresponding ethyl ester*, bp 132.5–133° (17 mm), was obtained in 80% yield.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.0; H, 10.0. Found: C, 66.3; H, 10.1.

4-Methyl-5,5-pentamethylene-2-oxazolidone*.—A solution of 37.2 g of the above methyl ester in 100 ml of 1-propanol and 14 ml of anhydrous hydrazine was refluxed for 24 hr. After removal of solvent on a rotary evaporator the residue was taken into cold chloroform. The crude hydrazide was extracted with two 150-ml portions of cold 3 *M* hydrochloric acid. These extracts were treated in an ice bath with a solution of 14 g of sodium nitrite in 100 ml of water. After the excess nitrite was destroyed with bisulfite, the crude azide was extracted with chloroform. After washing with saturated salt solution, the chloroform extract was added dropwise to a heated flask to effect rearrangement of the azide. After removal of solvent the residue was recrystallized from 9:1 cyclohexane–benzene to yield 30.5 g (92%) of colorless oxazolidone, mp 109–110°.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.9; H, 8.9; N, 8.2. Found: C, 64.1; H, 8.9; N, 8.1.

3-Nitroso-4-methyl-5,5-pentamethylene-2-oxazolidone* (3).—This compound was prepared essentially as described for similar compounds[3b] in 90% yield as orange, elongated prisms, mp 43–44°, from 9:1 pentane–cyclohexane. This compound was used immediately after preparation because it was fairly unstable at room temperature. All samples sent for analysis decomposed in transit. However, the ir (5.55 μ) and nmr ($CDCl_3$) {τ 8.80 (d, J = 6.5 Hz, 3, $CHCH_3$), 8.34 [broad m, 10, $-(CH_2)_5-$], 5.78 (q, J = 6.5 Hz, 1, $CHCH_3$)} were consistent with the proposed structure.

3-Nitroso-4,5,5-trimethyl-2-oxazolidone* (11).—This compound, mp 88–89°, was prepared in 93% yield as described.[3b,10]

Methyl 3-Hydroxy-2,3,4,4-tetramethylpentanoates (15).—About 100 ml of benzene was distilled from the reaction flask containing 70 g of activated zinc.[9] On cooling, 200 ml of dry ether and 0.5 g of iodine were added. To the reheated solution was added dropwise a solution of 101 g of methyl *tert*-butyl ketone and 175 g of methyl 2-bromopropanoate in 200 ml of ether. Once the exothermic reaction had commenced, heating was discontinued and the rate of addition was adjusted to control the reaction. After about half had been added 250 ml of ether was added. The mixture was stirred for 45 min at the end (until most of the zinc had reacted). After 400 ml of ammoniacal concentrated ammonium chloride solution was added, the solids were filtered and the filtrate was worked up in a conventional way to yield 122 g (65%) of **15**, bp 93–95° (15 mm). Nmr analysis indicated that a mixture of the diastereoisomers of **15** (about 9:2) was present. Pure samples of each were obtained by preparative glpc using 10% FFAP on Chromosorb W at 135°.

Isomer I had nmr [$(CH_3)_4Si$-10] τ 9.10 [s, 9, $C(CH_3)_3$], 8.92 (s, 3, CH_3COH), 8.83 (d, J = 7.0 Hz, 3, CH_3CH), 7.27 (q, J = 7 Hz, 1, $CHCH_3$), 6.7 (broad s, 1, OH), 6.34 (s, 3, OCH_3). Isomer II was similar except that the OH was at τ 8.14. The bands at τ 8.14 and 6.7 were used to estimate the proportions of I and II.

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.8; H, 10.6. Found (for I): C, 64.0; H, 10.5. Found (for II): C, 63.8, H, 10.8.

α,β,β,γ-Tetramethyl-γ-valerolactone (16).—When the Reformatsky reaction described above was carried out with excess zinc and bromo ester and the reaction mixture was refluxed for 8 hr the product boiled mostly at 105–110° (10 mm). On standing

(8) All compounds marked with an asterisk had nmr spectra [CCl_4, $(CH_3)_4Si$] and apparent peak (mass spectrum) consistent with the assigned structures. We thank Mr. Richard Weisenberger for the mass spectra.

(9) L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.*, **62**, 576 (1940).

(10) See Ph.D. Thesis of W. Liang, The Ohio State University, 1972, for details.

16 crystallized in large crystals: mp 64–65°; nmr ($CDCl_3$) τ 9.10 (s, 3, CH_3CH_3CO–), 8.95 (s, 3, CH_3CH_3CO), 8.90 (d, J = 7 Hz, 3, CH_3CH), 8.65 [s, 6, $(CH_3)_2C$], 7.3 (q, J = 7 Hz, 1, CH_3CH); ir (KBr) 3450 (due to enolization of carbonyl), 1745 cm^{-1} (C=O); mass spectrum m/e 156.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 69.4; H, 10.3.

The same lactone was obtained in 90% yield when a mixture of 17.3 g of **15**, 4 ml of 98% H_2SO_4, and 80 ml of water was refluxed for 4 hr.

3-Nitroso-4,5-dimethyl-5-*tert*-butyl-2-oxazolidone (12).—In a typical experiment a solution of 93 g of the diastereoisomers **15**, 80 ml of hydrazine, and 200 ml of 1-propanol was slowly warmed to reflux and held there for 24 hr. After removal of solvent on a rotary evaporator the residue was triturated with pentane. The solid (60 g, 65%) was collected and kept over H_2SO_4 in a desiccator overnight. No attempts were made to process the hydrazide in the mother liquor. The crude hydrazide (40 g) was added to a cold solution of 40 ml of 35% HCl in 400 ml of water layered with 100 ml of chloroform. A solution of 14 g of sodium nitrite in 60 ml of water was dropped in (cold) and the mixture was well stirred for 40 min. The yellow $CHCl_3$ layer was separated, washed twice with saturated salt solution, and then added slowly to refluxing benzene (100 ml). The resulting product on distillation, 175–180° (1 mm), yielded a yellow solid which on crystallization from 10:1 Skellysolve B–benzene afforded 32.0 g (88% based on hydrazide) of 4,5-dimethyl-5-*tert*-butyl-2-oxazolidone, mp 108–109°, as colorless crystals: nmr ($CDCl_3$) τ 9.0 [s, 9, $(CH_3)_3C$], 8.76 (d, J = 7 Hz, 3, CH_3-CH), 8.70 [s, 3, $CH_3CC(CH_3)_3$], 5.96 (q, J = 7 Hz, 1, CH_3CH), 2.92 (broad m, 1, NH); ir (KBr) 3250 (NH), 1725 cm^{-1} (C=O).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.2; H, 10.0. Found: C, 63.4; H, 10.0.

Nitrosation according to method B[3a] yielded **12** in 82% yield after recrystallization from pentane as yellow crystals: mp 48–49°; nmr ($CDCl_3$) τ 9.0 [s, 9, $(CH_3)_3C$], 8.71 (d, J = 7 Hz, 3, CH_3CH), 8.70 [s, 3, $CH_3CC(CH_3)_3$], 5.6 (q, J = 7 Hz, 1, CH_3CH); ir (KBr) 1800 cm^{-1} (C=O). Suitable microanalyses were not obtained because of deterioration of the samples en route.

Alkaline Treatment of 3.—In a typical experiment 35 ml of a 1.2 *M* solution of sodium 2-methoxyethoxide in 2-methoxyethanol was added dropwise during 15–20 min to a solution of 7.42 g of **3** in 30 ml of 2-methoxyethanol. About 85–90% of the theoretical nitrogen was collected. The reaction mixture was added to saturated salt solution and the organic products were extracted with ether. The ether was removed by distillation through a 6 ft × 0.5 in. glass helices packed column and the residue was distilled at 17 mm to yield the following five fractions: I, up to 41°, 4.0 g; II, 133–140°, 0.92 g; III, 158–167°, 0.72 g; IV, 167–177°, 0.96 g; and V, 188–198°, 3.65 g. Fractions I–IV were analyzed by glpc on a 10 ft × 0.25 in. column (column A) packed with 10% SF-96 (a silicone) on firebrick (Chromosorb P) with a helium flow of 50–60 ml/min at temperatures of 125–145°. In fraction I (mainly solvent) there was pentamethyleneallene (**4**) in 15–20% yield based on starting **3**, proved by comparison with an authentic[4] sample by ir, glpc retention time, and nmr. From II there were three peaks with retention times of 1.5, 2.0, and 2.5 min (column T, 135°). The first two peaks were shown to be vinylcyclohexene[5] (**5**) and methyl cyclohexyl ketone (**9**) (Chemical Samples Co.) by comparison with authentic samples. Each was present in about 5% yield based on starting **3**.[11] Preparative glpc of the 2.5-min fraction on a 9.5 ft × 0.25 in. column (column B) packed with Carbowax 4000 monostearate on Chromosorb W at 120° (helium flow 40 ml/min) gave a 1.4-min (retention time) fraction shown to be **6a** and a 2.3-min fraction shown to be **10**. Each was present in about 5% yield based on **3**. Authentic **6a** was prepared in 25% yield from **3** and sodium methoxide in methanol as a colorless liquid: bp 90–97° (100–110 mm); nmr ($CDCl_3$) τ 9–7.5 [m, 10, $-(CH_2)_5-$], 8.25 (s, 3, $CH_3C=$], 6.60 (s, 3, CH_3O).

Anal. Calcd for $C_9H_{16}O$: C, 77.1; H, 11.5. Found: C, 76.9; H, 11.5.

The identity of the 2.3-min fraction was established by comparison (ir, nmr, glpc) with authentic 2-methylcycloheptanone obtained from Professor R. Ouellette and M. S. Jerristaty.

Preparative glpc of fraction III and IV on a 10 ft × 0.25 in. column packed with SF 96 (a fluorinated silicone) on firebrick (Chromosorb P) at 145° with a helium flow of 50 ml/min yield a 7-min fraction and an 8-min fraction. The 7-min fraction was shown to be **7** by nmr, mass spectrum, and the formation of the 2,4-dinitrophenylhydrazone derivative identical with that formed from cyclohexyl methyl ketone*.[12] The 8-min fraction was shown to be **6** by nmr ($CDCl_3$) τ 9.0–7.5 [m, 10, $-(CH_2)_5-$], 8.20 (s, 3, $=CCH_3$), 6.6 (s, 3, OCH_3), 6.0–6.5 (m, 4, $-CH_2CH_2-$).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.7; H, 10.9. Found: C, 71.8; H, 11.0.

On treatment with 2,4-dinitrophenylhydrazone reagent, the 2,4-dinitrophenylhydrazone derivative, mp and mmp with an authentic sample[12] 138–139°, was obtained.

Fraction V was essentially pure **8** as shown by the following: ir (film) 1730 ($O_2C=O$), broad bands at 1175–1000 cm^{-1} (OC); nmr ($CDCl_3$) τ 9.0–7.5 [m, 10, $-(CH_2)_5-$], 8.85 (d, J = 7 Hz, 3, CH_3CH), 6.7–6.2 (m, 8, OCH_2CH_2O), 6.70 (s, 6, OCH_3), 6.1 (q, J = 7 Hz, 1, $CHCH_3$).

Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.2; H, 9.2. Found: C, 59.6; H, 9.1.

When 3.71 g of **3** in 40 ml of methanol was treated with a solution of sodium methoxide in methanol about 90% of the theoretical nitrogen was rapidly evolved. After a work-up similar to that described above two fractions, I, 1.2 g, bp up to 60° (100 mm), and II, 2 1 g, bp 80–115° (105 mm), were isolated. Fraction I consisted of a mixture of **4** and methanol. By glpc on column A it was estimated that a 10–15% yield of **4** was at hand. Analysis of fraction II on column A at 125° with a helium flow of 50 ml/min showed the presence of **4** (5% so that the total yield of **4** was 15–20%), 9.2 min, cyclohexyl methyl ketone (5–10%), 12.8 min, and a mixture of **10** (5–10%) and **6a** (20–25%), 14.7 min. The vinylcyclohexanol proved identical with an authentic sample[5] prepared by reduction of ethynylcyclohexanol over a Lindlar catalyst.[13]

When 7.9 g of **11** in 40 ml of propanol was treated with a solution of sodium propoxide in propanol 85% of the thoretical nitrogen was rapidly evolved. The mixture was then heated to 60° and a distillate consisting mostly of 1,1-dimethylallene (**13**) and propanol was obtained. The yield of **13** was determined to be about 6–7% by infrared analysis (using the band at 1950 cm^{-1} of solutions of authentic **13**[12] in propanol.

A solution of 10.0 g of **12** in anhydrous methanol was treated with sodium methoxide (85% N_2 formed) as in the case of **3**. After a similar work-up, distillation yielded two fractions, I, up to 45° (15 mm), and II, 45–60° (15 mm). Analysis of I by glpc on column A at 126–130° with a helium flow of 15–20 ml/min showed **14** in about 15% yield, retention time 5.5 min. The structure of **14** was established by comparison with an authentic sample: ir 840 cm^{-1} ($C=CH_2$), 1950 (C=C=C); nmr ($CDCl_3$) τ 8.98 [s, 9, $C(CH_3)_3$], 8.33 (m, 3, $CH_3C=$), 4.50 (m, 2, $=CH_2$). The authentic sample was synthesized from 2,3,3-trimethyl-1-butene and bromoform to yield 1,1-dibromo-2-methyl-2-*tert*-butylcyclopropane (45%) which on treatment with methyllithium afforded pure **14** in 80% yield.[14]

Anal. Calcd for C_8H_{14}: C, 87.2; H, 12.8. Found: C, 86.9; H, 12.7.

Anal. Calcd for $C_8H_{14}Br_2$: C, 35.6; H, 5.2; Br, 59.2. Found: C, 35.3; H, 5.1; Br, 59.1.

In addition to **14**, six other compounds were isolated by preparative glpc on column A. As each was present in 5–10% yield, no further description of them will be made.

Registry No.—**3**, 39922-49-1; **4**, 5664-20-0; **6**, 39922-51-5; **6a**, 26473-57-4; **8**, 39922-53-7; **11**, 39922-41-3; **12**, 39922-55-9; **13**, 598-25-4; **14**, 7417-50-7; **15**, 39922-57-1; **15** stereoisomer, 39922-58-2; methyl 3-hydroxy-2-methyl-3,3-pentamethylenepropanoate, 31042-01-0; ethyl 3-hydroxy-2-methyl-3,3-pentamethylenepropanoate, 39922-60-6; methyl 2-bromopropanoate, 5445-17-0; cyclohexanone, 108-94-1; 4-methyl-5,5-pentamethylene-2-oxazolidone, 16112-64-4;

(11) All percentages quoted on compounds analyzed for by glpc are calculated back to the starting nitrosooxazolidones.

(12) An authentic sample was obtained from Chemical Samples Co.

(13) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(14) L. Skattebøl and S. Solomon, *Acta Chem. Scand.*, **17**, 1683 (1963).

1-propanol, 71-23-8; methyl *tert*-butyl ketone, 75-97-8; 4,5-dimethyl-5-*tert*-butyl-2-oxazolidone, 39922-63-9; sodium 2-methoxyethoxide, 3139-99-9; 2,3,3-trimethyl-1-butene, 594-56-9; bromoform, 75-25-2; 1,1-dibromo-2-methyl-2-*tert*-butylcyclopropane, 39922-65-1; α,β,-β,γ-tetramethyl-γ-valerolactone, 39922-59-3.

Reactions of 5,5-Disubstituted 3-Nitrosooxazolidones. New Syntheses of Vinyl Azides, Vinyl Isothiocyanates, Vinyl Diethyl Phosphonates, and Divinyl Ethers[1]

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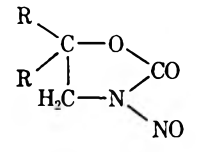
Evans Chemistry Laboratory of The Ohio State University, Columbus, Ohio 43210

Received February 8, 1973

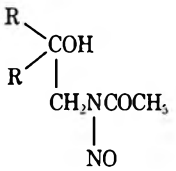
New syntheses of the α,β-unsaturated ketones, cyclohexylidenemethyl isopropyl ketone (**3**) and cyclohexylidenemethyl *tert*-butyl ketone (**4**), the divinyl ethers, 3-pentenyl ether (**6**) and cyclohexylidenemethyl 2,4-dimethyl-3-pentenyl ether (**7**), the vinyl azide, cyclohexylidenemethyl azide (**9**), the vinyl isothiocyanate, cyclohexylidenemethyl isothiocyanate (**10**), and the vinyl phosphonate, diethyl cyclohexylidenemethylphosphonate (**11**), result from the treatment of 1-(*N*-nitrosoacetylaminomethyl)cyclohexanol (**2a**) with bases in the presence of isobutyraldehyde, trimethylacetaldehyde, cyclohexanone, diethyl ketone, diisopropyl ketone, sodium azide, potassium isothiocyanate, and triethyl phosphite, respectively. The stereospecific cleavage of glyme to form 2-methoxyethyl *trans*-2,2,3-trimethyl-1-butenyl ether (**14b**) in 46% yield on treatment of 3-nitroso-5-methyl-5-*tert*-butyl-2-oxazolidone (**12**) with sodium phenoxide is explained by assuming the involvement of an unsaturated cationic intermediate. The reaction of 3-nitroso-4,5,5-trimethyl-2-oxazolidone (**15**) in 2-methoxyethanol containing sodium 2-methoxyethoxide yields 2-methoxyethyl 3-methyl-1-buten-3-yl carbonate (**16**, 22%) and other products in smaller yields.

In earlier work the products obtained on treating 5,5-disubstituted 3-nitrosoxazolidones (**1**) and nitrosoacetylaminomethylcarbinols (**2**) with alkaline reagents in the presence of other reactants were determined and their formation was explained by assuming the involvement of unsaturated cations (A)[3] or unsaturated carbenes (B).[4] In this paper further work designed to elucidate the reaction mechanisms involved and to expand the utility of the reactions for new syntheses is described.



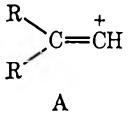
1

1a, RR = $-(CH_2)_5-$

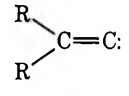


2

2a



A

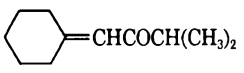


B

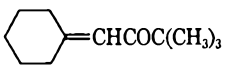
C, $R_1R = -(CH_2)_5-$

The reactions of **1a** and **2a** with alkali in the presence of cyclohexene to yield bicyclo[4.1.0]hept-7-ylidenecyclohexane have been reported and explained by assuming the intervention of cyclohexylidenecarbene (C).[5] We wished to see if reaction of 1-(*N*-nitrosoacetylaminomethyl)cyclohexanol **2a** with the carbonyl group of aldehydes and ketones would yield allene epoxides.

When a solution of **2a** and isobutyraldehyde in pentane containing Aliquat 336[6] was treated with aqueous sodium hydroxide at −10° the evolution of nitrogen was vigorous. From the reaction mixture a 36% yield of cyclohexylidenemethyl isopropyl ketone (**3**) was isolated. In a similar reaction involving tri-



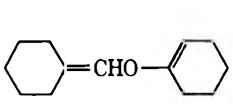
3



4

methylacetaldehyde, only a 4.4% yield of cyclohexylidenemethyl *tert*-butyl ketone (**4**) was obtained. These reactions represent a new route to α,β-unsaturated ketones. Until further work is done on this reaction, speculation as to the mechanism will not be made.

When **2a** was treated under similar conditions with cyclohexanone, diethyl ketone, and diisopropyl ketone there were obtained cyclohexylidenemethyl cyclohexenyl ether (**5**), cyclohexylidenemethyl 3-pentenyl



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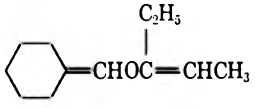

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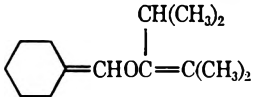


7

ether (**6**), and cyclohexylidenemethyl 2,4-dimethyl-3-pentenyl ether (**7**) in 32, 22, and 4.4% yields, respectively. Although the yields are low (no attempts at maximization were made), these reactions are of interest because they illustrate a new synthesis of acylic divinyl ethers, a type of ether apparently unknown except for the parent divinyl ether.[7] The formation

(1) This research was supported by Grant G12445X from the National Science Foundation.

(2) Further details can be found in the Ph.D. thesis of W. C. Liang, The Ohio State University, 1972.

(3) M. S. Newman and C. D. Beard, *J. Amer. Chem. Soc.*, **92**, 7564 (1970), and references cited therein.

(4) M. S. Newman and Z. ud Din, *Syn. Commun.*, **1**, 247 (1971).

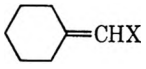
(5) M. S. Newman and C. D. Beard, *J. Amer. Chem. Soc.*, **92**, 4309 (1970).

(6) Methyl tricaprylylammonium chloride, General Mills Chemicals, Kankakee, Ill.

(7) J. U. Nef, *Justus Liebigs Ann. Chem.*, **298**, 327 (1897).

of vinyl ethers by the metal-catalyzed reaction[8] of ethyl diazoacetate with acetone and cyclohexanone and by pyrolysis[9] have been reported.

Since the reaction of nitrosooxazolidones (**1**, **1a**) with base in the presence of chloride, bromide, and iodide ions afforded high yields of terminal vinyl chlorides, bromides, and iodides,[5] classes of compounds not readily obtained by other methods, similar reactions were carried out with **2a** in the presence of iodide ion. Since a 72% yield of cyclohexylidenemethyl iodide (**8**) was obtained, we were encouraged to try similar reactions of **2a** in the presence of other nucleophilic reagents. When the reaction was carried out in the presence of azide ions a 56% yield of cyclohexylidenemethyl azide (**9**) was obtained. Thus a valuable synthesis of terminal azides is at hand. This new route to vinyl azides complements known methods.[10]



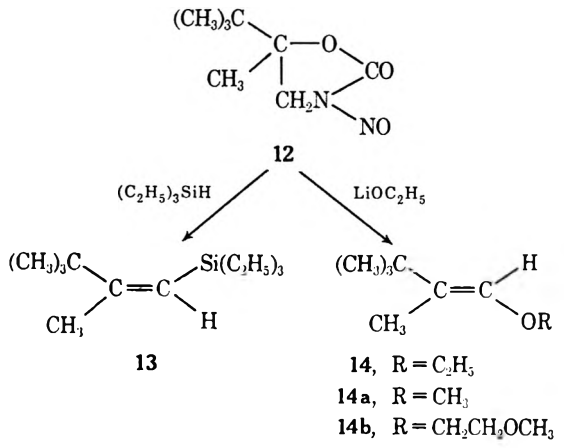
9, X = N_3
10, X = SCN
11, X = $PO(OC_2H_5)_2$

Similar reaction of **2a** with potassium thiocyanate afforded cyclohexylidenemethyl isothiocyanate (**10**) in 39% yield. This constitutes a new synthesis of terminal vinyl isothiocyanates, a class of compounds generally unknown except for the parent, vinyl isothiocyanate.[11]

When triethyl phosphite was used, **2a** reacted to form cyclohexylidenemethyldiethyl phosphonate (**11**) in 42% yield. Thus a new synthesis of phosphonates, quite different from all other methods,[12] is at hand. This and the above new reactions demonstrate anew the versatility of nitrosoacetylaminomethylcarbinols for the synthesis of substituted vinyl compounds. Although the syntheses of vinyl azides, isothiocyanates, and vinyl phosphonates have been demonstrated only with **2a**, undoubtedly similar reactions would occur with the nitrosooxazolidones (**1**). In our limited experience it is difficult to predict whether a better yield of product will be obtained by starting with a nitrosooxazolidone or a nitrosoacetylaminomethyl alcohol.[13]

In earlier work, the steric course of reactions in the carbenic and cationic modes of reaction of 5-methyl-5-*tert*-butyl-2-nitrosooxazolidone (**12**) were studied. In both cases, the intermediate was attacked at the position trans to the *tert*-butyl group.[14]

Evidence that the intermediate leading to **13** was an unsaturated carbene (B) was presented.[14] However, **14** could have been formed from A or B. Furthermore, under the reaction conditions (lithium ethoxide) designed to allow capture of a carbene by an allene, a 7% yield of **14** was obtained as a by-product.[14] We now show that treatment of **12** with sodium methoxide in methanol affords an 86% yield of a mixture of *trans*-**14a** (97%) and *cis*-**14a** (3%). As mentioned,[15] we cannot be sure whether an unsaturated carbene or cation is involved in the formation of vinyl ethers. In order to determine unequivocally the steric course of reaction in which an unsaturated cation was the intermediate, we treated **12** with sodium phenoxide in glyme as described for an analogous case.[3] A 46% yield of 2-methoxyethyl *trans*-2,2,3-trimethyl-1-butenyl ether (**14b**) and a 53% yield of anisole were produced. Thus, the unsaturated cation formed from **12** reacted stereospecifically trans to the *tert*-butyl group. Interestingly, a small yield (7–8%) of methyl *tert*-butyl acetylene was produced (compare ref 3 and 13) in this reaction.

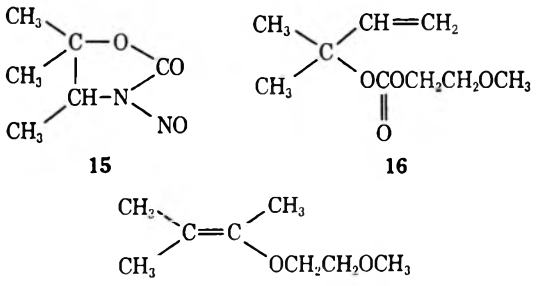


12

13

14, R = C_2H_5
14a, R = CH_3
14b, R = $CH_2CH_2OCH_3$

Since previous work on the alkaline treatment of nitrosooxazolidones had been confined almost exclusively to 5,5-dialkyl derivatives, we thought it of interest to study a case in which a 4-alkyl substituent was present because such a compound could not give rise to an unsaturated carbene.[16] Furthermore, the behavior of a trialkyl-substituted unsaturated cation compared to that of the unsymmetrical disubstituted variety (A) would be of interest. Accordingly, 3-nitroso-4,5,5-trimethyl-2-oxazolidone (**15**) was prepared. When a solution of **15** in 2-methoxyethanol saturated with sodium iodide was treated with sodium 2-methoxyethoxide,[5] no vinyl iodide was obtained. The main product obtained was 2-methoxyethyl 3-methyl-1-buten-3-yl carbonate (**16**) together with



15

16

18

(8) M. S. Kharasch, T. Rudy, W. Nudenberg, and G. Buchi, *J. Org. Chem.*, **18**, 1030 (1953).
(9) C. D. Gutsche and M. Hillman, *J. Amer. Chem. Soc.*, **76**, 2236 (1954).
(10) "The Chemistry of the Azido Group," S. Patai, Ed., Wiley-Interscience, New York, N. Y., 1971, p 80 ff.
(11) (a) J. C. H. Hwa, *J. Amer. Chem. Soc.*, **81**, 3604 (1959); (b) E. Tobler and D. Foster, *Z. Naturforsch.*, **17**, 136 (1962).
(12) (a) Y. L. Gefter, "Organophosphorous Monomers and Polymers," Pergamon Press, Elmsford, N. Y., 1962, pp 26–27, and references cited therein; (b) W. H. Woodstock, U. S. Patent 2,471,472 (1949); *Chem. Abstr.*, **43**, 7499 (1949); (c) G. M. Kosolapoff, U. S. Patent 2,389,576 (1946); *Chem. Abstr.*, **40**, 1536 (1946); (d) D. Y. Wysocki, *Diss. Abstr.*, **B28** (4), 1437 (1967); (e) P. Tavs and H. Weitkamp, *Tetrahedron*, **26**, 5529 (1970).
(13) Compare M. S. Newman and S. J. Gromelski, *J. Org. Chem.*, **37**, 3220 (1972).
(14) M. S. Newman and T. B. Patrick, *J. Amer. Chem. Soc.*, **92**, 4312 (1970).
(15) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).
(16) For one example of such a reaction see ref 15.

small amounts of 3-methyl-2-butanone (**17**) and 2-methoxyethyl 3-methyl-2-butenyl ether (**18**). When **15** in glyme was treated with sodium phenoxide, only a 2.6% yield of **18** and a corresponding 3.9% yield of anisole resulted. Hence the cleavage of glyme by the trimethylvinyl cation occurred to a very slight extent.[3] The above experiments indicate either that the trimethylvinyl cation is much less reactive than the disubstituted type (A) or that very little is formed because of competing reactions.

Experimental Section[17]

Cyclohexylidenemethyl Isopropyl Ketone (3).—To a stirred solution of 2.5 g (0.0125 mol) of **2a**[4] and 9 g (0.125 mol) of isobutyraldehyde in 15 ml of pentane containing 1 g of Aliquat 336[6] was added dropwise at −10° a 50% solution of sodium hydroxide in water. The theoretical amount of nitrogen was collected in 15 min. The mixture was then poured into 75 ml of a saturated sodium chloride solution and worked up as usual. Distillation at 60–137° (0.2 mm) yielded 2.18 g of colorless product. From the preparative vpc (column B, 125°, helium flow 120 cc/min, retention time 5.5 min) there was isolated 0.74 g (35.7%) of cyclohexylidenemethyl isopropyl ketone (**3**): ir (neat) 5.94 (C=O), 6.15 (C=C), and 6.90 μ [doublet, $(CH_3)_2$-CH−]; nmr (CCl_4) τ 8.97 [d, J = 7 Hz, 6, $-CH(CH_3)_2$], 8.38 (m, 6, $-CH_2-$), 7.84 (m, 2, $CH_2C=$), 7.36 [m, J = 7 Hz, 1, $-CH(CH_3)_2$], 7.26 (m, 2, $CH_2C=$), 4.10 (m, 1, =CH); uv (absolute EtOH) 241 mμ (ε 11,200); mass spectrum m/e 166.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.2; H, 11.1.

The 2,4-dinitrophenylhydrazone, mp 127.5–128.0°, mass spectrum m/e 346, was prepared.

Cyclohexylidenemethyl *tert*-Butyl Ketone (4).—In an analogous experiment involving 2.5 g of **2a** and 4.4 g of 2,2-dimethylpropanol was isolated by preparative vpc (column B, 135°, helium flow 130 cc/min) 0.10 (4.4%) of **4**: ir 5.87, 5.98, 6.20 μ (C=C); nmr (CCl_4) τ 8.87 [s, 9, $(CH_2)_3C-$], 8.36 (m, 6, $-CH_2-$), 7.80 (m, 2, $CH_2C=$), 7.25 (m, 2, $-CH_2C=$), 3.79 (m, 1, =CH); mass spectrum m/e 180, exact mass measurement 180.1517 (calcd, 180.1519); uv (absolute EtOH) 241 mμ (ε 12,700). The 2,4-dinitrophenylhydrazone, mp 125.5–127.0°, mass spectrum m/e 360, was prepared.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11:12. Found: C, 80.25; H, 11.19.

Cyclohexylidenemethyl Cyclohexenyl Ether (5).—To a stirred solution at 0–10° of 5.0 g of **2a** and 19.6 g of cyclohexanone in 30 ml of pentane containing Aliquat 336 was added 50% aqueous sodium hydroxide in tiny drops until about 95% of the theoretical nitrogen evolution had occurred (less than 30 min). The mixture was then treated with 100 ml of saturated sodium chloride solution and was worked up as usual to yield 2.1 g of colorless oil on distillation at 60–94° (0.05 mm). By glpc analysis the mixture was shown to contain approximately 1.6 g (32%) of **5**:[18] ir (neat) 6.00 and 8.50 μ; nmr (CCl_4) τ 8.44 (m, 10, ring $-CH_2-$), 7.92 (m, 8, $-CH_2C=C$), 5.28 (m, 1, $=CH_2C-$), 4.10 (m, 1, =CHO−); mass spectrum exact mass 192.1514 (calcd, 192.1516).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.3; H, 10.5. Found: C, 81.3; H, 10.3.

Cyclohexylidenemethyl 3-Pentenyl Ether (6).—In an experiment similar to the above with 4.9 g of **2a** and 21 ml of diethyl ketone in 25 ml of pentane was obtained 22% of **6**. By preparative glpc on a 10 ft × 0.125 in. 5% SE-30 on Chromosorb W at 138° on a F & M Model 609 chromatograph was isolated a sample of **6** which showed two components, undoubtedly the cis and trans isomers (no attempt at separation was made), and had the following properties: ir (neat) 5.45 and 8.40 μ; nmr (CCl_4) τ 8.97, 8.92 (two triplets, J = 7 Hz, 3 CH_2CH_3), 8.42 [m, 9, $-(CH_2)_3-$ and $CH_3C=C$], 7.90 (m, 6, $-CH_2C=C$), 5.50 5.35 (2 q, J = 7 Hz, 1, $CH_3CH=$), 4.14 (m, 1, =CH); mass spectrum exact mass 180.1515 (calcd, 180.1514). After treatment with dilute hydrochloric acid a mixture of 2,4-dinitrophenylhydrazone, of diethyl ketone, m/e 266, and cyclohexanecarboxaldehyde, m/e 292, was obtained.

Cyclohexylidenemethyl 2,4-Dimethyl-3-pentenyl Ether (7).—In a similar experiment (2.5 g of **2a**, 14 g of diisopropyl ketone) there was obtained 0.12 g (4.4%) of **7**: ir (neat) 6.00 and 8.45 μ; nmr (CCl_4) τ 9.00 [d, J = 7 Hz, 6, $-CH(CH_3)_2$], 8.38 [m, 12, $-(CH_2)_3-$ and $=C(CH_3)_2$], 8.02 (m, 2, trans $CH_2C=CO-$), 7.78 (m, 2, cis $CH_2C=CO-$), 7.18 [m, 1, $-CH(CH_3)_2$], 4.34 (m, 1, =CH); m/e 208 (calcd, 208).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.7; H, 11.6. Found: C, 80.4; H, 11.6.

Reactions with 2a with Nucleophiles.—A solution of 2.50 g of **2a** in 15 ml of pentane was dropped into a stirred mixture of 20 g of sodium iodide, 1 g of sodium hydroxide, 0.75 g of Aliquat 336,[6] and 10 g of water held at 3–5°. After the usual work-up, distillation afforded 2.00 g (72%) of iodomethylenecyclohexane, identified by nmr and ir which were identical with those of the known compounds.[5] In a similar experiment, except that 10 g of sodium azide was used instead of sodium iodide, there was isolated 2.2 g of crude reaction product. Chromatography over 30 g of Woelm alumina, grade I, with hexane yielded 0.95 g (56%) of azidomethylenecyclohexane (**9**) as a pale yellow liquid: ir (neat) 4.75 (=CN_3), 6.00 μ (C=C), nmr (CCl_4) τ 8.48 [m, 6, $-(CH_2)_3-$], 7.92 (m, 4, $-CH_2C=$), 4.16 (m, 1, =CH). An analytical sample was obtained by bulb-to-bulb distillation at 0.1 mm.

Anal. Calcd for $C_7H_{11}N_3$: C, 61.3; H, 8.1; N, 30.6. Found: C, 61.4; H, 8.2; N, 30.8.

In a similar experiment except that 12.1 g of potassium thiocyanate was used, distillation of the crude product yielded 0.78 g (41%) of colorless cyclohexylidenemethyl thiocyanate (**10**) (>95% pure by glpc). A purer sample was obtained by preparative glpc (column A, 140°, helium flow 100 cc/min, retention time 5 min). Pure **10** had ir bands at 4.65 (=CSCN), 6.20 μ (C=C, weak); nmr (CCl_4) τ 8.39 [m, 6, $-(CH_2)_3-$], 7.70 (m, 4, $-CH_2C=$), 4.28 (m, 1, =CH); m/e 153 (calcd, 153).

Anal. Calcd for $C_8H_{11}NS$: C, 62.7; H, 7.2; N, 9.1; S, 20.9. Found: C, 62.6; H, 7.1; N, 9.3; S, 20.9.

A solution of 2.5 g of nitrosoamide **2a** in 25 ml of pentane was added dropwise to a stirred, ice-cold mixture of 10.4 g of triethyl phosphite, 1 g of sodium hydroxide, 1.5 g of water, and 1 g of Aliquat 336 during 25 min. After the evolution of nitrogen (72% of the theoretical amount in 15 min) the mixture was worked up as usual. Distillation of the residue at 55–120° (0.1 mm) yielded 1.75 g of products which by glpc (column B) showed three components at a column temperature of 115° (helium flow 87 cc/min) and one main component at a column temperature of 190° (helium flow 75 cc/min), 6 min, 1.22 g (42%) of cyclohexylidenemethyl diethyl phosphonate (**11**). Pure **11** had ir (neat) 6.14 (C=C), 8.07 (P=O), 9.50, 9.75, 10.45 μ (POC); nmr (CCl_4) τ 8.68 (t, J = 7 Hz, 6, $-CH_3$), 8.34 [m, 6, $-(CH_2)_3-$], 7.76 (m, 2, trans $CH_2C=CP$), 7.30 (m, 2, cis $CH_2C=CP$), 5.97 (m, J = 7 Hz, 4, $-CH_2CH_3$), 4.78 (d, J = 17 Hz, 1, =CHP); mass spectrum exact mass, 232.1226 (calcd, 232.1228).

Anal. Calcd for $C_{11}H_{21}O_3P$: C, 56.9; H, 9.1; P, 13.3. Found: C, 56.8; H, 9.5; P, 13.5.

(17) All melting and boiling points are uncorrected. Melting points were taken with a Thomas-Hoover capillary melting point apparatus. The thermometers for boiling point determination were not standardized. Microanalyses were performed by the M-H-W Laboratories, Garden City, Mich., and Chemalytics, Tempe, Ariz. Infrared absorption spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance spectra relative to τ 10 for TMS were recorded on A-60 and A-60A nmr spectrophotometers, Varian Associates, Palo Alto, Calif. Vapor phase chromatographic analyses were recorded on a Varian Aerograph Model 1200 flame ionization gas chromatograph and a Varian Aerograph Model A-90P-3 gas chromatograph. A Varian Aerograph Autoprep, Model A-700, was used for preparative vapor phase chromatography. Column A represents a 10 ft × 0.375 in. column of 10% Carbowax 20M on Chromosorb W; column B represents a 5 ft × 0.25 in. column of 10% SE-30 on Chromosorb W. All vpc yields were based on the moles of the nitroso compounds used before decomposition. Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 uv spectrophotometer. Mass spectra were recorded on an AEI Model MS-9 instrument by Mr. Richard Weisenberger. The phrase "worked up as usual" means that the reaction mixture was diluted with ice water and the products were extracted into ether. The ethereal extracts were washed with a saturated salt solution, and dried by filtration through a cone of anhydrous magnesium sulfate or by the addition of anhydrous magnesium sulfate followed by filtration through a pad of Celite. The solvents were removed by distillation or on a rotary evaporator. Unless otherwise specified, the nitrogen evolution usually finished as soon as all of the base had been added.

(18) In all of the experiments with **2a** minor amounts of cyclohexanone, cycloheptanone, and cyclohexanecarboxaldehyde were obtained and identified by retention times, formation of the known 2,4-dinitrophenylhydrazones, or mass spectral results.

3-Nitroso-5-methyl-5-*tert*-butyl-2-oxazolidone (12) was prepared as described.[14]

Ethyl 2,3-Dimethyl-3-hydroxybutanoate.—To a refluxing stirred mixture of 130 g of activated zinc,[19] 250 ml of benzene, 105 g of acetone, and 250 ml of ether was added 362 g of ethyl α-bromopropionate during 3 hr. After a further 1 hr at reflux a conventional work-up afforded 214 g (74%) of desired ester, bp 77–78° (10 mm).

Anal. Calcd for $C_8H_{16}O_3$: C, 60.0; H, 10.0. Found: C, 59.9; H, 10.1.

2,3-Dimethyl-3-hydroxybutanoic Acid Hydrazide.—To 194 g of the above ester was added 58 g of anhydrous hydrazine at 0–20°. After 1 day the excess hydrazine was removed in a vacuum desiccator over concentrated H_2SO_4. Recrystallization from 95% ethanol–chloroform yielded 112 g (63%) of colorless hydrazide, mp 124–125°.

Anal. Calcd for $C_6H_{14}N_2O_2$: C, 49.3; H, 9.6. Found: C, 49.5; H, 9.6.

4,5,5-Trimethyl-2-oxazolidone.—To a stirred solution of 73.1 g of hydrazide in 250 ml of 2 *N* hydrochloric acid was added a solution of 41.4 g of sodium nitrite in 120 ml of water during 3 hr while maintaining a temperature near 5°. The mixture was extracted with benzene–chloroform (3:1) and the cold extract was washed with cold saturated sodium chloride solution. This extract was then added during 1 hr to 100 ml of refluxing benzene. After removal of solvent on a rotary evaporator, distillation at about 105° (0.15 mm) yielded a solid which, on crystallization from benzene–petroleum ether (bp 65–70°), yielded 54 g (83%) of oxazolidone: mp 61.0–61.5°; ir (KBr) 3.03 (NH), 5.77 μ (C=O); nmr ($CDCl_3$) τ 8.80 (d, J = 7 Hz, 3, $-CHCH_3$), 8.64 (s, 3, CH_3), 8.52 (s, 3, CH_3), 6.30 (q, J = 7 Hz, 1, $CHCH_3$), 3.52 (m, 1, NH).

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.8; H, 8.5. Found: C, 56.0; H, 8.7.

***N*-Nitroso-4,5,5-trimethyl-2-oxazolidone (15).**—To a stirred solution at 5° of 42 g of the above oxazolidone in 150 ml of 6 *N* hydrochloric acid was dropped a solution of 26.8 g of sodium nitrite in 100 ml of water. The yellow precipitate was collected, washed thoroughly with ice water, and dried *in vacuo* over P_2O_5. Recrystallization from ether–pentane afforded 47.7 g (93%) of **15**, mp 88–89° dec, ir (KBr) 5.57 μ (C=O). On standing at room temperature this compound decomposes so that a suitable C and H analysis could not be obtained.

Reactions of 12 with Nucleophiles. A. Decomposition with Sodium Methoxide in Methanol.—A slurry of 5.59 g (0.03 mol) of **12** in 30 ml of absolute methanol (freshly distilled over magnesium) was treated dropwise at 4° during 0.5 hr with a solution of 1.78 g (0.033 mol) of sodium methoxide in 10 ml of absolute methanol. After the theoretical amount of nitrogen had been evolved the mixture was worked up as usual. The residue was distilled to give 3.15 g (82%) of colorless materials at 63–65° (50 mm), which by vpc (column A, 40°, helium flow 100 cc/min) consisted of 97% of methyl *trans*-2,3,3-trimethyl-1-butenyl ether (**14a**) {ir (neat), bands at 5.95 (C=C), 8.90 μ ($C=COCH_3$); nmr (CCl_4) τ 8.98 [s, 9, $C(CH_3)_3$], 8.45 (d, J = 1 Hz, 3, $3H_3$), 6.49 (s, 3, $-OCH_3$), 4.27 (m, J = 1 Hz, 1, =CH); mass spectrum, mol wt 128, exact mass measurement 128.1202 (calcd, 128.1201)} and 3% of a compound which was undoubtedly the cis isomer.

Anal. Calcd for $C_8H_{16}O$: C, 74.9; H, 12.6. Found: C, 74.9; H, 12.6.

B. Decomposition with Sodium Phenoxide in Phenol–Glyme.—To a stirred solution of 5.1 g (0.044 mol) of sodium phenoxide and 33.6 g (0.4 mol) of phenol in 20 g of glyme was added dropwise at room temperature during 5 min a solution of 7.45 g (0.04 mol) of **12** in 16 g of glyme. The evolution of nitrogen was very slow. The theoretical amount was obtained only after 18 hr. After the usual work-up, which included four washes with 10% KOH, distillation gave three fractions. Preparative vpc (column A, helium flow 150 cc/min) gave pure materials from each of the fractions described below.

Fraction 1, bp 78–103°, column temperature 50°, 1.4 min, yielded 0.297 g (7.7%) of 2,2-dimethyl-3-pentyne identical with an authentic sample obtained from the Chemical Samples Co.

Fraction 2, bp 48–108° (20 mm), column temperature 110° (A) 3.5 min, yielded 2.28 g (52.7%) of anisole, identified by comparison with an authentic sample and (B) 4.7 min, yielded 3.15 g (45.7%) of 2-methoxyethyl *trans*-2,3,3-trimethyl-1-butenyl ether (**14b**): ir (neat) bands at 6.00 (C=C), 8.58, 8.92 μ; nmr (CCl_4) τ 8.97 [s, 9, $C(CH_3)_3$], 8.45 (d, J = 1.5 Hz, 3, $CH_3C=$), 6.67 (s, 3, $-OCH_3$), 6.10–6.63 (two groups of broad peaks, $-OCH_2-CH_2OCH_3$), 4.13 (m, 1, =CH); mass spectrum m/e 172 (calcd, 172).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.8; H, 11.6. Found: C, 70.1; H, 11.8.

Reactions of 3-Nitroso-4,5,5-trimethyl-2-oxazolidone (15) with Nucleophiles. A. In 2-Methoxyethanol Containing Sodium Iodide.—A 20% solution of sodium 2-methoxyethanolate in 2-methoxyethanol (20 g) was added dropwise during 10 min to a well-stirred solution of 2.37 g of **15** in 50 ml of 2-methoxyethanol saturated with sodium iodide (18 g/50 ml). The theoretical amount of nitrogen was evolved in 10 min. The temperature was maintained below 30° by cooling. The mixture was worked up as usual. Two fractions were collected by distillation. Pure samples were obtained by preparative vpc (column A).

Fraction 1, bp 35–70° (35 mm), column temperature 100°, helium flow 100 cc/min, <1 min, yielded 0.091 g (8.2%) of 3-methyl-2-butanone (**17**), identical with an authentic sample.

Fraction 2, bp 85–122° (35 mm), column temperature 132°, helium flow 100 cc/min, yielded (A) 1 min, 0.153 g (7.1%) of 2-methoxyethyl 3-methyl-2-butenyl ether (**18**) {ir (neat), 5.93 (C=C), 8.52 (C=CO–), 8.85 μ; nmr (CCl_4) τ 8.43 [broad s, 6, $(CH_3)_2C=$], 8.26 (broad s, 3, $CH_3C=$), 6.69 (s, 3, $-OCH_3$), 6.30–6.57 (complex m, 4, $-OCH_2CH_2OCH_3$); exact mass measurement, 144.1152 (calcd, 144.1150)} and (B) 3.5 min, 0.631 g (22.4%) of 2-methoxyethyl 3-methyl-1-buten-3-yl carbonate (**16**) {ir (neat), 5.73 (C=O), 6.10 (C=C, weak band), 7.90, 8.80 μ; nmr (CCl_4) τ 8.48 [s, 6, $(CH_3)_2C$], 6.68 (s, 3, $-OCH_3$), 5.74–6.60 (complex m, 4, $-OCH_2CH_2OCH_3$), 3.65–5.10 (multiple peaks, $-CH=CH_2$); mass spectrum mol wt 188}.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.4; H, 8.6. Found: C, 57.4; H, 8.6.

For further identification a 2,4-dinitrophenylhydrazone, mp and mmp 119–120° with the 2,4-dinitrophenylhydrazone prepared from 3-methyl-2-butanone (**17**), was prepared from **18**.

Registry No.—**2a**, 37150-64-4; **3**, 39922-26-4; **3** DNPH, 39922-27-5; **4**, 775-10-0; **4** DNPH, 39922-29-7; **5**, 39922-30-0; *cis*-**6**, 39922-31-1; *trans*-**6**, 39922-32-2; **7**, 39922-33-3; **9**, 39922-34-4; **10**, 39922-35-5; **11**, 39922-36-6; **12**, 29558-58-5; *cis*-**14a**, 39922-38-8; *trans*-**14a**, 39922-39-9; *trans*-**14b**, 39922-40-2; **15**, 39922-41-3; **16**, 39922-42-4; **16** DNPH, 39922-45-7; **17**, 563-80-4; **17** DNPH, 3077-97-2; **18**, 39922-44-6; isobutyraldehyde, 78-84-2; Aliquat 336, 13275-89-3; 2,2-dimethylpropanal, 630-19-3; cyclohexanone, 108-94-1; diethyl ketone, 96-22-0; diisopropyl ketone, 565-80-0; sodium azide, 12136-89-9; potassium thiocyanate, 333-20-0; triethyl phosphite, 78-38-6; ethyl 2,3-dimethyl-3-hydroxybutanoate, 34849-39-3; ethyl α-bromopropionate, 535-11-5; 2,3-dimethyl-3-hydroxybutanoic acid hydrazide, 5454-77-3; hydrazine, 302-01-2; 4,5,5-trimethyl-2-oxazolidone, 39922-48-0; sodium methoxide, 124-41-4; sodium phenoxide, 139-02-6; 2,2-dimethyl-3-pentyne, 999-78-0.

(19) L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.*, **62**, 576 (1940).

Reactions of Isocyanates with Carbonyl Azides and Carbonylnitrenes[1]

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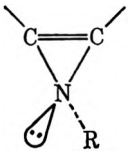
Received January 31, 1973

Photolysis and thermolysis of alkyl azidoformates in isocyanates leads to two reactions: a nitrene addition to the C=N bond of the isocyanate, forming 2-alkoxy-4-alkyl-1,3,4-oxadiazolin-5-ones, and an azide addition to the isocyanate, followed by attack of a second molecule of isocyanate and resulting in the formation of 1,4-dialkyl-2-alkoxycarbonylurazoles. The latter reaction predominates in the azidoformate system, but is not detected when aroyl azides are decomposed in alkyl isocyanates. A formal retro Chapman rearrangement takes place when 1,4-dialkyl-3-alkoxy-1,2,4-triazolin-5-ones are passed over a vpc column.

Carbonylnitrenes, RCON, are known to add to a variety of unsaturated functions with the formation of three- or five-membered rings.[2] For example, olefins give aziridines, alkynes give oxazoles, and nitriles give oxadiazoles. The formation of three-membered rings by addition to triple bonds has not been observed, perhaps because the resulting systems, such as **1** and **2**, would be antiaromatic. In such



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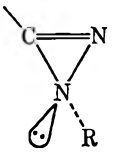

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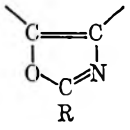
cases inclusion of the carbonyl group leads to stable five-membered rings, *e.g.*, **3** and **4**.



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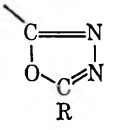

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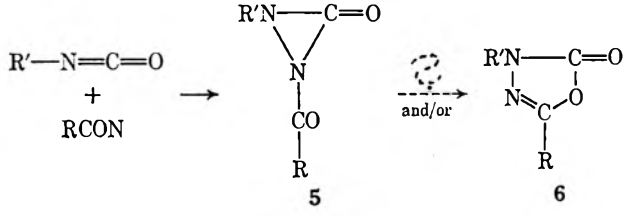
The addition of carbonylnitrenes to isocyanates, however, seemed to allow the formation of stable three-membered as well as five-membered rings. We



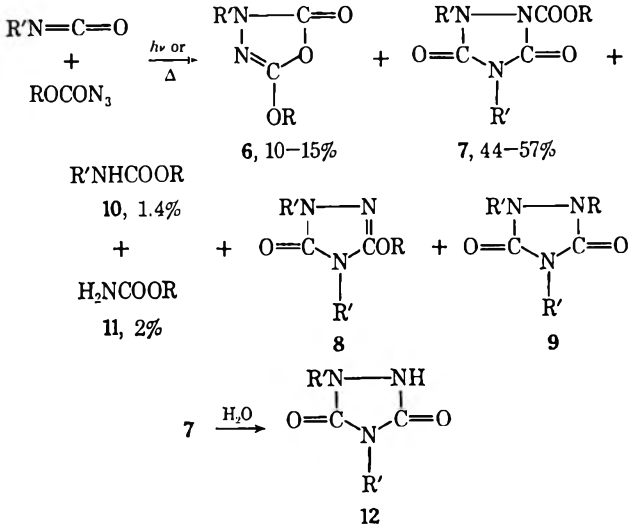
5 **6**

report here on the decomposition of various nitrene precursors in the presence of aliphatic isocyanates.

Results

Alkyl Azidoformates.—Thermolyses and photolyses of methyl azidoformate, dissolved in alkyl isocyanates, gave mixtures of six products in ratios dependent on the reaction conditions. Ethyl azidoformate gave entirely analogous products and product ratios. Scheme I summarizes the products and Table I gives the yields (measured by vpc) of the products under various conditions, together with those obtained when alkoxy-

SCHEME I[a]



[a] The yields given are for R = CH_3 and R′ = C_2H_5 (*cf.* text).

TABLE I

REACTIONS OF ISOCYANATES WITH ALKOXYCARBONYLNITRENE PRECURSORS

Product	Conditions	Yield, % (based on the precursor) R = Me; R′ = Et	R = R′ = Et	R = Et; R′ = Me
6	*hν*, 254 nm	10–15	13.2	9.4
	hν, 300 nm	4.5		
	Thermolysis, 120°	7		
	α-Elimination	2.7		7
7	*hν*, 254 nm	50	52	48
	hν, 300 nm	46		
	Thermolysis, 120°	68		
	α-Elimination	0		0
8[a]	*hν*, 254 nm	*b*	0.2	*b*
9[a]	*hν*, 254 nm	*b*	1.8	*b*
10	*hν*, 254 nm	1.4	1.5	*b*
	hν, 300 nm	1.0		
	Thermolysis, 120°	1.0		
	α-Elimination	1.8		
11	*hν*, 254 nm	2.2	2.5	
	hν, 300 nm	2.0		
	Thermolysis, 120°	2.6		
	α-Elimination	6.7		

[a] A secondary product; exact yields depend on the vpc conditions used in work-up; see text. [b] Not determined.

carbonylnitrenes were generated by α-elimination, rather than by azide decomposition (see below).

The expected 4-ethyl-2-methoxy-1,3,4-oxadiazolin-5-one (**6a**) was formed in 10–15% yield when methyl azidoformate was photolyzed in ethyl isocyanate solution, using light of 254-nm wavelength. Using light with a peak intensity at 300 nm, only a 4.5% yield

(1) A preliminary account of this work was given in a lecture reprinted in the *Trans. N. Y. Acad. Sci., Ser. II*, **33**, 259 (1971). This paper is based in part on a part of the Ph.D. Thesis by S. M. A. Hai, New Mexico State University, 1969.

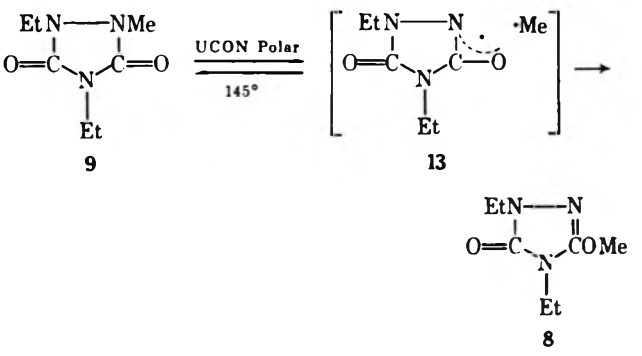
(2) *Cf.* W. Lwowski in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, Chapter 7.

of **6a** was obtained, and thermolysis of the azide at 120° gave only a 7% yield. The structures of **6a** (R = Me; R′ = Et), **6b** (R = R′ = Et), and **6c** (R = Et; R′ = Me) were derived from their elemental analyses, ir, nmr, and mass spectra, and chemical degradation. Catalytic hydrogenation failed, making unlikely the diaziridinone structure **5**. Hydrolysis of **6a** with 0.1 *N* NaOH gave methyl 2-ethylcarbazate in quantitative yield, establishing the presence of a N–N bond. Treating **6a** with sodium methoxide gave quantitatively the expected dimethyl *N*-ethylhydrazinedicarboxylate. Furthermore, **6a** and **6b** were independently synthesized from the corresponding 2-alkylcarbazates and phosgene.[3,4]

The major product, **7**, contains the elements of one ROOCN plus two R′NCO. Thermolytic reactions favor the formation of **7** and disfavor that of **6**. Photolysis of **6a** in dichloromethane and in ethyl isocyanate solutions failed to produce any **7a**. Also, subjecting a mixture of **6a** and ethyl isocyanate to our work-up procedure, including vpc, did not produce any **7a**. During one photolysis run, eight samples were withdrawn and analyzed by vpc. The yields of **6a** and **7a** (based on the nitrogen evolved at the particular sampling time) stayed virtually constant over 41 hr. We thus conclude that both **6** and **7** are primary products.

The structure of **7a** was derived from its elemental analysis and ir, nmr, and mass spectra and by chemical degradation and independent synthesis as that of 1,4-diethyl-2-methoxycarbonyl-1,2,4-triazolidine-3,5-dione. Mild hydrolysis gave 1,4-diethyl-1,2,4-triazolidine-3,5-dione (**12**) (commonly called 1,4-diethylurazole) (see Scheme I). Compound **12** was synthesized independently by pyrolysis of 1,1,4-triethyl-1,2,4-triazolidine-3,5-dion-1,2-ylide,[5] and also by exhaustive diazoethane ethylation of urazole, followed by separation of the isomeric (N and O) triethylurazoles. Their structures can be unequivocally assigned by nmr spectroscopy. Hydrolysis of the 1,4-diethyl-*O*-ethylurazole gave the desired **12**.[6] Treating **12** with potassium sand and then methyl chloroformate gave **7a**.

Separation by vpc (UCON Polar, 140°) of the reaction mixtures gave two minor products possessing the 1,2,4-triazole skeleton. However, careful scrutiny of the spectra of the crude reaction mixtures before vpc showed the absence of these two products, **8** and **9**. They are produced during vpc from **7**, by loss of the elements of carbon dioxide. Treating **12** with diazomethane gave **8** and **9** in approximately equal amounts. This result, together with the nmr, ir, and mass spectra, led to the structure assignments of 1,4-diethyl-2-methylurazole for **9**, and 1,4-diethyl-3-methoxy-1,2,4-triazolin-5-one for **8**. Both compounds are stable to heating, by themselves, to 150–160° for a few hours. However, **9** is converted to a small extent (0.5%) to **8** when passed through an 8-ft 20% UCON Polar column at 145°. This reaction is formally a retro Chapman rearrangement. It might involve dissociation of **9** to a paired intermediate, such as the radical pair **13**. Recombination would



9 **13** **8**

then give **8** and **9**. Loss of methyl is prominent in the mass spectral fragmentation of **9**, but could also arise from processes other than the formation of a dissociated form of **13**. The formation of **8** and **9** from **7** might well involve an intermediate common to that in the retro Chapman rearrangement, perhaps **13**.

The two open-chain products **10** and **11** were identified by comparison with authentic samples. Carbamates **11** ($ROOCNH_2$) are always found in alkoxycarbonylnitrene reaction and arise by hydrogen abstraction.[3] The origin of the *N*-alkylcarbamates **10** is not clear, except that the group on nitrogen must come from the isocyanate.

Methoxycarbonylnitrene Generated by α-Elimination.—The base-induced decomposition of methyl *N*-(*p*-nitrobenzenesulfonyloxy)carbamate (**14**, $MeOOCNHOSO_2C_6H_4NO_2$-*p*) is known[3] to give the nitrene MeOOCN in its singlet state (by analogy with the well-studied EtOOCN system). In order to test for the intervention of ROOCN in the formation of **6** or **7** or both, **14** was decomposed by triethylamine in a 1.6 *M* solution of ethyl isocyanate in dichloromethane, and also in undiluted ethyl isocyanate. Small yields of **6a**, **10a**, and **11a** were formed (see Table I and Experimental Section), but no trace of **7a** could be detected. In a control experiment, added **7a** survived the whole reaction process and 90% of it was recovered. Thus, we conclude that **7a** is formed from the azide, but not from the corresponding nitrene, while **6a** is the product of a nitrene reaction.

Aroyl Azides.—Horner[7] has shown that the photolysis of aroyl azides gives mixtures of aryl isocyanates and aroylnitrenes. Photolysis of benzazide in a tenfold molar excess of ethyl isocyanate at −16° gave a 93% yield of nitrogen, about a 50% yield of phenyl isocyanate, and 4-ethyl-2-phenyl-1,3,4-oxadiazolin-5-one (**15**) in about 25% yield. The novel aryloxadiazolinones **16** and **17** (from *p*-methoxybenzazide and *p*-nitrobenzazide, respectively) were formed analogously in 11.5 and 10% yields, respectively. Their identities were established by independent synthesis using Freund's method.[3,4] Compounds with the spectral characteristics of the urazoles (corresponding to **7**) were not found among the products of the aroyl azide–ethyl isocyanate photolyses. One, 1,4-diethyl-2-*p*-nitrobenzoylurazole (**18**), was prepared independently. It could have been easily detected in the photolysis reaction mixture. As expected from Horner's results,[7] thermolysis of our aroyl azides in ethyl isocyanate gave neither oxadiazolinones nor urazoles, only the aryl isocyanates.

(3) M. Freund and B. B. Goldsmith, *Ber.*, **21**, 1240, 2456 (1888).

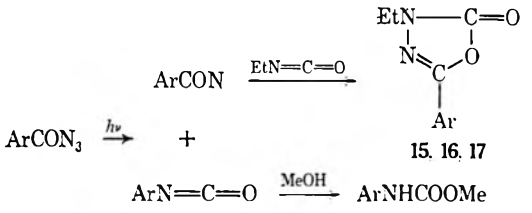
(4) A. Stern, *J. Prakt. Chem.*, **60**, 235 (1899); A. Dornow and K. Bruncke, *Chem. Ber.*, **82**, 121 (1949).

(5) W. Lwowski, R. A. de Mauriac, R. A. Murray, and L. Lünow, *Tetrahedron Lett.*, 425 (1971).

(6) R. A. de Mauriac, Ph.D. Thesis, Yale University, 1967.

(7) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963); L. Horner, G. Bauer, and J. Dörges, *ibid.*, **98**, 2631 (1965).

Photolysis of benzazide in equimolar mixtures of ethyl isocyanate and cyclohexane gave the oxadiazolinone **15** and *N*-cyclohexylbenzamide (**19**), the C–H insertion product from C_6H_5CON and cyclohexane. The average ratio of **15**:**19** was 1.42, not much affected by the reaction conditions or by addition of nitrobenzene or *m*-dinitrobenzene. The latter two compounds, added in small quantities, raise the yields of some C–H insertion reactions of ethoxycarbonylnitrene.[8] Typically, one run gave yields of 13.9% of **15**, 10.5% of **19**, and 48.3% of phenyl isocyanate (determined as its methanol adduct). If one neglects the ethyl group (insertion products into which were not detected), the 12 C–H bonds of the cyclohexane compete with each isocyanate function of the ethyl isocyanate. Thus, the relative reactivity of the functions –NCO *vs.* C–H is about 17.



The aroyl azide systems were not studied in any more detail, because of their apparently limited synthetic utility and because of external circumstances.

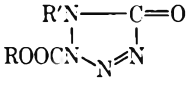
Discussion

Our results indicate that the oxadiazolinones **6**, and their aroyl analogs, are produced from carbonylnitrenes and isocyanates, while the formation of the urazoles **7** is not a nitrene reaction and occurs only with azidoformates, not with aroyl azides. No urazoles were found when alkoxycarbonylnitrenes were generated by α-elimination, and none were found in the aroyl azide photolyses, where the presence of aroylnitrenes is demonstrated by the formation of the C–H insertion product **19**. The urazole formation must be a reaction peculiar to the azidoformates, with which competing thermal reactions are relatively slow. Such reactions are nitrene formation and the Curtius rearrangement (with migration of RO from C to N). This Curtius rearrangement is about 10–20 times slower than nitrene formation.[9] In the aroyl azides, thermal Curtius rearrangement (with aryl migration) is the most facile reaction, to the exclusion of all other reaction paths. In the aroyl azide photolyses, rearrangement and nitrene formation seem to compete about evenly.[7]

Photolysis of methyl azidoformate in ethyl isocyanate gives more of the urazole **7a** and less of the oxadiazolinone **6a** when light of 300- rather than 254-nm wavelength is used. This agrees with the assumption that short-wavelength light produces more of the nitrene (and from it **6a**), than light of longer wavelength. Pending more intensive studies, one might conclude that the vibrationally highly excited state of the first excited singlet of the azide preferentially undergoes nitrogen elimination to the nitrene, while the cooler electronically excited azide, produced by absorption of 300-nm light, does not dissociate equally readily but undergoes internal conversion to a highly vibrationally excited molecule in its electronic ground state. Since the ethyl isocyanate (used as the solvent) is the most abundant quencher for the vibrationally hot ground state azide, the same reaction occurs (formation of **7a**) as is observed by merely heating the azide–isocyanate mixture. Earlier work indicates that alkoxycarbonylnitrenes, once formed, do not reflect in their reactions the wavelength of the light used to generate them.[10] For example, the stereospecificity of the addition of ethoxycarbonylnitrene to *cis*-4-methylpent-2-ene does not change when the photolysis wavelength is changed over the range from 250 to 300 nm. The nitrene seems to equilibrate thermally before it reacts, a contention well in accord with the selectivity observed for the nitrene.[2]

The mechanism of the oxadiazolinone formation might well be straightforward 1,3-cycloaddition. The intermediacy of a three-membered ring adduct **5** cannot be ruled out by our data, but in view of Greene's work,[11] we feel that we should have been able to detect diaziridinones if they had been present. Comparison of the ir and nmr spectra of the crude reaction mixtures before and after molecular distillation and then vpc (collecting all peaks together) showed that the final products **6**, **7**, **10**, and **11** were present in the crude mixtures, while **8** and **9** were formed during the vpc separation. No major product could have disappeared during this work-up.

The formation of the urazoles **7** must involve an intermediate 1:1 adduct which is not an oxadiazolinone **6** (see above). The tetrazolinones **20** and **21** are excluded as intermediates by L'abbé,[12] who obtained 1,4-disubstituted tetrazolinones from isocy-



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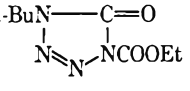


21

anates and azides. He found **21** and similar compounds to be stable at temperatures higher than those used in this work. Furthermore, cycloreversion at 150° resulted in equilibria between starting materials and adduct, not in loss of nitrogen and urazole formation. This does not rigorously exclude **20** as a possible cyclic intermediate. However, L'abbé always found the N_α of the azide group bound to the isocyanate carbonyl, and his compounds (such as **21**) formed in slow reactions (*e.g.*, 30 days at 55°). It is therefore unlikely that in our cases rapid formation of **20** should take place, and be followed by rapid decomposition. Formation of **7** *via* prior trimerization of the isocyanate, followed by attack of the azide, is also unlikely; no trimer was observed, although the reactions were run in an excess of isocyanate. The mechanism that seems most likely to us involves successive nucleo-

(8) D. S. Breslow and E. I. Edwards, *Tetrahedron Lett.*, 2123 (1967); D. S. Breslow, T. J. Prosser, A. F. Marcantonio, and C. A. Genge, *J. Amer. Chem. Soc.*, **89**, 2384 (1967).

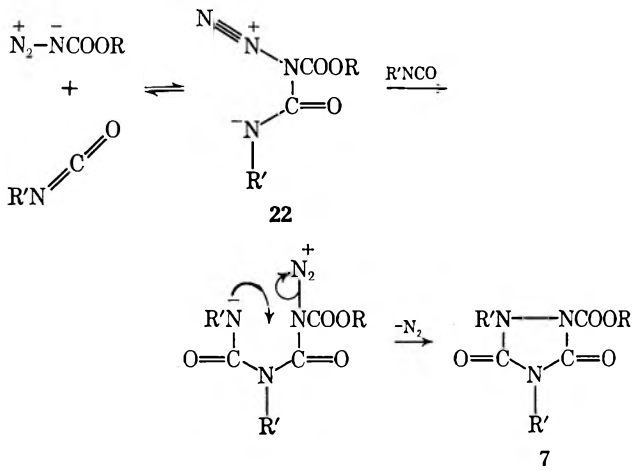
(9) W. Lwowski, R. de Mauriac, T. W. Mattingly, Jr., and E. Scheiffele, *Tetrahedron Lett.*, 3285 (1964).

(10) G. R. Felt, Ph.D. Thesis, New Mexico State University, 1971.

(11) F. D. Greene and J. C. Stowell, *J. Amer. Chem. Soc.*, **86**, 3569 (1964); F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969).

(12) J-M. Vandensavel, G. Smets, and G. L'abbé, *J. Org. Chem.*, **38**, 675 (1973).

philic attacks on isocyanate carbonyls by the N_α of the azides. Apparently, the intermediate 1:1 adduct **22** does not cyclize to a five-membered ring (similar to **21**), or to a three-membered one (the diaziridinone **5**). Rather, **22** attacks a second isocyanate molecule at its carbonyl group, to give a second intermediate in which cyclization to a five-membered ring is favored.



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7

Operation of this mechanism depends on a delicate balance. Competing thermal reactions must be relatively slow, and the azide N_α must be sufficiently nucleophilic, so that the equilibrium between starting materials and **22** contains enough of the latter. This might account for our failure to observe urazole formation using phenyl azide and benzenesulfonyl azide with ethyl isocyanate.

Experimental Section

Photolyses were carried out in silica vessels equipped with cooling fingers, in Rayonet photochemical reactors. Unless specified, low-pressure mercury lamps were used, emitting most of their light at 254 nm. The 300-nm irradiations were carried out using fluorescent lamps (RPR-3000), emitting light in a band from 280 to 340 nm. Infrared spectra were taken in carbon tetrachloride solution, nmr spectra in deuteriochloroform. Quantitative vpc analyses were evaluted planimetrically, after calibration of the detector response by injecting weighed pure samples.

Photolyses of Alkyl Azidoformates.—Typically, 6.66 g (66 mmol) of methyl azidoformate in 50 ml of redistilled ethyl isocyanate was irradiated until 70–90% of the calculated volume of nitrogen was evolved (24 hr). Removal *in vacuo* of the volatile constituents left 7.77 g of a viscous liquid. Tlc on silica gel with acetone–nitromethane–benzene (1:3:10) eluent separated **6a** (R_f 0.278), identified by comparison with an authentic sample. Vpc on a 20% UCON Polar 50HB2000 on 50/60 mesh Anakrom ABS (4 ft × 0.25 in.) separated all the components, in the order **10**, **11**, **6**, **8**, **9**, **7**.

Thermolyses of Alkyl Azidoformates.—Typically, 1.01 g (0.01 mol) of methyl azidoformate and 8.98 g (0.128 mol) of ethyl isocyanate in a 50-ml stainless steel cylinder were heated to 120°. After removal of the excess ethyl isocyanate, vpc separation (as above) was used to determine the yields (*cf.* Table I).

Alkoxycarbonylnitrenes by α-Elimination.—Adding slowly 1.25 ml (0.1 mol) of triethylamine to a solution of 2.67 g (0.01 mol) of methyl *N*-(*p*-nitrobenzenesulfonyloxy)carbamate (**14**) in 7.1 g (0.1 mol) of ethyl isocyanate, evaporation of the excess isocyanate and triethylamine, and vpc analysis (as above) gave **6a** in 2.7%, **10** in 1.8%, **11** in 6.7%, and dimethyl hydrazodiformate in 19% yield. The urazole **7a** could not be detected. Running the reaction in dichloromethane solution (typically 170 ml of dichloromethane and 60 ml of ethyl isocyanate) gave lower yields of **6a**.

4-Ethyl-2-methoxy-1,3,4-oxadiazolin-5-one[13] **(6a)**, isolated from the reaction mixtures as described above, shows characteristic ir absorption at 1805 and 1660 cm^{-1}, nmr signals at δ 1.30 (t, 3 H), 3.67 (q, 2 H), and 4.0 (s, 3 H), and in the mass spectrum P 144 (42%), P + 1/P 6.38% (calcd, 6.41%). Major cleavages are to *m/e* 59 (100%, $MeOCO^+$) and 85 (13.5%, EtN_2CO^+), the latter cleavaging further. A metastable ion peak at *m/e* 115.5 corresponds to P − CH_3. In the uv spectrum only end absorption near 200 nm was observed. In the synthesis of **6a** by Freund's method,[3] 0.673 g (5.7 mmol) of methyl 3-ethylcarbazate in 100 ml of benzene was treated with 240 ml (10 mmol) of phosgene gas and heated to reflux for 30 min. After washing with sodium bicarbonate solution, drying, and removal of the solvent, the brown residue was subjected to vpc separation (as above) to give a 34% yield of **6a**, identical in all respects with the material obtained from methyl azidoformate and ethyl isocyanate.

2-Ethoxy-4-ethyl-1,3,4-oxadiazolin-5-one (6b)[13] was synthesized independently by the same method as used for **6a**, in 38% yield. The ir spectrum showed absorptions at 1805 and 1640 cm^{-1}, and the nmr spectrum had signals at δ 1.28 (t), 1.43 (t), 3.6 (q), and 4.3 (q). The parent peak in the mass spectrum was at *m/e* 158 (40.9%); P + 1/P = 7.82% (calcd 7.52%); base peak at 130, metastable ion peak at 107 (P − C_2H_4 = 130).

2-Ethoxy-4-methyl-1,3,4-oxadiazolin-5-one (6c)[13] was not synthesized independently. Its properties were analogous to those of **6a** and **6b** and its methanolysis gave ethyl 3-methyl-3-methoxycarbonylcarbazate, ir spectrum 1805 and 1640 cm^{-1}, nmr spectrum δ 1.43 (t, 3 H), 3.28 (s, 3 H), 4.3 (q, 2 H).

Hydrolysis of 6a.—A 114-mg (0.79 mmol) portion of **6a** in 5 ml of dioxane was refluxed for 10 hr with 1 equiv of sodium hydroxide. The residues of ether and chloroform extracts of the neutralized reaction mixture upon vpc (20% silicone gum SE-30, 5 ft, 100°) gave methyl 3-ethylcarbazate, identical with an authentic sample.[9]

Methanolysis of 6a.—A 127-mg (0.88 mmol) portion of **6a** in 15 ml of ether was treated with 88 ml of 0.1 *N* methanolic sodium hydroxide for 4.5 hr. Neutralization, extraction with ether, and vpc separation (SE-30, 142°) gave dimethyl *N*-ethylhydrazodiformate identical with an authentic sample.[14]

Methanolysis of 6c, in the same manner, gave ethyl 3-methyl-3-methoxycarbonylcarbazate, ir 1709 cm^{-1}, nmr spectrum δ 1.28 (t, 3 H), 3.12 (s, 3 H), 3.71 (s, 3H), 4.14 (q, 2 H), 7.5 (broad, 1 H).

1,4-Diethyl-2-methoxycarbonylurazole (7a),[13] a colorless oil, was isolated as described above: ir spectrum 1828, 1802, and 1730 cm^{-1} (all strong); nmr spectrum δ 1.10 (t), 1.25 (t), 3.08 (q), 3.55 (q), 3.92 (s); integrals of these overlapping signals, CH_3 + $2CH_2$, 7 H, $2CH_3$, 6 H; mass spectrum P = 215, P + 1/P = 10.0% (calcd 9.88%); major fragmentations P − CH_3-COO, P − CO_2, P − (CH_3COO + EtNCO), P − (CO_2 + C_2H_4).

Synthesis of 1,4-Diethylurazole.[5,6]—Irradiation (254 nm) of 3.16 g (22.3 mmol) of diethylcarbamoyl azide in 35.5 g of ethyl isocyanate to give 47% of the calculated amount of nitrogen and removal of the volatile components gave, after recrystallization from ether, a 24% yield of 1,1,4-triethylurazole-1,2-ylide. Its pyrolysis (160°, 8 hr) gave 0.6 g of 1,4-diethylurazole. This was treated with potassium sand in refluxing benzene, followed by methyl chloroformate, to give **7a**, identical in all respects with the material obtained from methyl azidoformate and ethyl isocyanate. Very mild hydrolysis of **7a**, such as upon tlc on wet silica gel, led back to 1,4-diethylurazole.

1,4-Diethyl-2-ethoxycarbonylurazole (7b)[13] was isolated as described above from the photolysis reaction mixtures from ethyl azidoformate and ethyl isocyanate, in 52.3% yield: ir spectrum 1824, 1800, and 1738 cm^{-1}; nmr spectrum (overlapping signals) δ 1.12 (t), 1.27 (t), 1.42 (t) (9 H), 3.58 (q), 3.84 (q) (4 H), 4.38 (q, 2 H); mass spectrum P = 229, P + 1/P 10.52% (calcd 10.98%); major fragmentations P − (CO_2, C_2H_4) = 157 (100%), 157 − NH = 142 (48%, metastable ion peak 128.3), 142 − CO = 114 (metastable ion peak at 91.5), P − 28 = 129 (metastable ion peak at 106), 129 − EtNCO; 129 − 28 (metastable ion peak at 79.0).

1,4-Dimethyl-2-ethoxycarbonylurazole (7c)[13] was isolated as described from photolyses of ethyl azidoformate in methyl isocyanate in 48% yield: ir spectrum 1825, 1805, and 1725 cm^{-1}; nmr spectrum δ 1.42 (t, 3 H), 3.16 (s, 3 H), 3.30 (s, 3 H), 4.37 (q, 2 H).

Decomposition of 7a upon gas chromatography on a 8 ft × 0.25

(13) Compound gave elemental analysis within ±0.3% of the calculated value.

(14) D. C. Morrison, *J. Org. Chem.*, **23**, 1072 (1958).

in. 20% UCON Polar 50 HB 2000 column at 145° led to 90% recovery of **7a** and the formation of **8a** (1.3%) and **9** (6–7%).

1,4-Diethyl-3-methoxy-1,2,4-triazolin-5-one (8a),[13] a colorless oil, showed no ir absorption above 3000 cm^{-1} but bands at 1718 and 1608 cm^{-1}; nmr spectrum δ 1.27 (m, 6 H), 3.6 (m, 4 H), 3.95 (s, 3 H); mass spectrum P = 171, P + 1/P = 9.09% (calcd 8.78%); major fragmentations P − CH_3 = 156 (100%), 156 − EtNCO = 85 (75%), 156 − 28 = 128 (18%), P − 29 = 142 (18%), 142 − 28 = 114 (4%), P − 28 = 143 (16%), 143 − 28 = 115 (18%, metastable ion peak at 92.5), 115 − MeOCN = 58 (36%). Heating **8a** to 158° for 4 hr or passing it through the UCON Polar column (as above) left it unchanged, as indicated by its vpc and tlc.

1,4-Diethyl-2-methylurazole (9a),[13] a colorless liquid, had no ir absorption above 3000 cm^{-1} but bands at 1770 and 1710 cm^{-1}; nmr spectrum δ 1.17 (m, 6 H), 3.5 (m, 4 H), 3.03 (s, 3 H); mass spectrum P = 171, P + 1/P = 8.90 (calcd 8.78%); major fragmentations P − CH_3 = 156 (52%), 156 − EtNCO = 85 (95%), P − 28 = 143 (60%), 143 − 28 = 115 (83%), 115 − MeNCO = 58 (33%), MeNCO = 57 (17%). Heating to 150° for 2.5 hr in a sealed tube did not change **9a**, but passing it over a UCON Polar vpc column at 145° converted 0.5% of it to **8a**.

Synthesis of 8a and 9a was accomplished by treating 1,4-diethylurazole (**12a**) with diazomethane in ether solution. About equal amounts of **8a** and **9a** were formed; they were separated by vpc and identified by comparison with the compounds described above.

1,4-Diethyl-3-ethoxy-1,2,4-triazolin-5-one (8b)[13] was separated as described from the reaction mixture from the photolysis of ethyl azidoformate in ethyl isocyanate. It had no ir absorption above 3000 cm^{-1}, carbonyl absorption at 1720 cm^{-1}, C=N at 1605 cm^{-1}; nmr spectrum δ 1.28 (m, 9.6 H), 3.6 (m, 3.9 H), 4.3 (q, 2.0 H). The compound was identical in its properties with a sample synthesized by exhaustive diazomethane treatment of urazole, separation of the triethyl urazules by vpc, and identification by the unequivocal nmr spectra.[6]

1,2,4-Triethylurazole (9b)[13] was separated as described from the reaction mixture from the photolysis of ethyl azidoformate in ethyl isocyanate. The ir spectrum showed no absorption above 3000 cm^{-1}, but bands at 1770 and 1705 cm^{-1}; nmr spectrum δ 1.2 (m), 3.52 (m). The compound was independently synthesized by exhaustive treatment of urazole with diazoethane and vpc separation on a 5 ft × 0.25 in. 15% QF-1 fluorosilicon column at 135°.[6]

Aroyl azides were photolyzed with light of 254 nm as described above, in ethyl isocyanate, at −16°. Aryl isocyanates were formed in about 40% yield. These isocyanates were converted to methyl *N*-arylcarbamates by treatment of the reaction mixture with an excess of methanol for 12 hr at 35°, and were determined as such by vpc analysis on 2 ft × 0.25 in. 20% UCON Polar or 2 ft × 0.25 in. 15% OV-3 silicone columns at 140°. No aroyl amides were detected in the reaction mixtures, nor any of the urazoles (2-aroyl-1,4-diethyl-1,2,4-triazolidine-3,5-diones) or their conversion products. Products were identified by comparison of their spectra and vpc retention times with those of authentic samples. The oxadiazolinones were synthesized independently by Freund's method[4] (see above).

Benzazide, photolyzed at −16° in a tenfold excess of ethyl isocyanate, gave a 25.9% yield of **4-ethyl-2-phenyl-1,3,4-oxadiazolin-5-one (15)**, a 43% yield of phenyl isocyanate (determined as methyl *N*-phenylcarbamate), and a 93% yield of nitrogen. No product with the spectral characteristics of an arylurazole was detected. The 4-ethyl-2-phenyl-1,3,4-oxadiazolin-5-one (**15**),[13] mp 46–47°, showed in the ir spectrum CH at 3072, 2988, 2984, and 2880 cm^{-1}, other bands at 1865 (w), 1800 (s), 1780 (s), 1612 cm^{-1}; nmr spectrum δ 1.40 (t, 3 H), 3.85 (q, 2 H), 7.53 (m, 3 H), 7.83 (m, 2 H); mass spectrum P = 190 (100%), P + 1/P = 12% (calcd 11.8%); major fragmentations P − EtN_2CO = 105 (41%), P − EtN_2H_2 = 131 (48%), P − 28 = 146 (5%); major fragments C_6H_5 = 77 (39%), CO, C_2H_4 = 28 (93%).

Competition reactions were performed as described above, except that 10 mmol of benzazide and 100 mmol each of ethyl isocyanate and cyclohexane (purified) were used. Analysis by vpc (2 ft × 0.25 in. 15% OV-13 on Anachrom ABS at 140°), using weighed authentic samples for calibration, gave a 1.42 ratio of *N*-cyclohexylbenzamide to **15**. Addition of 1 mmol of *m*-dinitrobenzene or hydroquinone, or 100 mmol of nitrobenzene or hydroquinone, did not affect the ratio. However, yields decreased at the 100-mmol addend level.

2-Anisyl-4-ethyl-1,3,4-oxadiazolin-5-one (16) was obtained in 11.5% yield from the photolysis of 1.77 g (10 mmol) of anisoyl azide in 7.1 g (100 mmol) of ethyl isocyanate at −20°, together with a 49% yield of anisyl isocyanate. No 2-anisoyl-1,4-diethylurazole could be detected. The oxadiazolinone **16** (colorless crystals, mp 92°) was prepared for comparison, as described above: ir spectrum bands at 3080, 3000, 2945, 2845, 1790 (sh), and 1780 cm^{-1} (s); nmr spectrum δ 1.40 (t, 3 H), 3.87 (q) and 3.90 (s) (5 H), 6.9–7.9 (m, 4 H).

***p*-Nitrobenzoyl azide** photolyzed until 39% of the calculated amount of nitrogen had been evolved, and gave four major products, none of them 1,4-diethyl-2-*p*-nitrobenzoylurazole. The isocyanate was formed in 10.7% yield, and **4-ethyl-2-*p*-nitrophenyl-1,3,4-oxadiazolin-5-one (17)** in 10% yield. Treating 1-ethyl-2-*p*-nitrobenzoylhydrazine with phosgene also gave **17**, ir spectrum 1775 (s), 1785 (sh), 1525, 1505, 1350, and 1330 cm^{-1}.

1,4-Diethyl-2-*p*-nitrobenzoylurazole (18) was prepared by treating 0.85 g (5.4 mmol) of 1,4-diethylurazole with 0.211 g of potassium sand in refluxing benzene for 4 hr, then with 5.4 mmol of *p*-nitrobenzoyl chloride, followed by vpc: ir spectrum 3110, 3052, 2980, 2875, 1770, 1715, 1540, and 1355 cm^{-1}; nmr spectrum δ 1.26 (2 t, 6 H), 3.4–4.2 (2 q, 4 H), 11.67 (m, 4 H). The compound could not be detected in the reaction mixture from the *p*-nitrobenzoyl azide–ethyl isocyanate photolysis. Thermolysis of 1.92 g (10 mmol) of *p*-nitrobenzoyl azide in 14.2 g (200 mmol) of ethyl isocyanate (132°, 24 hr) in a steel cylinder gave neither **17** nor **18**, just *p*-nitrophenyl isocyanate.

Registry No.—**6a**, 39636-00-5; **6b**, 39636-01-6; **6c**, 39636-02-7; **7a**, 39636-03-8; **7b**, 39636-04-9; **7c**, 39636-05-0; **8a**, 39636-06-1; **8b**, 39636-07-2; **9a**, 39636-08-3; **9b**, 39636-09-4; **10a**, 6135-31-5; **10b**, 623-78-9; **11a**, 598-55-0; **11b**, 51-79-6; **12a**, 39636-12-9; **15**, 21816-80-8; **16**, 39636-14-1; **17**, 39636-15-2; **18**, 39636-16-3; methyl isocyanate, 624-83-9; ethyl isocyanate, 109-90-0; methyl azidoformate, 1516-56-9; ethyl azidoformate, 817-87-8; ethyl 3-methyl-3-methoxycarbonylcarbazate, 39636-17-4; diethylcarbamoyl azide, 922-12-3; 1,1,4-triethylurazole-1,2-ylide, 32515-29-0; 1,4-diethylurazole, 39636-12-9; diazomethane, 334-88-3; benzazide, 582-61-6; *p*-anisoyl azide, 3532-17-0; *p*-nitrobenzoyl azide, 2733-41-7; 1-ethyl-2-*p*-nitrobenzoylhydrazine, 39636-23-2; phosgene, 75-44-5; *p*-nitrobenzoyl chloride, 122-04-3.

Acknowledgments.—We are greatly indebted to the National Institutes of Health for support of this work under Grant GM14638.

Benzonitrile Formation in the Pyrolysis of Aromatic Nitrogen Compounds

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Received February 22, 1973

Benzonitrile is one of the major nitrogen-containing products obtained from the 700° pyrolysis of various nitroarenes (including nitrobenzene, nitrophthalic acids, and isomeric nitrotoluenes), nitrosobenzene, and *N*-methyleneaniline. Since the thermolysis of *N*-methyleneaniline, a possible interaction product of phenylnitrene and carbene, gave larger benzonitrile conversions than either nitroarene or phenyl azide pyrolyses, it is suggested that such an interaction contributes to benzonitrile formation.

In an investigation of the pyrolyzate composition of substituted phthalic acids, it was found that the major component of the neutral fraction obtained from the pyrolysis of 3- and 4-nitrophthalic acids at 700° was benzonitrile.[1] This and the observations that *N*-sulfinylaniline[2] at 1000° and phenyl azide[3] at 700° both produce benzonitrile suggest that benzonitrile formation might be a general reaction of *N*-aryl compounds during pyrolysis and that this formation might involve nitrene intermediates. Because previous studies of the pyrolysis of nitroarenes under a variety of conditions[4] and of nitrosobenzene[5] did not report the formation of benzonitrile, we have reinvestigated these pyrolyses at 700°.

Tables I–III summarize the results of the pyrolyses of nitrobenzene, nitrosobenzene, and isomeric nitrotoluenes at 700°. Results obtained in the pyrolysis under identical conditions of phenyl azide and *N*-methyleneaniline, a possible intermediate in benzonitrile formation, are included for comparison. Benzonitrile was also produced from nitrobenzene (neat) over the temperature range 600–900°, from isomeric nitrotoluenes over the range 500–700°, and from nitrobenzene–benzene solutions at 700°. In experiments where mixtures of nitrobenzene and benzene (ratios ranging from 1:1 to 1:4) were pyrolyzed, the benzonitrile yield (based on total mixture pyrolyzed) was proportional to the nitrobenzene concentration in the mixture.

TABLE I

YIELDS[a] OF SELECTED COMPONENTS PRODUCED IN THE PYROLYSIS OF AROMATIC NITROGEN COMPOUNDS AT 700°

	Nitrobenzene	Nitrosobenzene	*N*-Methyleneaniline	Phenyl azide
Benzonitrile	1.2[b]	0.5	7.7	0.5
Nitrobenzene	0.6			
Naphthalene	0.4	0.2	*c*	0.2
Biphenyl	3.9	1.9	*c*	2.2
Dibenzofuran	3.3	1.4		
Phenol	5.2	3.0		
Aniline	0.04	0.01	11.7[d]	0.2
Diphenylamine	0.1	5.4	c	1.4
N-Methylaniline			0.9	
Hydrogen cyanide[e]	6.4	1.0	24.6	8.3

[a] Yields are reported as moles of compound per mole of substance pyrolyzed × 100 and were determined by glpc using internal standards. [b] Yields of benzonitrile from nitrobenzene at 600, 800, and 900° were 1.2, 1.8, and 1.1, respectively. [c] Not determined. [d] Some contribution to aniline yield arises from the hydrolysis of starting material during acid extraction (see Experimental Section). [e] Yields reported as grams of hydrogen cyanide per mole of substance pyrolyzed.

Possible modes of formation of the major nitrobenzene pyrolyzate constituents, excepting benzonitrile, have been discussed previously.[4,6]

The production of benzonitrile is likely the result of several simultaneous processes including the addition of hydrogen cyanide to benzyne, the coupling of phenyl and cyanide radicals and the decomposition and/or isomerization of phenylnitrene.[3,7] Although the formation of naphthalene in the *N*-aryl compound pyrolyses (see tables) suggests the intermediacy of benzyne, benzyne formation as compared to phenyl radical formation appears to represent a relatively minor path in the decomposition of nitrobenzene[4a] and nitrosobenzene.[4c]

Various oxygen acceptors such as alkyl phosphites,[8,9] metals, and activated charcoal[10] have been reported to convert aromatic nitro and nitroso compounds into nitrenes, and "intractable tars" apparently functioned in this way in the conversion of 2-nitro-*p*-terphenyl into 2-phenylcarbazole.[11] The facts that the pyrolyses of nitrobenzene and nitrosobenzene produce sizable quantities of tar and that carbon monoxide, carbon dioxide, aniline, pyridine, diphenylamine, and benzonitrile are present in the pyrolyzates are indicative of a phenylnitrene intermediate in these reactions. A comparison of benzonitrile yields from phenyl azide (a known phenylnitrene precursor[12]) and nitrobenzene (Table I) shows that benzonitrile formation in the nitrobenzene (and nitrosobenzene) pyrolyses involves additional or more efficient routes than those involved in the decomposition of phenylnitrene. A possible explanation for the higher benzonitrile yields in the nitrobenzene pyrolyses is that, in these experiments, phenylnitrene interacts further with "active" carbon fragments (carbenes) to produce *N*-methyleneaniline, which, after dehydrogenation, isomerizes to benzonitrile. If "tar"

(1) From 3-nitrophthalic acid (22.8 g) there was obtained 0.4 g of neutrals of which 34% was benzonitrile (glpc area %). Similarly 4-nitrophthalic acid (13.2 g) gave 0.15 g of neutrals of which 20% was benzonitrile.

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TABLE II

RELATIVE CONCENTRATIONS[a] OF PYROLYZATE CONSTITUENTS OBTAINED FROM AROMATIC NITROGEN COMPOUNDS AND FROM AN EQUIMOLAR MIXTURE OF *N*-METHYLENEANILINE AND PHTHALIC ANHYDRIDE AT 700°

Component	Nitrobenzene	Nitrosobenzene	Phenyl azide	*N*-Methyleneaniline	*N*-Methyleneaniline–phthalic anhydride[f]
		A. Neutral Fraction			
Benzene	7.9	6.3	1.8	2.2	4.1
Toluene				1.1	1.0
Styrene	0.3			0.2	0.6
Benzonitrile	10.4	4.4	20.8	68.3	33.8
Nitrobenzene	2.3				
Naphthalene	4.0	1.0	5.9	0.3	3.5
Cinnamonitrile	0.6[b]	0.3[b]			
Indole			2.2[c]		
Biphenyl	29.8	17.3	17.8	4.8	11.9
1-Naphthonitrile	0.3	0.4	4.5		
2-Naphthonitrile	0.4		2.8		
Dibenzofuran	23.7	13.4			
Carbazole	4.5	8.7	12.4	1.0[d]	0.2[g]
Diphenylamine[e]	1.9	45.2	9.8	0.8	0.2
Wt neutral fraction, g	2.3	6.1	1.5	2.4	3.1
		B. Base Fraction			
Pyridine	4.9		0.8	0.2	
Aniline	9.3	18.5	34.3	74.8	17.6
Quinoline	12.8	7.8	9.3	0.5	1.7
Isoquinoline	3.6	1.4	1.1		
Acridine	6.0	8.4	0.4		41.3
Phenanthridine	5.1		3.9	6.7	31.1
Quinaldine			0.7		
Diphenylamine		43.1	2.8		
N-Methylaniline				9.9	3.8
Wt base fraction, g	0.3	0.3	0.4	3.2	1.9
		C. Acid Fraction			
Phenol	83.6	89.7			
o-Cyanophenol	0.6				
o-Hydroxybiphenyl	10.5	7.9			
Wt acid fraction, g	1.3	1.1			
Wt compound pyrolyzed, g	9.0	14.4	3.8	6.5	12.1

[a] Relative concentrations are area % as determined by glpc analysis. [b] Glpc analysis does not separate indole and cinnamonitrile. Peak mainly cinnamonitrile on basis of spectra data. [c] Peak mainly indole on the basis of spectra data. [d] *N*-Methylcarbazole also observed in 1.1% concentration. [e] Found in both the neutral and base fraction due to incomplete separation. [f] Fluorene present in 0.9% concentration. [g] *N*-Methylcarbazole.

TABLE III

RELATIVE CONCENTRATION[a] OF BENZONITRILE IN NEUTRAL FRACTIONS OBTAINED ON PYROLYSIS OF ISOMERIC NITROTOLUENES AT 700°

Component	Ortho	Meta	Para
Benzonitrile	14.7	8.3	8.7
o-Tolunitrile	2.6		
m-Tolunitrile		1.9	
p-Tolunitrile			0.2
Naphthalene	5.4	0.1	0.9
Wt neutral fraction, g	2.3	2.4	4.0
Wt acid fraction, g	0.9	1.2	*b*
Wt base fraction, g	1.1	0.4	*b*
Wt substance pyrolyzed, g	10.3	11.5	69.6

[a] Relative concentrations are area % as determined by glpc. [b] Not determined.

formation is taken as a measure of "active" carbon production, then the nitrobenzene pyrolysis produces *ca.* twice the "active" carbon as does the phenyl azide pyrolysis and thus the greater benzonitrile yields. To test the efficiency of benzonitrile production from the probable nitrene–carbene interaction product, *N*-methyleneaniline was pyrolyzed at 500, 600, and 700°. The benzonitrile yields, 0.5, 5.1, and 7.7%, respectively, indicate that *N*-methyleneaniline could be a precursor to benzonitrile in nitrobenzene and nitrosobenzene pyrolyses.

The major nitrogen-containing products from the *N*-aryl compound pyrolyses (in addition to benzonitrile) include diphenylamine, carbazole, and phenanthridine (from *N*-methyleneaniline). The formation paths of diphenylamine and carbazole from phenylnitrene[3] and from nitrosobenzene and phenyl radicals[5] have been proposed previously. Although the conversion of diphenylamine into carbazole has been observed,[13] the extent of reaction is probably small.[14,15] Phenanthridine (low yield) and acridine are produced in the pyrolysis of *N*-benzalaniline[16] and *N*-benzylaniline,[15] respectively, which in turn could arise from the addition

$$Ar\cdot + ArN{=}CH_2 \longrightarrow ArN{-}CH_2Ar + Ar_2N{-}CH_2\cdot$$

of phenyl radicals to *N*-methyleneaniline. *N*-Methylcarbazole could also originate from such an addition followed by ring closure. Product production (phenan-

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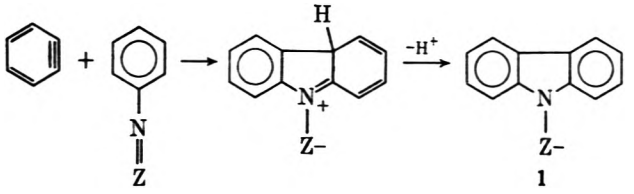
thridine, carbazole, *N*-methylcarbazole) in *N*-methyleneaniline pyrolysis is consistent with the proposed path. The pyrolysis of *N*-methylcarbazole under conditions used in the nitroarene experiments results in a 51% yield (isolated) of phenanthridine.

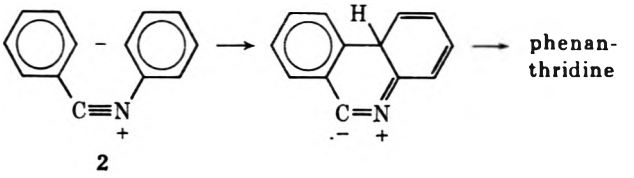
The report[17] that benzyne reacts with nitrosobenzene in tetrahydrofuran to form carbazoles suggests that a similar route to carbazoles from *N*-aryl compounds and benzyne might be available in the vapor phase. In the pyrolyses of nitrosobenzene and phenyl azide, **1**



Z = CH_2, CH·, N=N, O

loses oxygen and nitrogen, respectively, to form carbazole. In the pyrolysis of *N*-methyleneaniline, **1** couples with H to form *N*-methylcarbazole, loses methylene to form carbazole, or undergoes ring enlargement to form phenanthridine.

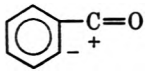
Isocyanides have been found to add to benzyne[18] and the adduct **2** arising from the interaction of phenyl



2

isocyanide and benzyne could produce phenanthridine on ring closure.

An equimolar mixture of *N*-methyleneaniline and phthalic anhydride (a benzyne precursor) was pyrolyzed to test the postulated benzyne–methyleneaniline interaction and subsequent phenanthridine production. While the pyrolysis produced enhanced phenanthridine yields (Table II), a substantial yield of acridine was also observed. Since acridine was not found in the pyrolysis of *N*-methyleneaniline, this experiment means either that benzyne interaction is not important in the *N*-methyleneaniline pyrolyses or that acridine formation (in the methyleneaniline–phthalic anhydride experiment) results from an interaction of *N*-methyleneaniline with a partial breakdown product of phthalic anhydride.



Experimental Section

Ultraviolet spectra were measured in cyclohexane using a Perkin-Elmer Model 202 spectrophotometer, infrared spectra were measured in chloroform or carbon tetrachloride using a Beckman IR-8 spectrophotometer equipped with a mirror beam condenser, and nmr spectra were measured in deuteriochloroform or carbon tetrachloride (TMS internal standard) using a Varian T-60 spectrometer. Mass spectra were determined on a Hitachi RMU-6E double focusing mass spectrometer using 70-eV ionizing energy with the inlet system at 200°. Glpc analyses and preparative separations of the pyrolyzate constituents were carried out on an F & M Model 810 gas chromatograph using a thermal conductivity detector.

Materials.—Nitrobenzene and nitrosobenzene were commercially available samples and were used as received. Nitrobenzene was redistilled prior to use and purity checked by glpc analysis. Phenyl azide was synthesized by the method of Lindsay and Allen,[19] bp 33–35° (1.2 mm), and *N*-methyleneaniline was synthesized by an adaptation of the procedure of Bigelow and Eatough.[20] The properties of the *N*-methyleneaniline were mp 142–144° (lit.[21] mp 140°); uv max (cyclohexane) 211, 253 nm; ir (CCl_4) 2840, 1600, 1495, 700 cm^{-1}; nmr ($CDCl_3$) δ 7.3 (m, 5), 4.85 ppm (s, 2); mass spectrum[22] *m/e* (rel intensity) 105 (MI, 98), 104 (94), 78 (16), 77 (100), 76 (8), 75 (7), 74 (11), 65 (8), 64 (5), 63 (12), 62 (6), 52.5 (10), 52 (25), 51.5 (1), 51 (51), 50 (28), 39 (19), 38 (12), 37 (9), 28 (6), 27 (10).

Pyrolyses.—The pyrolyses were carried out in the apparatus previously described[23] using 14 ml of Berl saddles or Vycor beads, a nitrogen flow of 100 ml/min, and a rotating screw device (driven by a Troemner monodrum unit) for the introduction of the solid samples (or syringe for liquids) into the pyrolysis tube. Samples were introduced at the same rate and contact times were *ca.* 24 sec. The liquid products were collected in two traps, each of which was cooled in a Dry Ice–chloroform–carbon tetrachloride mixture, dissolved in ether, and separated into neutral, acid, and base fractions by extraction with 5% HCl and 5% NaOH (each saturated with NaCl). Separate pyrolysis experiments in which cold traps were eliminated were used in the determination of gaseous products. Hydrogen cyanide was identified by comparison of its infrared spectrum with that obtained from an authentic sample and the quantity produced determined by the Liebig method[24] after trapping in NaOH solution.

Separation and Identification of Components.—Components of the neutral, base, and acid fractions were separated by glpc using a 25 ft × 0.375 in. 20% Apiezon L (Anakrom 50/60 U) column heated at 90° for 8 min and then programmed at 2°/min to 280°.

Identification of components is based on comparisons of glpc retention times and ultraviolet spectra with those obtained from authentic samples. The identities of the following components were additionally confirmed by comparisons of the indicated spectral data with that obtained from authentic materials: ir and nmr, benzonitrile, naphthalene, phenol, diphenylamine; ir, aniline, indole, cinnamonitrile; nmr, *N*-methylaniline, acridine, phenanthridine, biphenyl, dibenzofuran; mass, *o*-cyanophenol, *o*-hydroxybiphenyl. Estimation of relative abundance of constituents are based on area per cent values obtained from glpc using a 12 ft × 0.125 in. Hewlett-Packard Hi-pak Apiezon L column for the neutral and base fractions and a 12 ft × 0.125 in. 2% polyphenyl ether (six ring) column for the acid fraction. The results are reported in Tables II and III. The average deviation of the results of three pyrolyses of nitrobenzene was ±10% of the figure quoted. Yields of selected components were determined in the acid, base, and neutral fractions using the internal standard method. 2-Methylnaphthalene was used as internal standard in the neutral and base fraction analyses and naphthalene in the acid fraction analysis. The results are reported in Table I.

Pyrolysis of *N*-Methylcarbazole.[25]—The pyrolysis of *N*-methylcarbazole (0.70 g), using the conditions above, produced 0.61 g of pyrolyzate. Analysis (glpc) using a 6 ft × 0.125 in. Carbowax 20M column showed the following substances: phenanthridine (63%), carbazole (21%), and *N*-methylcarbazole (14%). The pyrolyzate was separated into a base and neutral fraction by extraction with 5% HCl (saturated with NaCl). Work-up of the base fraction gave 0.36 g of solid which showed only one peak on glpc and had a glpc retention time and uv and ir spectra identical with those of phenanthridine. Carbazole in

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(21) M. M. Sprung, *Chem. Rev.*, **26**, 311 (1940).
(22) Reference 21 reports that *N*-methyleneaniline exists as a cyclic trimer in the solid phase and as a monomer in the vapor phase.
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(25) The authors are indebted to Dr. C. F. Mayer for carrying out this pyrolysis.

the neutral fraction was tentatively identified by its glpc retention time.

Hydrolysis of *N*-Methyleneaniline.—A solution of 4.9 g of *N*-methyleneaniline in 200 ml of ether was extracted with three 300 ml-portions of 5% HCl. The acid extracts were combined and made alkaline by the addition of NaOH pellets. The basic solution was extracted with ether and the ether extract dried over Na_2SO_4. Removal of the ether produced 3.8 g (78%) of oil, identified as aniline by nmr spectroscopy.

Registry No.—Benzonitrile, 100-47-0; nitrobenzene, 98-95-3; nitrosobenzene, 586-96-9; *N*-methyleneaniline, 100-62-9; phenyl azide, 622-37-7; *N*-methylcarbazole, 1484-12-4; *o*-nitrotoluene, 88-72-2; *m*-nitrotoluene, 99-08-1; *p*-nitrotoluene, 99-99-0.

Acknowledgment.—This study was carried out under Contract No. 12-14-100-9575-(73) with the Agricultural Research Service, U. S. Department of Agriculture, administered by the Athens, Georgia Area, Richard B. Russell Agricultural Research Center, Athens, Georgia 30604.

Synthesis of [1]Benzothieno[3,2-*d*]pyrimidine Derivatives

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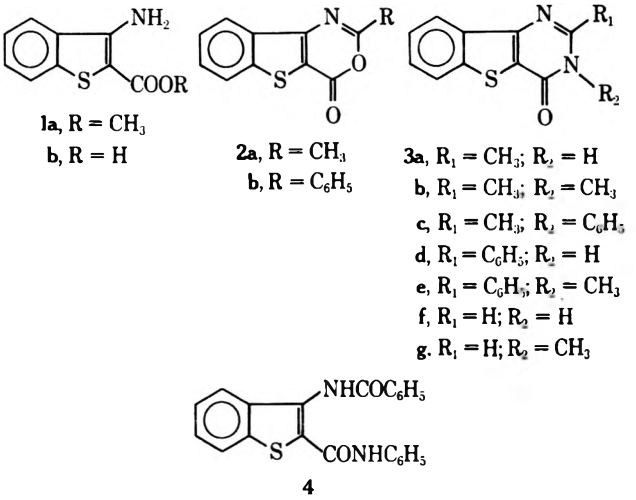
Received March 23, 1973

[1]Benzothieno[3,2-*d*]pyrimidine and several of its derivatives have been synthesized. Also described is the first reported example of the [1]benzothieno[3,2-*d*]-*v*-triazine ring system.

The literature contains only scattered reports concerning the synthesis of [1]benzothieno[3,2-*d*]pyrimidines. McCelland and Stammers[1] described the preparation of 2-methyl-4*H*-[1]benzothieno[3,2-*d*][1,3]oxazin-4-one (**2a**) from 3-acetamidobenzo[*b*]thiophene-2-carboxylic acid by treatment with acetic anhydride. The oxazinone was then converted to the corresponding pyrimidinone (**3a**) by reaction with ammonia. Travin and Magidson[2] later synthesized 4-chloro-2-methyl[1]-benzothieno[3,2-*d*]pyrimidine by treatment of **3a** with phosphorus oxychloride. Mamaev and Lyubimova[3] reported the synthesis of 3,4-dihydro-4-phenyl[1]benzothieno[3,2-*d*]pyrimidin-2(1*H*)-one 5,5-dioxide by the reaction of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide with 1,1′-benzylidenediurea.

In a recent paper[4] we described a facile synthesis of methyl 3-aminobenzo[*b*]thiophene-2-carboxylate esters from *o*-nitrobenzonitriles. The synthesis involved nucleophilic displacement of an activated nitro function by methyl thioglycolate anion followed by base-catalyzed ring closure. Using these esters and their corresponding amides as starting materials, we set out to synthesize a variety of [1]benzothieno[3,2-*d*]-pyrimidine derivatives.

Saponification of the methyl ester **1a**[4] with potassium hydroxide in aqueous alcohol yielded 3-aminobenzo[*b*]-thiophene-2-carboxylic acid (**1b**),[5] characterized as its potassium salt (87% yield). Treatment of **1b** (potassium salt) with acetic anhydride in pyridine produced the previously described oxazinone **2a** (90%). Similar treatment with benzoyl chloride formed the oxazinone **2b** (46%). Reaction of **2a** with ammonia, methylamine, and aniline, respectively, produced **3a** (70%), **3b** (85%), and **3c** (28%). Condensation of **2b** with ammonia yielded **3d** (72%) and with methylamine gave **3e** (98%). Similar treatment with aniline, however, yielded the uncyclized product **4**. All attempts to cyclize **4** to the pyrimidinone were unsuccessful.



When the methyl ester **1a** was allowed to react with formamide at reflux temperature, the product formed was the pyrimidinone **3f** (59%).[6] Alkylation of **3f** with methyl iodide in base gave **3g** (75%). The position of methylation was ascertained by comparison of the nmr, ir, and uv spectra of **3g** and **3b**. They were nearly identical, thus ruling out methylation at the 1 position of **3f**. The chloropyrimidine **5a** (82%)[6a,b] was formed by treatment of **3f** with phosphorus oxychloride. Nucleophilic displacement of the active chlorine of **5a** gave the substituted pyrimidines **5b** (81%), **5c** (82%), and **5d** (92%).[6b] Catalytic hydrogenation of **5a** in the presence of sodium acetate yielded [1]benzothieno-[3,2-*d*]pyrimidine (**5e**, 94%).[6a]

For the preparation of other [1]benzothieno[3,2-*d*]-pyrimidines, it was necessary to synthesize carboxamide analogs of the methyl ester **1a**. Conditions could not be found for the direct conversion of **1a** to the amide **6a** by

(1) E. W. McClelland and D. W. Stammers, *J. Chem. Soc.*, 78 (1948).

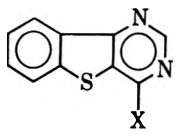
(2) A. I. Travin and O. Y. Magidson, *Khim. Geterctsikl. Soedin.* (Engl. trans.), **3**, 54 (1967).

(3) V. P. Mamaev and E. N. Lyubimova, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 96 (1969); *Chem. Abstr.*, **71**, 70566 (1969).

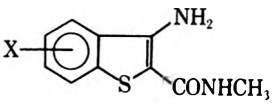
(4) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972).

(5) P. Friedlander and A. Laske, *Justus Liebigs Ann. Chem.*, **351**, 412 (1907).

(6) During the writing of this manuscript, two similar preparations of **3f** were reported: (a) M. Robba, P. Touzot, and R. M. Riquelme, *Tetrahedron Lett.*, 4549 (1972); (b) G. G. De Angelis and H. E. Hess, U. S. Patent 3,706,747 (1972).



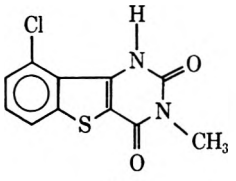
5a, X = Cl
b, X = OCH_3
c, X = SCH_3
d, X = $N(CH_3)_2$
e, X = H



6a, X = H
b, X = 4-Cl
c, X = 6-Cl

reaction with methylamine. Reaction of *o*-nitrobenzonitrile with mercapto-*N*-methylacetamide[7] in the presence of base did produce **6a**, but only in 8% yield. However, similar treatment of 2-chloro-6-nitrobenzonitrile gave **6b** in 86% yield and 4-chloro-2-nitrobenzonitrile gave **6c** in 78% yield.

Reaction of **6b** with phosgene in refluxing chlorobenzene produced the pyrimidinedione **7** (90%). Condensation of **6b** with benzaldehyde formed the dihydropyrimidinone **8a** (76%), which was alkylated with methyl iodide to give **8b** (60%). The reaction of **6b** with nitrous acid resulted in the formation of 9-chloro-3-methyl[1]benzothieno[3,2-*d*]-*v*-triazin-4(3*H*)-one (**9**),



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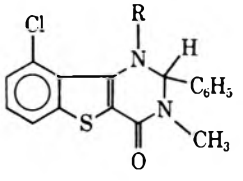
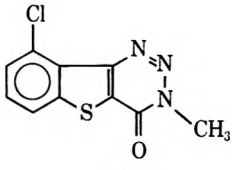


8a, R = H
b, R = CH_3



9

which represents the first reported example of this ring system.

Experimental Section[8]

3-Aminobenzo[*b*]thiophene-2-carboxylic Acid (1b) Potassium Salt.—A solution containing 5.0 g of **1a**[4] (24.2 mmol) and 3.0 g of potassium hydroxide in 75 ml of alcohol was refluxed for 0.5 hr. The mixture was cooled and filtered to yield 4.8 g (87%) of product, mp >300°.

Anal. Calcd for $C_9H_6KNO_2S$: C, 46.73; H, 2.61; N, 6.06. Found: C, 46.59; H, 2.63; N, 5.92.

2-Methyl-4*H*-[1]benzothieno[3,2-*d*][1,3]oxazin-4-one (2a).—A solution containing 5.0 g of **1b** (21.6 mmol) in 75 ml of pyridine and 25 ml of acetic anhydride was refluxed for 0.5 hr. The mixture was poured into ice–water and the solid was collected. Crystallization from absolute alcohol yielded 4.2 g (90%) of product, mp 179–181° (lit.[1] mp 179°).

Anal. Calcd for $C_{11}H_7NO_2S$: C, 60.82; H, 3.25; N, 6.45. Found: C, 60.61; H, 3.25; N, 6.67.

2-Phenyl-4*H*-[1]benzothieno[3,2-*d*][1,3]oxazin-4-one (2b).—A mixture of 20.0 g of **1b** (87 mmol) and 20 ml of benzoyl chloride in 200 ml of pyridine was refluxed for 20 hr and then poured into ice–water. The solid was collected and crystallized from methyl ethyl ketone to yield 11.0 g (46%) of product, mp 208–210°.

Anal. Calcd for $C_{16}H_9NO_2S$: C, 68.80; H, 3.25; N, 5.01. Found: C, 68.79; H, 3.17; N, 4.96.

2-Methyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3a).—A mixture of 4.5 g of **2a** (20.7 mmol) and 15 ml of concentrated ammonium hydroxide in 100 ml of alcohol was refluxed for 3.5 hr. The solution was cooled and filtered to yield 3.1 g (70%) of product, mp >350° (lit.[1] mp 340–345° dec).

Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95. Found: C, 60.84; H, 3.55; N, 13.10.

2,3-Dimethyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3b).—A solution containing 3.1 g of **2a** (14.3 mmol) and 15 ml of 40% aqueous methylamine solution in 100 ml of alcohol was refluxed for 3 hr. Water (10 ml) was added and the solution was cooled and filtered to yield 2.8 g (85%) of product, mp 177–179°.

Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.31; H, 4.24; N, 11.88.

2-Methyl-3-phenyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3c).—Aniline (18 ml) and 4.0 g of **2a** (18.4 mmol) were stirred and heated at 165° for 0.5 hr. The crude reaction mixture was crystallized from alcohol–water to yield 1.5 g (28%) of product, mp 239–241°.

Anal. Calcd for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58. Found: C, 69.57; H, 3.93; N, 9.32.

2-Phenyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3d).—Ammonia was slowly bubbled into a refluxing solution containing 3.5 g of **2b** (12.5 mmol) in 100 ml of absolute alcohol for 24 hr. The mixture was cooled and filtered and the crude product was crystallized from DMF–water to yield 2.5 g (72%) of product, mp 328–329°.

Anal. Calcd for $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.06. Found: C, 68.83; H, 3.82; N, 10.12.

3-Methyl-2-phenyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3e).—Methylamine (15 ml of 40% aqueous solution) and 3.3 g of **2b** (11.8 mmol) in 100 ml of absolute alcohol was heated at reflux temperature for 12 hr. Water (20 ml) was added and the solution was cooled and filtered to yield 3.4 g (98%) of product, mp 245–246°.

Anal. Calcd for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58. Found: C, 69.80; H, 4.37; N, 9.87.

3-Benzamidobenzo[*b*]thiophene-2-carboxanilide (4).—Aniline (8 ml) and 4.0 g of **2b** (14.3 mmol) were stirred and heated at 185° (oil bath) for 0.5 hr. The solution was cooled and triturated with hot acetone. The material crystallized and was collected to yield 3.2 g (60%) of product, mp 312–314°.

Anal. Calcd for $C_{22}H_{16}N_2O_2S$: C, 70.95; H, 4.33; N, 7.52. Found: C, 70.68; H, 4.50; N, 7.71.

[1]Benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3f).—A solution containing 18.0 g of **1a** (87 mmol) in 150 ml of formamide was refluxed for 6.5 hr. The mixture was cooled and the crude product was collected and washed with water. Crystallization from *n*-butyl acetate yielded 12.0 g (59%) of product, mp 308–309° (lit.[8a] mp 290°).

Anal. Calcd for $C_{10}H_6N_2OS$: C, 59.39; H, 2.99; N, 13.85; S, 15.85. Found: C, 59.14; H, 2.97; N, 13.79; S, 15.50.

3-Methyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3g).—To a solution containing 5.0 g of **3f** (24.8 mmol) and 3.0 ml of methyl iodine in 100 ml of DMF was added slowly at room temperature a solution containing 1.6 g of potassium hydroxide in 30 ml of water. The mixture was stirred for 1 hr, cooled, and allowed to crystallize yielding 4.0 g (75%) of product, mp 195–196°.

Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.78; N, 12.95. Found: C, 60.86; H, 3.59; N, 13.23.

4-Chloro[1]benzothieno[3,2-*d*]pyrimidine (5a).—Phosphorus oxychloride (250 ml) and 15.0 g of **3f** (74 mmol) were heated at reflux temperature for 45 min. Excess phosphorus oxychloride was removed by vacuum distillation and the crude solid was crystallized from DMF–water to yield 13.4 g (82%) of product, mp 142–144° (lit.[8a] mp 138°).

Anal. Calcd for $C_{10}H_5ClN_2S$: C, 54.43; H, 2.28; N, 12.69; Cl, 16.07. Found: C, 54.62; H, 2.48; N, 12.92; Cl, 16.23.

4-Methoxy[1]benzothieno[3,2-*d*]pyrimidine (5b).—A mixture containing 4.4 g of **5a** (20 mmol) and 1.2 g of sodium methoxide (22 mmol) in 100 ml of methanol was refluxed for 6 hr and then poured into ice–water. The crude solid was collected and crystallized from alcohol–water to yield 3.5 g (81%) of product, mp 140–142°.

Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.30; H, 3.66; N, 12.80.

(7) J. W. Haefele and R. W. Broge, *Proc. Sci. Sect. Toilet Goods Assoc.*, 52 (1959); *Chem. Abstr.*, **54**, 17233 (1960).

(8) Melting points were determined on a Mel-Temp apparatus and are uncorrected.

4-Methylthio[1]benzothieno[3,2-*d*]pyrimidine (5c).—To a solution containing 4.4 g of 5a (20 mmol) and excess methanethiol in 150 ml of DMF was added slowly a solution of 2.0 g of potassium hydroxide in 20 ml of water, at a rate so as to maintain the temperature at 35–40°. The mixture was stirred at room temperature for 2 hr and poured into ice–water. The crude solid was collected and crystallized from alcohol–water to yield 3.8 g (82%) of product, mp 125–126°.

Anal. Calcd for $C_{11}H_8N_2S_2$: C, 56.87; H, 3.47; N, 12.06; S, 27.60. Found: C, 56.85; H, 3.63; N, 12.28; S, 27.33.

4-(Dimethylamino)[1]benzothieno[3,2-*d*]pyrimidine (5d).—Dimethylamine was bubbled slowly into a refluxing solution of 5.5 g of 5a (24.9 mmol) in 70 ml of DMF for 2 hr. The mixture was cooled and poured into ice–water. Filtration yielded 5.1 g (91%) of product, mp 113–114°.

Anal. Calcd for $C_{12}H_{11}N_3S$: C, 62.86; H, 4.84; N, 18.30. Found: C, 62.87; H, 4.81; N, 18.20.

[1]Benzothieno[3,2-*d*]pyrimidine (5e).—A solution containing 2.2 g of 5a (10 mmol), 0.85 g of anhydrous sodium acetate, and 0.5 g of 5% palladium on carbon in 100 ml of absolute alcohol was placed in a pressure bottle and hydrogenated for 2 hr using a Parr shaker at an initial hydrogen pressure of 45 psi. The solution was filtered and cooled to yield 1.15 g of product, mp 139–140° (lit.[6a] mp 144°). Concentration of the mother liquors yielded 0.6 g of product, mp 138–140°. The total yield was 1.75 g (94%).

Anal. Calcd for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.04. Found: C, 64.23; H, 3.35; N, 14.83.

General Procedure for Preparation of 6a, 6b, and 6c.—To a cold solution containing 30 mmol of the appropriate o-nitrobenzonitrile and 30 mmol of mercapto-*N*-methylacetamide[7] in 60 ml of DMF was added dropwise a solution containing 3.0 g of potassium hydroxide in 15 ml of water. The mixture was stirred in the cold for 1.5 hr and poured into ice–water. The product was collected and crystallized. The following were obtained (yield, melting point, and crystallization solvent): 6a (8%, 163–164°, alcohol–water); 6b (86%, 134–135°, alcohol–water); 6c (78%, 156–157°, benzene–hexane).

Anal. Calcd for $C_{10}H_{10}N_2OS$ (6a): C, 58.23; H, 4.89; N, 13.58. Found: C, 58.26; H, 4.62; N, 13.44. Calcd for $C_{10}H_9ClN_2OS$ (6b): C, 49.91; H, 3.77; N, 11.64. Found: C, 49.71; H, 3.70; N, 11.90. Calcd for $C_{10}H_9ClN_2OS$ (6c): C, 49.91; H, 3.77; N, 11.64. Found: C, 50.03; H, 3.75; N, 11.64.

9-Chloro-3-methyl[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7).—Phosgene was bubbled slowly into a refluxing solution containing 6.5 g of 6b (27 mmol) in 150 ml of chlorobenzene for 1 hr. The mixture was cooled to yield 6.45 g (90%) of product, mp 309–312°.

Anal. Calcd for $C_{11}H_7ClN_2O_2S$: C, 49.54; H, 2.65; N, 10.50; Cl, 13.29. Found: C, 49.32; H, 2.35; N, 10.69; Cl, 13.21.

9-Chloro-1,2-dihydro-3-methyl-2-phenyl[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)-one (8a).—A mixture of 4.5 g of 6b (18.7 mmol), 2.1 g of benzaldehyde (19.8 mmol), and 100 mg of *p*-toluenesulfonic acid in 100 ml of benzene was refluxed (water removed using a Dean-Stark trap) for 4 hr. The mixture was cooled and the product was collected and crystallized from DMF–water to yield 4.7 g (76%) of product, mp 245–247°.

Anal. Calcd for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.99; N, 8.52; Cl, 10.78. Found: C, 61.96; H, 4.04; N, 8.50; Cl, 10.56.

9-Chloro-1,2-dihydro-1,3-dimethyl-2-phenyl[1]benzothieno-[3,2-*d*]pyrimidin-4(3*H*)-one (8b).—To a solution containing 4.0 g of 8a (12.2 mmol) and 4.0 ml of methyl iodide in 100 ml of DMF was added slowly a solution of 1.6 g of potassium hydroxide in 25 ml of water. The mixture was stirred at room temperature for 1 hr and poured into ice–water. Crystallization from DMF–water yielded 2.5 g (60%) of product, mp 188–192°. An analytical sample, mp 191–193°, was recrystallized from alcohol–water.

Anal. Calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17; Cl, 10.34. Found: C, 62.82; H, 4.46; N, 8.04; Cl, 10.50.

9-Chloro 3-methyl[1]benzothieno[3,2-*d*]-*v*-triazin-4(3*H*)-one (9).—To a cold vigorously stirred mixture of 0.7 g of sodium nitrite (10 mmol) in 10 ml of concentrated sulfuric acid was added slowly a solution containing 2.4 g of 6b (10 mmol) in 25 ml of acetic acid, while the reaction temperature was maintained at 20–25°. The mixture was stirred at room temperature for 0.5 hr and poured into ice–water. The crude solid was crystallized from acetic acid to yield 2.15 g (86%) of product, mp 269–271°.

Anal. Calcd for $C_{10}H_6ClN_3OS$: C, 47.72; H, 2.40; N, 16.70. Found: C, 47.59; H, 2.47; N, 16.93.

Registry No.—**1a**, 35212-85-2; **1b**, 40142-71-0; **1b** K salt, 40139-58-0; **2a**, 40139-59-1; **2b**, 40139-60-4; **3a**, 40139-61-5; **3b**, 40139-62-6; **3c**, 40139-63-7; **3d**, 40139-64-8; **3e**, 40139-65-9; **3f**, 40142-89-0; **3g**, 40139-67-1; **4**, 40139-68-2; **5a**, 36822-09-0; **5b**, 40139-70-6; **5c**, 40127-47-7; **5d**, 40127-48-8; **5e**, 245-16-9; **6a**, 40127-50-2; **6b**, 40127-51-3; **6c**, 40127-52-4; **7**, 40127-53-5; **8a**, 40127-54-6; **8b**, 40127-55-7; **9**, 40127-56-8; *o*-nitrobenzonitrile, 612-24-8; 2-chloro-6-nitrobenzonitrile, 6575-07-1; 4-chloro-6-nitrobenzonitrile, 34662-32-3; mercapto-*N*-methylacetamide, 20938-74-3.

Acknowledgments.—The authors wish to thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Alkylation of Ethyl 4-Thiomorpholineacetate and Ethyl 1-(4-Methylpiperidine)acetate with Ethyl Bromoacetate

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Received March 6, 1972

The alkylation of ethyl 4-thiomorpholineacetate (I) and ethyl 1-(4-methylpiperidine)acetate (II) at 30, 40, 50, and 60° with ethyl bromoacetate in absolute methanol follows second-order kinetics. The quaternization of reactant I was complicated by a competing reaction of sulfonium salt formation. The k_2 and ΔE and ΔS values at 40° are 3.75 and 34.4 × 10^{-6} l./(mol sec), 16.4 and 16.7 kcal/mol, and −33.4 and −27.6 eu, respectively, for the quaternization of the I and II amines. The k_2' and ΔE and ΔS values for the sulfonium salt formation at 40° were 10.6 × 10^{-6} l./(mol sec), 18.5 kcal/mol, and −24.2 eu, respectively.

This study investigated the quaternization of ethyl 4-thiomorpholineacetate (I) and ethyl 1-(4-methylpiperidine)acetate (II) with ethyl bromoacetate in absolute methanol. The reaction rate constants, energies of activation, and entropies of activation were determined and compared to literature values for ethyl 1-piperidineacetate (III) and ethyl 4-morpholineacetate (IV).[1]

The kinetics of the reaction were determined by potentiometric titration of the bromide ion with a Sargent Model C constant rate buret capable of delivering 0.05-ml increments of titrant with an accuracy of 0.05% as determined in this laboratory. Sample preparation, sample aliquots, and experimental determinations were performed in the same manner as previously described.[1] The rate constants were obtained from the second-order reaction plots and by a CHEM/2 Fortran IV G computer program developed at Illinois State University for the treatment of second-order reaction data.

Activation energies were determined from the Arrhenius equation, and the entropies of activation were calculated from the Eyring equation.

Results

The experimental rate constant data for the quaternization reaction are summarized in Table I. The bimolecular rate constant, k_2, is defined by the familiar equation

$$\frac{dx}{dt} = k_2(a - x)^2 \qquad (1)$$

where a is the initial molar concentration of ethyl bromoacetate and the tertiary amine in absolute methanol, and x is the concentration of the bromide ion.

Fractional lifetime analysis of the initial products of II by the Fortran program indicated the reaction followed second-order kinetics. Output included several estimates of the reaction order based on pairs of time intervals during which the concentrations of the reactants decreased by 25%. First and second indications of the 40° reaction order for II were calculated to be 2.3 and 1.9, respectively. These were typical data for the results obtained.

The data for II represents quaternization reactions of 59% completion at 30°, 81% at 40°, 84% at 50°, and 74% at 60°. The average percentage error in determining the concentration between three identical samples was 2.3% with a standard deviation of 2.8%.

TABLE I

REACTION RATE CONSTANTS[a] FOR THE QUATERNIZATION OF X⟨ ⟩NCH$_2$CO$_2$Et[b] WITH BrCH$_2$CO$_2$Et

Temp, °C (±0.1°)	k_I × 10^6	k_{II} × 10^6	k_{III} × 10^6 [c]	k_{IV} × 10^6 [c]
30	1.69 ± 0.12[e]	12.9 ± 0.5	13.2[d]	1.33[d]
40	3.75 ± 0.13	34.4 ± 0.3	33.9	4.00
50	8.43 ± 0.43	69.8 ± 1.1	80.5	10.0
60	17.6 ± 0.1	171.0 ± 1.0	150.0	23.1

Comparison of Reaction Rates

Temp, °C (±0.1°)	k_I/k_{IV}	k_{II}/k_{IV}	k_{III}/k_{IV}	k_{III}/k_{II}	k_{III}/k_I
30	1.27	9.69	9.92	1.02	7.80
40	0.937	8.63	8.46	0.986	9.04
50	0.843	6.98	8.08	1.15	9.53
60	0.762	7.41	6.46	0.888	8.82

[a] Average and average deviations of three determinations unless otherwise noted. [b] I, X = S; II, X = CHCH$_3$; III, X = CH$_2$; and IV, X = O. [c] Data from ref 1. [d] The reaction rate was calculated from the linear plot of $-\log k$ *vs.* $1/T$ from data at 20, 25, 40, 50, and 60° (ref 1). [e] Value extrapolated from the linear plot of $-\log k_2$ *vs.* $1/T$ (Figure 2).

This is based on a population of 144 samples for the four different temperatures.

The reaction data indicated a positive deviation from linearity at 60° after 110 hr (78% reaction). This discrepancy can be attributed to two possible sources: evaporation of the solvent and the competing methanolysis of ethyl bromoacetate which was found to be 6.68% at 60° after 240 hr and 0.55% at room temperature.[1]

The points for the 30° reaction became scattered after 1000 hr (70% reaction) but seemed to indicate a downward curvature with a 25% deviation from the initial slope after 2700 hr (82% reaction). The reaction of pyridine with isopropyl iodide in nitrobenzene has been reported to proceed to an equilibrium at 60 and 121°;[2] however, this explanation is questionable in this study because the downward curvature was not observed at the higher temperatures. Consequently, in order to calculate accurate rate constants only the linear portion of the rate curves were utilized.

Second-order plots of the data for I are shown in Figure 1. These graphs indicate complex kinetics by curving downward until approximately 30% of each reaction is complete. At this time a linear slope develops which eventually increases in the 50 and 60° reactions. The final upward trend is undoubtedly

(1) R. C. Duty and R. L. Gurnea, *J. Org. Chem.*, **35**, 1800 (1970).

(2) K. Laidler and C. N. Henshelwood, *J. Chem. Soc.*, 858 (1938).

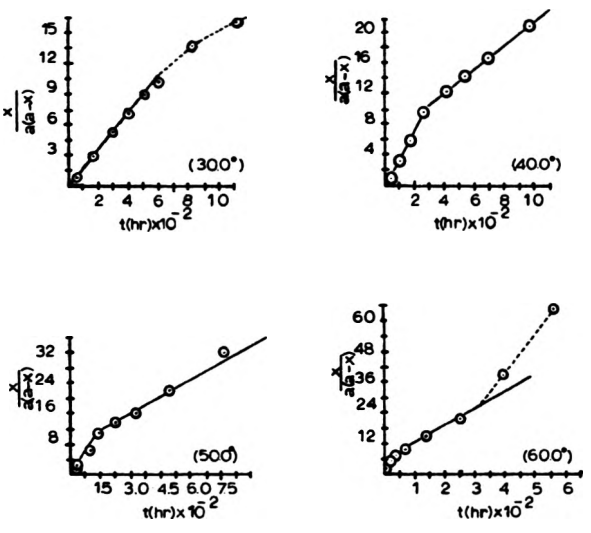
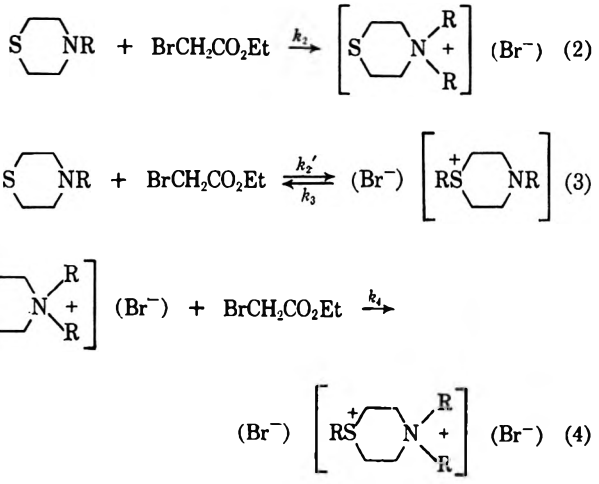


Figure 1.—Second-order kinetic plots for ethyl 4-thiomorpholineacetate with ethyl bromoacetate.

evidence for the methanolysis reaction noted previously.[1] The time required to reach the linear region of the curves is inversely related to the increase in temperature and is barely evident at the lower reaction temperature of 30°.

Since sulfides are known to form sulfonium salts with alkyl halides, the above observations suggest that the quaternization reaction of I_s is complicated by the formation of a sulfonium salt formed from the electrophile, ethyl bromoacetate. Thin layer chromatographic analysis of the salts (see Experimental Section) recrystallized from reaction I solutions definitely established that two products were formed. The following reactions, therefore, may be written for the above observations.



Equation 4 undoubtedly occurs to a negligible extent since the positive charge produced in eq 3 would reduce the reactivity of the heterocyclic ring to further electrophilic attack. Additionally, the thin layer chromatograms revealed only two products instead of three.

Equation 3 is written as an equilibrium reaction because the literature supports a reversible reaction of sulfonium salts as reported by Balfe and coworkers.[3] They found that 1-ethylmethylphenacylsulfonium mercuritetraiodide readily racemized in an acetone solution and contributed this racemization to the following equilibria

$$(PhCOCH_2SMeEt)_2HgI_4 \rightleftharpoons 2(PhCOCH_2\overset{+}{S}MeEt) + HgI_3^- + I^- \quad (5)$$

$$(PhCOCH_2\overset{+}{S}MeEt) + I^- \rightleftharpoons PhCOCH_2SMe + EtI \quad (6)$$

Consequently, one can justify the reversible reaction in eq 3 based on the equilibrium reaction of eq 6 above. Equation 2 is not written as a reversible reaction because aliphatic quaternary ammonium salts, as reported by Coleman and Fuoss,[4] are typically nonreversible and follow second-order kinetics in their formation.

Reactions 2, 3, and 4 enable the following rate equation to be written

$$\frac{dx}{dt} = k_2(A)(B) + k_2'(A)(B) - k_3(C)(x) \quad (7)$$

where $(x) = [Br^-]$, $(A) =$ [amine], $(B) = [BrCH_2CO_2Et]$, and $(C) =$ [sulfonium ion], along with the equilibrium constant equation

$$K_e = \frac{k_2'}{k_3} = \frac{(C)(x)}{(A)(B)} \quad (8)$$

Equations 7 and 8 combine to produce the second-order equation

$$\frac{dx}{dt} = k_2(A)(B) = k_2(a - x)^2 \quad (9)$$

where a is the initial concentration of A and B.

It is seen from these assumptions that, once equilibrium is established, the rate of bromide ion formation is related to second-order kinetics through eq 9. The concentration of the sulfonium ion is small during the initial stages and produces a nonlinear graph. However, once the sulfonium salt concentration has reached equilibrium, a plot of $x/a(a - x)$ *vs.* time should become linear. The experimental plots for these reactions (Figure 1) are in agreement with this hypothesis. Since the 30° reaction had evidently not reached equilibrium, only the 40, 50, and 60° reactions produced a linear region. The 30° graph represents data for 44% conversion to the quaternary salt, the 40° graph 50%, the 50° graph 61%, and the 60° graph 75%. The average percentage error between three identical samples was 1.5% with a standard deviation of 1.9%. This was based on a total population of 128. For the calculation of the rate constants for compound I in Table I, the average percentage error for the 36 samples was 1.9% with a standard deviation of 2.0%.

A more careful examination of eq 7 above reveals that at the beginning of the reaction the term $k_3(C)(x)$ is quite small and enables the rate equation to be expressed as

$$\lim_{t \to 0} \frac{dx}{dt} = (k_2 + k_2')(A)(B) \quad (10)$$

Consequently, we constructed tangents to the initial slopes of the curves in Figure 1 and calculated the term $(k_2 + k_2')$ for temperatures of 30, 40, 50, and 60°. Since we had previously determined the rate constants, k_2, from the linear portion of the curves of Figure 1, values for the reaction rate constants for the sulfonium

(3) M. P. Balfe, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 2554 (1930).

(4) B. D. Coleman and R. M. Fuoss, *J. Amer. Chem. Soc.*, **77**, 5472 (1955).

salt formation (k_2') could be calculated. These rate constants are given in Table II along with their limits of error.[5]

TABLE II
REACTION RATE CONSTANTS FOR THE FORMATION OF QUATERNARY AND SULFONIUM SALTS OF

WITH $BrCH_2CO_2Et$[a]

Temp, °C (±0.1°)	$(k_2 + k_2') \times 10^6$	$k_2' \times 10^6$
30	5.85 ± 0.01	4.16 ± 0.13
40	14.3 ± 0.6	10.6 ± 0.7
50	35.5 ± 1.3	27.1 ± 1.7
60	71.6 ± 0.9	54.0 ± 1.0

[a] See eq 2 and 3.

Since the tangents to each graph coincided with the initial experimental points in the Figure 1 graphs, experimental errors were calculated by constructing tangential graphs through the limits of error of the first experimental points of each graph.

The energies of activation (E_a) for the I and II quaternization reactions were calculated from an Arrhenius plot of the rate constants at the different temperatures. In the case of I, only three rate constants were available because of the inability to establish a reversible sulfonium salt equilibrium at 30° (see Figure 2). The values for E_a were calculated as the average of the minimum and maximum slopes drawn in such a manner that the lines passed through the areas of deviation of each point.[6] The close agreement of the activation energy of I with II, III and IV, which are given in Table III, lends additional support for the above reaction scheme.

An Arrhenius plot of $-\log k_2'$ *vs.* $1/T$ is also shown in Figure 2. A straight line resulted which helps support the interpretation of the kinetic data for the equilibration of the sulfonium salt. The datum point at 60° is slightly higher than the linear slope and is undoubtedly the result of contributions from the term, (C)(x), which was assumed to be negligible (see eq 10). The 60° second-order kinetic plot (Figure 1), also suggests the term (C)(x) would be significant during the early stages of the reaction. The limits of error were established in the same manner as for the quaternization reaction using three experimental temperatures of 30, 40, and 50°.

The entropies of activation, $\Delta S^{\pm}$ (Table III), were calculated by the method of Eyring[7] with the experimental errors calculated from the differential changes in the independent variables.[8]

$$\Delta S^{\pm} = \frac{E_a}{T} + 2.3R\left(\log k - \log \frac{k'T}{h}\right) - R$$

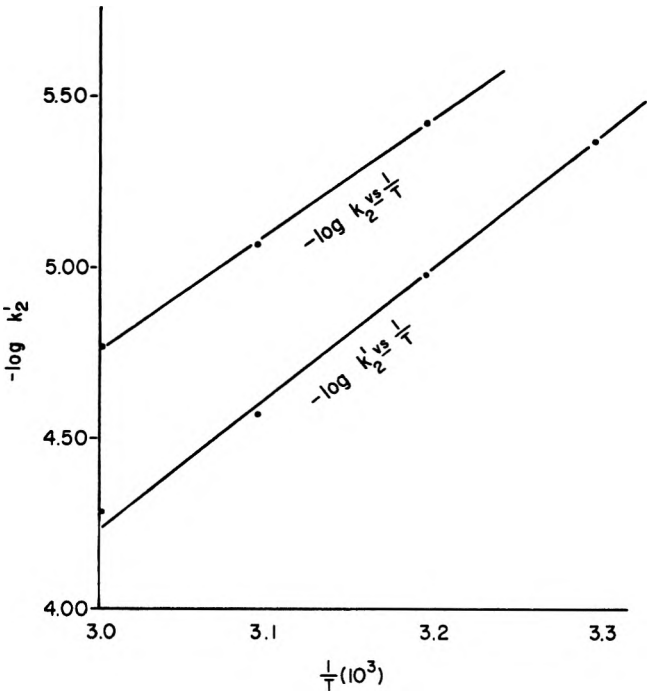


Figure 2.—Arrhenius plot for the sulfonium salt reaction (k'_2) and the quaternization reaction (k_2) with ethyl bromoacetate.

Ratios of the rate constants for I and II as compared with ethyl 1-piperidineacetate (III) and ethyl 4-morpholineacetate (IV) are given in Table I.

Discussion of Results

The reaction ratios for II and III (k_{III}/k_{II}), Table I, fluctuate about unity and are consistent with the postulate that the polar effect of the methyl substituent in II is equal to that of hydrogen. The inductive effect of the methyl group has traditionally been described as electron donating in solution. Such an effect is well established when the methyl group is directly bonded to an unsaturated system, but the picture is not so clear with saturated systems. Recent experimental evidence seems to support the view that the polar effect of the methyl substituent is small and electron withdrawing when bonded to an sp^3 hybridized carbon.[9-11] In a study of the dissociation constants of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids, Holtz and Stock determined σ_I of the methyl group to be −0.008.[12] Such a low value indicates the polar influence of the methyl group is minor.

In addition, the three carbon bonds separating the substituent from the nucleophilic nitrogen would also diminish the electronic effect of the methyl group. It is pertinent also to note that analyses have shown that the inductive effect is completely dampened by three carbon–carbon bonds.[13] Quadrupole resonance spectra of 1-chloroparaffins have established that the methyl group has no effect on the charge distribution of the chlorine nucleus when separated by more than two carbons.[14] Therefore, the small rate differences found

(5) A point considered by a reviewer was that the sulfonium salt reaction would not establish equilibrium if k_2' is only three times faster than k_2. Consequently, we calculated Ke by a numerical integration of eq 7, and the computer results will appear immediately following this article in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-73-2453. Remit check or money order for $3.00 photocopy or $2.00 for microfiche.

(6) D. P. Shoemaker and C. W. Garland, "Experiments in Physical Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1967, p 34.

(7) K. J. Laidler, "Chemical Kinetics," 2nd ed, McGraw-Hill, New York, N. Y., 1965, p 90.

(8) F. Daniels, J. W. Williams, P. Bender, R. A. Alberty, and C. D. Cronwell, "Experimental Physical Chemistry," McGraw-Hill, New York, N. Y., 1962, p 398.

(9) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 4194 (1964).

(10) V. W. Laure and J. S. Muenter, *ibid.*, **88**, 2883 (1966).

(11) H. Kwart and L. J. Miller, *ibid.*, **83**, 4552 (1961).

(12) H. D. Holtz and L. M. Stock, *ibid.*, **87**, 2404 (1965).

(13) K. Bowden, *Can. J. Chem.*, **41**, 2781 (1963).

(14) H. O. Hooper and P. J. Bray, *J. Chem. Phys.*, **33**, 334 (1960).

TABLE III
ACTIVATION ENERGIES AND ENTROPIES FOR THE QUATERNIZATION REACTION OF TERTIARY AMINES WITH ETHYL BROMOACETATE AT 40°

Amine	ΔE_a, kcal/mol	$-\Delta S$, eu	ΔE_a,[a] kcal/mol	$-\Delta S$,[a] eu
Ethyl 4-thiomorpholineacetate (I)	16.4 ± 0.4	33.4 ± 0.8	18.5 ± 1.1	24.2 ± 1.3
Ethyl 1-(4-methylpiperidine)acetate (II)	16.7 ± 0.3	27.6 ± 1.0		
Ethyl 1-piperidineacetate (III)[b]	17.2	26.0		
Ethyl 4-morpholineacetate (IV)[b]	18.1	27.6		

[a] Sulfonium salt formation. [b] Reference 1.

above (k_{III}/k_{II}) cannot be assigned to a polar effect of the methyl substituent.

The reaction rate ratio for I and III (k_{III}/k_{II}) is 9.04 at 40° and remains essentially constant with temperature. This trend is in agreement with an inductive model for the thioether group which exhibits electron-withdrawing ability. Taft's inductive constant, σ_I, is reported as +0.19 for $-SCH_3$,[15] and Hall reported that the pK_a of thiomorpholine is 2.31 units less than for piperidine.[16]

The fact that the rate constants of IV are predominantly greater than those of I ($k_I/k_{IV} < 1$) indicates that other factors in addition to an inductive effect are operative. The Taft inductive constants for $-OCH_3$ and $-SCH_3$ are +0.27 and +0.19, respectively,[15] and the pK_a for thiomorpholine and morpholine are 9.00 and 8.36, respectively.[16] These data suggest that the ratio (k_I/k_{IV}) should be greater than one, which is only true for the 30° reaction.

One of the original purposes of this research was to substantiate a hypothesis that the temperature-dependent ratio, k_{III}/k_{IV}, was caused by a reversed substituent effect.[17] The previous study[1] explained the smaller ratios at higher temperatures as the result of an increasing contribution of the field effect to the total polar effect of the oxygen atom. Since a greater percentage of the boat conformation of the six-membered ring occurred at higher temperature, the direct electrostatic repulsion of the nitrogen electron cloud by oxygen would increase and, consequently, enhance the rate of quaternization for IV over that for II and III. If sulfur replaced oxygen in the six-membered ring, this would lessen the reversed substituent effect by raising the activation energy of the ring inversion.

It is well known that six-membered rings exist in equilibrium mixtures of boat and chair conformations with the chair form the more stable.[18] When one substitutes a sulfur atom for a carbon atom in a carbocyclic ring, the barrier to ring inversion is increased whereas for oxygen the opposite is true.[19] In addition, it is also known that replacement of ring hydrogens with an alkyl substituent raises the barrier of ring inversion.[20] Therefore, it is not unreasonable to assume that at any one temperature the concentration of boat conformers for III and IV would exceed those for I and II.

One can observe from Table I that the ratio k_{III}/k_I does not change appreciably with temperature whereas the ratio k_I/k_{IV} decreases by 40% from 30 to 60° and the ratio k_{III}/k_{IV} has decreased 35%. These decreases indicate the reaction rate of the oxygen analog, k_{IV}, is increasing faster with temperature than the reaction rate for the sulfur analog, k_I, and the methylene analog, k_{III}. If the larger size of the atom is decreasing the boat conformer concentration relative to that for the oxygen heterocylic ring, this decrease in reaction rate ratio is understandable if one examines the field effect model. In the field effect model of IV,[1] the other dipole moment in the boat conformation enhances the reaction rate (k_{IV}) in parallel with a temperature increase. The sulfur dipole for I operates predominantly from a chair conformation and, consequently, its rate enhancement ability with temperature does not increase as is reflected in the reaction rate ratios. These conclusions are certainly not unequivocal proof for the field effect, but it does impart a reasonable explanation for the reaction ratios.

The activation energies reported for I and II (Table III) are in agreement with those reported in the earlier study.[1] The entropy value for I (−33.4 eu) is 23% more negative than the average of the three other amines. This entropy term is undoubtedly more negative because of the steric interference that results from the heterosulfur atom and the two *N*-carbethoxymethyl groups in the final product. The entropy term is even more enhanced for the sulfur atom in I than the oxygen atom in IV because of the difference in sizes of the two atoms (S = 1.04 Å and O = 0.66 Å).[21]

The rate constants, activation energy, and entropy for the sulfonium salt formation, to our knowledge, are the first to be reported for this type of reaction. Consequently, no comparison of these parameters can be made with literature values. The only comparison that appears to be reasonable is the comparison between the quaternization reactions of this study. Compound IV makes a reasonable model because it has an oxygen atom in the 4 position for the quaternization reaction, and a tertiary nitrogen in the 4 position of compound I for the sulfonium salt reaction. For these two compounds, surprisingly close agreement exists between the activation energies and entropies whereas the rate constants are three orders of magnitude larger for the sulfonium salt formation.

Experimental Section

Compound I, bp 83° (0.5 mm), was prepared by reacting $BrCH_2CO_2Et$ (0.068 mol) (Eastman White Label) with one molar excess of thiomorpholine (0.133 mol) in refluxing CH_3CO_2Et for 1 hr. Fraction distillation yielded 7.9 g (28%) of I. Compound I was further purified by preparative vpc on a Beckman GC-2A chromatograph with a 3 ft × $^5/_8$ in. o.d. column packed with 10% SE-30 substrate on a Chromosorb P (60/80 mesh) sup-

(15) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).
(16) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956).
(17) R. Golden and L. M. Stock, *ibid.*, **88**, 5928 (1966).
(18) J. B. Hendrickson, *ibid.*, **83**, 4537 (1961).
(19) F. G. Riddel, *Quart. Rev., Chem. Soc.*, **21**, 364 (1967).
(20) E. L. Eliel, N. L. Allinger, S. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1967, p 42.
(21) F. A. Cotton and G. Wilkenson, "Advanced Inorganic Chemistry," 2nd ed, Interscience, New York, N. Y., 1966, p 103.

port. Purity of the sample as checked by vpc was 99%. The ir spectrum confirmed the structure by comparison with the ir spectrum of compound IV:[1] ir ν (film) 2945, 2840, 1740, 1460, 1425, 1190, 1040, 965, and a weak 663-cm^{-1} band (C–S–C) (lit.[22] 658 cm^{-1}); nmr ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.3 Hz, OCH_2CH_3), 2.75 (m, 8 H, methylene ring protons), 3.35 (s, 2 H, NCH_2CO_2Et), and 4.18 ppm (m, 2 H, J = 7.3 Hz, OCH_2CH_3).

Thiomorpholine was prepared by the $LiAlH_4$ reduction of thiomorpholin-3-one (Aldrich). A 105-g (0.896 mol) sample of thiomorpholin-3-one was slowly shaken into an ether solution of 48.5 g (1.28 mol) of $LiAlH_4$ (Ventron). After the excess $LiAlH_4$ was decomposed and the solid was filtered, the solution was rotary evaporated and vacuum distilled to yield 14.0 g (14.6% yield) of thiomorpholine, bp 82–83° (2.9 mm).

Compound II, bp 51° (0.2 mm), was prepared by adding $BrCH_2CO_2Et$ (0.302 mol) (Aldrich) to an excess of 4-methylpiperidine (0.510 mol) (Aldrich) dissolved in CH_3CO_2Et. Fractional distillation of the mother liquor produced a 75% yield of product. Preparative gas chromatographic analysis as previously described for compound I produced 7.2 ml of product of 99.7% purity. The ir spectrum compared favorably with that for compound III:[1] ir ν (film) 2940, 2820, 1740, 1460, 1380, 1190, 990, and 830 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (m, 11 H, ring hydrogens and methyl hydrogens), 2.70 (m, 4 H, ring hydrogens adjacent to nitrogen, 3.35 (s, 2 H, NCH_2CO_2Et) and 4.25 (m, 4 H, J = 7.0 Hz, OCH_2CH_3).

Kinetic Procedure.—Initial concentration for the amines and $BrCH_2CO_2Et$ was 0.0500 M. Three independent samples of each compound were prepared and studied at the same time. Sample preparations and potentiomatic titrations were similar to the procedures as reported in the previous study.[1]

Reaction Products *via* Tlc.—In order to establish that two products were formed in the quaternization of I, a 50-ml sample of 0.0500 M reaction solution was heated at 60° for 427 hr. After removal of the solvent the product was recrystallized into fine white crystals from a solvent of ethyl acetate and ether (2:1) containing a small amount of methanol. The crystals (60-μg spots) were chromatographed on 4 × 7¾ in. glass plates coated with Silicar TLC 7G (Mallinckrodt). The mobile phase was absolute CH_3OH, and the plates were developed in an I_2 chamber. The R_f values for the two compounds were 0.64 ± 0.03 and 0.57 ± 0.02 (average and average deviation for two plates containing three spots per plate).

A similar tlc analysis was made from the reaction product of II. However, only one compound was resolved with R_f value of 0.51 ± 0.03.

Registry No.—Compound I, 39981-80-1; compound II, 39981-81-2; ethyl bromoacetate, 105-36-2; thiomorpholine, 123-90-0; thiomorpholin-3-one, 20196-21-8; 4-methylpiperidine, 626-58-4.

Acknowledgment.—The facilities at the Universidad Autonoma de Guadalajara, Guadalajara, Mexico, were generously made available for the writing of this manuscript by R. C. D. during a sabbatical leave (1971–1972). The authors also wish to acknowledge the assistance of Dr. Richard Reiter for his help in formulating the computer program.

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Reaction Kinetics of 2-Thiophenesulfonyl Chloride with Anilines in Methanol

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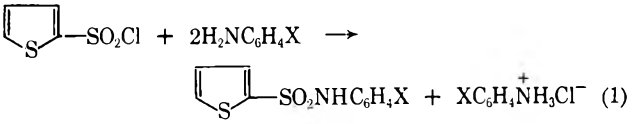
Received January 29, 1973

The reaction rate constants of 2-thiophenesulfonyl chloride with some substituted anilines have been measured in methanol at different temperatures. The reaction is second order overall and pseudo first order with respect to each reactant. The rate constants value is greater with electron-donating substituents, while it is lower with electron-withdrawing groups. The activation parameters and the slopes of the Hammett (−2.25) and Brønsted (0.53) plots are similar to those of the reaction of benzenesulfonyl chloride with anilines, showing that the reaction mechanism is the same for the two substrates, although 2-thiophenesulfonyl chloride reacts more slowly. The Tommila equation points out that the sulfur atom, the reaction center, is less positively charged, and thus less reactive toward nucleophiles, than that of benzenesulfonyl chloride.

Previously the mechanism of the reaction of 2-thenoyl chloride with some meta- and para-substituted anilines was investigated.[1] Following this research we report in this paper the kinetics of the reaction of 2-thiophenesulfonyl chloride with a series of substituted anilines to verify the reactivity in comparison with the analogous reaction of benzenesulfonyl chloride, which have been widely studied recently.[2–7]

The reaction between 2-thiophenesulfonyl chloride and aniline in methanol takes place quantitatively according to eq 1.



$$\text{2-thiophene-SO}_2\text{Cl} + 2\text{H}_2\text{NC}_6\text{H}_4\text{X} \rightarrow \text{2-thiophene-SO}_2\text{NHC}_6\text{H}_4\text{X} + \text{XC}_6\text{H}_4\overset{+}{\text{N}}\text{H}_3\text{Cl}^- \quad (1)$$

X = H, *m*-CH_3, *p*-CH_3, *m*-OCH_3, *p*-OCH_3, *m*-Cl, *p*-Cl

The rate of reaction 1 was measured by continuous titration of the acid produced (see Experimental Section).

We found that the reaction of 2-thiophenesulfonyl chloride with anilines follows second-order kinetics, first order with respect to each reactant.

By the comparison of the slopes of the Hammett and Brønsted plots it seems that the reaction mechanism is the same as for benzenesulfonyl chloride and anilines,[2] although the rates observed with 2-thiophenesulfonyl chloride are lower, probably because of the thiophene conjugative effect on the sulfonyl group which also makes the sulfur atom less electrophilic than that of benzenesulfonyl chloride as the Tommila equation shows.

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(7) E. Ciuffarin, L. Senatore, and M. Isola, *J. Chem. Soc., Perkin Trans. 2*, 468 (1972).

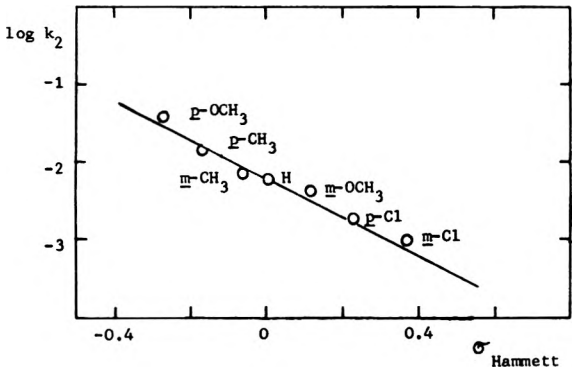


Figure 1.—Hammett plot for the reaction of 2-thiophenesulfonyl chloride with substituted anilines in methanol at 25°.

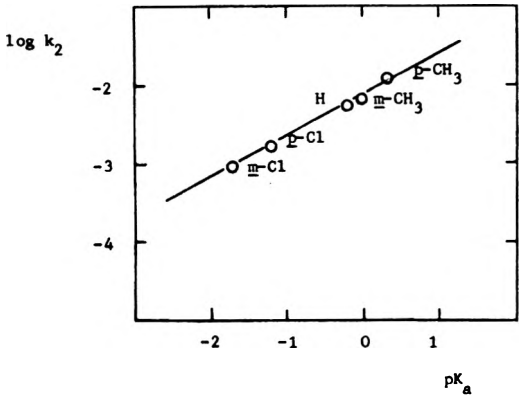


Figure 2.—Plot of log k_2 at 25° for the reaction of 2-thiophenesulfonyl chloride with substituted anilines in methanol against the pK_a of protonated anilines in methanol at 25° (Brønsted plot).

Results and Discussion

The reaction of 2-thiophenesulfonyl chloride with a large excess of aniline in methanol is pseudo first order with respect to 2-thophenesulfonyl chloride.

The plot of pseudo-first-order rate constants at 25° against aniline concentration is linear (Table I),

TABLE I
RATE CONSTANTS FOR THE REACTION OF 2-THIOPHENESULFONYL CHLORIDE WITH ANILINE IN METHANOL AT 25°

No.	Initial concn of reagents, mol l.$^{-1}$: Sulfonyl chloride	Aniline	$k_1 \times 10^4$, sec^{-1}	$k_2 \times 10^4$, l. mol^{-1} sec^{-1}
1	0.00158	0.0390	2.14	5.49
2	0.00308	0.0915	5.29	5.78
3	0.00393	0.127	7.28	5.73
4	0.00467	0.143	7.83	5.48

showing that the reaction is first order also with respect to aniline and that the rate constants do not change appreciably with the dilution.

The kinetics of the reaction is thus as expected from eq 1 with the rate law eq 2.

$$\text{rate} = k_2[C_4H_3SSO_2Cl][H_2NC_6H_4X] \quad (2)$$

The reaction was studied at different temperatures; the second-order overall rate constants, obtained by dividing the first-order observed rate constants by aniline concentration, are reported in Table II.

This assumption results in little error since k_{solv} is negligible[8] (eq 3).

$$k_{obsd} = k_{solv} + k_2[\text{aniline}] \quad (3)$$

The activation parameters are listed in Table III, together with the standard deviations (s) and the linear correlation coefficients (r).

Small amounts of water in methanol have no effect on the observed first-order rate constants, since duplicate runs in methanol containing 2% water gave only slightly higher rate constants.

It was not possible to consider the m- and p-nitroaniline rate constants, because, with these scarcely reactive anilines, apparently there is competition with solvolysis reactions.

Table II shows that electron-donating substituents in aniline increase the rate, while electron-withdrawing groups decrease the rate.

Figure 1, in which the Hammett plot is reported, shows that the reaction rate depends on the electron density on the nitrogen atom of aniline. The sensitivity of the rates to substituents in the aniline (ρ −2.25) is comparable with that found for other analogous reactions.[2,9] Moreover, we found that the activation energies (Table III) are linearly correlated with the substituent constants; in fact, the substituent of larger electronic availability and the more reactive (p-OCH_3) shows the lowest activation energy, while, on the contrary, the most deactivating substituent (m-Cl) shows the highest E_a.

The large negative entropies of activation are as expected for bimolecular reactions with a highly polar transition state.[10]

The slope of the Brønsted plot (Figure 2), obtained using the pK_a values of anilines calculated in methanol,[11] gives the reaction sensitivity to the basicity of the nucleophile and is related to the relative amount of bond formation in the transition state.[12]

The value obtained (β 0.53) can be ascribed to the partial formation of the sulfur–nitrogen bond in the transition state;[13] this value is comparable with that calculated by us from Rogne data[2] using the pK_a values of anilines in methanol, for the reaction of benzenesulfonyl chloride with anilines (β 0.52).

The reaction rate constants ratio of benzenesulfonyl chloride and 2-thiophenesulfonyl chloride with anilines ($k_{PhSO_2Cl}/k_{ThSO_2Cl}$ = 13.5 ± 1.5) is higher than that of benzoyl chloride and thenoyl chloride (k_{PhCOCl}/k_{ThCOCl} = 2.5 ± 0.5) with anilines.[1]

The lower reaction rate of 2-thiophenesulfonyl chloride with respect to benzenesulfonyl chloride can be ascribed to the greater conjugative effect of the thiophene ring system on the sulfonyl group, which makes the sulfur atom less reactive toward nucleophiles. The Tommila equation[14] points out that

(8) O. Rogne, *J. Chem. Soc. B*, 727 (1970).

(9) E. Ciuffarin and L. Senatore, *J. Chem. Soc. B*, 1680 (1970).

(10) A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 7.

(11) M. Kilpatrick and C. A. Aremberg, *J. Amer. Chem. Soc.*, **75**, 3812 (1953).

(12) J. E. Leffler and F. Grunwald, "Rates and Equilibria of Organic Reaction," Wiley, New York, N. Y., 1963, pp 238–242; R. A. Marcus, *J. Phys. Chem.*, **72**, 891 (1968).

(13) L. T. Stangeland, L. Senatore, and E. Ciuffarin, *J. Chem. Soc., Perkin Trans.*, **2**, 852 (1972).

(14) E. Tommila and T. Vihavainen, *Acta Chem. Scand.*, **22**, 3224 (1968).

Table II

Second-Order Rate Constants for the Reaction of 2-Thiophenesulfonyl Chloride with Meta- and Para-Substituted Anilines in Methanol

Registry no.	No.	Substituent	pK_a (25°) Water[a]	pK_a (25°) Methanol[b]	$k_2 \times 10^3$, l. mol^{-1} sec^{-1} 15°	25°	35°	40°	45°
62-53-3	1	H	4.596	−0.195	2.616	5.620	11.05		20.80
108-44-1	2	*m*-CH_3	4.712	−0.0079	3.608	6.901	15.18		25.52
106-49-0	3	*p*-CH_3	5.084	0.3426	6.705	13.52	26.38		45.32
536-90-3	4	*m*-OCH_3	4.200		1.747	4.035	7.336		15.72
104-94-9	5	*p*-OCH_3	5.357		18.98	32.82	56.54	69.81	87.30
108-42-9	6	*m*-Cl	3.521	−1.727		0.9739	2.441	3.294	4.892
106-47-8	7	*p*-Cl	3.982	−1.199	0.6325	1.794	3.746		6.789

[a] P. D. Bolton and F. M. Hall, *Aust. J. Chem.*, 20, 1797 (1967); 21, 939 (1968); *J. Chem. Soc. B*, 259 (1969). [b] M. Kilpatrick and C. A. Aremberg, *J. Amer. Chem. Soc.*, 75, 3812 (1953).

Table III

Activation Parameters for the Reaction Rates in Table II

Substituent	E_A, kcal mol^{-1}	*s*	*r*	ΔS^* at 25°, cal mol^{-1} °K^{-1}	Log *A*
H	12.50	0.03	0.9999	−28.70	6.95
m-CH_3	12.08	0.12	0.9980	−30.10	6.76
p-CH_3	11.61	0.06	0.9995	−29.95	6.68
m-OCH_3	13.02	0.11	0.9984	−27.69	7.18
p-OCH_3	9.28	0.03	0.9996	−36.03	5.35
m-Cl	15.00	0.15	0.9978	−23.70	8.05
p-Cl	14.29	0.22	0.9950	−25.16	7.73

the reaction center is less positively charged in the thiophene derivative. This is depicted in eq 4 below

$$\ln \frac{k_s}{k_u} = -\frac{e_x \delta e_s}{RTr_1} + \frac{e_y \delta e_s}{RT}\left(\frac{1}{r_0} - \frac{1}{r_2}\right) - \frac{\Delta W}{RT} \qquad (4)$$

where k_s = the rate constant of the substituted compound, k_u = the rate constant of the unsubstituted compound, e_x, e_y, e_s = the effective electric charge on the attacking agent, on the leaving group, and on the atom reaction center, respectively, δe_s = the positive or negative incremental change in charge e_s by the substituent introduced in the substrate molecule, r_0 = the distance S–Y in the unperturbed substrate molecule, r_1 and r_2 = the distances X–S and S–Y in the transition state, and $\Delta W/RT$ is the nonelectrostatic part of ln (k_s/k_u) in the reaction

$$X + S\overset{r_0}{-}Y \longrightarrow X\overset{r_1}{-}S\overset{r_2}{-}Y \longrightarrow \text{products}$$

where S is the center of the reaction, X is the attacking agent, and Y is the leaving group.

In Table IV the ratio ln (k_s/k_u) at 25° for the reaction of some benzenesulfonyl chloride derivatives[2]

Table IV

Sulfonyl chloride	X	ln (k_s/k_u)[a]
X–C$_6$H$_4$–SO_2Cl	*p*-NO_2	1.81
	H	0.00
	p-CH_3	−0.37
	p-OCH_3	−0.91
2-thiophenesulfonyl chloride		−2.50

[a] k_u = reaction rate constant of benzenesulfonyl chloride with aniline.

and 2-thiophenesulfonyl chloride with aniline are reported.

According to eq 4, since e_x is negative, the term $-e_x/RTr_1$ is positive. Thus, if the increment δe_s is positive, and if the term $-e_x\delta e_s/RTr_1$ is greater than the terms $e_y\delta e_s/RT(1/r_0 - 1/r_2)$ and $\Delta W/RT$, ln (k_s/k_u) is positive; if the increment δe_s is negative, also ln (k_s/k_u) is negative, which is in accordance with the experimental results (Table IV).

The ln (k_s/k_u) value for 2-thiophenesulfonyl chloride (−2.50) is more negative than that of benzenesulfonyl chloride, showing that the reaction center in the thiophene derivative is less positively charged.

Experimental Section

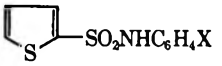
Materials.—2-Thiophenesulfonyl chloride was obtained according to the Hartough procedure,[15] bp 92–93° (1 mm), mp 32–33° from petroleum ether (bp 30–60°).

The various anilines are commercial products which were purified to constant melting point or boiling point by recrystallization or distillation. Methanol containing ~0.04% water (Carlo Erba) was used throughout.

All the sulfonanilides were synthesized by adding to a solution containing 0.065 mol of aniline in methanol (50 ml) 0.030 mol of 2-thiophenesulfonyl chloride in methanol (10 ml). The reaction was kept until completion; then the methanol was evaporated and the residue was treated with aqueous 40% sodium hydroxide and extracted twice with ether or filtered. The aqueous layer was acidified and the precipitate was filtered off, washed, and crystallized. In all cases the yield was ~95% in agreement with eq 1. The physical constants of sulfonanilides are reported in Table V.

Table V

Physical Constants of 2-Thiophenesulfonanilides[a]



No.	Registry no.	X	Mp, °C	Formula
1	39810-46-3	H[b]	99–100	
2	39810-47-4	*m*-CH_3[c]	88–89	$C_{11}H_{11}NO_2S_2$
3	39810-48-5	*p*-CH_3[c]	115	$C_{11}H_{11}NO_2S_2$
4	39810-49-6	*m*-OCH_3[c]	72–73	$C_{11}H_{11}NO_3S_2$
5	39810-50-9	*p*-OCH_3[c]	104	$C_{11}H_{11}NO_3S_2$
6	39810-51-0	*m*-Cl[c]	114	$C_{10}H_8ClNO_2S_2$
7	39810-52-1	*p*-Cl[c]	115	$C_{10}H_8ClNO_2S_2$

[a] All the compounds were crystallized from aqueous ethanol. [b] L. Weitz, *Ber.*, 17, 799 (1884); A. P. Terent'ev and G. M. Kadatskii, *Zhr. Obshch. Khim.*, 22, 153 (1952); *Chem. Abstr.*, 46, 11178 (1952). [c] Satisfactory combustion analytical data for C, H, N (±0.2%) were provided for these compounds: Ed.

Kinetic Procedure.—Rate measurements were done by a pH meter Jonosis type pH-Q_3 by titration of the acid produced with 0.1 *N* sodium hydroxide. The pH meter was standardized before each run with a buffer. The electrode was combined (glass, saturated calomel) type Ingold. The reaction vessel was sur-

(15) H. D. Hartough, "Thiophene and Its Derivatives," Interscience, New York, N. Y., 1952, p 513.

rounded by a jacket for circulation of water at constant temperature (±0.05°) and mounted on a magnetic stirrer.

In a typical run a solution of *ca.* 0.01 mol of aniline in methanol (90 ml) was placed in the reaction vessel. The reaction was started by adding a solution of *ca.* 0.0003 mol of 2-thiophenesulfonyl chloride in methanol (10 ml). At the initial time, the reagents concentrations were *ca.* 0.003 mol/l. for 2-thiophenesulfonyl chloride and *ca.* 0.08–0.16 mol/l. for the various anilines.

The observed pseudo-first-order rate constants were calculated from conventional plots of log $(a - x)$ against time from the slope obtained using the least squares method. The correlation coefficients were always 0.995. In all cases the reaction follows the pseudo-first-order kinetics well to at least 70% completion. All rates were run in duplicate. The experimental data are well reproducible within ±4%.

The second-order rate constants were obtained by dividing the pseudo-first-order rate constants by the aniline concentration.

The activation energies and log A values were calculated in the usual way from an Arrhenius plot by the least squares method.

The entropies of activation, ΔS^*, were computed for 25° by eq 5.[16]

$$\Delta S^* = 4.576 (\log A - \log T) - 49.21 \quad (\text{cal/mol°K}) \quad (5)$$

Registry No.—2-Thiophenesulfonyl chloride, 16629-19-9.

Acknowledgment.—The authors are grateful to the Consiglio Nazionale delle Ricerche (C. N. R.) for the financial support.

(16) M. Simonetta, "Chimica Fisica," Vol. I, Manfredi, Ed., Milano, 1966, p 278.

Kinetics and Mechanisms of Electrophilic Addition. I. A Comparison of Second- and Third-Order Brominations

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Received February 6, 1973

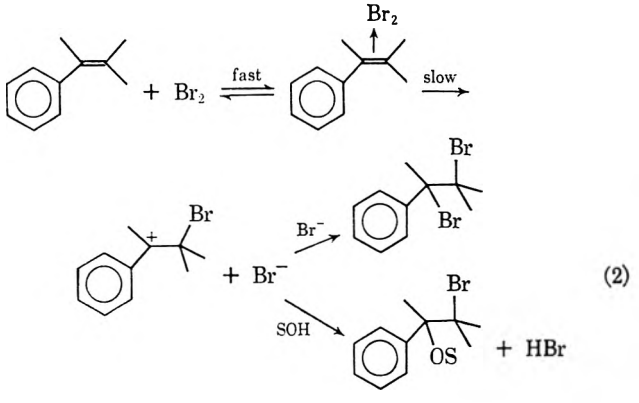
The rates of bromination of several ring-substituted styrenes have been measured as a function of temperature under both dominant second-order (k_2) and dominant third-order (k_3) conditions in acetic acid. The k_2 process is enthalpy controlled, while k_3 is entropy controlled. The ρ values (*vs.* σ^+) for each process are nonetheless very similar (for k_2, $\rho = -4.8$; for k_3, $\rho = -4.6$) suggesting that similar cationic intermediates are involved. This is supported by product analysis, which shows virtually identical dibromide–acetoxybromide distribution under either k_2 or k_3 conditions. The most probable mechanism of the k_3 process is proposed.

The rates of bromine addition to typical olefins (or acetylenes) in polar solvents can be described by the general rate equation[1] (1). Thus bromination

$$-d[Br_2]/dt = [\text{olefin}](k_2[Br_2] + k_3[Br_2]^2 + k_{Br^-}[Br_2][Br^-]) \quad (1)$$

(to give dibromides and solvent-incorporated products) can arise from one or more of several competing mechanistic pathways, depending on the reaction conditions.

The last term (involving k_{Br^-}) is only important in the presence of significant bromide concentrations and has been ascribed to either a bromide ion catalyzed AdE3 process[2] or to a kinetically equivalent AdE2 mechanism[3,4] involving tribromide as the electrophile. In the absence of bromide, and at low bromine concentrations ($<10^{-3}$ M), only the first term (involving k_2) is important. This simple second-order process has been the most widely investigated mechanistically. Based on a combination of kinetic studies,[4-7] product regiospecificity[8,9] and stereochemistry,[10] and spectral evidence,[11,12] this mechanism of bromination of styrenes can be formulated as an AdE2 reaction proceeding through a bromine–olefin charge-transfer complex to give an essentially open (or at most a weakly bridged) carbonium ion intermediate[13] (eq 2). However, much



(2)

less is known[15] about the corresponding higher order process (k_3) which becomes important at higher bromine concentrations ($\gtrsim 10^{-2}$ M), mainly because the observed rates are very high under these conditions. Nonetheless, many early kinetic studies[1,14] and most preparative brominations have been carried out under conditions where this process would have been significant or even predominant. It is therefore important to determine and compare the characteristics

(1) I. K. Walker and P. W. Robertson, *J. Chem. Soc.*, 1515 (1939); I. Ting and P. W. Robertson, *ibid.*, 628 (1947).

(2) N. Kanyaev, *J. Gen. Chem. USSR*, **29**, 825 (1959); J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 3332 (1970).

(3) J. R. Atkinson and R. P. Bell, *J. Chem. Soc.*, 3260 (1963); R. P. Bell and M. Pring, *J. Chem. Soc. B*, 1119 (1966).

(4) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1483 (1969).

(5) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 2944 (1970).

(6) K. Yates and W. V. Wright, *ibid.*, **45**, 167 (1967).

(7) C. Gebelein and G. D. Frederick, *J. Org. Chem.*, **37**, 2211 (1972).

(8) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

(9) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1469, 1477 (1969).

(10) These product analyses have been carried out under conditions where the k_2 process is predominant.[9]

(11) J. E. Dubois and F. Garnier, *J. Chim. Phys.*, **63**, 351 (1966); *Spectrochim. Acta*, **23A**, 2279 (1967).

(12) J. E. Dubois and F. Garnier, *Tetrahedron Lett.*, 3961 (1965).

(13) For additions to simple alkenes such as 2-butenes, this intermediate is, on the contrary, a more or less symmetrically bridged cyclic bromonium ion[9] of the type first proposed by Roberts and Kimball.[14]

(14) I. Roberts and G. E. Kimball, *J. Amer. Chem. Soc.*, **59**, 947 (1937).

(15) (a) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, Amsterdam, 1966. See also B. E. Swedlund and P. W. Robertson, *J. Chem. Soc.*, 630 (1947). (b) The corresponding second- and third-order processes in aromatic bromination have been studied by R. M. Keefer and R. J. Andrews, *J. Amer. Chem. Soc.*, **78**, 255, 3637 (1956), and U. P. Zimmerman and E. Berliner, *ibid.*, **84**, 3953 (1962).

TABLE I

SECOND-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE BROMINATION OF STYRENES IN ACETIC ACID

Substituent	n^a	t, °C	k_2, M^{-1} sec^{-1}	$\Delta H^{\ddagger}$,[b] kcal mol^{-1}	$\Delta S^{\ddagger}$,[b] cal deg mol^{-1}
4-NO_2[c]	2	25.0	3.58×10^{-3}		
	2	45.0	9.95×10^{-3}	9.0	−39.5
3-NO_2[c]	2	25.0	9.61×10^{-3}		
3,4-di-Cl[c]	3	25.0	8.33×10^{-2} [d]		
	1	29.0	1.21×10^{-1}		
	3	33.0	1.52×10^{-1}	8.5 ± 1.1[d]	−34.8 ± 3.6[d]
	3	40.0	1.94×10^{-1}		
	2	45.0	2.30×10^{-1}		
3-Cl[c]	3	25.0	2.15×10^{-1}		
4-Br[e]	2	25.1	2.53		
H[e]	2	18.0	11.0		
	3	25.0	14.3	4.7 ± 0.7	−37.6 ± 2.3
	2	34.9	18.2		
4-F[e]	3	25.1	25.3		
4-Me[e]	4	25.1	1.07×10^{3}		

[a] Number of kinetic runs. [b] Errors quoted are standard deviations. [c] Data from ref 5. [d] Values corrected from those previously reported incorrectly for this compound in ref 5. [e] This work. Registry numbers are, respectively, 2039-82-9, 100-42-5, 405-99-2, and 622-97-9.

of the k_3 (or termolecular) bromination process with those of the simpler k_2 (or bimolecular) process.

The main objective of the present study was to use the stopped-flow technique to study the rates of the k_3 process for ring-substituted styrenes and to compare its structure-reactivity dependence with that of the k_2 process. Secondary aims were to compare the activation parameters and product distributions for the two parallel bromination processes.

Results and Discussion

Rate Constants.—A previously reported correlation[5] of log k *vs.* σ^+ for bromination of styrenes in acetic acid ($\rho = -4.7$, $r = 0.997$) was based largely on deactivated styrenes, because of the high rates of bromination of the more activated compounds. This linear free-energy relationship has now been extended, using stopped-flow measurements, by determining several second-order bromination rate constants for more reactive olefins, also in acetic acid. These new values are listed in Table I, along with those reported previously. One value of k_2 previously reported incorrectly[5] (for 3,4-dichlorostyrene) has been corrected. These rate constants now extend over about six powers of ten in reactivity. The present values of k_2 for the eight substituted styrenes, listed in Table II, also correlate well[16] with σ^+ ($\rho = -4.8$, $r = 0.997$). Considerably more scatter is obtained by plotting these log k_2 values *vs.* σ ($\rho = -5.3$, $r = 0.985$).

Values of the third-order rate constants (k_3) for bromination of seven of the eight substituted styrenes have also been determined in acetic acid and are reported in Table III. Correlation of these log k_3 values with σ^+ again gives significantly less scatter ($\rho = -4.6$, $r = 0.995$) than a corresponding plot *vs.* σ ($\rho = -5.0$, $r = 0.988$). The values of k_3 obtained at 25° are also listed in Table II with the corresponding values of k_2 for comparison.[17]

TABLE II

LINEAR FREE-ENERGY RELATIONSHIPS FOR SECOND- AND THIRD-ORDER BROMINATIONS OF STYRENES IN ACETIC ACID AT 25°

Substituent	Log k_2[a]	Log k_3[b]	σ[c]	σ^+[d]
4-NO_2	−2.45		0.778	0.790
3-NO_2	−2.02	1.12	0.710	0.674
3,4-Cl_2	−1.08	2.12	0.572[e]	0.476[e]
3-Cl	−0.67	2.49	0.373	0.399
4-Br	+0.40	3.585	0.232	0.150
H	+1.155	4.39	0	0
4-F	+1.40	4.63	0.062	−0.073
4-Me	+3.03	5.69	−0.170	−0.311
	k_2 *vs.* σ	k_2 *vs.* σ^+	k_3 *vs.* σ	k_3 *vs.* σ^+
ρ values	−5.29	−4.83	−4.98	−4.63
	0.985	0.997	0.988	0.9995

[a] Units in M^{-1} sec^{-1}. [b] Units in M^{-2} sec^{-1}. [c] From D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958). [d] From ref 25. [e] From ref 4. [f] Correlation coefficient.

The large negative ρ value previously reported[4,5,18] for the k_2 process, the correlation with σ^+ rather than σ, the nonstereospecific nature of the addition to the analogous *cis*- and *trans*-1-phenylpropenes,[9,19] and the completely regiospecific mode of addition[6,9] (in the Markovnikov sense) for the solvent-incorporated products have all been interpreted in terms of a transition state leading to an essentially open α-phenylcarbonium ion intermediate. The very similar behavior of the rate constants for the k_3 process in the ρ–σ^+ relationship[20] points to a transition state for the termolecular bromination having a very similar struc-

(16) The point for the 4-methyl compound is significantly off the line. The reasons for this are not understood. In a similar correlation of bromination rates in methanol by Dubois and coworkers,[18] albeit using global rate constants, the point for 4-methyl does not deviate. This suggests that the present deviation is not mechanistically significant. The present correlation is significantly improved by omitting the 4-methyl point ($\rho = -4.6$, $r = 0.9996$).

(17) Comparison of the expected rates of these competing bimolecular and termolecular brominations shows that, in general, the first would dominate the observed rate for bromine concentrations $< 5 \times 10^{-3}$ M, whereas the second would be predominant at $[Br_2] > 10^{-3}$ M.

(18) J. E. Dubois and A. Schwarcz, *Tetrahedron Lett.*, 2167 (1964).

(19) R. C. Fahey and H. J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1967).

(20) It is reassuring that a linear free-energy relationship is also obeyed for the termoleecular process, despite a previous report[4] that the k_3 process did not follow the Hammett equation very well. However this was based on an attempted separation of the k_2 and k_3 rate constants in a bromine concentration region where the k_3 process was a minor contributor to the overall rate.

TABLE III
THIRD-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE BROMINATION OF STYRENES IN ACETIC ACID

Substituent	n^a	t, °C	k_3, M^{-2} sec^{-1}	$\Delta H^{\ddagger}$,[b] kcal mol^{-1}	$\Delta S^{\ddagger}$,[b] cal deg mol^{-1}
3-NO_2	2	18.3	12.6		
		25.0	(13.3)[c]	0.87	−50.5
	2	45.0	15.6		
3,4-Cl_2	4	17.9	1.15×10^2		
	4	25.0	1.13×10^2		
	3	31.9	1.25×10^2	0.93 ± 0.24	-45.8 ± 0.8
	3	39.1	1.40×10^2		
	5	45.1	1.49×10^2		
3-Cl	3	25.1	3.09×10^2		
4-Br	4	25.1	3.85×10^3		
H	4	18.5	2.30×10^4		
	2	25.0	2.44×10^4		
	2	35.1	2.41×10^4	0.01 ± 0.28	-38.5 ± 0.9
	4	45.1	2.53×10^4		
4-F	2	16.9	4.19×10^4		
	3	24.9	4.25×10^4		
	3	34.9	4.65×10^4	1.14 ± 0.36	-33.5 ± 1.2
	2	45.1	5.38×10^4		
4-Me[d]	1	25.1	4.9×10^5		

[a] Number of kinetic runs. [b] Errors quoted are standard deviations. [c] Value estimated from rate constants at other temperatures. [d] This compound reacts at a rate near the limit of the stopped-flow apparatus. Estimated error in this single determination is ~10%.

ture and charge development to that for the bimolecular process, at least as far as the cationic portion is concerned.

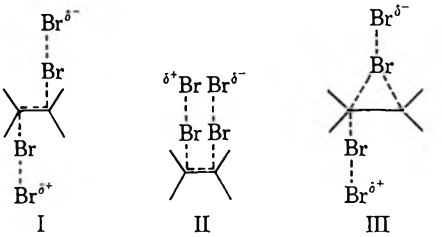
Activation Parameters.—Values of k_2 and k_3 measured at various temperatures are reported in Tables I and III, respectively, for several of the substituted styrenes, along with the activation parameters calculated from these data by standard methods.[21] It can be seen from Table I that $\Delta S^{\ddagger}$ is essentially independent of structure for the bimolecular process ($\Delta S^{\ddagger} \sim -37 \pm 3$ cal deg mol^{-1})[22] with structural effects on rate being reflected in the $\Delta H^{\ddagger}$ values. Thus electron-withdrawing groups retard the bimolecular electrophilic addition reaction by increasing $\Delta H^{\ddagger}$ significantly.

In contrast, the $\Delta H^{\ddagger}$ values for the third-order process are very low and essentially independent of structure ($\Delta H^{\ddagger}_{ave} \approx 0.7$ kcal mol^{-1}), while the large unfavorable negative $\Delta S^{\ddagger}$ values dominate the reaction rate. In fact the k_3 series is essentially isoenthalpic while the second-order rates appear to form an isoentropic series. Such large negative values of $\Delta S^{\ddagger}$ (−34 to −51 cal deg mol^{-1}) have previously been observed[24] for the third-order bromination of acetylenes and are not unexpected for a highly polarized termolecular transition state. Very low values of $\Delta H^{\ddagger}$ for the k_3 process were suggested by early workers,[1] who observed temperature coefficients for the rate of this process which were very close to zero or even negative. These workers[1,15a] further suggested that this was indicative of an initial preequilibrium step, followed by rate-determining attack of a third molecule.

Product Distributions.—The products of bromine addition to styrene and to 3,4-dichlorostyrene in acetic acid were analyzed first under conditions where the second-order process dominates the rate and then where the third-order process is predominant. Both processes give a mixture of 1,2-dibromophenylethanes (dibromides) and 1-acetoxy-2-bromophenylethanes (acetoxybromides). The ratio of dibromide to acetoxybromide for bromination of styrene under k_2 conditions ($[Br_2]_0 < 10^{-3}$ M) was 79:21 and under k_3 conditions ($[Br_2]_0 \geq 10^{-2}$ M) was 83:17. For 3,4-dichlorostyrene the corresponding product ratios were 77:23 under k_2 conditions and 78:22 under k_3 conditions. These nearly identical product distributions again imply that very similar intermediates and product-determining steps are involved in the two processes. Although no stereochemical information can be obtained from styrene additions, it has been previously shown[9] that product stereoselectivity is essentially independent of bromine concentration for bromine additions to *cis*- and *trans*-1-phenylpropenes in acetic acid. Thus it seems reasonable that each process (k_2 and k_3) gives almost identical product distribution and stereochemistry.

Proposed Mechanism of Third-Order Bromination.—The above results for analogous k_2 and k_3 brominations may now be discussed in terms of possible mechanisms for the latter process. Firstly, the very similar ρ–σ^+ correlations point to considerable positive charge development on the α carbon at the k_3 transition state and are also similar to those typically observed in SN1 type solvolyses (*e.g.*, cumyl chloride solvolysis in ethanol has $\rho = -4.67$).[25] This is also supported by the observed regiospecificity of the solvent-incorporated products in the k_3 process. Similarly the identical stereoselectivity observed under either k_2 or k_3 conditions points to a similar degree of openness in the product-determining carbonium ion intermediates.

These kinetic and product results do not support transition states[14] in which both nucleophilic and electrophilic bromine attack occurs at the two olefinic carbons, as in structures I–III. It would be expected



I II III

that these AdE3 type transition states would have a considerably different charge distribution[26] from that in the k_2 process (which involves an AdE2 mechanism). Further, such transition states would lead to stereospecific (anti from I and III, syn from II) addition for the k_3 process only, whereas both k_2 and k_3 processes show variable stereoselectivity.[9] In addition, solvent

(21) J. F. Bunnett, in "Technique of Organic Chemistry," Vol. VIII, part 1, S. L. Friess, E. S. Lewis and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, p 199.

(22) These values are significantly more negative than those reported[23] for the second-order brominations of symmetrically substituted dialkyl- and diphenylethylenes, where $\Delta S^{\ddagger} \approx -24$ cal deg mol^{-1}. This may indicate more charge development and increased solvent restriction in the styrene transition states.

(23) K. Yates and R. S. McDonald, *J. Amer. Chem. Soc.*, **93**, 6297 (1971).

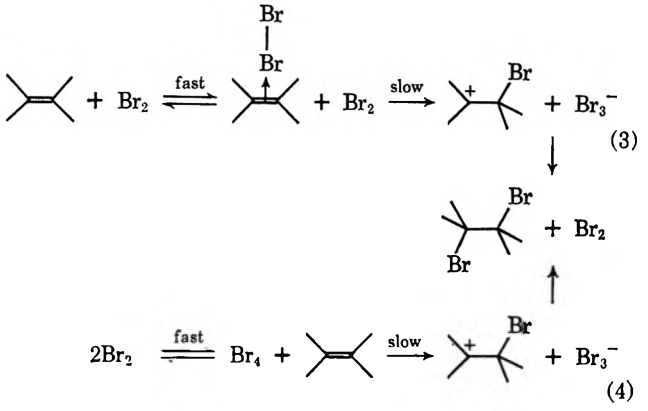
(24) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 3332 (1970).

(25) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(26) For example, the bromide-catalyzed addition of bromine to phenylacetylene, which involves a similar AdE3 process, has a considerably different ρ value from that in the analogous, simple second-order addition, is completely anti stereospecific, and gives no solvent-incorporated products.[24]

incorporation occurs to the same extent in both processes, whereas I–III would be expected to give no solvent-incorporated products.

A fully synchronous termolecular process is unlikely, and probably few if any truly termolecular processes are known. The very low $\Delta H^{\pm}$ values for k_3 are more easily interpreted in terms of an initial preequilibrium association, followed by rate-determining attack of a third molecule. However, two kinetically indistinguishable mechanisms of this type have been suggested.[1,15a] These involve rate-determining bromine attack on a bromine-olefin complex (mechanism 3) or bromination of the olefin by a Br_4 species (mechanism 4). Although 1:1 bromine–olefin com-



plexes have been observed spectroscopically,[11,12] evidence that these intermediates lie on the reaction coordinate for bromination is largely circumstantial.[7,11,27] The analogous iodine–olefin complexes are well characterized[23] and are known to be formed exothermically. Also, semiempirical MO calculations predict favorable associations between olefins and halogens.[29]

The kinetic importance of a Br_4 species is difficult to assess. While such species are believed to be present in the pure solid and liquid phases of halogens,[30] there is no evidence for such association in the gas phase or in solution. Even in a solvent as weakly polar as acetic acid, bromine–solvent interactions would be expected to be stronger than those between Br_2 molecules. Thus, in fact there is no evidence for Br_4 species in solution while good evidence for bromine–olefin complexes does exist.

Evidence has been discussed previously that the bimolecular k_2 process proceeds *via* olefin–bromine charge-transfer-complex formation followed by rate-determining solvent-assisted bromine–bromine bond cleavage. This would occur most readily in solvents capable of solvating an anionic centre. In solvents incapable of such solvent stabilization, the k_3 term becomes predominant even at low $[Br_2]$. Thus, one may envisage that, in the k_3 process, a bromine molecule is serving the function of catalytically aiding the Br–Br bond cleavage[31] by forming a charge dispersed tribromide ion. Such a bromine assised AdE2 process would lead to the well-documented tribromide ion[32] and a similar cationic intermediate (the β-bromophenylethyl cation) to that involved in the simpler k_2 process.

The characteristics of the k_2 and k_3 bromination processes are summarized in Table IV. A major point of

TABLE IV
CHARACTERISTICS OF k_2 AND k_3 BROMINATION PROCESSES FOR SUBSTITUTED STYRENES

	k_2	k_3
Rate constants[a]	10^{-2}–10^{3} M^{-1} sec^{-1}	10^{1}–10^{6} M^{-2} sec^{-1}
Region of predominance	$[Br_2] < 5 \times 10^{-3}$ M	$[Br_2] > 10^{-2}$ M
Dibromide:acetoxybromide	79:21[b]	83:17[b]
	77:23[c]	78:22[c]
Stereoselectivity	Anti > syn[d]	Anti > syn[d]
Regioselectivity	Regiospecific (M)	Regiospecific (M)
ρ value (*vs.* σ^+)	−4.8	−4.6
$\Delta H^{\pm}$ range	5–10 kcal	~1 kcal
$\Delta S^{\pm}$ range	*Ca.* −37	−(34–51)

[a] In anhydrous acetic acid. [b] For styrene. [c] For 3,4-dichlorostyrene. [d] See ref 9.

difference between the k_2 and k_3 processes is the more negative $\Delta S^{\pm}$ range for k_3. This is understandable in terms of the proposed mechanism, since not only is a third molecule involved, but also the incipient tribromide ion formation probably requires a fairly rigid linear arrangement of the four bromine atoms.

Experimental Section

The sources and purification of the substituted styrenes, bromine, and the solvent, anhydrous acetic acid, have been previously described.[9]

Kinetic Studies.—The second- and third-order rate constants were measured on a Durrum Gibson stopped-flow kinetics spectrophotometer. The output was coupled into a Tektronix storage oscilloscope which was frequently calibrated on the vertical (per cent transmittance) and horizontal (time) axes. The instrument had a mixing time of 2–3 msec and a 2-cm observation cell. The reaction was monitored by observing the decrease in bromine absorbance at 490 nm using a 0.1-mm slit width. The time constant setting was routinely ≤0.1 of the time/division setting on the horizontal scope axis. Temperature control was achieved by the use of a Tamson TE-9 constant-temperature circulating bath equipped with a PBC-4 bath cooler. The temperature remained fairly constant (±0.05°) during the equilibration period. The instrument was allowed to stabilize and the system equilibrated thermally for 3–4 hr before any kinetic runs were attempted. The flow system was thoroughly flushed with anhydrous acetone and then with anhydrous acetic acid. The 0% and 100% transmittance readings were adjusted on the scope.

One drive and one reservoir syringe was used for the bromine solution and the other pair of syringes for the olefin solution. The system was flushed with a stock bromine solution (in twice the concentration of that of the initial bromine concentration in the kinetic run) until a constant per cent transmittance reading was observed. Knowing the absorbance of the stock bromine solution and the extinction coefficient of bromine at 490 nm, the initial bromine concentration during the kinetic run could be calculated. The stock olefin solution was prepared by weighing an appropriate amount of styrene into a volumetric flask and diluting to the mark with acetic acid. The stock olefin concentration was twice the desired concentration during the kinetic run. To simplify the kinetics, the value of $[olefin]_0$ was always at least in 20-fold excess over that of $[Br_2]_0$ so that all runs were

(27) R. Foster, "Organic Charge-Transfer Complexes," Academic Press, New York, N. Y., 1969, p 322.
(28) J. G. Traynham and J. R. Olechowski, *J. Amer. Chem. Soc.*, **81**, 571 (1959).
(29) B. Nelander, *Theor. Chim. Acta*, **25**, 382 (1972).
(30) R. S. Mulliken, *J. Amer. Chem. Soc.*, **72**, 600 (1950).
(31) Thus lowering the enthalpy of activation.
(32) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. II, Oxford University Press, London, 1950, p 1142, 1143. E. H. Wiebenga, E. E. Havinga, and K. H. Boswijk, *Advan. Inorg. Chem. Radiochem.*, **3**, 133 (1961).

pseudo first order in bromine. The flow system was flushed thoroughly with the olefin solution and the scope line normally returned to the 100% transmittance reading previously set. The drive syringes were then filled with the solutions to be mixed and allowed to equilibrate thermally for 30–45 min.

The second-order kinetic runs were carried out using $[Br_2]_0 < 5 \times 10^{-4}$ M to ensure that only the contribution from the bimolecular process was significant over most of the kinetic run. This necessitated use of the expanded transmittance scales such that the reaction was monitored over the 100–90 or 100–95% transmittance range. The total absorbance change was usually 0.05 absorbance units.

After the equilibration period, a few trial runs were carried out to optimize the extent of reaction followed (usually 2–3 half-lives were recorded). After several reproducible traces were obtained, the stored scope output was erased, the next run stored, and the bath temperature recorded. An infinity trace was recorded after at least 10 half-lives. The absorbance-time data were obtained from a photograph of the oscilloscope trace.

Integration of the second-order rate expression for the bromination of an olefin (under pseudo-first-order conditions) gives a linear relationship between log $(A - A_\infty)$ and time, with k_2 being obtained from the slope of the line. The kinetic plots normally were good straight lines at $[Br_2] \leq 3 \times 10^{-4}$ M over 75% reaction. The occasional problem of a varying infinity value was surmounted by the use of the Guggenheim method.[33] The k_2 values were calculated using the average olefin concentration during the run; even using as low as a 20-fold excess of olefin, this would introduce an error of only 2.5% in k_2.

The third-order rate constants were measured by an analogous method. To ensure that the k_3 process was predominant, the initial $[Br_2]$ was $\approx 1.2 \times 10^{-2}$ M and was monitored down to $\simeq 6 \times 10^{-3}$ M. This corresponded to an absorbance change from 1.5 to 0.7 units. At this lower concentration, the k_2 term began to contribute significantly to the observed rate. The reaction was followed using the expanded scale attachment such that full scale corresponding to 0–10 or 0–20% T. Again the extent of reaction followed was optimized, the run recorded and an infinity value taken on the 100–0% transmittance scale. Operation of the instrument was carried out as previously described and absorbance-time data during the run was obtained in an exactly analogous manner to above.

Integration of the third-order rate expression for the bromination of an olefin (under pseudo-second-order conditions) gives a linear relationship between $(A - A_\infty)^{-1}$ and time, with k_3 being obtained from the slope of the straight line. Some initial curvature in the plots for the reactive styrenes at very short reaction times (≤ 3 msec) was taken to be indicative of incomplete mixing. Some curvature at longer reaction times, and hence at lower bromine concentrations, was routinely encountered and taken to be due to the increasing relative importance of the second-order process.

Two methods were used to calculate the third-order rate constants. For those olefins where the k_2 values were not determined in the same series of runs (for all styrenes except the 4-bromo- and 4-methyl-substituted compounds), the k_3 values were calculated from the slopes of the visibly linear portions of the $(A - A_\infty)^{-1}$ *vs.* t plots. For the other two substrates, two series of runs at 25° were carried out, one set under predominant k_2 and the other under predominant k_3 conditions. At least two different initial olefin concentrations were used for each set. A nonlinear least-squares regression analysis was then performed on each pair of k_2–k_3 runs by an iterative technique, minimizing the variance for the two runs. Thus one set of "best" k_2 and k_3 values could be determined, the second-order contribution having been eliminated from the k_3 process and vice versa. This technique was also carried out for styrene and the 4-fluorostyrene but the rate constants quoted for these compounds are from a subsequent variable temperature series of runs. The "pure" k_3 values generally corresponded to within 5–10% of those calculated from the nonlinear correlations. Thus an estimated error of 10% in the k_3 values appears reasonable for these rapid reactions, which require the use of expanded oscilloscope scales and are complicated by competing rate processes.

Duplicate traces were normally recorded for each kinetic run and usually two–four different initial olefin concentrations were used. The errors in the quoted rate constants were generally $\leq$6–7%.

For the styrenes for which activation parameters were required, rate constants were measured at three–four temperatures in the 17–45° range. Plots of log k/T *vs.* $1/T$ yielded straight lines with $\Delta H^{\ddagger}$ being obtained from the slope and $\Delta S^{\ddagger}$ from the intercept. Each individually determined rate constant was included in the correlation, since small temperature fluctuations did occur on the duplicate runs and the same number of runs was usually not carried out at each temperature.

All final calculations of the rate constants and activation parameters were performed on a computer or a desk top programmable calculator using a linear least-squares regression program.

Product Studies.—The product runs were under second-order bromination conditions were carried out by the slow, dropwise addition of an equivalent amount of bromine in 20 ml of acetic acid to a stirred solution of 1.0 g of the styrene in 20 ml of solvent. The reaction was protected from light in an aluminum foil wrapped flask and each drop of bromine solution added was allowed to react completely before another drop was added. After the addition was complete, the solution was stirred for 1 hr and poured into a separatory funnel containing 50 ml each of pentane and water. Any excess bromine was destroyed by the addition of a crystal of $Na_2S_2O_3$, the mixture was shaken, and the pentane layer was removed. Successive washings with water, saturated $NaHCO_3$ solution until neutral, and again with water were followed by drying of the pentane layer with $MgSO_4$. The drying agent was removed by filtration and the solution was concentrated on a rotary evaporator.

The product run under third-order bromination conditions was carried out by an analogous slow, dropwise addition of the olefin solution to the stirred, light-protected solution of bromine in acetic acid. After complete addition, the reaction mixture was worked up in exactly the same manner as that described above.

The crude products in CCl_4 solutions were analyzed directly on a Varian T-60 nmr spectrometer. Only two products could be observed from the bromination runs; these were the dibromo- and α-acetoxy-β-bromo adducts which have been previously characterized.[9] The ratios of the products were determined by repeated integrations in the methylene and methine hydrogen regions of the two compounds. The spectra are well separated in these regions.

Registry No.—Bromine, 7726-95-6.

Acknowledgments.—The continued financial support of the National Research Council of Canada is gratefully acknowledged, as is the award of studentships and scholarships to R. S. M.

(33) K. J. Laidler, "Chemical Kinetics," 2nd ed, McGraw-Hill, New York, N. Y., 1965, p 14.

Kinetics and Mechanisms of Electrophilic Addition. II. A Thermochemical–Kinetic Approach to Transition-State Structure

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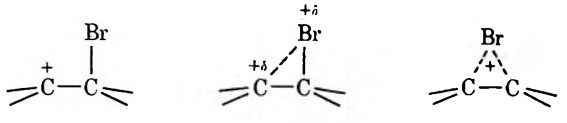
Received February 6, 1973

The enthalpies of isomerization (ΔH_i) of six pairs of geometrically isomeric 1,2-disubstituted ethylenes were either determined directly from heat of combustion measurements or obtained from literature values. These ΔH_i values were corrected to acetic acid conditions by measuring heats of solution in that solvent. Bimolecular rate constants (k_2) for bromination of ten of the above olefins, and several more of interest, were determined at several temperatures in acetic acid using stopped flow methods in most cases. Values of $\Delta H^{\pm}$ and $\Delta S^{\pm}$ were obtained for each isomer. These reactions were also analyzed for dibromide–acetoxybromide product distribution and product stereochemistry. In some cases stereospecific anti addition was observed, and in others variable stereoselectivity was obtained. However, in all cases the initial enthalpy difference between starting cis and trans isomers was increased at the bromination transition state. It is concluded that, although bridged transition states are involved in all cases, these may lead to either bridged or open cationic intermediates, depending on the nature of the attached groups. It is also shown that in these reactions large values of $\Delta\Delta H$ and $\Delta\Delta F$ (cis–trans) for the reactants do not generally decrease monotonically along the reaction coordinate as small $\Delta\Delta H$ and $\Delta\Delta F$ values for the diastereomeric products are approached.

For a long time, electrophilic bromine additions to olefins were considered to be generally stereospecific and anti, which was explained in terms of the well-known cyclic bromonium ion intermediate of Roberts and Kimball,[1] but it is now clear that these reactions can show variable stereoselectivity, ranging all the way from predominant syn to exclusive anti addition.[2] The nature of the intermediate has been shown to depend strongly on starting olefin structure and on the solvent, and it is now more reasonable to propose a spectrum of possible ionic intermediates, of which I and III are extremes.



I (free rotation) II (restricted rotation) III (no rotation)

It has proved difficult to obtain unequivocal evidence about the structures of these cationic intermediates, and more particularly about the transition states which precede and presumably closely resemble them. Stereochemical studies give information only about the structure of the product determining intermediates. Similarly kinetic studies give information only about the charge distribution in the preceding transition states. We have therefore been interested in developing alternative methods of assessing the importance of bromonium ion structures, both as intermediates and as transition states, and have reported[3] some preliminary results using a combined thermochemical–kinetic product study approach.

The approach is based on a comparison of the reactions of pairs of cis- and trans-disubstituted ethylenes. In comparing such systems the considerable difference in steric interactions between the groups R is reflected in the heats of combustion of the isomers. The cis group interactions result in values of ΔH_c for the cis isomers which are higher than those for the trans by ~1–10 kcal for typical olefins.[4] It is therefore of interest to try to determine to what extent these steric differences are retained at the transition states for electrophilic addition. If the transition state resembles I, the steric repulsions in the cis case would be relieved by a combination of bond length and hybridization changes (see Appendix) and could also be further relieved by a small rotation of the C–C bond, thus significantly reducing the ground-state enthalpy difference between cis and trans olefin.[5]

If the transition state resembles III, then this difference in steric repulsions would either be retained or more probably accentuated (see Appendix) as the groups R are forced together owing to a combination of bond length and hybridization changes. Thus the initial isomeric enthalpy difference would be maintained or increased at the transition state.

Therefore, by appropriately combining ΔH_c values for pairs of geometrical isomers with values of $\Delta H^{\pm}$ for bromination it should be possible to determine to what extent the transition state geometry resembles the extremes I or III, for different types of olefinic substrates.

Results and Discussion

Choice of Substrates.—The pairs of olefins studied were all 1,2-disubstituted ethylenes, chosen to span a wide range of bromination reactivity and of ground-state stability difference. Several highly reactive 1,2-dialkylethylenes (diisopropyl, *tert*-butylethyl and di-*tert*-butyl) were used as model substrates of the type expected to lead to cyclic bromonium ion intermediates.[7] The cyclooctenes were investigated to determine whether the severe ring distortion which destabilizes the trans relative to the cis isomer would cause this pair to behave differently from "normal"

(1) I. Roberts and G. E. Kimball, *J. Amer. Chem. Soc.*, **59**, 947 (1937).

(2) See, for example, R. E. Buckles, J. M. Bader, and R. J. Thurmaier, *J. Org. Chem.*, **27**, 4523 (1962); R. E. Fahey and C. Shubert, *J. Amer. Chem. Soc.*, **87**, 5172 (1965); J. H. Rolston and K. Yates, *ibid.*, **91**, 1469, 1477, 1483 (1969).

(3) K. Yates and R. S. McDonald, *J. Amer. Chem. Soc.*, **93**, 6297 (1971).

(4) H. F. Bartolo and F. D. Rossini, *J. Phys. Chem.*, **64**, 1685 (1960), and references therein.

(5) There is already evidence that this can occur for type I transition states, based on the acid-catalyzed hydrations of *cis*- and *trans*-stilbenes.[6] In this case, the rate-determining step is proton transfer to give an open carbonium ion. An initial ground-state difference of 5.7 kcal between the two isomers was found to decrease to only 2.7 kcal at the transition state.

(6) D. R. Hartter, Ph.D. Dissertation, University of California, Berkeley, 1964.

(7) Alkyl-substituted ethylenes are known to give essentially 100% stereospecific anti addition of bromine and yield virtually no solvent-incorporated products in solvents such as acetic acid.[2]

TABLE I

ENTHALPY OF COMBUSTION, ENTHALPY OF FORMATION, AND ENTHALPY OF ISOMERIZATION ON ISOMERIC PAIRS

Compound[a]	No. of runs	$-\Delta E_c°$ [b,c]	$-\Delta H_c°$ [c,d]	$-\Delta H_f°$ [c,e]	$-\Delta H_i$ [f,g]
trans-Diisopropylethylene	5	1258.50 ± 0.35	1260.87 ± 0.35	38.07 ± 0.35	−1.96 ± 0.30
cis-Diisopropylethylene	6	1260.47 ± 0.44	1262.83 ± 0.44	36.11 ± 0.44	
trans-tert-Butylethylethylene	6	1258.85 ± 0.48	1261.22 ± 0.48	37.72 ± 0.48	−5.12 ± 0.38
cis-tert-Butylethylethylene	6	1263.96 ± 0.37	1266.34 ± 0.37	32.60 ± 0.37	
trans-β-*tert*-Butylstyrene	3	1667.37 ± 0.99	1669.74 ± 0.99	5.40 ± 0.99	−7.79 ± 0.92
cis-β-*tert*-Butylstyrene	3	1675.16 ± 0.50	1667.53 ± 0.50	−2.39 ± 0.50	

[a] Registry numbers are, respectively, 692-70-6, 10557-44-5, 690-93-7, 690-92-6, 3846-66-0, 3740-05-4. [b] Standard heat of combustion in kcal/mol. [c] Errors quoted are standard deviations of the mean and include uncertainty in calorimeter calibration value. [d] Standard enthalpy of combustion in kcal/mol. [e] Standard enthalpy of formation in kcal/mol. [f] Enthalpy of isomerization in kcal/mol [$\Delta H_f°$(trans) − $\Delta H_f°$(cis)]. [g] Errors quoted are standard deviations of the difference and do not include calorimeter calibration uncertainty.

1,2-dialkylethylenes. A number of phenyl-substituted systems were also studied. The stilbenes were chosen since the cis isomer is known to give nonstereospecific addition in acetic acid.[8] Thus, this isomer at least must form an open ion intermediate before the product-determining step. The β-methylstyrenes are known to react *via* open or only very weakly bridged ions.[9] To destabilize the cis isomer further relative to the trans, the β-*tert*-butylstyrenes were also investigated as being good models for substrates producing open ion intermediates.

Heats of Combustion.—The heats of combustion of each isomer of three pairs of 1,2-disubstituted olefins were carefully and repeatedly determined using an adiabatic bomb calorimeter and are reported in Table I. These data were used to obtain values of the standard enthalpies of combustion ($\Delta H_c°$) and formation ($\Delta H_f°$) of the olefins, which are also listed in Table I. All values refer to the idealized process at 1.0 atm and 25°. Values of the enthalpies of isomerization, ΔH = [$\Delta H_f°$(trans) − $\Delta H_f°$(cis)] are collected in Table II, along with values obtained from literature data on heats of combustion or hydrogenation for a number of other isomeric olefins of interest.[10-17] With one exception there is good agreement between ΔH_i values based on combustion and hydrogenation. There is some conflict between the reported values for the enthalpy (and free energy) difference between *cis*- and *trans*-stilbene. Thermal isomerization of the trans isomer to give an equilibrium mixture yielded a ΔG_i value of −3.0 kcal/mol at 330°.[18] A study of the iodine-catalyzed isomerization of stilbenes and measurement of the equilibrium constant as a function of temperature gave ΔG_i and ΔH_i values of −3.7 and −2.9 kcal/mol, respectively, in methylcyclohexane at 27°.[19] The enthalpy difference between the solid trans isomer and the liquid cis isomer is −12.85 kcal/mol from hydrogenation measurements[15] and −10.29 kcal/mol from combustion results.[14] When corrected for the heat of fusion of the trans isomer (7.19 kcal/mol),[17] the ΔH_i values for the pure liquids listed in Table II are obtained. The discrepancy between the hydrogenation value and the other results will be discussed later.

TABLE II

COLLECTED VALUES OF ENTHALPY OF ISOMERIZATION FOR CIS- AND TRANS-1,2-DISUBSTITUTED ETHYLENES

1,2 substituents[a]	ΔH_i, kcal mol^{-1} [b] $\Delta\Delta H_c$[c]	Ref	$\Delta\Delta H_h$[d]	Ref
Methyl, methyl*	−0.75[e]	10	−0.95[e]	11
Methyl, *n*-propyl*	−0.39	4		
Methyl, isopropyl*	−1.08	4	−0.94	12
Ethyl, ethyl*	−1.70	4		
Methyl, *tert*-butyl*	−3.92	13	−4.29	12
Ethyl, *tert*-butyl	−5.12			
Isopropyl, isopropyl	−1.96			
tert-Butyl, *tert*-butyl*	−10.51		−9.37	12
tert-Butyl, phenyl	−7.79			
Phenyl, phenyl*	−3.10[f]	14	−5.66[f]	15
Cyclooctene*			+9.26	16
Cyclononene*			+2.87	16
Cyclodecene*			+3.34	16

[a] Registry numbers pertaining to asterisked entries, cis (trans), are, respectively, 590-18-1 (624-64-6), 7688-21-3 (4050-45-7), 691-38-3 (674-76-0), 7642-09-3 (13269-52-8), 762-63-0 (690-08-4), 692-47-7 (692-48-8), 645-49-8 (103-30-0), 931-87-3 (931-89-5), 933-21-1 (3958-38-1), 935-31-9 (2198-20-1). [b] The enthalpies of isomerization refer to the process cis olefin → trans olefin with both isomers in the liquid phase at 25°, unless otherwise noted. [c] Derived from enthalpies of combustion [ΔH_c(trans) − ΔH_c(cis)]. [d] Derived from enthalpies of hydrogenation [ΔH_h(trans) − ΔH_h(cis)]. [e] ΔH_i values refer to the gas phase. [f] Corrected for the latent heat of fusion of the trans isomer, 7.19 kcal/mol.[17]

It can be seen from the ΔH_i values in Table II that for simple olefins the cis isomer is significantly destabilized (by up to 10.5 kcal) with respect to the trans in every case (except the cyclic olefins). This is particularly notable when one or more of the adjacent groups is *tert*-butyl. It should therefore be easy to detect what happens to these large steric differences, as the bromination transition states are approached, by measuring $\Delta H^{\ddagger}$ values for each isomer, and thus obtain information about their structures.

Although ideally comparisons should be made on both an enthalpy and free-energy basis, entropy of isomeriza-

(8) R. E. Buckles, J. M. Bader, and R. J. Thurmaier, *J. Org. Chem.*, **27**, 4523 (1962).

(9) These olefins give nonstereospecific bromine addition in acetic acid and significant yields of solvent-incorporated products, which are formed completely regiospecifically in the Markovnikov sense.[2]

(10) E. J. Prosen, F. W. Mason, and F. D. Rossini, *Nat. Bur. Stand. J. Res.*, **46**, 106 (1951).

(11) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **57**, 876 (1935).

(12) R. B. Turner, D. E. Nettleton, and M. Perelman, *J. Amer. Chem. Soc.*, **80**, 1430 (1958).

(13) J. D. Rockenfeller and F. D. Rossini, *J. Phys. Chem.*, **65**, 267 (1961).

(14) J. Coops and G. J. Hoijtink, *Recl. Trav. Chim. Pays-Bas*, **69**, 538 (1950).

(15) R. B. Williams, *J. Amer. Chem. Soc.*, **64**, 1395 (1942).

(16) R. B. Turner and W. R. Meadar, *J. Amer. Chem. Soc.*, **79**, 4133 (1957).

(17) International Critical Tables, Vol. V, National Research Council, E. W. Washburn, Ed., McGraw-Hill, New York, N. Y., p 134.

(18) G. B. Kistiakowsky and W. R. Smith, *J. Amer. Chem. Soc.*, **56**, 368 (1934).

(19) G. Fischer, K. A. Muszkat, and E. Fischer, *J. Chem. Soc.*, **94**, 4580 (1972), and references cited therein.

TABLE III

HEATS OF SOLUTION AND ENTHALPIES OF ISOMERIZATION IN ACETIC ACID[a]

Compound	ΔE_{soln}[b]	$\Delta\Delta H_{soln}°(\infty)$[c]	ΔH_i[d]	ΔH_i (soln)[e]
trans-Diisopropylethylene	0.71	−0.04 ± 0.02[f]	−1.96 ± 0.30[g]	−2.00
cis-Diisopropylethylene	0.75			
trans-tert-Butylethylethylene	1.01 ± 0.05	+0.20 ± 0.03	−5.12 ± 0.38[g]	−4.92
cis-tert-Butylethylethylene	0.81 ± 0.04			
trans-Di-*tert*-butylethylene	1.42 ± 0.09	+0.31 ± 0.05	−10.51 ± 0.36	−10.20
cis-Di-*tert*-butylethylene	1.11 ± 0.06			
trans-β-Methylstyrene	0.36 ± 0.02	−0.02 ± 0.02		
cis-β-Methylstyrene	0.38 ± 0.02			
trans-β-*tert*-Butylstyrene		+0.20[h]	−7.79 ± 0.92[g]	−7.6
cis-β-*tert*-Butylstyrene				
trans-Stilbene	5.89 ± 0.30	+5.26 ± 0.30	−10.29 ± 0.22	−5.03
cis-Stilbene	0.63 ± 0.04			

[a] All values given in kcal mol^{-1}. [b] The observed heat of solution (ΔE_{soln}) is assumed to be identical with the standard enthalpy of solution at infinite dilution [$\Delta H_{soln}°(\infty)$]. The errors quoted include the assumed uncertainty in the heat of solution of the reference compound (see Experimental Section for details). [c] $\Delta\Delta H_{soln}°(\infty) = \Delta H_{soln}°(\infty)(\text{trans}) - \Delta H_{soln}°(\infty)(\text{cis})$. The errors quoted are standard deviations of the difference. [d] The enthalpy of isomerization for the neat compounds at 25.0. Values are all derived from combustion data. References to literature data are given in Table VI. The error quoted is the standard deviation of the difference [$\Delta H_f°(\text{trans}) - \Delta H_f°(\text{cis})$]. [e] The enthalpy of isomerization in acetic acid solution at 25.0° [$\Delta H_i(\text{soln}) = \Delta H_i + \Delta\Delta H_{soln}°(\infty)$]. [f] Estimated error. [g] This work. [h] This value is estimated (see text).

tion (ΔS_i) values are not easy to obtain from non-equilibrium measurements.[20] The instrumental techniques required for the extensive heat capacity (C_p) measurements from 0–298°K were not available; so it was decided to make comparisons on a purely enthalpic basis. It is known, however, that the ΔS_i values of cis–trans isomeric olefins are very small, in general, in the range of −1 to −2 cal/deg mol[21] (corresponding to a ΔG_i contribution of $\leq$0.6 kcal/mol at 25°). Although this normally tends to reduce (make less negative) the ΔG_i difference from that reflected by the ΔH_i values (the trans isomer has a lower standard entropy than the cis), the trans isomer will be more stable than the cis on both an enthalpy and free-energy basis.

Heats of Solution.—Since all kinetic work was carried out in acetic acid, differences in activation parameters therefore refer to that solution. Thus, ground-state enthalpy values (or differences) in the previous section may need to be adjusted for heats of solution of the olefins in acetic acid. Heats of solution of selected olefins were measured in acetic acid. The heats of solution (ΔE_{soln}), assumed to be identical (see Experimental Section) with the enthalpies of solution at infinite dilution [$\Delta H_{soln}(\infty)$], of five olefin pairs are collected in Table III. The $\Delta\Delta H_{soln}$ values required to correct the enthalpies of isomerization of the neat substrates to acetic acid solution are also given in Table III.

The β-methylstyrenes were chosen as models for the β-*tert*-butylstyrenes since only limited quantities of the latter compounds were available. The cis and trans isomers of the β-methylstyrenes and the diisopropylethylenes have essentially identical ΔH_{soln} values. In fact, only where the ground-state enthalpy differences become fairly large (where one of the ethylene substituents is a *tert*-butyl group) do the $\Delta\Delta_{soln}$ values become appreciable. (The difference is large in the case of the stilbenes only because the trans isomer is dissolved as a solid.) A prediction may be made of the $\Delta\Delta H_{soln}$ for the β-*tert*-butylstyrenes from these results. Since the β-methylstyrenes have a $\Delta\Delta H_{soln}$ value of essentially zero, and, since it appears that a *tert*-butyl substituent interacting with a non-*tert*-butyl substituent leads to $\Delta\Delta H_{soln}$ value of $\simeq$0.2 kcal/mol, then a $\Delta\Delta H_{soln}$ value for the β-*tert*-butylstyrenes may be assumed to be roughly 0.2 kcal/mol.

From the $\Delta\Delta H_{soln}$ values of the other isomeric pairs, it would be expected that the heats of solution of the stilbenes, if both were in the liquid phase, would be the same to within a few tenths of a kilocalorie. However, in order that our heat of solution data be compatible with the only available value[17] for the heat of fusion of the trans isomer (7.19 kcal/mol), the heat of solution of liquid *trans*-stilbene would have to be roughly −1.3 kcal/mol. Such a fairly large, negative ΔE_{soln} would be totally unexpected since all the other olefins have positive values. This suggests that the very old heat of fusion value is probably in error by 1–2 kcal/mol.

As mentioned previously there is a serious discrepancy between the value of ΔH_i for stilbenes based on hydrogenation data and those based on other approaches, including heats of combustion. Also, the hydrogenation work[15] involved use of *cis*-stilbene of questionable purity. Since our heat of solution results do take into consideration that the trans isomer is dissolved as a solid, correcting the combustion values to acetic acid solution leads to a ΔH_i(soln) value of −5.03 kcal/mol, which is free of the above uncertainty in the reported heat of fusion value. Further, if it is assumed that the ΔH_i(soln) of the β-*tert*-butylstyrenes ($\simeq$−7.6 kcal/mol) is roughly midway between that for the stilbenes and the di-*tert*-butylethylenes (−10.2 kcal mol^{-1}), as seems reasonable, the ΔH_i(soln) for the stilbenes should be roughly −5 kcal. This is very close to the value obtained by correcting the combustion data to acetic acid conditions and suggests that the combustion results are the more reliable. These will be used wherever possible for comparisons of isomeric olefins. The enthalpies of isomerization in acetic acid for the isomeric

(20) The choice of olefins in this study precludes the use of equilibrium measurements, since only one of the olefin pairs of interest has an enthalpy (and probably free energy) difference less negative than −4 kcal/mol. A ΔG_i of −4.1 kcal/mol between a pair of cis–trans olefins corresponds to an equilibrium constant of 10^3. Thus, a method of analyzing accurately for 0.1% or less of the cis olefin in the presence of 99.9% or more of the trans would be required.

(21) H. Akimoto, J. L. Sprung, and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, **94**, 4850 (1972), and references cited therein.

olefins of principal interest in the present study are listed in Table III.

Bromination Rates.—Of the six olefin pairs originally chosen for a complete kinetic study, work on one pair (the cyclooctenes) was discontinued since the trans isomer reacted too rapidly to be followed even by the stopped-flow technique. The bimolecular rate constants (k_2) for the other five olefinic pairs were measured at a series of temperatures by either stopped-flow or conventional spectrophotometric methods, as described in the Experimental Section. The bimolecular rate constants determined for these five olefin pairs and for several other olefins of interest are collected in Table IV. It can be seen that the 1,2-dialkylethylenes react very rapidly with bromine in acetic acid with rate constants (k_2) in the range of 10^2–10^3 M^{-1} sec^{-1}. Styrenes react less rapidly, but are still very reactive (with k_2 in the range of 10^2–10^{-1} m^{-1} sec^{-1}). The stilbenes are much less reactive ($k_2 \sim 10^{-1}$–10^{-2} M^{-1} sec^{-1}). These rate differences are qualitatively explicable in terms of the electrophilic nature of the additions and the combined inductive and conjugative effects of the substituent groups on both the olefin and its transition state.

Apart from two pairs of olefins in Table IV, the cis:trans rate ratios fall in the range of 0.15–3, as shown in Table V. These small rate ratios correspond to differences in free energy of activation ($\Delta\Delta G^{\pm}$) in the range of -1 to $+1$ kcal/mol. It has been previously assumed that the often observed fact that a cis olefin reacts more rapidly than its trans isomer (indicative of a closing of the free-energy gap between the starting olefin pair, since ΔG_i is usually <0), is caused by relief of steric strain in the cis olefin in going from the ground state to the transition state. In fact for three of the nine isomeric pairs listed in Table V, this free-energy difference actually increases (the ΔG_i gap becomes more negative). Thus it is dangerous to draw much mechanistic conclusions from these generally small and variable rate ratios (or free-energy differences) which are in any case composites of enthalpy and entropy contributions.[22]

In addition the large steric differences between cis and trans isomers are reflected mainly in the enthalpy terms (ΔH_i). It is therefore of more interest to examine the individual activation parameters $\Delta H^{\pm}$

TABLE IV

BIMOLECULAR RATE CONSTANTS (k_2) FOR THE BROMINATION OF SOME 1,2-DISUBSTITUTED OLEFINS IN ANHYDROUS ACETIC ACID

Compound	No. of runs	t, °C	k_2,[a] M^{-1} sec^{-1}
cis-Diisopropylethylene	2	17.8	(2.08 ± 0.07) × 10^2
	3	25.0	2.68 ± 0.08
	2	32.2	4.56 ± 0.13
	2	38.4	5.36 ± 0.35
	2	44.3	5.87 ± 0.30
	2	45.2	6.19 ± 0.28
trans-Diisopropylethylene	2	18.0	(4.80 ± 0.30) × 10^2
	2	25.0	6.37 ± 0.27
	2	32.1	7.79 ± 0.56
	2	38.3	10.04 ± 0.35
	3	44.5	12.53 ± 0.10
cis-*tert*-Butylethylethylene	3	18.4	(7.28 ± 0.35) × 10^2
	2	25.0	11.17 ± 0.07
	2	32.1	11.76 ± 0.57
	2	38.3	16.53 ± 0.37
	2	44.4	21.08 ± 0.22
trans-*tert*-Butylethylethylene	2	17.9	(3.31 ± 0.12) × 10^2
	2	25.0	4.47 ± 0.08
	3	32.2	6.47 ± 0.21
	2	38.4	7.91 ± 0.48
	4	44.5	9.12 ± 0.09
cis-Di-*tert*-butylethylene	2	20.0	(4.58 ± 0.15) × 10^2
	2	25.0	5.29 ± 0.07
	2	32.0	7.59 ± 0.06
	2	38.0	9.72 ± 0.20
trans-Di-*tert*-butylethylene	2	20.0	8.18 ± 0.10
	2	25.0	11.4 ± 0.3
	3	32.1	12.2 ± 0.4
	3	38.0	14.4 ± 0.5
cis-Stilbene	3	25.1	(5.44 ± 0.10) × 10^{-2}
	2	30.3	7.45 ± 0.09
	4	35.2	10.87 ± 0.44
	2	43.1	19.78 ± 0.35
trans-Stilbene	2	25.1	(1.84 ± 0.04) × 10^{-2}
	3	30.4	2.62 ± 0.11
	2	35.2	3.40 ± 0.04
	4	43.2	6.43 ± 0.24
cis-β-*tert*-Butylstyrene	2	25.0	2.97 ± 0.08
	2	32.0	3.70 ± 0.12
	2	38.0	4.37 ± 0.11
	2	45.2	5.18 ± 0.42
trans-β-*tert*-Butylstyrene	2	20.0	18.4 ± 0.6
	2	25.0	19.6 ± 0.9
	3	32.1	20.7 ± 1.6
	2	38.0	22.8 ± 0.7
cis-Cyclooctene	2	25.0	(8.42 ± 0.18) × 10^2
trans-Cyclooctene		25.0	≥5 × 10^5[b]
cis-2-Butene	3	25.1	(11.62 ± 0.42) × 10^2
trans-2-Butene	2	25.1	(9.23 ± 0.43) × 10^2
cis-3-Hexene	2	25.0	(21.7 ± 1.3) × 10^2
trans-3-Hexene	2	25.0	(19.6 ± 0.8) × 10^2
1-Hexene	4	25.1	31.8 ± 2.1

[a] The errors quoted are standard deviations. [b] This compound reacted too rapidly to be followed by stopped flow. The number quoted is a lower limit for the rate constant.

TABLE V

CIS:TRANS RATE CONSTANT RATIOS AND CORRESPONDING DIFFERENCES IN FREE ENERGY OF ACTIVATION FOR THE BROMINATION OF ISOMERIC OLEFIN PAIRS

Isomeric pair	k_c/k_t	$\Delta\Delta G^{\pm}$,[a] kcal/mol	Effect on isomeric ΔG difference at transition state
2-Butenes	1.26	+0.14	Decrease
3-Hexenes	1.11	+0.06	Decrease
Diisopropylethylenes	0.42	−0.51	Increase
tert-Butylethylethylenes	2.35	+0.51	Decrease
Di-*tert*-Butylethylenes	51.9	+2.34	Decrease
Cyclooctenes	<0.002	<−3.7[b]	Decrease
Stilbenes	2.96	+0.64	Decrease
β-Methylstyrenes[c]	0.72	−0.19	Increase
β-*tert*-Butylstyrenes	0.15	−0.12	Increase

[a] $\Delta\Delta G^{\pm}[\Delta G^{\pm}(\text{trans}) - \Delta G^{\pm}(\text{cis})] = RT \ln k_c/k_t$. A negative $\Delta\Delta G^{\pm}$ value shows that the isomeric free energy difference (ΔG_i) is accentuated at the transition state (one exception is the cyclooctene case; see *b*). [b] In this case, the ground state ΔG_i is positive (the cis isomer is more stable than the trans) and the negative $\Delta\Delta G^{\pm}$ value implies that the free-energy gap is closing at the transition state. [c] From ref 2.

(22) Since steric differences between cis and trans olefins can be as high as 10 kcal, it is evident from the small rate ratios in Table VI that relief of steric strain can not be an important factor in these reactions, even where $k_c/k_t > 1$.

TABLE VI

ENTHALPY AND ENTROPY OF ACTIVATION TERMS FOR BROMINATION OF ISOMERIC OLEFIN PAIRS[a]

Isomeric pair	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, cal/deg mol	$\Delta\Delta H^{\pm}$,[b] kcal/mol	$-T\Delta\Delta S^{\pm}$,[b,c] kcal/mol	$\Delta\Delta G^{\pm}$,[b,c,d] kcal/mol
cis-Diisopropylethylene	6.96 ± 0.53	−23.9 ± 1.7	−0.96 ± 0.60	+0.51 ± 0.57	−0.45
trans-Diisopropylethylene	6.00 ± 0.28	−25.6 ± 0.9			
cis-tert-Butylethylethylene	6.56 ± 0.53	−22.9 ± 1.8	−0.29 ± 0.62	+0.72 ± 0.63	0.43
trans-tert-Butylethylethylene	6.27 ± 0.32	−23.0 ± 1.0			
cis-Di-*tert*-butylethylene	6.83 ± 0.29	−23.0 ± 1.0	−2.38 ± 0.67	+4.77 ± 0.66	+2.39
trans-Di-*tert*-butylethylene	4.45 ± 0.60	−39.0 ± 2.0			
cis-Stilbene	12.78 ± 0.45	−21.5 ± 1.5	−0.29 ± 0.67	+0.78 ± 0.66	+0.49
trans-Stilbene	12.49 ± 0.49	−24.1 ± 1.6			
cis-β-*tert*-Butylstyrene	4.58 ± 0.50	−41.0 ± 1.6	−3.19 ± 0.77	+2.09 ± 0.75	−1.10
trans-β-*tert*-Butylstyrene	1.39 ± 0.58	−48.0 ± 1.9			

[a] Errors quoted are standard deviations, or standard deviations of the difference (for the ΔΔ quantities). [b] $\Delta\Delta X^{\pm}$ refers to the difference $\Delta X^{\pm}$(trans) − $\Delta X^{\pm}$(cis). [c] At 25.0°. [d] $\Delta\Delta G^{\pm} = \Delta\Delta H^{\pm} - T\Delta\Delta S^{\pm}$ at 25.0°.

and $\Delta S^{\pm}$ in attempting to obtain mechanistic information.

Activation Parameters.—The enthalpies ($\Delta H^{\pm}$) and entropies ($\Delta S^{\pm}$) of activation for five olefin pairs were calculated from correlations of log k_2/T *vs.* $1/T$ using the rate data in Table IV. These values are given in Table VI along with the differences [$\Delta X^{\pm}$(trans) − $\Delta X^{\pm}$(*cis*)] in these values and their relative contributions to the total difference in free energy of activation.[23]

The most striking observation on separating the enthalpy–entropy contributions is that, regardless of the direction or magnitude of the isomeric difference in free energy of activation, all of the enthalpy differences are negative and all of the corresponding entropy contributions are positive. For all of these pairs, ΔG_i is negative (the trans isomer is thermodynamically more stable than the cis isomer). Thus, while three of the pairs, the stilbenes and the *tert*-butylethyl- and di-*tert*-butylethylenes, tend to lower this free-energy difference, the other two pairs tend to increase the ΔG_i gap, at the bromination transition state. However, for all of the pairs, the entropy of activation of the cis isomer is always less negative than that for the trans compound. In each case the entropy difference has a compensating effect (positive contribution to the $\Delta\Delta G^{\pm}$ value, as in column 4, Table VI). In terms of rates, the enthalpy term favors the trans isomer to react *more* rapidly in every case, but its entropy term is more negative and thus less favorable, which in some cases results in a lower rate for this isomer.

The enthalpy effects arise primarily from a combination of bond-making and bond-breaking effects which occur in the activated complex. However, in the absence of steric effects these should be very similar for a cis–trans olefin pair. Thus any observed enthalpy effects can be interpreted mechanistically in terms of the initial premise concerning various transition state structures and their steric effects.

Transition-State Geometry and Product Stereochemistry.—The prediction that olefin pairs which proceed *via* bromonium ion type transition states should show a widening of the enthalpy gap in going from the ground to the bromination transition state is borne out here in the observed enthalpy effects [in each case, $\Delta H^{\pm}$(cis) > $\Delta H^{\pm}$(trans)]. This must mean, at least, that no rotation is occurring at the transition states and that the isomeric enthalpy gap is being increased by more severe steric interactions in the cis transition state. This is consistent with a bridged transition state leading to some type of cyclic bromonium ion intermediate. However, very surprisingly, this occurs for all pairs of substrates studied, even the β-*tert*-butylstyrenes and stilbenes. Although the enthalpy changes at the transition state are small where the initial enthalpy differences of the olefins are also small (*i.e.*, where ΔH_i is less negative than −5 kcal/mol), the $\Delta\Delta H^{\pm}$ is large (−2.38 kcal) for the di-*tert*-butylethylenes where ΔH_i is −7.8 kcal. The fact that in all five cases the enthalpy (or entropy) effects occur in a similar direction supports the idea that these changes, even when small, are real.

i. Dialkylethylenes.—The original postulate concerning the intermediacy of the bromonium ion[1] arose through studies of the stereochemistry of the olefin bromination products. The products of bromination of the cis–trans olefin pairs determined in this study and of two pairs from the literature are summarized in Table VII. In general, it is observed that the 1,2-dialkylethylenes give essentially 100% anti addition, indicative of a bridged intermediate in all of these cases. In fact the four cis isomers of this type give completely stereospecific anti-addition products. These isomers would be expected to allow rotation to relieve the ground-state steric effects and lead to nonstereospecific products, if open-ion intermediates were involved. In general, only anti-addition products are observed from the trans alkenes as well, but some unidentified product is observed in bromination of *trans*-diisopropylethylene and *trans*-di-*tert*-butylethylene. These are not, however, the products of syn addition and are probably addition–elimination products or products of the further bromination of these compounds (see Experimental Section). *trans*-Di-*tert*-butylethylene is anomalous in its behavior. Although no products of syn addition are observed, very little meso dibromide is formed. The predominant product is a rearranged bromo olefin or products from the secondary bromination of this compound. However, this olefin appears to be formed *via* a stereospecific methyl shift to a bromonium ion centre analogous to reported chlorination results.[24] The transition state for both the *cis*- and *trans*-di-*tert*-butylethylene is pro-

(23) The $\Delta\Delta G^{\pm}$ values in Table VI are slightly different from those in Table V which were calculated directly from the rate constant ratios at 25°, but the differences are negligible (≤0.15 kcal).

(24) R. C. Fahey, *J. Amer. Chem. Soc.*, **88**, 4681 (1966).

TABLE VII

SUMMARY OF PRODUCTS FROM THE BROMINATION OF SOME OLEFIN PAIRS IN ACETIC ACID AT 25°[a]

Compound	Dibromides, %		Acetoxybromides, %			Anti addition, %[c]
	Meso or erythro	*dl* or threo	Erythro	Threo	Other[b]	
cis-2-Butene[d]		98		2		99.5
trans-2-Butene[d]	98		2	*h*		99.5
cis-Diisopropylethylene		>99[e]				≥99
trans-Diisopropylethylene	83[f]		~4[g]		13	≥99
cis-*tert*-Butylethylene		92[i]	*k*	8		>99
trans-*tert*-Butylethylethylene	>99[j]			*l*		>99
cis-Di-*tert*-butylethylene		>99[m]		*n*		>99
trans-Di-*tert*-Butylethylene	≤5				~95	(>99)[u]
cis-Cyclooctene		~90[o,v]	~2–3		~7	
trans-Cyclooctene		~20[v]	Total ~5		~75	
cis-Stilbene	Predominant	Present	Present	Present		<50
trans-Stilbene	>95[p]		Present			>95
cis-β-Methylstyrene[d]	22	59		20		79
trans-β-Methylstyrene[d]	64	13	23			87
cis-β-*tert*-Butylstyrene	55[q]	25[r]	18[s]	2[t]		27
trans-β-*tert*-Butylstyrene	75	23	2			77

[a] A blank indicates that none of this compound is detectable (≤0.5%). [b] Includes bromo olefin or its secondary reaction products and unidentified material (see Experimental Section for details). [c] Based on dibromide and acetoxybromide products only. [d] From ref 2. [e–t] Registry numbers. [e] 40084-92-2. [f] 40084-93-3. [g] 40084-94-4. [h] 40084-95-5. [i] 40084-96-6. [j] 40084-97-7. [k] 40084-98-8. [l] 40084-99-9. [m] 40085-00-5. [n] 40085-01-6. [o] 34969-65-8. [p] 13440-24-9. [q] 40085-04-4. [r] 40085-05-0. [s] 40085-06-1. [t] 40037-04-5. [u] No syn addition is observed in this case, but only ~15% of the total product mixture was identified. [v] This compound is the *trans*-1,2-dibromocyclooctane from an anti addition to the cis isomer or from a net syn addition to the trans isomer.

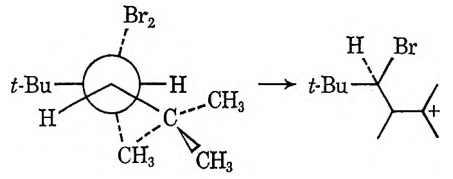
posed to resemble that for the other dialkylethylenes. However, special conformational effects must be occurring at the transition state for the trans olefin. While the trans isomer reacts 50-fold more slowly than the cis isomer, this is reflected not in the enthalpy term which actually favors the trans isomer by 2.4 kcal/mol, but in the entropy term which is unfavorable by 4.8 kcal/mol. The difference in $\Delta S^{\pm}$ of 16 cal/deg mol between the cis and trans isomers cannot be simply explained in terms of differences in solvation of the corresponding transition states.[25] The cis isomer behaves normally with respect to its bromination rate, activation parameters, and product stereochemistry.

Thus the thermochemical–kinetic and stereochemical studies presented here point strongly toward a bromonium ion type transition state leading to a bridged ion intermediate for the acyclic 1,2-dialkylethylenes.

ii. Stilbenes.—The previous compounds, adopted as models which are believed to brominate through cyclic bromonium ion intermediates, showed enthalpy effects which were interpretable in terms of a transition state leading to such an ion. However, the stilbenes also show similar effects. This is surprising, since in these cases an open ion could be resonance stabilized by one of the phenyl groups. Thus, the enthalpy gap between the isomers is found to increase by 0.29 kcal/mol and the trans isomer is found to have a $\Delta S^{\pm}$ value 2.6 cal/deg mol less than that of the cis isomer. These values are, in fact, very similar to those observed for the *tert*-butylethylethylene pair (which has a similar ΔH_i value) and point toward a bromonium ion type transition state for the stilbene also. However, referring to Table VII stereospecific anti addition is observed only for the trans isomer. The cis isomer gives stereoselective syn addition and isomerizes in the presence of bromine. Nonstereospecific bromine addition to stilbenes has also been reported previously.[8] An open-ion intermediate is required to explain these results, but, at the transition state leading to this ion, no rotation to relieve the steric interaction between the cis substituents is allowed. Thus, the neighboring substituent interaction actually increases slightly.

What the kinetic and stereochemical studies then imply is that both stilbenes react *via* initial formation of an essentially symmetrical charge-transfer complex with little, if any, change in steric effects in the cis olefin. Both then proceed *via* a rate-determining transition state, either with unassisted or solvent-assisted bromine–bromine bond cleavage, in which the interacting substituents in the cis olefin are forced slightly together and in which no rotation to relieve this interaction is allowed. In the case of the trans olefin, this activated complex may lead to a bromonium ion which reacts further to give products. The complex from the cis olefin probably proceeds to the formation of an open or weakly bridged ion. Thus, an unsymmetrically bridged transition state (type II) can be envisaged for these olefins. In nonpolar solvents, the unsymmetrically bridged ion does not open and only anti addition is observed.[8,26] In solvents capable of stabilizing a carbonium ion center by solvation, bridging is sufficiently weakened to allow C_α–C_β bond rotation, resulting in nonstereospecific addition. Since the relative rate of bromine addition to *cis*-stilbene and its rate of bromine-catalyzed isomerization are not known, the question arises as to what extent nonstereospecific addition is due to collapse of this open

(25) A referee has suggested that this large difference may point to a quite different transition state for *trans*-di-*tert*-butylethylene, because the incoming bromine cannot avoid the bulky groups by attacking off the perpendicular,



as it could in the cis isomer. This could lead directly to a different intermediate and the observed rearranged product.

(26) G. Heublein, *J. Prakt. Chem.*, **31**, 84 (1966).

ion with bromide (leading predominantly to meso dibromide) or to prior isomerization to the trans olefin which is known to brominate anti to give the meso dibromide. In any event, a similar open α-bromocarbonium ion would be required as an intermediate for the cis olefin isomerization to that required to explain nonstereospecific addition.

iii. β-*tert*-Butylstyrenes.—Even more surprising than the stilbene results are those for the β-*tert*-butylstyrenes. Evidence requiring an open benzylic carbonium ion or, at most, a weakly bridged bromonium ion intermediate in the bromination of the β-methylstyrenes has been discussed previously. A summary of the nonstereospecific adducts in acetic acid is found in Table VII. Our model for the transition state leading to an essentially open ion was the β-*tert*-butylstyrene system. In this case, the 7.6-kcal/mol strain energy in the cis isomer would provide an even larger driving force (than in the β-methylstyrene case) for the rotation apart of the cis substituents, leading to nonstereospecific products.

The stereochemical studies, outlined in Table VII bear out this idea. *trans*-β-*tert*-Butylstyrene gives only 77% anti-addition products relative to 87% for *trans*-β-methylstyrene. An open-ion intermediate is strongly suggested, since even a weakly bridged ion would probably not open and rotate since this would increase any steric interactions. The open ion appears to be attacked predominantly from the side opposite that to which the bromine is first attached, by bromide ion rather than acetic acid, before rotation occurs. A very similar total erythro:threo product ratio is observed for the cis isomer [erythro:threo (cis) = 73:27; erythro:threo (trans) = 77:23]. The predominant syn addition to the cis olefin is strong evidence for the intermediacy of an open ion which tends to rotate to an energetically more favorable conformation before ion-pair collapse or solvent attack occurs. (Neither olefin isomerizes under the reaction conditions, so that the syn-addition products do not arise from isomerization followed by anti addition.) However, the same intermediate and complete equilibration of all ion pairs from both olefins evidently does not occur since nonidentical product distributions are observed. For example, very little solvent incorporation is observed from the trans olefin.

Despite the fact that an open-ion intermediate is clearly involved in the case of the β-*tert*-butylstyrenes, the thermochemical–kinetic results demonstrate that this pair shows very similar trends in both enthalpy and entropy of activation terms to the other olefin pairs. Thus, the $\Delta H^{\ddagger}$ of the cis isomer is significantly larger than that for the trans, and the enthalpy difference between the isomers increases from 7.6 kcal/mol to 10.8 kcal/mol in going from initial to transition state.

Again, this demonstrates that not only is no rotation allowed at the transition state leading to the open ion, but also that the interacting cis substituents are forced more closely together. The favorable enthalpy of activation with respect to the trans isomer outweighs its more unfavorably negative entropy of activation and the difference in free energy of activation is negative (leading to a $k_c/k_t < 1$). Thus, even in cases where the bromination intermediate is clearly either an open or at best very weakly bridged ion, the transition state nevertheless more closely resembles a cyclic bromonium ion structure (type II or III).

iv. Cyclooctenes.—This cyclic olefinic pair can only be considered through product stereochemical studies since rate studies were not possible. Previous work[27] has shown that the cis isomer reacts normally, probably *via* a cyclic bromonium ion leading to the *trans*-1,2-dibromocyclooctane, essentially exclusively. A small amount of addition–elimination[27b] and transannular rearrangement[27c] has been observed. Such a scheme would be reasonable for this olefin, the more stable of the pair. Also, as previously reported,[27a,c] the trans isomer gives a very complex product mixture. However, in this case also, the mechanism has been proposed to involve a cyclic bromonium ion intermediate, at least initially.[27c] However, the observation, in the present study, of the presence of some trans 1,2 dibromide (by a syn addition) would require olefin isomerization in the presence of bromine or that an open ion must be formed before the product-forming step. Such conclusions remain very tentative.

Overall Reaction Profiles.—Little information can be obtained from the literature on the differences in overall ΔG and ΔH of reaction during the bromination of isomeric olefin pairs because the relative ground-state enthalpies of the diastereomeric dibromide adducts is not generally available. However, some data is available in the case of the 2-butenes and the stilbenes. The gas phase brominations of *cis*- and *trans*-2-butene lead to the diastereomeric *dl*- and *meso*-2,3-dibromobutanes, respectively. It is found that the enthalpy difference of the olefins (−0.95 kcal/mol)[11] is completely removed on formation of the products[28] (within experimental error, the enthalpy difference of the adducts is zero). In the case of the silbenes, the ground-state free-energy difference between the olefins of −3.7 kcal[19] is reduced to only −0.8 kcal on forming the corresponding dibromides.[29] Therefore there is probably only a very small enthalpy difference between the diastereomeric products.[30] It thus seems reasonable that both enthalpy and free-energy differences will generally be small at the product stage of these electrophilic additions.

It is now possible to construct overall reaction profiles on both an enthalpy and free-energy basis, as shown schematically in Figure 1a for the bromination of *cis*- and *trans*-stilbene. These show the following general characteristics. The significant isomeric enthalpy gap which exists at the reactant stage is either retained or shows a definite increase at the transition state in all cases and is then reduced almost to zero at the product stage. (Also the larger the initial enthalpy difference, the more it seems to be increased as the transition state is approached.) On the other hand, the initial *free-energy* difference may decrease smoothly from reactants to products in some cases (*e.g.*, for the

(27) (a) A. C. Cope, R. A. Pike, and C. F. Spenser, *J. Amer. Chem. Soc.*, **75**, 3213 (1953); (b) G. Wittig and H-l Dorsch, *Justus Liebigs Ann. Chem.*, **711**, 46 (1968); (c) K. Ziegler and H. Wilms, *ibid.*, **869**, 1 (1950).

(28) J. B. Conn, G. B. Kistiakowsky, and E. A. Smith, *J. Amer. Chem. Soc.*, **60**, 2764 (1938).

(29) W. K. Kwok, I. M. Mathai, and S. I. Miller, *J. Org. Chem.*, **35**, 3420 (1970).

(30) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw Hill, New York, N. Y., 1962: Chapter 6, pp 138–139. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965. Chapter 1, pp 23–26.

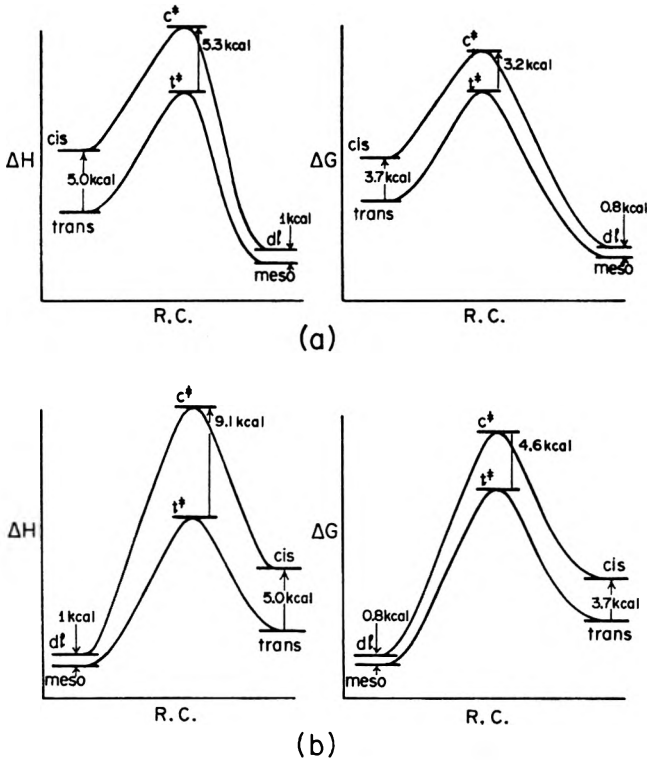


Figure 1.—Schematic representations of enthalpy and free-energy differences along the reaction coordinate for (a) bromine additions to *cis*- and *trans*-stilbene in acetic acid (this work) and (b) LiBr-catalyzed debrominations of *dl*- and *meso*-stilbene dibromides in DMF (ref 29).

stilbenes as shown in Figure 1a) yet in others show a definite increase (*e.g.*, for the *tert*-butylstyrenes or di-*tert*-butylethylenes) at the transition state.

Although halide ion catalyzed debrominations are not exactly the microscopic reverse of the above additions, Miller and coworkers have observed[29,31] analogous results for these reactions. In several cases, they found that the free-energy differences of the reactants (*meso*- and *dl*-stilbene dibromide; $\Delta G = -0.8$ kcal/mol) and the products (*trans*- and *cis*-stilbene, $\Delta G = -3.7$ kcal/mol) did not bracket the difference found at the transition state.[32] That is, transition-state free-energy differences of less than -3.7 kcal/mol were observed. If the enthalpy difference of the dibromides is also fairly small, say, approximately equal to -1 kcal/mol, with the enthalpy difference of the stilbenes known to be -5.0 kcal/mol, then a similar result is found on an enthalpy basis in Miller's work as shown in Figure 1b. For the NaI-[31] and the LiBr-catalyzed[29] debrominations of stilbene dibromides in dimethylformamide, the enthalpy differences at the transition states are -6.8 and -9.1 kcal/mol, respectively. Results from the present study on bromination of this olefin pair show the enthalpy difference to increase by 0.3 kcal/mol and the free-energy difference to decrease by 0.5 kcal/mol from the ground-state olefins to the bromination

(31) I. M. Mathai and S. I. Miller, *J. Org. Chem.*, **35**, 3416 (1970); W. K. Kwok and S. I. Miller, *J. Amer. Chem. Soc.*, **92**, 4599 (1970).

(32) Although Miller has stated that such results are contrary to Hammond's postulate, the very similar results observed in the present study appear to have a reasonable mechanistic interpretation. However, Miller also pointed out that this type of result is analogous to a Brønsted α outside the range of 0–1. If it were generally found that $\Delta\Delta G^{\pm}$ need not lie between $\Delta\Delta G$ (reactants) and $\Delta\Delta G$ (products) this would cast further serious doubt[33] on the validity of Brønsted relationships.

(33) F. G. Bordwell and W. J. Boyle, *J. Amer. Chem. Soc.*, **93**, 511 (1971).

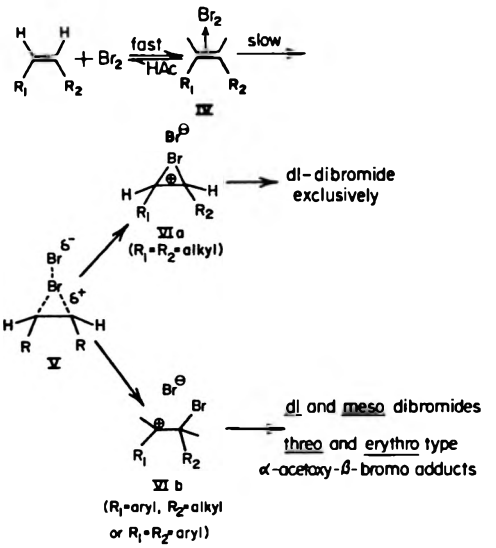


Figure 2.—General mechanistic scheme for bromine additions to cis-1,2-disubstituted olefins.

transition state. These effects may be seen more clearly in Figures 1a and 1b where the enthalpy and free energy are plotted schematically *vs.* the reaction coordinate for the olefin brominations in acetic acid (this work) and for the LiBr-catalyzed debromination of the stilbene dibromides in DMF.[29]

Thus the findings of this study in which the ground-state enthalpy difference between a pair of isomeric olefins is found to increase initially at the bromination transition state and then to decrease on formation of the products are not without parallel. All the results appear to be consistent with the general mechanistic scheme, shown for a cis olefin in Figure 2. An analogous scheme can be written for the trans isomer. The first step is a rapid preequilibrium formation of a charge-transfer complex (IV). This then proceeds to a highly dipolar transition state (V), which possesses a cyclic bromonium ion like geometry in which the groups R are forced somewhat closer together than in the starting olefin. If the groups R are both either hydrogen or alkyl, continued solvent stabilization allows formation of the bromonium bromide ion-pair intermediate (VIa). Bromine bridging is still retained, in the absence of any more effective mode of stabilization than by the alkyl groups. This ion pair can then collapse directly (without rotation), by bromide attack on the opposite face, to give exclusively the *dl* dibromide.[34]

If one or more of the groups R is a phenyl group, the bromonium ion like transition state (V) proceeds to an essentially open α-bromocarbonium ion intermediate (VIb) in which conjugative stabilization is gained and in which rotation is possible. This ion pair can then collapse to give both *dl* and meso dibromide, whose relative amounts depend on starting olefin structure and solvent. Also solvent attack can occur at the α carbon to give both diastereomeric solvent-incorporated products, which are both completely regiospecifically formed (*i.e.*, exclusively α-acetoxy-β-bromo derivatives).

(34) In the presence of external added nucleophile, the bromide ion can be replaced in this ion pair, to give mixed products. However, although such counterion exchange presumably involves solvent-separated ion pairs also, solvent does not attack the bromonium ion to give any significant amount of solvent incorporated product.

Experimental Section

All melting and boiling points are uncorrected. Nmr spectra were measured with a Varian A-60 or T-60 spectrometer using samples of roughly 10% solution in CCl_4 containing 1% TMS. A Varian HA-100 instrument was used to measure coupling constants and ^{13}C–H coupling side-band spectra. Liquid samples were purified by repeated distillation through a 24 in. spinning-band column. Analytical glpc was carried out on a Carlo Erba Fractovap Model GI gas chromatograph equipped with a flame ionization detector and disc integrator.

Materials.—The purification of acetic acid has been described previously. Only samples with fp $\geq$16.55° (lit.[35] fp 16.63°) were used as solvent in the kinetic experiments. Commercially available bromine (Anachemia) was used without further purification.

trans-Stilbene (BDH) was recrystallized from ethanol and dried over P_2O_5 at 100° under high vacuum: mp 126.5–126.7° (lit.[36] mp 124.5–124.8°). *cis*-Stilbene was distilled and a colorless center fraction was used for kinetic measurements: bp 106° (17 mm) [lit.[15] bp 145° (10 mm)]. Each isomer was found to be $\geq$99.8% pure by glpc analysis (6 ft × 0.25 in. 20% DGGS on Chromosorb W, 200°, He flow rate 170 ml/min).

cis-Diisopropylethylene (2,5-dimethyl-3-hexene) (Chemical Samples) was distilled: bp 95.0–95.5°, d^{25}_4 0.6896 g/ml. The trans isomer (Chemical Samples) was also distilled: bp 98.5° (lit.[37] bp 102°), d^{25}_4 0.7065 g/ml (lit.[37] 0.706 g/ml). Glpc analysis [13 ft × 0.25 in. Tide (Procter and Gamble), 71°, 65 ml/min] showed no detectable (<0.5%) impurities in either isomer.

cis-tert-Butylethylethylene (2,2-dimethyl-3-hexene) (Aldrich) was carefully distilled: bp 102.0–102.6° (lit.[37] bp 105.4°), d^{25}_4 0.7080 g/ml (lit.[38] 0.7086 g/ml). Glpc analysis under the above conditions showed 0.8% of the trans isomer to be present as the only detectable impurity. This amount has a negligible effect on combustion, solution and kinetic results. The trans isomer (Aldrich) was also distilled: bp 96.5–97.0° (lit.[37] bp 100.9°), d^{25}_4 0.6965 g/ml (lit.[37] 0.6995). Glpc analysis showed the only detectable impurity was 0.3% of the cis isomer. Further purification was not attempted.

cis-Di-*tert*-butylethylene (2,2,5,5-tetramethyl-3-hexene) was prepared by the method of Hennion and Banigan.[38] Repeated careful distillation of the final product gave bp 139.0–135.5° (lit.[38] bp 144.2–144.4°); nmr spectrum δ 1.17 (s, 9 H), 5.15 (s, 1 H); ir peaks at 1635 (w), characteristic of nonconjugated C=C stretching, and at 730 cm^{-1} (s), characteristic of *cis*-C=C—H out-of-plane deformation. Glpc analysis (6 ft × 0.25 in. 20% Apiezon L on Chromosorb P, 150°, 100 ml/min) showed the product to be 99.8% pure. *Anal.* Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.62; H, 14.43. *trans*-Di-*tert*-butylethylene was prepared by the method of Puterbaugh and Newman.[39] Purification of the final product by column chromatography (2 ft × 1.8 in. Florisil column, pentane) yielded material with bp 124–126° (lit.[39] bp 125.0°); nmr spectrum δ 0.99 (s, 9 H), 5.32 (s, 1 H); ir negligible absorption in the C=C stretching region, but a strong peak at 980 cm^{-1}, characteristic of a *trans*-HC=CH grouping. Repeated, careful distillation increased the isomer purity to 99% and no further purification was attempted.

cis-Cyclooctene (Matheson Coleman and Bell) was distilled: bp 137° (lit.[38] bp 138°). Glpc analysis (Apiezon L, 110°, 100 ml/min) showed roughly 1% impurity with longer retention time than that of the cis olefin (which is probably not the trans isomer). No further purification was attempted. The trans isomer was synthesized by the method of Cope and coworkers.[27a] Final distillation of the product yielded pure *trans*-cyclooctene: bp 61–62° (43 mm), 142–144° (760 mm) [lit.[36] bp 143° (760 mm)]; nmr δ 0.5–2.9 (m, 12 H), 5.1–5.9 (m, 2 H), no detectable cis peaks; ir strong absorption at 845 and 790 cm^{-1}, characteristic of the trans olefin but only very small peaks at 890 and 755 cm^{-1} due to cis impurity. *Anal.* Calcd for C_8H_{15}: C, 87.19; H, 12.81. Found: C, 87.30; H, 12.76. The trans olefin was purified again immediately before use.

cis-β-*tert*-Butylstyrene (3,3-dimethyl-1-phenyl-1-butene) was synthesized by the catalytic hydrogenation of the corresponding acetylene, prepared as follows. To a solution of ethyl magnesium bromide (1.0 mole) in 200 ml of ether, cooled to 0°, was added dropwise, a solution of 91.0 g (0.89 mol) of phenylacetylene (Aldrich) in 100 ml of ether. The solution was then allowed to warm to room temperature and was refluxed with stirring, for 14 hr. To this solution, cooled in ice, 113.2 g (0.83 mol) of *tert*-butyl bromide in 100 ml of ether was added dropwise (4 hr). After warming to room temperature, the solution was refluxed for 20 hr and allowed to cool. Work-up was achieved by cautiously pouring this solution into 500 ml of ice and 1 *N* HCl and was followed by extraction with ether. Concentration of the dried ether extracts, followed by vacuum distillation, gave two fractions. The first fraction, boiling range of 43–53° (17 mm), consisted of unreacted phenylacetylene, 31.6 g (0.31 mol). The second fraction, boiling range of 83–97° (17 mm), consisted mostly of the desired *tert*-butylphenylacetylene: 64.6 g (0.41 mol, 45% yield); nmr δ 1.31 (s, 9 H), 7.0–7.5 (m, 5 H). This crude material was used directly in the hydrogenation. Optimum conditions involved shaking a mixture of 50.1 g of *tert*-butylphenylacetylene (0.25 mol), 1 g of freshly prepared Raney nickel catalyst, and 150 ml of 95% ethanol with an average H_2 pressure of 55 psi until 1.1 equiv of H_2 had been consumed (6 hr). This yielded 36 g of crude material which was analyzed by nmr and glpc, which revealed the presence of roughly 65% *cis*-β-*tert*-butylstyrene, 10% unreacted acetylene, 20% 3,3-dimethyl-1-phenylbutane, and 5% *trans*-β-*tert*-butylstyrene. The four compounds were cleanly separable by glpc (Carlo Erba, DEGS column at 125°, He flow rate 130 ml/min). The product was purified by two careful spinning-band distillations with the cis olefin being concentrated in the initial fractions. The final distillation yielded 12 g of the pure *cis*-β-*tert*-butylstyrene: bp 81–82° (14 mm) [lit.[40] bp 80.5–81.0° (16 mm)]. Glpc analysis on the DEGS column at 110° showed that no detectable impurities were present (>99.9% pure). A strong ir absorption at 698 cm^{-1}, characteristic of the C—H out-of-plane deformation frequency of the *cis*-HC=C—H grouping, was present. The nmr spectrum [δ 0.98 (s, 9 H), 5.55 (d, J = 12.8 Hz, 1 H), 6.40 (d, J = 12.8 Hz, 1 H); 7.17 (s, 5 H)] is consistent with the cis structure. The olefin hydrogens appear as an AB quartet; the cis-olefinic coupling of 12.8 Hz is in the range expected. *Anal.* Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.92; H, 9.91. *trans*-β-*tert*-Butylstyrene was prepared by the acid-catalyzed isomerization of the cis isomer. About 15 g of a hydrocarbon mixture from the cis-olefin preparation, enriched in the cis isomer, was refluxed in 20 ml of acetic acid with a catalytic amount of *p*-toluenesulfonic acid. After 18 hr, the solution was cooled and poured into a mixture of 50 ml of pentane and 50 ml of water. Work-up was achieved in the usual way. Concentration of the dried pentane solution yielded *trans*-β-*tert*-butylstyrene: bp 91–92° (11 mm) [lit.[40] bp 90–91° (13 mm)]. Glpc analysis on the DEGS column at 110° showed no detectable impurities were present (>99.9% pure). A strong ir absorption at 967 cm^{-1}, characteristic of the C—H out-of-plane deformation frequency in the *trans*-H—C=C—H arrangement, was present. The nmr spectrum showed δ 1.13 (s, 9 H), 6.22 (s, 2 H), 7.0–7.5 (m, 5 H). The olefinic hydrogens appear to be almost coincident. At higher amplitude however, two weak peaks 16.5 Hz to either side of the δ 6.22 are detectable. Thus, these two hydrogens are not identical; the very tightly coupled AB spectrum indicates roughly a 16.5-Hz coupling, indicative of the trans structure. Similarly, the fact that the *tert*-butyl in the trans olefin occurs at lower field than that in the cis olefin (δ 1.13 *vs.* 0.98, respectively) supports the assigned geometry. *Anal.* Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.89; H, 10.04.

The *cis*- and *trans*-2-butenes were commercially available and used without further purification (in previous studies[2] they were found to be <99.5% pure). The 3-hexenes and 1-hexene (Chemical Samples) were spinning band distilled before use.

Heats of Combustion.—All heats of combustion were mea-

(35) "Techniques of Organic Chemistry," Vol. III, 2nd ed, p 145. A. Weissberger, E. S. Proskauer, J. A. Riddick, and E. E. Toops, Ed., Interscience, New York, N. Y., 1955.

(36) "Handbook of Chemistry and Physics," 51st ed, R. C. Weast, Ed, Chemical Rubber Co., Cleveland, Ohio, 1970.

(37) R. R. Dreisbach, "Physical Properties of Organic Compounds," *Advan. Chem. Ser.*: Vol. I (1955), Vol. II (1959), Vol. III (1961). "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," NBS Circular C461, API Project 44, Washington, D. C., 1947.

(38) G. F. Hennion and T. F. Banigan, *J. Amer. Chem. Soc.*, **68**, 1202 (1946).

(39) W. H. Puterbaugh and M. S. Newman, *J. Amer. Chem. Soc.*, **81**, 1611 (1959).

(40) K. Yasufuku, S. Hirose, S. Nozakura, and S. Murahadu, *Bull. Chem. Soc. Jap.*, **40**, 2139 (1967).

sured with a Parr 1231 oxygen bomb calorimeter equipped with a Model 2601 adiabatic control unit. A Parr 1111 oxygen bomb was used to contain samples, and temperatures were measured with Parr 1622 calibrated 24–30° thermometers. Solid samples were pelletized and ignited in open stainless steel crucibles. Liquid samples were sealed in a volatile sample holder (Parr A 158A) immediately after weighing to prevent evaporation losses. Samples were weighed and stored in the presence of P_2O_5 to prevent absorption of atmospheric water. Combustions were normally performed using 30-atm O_2 pressure, except for the *β-tert*-butylstyrenes where 35 atm was found necessary to prevent considerable soot formation, indicating incomplete combustion. Corrections for small amounts of soot formation were made in all cases. Corrections were made for combustion of residual N_2 in the bomb by titrating for nitrous and nitric acids.[41] The calorimeter was carefully calibrated using Parr-certified benzoic acid pellets, which yielded under standard bomb conditions (30-atm O_2; reference $T = 25°$; bomb volume 0.360 l.) a heat of combustion value of -6323.6 cal g^{-1}.[41] All calibration runs were corrected to standard bomb conditions using the "Washburn" correction terms, as recently revised and expanded.[42] Full experimental details and typical experimental data and calculations are available sn the Ph.D. thesis of R. S. M. (University of Toronto).

Heats of Solution.—Heats of solution were measured by rapidly dissolving weighed amounts of the olefins in a fixed quantity of anhydrous acetic acid, using a simple calorimeter. (The calorimeter was calibrated using pyridine whose heat of solution at infinite dilution at 25° is known. The reported value[43] of 6.50 kcal mol^{-1} was assumed to be accurate to within 5%.) This consisted of a 250-ml dewar flask, tightly covered with a two-hole stopper. One hole was fitted with a Parr certified 24–30° thermometer and the other was used for syringe injection of the olefin samples. Solvent was added to the calorimeter and thermal equilibration at or near 25° was allowed, with continuous (magnetic) stirring. After the equilibration period "initial" temperature readings were taken every 1–2 min to the nearest 0.001°. These usually drifted very slightly but linearly, with time, typical drifts being of the order of ±0.003–0.006°/min. The last "initial" temperature was noted and the olefin sample (1–2 g) was then injected rapidly, solution being complete within a few seconds as noted by the rapid temperature changes. The first "final" temperature reading was taken after 1 min and time–temperature readings were continued for 20–25 min. The initial and final calorimeter temperatures were then obtained by extrapolation to the mixing time, by use of the linear time–temperature plots before and after solution of the olefin. For each experiment a temperature correction was made because the olefin and solvent were at different initial temperatures. This was based on the known specific heats of the acid and olefins.[37,44]

Multiple injections of sample into the same solution, use of different sample sizes, and different initial temperatures showed no trends in the calculated heats of solution. This confirms that the measured heats of solution are effectively those at infinite dilution. These were reproducible to within 0.1 kcal mol^{-1}, except for *trans*-stilbene. This was the only solid olefin used, and the results were more difficult to obtain accurately. In this case reproducibility to within only 0.3 kcal mol^{-1} could be obtained.

Kinetic Measurements.—The experimental details involved in the stopped-flow kinetic measurements of the bromination of the more reactive olefins have been previously described.[45] Pseudo-first-order rate plots (*i.e.*, with 50–200-fold excess olefin) were linear over at least 75% reaction, with correlation coefficients of 0.999 or better. Initial bromine concentrations were kept in the range $2.5–5.0 \times 10^{-4}$ M to minimize any contribution from the parallel third-order process (see accompanying paper). Unfortunately *trans*-cyclooctene reacted too rapidly to give reliable rate plots and probably has $k_2 \geq 5 \times 10^5$ l. m^{-1} sec^{-1}. The rates of bromination of the less reactive olefins (*i.e.*, stilbenes) were measured conventionally using a Cary 16 spectrophotometer, by following the disappearance of Br_2 absorption at 490 nm, again under pseudo-first-order conditions.

Product Analysis.—The main purpose of the product studies on the olefinic pairs was to determine the degree of stereospecificity of the dibromides and acetoxybromides formed in the bromination process. Nonstereospecific addition was accompanied by checks on starting isomer stability under the reaction conditions. Analyses were routinely carried out by combined glpc–nmr techniques and extensive purification and physical property measurements were usually not attempted. Yields quoted are those from nmr or glpc analyses.

Product runs in acetic acid under conditions where the second-order process is dominant were carried out as follows. One gram of the olefin in a rapidly stirred solution in 20 ml of acetic acid was protected from the light while 1 equiv of bromine in 20 ml of acetic acid was added dropwise. The bromine concentration was kept as low as possible during addition so that the k_2 term would dominate.[45] This was easily controlled with the reactive olefins and addition was normally complete after 2–3 hr. Work-up was achieved by pouring the solution into a 50% mixture of water and pentane. Any excess bromine was destroyed by the addition of a few crystals of $Na_2S_2O_3$. The pentane layer was removed and washed successively with water, saturated aqueous $NaHCO_3$ until neutral, and finally with water. Drying over $MgSO_4$ and then evaporation yielded the crude product. The rather insoluble stilbene dibromides were isolated by pouring the acetic acid solution into water and filtering off the precipitate. The solid was washed with water and acetic acid and finally air dried. Analyses were performed by nmr on the reaction mixtures themselves.

Diisopropylethylenes.—The major product of the bromination of the trans isomer in acetic acid is the meso dibromide: 83% yield by glpc analysis (5-ft DEGS column at 105°, He 65 ml/min). Preparative glpc (13-ft TIDE column at 80°, He 65 ml/min) yielded a white crystalline solid: mp 53–54° (for the meso dibromide, lit.[46] mp 54–55°). *Anal.* (of the purified dibromide): Calcd for $C_8H_{16}Br_2$: C, 35.32; H, 5.93; Br, 58.75. Found: C, 35.76; H, 5.85; Br, 56.89. Some of the dibromides became slightly yellowish shortly after purification, owing to loss of bromine. Thus, some of the bromine analyses were too low. The nmr spectrum showed δ 0.91 (d, J = 6.5 Hz, 6 H), 1.08 (d, J = 6.5 Hz, 6 H), 2.53 (m, 2 H), 4.16 (t, J = 1.0 Hz, 2 H). The isopropylmethine hydrogen appears as a septet with further splitting by the bromomethine hydrogen. The isopropyl methyls, adjacent to the asymmetric center, are nonequivalent. The theoretical 12-line AA′XX′ spectrum[47] appears as an A_2X_2 where the equivalent bromomethine hydrogens show an apparent average coupling of 1.0 Hz with the isopropylmethine hydrogens. Decoupling the multiplet centered at δ 2.53 sharpens the 4.16 to a singlet, while decoupling the 4.16 triplet gives a sharp septet at 2.53. The magnitude of the vicinal coupling constant between the bromomethine hydrogens has frequently been used[2,44,46,48] as a criterion for distinguishing meso-*dl* and erythro-threo diastereomeric pairs. An examination of the steric and electrostatic interactions reveals that in the preferred rotamer of the meso dibromide, the vicinal hydrogens bear an anti relationship to one another. Anti-hydrogen couplings for compounds of this type are normally in the range 10–11 Hz while gauche couplings are usually 2–4 Hz. Thus, a large vicinal coupling constant would be expected for the meso dibromide. (No clear-cut distinction is possible on the basis of relative rotamer populations for the *dl* dibromide.) The nmr spectrum of a very concentrated solution of the purified meso dibromide in the ^{13}C–H splitting side-band regions ($J_{^{13}C-H}$ = 153 Hz) of the bromomethine hydrogens gave a doublet of doublets (J = 11.8 and 1.9 Hz) for the H–^{13}C(Br)–^{12}C(Br)–H grouping. The larger coupling is assigned to the vicinal $J_{AA'}$ coupling while the smaller must be the J_{AX} splitting. If $J_{AX'}$ is zero, then the observed average $J_{AX(X')}$ for the A_2X_2 system would be $(1.9 + 0)2 \simeq 1.0$ Hz, as observed. An nmr spectrum of the crude product from the trans olefin revealed the presence of 20% meso dibromide and 80% acetoxybromide. This latter compound was purified by preparative glpc on the Tide column to yield a colorless oil. The ir spectrum showed the intense sharp carbonyl

(41) J. Coops, R. S. Jessup, and K. van Nes, "Experimental Thermochemistry," Vol. I, F. D. Rossini, Ed., Interscience, New York, N. Y., 1956, Chapter 3.

(42) E. W. Washburn, *Nat. Bur. Stand. J. Res.*, **10**, 525 (1933), and ref 41, Chapter 5.

(43) Reference 17, p 152.

(44) Reference 17, pp 101–113.

(45) K. Yates, R. S. McDonald, and S. A. Shapiro, *J. Org. Chem.*, **38**, 2460 (1973); see accompanying paper.

(46) J. R. Chretien, Doctoral Thesis, University of Orleans, France, 1971.

(47) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, Elmsford, N. Y., p 392.

(48) C. A. Kingsbury and D. C. Best, *J. Org. Chem.*, **32**, 6 (1967).

absorption at 1750 cm^{-1}; nmr spectrum δ 0.8–1.1 (m, 12 H), 2.03 (s, 3 H), 2.1–2.7 (m, 2 H), 3.91 (d of d, J = 2.0, 10.2 Hz, 1 H), 5.08 (d of d, J = 2.8, 10.2 Hz). The methyl peaks near δ 1 are an overlapping series of four doublets, since all are nonequivalent. The bromomethine hydrogen causes the δ 4 resonance, and the acetoxymethine the δ 5 peak. The vicinal dimethine coupling is 10.2 Hz, and, by similar arguments on the basis of rotamer populations to those above, this acetoxybromide can be assigned the erythro stereochemistry.

The acetoxybromides from *trans*- and *cis*-diisopropylethylene were prepared following the method of Jovtscheff.[49] Bromination of the cis olefin in acetic acid gave a white crystalline solid which appeared to be a single compound (>99% pure) by glpc analysis. A sublimed sample had mp 73–74° (for the *dl* dibromide, lit.[46] mp 73°). *Anal.* Calcd for $C_8H_{16}Br_2$: as above. Found: C, 35.46; H, 5.96; Br, 58.17. No carbonyl absorption was observed in the ir spectrum of the crude product in a Nujol mull. Analysis by glpc revealed the absence of the meso dibromide and the erythro and threo acetoxybromides. The nmr spectrum of purified sample showed δ 1.02 (d, J = 6.5 Hz, 6 H), 1.15 (d, J = 6.5 Hz, 6 H), 2.0–2.4 (m, 2 H), 3.70–3.85 (m, 2 H). On the basis of steric and electrostatic effects, no one conformation is clearly predominant for the *dl* dibromide and the $J_{AA'}$ coupling should be smaller than that observed for the meso dibromide. An nmr spectrum of the pure dibromide from the cis olefin in the ^{13}C–H side-band regions ($J_{^{13}C-H}$ = 146 Hz) of the bromomethine multiplet centered at δ 3.77 showed the H–^{13}C–^{12}C–H grouping to give a doublet of doublets (J = 3.5 and 8.2 Hz). The 3.5-Hz coupling was assigned to the isopropyl methine–bromomethine splitting. Thus, the vicinal bromomethine coupling is at most 8.2 Hz, lower than that obtained in the meso dibromide. This dibromide is assigned the *dl* stereochemistry.

The acetoxybromide from the cis olefin, prepared by the method outlined above, was free from any major impurities by glpc analysis. Short-path distillation yielded a colorless liquid: bp 46–47° (0.1 mm). *Anal.* Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62; Br, 31.82; O, 12.74. Found: C, 47.84; H, 7.32; Br, 32.83; O (by difference), 12.40. The nmr spectrum showed δ 0.8012 (m, 12 H), 1.65–2.25 (m, 2 H), 1.99 (s, 3 H), 3.91 (d of d, J = 5.0, 5.9 Hz, 1 H), 4.87 (d of d, J = 5.0, 6.7 Hz, 1 H). An intense carbonyl peak was observed at 1745 cm^{-1} in the ir spectrum. The 5.0-Hz coupling is assigned to the vicinal bromomethine–acetoxymethine splitting. This is lower than the analogous 10.2-Hz coupling found in the erythro isomer; so this compound is assigned the threo-acetoxybromide stereochemistry. None of this compound was detected in either the trans- or cis-olefin product from addition of bromine in acetic acid. The four compounds were separable by glpc (6-m DEGS column at 93°, He 120 ml/min).

***tert*-Butylethylethylenes.**—Bromination of the trans olefin in acetic acid gave one major component in <99% yield by glpc analysis (DEGS column at 90°, He flow rate 100 ml/min). Some addition–elimination products were detected but in trace amounts (<1%). Short-path distillation of the crude reaction mixture yielded a colorless liquid: bp 47–48° (0.13 mm). *Anal.* for a dibromide. Calcd for $C_8H_{16}Br_2$: C, 35.2; H, 5.93; Br, 58.75. Found: C, 35.59; H, 5.94; Br. 58.49. The nmr spectrum showed δ 1.97 (t, J = 7 Hz, 3 H), 1.15 (s, 9 H), 1.7–2.2 (m, 2 H), 4.23 (d of t, J = 6.2, 1.9 Hz, 1 H), 4.38 (d, J = 1.9 Hz, 1 H). The vicinal coupling constant, observed directly from the *tert*-butyl bromomethine hydrogen resonance, is 1.9 Hz, low even for a pure gauche coupling. Very low vicinal coupling constants have been previously observed for the erythro dibromide and dichloride adducts of *tert*-butylmethylethylene (*i.e.*, 2.4 and 2.0 Hz, respectively[48]). Comparing our results with those of these workers, on the basis of both the erythro and threo adducts, this compound is assigned the erythro-dibromide structure. By combined nmr and glpc analysis, under the above conditions, it was found that <1% threo dibromide or either of the acetoxybromides, all independently synthesized, could be present in the bromination product. The acetoxybromide of the trans olefin was prepared by the method outlined above[49] and subjected to short-path distillation: bp 46–47° (0.12 mm). Glpc analysis showed the presence of roughly 5% erythro dibromide in this acetoxybromide, but also that this compound was not present in the trans-olefin product run. No further purification was attempted. The ir spectrum showed an intense carbonyl absorption at 1735 cm^{-1}. The nmr spectrum confirmed the acetoxybromide structure: δ 1.03 (t, J = 7.4 Hz, 3 H), 1.13 (s, 9 H), 1.5–2.0 (m, 2 H), 2.03 (s, 3 H), 3.99 (d, J = 3.1 Hz, 1 H), 4.7–5.1 (m, 1 H). The bromomethine hydrogen on an alkyl substituted carbon is found to resonate in the range of 3.7 4.5[46] while the acetoxymethine hydrogen occurs at 2.7–5.1. In this acetoxybromide the bromomethine hydrogen appears as a doublet (and thus must be on the carbon with the *tert*-butyl substituent) from which the vicinal coupling constant, 3.1 Hz, may be obtained directly. Again, this low coupling constant, characteristic of a gauche hydrogen arrangement, is larger than that in the acetoxybromide obtained from the cis olefin and is assigned the "erythro"[50] stereochemistry. Thus, regiospecific and stereospecific acetoxybromide formation has occurred from the trans olefin. Only one acetoxybromide is observed by glpc or nmr.

Glpc analysis of the crude product from the bromination of the cis olefin showed the presence of two components in the ratio of 92:8. Retention times and nmr spectra of these components were different from those of either of the two compounds characterized above. In fact, <1% erythro dibromide or "erythro" acetoxybromide could be present from glpc and nmr analyses. Short-path distillation yielded a colorless liquid, bp 45–46° (0.08 mm), with no separation of these two components. The nmr of the major component is strongly suggestive of a dibromide: δ 0.8–1.2 (m, 3 H) 1.18 (s, 9 H), 1.6–2.3 (m, 2 H), 3.93 (d, J = 1.6 Hz, 1 H), 3.9–4.3 (m, 1 H). The vicinal coupling constant, 1.6 Hz, is smaller than that observed in the erythro dibromide; so this compound is assigned the threo-dibromide stereochemistry. The structure of the minor component of the reaction mixture was proved by independent synthesis. Treatment of the cis olefin with NBS in acetic acid, followed by work-up and distillation, yielded a colorless liquid: bp 44.0–44.5° (0.12 mm). The ir spectrum revealed an intense carbonyl absorption at 1735 cm^{-1}. Glpc analysis showed the presence of only one component (>99%). Analysis confirmed the compound was the acetoxybromide. *Anal.* Calcd for $C_{10}H_{19}O_2Br$: C, 47.82; H, 7.62; Br, 31.82; O, 12.74. Found: C, 47.80; H, 7.63; Br, 32.08; O (by difference), 12.49. The nmr spectrum [δ 0.6–1.2 (m, 3 H), 1.08 (s, 9 H), 1.3–1.8 (m, 2 H), 2.02 (s, 3 H), 3.89 (d, J = 1.1 Hz, 1 H), 5.00 (d of t, J = 6.9, 1.1 Hz, 1 H)] supports the acetoxybromide structure, where the *tert*-butyl and bromine are attached to the same carbon. The vicinal coupling constant, 1.1 Hz, is lower than that obtained from the "erythro" acetoxybromide; so this compound is assigned the "threo"-acetoxybromide structure. This compound was identified, by comparison of glpc retention times and nmr spectra, as the 8% component in the product run on the cis olefin. These four compounds were all separable by glpc (DEGS column at 90°, He 100 ml/min).

Di-*tert*-butylethylenes.—Work-up of the bromination product of the cis olefin yielded a white crystalline solid which, by glpc analysis (DEGS column at 100°, He 120 ml/min), was >99% a single component. A sample, purified by sublimation, had mp 57–58° and analyzed for a dibromide. *Anal.* Calcd for $C_{10}H_{20}Br_2$: C, 40.02; H, 6.72; Br, 53.26. Found: C, 40.01; H, 6.65; Br, 52.94. The nmr spectrum showed only two hydrogen absorptions: δ 1.13 (s, 9 H), 4.19 (s, 1 H). The high amplitude spectrum in the ^{13}C–H splitting side-band regions of the bromomethine hydrogens ($J_{^{13}C-H}$ = 145 Hz) revealed a doublet (J = 1.0 Hz) for the H–^{13}C(Br)–^{12}C(Br)–H grouping. From this very low vicinal coupling constant, close to that observed for the analogous dichloride assigned the *dl* stereochemistry[24] (0.8 Hz), the *dl*-dibromide structure was assigned to this compound. Treatment of the cis olefin with NBS in acetic acid and nmr analysis of the crude reaction work-up revealed that the major product, an acetoxybromide, was not present in >0.5% yield in the above product run: nmr spectrum of the acetoxybromide δ 0.98 (s, 9 H), 1.05 (s, 9 H), 2.05 (s, 3 H), 3.97 (d, J = 1.0 Hz, 1 H), 4.95 (d, J = 1.0 Hz, 1 H). The very low vicinal coupling constant, 1.0 Hz, again prompted the assignment of the threo stereochemistry. The addition of 1 equiv of bromine to a stirred, light-protected solution of the trans olefin in acetic acid gave a very complex product mixture. Glpc analysis of the crude product showed, other than unreacted trans olefin,

(49) A. Jovtscheff and S. L. Spassov, *Monatsh. Chem.*, **98**, 2272 (1967).

(50) Although the terms erythro and threo are not strictly applicable to these unsymmetrical ($R_1 \neq R_2$) acetoxybromides, the terms "erythro" and "threo" will be used here so that the stereochemistry of the acetoxybromides can be related directly to that of the analogous dibromides.

four major components with retention times of 1.8, 9.4, 12.4, and 16.5 min. Neither the *dl* dibromide nor the threo acetoxybromide, obtained above from the cis olefin, could be detected by glpc or nmr analysis. The nmr spectrum was similarily uninformative; other than peaks corresponding to the trans olefin (≃40% after addition of 1 equiv of bromine) there were complex absorptons in the regions of δ 0.9–1.4, 1.6–2.1, and 3.8–4.2. Little, if any, solvent incorporation appeared to have occurred. Complete bromination of the product mixture resulted in the disappearance of the starting material peak and that at 1.8 min in the glpc analysis. This fact, combined with the very short retention time, suggested that this component was a bromo olefin. Treatment of the trans olefin with NBS in acetic acid gave as the major product (>90%), a compound having a retention time of 1.8 min. Purification by preparative glpc (20% SE-30 on Chromsorb P at 200°, He flow rate 70 ml/min) yielded a colorless liquid which, from the elemental analysis and nmr spectrum, was concluded to be the rearranged bromo olefin, 4-bromo-2,3,5,5-tetramethyl-1 hexene. A rearranged chloro olefin of exactly analogous structure has been observed from the chlorination of the trans olefin in CCl_4.[24] *Anal.* Calcd for $C_{10}H_{19}Br$: C, 54.80; H, 8.74; Br, 36.46. Found: C, 55.08; H, 8.75; Br, 36.50. Comparison of the glpc retention time and nmr spectrum of this compound with that of the crude trans-olefin bromination product revealed that this compound was present in the product in roughly 15% yield. No acetoxybromide was observed from the trans-olefin reaction with NBS in acetic acid. An attempt was made to collect pure samples of the longer retention time components from the reaction mixture but the severe glpc conditions required (column temperature <220°) caused considerable decomposition.

Stilbenes.—The crude solid product from the bromination of the trans isomer in acetic acid was highly insoluble in most organic solvents in which an nmr spectrum could be obtained. The solid had a high, sharp melting point, 239–240°, close to that for an independently synthesized sample of the meso dibromide: mp 242–243° (prepared in CH_2Cl_2) (lit.[8] mp 237–239°). The ir spectrum of the crude sample (KBr pellet) gave absorptions at 601 and 551 cm^{-1}, characteristic of the meso dibromide. Those chracteristic of the *dl* dibromide, also synthesized independently [mp 114–115° (lit.[8] mp 110–111°)], at 668 and 574 cm^{-1} were absent. A high amplitude nmr spectrum of a saturated solution of the crude product in CCl_4 showed a very weak resonance near δ 2 characteristic of an acetate. Thus, the trans olefin brominates to form predominantly the meso dibromide with a trace of acetoxybromide, unaccompanied by *dl* dibromide. This is in accord with previous studies by other workers.[8]

The crude product from the bromination of the cis olefin under identical conditions gave a solid which showed softening near 111–112°, the bull of the material melting above 235°. The ir spectrum showed strong absorption characteristic of the meso dibromide, and small *dl*-dibromide peaks. A saturated solution of the crude adduct in CCl_4 gave nmr peaks at δ 1.78 and 2.03 which could be characteristic of the two diastereomeric acetoxybromides. Although no quantitative information can be obtained from this data, it does appear that nonstereospecific but stereoselective syn addition has occurred.[8] A check for olefin isomerization during this run was very informative. An 0.23 *M* solution of *cis*-stilbene in acetic acid was stirred for 2–3 hr at room temperature. There was no detectable isomerization by glpc (DEGS column at 200°, He 170 ml/min). After addition of 1% of the equivalent amount of bromine and stirring until complete reaction, it was found that 6–7% of the olefin was *trans*-stilbene. These conditions would closely resemble those in a kinetic run. No further change in olefin ratio occurred after 3 hr. After addition of 5% of the bromine, roughly 25% isomerization had occurred after 0.5 hr and no further change up to 17 hr took place. After addition of 50% of the equivalent amount of bromine, 90% of the unreacted olefin was the trans isomer after 0.5 hr, while, after 24 hr and complete reaction, all unreacted olefin was the *trans*-stilbene. Thus, it is likely that the lack of stereospecific addition to the cis olefin is at least partly due to isomerization under the bromination conditions.

β-*tert*-Butylstyrenes.—Both isomers were stable in acetic acid for 24 hr. Less than 1% of the other isomer could be detected by glpc or nmr analysis. The dibromides and acetoxybromides were too involatile for glpc analysis; thus all analyses were carried out by nmr. The dibromides were prepared by the slow addition of a bromine to the stirred, light-protected olefin solution in CCl_4. Oxygen was continuously bubbled through the solution during the reaction. Work-up simply involved removal of the solvent by evaporation. The acetoxybromides were prepared by the NBS–acetic acid method[49] previously described. All adducts were of the 3,3-dimethyl-1 phenyl 1,2 dibromo (or 1 acetoxy 2 bromo) butane type. Both the erythro and threo diastereomers of both compounds were observed and characterized by their nmr spectra. No peaks other than those attributed to these four compounds or unreacted starting material were observed. Product ratios were measured by repeated integrations of the appropriate nmr resonances.

Two dibromides were produced in a 4:1 ratio from the bromination of the trans-olefin in CCl_4. The fact that major dibromide has the larger vicinal coupling constant, 4.6 Hz, relative to 2.0 Hz for the minor component, led to the assignment of the erythro stereochemistry to this major product. The minor component is assigned the threo-dibromide structure. The same two dibromides are formed in a 2:1 ratio from the bromination of the cis isomer in CCl_4. Again the erythro dibromide is the major product, but now a higher proportion of the threo adduct formed supports the stereochemical assignments.

The NBS method on the trans olefin produced two acetoxybromides in the ratio of 11.5:1. The nmr data again suggest the predominant product is the "erythro" acetoxybromide since it has the large vicinal coupling constant, 6.7 Hz, relative to 1.9 Hz for the minor component, assigned the "threo" acetoxybromide structure. These diastereomers are produced in a 1:6.7 ratio from the cis olefin; again the higher proportion of the "threo" adduct supports the assigned structures.

The bromination of these olefins in acetic acid (under predominant k_2 conditions[46]) gave all of the above adducts. The trans isomer produced a 3.3:1 ratio of the erythro and threo dibromides, respectively (98% of the product), along with 2% "erythro" acetoxybromide. The cis isomer produced a 2.2:1 ratio of these dibromides (80% of the product) and a 9:1 ratio of the "erythro" and "threo" acetoxybromides, respectively.

Aliquots of one of the bromination runs of the cis olefin in acetic acid were checked by nmr to test for isomerization. No detectable (>5%) isomerization of the cis to trans olefin had occurred up to 60% reaction. Thus, the lack of stereospecificity is not due to isomerization of the starting material.

Cyclooctenes.—Bromination of the cis isomer in acetic acid gave one major product (>90%) by glpc (DEGS column at 135°, He 130 ml/min). Short path distillation of the crude product afforded a colorless liquid, bp 63–66° (0.02 mm) [for *trans*-1,2-dibromocyclooctane, lit.[27a] bp 89–91° (at 0.5 mm)], which turned yellow on standing. The dibromide appears to liberate bromine spontaneously. The nmr of the freshly distilled compound was taken: δ 1.2–2.8 (m, 12 H), 4.3–4.8 (m, 2 H). The crude product also showed a small acetate signal at δ 1.93 which may be present in 2–3% yield. No elimination products were detectable.

Bromination of the trans olefin in acetic acid proceeded with HBr evolution indicative of considerable solvent incorporation or addition–elimination. The crude work-up revealed, by glpc analysis, the presence of at least nine components other than unreacted olefin. The complex nmr spectrum revealed only very small peaks near δ 2 indicative of very little solvent incorporation. Three peaks of retention time ≤2.5 min reveal the presence of significant amounts of elimination products (bromo olefins, ≃35% yield). One such product could be 3-bromocyclooctene,[27b] but transannular reactions also have been reported during the bromination of medium-ring olefins.[27c] Thus, other olefins formed by a 1,4 hydride transfer followed by elimination could be present. Three peaks of retention times expected for the dibromides (8.3, 9.8, and 11.3 min) were also detected. The latter has the same retention time as the trans dibromide obtained from the cis isomer. None of the cis-1,2 dibromide has been previously detected but two rearranged dibromides, 1,3-dibromo-2-methyl- and 1,4-dibromo-5-methylcycloheptane, have been detected.[51] These dibromides account for 60% of the product mixture; the remaining 5% is probably an acetoxybromide or a secondary reaction product of the bromo olefins. Such a complex reaction mixture from the trans olefin, together with Hbr formation, has been previously reported.[27c,51] Not all of the products have been characterized and extensively studied here since the kinetic work on this olefin could not be carried out.

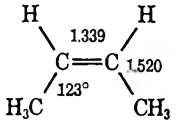
(51) N. L. Allinger and L. A. Tushams, *Tetrahedron*, **23**, 2051 (1967).

Registry No.—4-Bromo-2,3,5,5-tetramethyl-1-hexene, 40087-55-6; *trans*-β-methylstyrene, 873-66-5; *cis*-β-methylstyrene, 766-90-5; 1-hexene, 592-41-6.

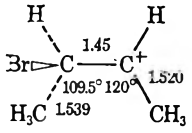
Appendix

Geometrical Calculations.—The reasonable assumption is made that all of the ground-state enthalpy difference between cis- and trans-1,2-disubstituted ethylenes is due to the unfavorable steric interaction between substituent groups in the cis isomer. The trans isomer and its possible reaction intermediates should be essentially free of such steric effects. Thus formation of intermediates (or transition states) from the cis olefin, in which the distance between the 1,2 substituents has decreased, should result in an increase in the isomeric enthalpy difference established in the initial states, while, for those in which this distance is increased, there should be a decrease (or even disappearance) of the isomeric enthlapy difference.

In an attempt to test the premise that type I intermediate geometry (*i.e.*, open α-bromocarbonium ion) would decrease the steric effects from those present in the olefins, whereas type III geometry (cyclic bromonium ion) would increase them, calculations of interatomic distances were carried out using the 2-butene system as a model. Geometries of molecules were taken from the literature;[52] those for ionic species were estimated using standard trigonal or tetrahedral bond angles and bond lengths optimized from *ab initio* calculations.[53] Based on the geometry shown for *cis*-2-butene, the methyl(carbon)–methyl(carbon) distance is 2.995 Å, whereas, in the trans isomer, this distance is 3.933 Å.

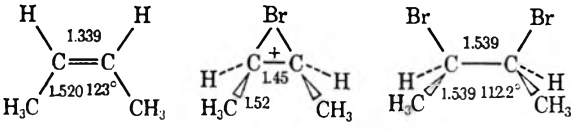


The geometry of an initially formed (*i.e.*, before rotation) α-bromocarbonium ion was taken to be as shown, where the methyl group on the tetrahedral carbon is 30° below the plane of the other three carbons. The methyl–methyl distance[54] in this ion is 3.057 Å, which increases to 3.154 and 3.255 Å, with small



rotations of 10 and 20°, respectively, about the central C–C bond, in the direction which relieves steric effects. Thus, even if no rotation were allowed at the transition state leading to the open ion, it seems clear that the steric interaction between adjacent groups would be expected to decrease from that in the starting olefin. Even assuming central bond length of 1.41 Å for this ion, which is very short for a C(sp²)–C(sp³) bond, the distance between the *cis*-methyl groups is still significantly greater (3.017 Å) than in the olefin.

Calculation of the corresponding methyl–methyl distance in the cyclic bromonium ions (of type III) is more difficult. The problem is to estimate a reasonable geometry for this ion. The central carbon–carbon bond length was taken to be 1.45 Å. This is the same as the C(sp³)–C(sp²) bond length estimated for the open ion, and also the value obtained from an optimization of the energy for protonated ethylene.[55] (This estimated bond length seems very reasonable, since, in the following three-membered cyclic heterocycles, the C–C bond length decreases smoothly with the electronegativity of the heteroatom or group X, *e.g.*, cyclopropane (X = CH_2) 1.562 Å, ethylene sulfide (X = S) 1.492 Å, ethyleneimine (X = NH) 1.48 Å, and ethylene oxide (X = 0) 1.467 Å.[52] The electronegativity of Br^+ in the cyclic bromonium ion would be expected to be greater than that of oxygen in ethylene oxide.) However, the extent of rehydridization at the olefinic carbons must be estimated. Thus, while the bond length increases from 1.339 to 1.539 Å from the olefin to the product, 2,3-dibromobutane, the bond angle decreases from the roughly trigonal 123 to the roughly tetrahedral 112.2° (see figures below). A methyl–carbon bond



length of 1.52 Å appears reasonable. Methyl–methyl distance calculations were then made for several methyl–carbon–carbon bond angles near 120°. Assuming only a small amount of bond angle change at the transition state (*i.e.*, a methyl–carbon–carbon bond angle of 120°) the methyl–methyl distance is 2.96 Å. An angle of 119° leads to a distance of 2.91 Å. Thus, the calculations again indicate that the steric interactions become more severe at the transition state leading to the bridged ion.

A second approach is based on a comparison of initial olefin and final product geometries. The factors affecting the methyl–methyl distance in the bromonium ion are the central carbon–carbon bond length and the methyl–carbon–carbon bond angle. The geometries estimated for the olefin and the dibromo adduct, given above, are believed to be quite precise. Remembering that no rotation is allowed about the central carbon–carbon bond in a bridged ion, then, if the bond length and bond angle changes from olefin to product occur synchronously and smoothly, the methyl–methyl distance at the transition state (geometry resembling type III) should be somewhere intermediate between that in the olefin (2.995 Å) and the all-cis eclipsed form of the product (2.702 Å).

Finally, an estimate can be made from the known geometries of analogous three-membered-ring heterocyclic systems.[52] Based on the parent molecules ethylene oxide, ethyleneimine, and enthylene sulfide the methyl–methyl distance in the cis-1,2-disubstituted systems can be estimated to be 3.03 (oxide), 2.96

(52) Tables of Interatomic Distances and Configuration in Molecules and Ions, *Chem. Soc. Spec. Publ. (London)*: No. 11 (1958); No. 18 (1965).

(53) R. Sustmann, J. E. Williams, M. J. S. Dewar, L. C. Allen, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 5350 (1969); J. E. Williams, V. Buss, and L. C. Allen, *ibid.*, **93**, 6867 (1971).

(54) The methyl–methyl distance in all these calculations refers to the carbon–carbon distance.

(55) D. T. Clark and D. M. J. Lilley, *J. Chem. Soc. D*, 549 (1970).

(imine), and 2.95 Å (sulfide). Thus, if the cyclic bromonium ion geometry resembles these analogous heterocycles, the cis methyl–methyl distance would either be expected to remain roughly the same as that in the olefin, or decrease. Because of the longer bond lengths to the heteroatom and greater distortion of the three-membered-ring system from the equilateral cyclopropane structure, the ethylene sulfide is probably the best model for the cyclic bromonium ion. Therefore, all three methods of estimating its geometry suggest that the steric interactions between *cis*-1,2-methyl groups in a cyclic bromonium ion would either be as severe or, more probably, be increased over those present in the parent olefin.

Kinetics of Thermal Electrocyclic Ring Closure. Alkyl-1,3,5-hexatrienes[1]

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Received October 12, 1972

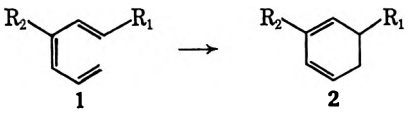
Kinetic studies of thermal electrocyclization of a series of 1- and 3-alkyl-1,3,5-hexatrienes (R = Me, Et, *t*-Bu) yielded the following relative rates: 3-*t*-Bu > 3-Et, 3-Me > 1-Et > 1-Me, H. The activation enthalpies of the 3-alkyl series were, in general, 3 kcal/mol less than either the 1-alkyl counterparts or the parent hydrocarbon. These results can be interpreted in terms of the donative ability of alkyl groups, steric retardation at the reaction sites, and differences in ground-state energies and/or conformation.

Thermal electrocyclic ring closure of various systems containing $4n + 2$ π electrons has been studied extensively during the past few years.[2,3] However, although the kinetics of isolated examples have been reported,[4-8] no comprehensive study has yet been reported which evaluates the magnitude of substituent effects as a function of chain position.[9] The Woodward–Hoffmann description[2] of this reaction as a disrotatory, concerted process has been confirmed repeatedly in the literature, but primarily in terms of stereochemistry. Few predictions concerning the ability or inability of substituents to affect the course or energetics of this process have been forthcoming, even though an examination of the scattered published examples[3-8] indicates possible substituent participation in the reaction.

In order to demonstrate the existence or absence (and/or magnitude) of substituent effects in the $4n + 2$ π system, we have studied the thermal ring closure of a series of 1- and 3-alkyl-1,3,5-hexatrienes (alkyl = Me, Et, *i*-Pr, *t*-Bu) in the temperature range 348–423° K, resulting in the formation of 5-alkyl- and 2-alkyl-1,3-cyclohexadienes, respectively, as shown in Scheme I.

Pure substituted 1,3,5-hexatrienes were prepared from appropriately substituted hexadienols essentially by the method of Hwa, *et al.*,[10] which we have also used previously.[11,12] This is illustrated in Scheme II.

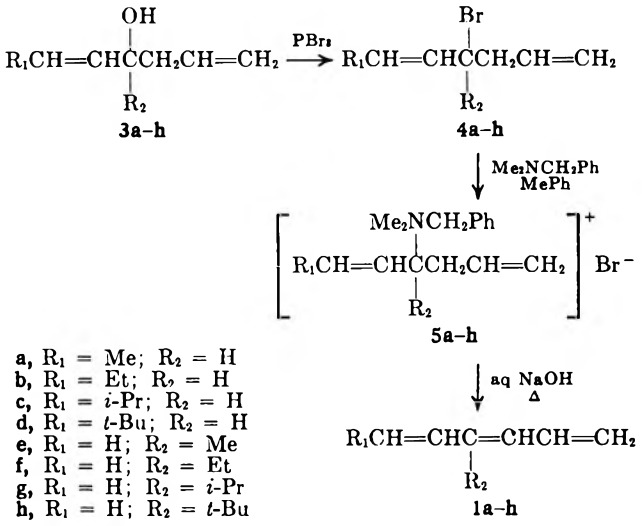
SCHEME I



1 **2**

1a, R_1 = Me; R_2 = H
b, R_1 = Et; R_2 = H
c, R_1 = *i*-Pr; R_2 = H
d, R_1 = *t*-Bu; R_2 = H
e, R_1 = H; R_2 = Me
f, R_1 = H; R_2 = Et
g, R_1 = H; R_2 = *i*-Pr
h, R_1 = H; R_2 = *t*-Bu

SCHEME II



3a-h **4a-h** **5a-h** **1a-h**

a, R_1 = Me; R_2 = H
b, R_1 = Et; R_2 = H
c, R_1 = *i*-Pr; R_2 = H
d, R_1 = *t*-Bu; R_2 = H
e, R_1 = H; R_2 = Me
f, R_1 = H; R_2 = Et
g, R_1 = H; R_2 = *i*-Pr
h, R_1 = H; R_2 = *t*-Bu

The trienes were obtained free of contamination from either the ring-closure products (**2a–h**) or the corresponding aromatized products. In general, a mixture of geometric isomers may be expected from the Hwa procedure; however, as can be seen in Table I, several trienes were obtained geometrically pure.

It is obvious that the 1-*i*-Pr and 1-*t*-Bu trienes thus could not be included in the kinetic analysis. We have not been able to synthesize these trienes with a cis configuration about the central double bond.

The trends evident in the two series can be rationalized from consideration of the most probable ground-

(1) (a) Portions of this paper were presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972. (b) Taken in part from the Ph.D. dissertation of Thor P. Jondahl, Northern Illinois University, Dec 1971.

(2) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie-Academic Press, Weinheim/Bergstr., 1970.

(3) H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969).

(4) K. E. Lewis and H. Steiner, *J. Chem. Soc.*, 3080 (1964).

(5) E. N. Marvell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965).

(6) K. W. Egger, *Helv. Chim. Acta*, **51**, 422 (1968).

(7) E. Vogel, W. Grimme, and E. Dinné, *Tetrahedron Lett.*, 391 (1965).

(8) C. J. Gaasbeek, H. Hogeueen, and H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **91**, 821 (1972).

(9) The present discussion applies only to acyclic examples. The authors are aware of the many cyclic examples, but do not feel that their inclusion would be meaningful in that the complication of ring size and conformation obscures the presence or absence of steric and other secondary effects.

(10) J. C. H. Hwa, P. L. de Benneville, and H. J. Sims, *J. Amer. Chem. Soc.*, **82**, 2537 (1960).

(11) C. W. Spangler and G. F. Woods, *J. Org. Chem.*, **28**, 2245 (1963).

(12) C. W. Spangler and G. F. Woods, *ibid.*, **30**, 2218 (1965).

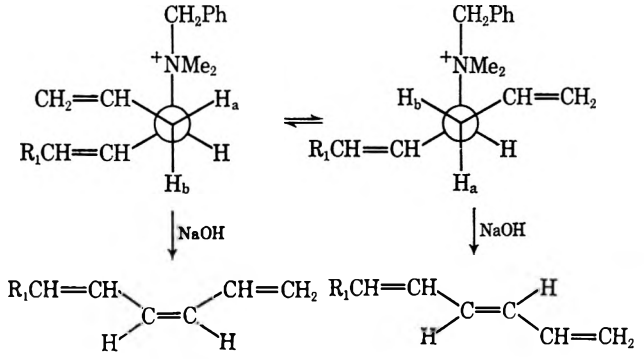
TABLE I
GEOMETRIC COMPOSITION OF TRIENES
$R_1CH{=}CHCR_2{=}CHCH{=}CH_2$

Substituents	Composition
R_1 = H; R_2 = Me	55% trans; 45% cis
R_1 = H; R_2 = Et	35% trans; 65% cis
R_1 = H; R_2 = *i*-Pr	25% trans; 75% cis
R_1 = H; R_2 = *t*-Bu	100% cis
R_1 = Me; R_2 = H	56% trans,trans; 44% cis,trans
R_1 = Et; R_2 = H	68% trans,trans; 32% cis,trans
R_1 = *i*-Pr; R_2 = H	100% trans,trans
R_1 = *t*-Bu; R_2 = H	100% trans,trans

state conformations of the intermediary ammonium salts which result from minimization of electronic and steric interactions.

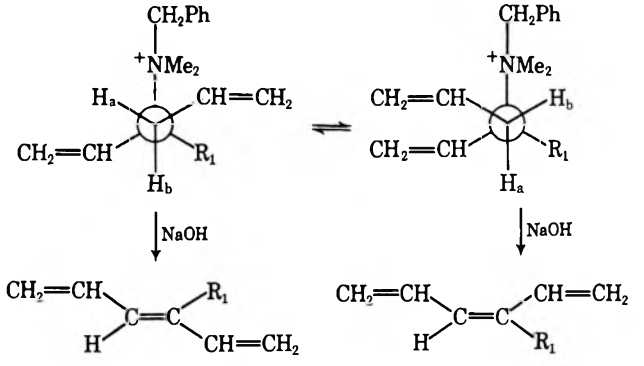
Thus, in Scheme III, as R_1 increases in bulk, the conformation leading to formation of a trans central

SCHEME III



double bond is preferred, while, in Scheme IV, the conformation yielding a cis configuration would predominate.

SCHEME IV



The pure trienes, usually a geometric mixture containing the isomer with a central cis configuration, were sealed in Pyrex capillary ampoules and placed in thermostatically controlled baths at various temperatures. The progress of the reaction was followed by measuring the loss of cis isomer, as well as the appearance of the appropriate 1,3-cyclohexadiene, by quantitative gas–liquid partition chromatography (glpc).

Lewis and Steiner[4] indicated in their study of the thermal behavior of pure *cis*- and pure *trans*-1,3,5-hexatriene that no cis–trans isomerization occurs below 460° K. However, other workers[5,13] have found that isomerization does occur to some extent with substituted trienes. In our studies we found isomerization occurring in the following trienes as well as ring closure: 1-Me, 3-Me, 1-Et, and 3-Et. For the larger groups, no thermal isomerization occurs below 410° K. Ring closure of 3-isopropyl-1,3,5-hexatriene was complicated by other thermal processes, primarily double-bond migration into the isopropyl group. Similarly, the 1-isopropyl counterpart was severely contaminated with a nonconjugated triene formed during the Hwa process. Thus the isopropyl members of the series were not amenable to clean kinetic analysis.

Since some cis–trans isomerization in the unreacted trienes (**1a,b,e,f,h**) occurs simultaneously with thermal ring closure, loss of cis isomer is not a simple first-order process.[14] However, corrections of this type are easily handled by digital computer, utilizing a program DRATE,[14] developed by Butterfield,[15] and modified by us for use with an IBM 360-67 system. The program incorporates a minimization technique developed by Rosenbrock and Story,[16] which minimizes the summed squared error between the calculated and experimentally measured data until the rate constants are changing by less than 1% on successive calculations.[17] *cis*-3-*tert*-Butyl-1,3,5-hexatriene followed simple first-order kinetics as determined by the least squares program. Similarly, temperature dependence of the rate constants calculated by the above methods and the corresponding Arrhenius parameters were determined by least squares analysis. Rate constants for thermal ring closure are shown in Table II, while the activation parameters are shown in Table III.[18]

Examination of the results leads to several interesting conclusions. It appears that introduction of an electron-donating group in the 3 position, relatively remote from the reaction centers, increases the cyclization rate: 3-*t*-Bu > 3-Et ~ 3-Me > H. Similarly, introduction of the same group in the 1 position, a reaction site, has a much smaller effect on the overall rate: 1-Et > 1-Me ~ H. Activation enthalpies show a similar trend, the compounds having 3 substituents having lower activation enthalpies than the parent 1,3,5-hexatriene, while the 1-substituted compounds are essentially the same. Activation entropies are all negative, indicating similar transition states for all trienes in this study.

The results can be interpreted as indicating the operation of several possible effects: (1) an increase in the polyene π-electron density by introduction of a substituent electron-donating group remote from the reaction center will increase the rate of ring closure and lower the activation enthalpy; (2) introduction of a group in the 3 position will alter the relative amounts of s-trans and s-cis conformations, thereby allowing an increase in cyclization rate as the relative percentage of

(13) P. Vander Burg, Ph.D. Dissertation, University of Leiden, 1970.

(14) The data may be fit to either of the following isomerization schemes: (a) trans $\rightleftharpoons$ cis $\rightarrow$ diene, or (b) trans $\rightarrow$ cis $\rightarrow$ diene. In either case, the rate constants for ring closure are identical. The mechanism for the isomerization process is obscure at present, but probably involves activation by the walls of the capillary tube. Cis–trans isomerization occurs only about the central 3,4 double bond; the configurations about the terminal double bonds remain fixed.

(15) R. O. Butterfield, *J. Amer. Oil Chem. Soc.*, **46**, 429 (1969).

(16) H. H. Rosenbrock and C. Story, "Computational Techniques for Chemical Engineers," Pergamon Press, Elmsford, N. Y., 1966, pp 64–68.

(17) A 360-67 source listing in Fortran IV and test data for a variety of first-order schemes will be sent to interested people on request.

(18) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 378–379.

TABLE II

RATE CONSTANTS[a] FOR ELECTROCYCLIZATION OF ALKYL-1,3,5-HEXATRIENES

Substituent	Temp, °C	$k \times 10^5$, sec^{-1}	Substituent	Temp, °C	$k_1 \times 10^5$, sec^{-1}
1-Me[b]	98.8	0.196	1-Et[d]	98.8	0.735
	109.8	0.815		115.0	2.03
	124.1	2.39		125.0	5.56
	140.0	11.9		135.0	15.5
	150.0	28.3		150.0	66.9
3-Me[c]	101.0	1.02	3-Et[e]	101.0	2.14
	109.9	3.03		115.7	6.74
	121.0	6.43		124.1	13.2
	131.2	21.9		135.0	42.4
	150.0	88.8		150.0	92.8
H[4]	150.0	24.1	3-*t*-Bu[f]	75.0	0.54
				85.0	1.68
				100.0	7.82
				115.0	31.9
				125.4	84.6

[a] All rate constants fitted to a minimum sum-squared error and change <1% on successive calculations. All temperatures maintained to within ±0.1°. [b] Thermolysis of mixture containing 56% trans,trans and 44% cis,trans. [c] 55% trans and 45% cis. [d] 68% trans,trans and 32% cis,trans. [e] 35% trans and 65% cis. [f] Cis isomer present initially in >99%.

TABLE III

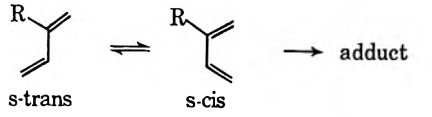
ACTIVATION PARAMETERS FOR ELECTROCYCLIZATION OF ALKYL-1,3,5-HEXATRIENES[a]

Substituent	Temp, °K	Log *A*, sec^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu (temp, °K)
1-Me	372–423	11.8	28.9 ± 0.2	−4.9 ± 0.5
		(11.6)[b]	(29.2)[b]	(374)
3-Me	374–423	11.7	26.1 ± 0.3	−12.4 ± 0.7
				(374)
1-Et	372–423	11.2	27.8 ± 0.4	−6.2 ± 1.2
				(372)
3-Et	374–423	9.9	26.0 ± 0.5	−11.3 ± 1.5
				(374)
3-*t*-Bu	348–398	11.9	26.7 ± 0.1	−11.3 ± 0.3
				(373)
H[4]	390–434	11.9	29.1 ± 0.5	−7.3

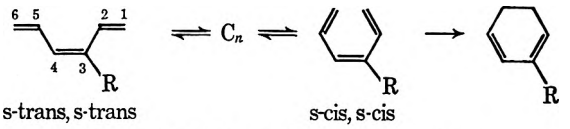
[a] Errors quoted are standard errors. See ref 18. [b] Reference 13.

s-cis conformations increase; (3) introduction of a group in the 1 position leads only to a very slight increase in rate, and no meaningful reduction in the enthalpy owing to a competing steric retardation at the reaction sites. That this retardation is not more dramatic supports our contention that alkyl groups are acting as electron donors in this reaction.

Craig and coworkers[19] have observed similar rate phenomena in their study of the reaction of 2-alkyl-1,3-butadienes with maleic anhydride (*t*-Bu > *i*-Pr > Et > Me > H). They attribute this rate increase to the increasing stability of the s-cis conformation relative to the s-trans. Thus as R increases in bulk, the s-cis conformation becomes more stable.



The situation with regard to this argument is more complicated. The most stable conformation of both *trans*- and *cis*-1,3,5-hexatriene is linearly extended.[20,21] Substitution of an alkyl group in the 3 position should produce effects similar to those observed by Craig,[19] since a group in the 3 position would destabilize the s-trans conformation as one goes from hydrogen to *tert*-butyl. However, two double bonds must achieve an s-cis conformation prior to ring closure, and only a partial enhancement of rate might be expected.[22,23] It is highly unlikely that the 3-alkyl group will affect the conformational equilibrium involving the 5,6-



C_n = other intermediate conformations

vinyl group. It is interesting to also note that Craig attributed partial rate enhancement in the 1- and 2-alkyl-1,3-butadienes to the electron-releasing character of the alkyl group (both 1-Me and 2-Me > H).

Since the enthalpy and entropy differences for the trienes in this study are relatively small, it is quite possible that they merely represent differences in ground-state energies. It is not immediately obvious, however, how one can account for a difference of 3 kcal/mol by this line of reasoning for the 3-alkyl trienes.

Thus we feel that substituents remote from the reaction site *do* affect the rates of electrocyclization and, to a lesser extent, the activation enthalpy. Groups at the 1 position display similar behavior, although at a much reduced level, primarily owing to the added phenomenon of steric retardation. It would be extremely interesting to examine the electrocyclization of trienes containing either strong electron-donating or withdrawing groups (OR, NR_2, NO_2, CN, Cl, etc.). However, these compounds have either not been produced in a pure state, or they are not particularly stable.[11,13,24] We believe that our results indicate that much more attention should be paid to perturbations in either the electron density or steric requirements of the electrocyclization transition state, although the latter has been recognized previously by some workers.[5,8,25] It is quite probable that investigations with strong donating or withdrawing groups, or with much greater steric interference at the reaction centers, will reveal much greater deviations than we have observed.

(19) D. Craig, J. Shipman, and R. Fowler, *J. Amer. Chem. Soc.*, **83**, 2885 (1961).

(20) E. Lippincott, C. White, and J. Siblia, *ibid.*, **80**, 2926 (1958).

(21) E. Lippincott and T. Kenney, *ibid.*, **84**, 3641 (1962).

(22) An excellent discussion on diene reactivity in general, and the effect of conformation on the rate of Diels–Alder addition in particular, may be found in J. Sauer, *Angew. Chem., Int. Ed., Engl.*, **6**, 16 (1967), and references cited therein.

(23) A referee has suggested that these arguments violate the Curtin–Hammett principle. However, this principle is usually invoked for the situation in which two conformations, in equilibrium with each other, produce different transition states which, in turn, produce different products which are not easily interconvertible. The reaction sequence in the case of conformational equilibrium of 3-alkyl-1,3,5-hexatriene allows only one conformation (s-cis,s-cis) to produce one transition state and one product. Thus the rate of formation of the transition state and product is directly proportional to the relative percentage of triene having an s-cis,s-cis conformation and the Curtin–Hammett principle is not violated.

(24) C. W. Spangler and R. P. Hennis, *Org. Prep. Proced.*, **2**, 75 (1970).

(25) R. Huisgen, A. Dahmen, and H. Huber, *Tetrahedron Lett.*, 1461 (1969).

Experimental Section[26]

1,3,5-Heptatriene (1a).—1,3,5-Heptatriene was prepared and purified essentially by the method of Spangler and Woods,[12] bp 30–32° (25 mm), n^{23}D 1.5231 [lit.[12] bp 115° (760 mm), n^{24}D 1.5239]. The triene was subjected to glpc analysis, which revealed a mixture of two isomers. Subsequent analysis showed this to be a mixture of 56% trans,trans and 44% cis,trans isomers. The nmr spectrum revealed τ 8.25 (d, 3 methyl protons, J = 5.5 Hz), 4.6–5.2 (m, 2 vinyl protons), 3.0–4.6 (m, 5 vinyl protons). The ir spectrum was consistent with the assigned structure.

5-Methyl-1,3-cyclohexadiene (2a).—A kinetics sample tube containing 1,3,5-heptatriene (56% trans,trans and 44% cis,trans) was heated at a constant temperature of 150° for 2 hr and then submitted to glpc analysis, revealing one new peak (*ca.* 36% conversion). The new product was collected by preparative glpc and assigned the structure of 5-methyl-1,3-cyclohexadiene based on its uv and nmr spectra. The uv spectrum contained one broad absorption at λ_{max} 258 nm (ϵ_{max} 4200) [lit.[27] λ_{max} 259 nm (ϵ_{max} 3700)]. The nmr spectrum revealed τ 9.0 (d, 3 methyl protons, J = 7.0 Hz), 7.3–8.3 (m, 4 allylic protons), 3.8–4.6 (m, 4 vinyl protons).

1,5-Octadien-4-ol (3b).—*trans*-2-Pentenal (63.0 g, 0.72 mol) dissolved in 200 ml of dry ether was added dropwise to chilled allylmagnesium bromide prepared from allyl bromide (145.0 g, 1.2 mol) and magnesium turnings (73.0 g, 3.0 g-atoms) in 500 ml of dry ether. Hydrolysis and isolation of *trans*-1,5-octadien-4-ol (75.1 g, 83%) was accomplished in the usual manner, yielding a colorless liquid, bp 66–67° (10 mm), n^{23}D 1.4523.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.52; H, 11.38.

The nmr spectrum revealed τ 9.0 (t, 3 methyl protons, J = 7.5 Hz), 8.12 (s, 1-OH proton), 7.5–8.2 (m, 4-allylic protons), 5.89 (q, 1 methine proton, J = 6.0 Hz), 3.75–5.15 (br m, 5 vinyl protons). The ir spectrum was consistent with the assigned structure.

Benzyldimethyl-4-(1,5-octadienyl)ammonium Bromide (5b).—1,5-Octadien-4-ol (75 g, 0.60 mol) in 200 ml of dry ether was added dropwise over a period of 2 hr with stirring to phosphorus tribromide (81 g, 0.3 mol). During the addition the reaction mixture was cooled in an ice bath. The work-up and isolation of the crude 4-bromo-1,5-octadiene (99 g, 87%) follows the procedure described by us previously[11,12] for allylic bromides.

A solution of the crude 4-bromo-1,5-octadiene (99 g, 0.52 mol) and *N,N*-dimethylbenzylamine (94.5 g, 0.70 mol) in 800 ml of dry toluene was prepared and allowed to stand overnight. The solution was then heated on a steam cone for 2–3 hr to complete salt formation. The product separated as a mixture of crystalline and brown glassy material (126 g, 75%). A small portion was recrystallized from ethyl acetate–ethanol, mp 141–142°.

Anal. Calcd for $C_{17}H_{26}BrN$: C, 62.96; H, 8.08; N, 4.32. Found: C, 62.62; H, 7.95; N, 4.55.

The combined crystalline–amorphous product was dissolved in 600 ml of water and the resulting aqueous solution was extracted several times with ether to remove suspended organic material. The yellow aqueous solution was heated to boiling to remove dissolved ether and then cooled to room temperature.

1,3,5-Octatriene (1b).—The above aqueous solution of benzyldimethyl-4-(1,5-octadienyl)ammonium bromide was added dropwise to a solution of sodium hydroxide (128 g in 800 ml of water) which was undergoing distillation. The product was extracted from the distillate in *ca.* 200 ml of ether and washed twice with 3 *N* HCl and twice with water before drying with anhydrous magnesium sulfate. After removal of the solvent, distillation at reduced pressure yielded 1,3,5-octatriene (12 g, 29%), bp 52–53° (23 mm), n^{23}D 1.5200 [lit.[28] bp 66–67° (60 mm), n^{20}D 1.517].

Anal. Calcd for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.78; H, 11.22.

Glpc analysis of the product indicated a mixture of two isomers. Subsequent analysis showed this to be a mixture of 68% *trans,trans*- and 32% *cis,trans*-1,3,5-octatriene. The nmr spectrum showed τ 9.0 (t, 3 methyl protons, J = 7.5 Hz), 7.6–8.2 (q, 2 methylene protons, J = 7.0 Hz), 2.8–5.2 (br m, 7 vinyl protons).

5-Ethyl-1,3-cyclohexadiene (2b).—A kinetics sample tube containing 1,3,5-octatriene (68% trans,trans and 32% cis,trans) was heated at 150° for 2 hr and then submitted to glpc analysis, revealing one additional product (*ca.* 50% conversion), 5-ethyl-1,3-cyclohexadiene, based on the uv and nmr spectra: λ_{max} 259 nm (ϵ_{max} 4000) [lit.[29] λ_{max} 259 nm (ϵ_{max} 4300)]; τ 8.9–9.3 (m, 3 methyl protons), 8.35–8.8 (m, 2 methylene protons), 7.7–8.0 (m, 3 allylic protons), 3.9–4.4 (br m, 4 vinyl protons).

7-Methyl-1,5-octadien-4-ol (3c).—*trans*-4-Methyl-2-pentenal (66.3 g, 0.68 mol), dissolved in 250 ml of anhydrous ether, was added slowly to a chilled solution of allylmagnesium bromide prepared from allyl bromide (194 g, 1.6 mol) in 600 ml of anhydrous ether and magnesium turnings (97 g, 4.0 g-atoms). The product, *trans*-7-methyl-1,5-octadien-4-ol, was obtained in the usual manner, bp 68–70° (7 mm), n^{22}D 1.4497 (72.7 g, 76%).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.55; H, 11.78.

The nmr revealed τ 9.02 (d, 6 methyl protons, J = 7.0 Hz), 8.11 (s, 1-hydroxyl proton), 7.5–8.1 (m, 3 allylic protons), 5.88 (q, 1 methine proton, J = 6.0 Hz), 3.8–5.13, (br m, 5 vinylic protons). The ir spectrum was consistent with the assigned structure.

Attempted Preparation of 7-Methyl-1,3,5-octatriene (1c).—7-Methyl-1,5-octadien-4-ol (72.5 g, 0.52 mol) in 200 ml of dry ether was added dropwise during a period of 2.5 hr to phosphorus tribromide (85.5 g, 0.32 mol) with cooling. The crude bromide (100 g, 94%) was isolated in the manner described previously.[11,12]

Crude 4-bromo-7-methyl-1,5-octadiene (100 g, 0.5 mol) and *N,N*-dimethylbenzylamine (81 g, 0.60 mol) were mixed in 800 ml of dry toluene. Heating on a steam cone for 3 days produced a brown residue which proved to be *N,N*-dimethylbenzylammonium bromide, indicating dehydrohalogenation rather than salt formation.

The toluene solution was washed several times with 3 *N* HCl to remove amine, then with water, and finally dried with anhydrous-magnesium sulfate. The volume of the solution was reduced to 100 ml with a rotary evaporator. The toluene–triene mixture was then steam distilled from a solution of phosphoric acid (5 ml of 85% phosphoric acid in 500 ml of water). The organic product was extracted into pentane and the resulting pentane solution was dried with anhydrous magnesium sulfate. Distillation at reduced pressure yielded crude 7-methyl-1,3,5-octatriene, bp 52–54° (15 mm), n^{21}D 1.4982 (10.4 g, 17% based on the bromo precursor), as a colorless liquid.

Glpc analysis of the crude product showed three peaks, the first of which (13%) proved to be toluene. The uv spectrum of the second product (25%) was that of a typical triene, λ_{max} 253.0, 262.5, 273.5 nm ($\epsilon_{max} \times 10^{-4}$ 2.93, 4.04, 3.27), and the nmr showed τ 8.9–9.0 (d, 6 methyl protons, J = 6.5 Hz), 7.0–7.4 (m, 1 allylic proton), 3.5–5.2 (br m, 7 vinyl protons). There was no ir absorption in the region 800–850 cm^{-1}. On the basis of these results, the structure was assigned as *trans,trans*-7-methyl-1,3,5-octatriene.

The ultraviolet spectrum of the third component (62%) revealed one absorption band, λ_{max} 238.5 nm ($\epsilon_{max} \times 10^{-4}$ 2.84), and the nmr showed τ 8.27 (s, 6 methyl protons), 7.14 (t, 2 allylic protons, J = 6.5 Hz), 3.4–5.2 (br m, 6 vinylic protons). On this basis the third component was assigned the *trans*-2-methyl-2,4,7-octatriene structure. The ir spectra of the two trienes were consistent with the assigned structures. An analytical sample was collected *via* glpc, and contained the two trienes.

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.32; H, 11.68.

7,7-Dimethyl-1,5-octadien-4-ol (3d).—*trans*-4,4-Dimethyl-2-pentenal (56 g, 0.50 mol) in 200 ml of anhydrous ether was added to chilled allylmagnesium bromide, prepared from allyl

(26) Gas–liquid partition chromatography (glpc) was performed with an Aerograph Model 202-1B dual column instrument equipped with a Hewlett-Packard Model 3370A electronic integrator for peak area measurement. Glpc conditions for all runs: 0.25-in. SS columns, 15 ft, 15% 1,2,3-triscyanoethoxypropane (TCEP), column temperature 50–75°, He pressure 60 psig, flow rate 60 ml/min. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer using Spectrograde isooctane as the solvent (λ_{max} values are reported in nanometers), and infrared spectra with Beckman IR-8 or IR-12 spectrophotometers. Nmr spectra were determined as solutions in $CDCl_3$ (TMS) using a Varian A-60A spectrometer. All trienic spectra were recorded for mixtures of geometric isomers unless otherwise stated. All boiling and melting points are uncorrected. C, H, and N analyses were obtained using a Perkin-Elmer Model 240 elemental analyzer. Assignment of the hydroxyl proton in the nmr spectra of alcohols was accomplished by D_2O exchange.

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bromide (135.5 g, 1.12 mol) and magnesium shavings (68 g, 2.8 mol) in 400 ml of dry ether. The product, *trans*-7,7-dimethyl-1,5-octadien-4-ol, bp 69–70° (5 mm), $n^{21.5}$D 1.4492, was obtained in the usual manner (71 g, 92%).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.63; H, 12.02.

The nmr spectrum revealed τ 9.0 (s, 9 methyl protons), 8.18 (s, 1 hydroxyl proton), 7.7 (t, 2 allylic protons, J = 6.5 Hz), 5.88 (q, 1 methine proton, J = 6.0 Hz), 3.9–5.15 (br m, 5 vinylic protons). The ir spectrum was consistent with the assigned structure.

7,7-Dimethyl-1,3,5-octatriene (1d).—A solution of 7,7-dimethyl-1,5-octadien-4-ol (70.5 g, 0.46 mol) in 100 ml of dry ether was added dropwise to phosphorus tribromide (81 g, 0.3 mol) with cooling. The crude bromide, 4-bromo-7,7-dimethyl-1,5-octadiene (95 g, 95%), was isolated in the usual manner.

Reaction of the crude bromide (95 g, 0.44 mol) with *N,N*-dimethylbenzylamine (91.5 g, 0.68 mol) in 750 ml of dry toluene at room temperature for 1 week, followed by heating on a steam cone for 72 hr, yielded only *N,N*-dimethylbenzylammonium bromide. The toluene solution was thus treated as described above for 7-methyl-1,3,5-octatriene, and 7,7-dimethyl-1,5-octatriene was obtained (12.4 g, 21%) by vacuum distillation, bp 45–47° (6 mm), n^{23}D 1.5052.

Glpc analysis showed only one peak, while the uv spectrum had λ_{max} 252.0, 261.5, 272.5 nm ($\epsilon_{max} \times 10^{-4}$ 3.30, 4.54, 3.60). The nmr spectrum showed τ 8.98 (s, nine methyl protons), 4.6–5.15 (m, 2 vinyl protons), 3.7–4.3 (m, 5 vinyl protons). On the basis of the above, and subsequent thermal behavior, the product is assigned as *trans,trans*-7,7-dimethyl-1,3,5-octatriene.

Attempted Cyclization of 7,7-Dimethyl-1,3,5-octatriene (1d).—A sealed Pyrex ampoule containing *trans,trans*-7,7-dimethyl-1,3,5-octatriene was heated at 135° for 24 hr. Glpc analysis showed that no reaction had occurred.

7,7-Dimethyl-1,3,5-octatriene (5.0 g, 0.037 mol) was thermolyzed by dropwise addition through a 22-mm Pyrex tube packed to a depth of 27 cm with glass helices and externally heated to 350° with a Lindberg Hevi-duty split-tube electric furnace (0.5 ml/min). The thermolysis product was collected in a flask immersed in a Dry Ice–acetone bath, and subsequently warmed to room temperature. Glpc analysis of the crude product (4.7 g, 94% recovery) revealed at least 11 components. Seven of these minor constituents (3% of total product) were not identified. The four remaining constituents were identified by collecting the glpc effluent emanating from the chromatograph for each peak and analyzing by uv, ir, and nmr spectrometry. The mixture consisted of 5% 2-*tert*-butyl-1,3-cyclohexadiene, 16% 5-*tert*-butyl-1,3-cyclohexadiene, 72% *trans,trans*-7,7-dimethyl-1,3,5-octatriene, and 4% *tert*-butylbenzene. No *cis,trans*-7,7-dimethyl-1,3,5-octatriene could be detected. The ir, uv, and nmr spectra were all consistent with these assigned structures.

3-Methyl-1,3,5-hexatriene (1e).—3-Methyl-1,3,5-hexatriene was prepared and purified essentially by the method of Spangler and Woods,[12] bp 28–29° (25 mm), n^{24}D 1.5189 [lit.[12] bp 74° (50 mm), n^{26}D 1.5198]. Glpc analysis indicated a mixture of two isomers. Subsequent analysis showed this to be a mixture of 55% *trans*- and 45% *cis*-3-methyl-1,3,5-hexatriene. The nmr spectrum revealed τ 8.15 (s, three methyl protons), 4.5–5.2 (br m, 4 vinyl protons), 2.7–4.2 (br m, 3 vinyl protons). The ir spectrum was consistent with the assigned structure.

2-Methyl-1,3-cyclohexadiene (2e).—A sealed ampoule of 3-methyl-1,3,5-hexatriene (55% trans, 45% cis) was heated at 150° for 1 hr. Glpc analysis indicated one new product (*ca.* 80% conversion). This component was isolated by preparative glpc and had λ_{max} 260.5 nm (ϵ_{max} 4200) (lit.[27] λ_{max} 261 nm). The nmr spectrum of the diene revealed τ 8.3 (d, 3 methyl protons, J = 1.5 Hz), 7.92 (narrow m, 4 allylic protons), 4.55 (br m, 1 vinyl proton), 4.22 (m, 2 vinyl protons); thus the structure was assigned as 2-methyl-1,3-cyclohexadiene.

3-Ethyl-1,5-hexadien-3-ol (3f).—1-Penten-3-one (100 g, 1.2 mol) in 250 ml of dry ether was added to chilled allylmagnesium bromide prepared from allyl bromide (218 g, 1.8 mol) and magnesium turnings (110 g, 4.5 g-atoms) in 900 ml of anhydrous ether. 3-Ethyl-1,5-hexadien-3-ol was obtained in the usual manner (74 g, 49%), bp 47–48° (25 mm), n^{25}D 1.4500.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.07; H, 11.22.

Benzyldimethyl-3-(3-ethyl-1,5-hexadienyl)ammonium Bromide (5f).—3-Ethyl-1,5-hexadien-3-ol (74 g, 0.59 mol) in 200 ml of anhydrous ether was added to phosphorus tribromide (80 g, 0.30 mol) cooled by an ice bath. The crude product, 3-bromo-3-ethyl-1,5-hexadiene, was obtained as described previously as an unstable lachrymatory liquid (87 g, 78%). The crude product was treated immediately with *N,N*-dimethylbenzylamine (85 g, 0.63 mol) in 800 ml of dry toluene. The reaction mixture was allowed to stand for several days at room temperature. The crystalline salt (90 g, 60%) was then dissolved in water (500 ml) and treated as described above. A small portion was recrystallized from ethyl acetate–ethanol, mp 112–113°.

Anal. Calcd for $C_{17}H_{26}BrN$: C, 62.96; H, 8.08; N, 4.32. Found: C, 62.75; H, 7.89; N, 4.23.

3-Ethyl-1,3,5-hexatriene (1f).—The above aqueous solution of benzyldimethyl-3-(3-ethyl-1,5-hexadienyl)ammonium bromide (90 g, 0.28 mol) in 500 ml of water was added dropwise to a solution of sodium hydroxide (96 g in 800 ml of water) undergoing distillation. The distillate was treated as has been described previously. 3-Ethyl-1,3,5-hexatriene (23 g, 78%) was obtained as a colorless liquid, bp 46–47° (25 mm), n^{24}D 1.5175.

Anal. Calcd for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.67; H, 11.33.

Glpc analysis showed the triene to be a mixture of two isomers of 3-ethyl-1,3,5-hexatriene and 3% 2-ethyl-1,3-cyclohexadiene. Subsequent analysis showed the triene fraction to be composed of 64% *cis*- and 33% *trans*-3-ethyl-1,3,5-hexatriene. The nmr revealed τ 8.7–9.2 (t of d, J_{ab} = 7.0, J_{ax} = 2.0 Hz, 3-methyl protons), 7.4–8.0 (quintet, 2 methylene protons, J = 7.0 Hz), 4.5–5.1 (br m, 4 vinyl protons), 2.8–4.2 (br m, 3 vinyl protons).

2-Ethyl-1,3-cyclohexadiene (2f).—An ampoule containing a mixture of geometric isomers of 3-ethyl-1,3,5-hexatriene (64% cis, 33% trans) was heated at 150° for 1 hr. Glpc analysis revealed the major product to be 2-ethyl-1,3-cyclohexadiene (*ca.* 86% conversion). The uv spectrum revealed one broad absorption, λ_{max} 259 nm (ϵ_{max} 4400), while the nmr showed τ 8.8–9.2 (t, some narrow, long-range splitting superimposed on triplet splitting, 3 methyl protons, J = 7.0 Hz), 7.55–8.3 (br m, 6 allylic protons), 4.4–4.7 (br, m, 1 vinyl proton), 4.05–4.25 (m, 2 vinyl protons).

A Typical Oxidation of 4-Methyl-1-penten-3-ol (6).—4-Methyl-1-penten-3-ol (20 g, 0.20 mol)[30] dissolved in 400 ml of ether and 140 ml of water was oxidized essentially by the method of Vanstone and Johnson[31] with Jones reagent.[32] Glpc analysis (6 ft, 15% Carbowax 20M on 60–80 mesh Chromosorb W columns at 90°) of the ether solution showed the product composition to be 68.5% 4-methyl-1-penten-3-one and 31.5% unreacted alcohol. A sample of the pure ketone was collected and converted to the 2,4-dinitrophenylhydrazone. This derivative was recrystallized from ethanol–ethyl acetate, mp 126–128°.

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.86; H, 5.40; N, 19.92.

Isolation of the pure ketone was not attempted on a large scale and the above crude product mixture was dried with anhydrous magnesium sulfate and utilized directly in the next step.

3-Isopropyl-1,5-hexadien-3-ol (3g). A Typical Preparation.—The crude reaction product from three oxidation runs of 4-methyl-1-penten-3-ol, reduced in volume to 200 ml, was added to chilled allylmagnesium bromide, prepared from allyl bromide (121 g, 1.0 mol) and magnesium turnings (73 g, 3 g-atoms). The product was isolated in the usual manner, yielding 3-isopropyl-1,5-hexadien-3-ol (20 g, 23% overall based on starting 4-methyl-1-penten-3-ol), bp 60° (25 mm), n^{25}D 1.4517.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.88; H, 11.44.

The nmr spectrum revealed τ 9.1 (d, 6 methyl protons, J = 7.5 Hz), 8.09 (s, 1 hydroxyl proton), 7.9–8.6 (m, 1 methine proton), 7.7 (d, 2, allylic protons, J = 7.0 Hz), 3.8–5.17 (br m, 6 vinylic protons). The ir spectrum was consistent with this structure.

Benzyldimethyl-3-(3-isopropyl-1,5-hexadienyl)ammonium Bromide (5g).—3-Isopropyl-1,5-hexadien-3-ol (67.9 g, 0.48 mol) dissolved in 100 ml of anhydrous ether was added dropwise to phosphorus tribromide (70 g, 0.26 mol) with cooling. The crude product, 3-bromo-3-isopropyl-1,5-hexadiene, was obtained as described previously as an unstable lachrymatory liquid (82 g, 90%). The crude bromide (82 g, 0.40 mol) was added to *N,N*-dimethylbenzylamine (67.6 g, 0.50 mol) in 800 ml of dry toluene. This mixture was allowed to stand at room temperature for 1

(30) K & K Laboratories, Plainview, N. Y.

(31) A. E. Vanstone and J. S. Whitehurst, *J. Chem. Soc. C*, 1972 (1966).

(32) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

week and the crystalline product was collected (97 g, 72%). A small sample was recrystallized from ethyl acetate–ethanol, mp 124–126°.

Anal. Calcd for $C_{18}H_{28}NBr$: C, 63.71; H, 8.61; N, 4.13. Found: C, 63.77; H, 8.64; N, 4.23.

3-Isopropyl-1,3,5-hexatriene (1g).—A solution of benzyldimethyl-3-(3-isopropyl-1,5-hexadienyl)ammonium bromide (97 g, 0.27 mol in 500 ml of water) was added to a solution of sodium hydroxide (96 g in 800 ml of water) undergoing distillation. The distillate was treated as has been described previously. 3-Isopropyl-1,3,5-hexatriene, bp 51–53° (25 mm), $n^{25}D$ 1.5012, was obtained as a colorless liquid (10 g, 29%).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.58; H, 11.42.

Glpc analysis indicated that the product was a mixture of two isomers. Subsequent analysis showed this to be a mixture of 75% cis and 25% trans isomers. The nmr revealed τ 8.75–9.05 (d, 6 methyl protons, J = 7.0 Hz), 6.7–7.5 (septet, 1 methine proton, J = 6.5 Hz), 4.4–5.15 (br m, 4 vinyl protons), 2.9–4.2 (br m, 3 vinyl protons).

2-Isopropyl-1,3-cyclohexadiene (2g).—An ampoule containing 3-isopropyl-1,3,5-hexatriene (75% cis, 25% trans) was heated at 150° for 0.75 hr. Glpc analysis indicated *ca.* 90% conversion to 2-isopropyl-1,3-cyclohexadiene. The uv spectrum showed one broad absorption, λ_{max} 258 nm (ϵ_{max} 5200). The nmr spectrum revealed τ 8.80–9.15 (d, 6 methyl protons, J = 6.5 Hz), 7.50–8.0 (br m, 5 allylic protons, 4.4–4.7 (m, 1 vinyl proton), 4.0–4.2 (m, 2 vinyl protons).

3-*tert*-Butyl-1,5-hexadien-3-ol (3h).—4,4-Dimethyl-1-penten-3-one[33] (74 g, 0.66 mol) in 250 ml of anhydrous ether was added to chilled allylmagnesium bromide, prepared from allyl bromide (2.8 g, 1.8 mol) and magnesium turnings (110 g, 4.5 g-atoms). 3-*tert*-Butyl-1,5-hexadien-3-ol was obtained in the usual manner (35 g, 34%), bp 59–60° (1 mm), $n^{24}D$ 1.4521.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.92; H, 12.17.

The nmr spectrum showed τ 8.8–9.5 (m, 9 methyl protons), 8.5 (s, 1 hydroxyl proton), 7.5–8.1 (m, 2 allylic protons), 3.79–5.25 (br m, 6 vinyl protons). The *tert*-butyl signal appeared as three singlets whose peak heights were in the ratio 1:1.5:5.7 (total of 9 protons by integration) and this is interpreted as representing preferred but unknown conformations of the *tert*-butyl group. The ir spectrum was conistent with the assigned structure for this alcohol.

Benzyldimethyl-3-(3-*tert*-butyl-1,5-hexadienyl)ammonium Bromide (5h).—3-*tert*-Butyl-1,5-hexadien-3-ol (68 g, 0.44 mol) in 100 ml of anhydrous ether was added dropwise to phosphorus tribromide (85.5 g, 0.32 mol) with cooling. The crude product, 3-bromo-3-*tert*-butyl-1,5-hexadiene, was obtained as described previously as an unstable, lachrymatory liquid (88 g, 92%). The crude bromide (88 g, 0.40 mol) was treated with *N,N*-dimethylbenzylamine (67.5 g, 0.50 mol) in 800 ml of dry toluene overnight, after which the white, crystalline product was obtained (96 g, 68%). A small sample was recrystallized from ethyl acetate–ethanol, mp 165–166°.

Anal. Calcd for $C_{19}H_{30}NBr$: C, 64.76; H, 8.58; N, 3.98. Found: C, 64.33; H, 8.52; N, 4.02.

3-*tert*-Butyl-1,3,5-hexatriene (1h).—A solution of benzyldimethyl-3-(3-*tert*-butyl-1,5-hexadienyl)ammonium bromide (96 g, 0.27 mol) in 800 ml of water was added to a solution of sodium hydroxide (96 g in 600 ml of water) undergoing distillation. The distillate was treated as has been described previously. 3-*tert*-Butyl-1,3,5-hexatriene, bp 57–58° (25 mm), $n^{25}D$ 1.4813, was obtained as a colorless liquid (18 g, 48%).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.49; H, 11.57.

Glpc analysis revealed two peaks, of which the first peak (61% of the total) was subsequently shown to be 3-*tert*-butyl-1,3,5-hexatriene, and the second peak (39%) 2-*tert*-butyl-1,3-cyclohexadiene. Lowering both the column and detector temperatures shifted this ratio to 79:21. The nmr spectrum of the distilled sample revealed the *tert*-butyl group at τ 8.83 (9 methyl protons); however, this signal was split into very closely spaced singlets whose ratio was temperature dependent. The vinylic portion, τ 4.45–5.25 (m, 4 protons) and 2.8–4.1 (m, 3 protons), was the only other absorption. Inspection of models of *cis*-3-*tert*-butyl-1,3,5-hexatriene indicates that there are preferred orientations of the methyl groups, suggesting a possible magnetic nonequivalence (theoretical limit 2:1). At 31° the observed ratio is 4.3:1, while at −60° this ratio is lowered to 2.3:1, which supports this interpretation. The uv spectrum of the distilled triene shows a single absorption with no fine structure, λ_{max} 241.0 nm ($\epsilon_{max} \times 10^{-4}$ 1.46). On the basis of the spectral characteristics and glpc behavior, the product is assigned the *cis*-3-*tert*-butyl-1,3,5-hexatriene structure, which undergoes partial conversion to the diene when submitted to glpc analysis.

2-*tert*-Butyl-1,3-cyclohexadiene (2h).—An ampoule containing 100% *cis*-3-*tert*-butyl-1,3,5-hexatriene was heated at 150° for 1 hr. Glpc analysis of the product revealed only one product, λ_{max} 258 nm (ϵ_{max} 4100), nmr τ 8.95 (s, 9 methyl protons), 7.8–8.0 (m, 4 allylic protons), 4.34–4.65 (m, 1 vinyl proton), τ 3.7–4.2 (m, 2 vinyl protons). The structure was assigned as 2-*tert*-butyl-1,3-cyclohexadiene based on these properties.

Kinetic Studies.—The rates of electrocyclic ring closure of the substituted hexatrienes were determined using appropriate mixtures of geometric isomers, as neat liquids, at five different temperatures for each substrate. Ampoules (Pyrex glass, 12 cm × 2 mm i.d.) containing *ca.* 60 μl of neat liquid were degassed and sealed under 20 mm pressure and placed in a paraffin oil bath whose temperature was controlled by a CRC Circu-Temp temperature controller equipped with a CRC Temp-Tact Thermoregulator Model E. Bath temperatures were maintained to within ±0.1°. The disappearance of triene and appearance of the corresponding diene were followed by glpc analysis of the contents of a series of ampoules as a function of time. Ampoules were removed from the bath and quenched by plunging into an ice bath prior to analysis. Pretreatment of the ampoules by acid or base washing or by passage of steam through the capillary tubing was found to have little effect upon the rate of ring closure. Rates were followed generally for >50% conversion to the diene except for the lowest temperatures. In most cases, some trans–cis conversion also occurred. Thus rate constants were calculated using a modified DRATE[15] program which was able to correct the concentration of *cis* isomer as a function of time. Activation parameters were obtained from a standard least squares plot of ln k *vs.* $1/T$. All errors quoted are standard errors.

Assignments of Geometric Configuration. Alkyl-1,3,5-hexatrienes.—In the generation of the 1-alkyl series (alkyl = Me, Et, *i*-Pr, *t*-Bu), the configuration about one double bond (5–6) is fixed by starting with the trans aldehyde. Thus conversion of dienols **3a–d** *via* the reaction sequence outlines in Scheme II to trienes **1a–d** could produce either 3-trans,5-trans or 3-cis,5-trans (or both). For **1a** and **1b** (1-Me and 1-Et trienes), two isomers are indeed obtained, while only one is obtained for **1c** and **1d** (1-*i*-Pr and 1-*t*-Bu). The assignments of geometric isomerism is based on the following basis.

A. Flash Thermolysis.—All four samples (synthetic **1a**, **1b**, **1c**, and **1d**) were passed over Pyrex helices at 250° in a previously described[22] flow system (contact time 1 sec). For **1a** and **1b** glpc revealed that one of the isomers had been converted to a new compound. Isolation of the new substance followed by uv, nmr, and ir analysis showed them to be 5-alkyl-1,3-cyclohexadienes (5-Me and 5-Et, respectively). Area integration of the glpc trace showed that the decrease in area of the one triene peak was directly proportional to the area corresponding to the newly formed 5-alkyl-1,3-cyclohexadiene. Since only isomers with a cis configuration about the 3,4 double bond can undergo ring closure under these conditions,[4] the two isomers of **1a** and **1b** were assigned 3-trans,5-trans and 3-cis,5-trans configurations, respectively. The single geometric isomers obtained for the 1-*i*-Pr and 1-*t*-Bu trienes (**1c** and **1d**) were inert to thermolysis, indicating a 3-trans,5-trans configuration. Details of this technique have previously been described.[27] Thermolyses in sealed tubes, described above, follow the same pattern as flash thermolysis, except that a small amount of trans–cis isomerization occurs. Isolation and structure assignment of the 5-alkyl-1,3-cyclohexadienes, however, is identical in all respects.

The syntheses of **1e–g** (3-Me, Et, and *i*-Pr) produced both cis and trans isomers, while only one isomer of 3-*t*-Bu (**1h**) was obtained. Flash thermolysis of all four trienes were conducted as described above, yielding 2-alkyl-1,3-cyclohexadienes from the isomer having a 3-cis configuration, the 3-trans isomer being totally inert. These results agree with the predicted thermal behavior of 3-cis- *vs.* 3-trans configurations based on the results of Lewis and Steiner.[4]

(33) S. Archer, W. B. Dickinson, and M. J. Unser, *J. Org. Chem.*, **22**, 92 (1957).

B. Comparison to Alkyl-1,3,5-hexatrienes Generated by Photochemical Ring Opening of Alkyl-1,3-cyclohexadienes.—Irradiation (2537 Å) of 5-alkyl-1,3-cyclohexadienes (**2a–d**) in pentane solution yields mixtures of 3-*cis*,5-*cis*- and 3-*cis*,5-*trans*-**1a–h**, as has been reported previously.[34,35] Similarly, irradiation of **2e–h** yields *cis*-**1e–h**. Prolonged irradiation produces mixtures containing all possible isomers, which are resolvable under the glpc conditions described herein.[26] Comparison of retention times and admixture of the synthetic samples with those generated photochemically confirmed the assignments based on the flash thermoylsis results.

C. Uv Spectra.—Uv analysis yields a great deal of pertinent information. Two observations seem to be of general[10,28,36,37] use in assigning geometric configuration. (1) Isomers having a cis arrangement of hydrogens display a red shift compared to those with trans configurations. In the case of 3-alkyl-1,3,5-hexatrienes, the isomers having a cis arrangement of the two most bulky groups display a red shift compared to those with trans configurations. (2) Isomers having all-trans configurations display much greater extinction than the corresponding isomers wiht all-cis configurations. Along with this observation, the two minima associated with the three maxima in the triene spectrum are *much* more pronounced for the isomers having a 3-trans configuration *vis-à-vis* a 3-cis configuration. This latter correlation, however, is most useful if one has spectra for all possible isomers.

The following spectra were obtained for samples collected by glpc and analyzed immediately. For the 1-alkyl series, the 3-cis,5-trans and 3-trans,5-trans spectra were obtained for both the synthetic and photochemically produced samples, while the 3-trans,5-cis and 3-cis,5-cis spectra were obtained from the photochemical sample *only*. The data are arranged as follows (Table IV).

TABLE IV

Triene	Isomer	$\lambda_{max}^{isooctane}$	$\epsilon_{max} \times 10^4$
1a	3-*t*,5-*t*	271.5, 260.0, 250.5, 242	3.82, 4.60, 3.43 sh
	lit.[31]	271.5, 261.0, 251.0, 242.5 sh	
1a	3-*t*,5-*c*	274.0, 263.5, 254.5	3.04, 3.67, 2.67
	lit.[36]	274.0, 263.5, 254.5	
1a	3-*c*,5-*t*	273.5, 263.0, 255.0	2.83, 3.60, 2.86
	lit.[36]	272.6, 262.2, 252.8	
1a	3-*c*,5-*c*	275.0, 265.0, 256.5	1.05, 1.34, 1.08
	lit.[36]	275.0, 265.0, 256.5	
1b	3-*t*,5-*t*	272.5, 261.5, 252.0, 241	3.15, 4.39, 3.48 sh
1b	3-*c*,5-*t*	274.0, 264.0, 254.0	2.68, 3.50, 2.86
1b	3-*t*,5-*c*	275.0, 264.5, 254.5	2.75, 3.60, 2.60
1b	3-*c*,5-*c*	276.0, 266.0, 256.5	1.10, 1.45, 1.15
1c	3-*t*,5-*t*	273.5, 262.5, 253.0, 242	3.27, 4.04, 2.93 sh
1c	3-*c*,5-*t*	274.0, 263.0, 253.5	2.83, 3.60, 3.08
1c	3-*t*,5-*c*	276.5, 266.0, 257.0	3.01, 3.70, 2.87
1c	3-*c*,5-*c*	277.0, 266.5, 257.0	1.17, 1.50, 1.29
1d	3-*t*,5-*t*	272.5, 261.5, 252.0, 241	3.60, 4.54, 3.30 sh
1d	3-*c*,5-*t*	274.0, 263.0, 253.5	2.77, 3.47, 2.79
1d	3-*t*,5-*c*	276.0, 264.5, 255.0	2.89, 3.53, 2.78
1d	3-*c*,5-*c*	278.0, 267.0, 257.5	1.07, 1.40, 1.19
1e	3-*c*	272.0, 261.5, 252.0	2.22, 2.86, 2.22
1e	3-*t*	273.5, 263.0, 253.0, 244	3.48, 4.39, 3.27 sh
1f	3-*c*	275.0, 265.5, 256.0	1.85, 2.46, 1.67
1f	3-*t*	277.0, 266.0, 257.0, 248.0	2.22, 2.97, 2.18 sh
1g	3-*c*	276.5, 266.0, 257.5	1.58, 2.12, 1.87
1g	3-*t*	279.0, 268.0, 259.0	2.20, 2.70, 2.37
1h	3-*c*	241.0	1.46

D. Ir Spectra.—1-Alkyl-1,3,5-hexatrienes with a cis configuration about the central double bond display ir absorption in the region 818–825 cm^{-1} which Lippincott, *et al.*,[20,21] have assigned to the cis out-of-plane CH deformation. The corresponding trans out-of-plane absorption occurs at *ca.* 940 cm^{-1}. Thus the 3-trans,5-trans and 3-cis,5-trans isomers can be distinguished. The single isomers obtained in the 1-*t*-Bu and 1-*i*-Pr cases do not absorb in the region 800–850 cm^{-1}, indicating a 3-trans,5-trans configuration, which agrees with our assignment based on the flash thermolysis results as well as the uv assignments.

Registry No.—3-*trans*,5-*trans*-**1a**, 17679-93-5; 3-*trans*,5-*cis*-**1a**, 30915-43-6; 3-*cis*,5-*trans*-**1a**, 24587-25-5; 3-*cis*,5-*cis*-**1a**, 30915-44-7; 3-*trans*,5-*trans*-**1b**, 33580-04-0; 3-*trans*,5-*cis*-**1b**, 33580-05-1; 3-*cis*,5-*trans*-**1b**, 40087-61-4; 3-*cis*,5-*cis*-**1b**, 40087-62-5; 3-*trans*,5-*trans*-**1c**, 40087-63-6; 3-*trans*,5-*cis*-**1c**, 40087-64-7; 3-*cis*,5-*trans*-**1c**, 40087-65-8; 3-*cis*,5-*cis*-**1c**, 40087-66-9; 3-*trans*,5-*trans*-**1d**, 40087-67-0; 3-*trans*,5-*cis*-**1d**, 40087-68-1; 3-*cis*,5-*trans*-**1d**, 40037-06-7; 3-*cis*,5-*cis*-**1d**, 40087-69-2; *cis*-**1e**, 24587-27-7; *trans*-**1e**, 24587-26-6; *cis*-**1f**, 40087-72-7; *trans*-**1f**, 40087-73-8; *cis*-**1g**, 40087-74-9; *trans*-**1g**, 40087-75-0; *cis*-**1h**, 40087-76-1; **2a**, 19656-98-5; **2b**, 40085-08-3; **2e**, 1489-57-2; **2f**, 40085-10-7; **2g**, 40085-11-8; **2h**, 40085-12-9; *trans*-**3b**, 40087-77-2; *trans*-**3c**, 40087-78-3; *trans*-**3d**, 40087-79-4; **3f**, 40085-13-0; **3g**, 40085-14-1; **3h**, 40085-15-2; *trans*-**4b**, 40087-80-7; *trans*-**4c**, 40087-81-8; *trans*-**4d**, 40087-82-9; **4f**, 40085-16-3; **4g**, 40085-17-4; **4h**, 40085-18-5; *trans*-**5b**, 40087-83-0; **5f**, 40087-84-1; **5g**, 40087-85-2; **5h**, 40087-86-3; *trans*-2-pentenal, 1576-87-0; *N*,*N*-dimethylbenzylamine, 103-83-3; *trans*-4-methyl-2-pentenal, 24502-08-7; *trans*-4,4-dimethyl-2-pentenal, 22597-46-2; 1-penten-3-one, 1629-58-9; 4-methyl-1-penten-3-ol, 4798-45-2; 4-methyl-1-penten-3-one dinitrophenylhydrazone, 40087-88-5; 4,4-dimethyl-1-penten-3-one, 2177-30-2.

(34) C. Spangler and R. Hennis, *J. Chem. Soc., Chem. Commun.*, 24 (1972).
(35) R. Hennis, Ph.D. Thesis, Northern Illinois University, 1972.
(36) K. Egger and M. Jola, *Int. J. Chem. Kinet.*, 265 (1970).
(37) T. Sorensen, *Can. J. Chem.*, **42**, 2781 (1964).

Provincialin, a Cytotoxic Germacradienolide from *Liatris Provincialis* Godfrey with an Unusual Ester Side Chain[1]

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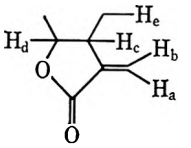
Received April 3, 1973

The isolation and structure determination of provincialin (1), a new cytotoxic germacradienolide from *Liatris provincialis* Godfrey, is reported. Provincialin belongs to the class of *trans*-$\Delta^{1,10}$,*cis*-$\Delta^{4,5}$-germacranolides and possesses an unusual C_{10} ester side chain made up of two C_5 acyl units. A revised stereochemistry is suggested for eucannabinolide.

In an earlier communication we reported the isolation of a new dihydrobenzofuran[2] from a chloroform extract of *Liatris provincialis* Godfrey, tribe Eupatoriae, family Compositae, a plant native to a few counties in north Florida.[3] The main component of the extract, however, was a new cytotoxic sesquiterpene lactone, provincialin, whose structure has now been elucidated as **1**.[4]

Provincialin (**1**), $C_{27}H_{34}O_{14}$, $[\alpha]D$ $-85°$, was a gum and various attempts to convert it into crystalline form proved unsuccessful. It was a conjugated γ-lactone (ir bands at 1760 and 1655 cm^{-1}; strong uv end absorption at 210 nm). The nmr spectrum exhibited the typical two doublets of H_a and H_b of partial structure A at 6.35 and 5.78 ppm, respectively. Spin-decou-



A

pling experiments involving H_a and H_b established the location of the narrowly split H_c multiplet at 2.91 ppm. Irradiation at the frequency of H_c collapsed a doublet of doublets at 5.93 ppm (J = 11.1 and 2.4 Hz) to a doublet and caused a change in the region around 5.3 ppm, where overlapping signals due to four hydrogens were located. Thus, H_d and H_e are at 5.93 and 5.3 ppm, respectively, or the reverse.

One narrowly split and one broadened three-proton signal at 1.83 and 1.77 ppm, respectively, in the nmr spectrum of provincialin indicated the presence of two vinylic methyl groups, both of which were coupled to protons giving rise to signals in the complex 5.3-ppm region. Epoxidation of **1** yielded a monoepoxide **2**, $C_{27}H_{34}O_{11}$, in whose nmr spectrum the signal at 1.77 ppm was replaced by a three-proton singlet at 1.47 ppm and one of the low-field signals was shifted upfield to 2.9 ppm.

The ir spectrum of provincialin had absorptions due to ester groups (1740 and 1730 cm^{-1}). One of the ester functions was obviously an acetate (nmr peak at 2.11 ppm). Provided that **1** was a sesquiterpene lactone, the molecular formula would require that the other ester substituent(s) comprised ten carbon atoms altogether.

Hydrolysis of **1** using methanol and K_2CO_3 afforded as the main component **3**, $C_{18}H_{26}O_6$. The nmr spectrum of **3** indicated the loss of one ester side chain; simultaneously one of the signals in the 5.3-ppm region had moved upfield to 4.07 ppm. The acetate group was still present, but the presence of a new three-proton singlet at 3.39 ppm and a two-proton signal centered at 3.67 ppm together with the disappearance of the signals due to H_a and H_b demonstrated that **3** was an 11,13-methanol adduct. These observations were supported by the mass spectrum, which displayed prominent peaks at m/e 338 (M), 306 (M − MeOH), 296 (M − ketene), 278 (M − HOAc), 260 (M − HOAc − H_2O), 246 (M − HOAc − MeOH), and 228 (M − HOAc − MeOH − H_2O). In view of the empirical formula of **3** the hydrolysis involved loss of one C_{10} side chain. Since the nmr spectra of **1** and **3** were similar in other respects, it was concluded that the hydrolysis had occurred without rearrangement.

Treatment of **3** with *m*-chloroperbenzoic acid afforded a monoepoxide **4**, $C_{18}H_{26}O_7$, whose nmr spectrum was amenable to extensive spin-decoupling experiments. Since **4** was an 11,13-methanol adduct, unambiguous identification of the signal due to H-7 (H_c) now had to be accomplished in the following manner. Irradiation at the frequency of the two H-13 protons (3.66 ppm) collapsed the H-11 multiplet to a doublet at 2.74 ppm. In turn, irradiation at the frequency of H-11 affected not only the signals due to the H-13 protons but also a multiplet located at 2.28 ppm, which could therefore be identified as the signal of H-7. In accordance with its now nonallylic nature, it was shifted upfield compared with its shift in the spectra of **1** and **2**.

In conformity with the results for **1** and **2** H-7 of **4** was coupled to a low-field doublet of doublets at 5.95 ppm, H-6 (H_d), and to a multiplet at 4.01 ppm, H-8 (H_e), ascribed to the proton on the carbon carrying the newly generated hydroxyl group. Hence, the C_{10} ester side chain was attached to C-8 in **1**. Conversely, irradiation at the frequency of H-8 collapsed the H-7 multiplet to a doublet of doublets and converted two doublets of doublets centered at 2.48 (J = 14.6 and 4.8 Hz) and 1.29 ppm (J = 14.6 and 1.9 Hz) to doublets. This indicated that H-8 was adjacent to a $-CH_2$ group, H-9a and H-9b.

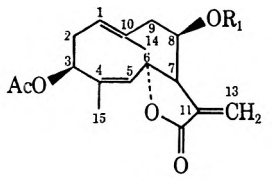
Spin-tickling experiments involving H-6, the lactone hydrogen, of **4** caused changes in another low-field doublet of doublets, H-5 (5.55 ppm; J = 11.0 and 1.2 Hz). The latter signal was collapsed into a doublet on irradiation at the frequency of the vinylic methyl doublet. In turn, the methyl doublet was

(1) (a) Part III in a series "Constituents of *Liatris* Species;" for part II, see W. Herz and I. Wahlberg, *Phytochem.*, in press. (b) This work was supported in part by U. S. Public Health Service Research Grant No. CA-13121 from the National Cancer Institute.

(2) W. Herz and I. Wahlberg, *Phytochem.*, **12**, 429 (1973).

(3) R. K. Godfrey, *Amer. Midland Naturalist*, **66**, 466 (1966).

(4) Provincialin showed significant cytotoxicity (ED_{50} = 3.5 μg/ml) against cells derived from the human carcinoma of the nasopharynx (KB). Cytotoxicity was assayed under the auspices of the National Cancer Institute.



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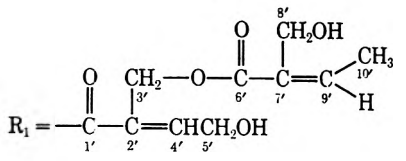

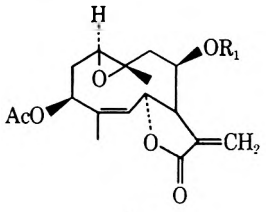

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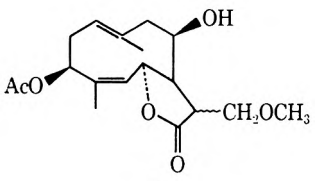

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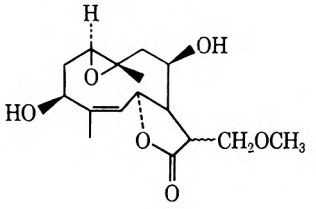

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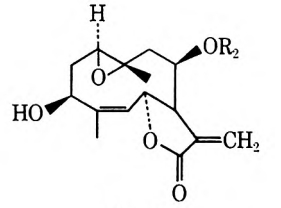
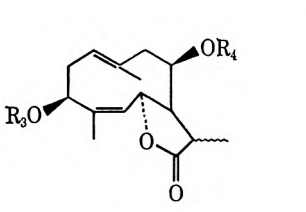
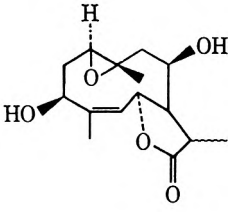


5a, R_2 = —C(=O)—C(=CH$_2$)—CH$_3$

b, R_2 = —C(=O)—C(=CH$_2$)—CH$_3$

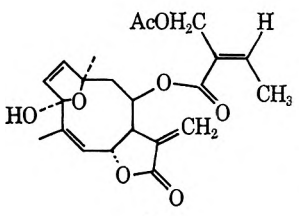




6, R_3 = Ac; R_4 = —C(=O)—C(=CH$_2$)—CH$_2$CH$_2$OH

7, R_3, R_4 = H

8



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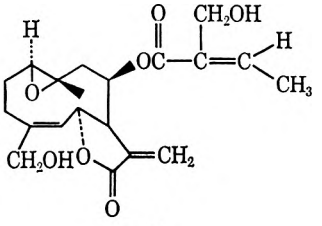

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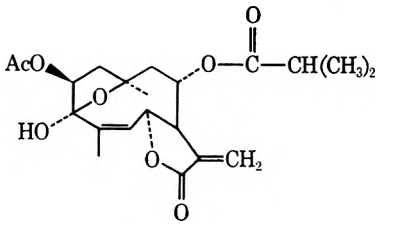

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converted into a singlet on irradiation at the frequency of H-5. Hence, **4** incorporates a 4,5 double bond and H-5 is a vinylic proton allylically coupled to the methyl group on C-4. On the basis of these spin-decoupling experiments it was concluded that the conversion of **3** into **4** involved epoxidation of the 1,10 double bond and that the 4,5 double bond, also adjacent to a methyl group, was not attacked.

The remaining low-field signal in the nmr spectrum of **4**, a narrowly split doublet of doublets at 5.23 ppm, was ascribed to a proton on a carbon carrying the acetate group. The multiplicity of the signal alone suggested that the proton was adjacent to two other protons, a requirement met if the acetate was attached to C-3 and not to C-2. This assignment was confirmed by further double irradiation experiments. Thus, the proton under the acetate grouping was coupled to two protons (H-2a and H-2b), which were represented by multiplets centered at 2.40 and 1.62 ppm. Irradiation at the frequency of each of these affected the other as well as the H-3 doublet of doublets and a doublet of doublets at 2.86 ppm due to H-1. Conversely, irradiation at the frequency of H-1 affected the signals ascribed to H-2a and H-2b and not that of H-3.

Information on the stereochemistry of the centers at C-3 and C-5 in **4** was obtained from NOE experiments. Thus, irradiation at the frequency of the vinylic methyl group at C-4 in **4** produced a 15% increase in the strength of the H-5 signal and a 9% increase in the strength of the H-3 signal. Hence, the 4,5 double bond is cis and H-3 is α oriented and cis to the methyl group at C-4, reminiscent of the stereochemistry of the corresponding centers in heliangine (**5a**)[5,6] and erioflorin (**5b**).[7]

In fact a comparison of the nmr spectral data revealed that the coupling constants of H-3 and H-5 as well as those of H-6, H-7, and H-8 in **4**, **5a**, and **5b** were very similar, indicating that these compounds had identical stereochemistry at all these positions.

Chemical evidence for the structure and stereochemistry of the sesquiterpene portion of provincialin was finally obtained as follows. Treatment of **1** with $NaBH_4$ resulted in the reduction of the 11,13 double bond and the formation of **6**, which incorporates a modified ester side chain (*vide infra*). Hydrolysis of **6** afforded in low yield the diol **7**, $C_{15}H_{22}O_4$, which on epoxidation furnished **8**. The latter compound was identical in all respects with dihydroheliangino, prepared from erioflorin (**5a**) on $NaBH_4$ reduction followed by hydrolysis.

Hence, the lactone ring in provincialin is trans-fused, the ester side chains attached to C-3 and C-8 are β oriented and the 4,5 double bond is cis, whereas the 1,10 double bond is trans.

We now turn to the structure of the ester side chain attached to C-8. On the basis of the results presented earlier it was concluded that the side chain incorporated ten carbon atoms. The nmr data of pro-

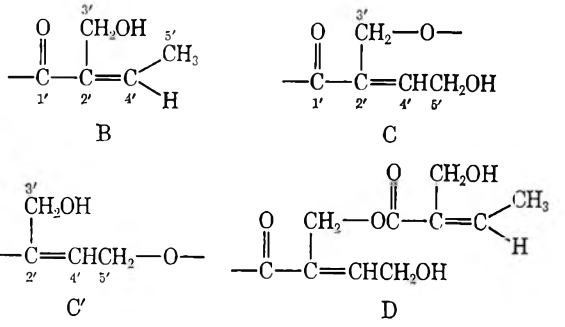
(5) H. Morimoto, Y. Sanno, and H. Oshio, *Tetrahedron*, **22**, 3173 (1966).

(6) M. Nishikawa, K. Kamiya, A. Takabatake, H. Oshio, Y. Tomiie, and I. Nitta, *Tetrahedron*, **22**, 3601 (1966). Contrary to its depiction as a *trans*-Δ^4-germacrenolide, this substance has a cis 4,5 double bond [*cf.* S. Neidle and D. Roberts, *Chem. Commun.*, 140 (1972)].

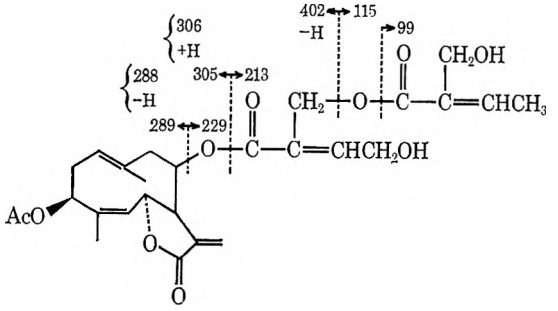
(7) S. J. Torrance, T. A. Geissman, and M. R. Chedekel, *Phytochem.*, **8**, 2381 (1969). The correlation of erioflorin with heliangine carried out by these authors requires that erioflorin be re-formulated as a *cis*-Δ^4-germacrenolide.

vincialin implied that these could be conveniently divided into two C_5 units. Thus, one of the units comprised a vinylic methyl group coupled to a vinylic proton (6.96 ppm, J = 7.3 Hz). This in turn was long range coupled to a two-proton broadened singlet at 4.32 ppm, which was assigned to a carbinol group, indicating that the first unit was of type B. In fact, the chemical shifts of all these protons agreed well with those published for the cis isomer of sarracinic acid.[8]

The other C_5 moiety was represented in the nmr spectrum of **1** by a two-proton doublet at 4.43 ppm coupled to a vinylic triplet at 7.02 ppm, which in turn showed a peak coupling to a two-proton signal centered at 4.93 ppm. It could therefore be formulated as C or C′. However, the relative chemical shifts of the two two-proton signals favored structure C, since the signal of the carbinol group is upfield from the signal of the hydrogens on the carbon carrying the ester group. The side chain was consequently of type D consisting of unit B esterified on C-3′ of unit C.



The mass spectral fragmentation of provincialin strongly supported this formulation. The base peak in the spectrum was due to a $C_5H_7O_2$ fragment of mass 99. Furthermore, abundant ions of masses 115 ($C_5H_7O_3$) and 402 (M − $C_5H_8O_3$) confirmed that unit B of the side chain was terminal (*cf.* molecular structure below



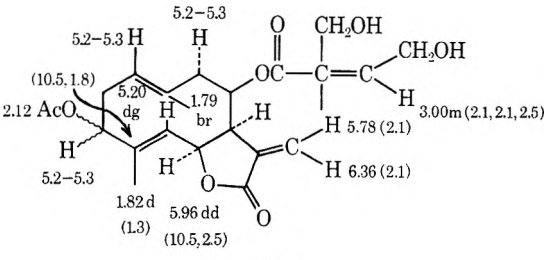
which summarizes the principal fragmentation reactions). The fragmentation also resulted in the formation of diagnostically important ions of masses 229.0711 ($C_{10}H_{13}O_5$) and 213.0788 ($C_{10}H_{13}O_5$) comprising the side chain or part of it, while charge retention on the sesquiterpene portion of the molecule led to fragments of masses 288, 289, 305, and 306. The latter ions decomposed further by elimination of ketene or acetic acid, giving rise to species of masses 228, 229, 246, 247, 264, 342, and 360.

Evidence for the structure of the side chain in **1** was also obtained by treatment of **1** with $NaBH_4$, which gave **6**, $C_{22}H_{30}O_7$. The reaction involved not only reduction of the 11,13 double bond but also simultaneous reduction of unit C and elimination of unit B of the side chain in a manner analogous to that reported for the acetylsarracinoyl residue in liatrin (**9**),[9] a conclusion which was confirmed by spectral data. The mass spectrum of **6** displayed peaks at m/e 99 ($C_5H_7O_2$), 307 (M − $C_5H_7O_2$), and 291 (M − $C_5H_7O_3$) demonstrating that the new side chain had the elemental composition $C_5H_7O_3$. Furthermore, the presence of peaks at m/e 230, 231, 248, 249, 290, and 291, shifted by two mass units compared with **1**, revealed the uptake of two hydrogen atoms by the sesquiterpene portion of the molecule. In harmony with these findings the nmr spectrum of **6** displayed a two-proton triplet at 3.70 ppm, assigned to the terminal carbinol group, now adjacent to a $-CH_2-$ group, whereas the terminal vinylic methylene group was represented by two narrowly split doublets at 6.23 and 5.72 ppm and the methyl group at C-11 by a new methyl doublet.

To our knowledge provincialin is the only sesquiterpene lactone encountered so far which possesses a C_{10} ester side chain comprising two C_5 acyl units. It is also noteworthy that one of these units is the cis isomer of sarracinic acid, since sarracinoyl type moieties are present in liatrin (**9**)[9] and punctatin (**10**)[1] as well as other sesquiterpene lactones[10] isolated from various *Liatris* species.

In conclusion, we wish to comment briefly on the values of $J_{7,13}$ in provincialin and related sesquiterpenoids which contain a trans-fused lactone ring closed to C-6 and incorporate a cis 4,5 double bond. In these compounds $J_{7,13}$ is less than 3 Hz, *e.g.*, for heliangin (**5a**, structure established by X-ray analysis[3,4]), $J_{7,13a}$ = $J_{7,13b}$ = 2 Hz; for erioflorin (**5b**, correlated with **5a**), $J_{7,13a}$ = $J_{7,13b}$ = 2 Hz; for liatrin (**9**, X-ray analysis[9]), $J_{7,13a}$ = $J_{7,13b}$ = 2.3 Hz; for punctatin (**10**),[1] $J_{7,13a}$ = 2.1, $J_{7,13b}$ = 1.4 Hz; for provincialin (**1**), $J_{7,13a}$ = 2.1, $J_{7,13b}$ = 1.9 Hz; and for woodhousin (**11**),[11] $J_{7,13a}$ = 2.4, $J_{7,13b}$ = 2.0. Thus, such compounds appear to constitute an important exception to the rule formulated by Samek[12] that in trans-fused lactones $J_{7,13} > 3$ Hz.

Samek's rule has been used in several instances to assign lactone ring stereochemistry in germacranolides, a procedure which in view of the observations recorded in the previous paragraph may be of dubious validity if the stereochemistry of the double bonds is not established with certainty. A particularly interesting example is eucannabinolide (**12a** or mirror image) where the assignment of stereochemistry was based solely on



12a

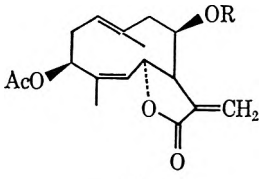
(8) J. D. Edwards, T. Matsumoto, and T. Hase, *J. Org. Chem.*, **32**, 244 (1967).

(9) S. M. Kupchan, V. H. Davis, T. Fujita, M. R. Cox, and R. F. Bryan *J. Amer. Chem. Soc.*, **93**, 4916 (1971).

(10) W. Herz and I. Wahlberg, unpublished results.

(11) W. Herz and S. V. Bhat, *J. Org. Chem.*, **37**, 906 (1972).

(12) Z. Samek, *Tetrahedron Lett.*, 671 (1970).



12b

nmr data.[13] The similarities of chemical shifts and coupling constants in the nmr spectra of eucannabinolide (taken from ref 13) and provincialin (1) (see Table I) are so striking that it is tempting to formulate eucannabinolide as **12b** rather than **12a**.

Experimental Section[14]

The isolation of crude provincialin from a chloroform extract of *L. provincialis* Godfrey has been described elsewhere.[2] Portions of this material were rechromatographed over silica gel (hexane–ethyl acetate 1:4) to give a gum, which was homogeneous on tlc. Various attempts to induce crystallization were unsuccessful. Provincialin (1) had $[\alpha]_D$ −85° (*c* 0.6, $CHCl_3$); ir 3420 (br), 1760, 1740, 1730, and 1655 cm^{-1}; strong uv end absorption at 210 nm; *m/e* (%, composition) 518 (M, 3, $C_{27}H_{34}O_{10}$), 402 (1, $C_{22}H_{26}O_7$), 360 (2, $C_{20}H_{24}O_6$), 342 (0.5, $C_{20}H_{22}O_5$), 306 (0.5, $C_{17}H_{22}O_5$), 305 (0.4, $C_{17}H_{21}O_5$), 289 (7, $C_{17}H_{21}O_4$), 288 (1.6, $C_{17}H_{20}O_4$), 264 (1, $C_{15}H_{20}O_4$), 247 (9, $C_{15}H_{19}O_3$), 246 (22, $C_{15}H_{18}O_3$), 229 (38, $C_{15}H_{17}O_2$), 229 (0.4, $C_{10}H_{13}O_6$), 228 (89, $C_{15}H_{16}O_2$), 213 (9, $C_{10}H_{13}O_5$), 115 (25, $C_5H_7O_3$), 99 (100, $C_5H_7O_2$), and 81 (30, C_5H_5O).

Anal. Calcd for $C_{27}H_{34}O_{10}$: mol wt 518.2149. Found: mol wt (mass spectrum) 518.2119.

Epoxyprovincialin (2).—A solution of 66 mg of 1 in 2 ml of chloroform was allowed to stand with 35 mg of *m*-chloroperbenzoic acid at room temperature for 6 hr. The reaction mixture was diluted with chloroform, washed, and evaporated. Chromatography over silica gel (hexane–ethyl acetate 1:1 → 1:3) gave 53 mg of epoxyprovincialin (2) as a gum, ir 3460 (br), 1750, 1740, 1720, and 1655 cm^{-1}.

Anal. Calcd for $C_{27}H_{34}O_{11}$: C, 60.67; H, 6.41; O, 32.92; mol wt 534. Found: C, 61.05; H, 6.72; O, 32.10; mol wt (mass spectrum) 534.

Hydrolysis of Provincialin.—A solution of 107 mg of 1 in 10 ml of aqueous methanol (80%) was stirred with 403 mg of potassium carbonate at room temperature under nitrogen for 3.5 hr. The solvents were evaporated *in vacuo* and the residue was diluted with water. Extraction with chloroform and chromatography over silica gel afforded as the main component 86 mg of **3**, which on recrystallization from isopropyl ether had mp 139–141.5°; ir 3520, 1770, and 1720 cm^{-1}; *m/e* (%) 338 (M, 2), 306 (0.1), 296 (2), 278 (3), 260 (2.5), 246 (4), 228 (7), and 31 (100).

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74; O, 28.37. Found: C, 63.53; H, 7.82; O, 28.19.

Epoxidation of 3.—A solution of 35 mg of **3** in 1.5 ml of chloroform was allowed to stand with 33 mg of *m*-chloroperbenzoic acid for 3 hr. The mixture was diluted with chloroform, washed with aqueous sodium hydrogen carbonate, and evaporated. Chromatography over silica gel yielded 18 mg of 4, which on recrystallization from hexane–ethyl acetate had mp 165–169°: ir 3550, 1770, and 1730 cm^{-1}; *m/e* (%) 354 (M, 0.1), 339 (1), 312 (5), 294 (8), 279 (4), 123 (92), 69 (75), 45 (98), and 43 (100). Scarcity of material prevented elemental analysis, but the high-resolution mass spectrum was in accord with the postulated empirical formula.

Anal. Calcd for $C_{16}H_{24}O_6$: M − C_2H_2O 312.1573. Found: 312.1584. Calcd for $C_{16}H_{22}O_5$: M − $C_2H_4O_2$ 294.1467. Found: 294.1466.

Sodium Borohydride Reduction of 1.—A solution of 1.6 g of 1 in 25 ml of methanol was stirred with 630 mg of sodium borohydride at 0° for 2 hr. The mixture was acidified and the solvents

TABLE I.—NMR SPECTRA OF PROVINCIALIN DERIVATIVES[a]

Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15[b]	H-3′	H-4′	H-5′[c]	H-8′[c]	H-9′	H-10′[b]	Ac
1	~5.3[d]	*d*	~5.3[d]	5.21 dd (11.1, 1.2)	5.93 dd (11.1, 2.4)	2.91 m $W_{1/2}$ ~ 8	~5.3[d]	*d*	6.35 d (2.1) 5.78 d (1.9)	1.77 br	1.83 d (1.2)	4.90 d (~12) 5.01 d (~12)	7.02 t (5.8)	4.43 d (5.8)	4.32 br	6.96 q (7.3)	1.90 d (7.3)	2.11
2	~2.9[d]	*d*	~5.3[d]	5.28 dd (11.1, 1.2)	6.18 dd (11.1, 2.4)	2.9[d]	~5.3[d]	*d*	6.35 d (2.1) 5.80 (1.9)	1.47	1.91 d (1.2)	4.90 d (~12) 5.01 d (~12)	7.03 t (5.8)	4.43 d (5.8)	4.31 br	6.96 q (7.3)	1.91 d (7.3)	2.16
3	~5.2[d]	*d*	~5.2[d]	5.39 dd (10.8, 1.2)	5.72 dd (10.8, 3.9)	*d*	4.07 m $W_{1/2}$ ~ 11	*d*	3.67 m[e] (3.39)[b]	1.83 br	1.81 (1.2)							2.06
4	2.86 (4.5, 10.3)	2.40 m 1.62 m	5.23 dd (2.2, 4.7)	5.55 dd (11.0, 1.2)	5.95 dd (11.0, 3.1)	2.28 m	4.01 m $W_{1/2}$ ~ 11	2.48 dd (14.6, 4.8) 1.29 dd (14.6, 1.9)	3.66 m[e] (3.39)[b]	1.58	1.88 d (1.2)							2.10
6	~5.2[d]	*d*	~5.2[d]	5.41 dd (11.0, 1.2)	5.86 dd (11.0, 2.2)	*d*	~5.2[d]	*d*	1.15 d (7)	1.79 br	1.86 d (1.2)	6.23 d (~1) 5.72 d (~1)	*d*	3.70 t (6.5)				2.09

[a] Run at 90 MHz in $CDCl_3$ solution on a Bruker nmr spectrometer using TMS as internal standard. Values are in ppm. Multiplicities are indicated by the usual symbols: d, doublet; t, triplet; q, quartet; br, broadened singlet; m, multiplet whose center is given. Unmarked signals are singlets. Figures in parentheses are coupling constants (*J*, in Hz) measured by spin decoupling. [b] Intensity three protons. [c] Intensity two protons. [d] Obscured signal.

(13) B. Drozdz, H. Grabarczyk, Z. Samek, M. Holub, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **37**, 1546 (1972).

(14) Melting points are uncorrected. Rotations were run in chloroform on a Perkin-Elmer 141 polarimeter, ultraviolet spectra in methanol on a Cary Model 14 recording spectrophotometer, and infrared spectra on a Perkin-Elmer Model 257 grating spectrophotometer. High-resolution mass spectra were run at 70 eV on a MS-9 mass spectrometer. Analyses were performed by F. Pascher, Bonn, Germany.

were evaporated under reduced pressure. Dilution with water, extraction with chloroform, and chromatography over silica gel (hexane–ethyl acetate 3:2 → 1:1) gave 312 mg of 6 as a gum: ir 3460 (br), 1760, 1740, and 1720 cm^{-1}; *m/e* (%, composition) 406 (M, 6, $C_{22}H_{30}O_7$), 307 (1, $C_{17}H_{23}O_5$), 291 (8, $C_{17}H_{23}O_4$), 290 (2, $C_{17}H_{22}O_4$), 249 (4, $C_{15}H_{21}O_3$), 248 (17, $C_{15}H_{20}O_3$), 231 (21, $C_{15}H_{19}O_2$), 230 (50, $C_{15}H_{18}O_2$), 175 (32, $C_{12}H_{15}O$), 157 (100, $C_{12}H_{13}$), 156 (41, $C_{12}H_{12}$), and 99 (56, $C_5H_7O_2$). The gum could not be purified satisfactorily, but the high-resolution mass spectrum was in accord with the postulated empirical formula.

Anal. Calcd for $C_{22}H_{30}O_7$: mol wt 406.1990. Found: mol wt (mass spectrum) 406.1989.

Hydrolysis of 6.—A solution of 300 mg of 6 in 10 ml of aqueous methanol (80%) was stirred with 229 mg of potassium hydroxide at room temperature under nitrogen for 24 hr. The solvents were removed and the residue was diluted with water. Extraction with chloroform and chromatography over silica gel (hexane–ethyl acetate 3:2) gave 39 mg of 7: mp 167–171°; ir 3460, 3400, and 1755 cm^{-1}; nmr (acetone-d_6) 1.19 (3 H, d, $J \sim 7$), 1.77 (3 H, d, $J \sim 1$), 1.92 (3 H, br) 4.10 (1 H, dd, $J \sim 2$ and 5), 4.22 (1 H, m), 5.11 (1 H, dd, $J \sim 11$ and 1), and 5.40 ppm (1 H, dd, $J \sim 11$ and 1); *m/e* (%) 266 (M, 11), 248 (26), 230 (18), and 95 (100).

Anal. Calcd for $C_{15}H_{22}O_4$: mol wt 266.1518. Found: mol wt (mass spectrum) 266.1501.

Epoxidation of 7.—A solution of 30 mg of 7 in 2 ml of chloroform was allowed to stand with 22 mg of *m*-chloroperbenzoic acid at room temperature for 1 hr. The reaction mixture was evaporated and chromatographed over silica gel (hexane–ethyl acetate 3:2) to give 10 mg of 8, mp 222–225° dec, undepressed on admixture with a sample of dihydroheliangino1 (8) prepared from erioflorin; the ir, nmr, and mass spectra were identical with those of the authentic sample.

Preparation of Dihydroheliangino1 (8) from Erioflorin (5b).—A solution of 391 mg of erioflorin in 10 ml of methanol was stirred with 390 mg of sodium borohydride at 0° for 0.5 hr. The reaction mixture was acidified, evaporated at reduced pressure, diluted with water, and extracted with chloroform. The crystalline residue obtained was dissolved in 20 ml of aqueous methanol (80%) and heated with 200 mg of potassium hydroxide on a steam bath under nitrogen for 4 hr. The reaction mixture was acidified and the solvents were removed under reduced pressure. Dilution with water and continuous extraction with ether for 48 hr afforded 264 mg of dihydroheliangino1 (8), which on recrystallization from ethyl acetate had mp 224–225° dec (reported mp 219–220° dec,[7] 202–203°[5]). The nmr spectrum was identical with that of an authentic sample, whereas the ir spectrum of our sample (KBr) differed in a few minor details from the spectrum recorded by Torrance, *et al.*[7] These discrepancies can probably be ascribed to differences in crystal forms of the two samples.

Registry No.—**1**, 40328-96-9; **2**, 40386-87-6; **3**, 40328-97-0; **4**, 40386-88-7; **6**, 40328-98-1; **7**, 40328-99-2.

Acknowledgments.—I. W. wishes to thank the Swedish Tobacco Company for a stipend. We are indebted to Professor T. A. Geissman for a generous sample of erioflorin and for reference spectra of dihydroheli-anginol.

The Total Synthesis of *dl*-Avenaciolide[1]

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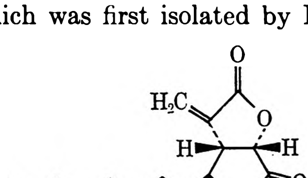
Received March 13, 1973

The total synthesis of the mold product avenaciolide (1) is reported using the following sequence. Acylative decarboxylation of tricarballylic acid with nonanoic anhydride afforded the dilactone (26) of 3-(1,1-dihydroxynonyl)glutaric acid. Reduction of this dilactone by means of alkaline borohydride then led to *trans*-tetrahydro-2-octyl-5-oxo-3-furanacetic acid (16) which was converted *via* its acid chloride to the pyrrolidine amide **32**. Carbomethoxylation of the latter compound afforded the amidolactonic ester **33**. Treatment of this material with sodium hypochlorite solution followed by boiling both the neutral and acidic products with aqueous hydrobromic acid led to the dilactone **35**. Carboxylation of **35** with methyl methoxymagnesium carbonate provided the dilactonic acid **40** which when treated with formaldehyde and diethylamine in buffered acetic acid yielded *dl*-avenaciolide (1).

Avenaciolide (1) is a naturally occurring antifungal compound which was first isolated by Brookes, Tidd,



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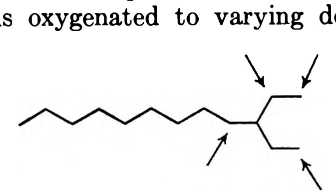
and Turner[2a] from *Aspergillus avenaceus* H. Smith. It was also subsequently obtained from cultures of *Aspergillus fischeri* var. glaber[2b] by investigators at the U. S. Department of Agriculture. The unique bislactonic structure 1, assigned to avenaciolide by Brookes, *et al.*,[2a] was later confirmed by a more detailed nmr study.[3] More recently 4-isoavenaciolide has been isolated[4] in small quantity during the large-scale preparation of 1. In addition, the same authors[4] have isolated ethisolide, the 4-isoethyl lower homolog of 1, from an unidentified species of *Penicillium*.

For the purposes of synthesis, the skeleton of avenaciolide can be looked upon as that of a γ-nonylpentane (2), which is oxygenated to varying degrees at the



2

points indicated by the arrows but which is lacking the methylene carbon atom of the second lactone ring. With the objective of simplifying the synthesis in its initial stages, we elected to introduce this latter group, last of all. Our initial synthetic attempts were geared therefore to the synthesis of a suitably oxygenated derivative of 3-nonylglutaric acid. An early attempt

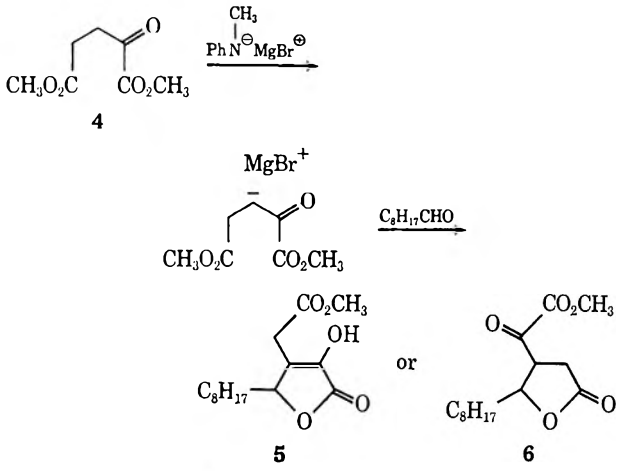
(1) A preliminary account of this work has already been published: W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, **91**, 7208 (1969).

(2) (a) D. Brookes, B. K. Tidd, and W. B. Turner, *J. Chem. Soc.*, 5385 (1963); (b) J. J. Ellis, F. H. Stodola, R. F. Vesonder, and C. A. Glass, *Nature (London)*, **203**, 1382 (1964).

(3) D. Brookes, S. Sternhell, B. K. Tidd, and W. B. Turner, *Aust. J. Chem.*, **18**, 373 (1965).

(4) D. C. Aldridge and W. B. Turner, *J. Chem. Soc.*, 2431 (1970).

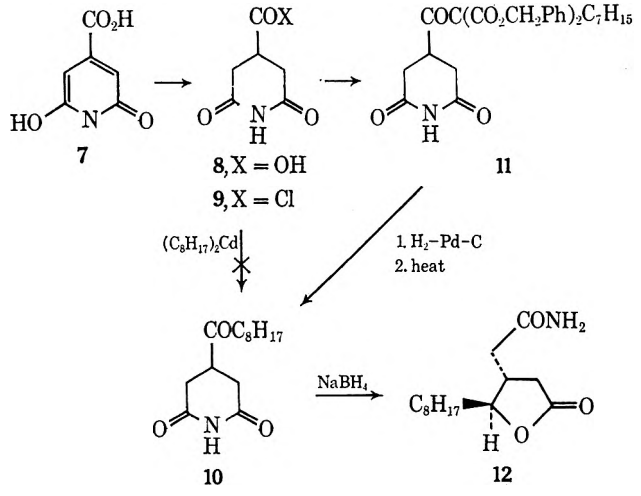
to do this involved the potential Nielsen condensation[5] between the magnesium bromide salt of dimethyl-2-oxoglutarate (4) and nonanal. However, neither of the expected lactonic compounds 5 or 6 could be isolated



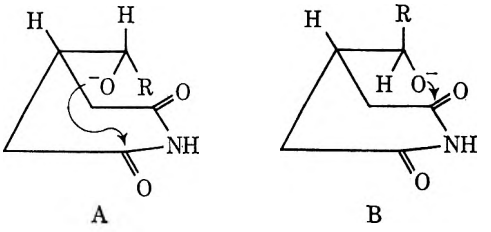
from the reaction. Equally abortive were the attempts to produce 5 or 6 by the diethylamine-catalyzed condensation of nonanal with 4. In each case the only product that could be isolated was the self-condensation product of nonanal.

Our second attempt at the synthesis of the desired carbon skeleton proved more successful. In this approach the objective was the lactone amide 12 which we thought might be subjected to the Barton lactone synthesis[6] for the construction of the second ring. The synthesis of the desired material was accomplished according to Scheme I.

SCHEME I

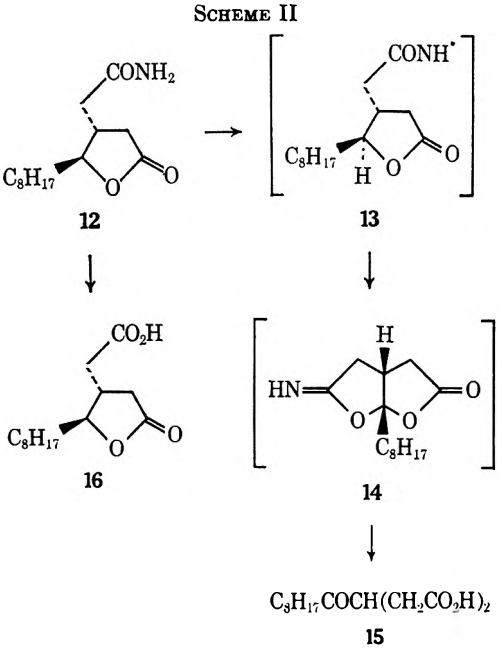


Hydrogenation of citrazinic acid as the sodium salt, using a variation of the literature procedure,[7] easily afforded 3-carboxyglutarimide (8) which could be converted almost quantitatively to the acid chloride 9 by means of thionyl chloride containing a trace of dimethylformamide. However, the direct conversion of 9 to the desired ketone 10 using di(*n*-octyl)cadmium could not be achieved, although several variations of the reaction conditions were tried. Nevertheless, the synthesis of 10 from 9 was accomplished in two steps, the first of which involved the acylation of the bromomagnesium salt of dibenzyl *n*-octylmalonate with the acid chloride. This afforded 11 which without further purification was subjected to reductive debenzylation using hydrogen and a palladium catalyst in ethyl acetate solution. Subsequently when this solution was boiled for a brief period, decarboxylation took place cleanly and 10 was produced in good yield. When 10 was treated with sodium borohydride in cold ethanolic solution, reduction and rearrangement occurred smoothly to give the sought-after lactonic amide 12 in good yield. That essentially only one isomer would be obtained in this reaction was anticipated. Attack by the intermediate oxy anion on one of the carbonyl groups of the imide would lead to a transition state (A) in which there is severe eclipsing between the octyl group and the developing acetamide residue. On the other hand, such an attack upon the other carbonyl group (B) leads to a transition state that is strain free.



Having a reasonable supply of 12 in hand it was subjected to the Barton lactonization reaction. Much to our chagrin, however, the carboxamido radical intermediate 13 chose selectively to remove the γ rather than an α proton of the butyrolactone ring. The final product of the reaction after treatment with base was 15, a compound easily obtained by the hydrolysis of 10. This reaction undoubtedly proceeds through the intermediate 14 (Scheme II) in keeping with the

SCHEME II



proposed mechanism.[6] This result, although disappointing, afforded some chemical proof of the stereochemistry assigned to 12. If 12 had been the cis isomer,

(5) A. T. Nielsen, C. Gibbons, and C. A. Zimmerman, *J. Amer. Chem. Soc.*, 73, 4696 (1951).

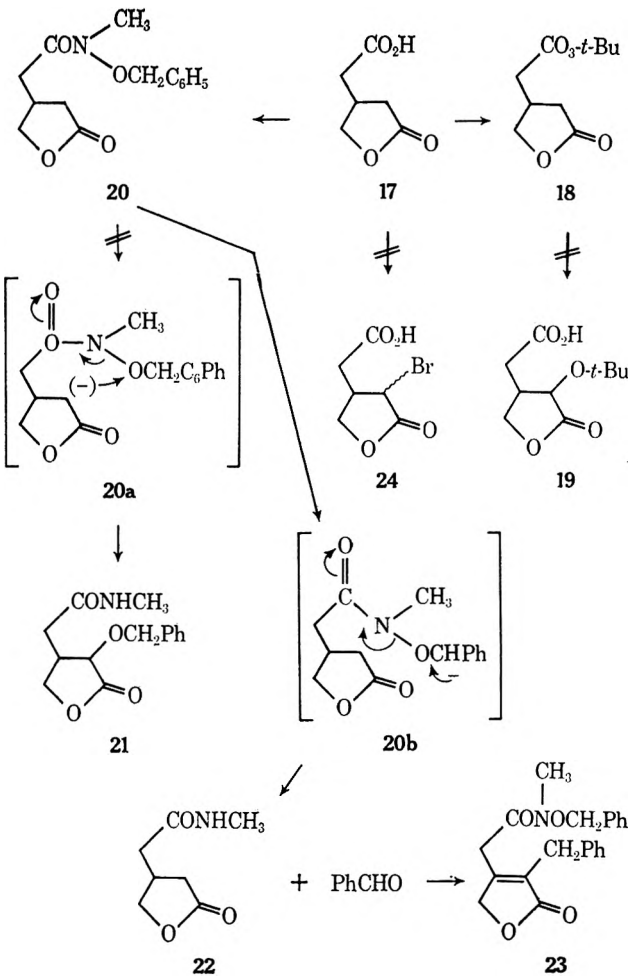
(6) D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965).

(7) A. L. Langis and R. Gaudry, U. S. Patent 2,874,158, (Feb 17, 1959).

it seems most unlikely that the γ-hydrogen atom of the butyrolactone ring would have been within reach of the carboxamido radical.

Despite this failure we still felt that the acetamide group of **12** or the corresponding acetic acid residue might be useful for the intramolecular functionalization of the lactone ring at the α position. Although the corresponding acetic acid **16** could be prepared by nitrous acid treatment of **12**, the overall route now appeared cumbersone and tedious, and we looked for an alterative method for its preparation. In the meantime we also examined the functionalization of the α position of the known[8] lactone, **17**, as a model system, since we had a supply of this material at hand from research on a different problem. With the idea of functionalizing the lactonic α position by an internal oxidation, we prepared first of all the per ester **18** and subjected it to the action of potassium *tert*-butoxide. This led only to the regeneration of the starting material **17** and afforded none of the desired product **19**. In a second variation of this procedure the hydroxamic acid derivative **20** was synthesized and subjected to a variety of basic conditions. Only when sodium dimsyl was used was any transformation product obtained. However, the reaction, instead of proceeding *via* **20a** to give the desired lactonic ether **21**, took a different course and the unexpected butenolide **23** (identified by its nmr spectrum) was obtained (Scheme III). The latter undoubtedly arises by the fragmentation

SCHEME III



(8) J. K. Mehrotra and A. N. Dey, *J. Indian Chem. Soc.*, **38**, 888 (1961).

depicted in **20b** followed by a condensation of starting material **20** and benzaldehyde.

The failure of these reactions is perhaps due more to a lack of certain geometrical requirements than to a lack of feasibility. Eschenmoser, *et al.*,[9] have shown recently that, for tetrahedral carbon at least, an SN2 reaction takes place easily only when the three centers involved have linear geometry. If this then were a necessary requirement for the transformation of **18** to **19** and of **20** to **21**, failure of the reaction could be anticipated. As to feasibility, although to the best of our knowledge no such intramolecular transfer of a functionalized oxygen atom has been reported, an analogous intermolecular example has been published recently by Zinner and Dybowski.[10] They have shown that 1-aminoadamantane when treated with benzoyl peroxide affords the hydroxylamine derivative **25**.

$$AmNH_2 \xrightarrow{(C_6H_5CO_2)_2} AmNHOCOC_6H_5$$
25

We also examined the direct functionalization of the α position of the lactone ring of **17**. Halogenation seemed a obvious choice but from the literature it can be gleaned that, although base-catalyzed reactions at this position can be carried out almost as easily as with ketones, acid-catalyzed reactions are extremely difficult to achieve. With respect to halogenation butyrolactones appear to approximate aliphatic esters in reactivity. It is perhaps not surprising then that we were unable to effect bromination of **17** under any of the conditions that we tried and that chlorination at high temperature afforded a complex mixture of products.

Further work, which now led to a successful synthesis of avenaciolide, was conducted with **16** for which a simpler synthesis had by this time been devised. The latter utilized the acylative decarboxylation of tricarballylic acid by acid anhydrides, a reaction which was discovered by Fittig[11] and subsequently was extended by Lawson.[12] It appears to be formally analogous to the later Dakin–West[13] reaction. Initially a discouraging aspect of this approach to **16** was the yields reported by these investigators. These appeared to decrease as the size of the alkyl group of the anhydride increased. Since the Dakin–West reaction and the related acylative decarboxylation of arylacetic acids[14] are both base-catalyzed, we examined the reaction of nonanoic anhydride with tricarballylic acid in the presence of powdered soft glass.[15] Much to our satisfaction the reaction proceeded to give the desired dilactone **26** in 49% yield accompanied by 9% of a highly insoluble self-condensation product of tricarballylic acid. This was identified by its elemental analysis and nmr spectrum as **27**.

The conversion of **26** to **16** was easily accomplished in 91% yield by dissolving it in aqueous potassium

(9) L. Tenud, S. Faroog, J. Siebl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).

(10) G. Zinner and U. Dybowski, *Arch. Pharm. (Weinheim)*, **303**, 488 (1970).

(11) R. Fittig, *Justus Liebigs Ann. Chem.*, **314**, 1 (1901).

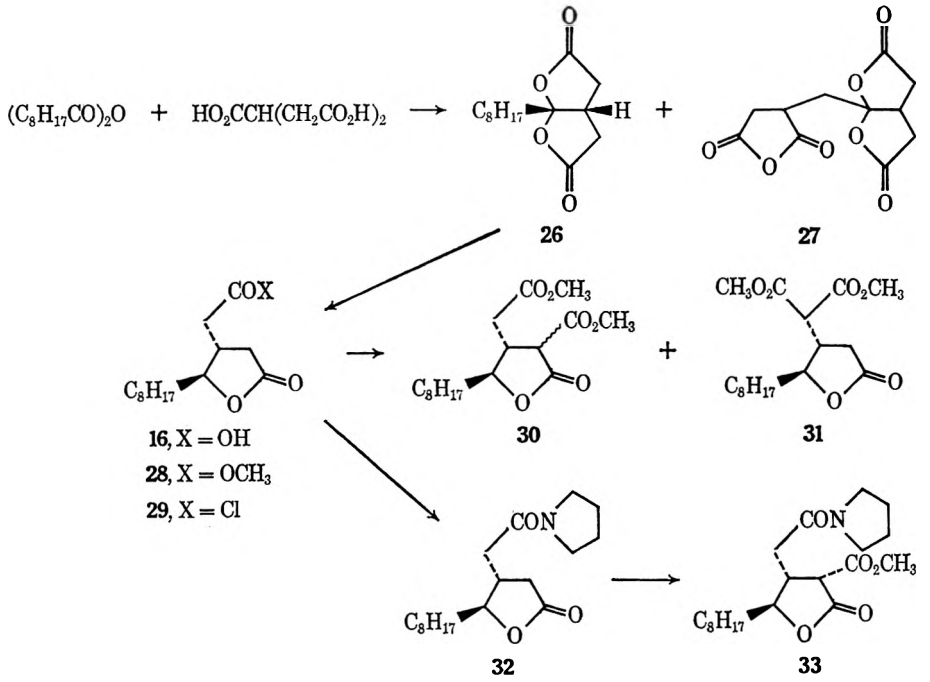
(12) A. Lawson, *J. Chem. Soc.*, 144 (1957).

(13) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91, 745, 757 (1928).

(14) J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.*, **73**, 4911 (1951).

(15) Subsequently we found that this could be omitted provided that the reaction flask had been washed out with a strongly alkaline detergent.

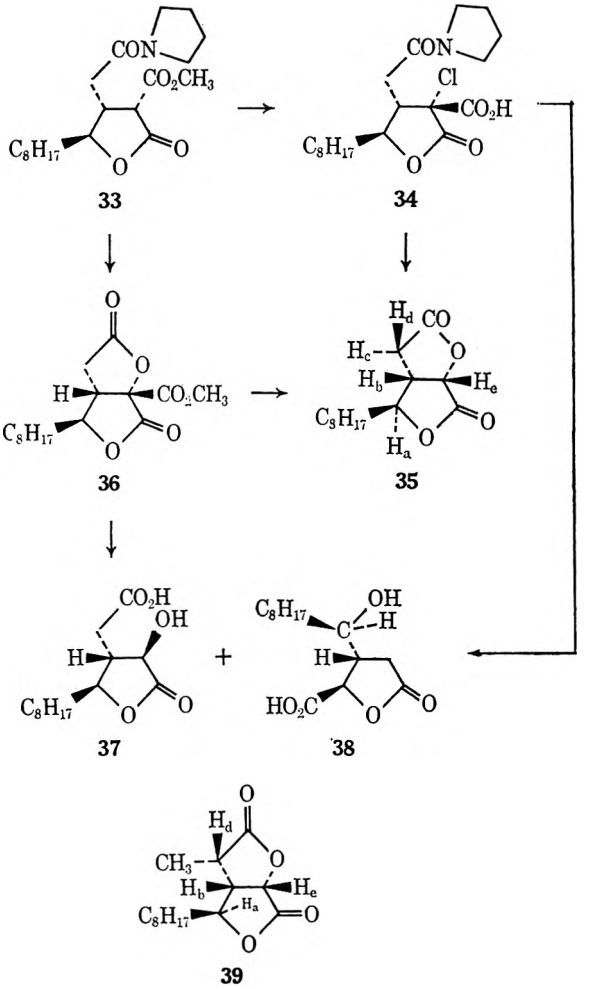
SCHEME IV



hydroxide solution and then adding sodium borohydride. Acidification afforded **16**.

Renewing now our attempts to functionalize the α position of the lactone ring of **16**, we attempted carbomethoxylation of **28** by means of sodium hydride in dimethyl carbonate (Scheme IV). This, however, could not be accomplished cleanly. Although the major product was obviously the desired ester **30**, it was accompanied by approximately 15% of the undesired isomer **31**. To prevent this carbomethoxylation of the acetic residue, we simply converted **16** to the amide[16] **32** *via* the acid chloride **29**. Carbomethoxylation of **32** then led smoothly and exclusively to **33**. We believe that the stereochemistry of **33** is that depicted since protonation of its sodium salt, formed in the reaction of **32** with dimethyl carbonate, should occur on the less hindered face and it could be expected therefore that the substituents at the α,β position of the butyrolactone ring should be cis related. In any event the substance both from its tlc and its nmr spectrum appears to be essentially a single compound. The nmr spectrum shows a very sharp acetate methyl peak at 3.75 ppm and a very minor peak at 3.72 ppm due to the presence of a trace of an isomeric impurity. At a later date the same product was also obtained[17] completely pure when **32** was carboxylated with Stiles' reagent (*vide infra*) and the acid thus produced was methylated with diazomethane. The carbomethoxylated amide **33** reacted rapidly with bromine or iodine in the presence of a weak base such as sodium acetate. However, a particularly convenient method of effecting halogenation of **33** consisted in shaking an ether solution briefly with aqueous sodium hypochlorite. This gave rise to a neutral fraction remaining in the ether layer and an acidic component, isolated from the aqueous phase by acidification. Chromatography of a sample of the neutral material led to a crystalline solid which was characterized by its physical data as the dilactone **36**. (Scheme V). Neighboring-group interactions of this type between amides and halogen and which lead to cyclic imino ethers or butyrolactones have been studied

SCHEME V



(16) Although probably any secondary amine could be used here to deactivate the methylene group of the acetic acid residue, our past experiences with enamines suggested that pyrrolidine would be the most effective.

(17) J. Martin, P. C. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970).

by Stirling.[18] Lactone formation involving a methanesulfonate group and a secondary amide has been noted in the sugar series by Kuzuhara and Fletcher.[19] The acidic fraction from the halogenation of **33** could be crystallized directly and its physical characteristics indicated it to be the acid **34**. The α orientation (below the plane of the ring) assigned to the halogen atom is conjectural but seems likely since no change takes place when **34** is boiled in ethanol. These conditions would be expected[18] to lead to lactone formation if the halogen atom were β oriented.

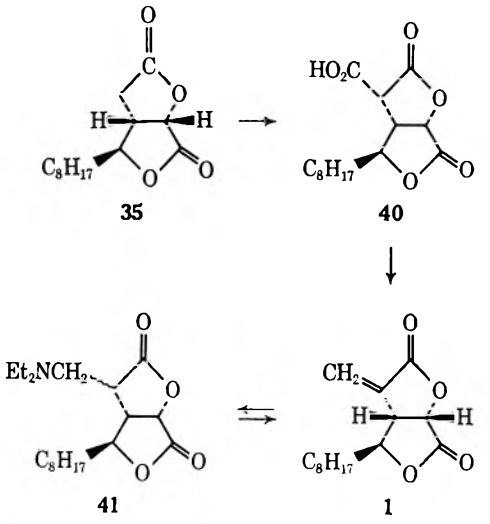
Treatment of either the acidic or the neutral fraction mentioned above with boiling aqueous hydrogen bromide in dioxane followed by azeotropic removal of water from the product gave rise to the desired neutral dilactone **35** and a new acidic fraction. Thus in general practice the total products from the halogenation of **33** were combined and treated as described above to give **35** in 57% yield. The new acidic fraction from this reaction appeared, from its physical characteristics and tlc behavior, to be a mixture of two lactones which probably have structures **37** and **38**. One of these was isolated in small yield by crystallization but no attempt was made to determine its structure.

The stereochemistry of the bislactone is assigned on the basis of a comparison of its nmr spectrum with that of dihydroavenaciolide (**39**). The H_a and H_e protons in both compounds occur at ~4.3–4.5 (multiplet) and at ~5.0 ppm (doublet, J = 7.2 Hz), respectively, and have the same line shapes. The stereochemistry of the methyl group in dihydroavenaciolide (**39**) was shown to be that depicted (*i.e.*, inside the envelope of the two lactone rings) by virtue of the fact that an NOE (~42%) could be observed for H_a when the methyl group was irradiated. This observation not only defines the mode of addition of hydrogen to **39** *but corroborates completely the original assignment*[1,3] *of stereochemistry made to avenaciolide itself.*

The preparation of **35** set the stage for the completion of the synthesis of **1**. We envisioned that, by the introduction of carboxylic function at the $-CH_2-$ group of the upper lactone ring of **35**, we should be able to complete the synthesis by employing the decarboxylative methylenation procedure used by van Tamelen and Bach[20] in the synthesis of protolichesterinic acid. However, initial attempts to carbomethoxylate **35** gave unsatisfactory results and we looked for an alternate method. The use of Stiles' reagent[21] seemed to offer a possible solution, and we were gratified in our expectations to find that the reaction proceeded[17] to give the desired acid, **40**, in excellent yield (Scheme VI). The stereochemistry of the carboxyl group in **40** is assigned the α position since protonation of the intermediate enolate could be expected to occur from the less hindered side, *i.e.*, the β face of the molecule.

Application of the conditions of van Tamelen and Bach[20] to **40** did not lead to avenaciolide. Modification of the procedure by simply treating **40** with diethylamine and aqueous formaldehyde gave mainly an oily material whose nmr and infrared spectra indicated it to be **41**, the diethylamine addition product of avenaciolide. Besides this material, traces of avenaciolide could be isolated but this preparation could hardly be called satisfactory. Consideration of the mechanism by which **41** arises from **40** (it is in fact a variation of the Cope condensation) suggested that the presence of a mild acid was essential, if avenaciolide was to become the major product. Repetition of the reaction in the presence of acetic acid led to complete evolution of carbon dioxide in 1 min. Further brief heating of the reaction mixture then afforded *dl*-avenaciolide in 66% yield identical in all respects, except that of optical activity, with the natural product.

SCHEME VI



Experimental Section

All melting points are corrected. Nmr spectra were recorded in deuteriochloroform on a Varian A-56-60, T60, or HA-100 spectrometer and are not calibrated with the exception noted. Infrared spectra were recorded as films or as Nujol mulls on a Perkin-Elmer 337 spectrometer.

3-Carboxyglutarimide (**8**).—Crude citrazinic acid (10.0 g), as supplied by Chas. Pfizer and Co., was dissolved in a solution of sodium bicarbonate (5.68 g) in water (150 ml). The solution was then hydrogenated at 26° over a 5% rhodium-on-alumina catalyst (0.416 g) under a hydrogen pressure that varied from 3.1 to 0.2 kg cm^{-2}, during the course of the reduction. After 18 hr absorption, which corresponded to 1 mol of hydrogen, ceased. The catalyst was removed by filtration through diatomaceous earth and the filtrate neutralized by the addition of sodium hydrogen sulfate (9.34 g). The solution was then evaporated to dryness under reduced pressure and the residue was extracted with boiling ethanol. Clarification of the solution with charcoal followed by concentration to 70 ml afforded 8.59 of a tan-colored solid which when recrystallized from the same solvent gave essentially pure 3-carboxyglutarimide (6.54 g), mp 211–212.5° (lit.[7] mp 211–212.5°). A somewhat purer product, mp 214.5–216°, could be obtained by additional crystallization from dioxane, but this was unnecessary for further work.

3-Chlorocarbonylglutarimide (**9**).—Very finely powdered 3-carboxyglutarimide (6.05 g) was added to thionyl chloride (100 g) containing 2–3 drops of dimethylformamide. The mixture was refluxed for 15 min during which time the solution became homogeneous. Removal of the thionyl chloride under reduced pressure afforded a pale yellow solid (6.8 g), mp 113.5° (lit.[22] 118–119°), which was used directly in the subsequent step. This acid chloride is extremely sensitive to moisture and attempts to recrystalize it under normal conditions caused partial conversion to the highly insoluble anhydride.

Dibenzyl Heptylmalonate.—Diethyl heptylmalonate (25.8 g) and benzyl alcohol (37 ml) were heated together in an oil bath at

(18) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960).
(19) H. Kuzuhara and H. G. Fletcher, *J. Org. Chem.*, **33**, 1816 (1968).
(20) E. E. van Tamelen and S. R. Bach, *J. Amer. Chem. Soc.*, **77**, 4683 (1955).
(21) H. L. Finkbeiner and M. Stiles, *J. Amer. Chem. Soc.*, **85**, 616 (1963).
(22) R. F. Struck, H. J. Schaeffer, C. A. Krauth, R. T. Kemp, F. Shealy, and J. A. Montgomery, *J. Med. Chem.*, **7**, 646 (1964).

240–245° until ethanol no longer distilled over. The excess benzyl alcohol was then removed at reduced pressure and the residual liquid was distilled through a short-path condenser to give the desired product (32.2 g), bp 193–201° (0.02 mm), yield 84%.

Anal. Calcd for $C_{24}H_{36}O_4$: C, 75.36; H, 7.19. Found: C, 75.28; H, 7.89.

3-(1-Oxononyl)glutarimide (10).—Dibenzyl heptylmalonate (14.70 g) was dissolved in dry tetrahydrofuran and the solution cooled to 0°. A solution (37.7 ml) of phenylmagnesium bromide (1.02 *M*) in ether–tetrahydrofuran (1:2) was added dropwise during 15 min. The solution which had reached 30° during this addition was again cooled to 0° and a solution of 3-chlorocarbonylglutarimide (6.8 g) in tetrahydrofuran (45 ml) was added over 30 min. Two hours after initiation of the reaction the solvents were removed *in vacuo*, and the residue was treated with water and benzene. The benzene layer was removed, washed with sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, and taken to dryness under reduced pressure. The resulting viscous oil (22.48 g) was dissolved in methylene chloride and the solution was passed down a column of silica gel (500 g). Elution of the column with methylene chloride (2 l.) afforded crude dibenzyl hepylmalonate (5.15 g) and subsequent elution with methylene chloride containing 20% ethyl acetate led to the desired C-acylated malonate 11 (14.16 g, yield ~100% based on unrecovered dibenzyl heptylmalonate). This material was dissolved in ethyl acetate (200 ml) and hydrogenated over a 10% palladium-on-charcoal catalyst (1.0 g) for 2 hr. The solution was filtered, a trace of copper powder was added, and the mixture was boiled until carbon dioxide evolution was complete (~0.5 hr). After the solution had been washed with saturated sodium hydrogen carbonate solution and then dried over anhydrous magnesium sulfate, the solvent was removed to give crude 3-(1-oxononyl)glutarimide (6.20 g) as a nearly white solid (86.6%). One recrystallization of this material yielded essentially pure material (5.0 g), mp 113.5°. A sample recrystallized for analysis had mp 115–116°. Its infrared spectrum showed imide NH absorption at 3100 and 3190 cm^{-1}, a ketonic bond at 1725 cm^{-1}, and an imide carbonyl doublet 1708 and 1685 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.4; H, 9.1; N, 5.6.

***trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetamide (12).**—3-(1-Oxononyl)glutarimide (2.94 g) and sodium borohydride (0.31 g) were dissolved in ethanol (100 ml), and the resulting solution was stirred at room temperature for 1.5 hr. The solvent was removed under reduced pressure at ~40° and the residue cautiously treated with hydrochloric acid (0.1 *N*, 100 ml). Isolation of the product by methylene chloride extraction yielded a white solid (2.94 g), mp 77–82°. One recrystallization gave 2.1 g of material, mp 84.5–87.5°, suitable for further work and a second gave analytical material, mp 87.5–88°. Its infrared spectrum showed amide NH_2 and carbonyl absorption at 3550, 3215, and 1685 cm^{-1}, respectively, and a γ-lactone band at 1773 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.81; H, 9.95; N, 5.70.

3-Carboxymethyl-4-oxolauric Acid (15).—The ketoimide 10 (12.2 mg) was heated with 5 *N* hydrochloric acid (10 ml) for 18 hr at ~90°. On cooling the crystalline precipitate which appeared was removed by filtration and dried. The solid (10.7 mg, mp 106.5–108°) after one crystallization from a mixture of ethyl acetate and cyclohexane gave analytically pure material, mp 109–109.5°. Its infrared spectrum had bands at 1715 (ketone) and 1700 cm^{-1} (carboxylic acid).

Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 62.00; H, 8.70.

Attempted Lactonization of *trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetamide.—Lead tetraacetate (1.335 g), iodine (0.778 g), and the lactone 12 (0.257 g) were added to benzene (6 ml), and the mixture was irradiated in a Pyrex vessel with a high-pressure mercury lamp for 5 hr while the mixture was stirred and cooled to 11°. The reaction mixture was diluted with benzene and filtered, and the solid collected was washed with chloroform. The combined filtrates were washed with water followed by saturated sodium hydrogen carbonate solution and were then dried over magnesium sulfate. Removal of the solvents left a partially crystalline residue (0.37 g) which was added to ethanol (20 ml) and water (5 ml) containing potassium hydroxide (1.25 g). The mixture was refluxed for 2 hr and the product after acidification was extracted with ether. The ether solution was in turn extracted with sodium hydrogen carbonate solution. The latter was acidified and the precipitate was collected by filtration and dried *in vacuo*. The faintly tan lustrous plates (0.186 g), mp 106–108°, had an infrared spectrum that was identical with that of the previously prepared 3-carboxymethyl-4-oxolauric acid and a mixture of the two showed no depression in melting point.

3-(1,1-Dihydroxynonyl)glutaric Acid Di-γ-lactone (26).—Nonanoic anhydride (467 g) was stirred and heated at 185° under nitrogen while tricarballylic acid (95.8 g) was added in three portions at 1-hr intervals. The theoretical amount of carbon dioxide (collected in a potassium hydroxide tower) was obtained 7 hr after the start of the reaction.

The reaction mixture was cooled to room temperature, 1 l. of hexane was added, and the resulting slurry was cooled to 0°. The solid material was removed by filtration and washed with hexane (250 ml), then dissolved in hot carbon tetrachloride (300 ml). The residual insoluble substance (5.99 g) had mp 191–194° and is the Fittig self-condensation product (27) of tricarballylic acid itself. Recrystallization from acetone afforded the pure material, mp 197.5–198°, whose infrared spectrum showed carbonyl bands at 1780, 1810, and 1845 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}O_7$: C, 51.98: H, 3.97. Found: C, 51.77; H, 3.96.

The carbon tetrachloride solution was taken to dryness under reduced pressure and the resulting solid (100 g) was recrystallized from ether–ethyl acetate. This led to the desired material (67.8 g, yield 49%), mp 84.5–85.5°, which was sufficiently pure for further work. A sample recrystallized for analysis from the same solvent pair had mp 86–87°. Its infrared spectrum showed γ-lactone absorption at 1786 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.06; H, 8.69.

***trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetic Acid (16) and Its Methyl Ester (28).**—(a) The dilactone 26 (65.0 g) was dissolved in hot 1.0 *N* potassium hydroxide solution (774 ml) and sodium borohydride (24.2 g) was added in small portions over 30 min with swirling. The mixture was then heated on a steam bath for 5 hr, cooled to room temperature, and acidified to pH 1 with concentrated hydrochloric acid (~145 ml). The solution was extracted with ether and the ether extract was washed with water, dried over magnesium sulfate, and concentrated to small bulk. Trituration of the oily residue with hexane yielded a crystalline solid (59.9 g, 91.4% yield), mp 55–56°, whose infrared spectrum displayed carbonyl absorption at 1695 and 1762 cm^{-1}. Further recrystallization did not improve the melting point.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.47; H, 9.38.

(b) *trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetamide (12, 45.3 mg) was refluxed in 5 *N* hydrochloric acid (20 ml) for 15.5 hr. The product (41.3 mg) was isolated by methylene chloride extraction. It solidified on standing, mp 45–51.5°, and on recrystallization from ether–hexane afforded the pure compound, mp 55–56°, whose infrared spectrum was identical with that of a specimen prepared according to method a above. Treatment of this acid with ethereal diazomethane afforded a quantitative yield of the methyl ester, mp 20–21.5°, whose infrared spectrum showed significant bands at 1737 and 1776 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.77; H, 9.65.

***trans*-β-(1-Hydroxynonyl)-δ-oxo-1-pyrrolidinevaleric Acid γ-Lactone (32).**—The lactonic acid 16 (4.50 g) was dissolved in thionyl chloride (8.5 ml) containing 2 drops of dimethylformamide. After 2 hr at room temperature the solution was heated briefly (3–4 min) on the steam bath and the excess thionyl chloride was removed *in vacuo*. The residue was dissolved in benzene (40 ml) and pyrrolidine (3.1 ml) was then added dropwise to this solution. After 30 min at room temperature the mixture was diluted with ether, washed with dilute hydrochloric acid then water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent left an oil which crystallized from hexane–benzene to give the desired material (4.36 g, 81%), mp 49–51°. A sample recrystallized several times from hexane afforded the pure compound, mp 51–52°, whose infrared spectrum showed bands at 1640 and 1775 cm^{-1}.

Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86; H, 10.10; N, 4.53. Found: C, 69.91; H, 10.15; N, 4.49.

Methyl [2-Hydroxy-1-(1-pyrrolidinylcarbonyl)methyl]decylmalonic Acid γ-Lactone (33).—(a) A 56% dispersion of sodium hydride in mineral oil (22.0 g) was washed free of the oil with petroleum ether (bp 30–60°) by decantation under dry nitrogen.

The residual hydrocarbon was removed by evaporation and dry dimethyl carbonate (450 ml) containing methanol (100 μl) was added. This mixture was stirred at ~80° while a solution of the lactonic amide **32** (32.0 g) in dimethyl carbonate was added dropwise during 30 min. The mixture was refluxed for 6 hr but after the first 20 min hydrogen evolution became so vigorous that the heating was reduced. The mixture was cooled to room temperature and glacial acetic acid (53 ml) was added to it slowly with stirring. The solution was diluted with water (350 ml) and the product extracted with ether. The ethereal solution was washed with sodium bicarbonate solution and water and then dried over anhydrous magnesium sulfate. Removal of the ether afforded oil (37.8 g) which was chromatographed on silica gel (600 g). Elution with ether and then ethyl acetate yielded **33** as a colorless oil (31.42 g, 82.6%), $n^{24.5}$D 1.4857, whose infrared spectrum (film) showed significant bands at 1777, 1739, and 1640 cm^{-1}. The nmr spectrum (CCl_4) showed a singlet at 3.73 ppm (OCH_3).

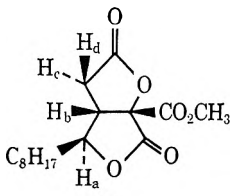
Anal. Calcd for $C_{20}H_{33}NO_5$: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.52; H, 9.15; N, 4.15.

(b) The lactonic amide **32** (1.0 g) was added to 5 ml of a solution (5 ml) of methyl methoxymagnesium carbonate[21] in dimethylformamide under nitrogen, and the solution was then heated for 6 hr at 130° while a slow stream of N_2 gas was bubbled through the liquid. The mixture was then poured into ice cold 6 *N* hydrochloric acid and ether and shaken thoroughly to dissolve the solid material. The ether extract was washed four times with water and dried ($MgSO_4$) and the ether removed under reduced pressure. The residual solid (0.9 g) had mp 92–98° and after two recrystallizations afforded the pure acid, mp 94.5–95.5°. The nmr spectrum of the compound shows a single fairly sharp peak in the low field region at 10.08 ppm (CO_2H) indicating the presence of only one carboxylic acid.

Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.56; H, 8.84; N, 3.96. Found: C, 64.12; H, 8.90; N, 4.25.

A specimen of the above acid (0.205 g) was treated briefly with diazomethane in ether. Isolation of the product in the usual way afforded a quantitative yield of the methyl ester whose physical and spectral characteristics were identical with those of specimen **33** prepared according to method a above. In particular the compound appeared completely homogeneous by tlc analysis.

2-Hydroxy-3-(1-hydroxynonyl)glutaric Acid Di-γ-lactone (35).—A solution of the carbomethoxylated amide **33** (30.45 g) in ether (625 ml) was shaken for 5 min with a solution of "Clorox" (1250 ml, 5.25% NaOCl). The ether layer was washed with water and brine and then dried over magnesium sulfate. Removal of the ether *in vacuo* afforded the oily neutral fraction (14.65 g). A sample of this material was chromatographed over silica gel. Elution of the column with ether–benzene mixtures afforded a solid which after several recrystallizations from hexane–benzene gave pure **36**, mp 78.5–79.5°, whose infrared



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spectrum (neat melt) showed bands at 1808, 1788, and 1740 cm^{-1}. Its nmr spectrum showed absorption at 0.89 [triplet, $(CH_2)_7CH_3$], 1.31 [$(CH_2)_7CH_3$], 2.4–3.4 (multiplet, H_b, H_c, H_d), 3.87 (singlet, OCH_3), and 4.39 ppm (multiplet, H_a). The multiplet for H_b, H_c, and H_d was approximately fitted with a computer, using the following chemical shifts (coupling constants): δ (H_b) 3.25, (H_c) 2.68, (H_d) 3.06 ppm (J_{ab} = 3.5, J_{ac} = J_{ad} = 0, J_{bc} = 1.5, J_{bd} = 9.5, and J_{cd} = −17.0 Hz).

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 61.23; H, 7.54.

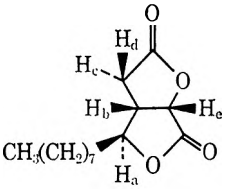
The aqueous phase from the chlorination reaction was acidified with concentrated hydrochloric acid and extracted with methylene chloride. The extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a very viscous oil (18 g). A sample of this material was crystallized from ethanol to give a pure specimen of **34**, mp 124–125° dec, whose infrared spectrum showed significant bands at 1778, 1757, and 1593 cm^{-1} (Nujol mull) and at 1784 and 1606 in $CHCl_3$. The nmr spectrum showed absorption at 8.67 (broad singlet, CO_2H), 3.50 (multiplet, $-CH_2CH_2N<$), and 1.94 ppm (multiplet, $CH_2CH_2N<$).

Anal. Calcd for $C_{19}H_{30}ClNO_5$: C, 58.84; H, 7.74; N, 3.61; Cl, 9.16. Found: C, 58.61; H, 7.85; N, 3.47; Cl, 9.14.

The neutral fraction described above was dissolved in dioxane (630 ml) and water (216 ml) containing 48% hydrobromic acid (54 ml). The mixture was refluxed for 48 hr and then concentrated *in vacuo*. The residue was taken up in benzene and refluxed until no more water was collected in a Dean–Stark trap. The benzene solution was extracted with sodium bicarbonate solution (retained) and then after drying ($MgSO_4$) was evaporated to give a neutral oil (4.88 g). An acidic fraction (7.29 g) was obtained from the bicarbonate solution on acidification.

When the crude acidic material **34** was treated with dilute hydrobromic acid in exactly the same way as for the neutral fraction, the yield of identical neutral oil was 7.14 g while an acidic fraction (1.85 g) was obtained from the alkaline wash.

The neutral fractions of these reactions were therefore combined affording a 57% yield of crude **35**. A sample of the material



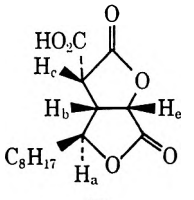
35

was chromatographed on silica gel and ether–benzene mixtures eluted the pure dilactone in excellent recovery, $n^{24.5}$D 1.4745. Its infrared spectrum (neat) showed bands at 1794, 1782, 1243, 1212, 1146, and 1071 cm^{-1}, while its nmr spectrum displayed absorption at 0.89 [triplet, $(CH_2)_7CH_3$], 1.31 [$(CH_2)_7CH_3$], 2.1–3.3 (multiplet, H_b, H_c, and H_d), 4.34 (multiplet, H_a), and 5.01 ppm (doublet, J = 7.2 Hz, H_e).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.99; H, 8.70.

The acidic materials from these hydrolysis reactions were not investigated in depth.

3-Hydroxy-2-(1-hydroxynonyl)-1,1,3,-propanetricarboxylic Acid 1,3-Di-γ-lactone (40).—The dilactone (**35**, 2.77 g) was added to a 2.6 *M* solution (22 ml) of methyl methoxymagnesium carbonate[21] in dimethylformamide and the mixture heated under a slow stream of dry nitrogen at 120° for 5 hr. The mixture was poured into a mixture of ice cold 6 *N* hydrochloric acid and ether and shaken until all of the precipitated solid had dissolved. The ether phase was washed with water and brine and then dried over magnesium sulfate. Removal of the ether under reduced pressure afforded an oil which after crystallization from hexane gave the dilactonic acid **40** (2.43 g, 75% yield), mp 78–80°.



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Further crystallization did not improve the melting point. Its infrared spectrum showed bands at 1790, 1734, 1288, 1140, and 1075 cm^{-1}, while the nmr spectrum shows, besides the typical characteristics of the C_8H_{17} chain, absorption at ~3.58 (multiplet, H_b), ~3.73 (doublet, J = 5 Hz, H_c), 4.54 (multiplet, H_a), 5.20 (doublet, J = 8 Hz, H_e), and 8.06 ppm (singlet, CO_2H).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.57; H, 7.58.

dl-**Avenaciolide (1).**—Sodium acetate (0.105 g) was dissolved in acetic acid (4 ml) and mixed with a solution of formalin (2.92 ml) and diethylamine (1.00 ml). The dilactonic carboxylic acid (0.295 g) was added to this solution (1 ml) and shaken vigorously until evolution of carbon dioxide ceased (*ca.* 1 min). The mixture was then heated on the steam bath for 5 min, cooled, and poured into water and ether. The ether phase was washed with water, saturated sodium bicarbonate solution, water again, and then dried ($MgSO_4$). Evaporation of the ether afforded a solid, mp 44–51°, which was chromatographed over silica gel. Elution with 5% ether in benzene (v/v) gave *dl*-avenaciolide (0.173 g,

66%), mp 54–57°. Material that had been recrystallized several times from ether–pentane mixtures melted at 55–56°. The infrared spectrum (CCl_4) showed significant bands at 1793, 1662, 1294, 1100, 1061, and 950 cm^{-1} and was identical in all respects with that of the natural material. The nmr spectrum (3% in CCl_4, calibrated) showed absorption at 6.32 (doublet, J = 2.3 Hz), 5.80 (doublet, J = 2.0 Hz), 4.97 (doublet, J = 8.3 Hz), 4.33 (multiplet), 3.57 (multiplet), 1.32, and 0.90 ppm (triplet) [lit.[3] (3% in CCl_4), 6.36 (doublet, J = 2.17 Hz), 4.98 (doublet, J = 8.54 Hz), 4.33 (multiplet), and 3.59 (multiplet)].

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.69; H, 8.26.

The synthetic and natural avenaciolide gave identical thin layer chromatograms on silica gel H being eluted with 20% ether in benzene (v/v).

Registry No.—**1**, 26057-70-5; **7**, 99-11-6; **8**, 6973-55-3; **9**, 39949-60-5; **10**, 39949-61-6; **11**, 39949-62-7; **12**, 39971-68-1; **15**, 39949-63-8; **16**, 39949-64-9; **26**, 39949-65-0; **27**, 39949-66-1; **28**, 39949-67-2; **32**, 39949-68-3; **33**, 39949-69-4; **33** free acid, 39949-70-7; **34**, 39949-71-8; **35**, 39949-88-7; **36**, 39949-89-8; **40**, 39949-90-1; dibenzyl heptylmalonate, 39949-91-2; diethyl heptylmalonate, 607-83-0; benzyl alcohol, 100-51-6; nonanoic anhydride, 1680-36-0; tricarballylic acid, 99-14-9.

Acknowledgment.—The authors would like to thank Drs. J. J. Ellis and F. H. Stodola for a culture of *Aspergillus fischeri* var. glaber, and Mr. P. C. Watts and Mr. L. G. Duquette for technical assistance. Thanks are due also to Dr. J. Martin for suggestions that contributed to the success of this work.

Synthesis of Yohimbines. I. Total Synthesis of Alloyohimbine, α-Yohimbine, and Their Epimers. Revised Structure of Natural Alloyohimbine

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Received February 13, 1973

The first total synthesis of alloyohimbine (**6a**) and its isomers **4i**, **4j**, and **8b** has been accomplished. Sodium borohydride reduction of the keto nitrile **3** yielded alcohols **4a** and **4b**, epimeric at C_{17}. The diastereoisomers **4i** and **4j** belonging to the epiallo series were derived from **4a** and **4b**. Epimerization of **4i** at C_3 furnished **6a** which proved to be identical with naturally occurring alloyohimbine except for melting point and optical activity. Compound **6a** could be converted to α-yohimbine under mild conditions, characteristic of those used for epimerization at C_{16}. On the basis of these facts, the structures for alloyohimbine and epialloyohimbine should be revised to **6a** and **4i**, respectively. The hydroxy ester **4j** does not lend itself to facile epimerization at C_3, and has not yet been found in nature.

Two products had been obtained from the catalytic reduction of the unsaturated nitrile ester **1** which had been prepared in the course of the total synthesis of yohimbine.[1] The main product, the trans 2,3-disubstituted nitrile ester, was used for the synthesis of yohimbine. It stood to reason, therefore, to utilize the cis fused isomer **2**, which was the minor product, for the preparation of yohimbines of the allo series, especially so since such bases had not been heretofore synthesized.

The nitrile ester **2** was converted in almost quantitative yield to the pentacyclic ketone **3** using potassium *tert*-butoxide in DMSO. This ketone is strongly enolized both in the solid and dissolved states, and on the basis of its spectral properties must exist mainly in the epiallo-trans (E_t) conformation.[2]

In the course of the earlier sodium borohydride reduction of the analogous ketone nitrile belonging to the normal series, three different nitrile alcohols were isolated out of the theoretically possible four. Under similar conditions (DMF–methanol), **3** furnished only two products, **4a** and **4b**, in a ratio of about 2:3.

From spectral evidence, both **4a** and **4b** must exist in the E_t conformation (Table I). It is also possible to establish the stereochemistry of the C_{17} hydroxyl function from the chemical shift of the C_{17} proton.[3]

TABLE I

NMR AND IR DATA

	Nmr,[a] δ		Ir,[b] cm^{-1}	Conformation		
Compd	C_{17} proton multiplet	C_{17} hydroxyl doublet	Bohlmann bands	C_{17} H	C_{17} OH	Skeleton
4a	4.05	5.25	2815, 2775, 2760	e[c]	a	E_t[d]
4b	3.55	5.45	2815, 2775	a[c]	e	E_t
4c	5.15		2815, 2775	e		E_t
4d	4.85		2815, 2780	a		E_t

[a] In DMSO-d_6 at 60 MHz. [b] In pyridine. [c] a = axial, e = equatorial. [d] See ref 2b.

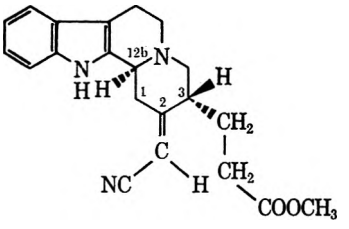
In isomer **4a** the equatorial C_{17} proton is at δ 4.05, while in **4b** the axial C_{17} proton is located higher upfield at δ 3.55. In view of the stable E_t conformation of the two isomers, it follows that the hydroxyl group in **4a** is α while in **4b** it is β. The corresponding O-acylated derivatives **4c** and **4d** were also prepared, and their spectra confirmed the correctness of the C_{17} assignments since the signals for the α protons are now shifted to δ 5.15 and 4.85, respectively. In accordance with the steric assignments, the rate of O-acetylation of **4b** was larger by an order of magnitude than that for the similar reaction of **4a**.

It had been observed in the course of the yohimbine synthesis[1] that the analogs of **4a** and **4b** belonging to the normal series readily epimerized at C-16, bearing the nitrile group, in the presence of aqueous alcoholic alkali at room temperature or under gentle heating. The ΔG value calculated from the equilibrium constants was in good agreement with the energy difference of a

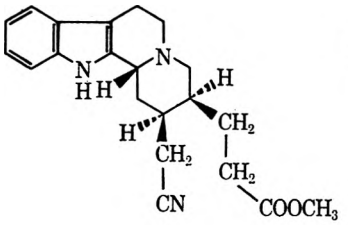
(1) Cs. Szántay, L. Töke, and K. Honty, *Tetrahedron Lett.*, 1665 (1965); L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, **102**, 3248 (1969).

(2) (a) W. F. Trager, C. M. Lee, and A. H. Becket, *Tetrahedron*, **23**, 365 (1967). (b) For the meaning of the symbols for the corresponding conformations of yohimban derivatives, see Cs. Szántay, *Magy. Kém. Lapja*, **26**, 490 (1971).

(3) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963).



1



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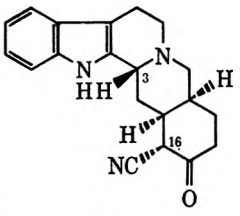

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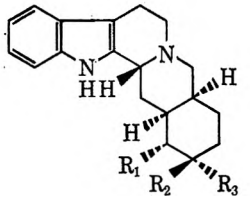
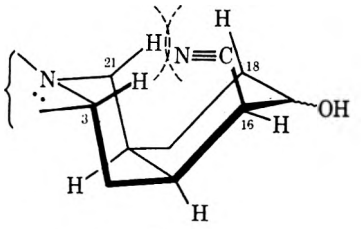


4

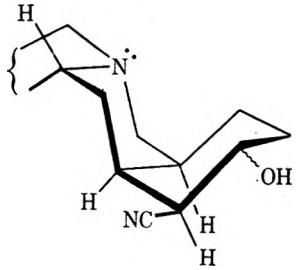
4	R_1	R_2	R_3	4	R_1	R_2	R_3
a	CN	H	OH	f	CN	OTs	H
b	CN	OH	H	g	$CONH_2$	H	OH
c	CN	OH	OAc	h	$CONH_2$	OH	H
d	CN	OAc	H	i	CO_2CH_3	H	OH
e	CN	H	OTs	j	CO_2CH_3	OH	H

nitrile group in the axial and equatorial positions of a cyclohexane system.[4] On the other hand, isomers **4a** and **4b** belonging to the epiallo series could not be epimerized with alcoholic alkali. This result can be readily rationalized by the realization that, if the nitrile group were to epimerize to the β position, it would interact with the axial hydrogens at C_3 and C_{21} in the E_t conformation (Chart I). If the molecule were to take the epiallo-cis (E_{c_1}) conformation to evade such steric interaction, then the indole ring would be placed in an axial position. One can see, then, that the energy difference between the α and β nitrile epimers would be much larger than the value of ~0.2 kcal/mol observed in the normal series.

CHART I



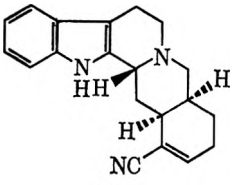
E_t



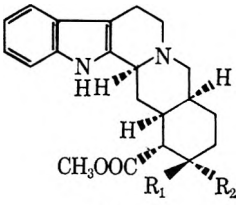
E_{c_1}

It should be mentioned, by way of comparison, that 3-epi-α-yohimbine (**9b**) in which the C_{16} substituent is β exists entirely in the epiallo-cis (E_{c_1}) conformation, and Bohlmann bands indicative of the E_t conformation are completely absent.

Neither can the epimerization of the nitrile alcohols be brought about by hot methanolic alkali. However, **4a** is converted relatively quickly, in about 30 min, to the unsaturated nitrile **5**, whereas **4b** undergoes this dehydration over a period of about 8 hr. This difference in rates of elimination is again in agreement with the structural assignments made.



5



6

6	R_1	R_2
a	H	OH
b	OH	H

The difference in the elimination rates when the tosylates **4e** and **4f** are heated in DMF parallels that for their hydroxyl precursors. This trend can also be observed in the mass spectra. In contradistinction to the spectrum of **4f**, the molecular peak of **4e** is not observed; rather only the ion for the dehydro species **5** is recorded.

By analogy with the behavior of the tosylate of 3-epi-α-yohimbine,[5] it was expected that in pyridine a quaternary salt could be derived from **4e**. The fact that such a transformation did not occur may be attributed to the elimination reaction in the nitrile proceeding at a considerably faster rate than that for the corresponding ester, so that quaternization does not appear as a concurrent reaction.

An answer can now be given as to why only two isomers are formed in the reduction of the ketone **3** belonging to the epiallo series, while it will be recalled that three alcohols are formed in the corresponding reaction in the normal series.

Considering the stereochemistry depicted in Chart I, in the ketone **3** the nitrile group can occupy solely an α position, contrary to the analogous keto nitrile belonging to the normal series where the nitrile in a β configuration is also present at equilibrium. It follows that attack by sodium borohydride leads to two alcohols, with a slight preference for attack from the convex side of the molecule.

As a further step in the synthesis, the nitrile groups in **4a** and **4b** were converted to ester functions. Similarly, in the normal series, direct hydrolysis did not yield the required results. Rather, the acid amides **4g** and **4h** were prepared using hydrogen peroxide in

(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 44.

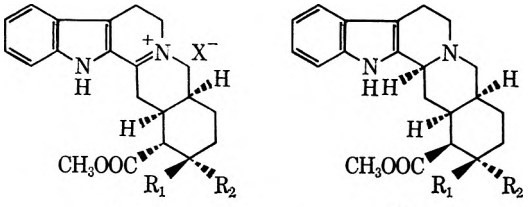
(5) P. E. Aldrich, P. A. Diassi, D. F. Dickel, C. M. Dylion, P. D. Hance, C. F. Huebner, B. Korzun, M. E. Kuehne, L. H. Liu, H. B. McPhillamy, E. W. Robb, D. K. Roychaudhuri, E. Schlittler, A. F. André, E. Van Tamelen, F. L. Weisenborn, E. Wenkert, and O. Wintersteiner, *J. Amer. Chem. Soc.*, **81**, 2481 (1959).

alkaline methanol, and from them the free acids were obtained by boiling with aqueous hydrochloric acid. Esterification of the two acid with diazomethane gave rise to esters **4i** and **4j**. Noteworthy was the observation that the isomers containing the C_{16}, C_{17} substituents in the cis relationship (**4a**, **4g**) hydrolyze more rapidly than in the trans compounds (**4b**, **4h**) on account of the effect of the hydroxyl group.

However, in the course of the hydrolysis of the acid amide **4g** with hydrochloric acid, epimerization at the C_3 site also occurred, so that in addition to **4i** belonging to the epiallo series, a smaller quantity of **6a** of the allo configuration was also formed. That **4i** and **6a** actually differ only at C_3 was proven by mercuric acetate oxidation, which furnished the same immonium salt, **7b**. Reduction of this salt with sodium borohydride gave **6a** as the main product, while **4i** was recovered from the zinc in acetic acid reduction.

Boiling with acid of **6a** with the allo configuration and subsequent methylation provided a 1:3 mixture of **6a** and **4i**, identical with that derived from the boiling with acid and methylation of the amide **4g**.

Following all of these transformations, it was somewhat unexpected to find that the chromatographic, spectral, and chemical properties of **6a** were identical with those of natural alloyohimbine to which the structure **8a** had been attributed in the literature.[6] The original structural assignment had been based on the finding that on boiling with potassium *tert*-butoxide alloyohimbine was converted to α-yohimbine (**8b**), the



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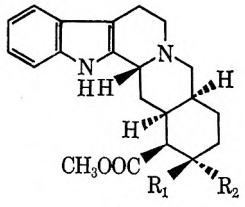

9

7, 8, 9,	R_1	R_2
a	OH	H
b	H	OH

structure of which had been firmly established.[7] Indeed, under such conditions, epimerization of the C_{17} hydroxyl can occur, as for example in the preparation of β-yohimbine from yohimbine. Thus, alloyohimbine was considered to be the C_{17} epimer of α-yohimbine.

To eliminate this apparent contradiction, we tried to bring about under mild conditions the epimerization of natural alloyohimbine, as well as of **6a** which we had synthesized. It was found that alloyohimbine can be readily converted to α-yohimbine at room temperature using sodium methoxide as base. Under such mild conditions, only the more acidic C_{16} hydrogen α to the carbomethoxy group can be pulled. For instance, yohimbine cannot epimerize under such conditions to β-yohimbine.

It follows then that the structural assignment for alloyohimbine, also strongly supported by nmr data, must be revised to **6a**. A corollary is that 3-epialloyohimbine is now correctly represented by expression **4i**. According to the literature, 3-epialloyohimbine should be represented by expression **9a**. The ir spectrum[7] of this alkaloid clearly shows Bohlmann ir bands, so that the molecule would then exist in the E_t conformation. Such a steric arrangement, however, would mean that the β carbomethoxy group would strongly interfere with the hydrogens at C_3, C_{18}, and C_{21}.

In support of our new assignments, it should be noted that Weisenborn indicated[8] as early as 1957 that epimerization at C_{16} of 3-epi-α-yohimbine (**9b**) occurred upon treatment with sodium methoxide to afford 3-epi-16-epi-α-yohimbine. The latter compound should be renamed 3-epialloyohimbine and must be represented by **4i**. Using Weisenborn's conditions, we have found that **9b** could be completely isomerized to the natural antipode of **4i**.

It is interesting to note that in the original literature[9] on alloyohimbine structure **6a** was considered as a possibility for the alkaloid, but was then rejected.

Another result of our stereochemical revisions concerns the nomenclature of the depyrroloalloyohimbine earlier synthesized by us.[10] The proper name for this berban derivative should now be 10,11-dimethoxydepyrrolo-14-epi-α-yohimbine.

From the hydroxy nitrile **4b**, we have also prepared, through the intermediacy of the amide **4h**, the methyl ester **4j**, which proved to be a very stable material, and did not epimerize even on boiling with concentrated acid. Sodium borohydride reduction of its Δ-3 immonium salt yielded, in addition to **6b**, which possesses the alloyohimbine skeleton, a substantial quantity of the isomer **4j**. Such a result could be expected since in **6b** either the indole ring (A_{c_1} conformer) or the C_{16} and C_{17} substituents on ring E (A_t conformer) must be in axial positions.

Following the present synthesis of alloyohimbine and 3-epialloyohimbine the total synthesis of all known yohimbine alkaloids can now be considered to have been achieved, especially since the conversions alloyohimbine → α-yohimbine[7] and α-yohimbine → 3-epi-α-yohimbine[11] are already known from the literature.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 221 and UR-10 spectrometer. Nuclear magnetic resonance spectra were obtained on a Perkin-Elmer R 12 (60 MHz) and on a Varian 300-MHz instrument located in Belgium, and are given in δ units downfield from internal tetramethylsilane. Mass spectra were recorded at 70 eV on AEI MS-902 double-focusing instrument

(6) J. E. Saxton in "The Alkaloids, Chemistry and Physiology," Vol. VII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p 55, and R. H. F. Manske, *ibid.*, Vol. VIII, 1965, p 705, and references cited therein.

(7) M. M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. Soc. Chim. Fr.*, 637 (1961).

(8) F. L. Weisenborn, *J. Amer. Chem. Soc.*, **79**, 4818 (1957).

(9) A. Le Hir, M. M. Janot, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1027 (1953).

(10) L. Szabó, K. Honty, L. Töke, and Cs. Szántay, *Chem. Ber.*, **105**, 3231 (1972).

(11) F. L. Weisenborn and P. A. Diassi, *J. Amer. Chem. Soc.*, **78**, 2022 (1956).

using direct insertion probe at 120–150°. High-resolution mass measurements were accurate to within 2 ppm.

Thin layer chromatography (tlc) was performed on silica gel G, E. Merck AG; silica gel $PF_{254+366}$, E. Merck AG, was used for preparative layer, and silica gel (0.05–0.2 mm), E. Merck AG, for column chromatography, unless otherwise noted.

Anhydrous magnesium sulfate was employed as the drying agent. All reactions utilizing strongly basic reagents were conducted in an oxygen-free dry nitrogen atmosphere. Melting points are uncorrected.

17-Oxo-3-epialloyohimban-16α-carbonitrile (3).—A solution of 3.35 g (9.5 mmol) of 2 (previously dried *in vacuo* with boiling toluene over phosphorus pentoxide for 12 hr) and 3.14 g (28 mmol) of sublimed potassium *tert*-butoxide in 15 ml of dry DMSO was allowed to stand at room temperature for 12 hr, in a carefully dried apparatus under nitrogen. In the meantime the potassium salt of **3** began to separate. The reaction mixture was poured into 100 ml of ice water made acidic to pH 7.5. The precipitate was collected, washed with water and then with methanol, and dried to give 2.95 g (97%) of crude product of satisfactory purity for use in the next step without further purification. Recrystallization from DMF–water gave an analytical sample, mp 285° dec.

Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.83; N, 13.16. Found: C, 74.94; H, 6.60; N, 12.99.

Ir (KBr) 3450–3050 (OH, NH), 2170 (C≡N conj), 2220 (C≡N, w), 1720 (C=O, w), and 2750 and 2810 cm^{-1} (Bohlmann bands); ir (DMF) 2200 cm^{-1} (C≡N).

17α-Hydroxy-3-epialloyohimban-16α-carbonitrile (4a) and 17β-Hydroxy-3-epialloyohimban-16α-carbonitrile (4b).—To a stirred suspension of 0.73 g (2.29 mmol) of **3** in 40 ml of DMF–methanol (1:1) under nitrogen was added 0.17 g (4.5 mmol) of sodium borohydride in small portions during 1 hr. Stirring was continued for an additional 3 hr and the progress of the reaction was followed by tlc (chloroform–methanol 5.0:0.7, R_f **4b** > **3** > **4a**). The excess of sodium borohydride was decomposed with acetic acid and the solvent was removed *in vacuo*. The residue was dissolved in water and basified with concentrated ammonium hydroxide to pH 8.5. The solid separating on cooling was washed with water to give 0.70 g (95%) of a mixture of **4a** and **4b** which was chromatographed over alumina (Brockmann, activity II–III). Elution with chloroform–methanol (99:1) afforded 0.27 g (37%) of **4b** which upon recrystallization from ethanol gave colorless crystals, mp 275° dec.

Anal. Calcd for $C_{20}H_{22}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.77; H, 7.29; N, 13.25.

Ir (KBr) 3500–3100 (OH, NH), 2820, 2760 (Bohlmann bands), 2240 cm^{-1} (C≡N); ir (pyridine) 2815, 2775 (Bohlmann bands), 2245 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.80 (s, 1, NH), 5.45 (d, 1, OH, J = 6 Hz, C_{17} OH), 3.55 (m, 1, C_{17} H).

Further elution with chloroform–methanol (98:2) gave 0.22 g (30%) of **4a** which was recrystallized from ethanol to give white needles, mp 265° dec.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.61; H, 7.31; N, 13.49.

Ir (KBr) 3420 (OH), 3340 (NH), 2820, 2760 (Bohlmann bands), 2250 cm^{-1} (C≡N); ir (pyridine) 2815, 2775, 2760 (Bohlmann bands), 2243 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.85 (s, 1, NH), 5.25 (d, 1, J = 6 Hz), C_{17} OH), 4.05 (m, 1, C_{17} H).

17α-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Acetate (4c).—A mixture of 0.10 g (0.31 mmol) of **4a**, 3.0 ml of anhydrous pyridine, and 0.3 ml (2.9 mmol) of acetic anhydride was allowed to stand at room temperature for 48 hr under nitrogen. The solid which separated was removed by filtration and washed with 2 ml of ether–petroleum ether (bp 30–60°) (1:1) to give 74 mg (68%). Crystallization from 15 ml of dioxane–water (1:1) gave 40 mg (36%) of **4c**: mp 290° dec; ir (KBr) 3360 (NH), 2815, 2780 (Bohlmann bands), 2245 (C≡N), 1740, 1230 cm^{-1} ($OCOCH_3$); ir (pyridine) 2815, 2774 (Bohlmann bands), 2245 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.95 (s, 1, NH), 5.15 (m, 1, C_{17} H), 2.05 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M^+), 362 (95), 320 (14), 304 (30), 303 (15), 302 (22), 277 (1.8), 276 (2.8), 184 (15), 170 (30), 169 (23), 156 (21).

17β-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Acetate (4d).—A mixture of 0.10 g (0.31 mmol) of **4b**, 3.0 ml of anhydrous pyridine, and 0.3 ml (2.9 mmol) of acetic anhydride was allowed to stand at room temperature for 24 hr under nitrogen. The dark solution was diluted with ice water and made basic with concentrated ammonium hydroxide. The solid was filtered and crystallized from ethanol to give 70 mg (68%) of **4d**: mp 268–270° dec; ir (KBr) 3350 (NH), 2815, 2770 (Bohlmann bands), 2245 (C≡N), 1745, 1245 cm^{-1} ($OCOCH_3$); ir (pyridine) 2815, 2780 (Bohlmann bands), 2250 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.85 (s, 1, NH), 4.85 (m, 1, C_{17} H), 2.0 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M^+), 362 (77), 320 (2.3), 304 (28), 303 (1.8), 302 (16), 277 (1.7), 276 (2.7), 184 (9.5), 170 (17), 169 (16), 156 (13).

17α-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Tosylate (4e).—A solution of 24.8 mg (0.077 mmol) of **4a** and 40 mg (0.21 mmol) of *p*-toluenesulfonyl chloride in 2 ml of dry pyridine was allowed to stand at room temperature for 12 hr under nitrogen. The product was separated by preparative tlc (methylene chloride–methanol (100:8), R_f **4e** > **4a**), yielding 9.5 mg of **4e**, mp 290° dec, which could not be obtained crystalline: mass spectrum (70 eV) *m/e* (rel intensity) 303 (90.3, M^+), 302 (100), 288 (2.4), 275 (2.7), 274 (2.9), 235 (1.5), 221 (3.6), 211 (6.7), 209 (6.2), 197 (5.2), 184 (13.8), 170 (11), 169 (17.6), 156 (27.2). Boiling **4e** (2 mg) in 1 ml of dry pyridine for 3 hr gave no change, while during the reflux in DMF for 1 hr elimination occurred and **5** was obtained as the sole product [tlc, chloroform–methanol (5.0:0.2), R_f **4e** > **5** > **4a**].

17β-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Tosylate (4f).—The conversion of 34.4 mg (0.107 mmol) of **4b** to **4f** was accomplished under the same conditions as for the preparation of **4e**. The yield of **4f** was 10 mg, mp 310° dec, which could not be obtained crystalline: mass spectrum (70 eV) *m/e* (rel intensity) 475 (1.4, M^+), 303 (94.9), 302 (100), 288 (2.3), 275 (2.8), 274 (3.2), 221 (3.7), 211 (6.7), 209 (6.2), 198 (4.1), 197 (5.5), 184 (13.2), 170 (10.7), 169 (16.5), 156 (26.4).

4f (2 mg) was refluxed in pyridine (1 ml). No product was formed after 3 hr. Reflux was continued in DMF. Analysis of the mixture by tlc showed that it consisted of **4f** and **5** in the ratio 4:6 after 11 hr [chloroform–methanol (5.0:0.2), R_f **4f** > **5** > **4b**)].

16,17-Dehydro-3-epialloyohimban-16-carbonitrile (5).—A solution of 10 mg (0.031 mmol) of **4a** in 5 ml of 1 *N* ethanolic potassium ethoxide solution was refluxed under nitrogen for 3 hr. After cooling the separated crystals were collected and recrystallized from ethanol to give **5** as colorless needles (8 mg, 85%): mp 233–235°; ir (KBr) 3340 (NH), 2210 (C≡N conj), 1630 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 303 (100, M^+), 302 (98), 288 (2.4), 275 (2.6), 274 (2.5), 221 (3), 211 (5.8), 209 (5.6), 198 (3.9), 197 (4.8), 184 (12), 170 (8.5), 169 (13.6), 156 (25).

17α-Hydroxy-3-epialloyohimban-16α-carboxamide (4g).—To a stirred mixture of methanol (28 ml), 1 *N* sodium hydroxide (5.0 ml), and 15% hydrogen peroxide solution (1.7 ml) was added 0.23 g (0.71 mmol) of **4a**. The suspension was refluxed under nitrogen to the disappearing of the starting material [about 75 min, tlc chloroform–methanol (5.0:1.5), R_f **4a** > **4g**]. The excess of the reagent was destroyed with sodium borohydride and the solvent was evaporated *in vacuo*. The tan residue was taken up with ice water (1.5 ml), filtered, and washed with water (2 × 0.5 ml), giving 0.20 g (79%) of white crystals of **4g**. An analytical sample was prepared by recrystallization from chloroform–methanol (100:1.5), mp 280–285° dec.

Anal. Calcd for $C_{20}H_{25}N_3O_2 \cdot H_2O$: C, 67.21; H, 7.61; N, 11.75. Found: C, 67.01; H, 7.38; N, 11.95.

Ir (KBr) 3450–3150 (OH, NH), 2820, 2760 (Bohlmann bands), 1665, 1590 cm^{-1} ($CONH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M^+), 338 (52), 321 (5), 295 (16), 277 (14), 267 (2.2), 235 (3.6), 223 (7.4), 221 (7), 209 (6), 197 (6), 184 (12), 170 (13), 169 (17), 156 (10).

17β-Hydroxy-3-epialloyohimban-16α-carboxamide (4h).—A solution of **4b** (0.24 g, 0.74 mmol) in methanol (23 ml), 1 *N* sodium hydroxide (7.0 ml), and 15% hydrogen peroxide (1.6 ml) was stirred and refluxed for about 75 min, after which time tlc showed the complete disappearance of **4b** [chloroform–methanol (5.0:1.5), R_f **4b** > **4h**]. Sodium borohydride was added to the solution to decompose excess hydrogen peroxide. Most of the solvent was then removed under reduced pressure, and the residue obtained was taken in cold water, washed, and filtered to give 0.19 g (73%) of **4h**. Recrystallization from chloroform–petroleum ether gave colorless crystals, mp 256–259° dec.

Anal. Calcd for $C_{20}H_{25}N_3O_2 \cdot H_2O$: C, 67.21; H, 7.61; N, 11.75. Found: C, 67.64; H, 7.36; N, 11.46.

Ir (KBr) 3450–3150 (OH, NH), 2800, 2760 (Bohlmann bands), 1660, 1615 cm^{-1} ($CONH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M^+), 338 (65), 321 (6), 295 (12), 277 (8),

267 (2.2), 235 (3.6), 223 (10), 221 (9.2), 209 (5.8), 197 (6.5), 184 (15), 170 (15), 169 (18.5), 156 (11).

Methyl 17β-Hydroxy-3-epialloyohimban-16α-carboxylate (4j).—A solution of 0.25 g (0.70 mmol) of **4h** in 40 ml of 18% hydrochloric acid was refluxed for 7–8 hr under nitrogen [tlc, benzene–methanol (4.0:1.7), R_f **4h** > the acid]. The solvent was removed *in vacuo* and after azeotropic removal of water with benzene and crude acid was suspended in methanol (5 ml) and treated with an excess of an ethereal solution of diazomethane. After 60 min the excess of the reagent was decomposed with acetic acid and the solvent was removed again. The residue was refluxed with 2 × 25 ml of chloroform and filtered and the combined extracts were concentrated to a small volume. The crude product was purified by chromatography on silica. Elution with methylene chloride–methanol (98:2) yielded 0.10 g (40.5%) of **4j** which upon recrystallization from methanol afforded colorless needles, mp 232–233°.

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.40; N, 7.92. Found: C, 71.10; H, 7.44; N, 8.03.

Ir (KBr) 3500–3200 (OH, NH), 2820, 2780 (Bohlmann bands), 1740 (CO_2CH_3), 1060 cm^{-1} (COH); ir ($CHCl_3$) 3620 (OH), 3470 (NH), 2815, 2775 (Bohlmann bands), 1730 (CO_2CH_3), 1050 cm^{-1} (COH); nmr ($CDCl_3$ at 300 MHz) δ 7.76 (s, 1, NH), 7.42 (d, 1, C_9 H), 7.27 (d, 1, C_{12} H), 7.12–7.0 (m, 2, C_{10}, and C_{11} H), 3.83 (m, 1, C_{17} H), 3.80 (s, 3, CO_2CH_3), 3.55 (m, 1, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (99), 339 (12), 337 (3.1), 335 (1.6), 325 (2.5), 323 (1.3), 305 (4.5), 295 (2.7), 277 (2.0), 184 (1.5), 170 (15), 169 (19), 156 (11), 144 (8.5).

Methyl 17α-Hydroxy-3-epialloyohimban-16α-carboxylate (4i) and Methyl 17α-Hydroxyalloyohimban-16α-carboxylate [6a, (±)-Alloyohimbine].—**4g** (0.11 g, 0.31 mmol) was refluxed in 20 ml of 18% hydrochloric acid for 4 hr [tlc, chloroform–methanol (5.0:1.5), R_f **4g** > acid] under nitrogen and then evaporated to dryness. The residue was dehydrated by azeotroping with benzene. The solid, which showed two spots on tlc, was taken up with methanol (5 ml) and treated with excess of an ethereal solution of diazomethane. After 60 min the excess reagent was destroyed with acetic acid. The residue after removal of solvents was treated with boiling chloroform (2 × 25 ml) and a small amount of insoluble material filtered off. The filtrate was taken to dryness *in vacuo*, leaving the mixture of **4i** and **6a**, which was separated by chromatography on silica; elution with methylene chloride–acetone (80:20) yielded **6a** (15 mg, 13%). Recrystallization from ethyl acetate following from ether gave an analytical sample of **6a**: mp 136–137°; ir (KBr) 3550–3200 (OH, NH), 2805, 2750 (Bohlmann bands), 1725 (CO_2CH_3), 1050 cm^{-1} (COH); ir ($CHCl_3$) identical with that of an authentic sample of natural alloyohimbine, 3615 (OH), 3470 (NH), 2805, 2760 (Bohlmann bands), 1715 (CO_2CH_3), 1050 cm^{-1} (COH); nmr ($CDCl_3$) δ 8.57 (s, 1, NH), 7.65–7.05 (m, 4, aromatic protons), 3.80 (axial C_{17} H signal coincident with methoxycarbonyl signal total intensity equivalent to four protons), 3.25 (m, 1, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (95), 339 (4.8), 337 (1.9), 335 (1.4), 323 (4.9), 295 (7.3), 277 (1.5), 267 (1.7), 184 (6.7), 170 (12), 169 (14), 156 (9.0), 144 (9.6).

Further elution with methylene chloride–acetone (65:35) afforded **4i** (50 mg, 43.7%). An analytical sample was recrystallized from ethyl acetate: mp 223–224° (sublimed at 226.5°); ir (KBr) 3550–3350 (OH, NH), 3460 (NH), 2815, 2775 (Bohlmann bands), 1720 (CO_2CH_3), 1060 cm^{-1} (COH); ir ($CHCl_3$) 3650–3500 (OH, NH), 3480 (NH), 2815, 2775 (Bohlmann bands), 1725 (CO_2CH_3), 1050 cm^{-1} (COH); nmr ($CDCl_3$ at 300 MHz) δ 7.72 (s, 1, NH), 7.45 (d, 1, C_9 H), 7.28 (d, 1, C_{12} H), 7.14–7.04 (m, 2, C_{10} and C_{11} H), 4.23 (s, 1, C_{17} H), 3.82 (s, 3, CO_2CH_3), 3.48 (m, 1, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (98), 339 (8.5), 337 (2.1), 335 (1.4), 323 (4.6), 295 (8.4), 277 (1.9), 267 (2.0), 184 (8.4), 170 (18), 169 (21), 156 (13), 144 (12).

3-Epi-α-yohimbine (9b).[11]—To a solution of 60 mg (0.17 mmol) of natural α-yohimbine (**8b**) in 4 ml of glacial acetic acid held at 60° was added 215 mg (0.67 mmol) of mercury (II) acetate. The course of the oxidation was followed by tlc [chloroform–methanol (5.0:0.5), under an ammonia atmosphere, R_f **8b** > the immonium salt of **8b**]. After completion of the reaction (*ca.* 90 min) the mercury(I) acetate was removed by filtration and washed with acetic acid (5 ml). The filtrate was heated to boiling, hydrogen sulfide gas was introduced, and the sulfides were filtered off. Zinc dust (0.30 g) was added to the solution, the reflux was continued for 2.5 hr, and the solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in water. Basification with concentrated ammonia followed by ethereal extraction yielded a crude product which was purified by chromatography on silica. Elution with chloroform gave 13.5 mg of α-yohimbine (**8b**). Then chloroform–methanol (90:10) eluted a 3,4-secoyohimbine fraction. Further elution with chloroform–methanol (85:15) afforded 10.8 mg of 3-epi-α-yohimbine (**9b**).

8b had mp 235–236°; mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (93), 339 (5.5), 337 (2), 336 (1.5), 335 (1.9), 323 (6), 295 (7.1), 184 (10), 170 (12), 169 (13), 156 (8.4).

9b had mp 225°; mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (94), 339 (10), 337 (3.9), 335 (2.6), 323 (6.3), 297 (9.3), 295 (10), 184 (18), 170 (19), 169 (21).

3,4-Secoyohimbine had mass spectrum (70 eV) *m/e* (rel intensity) 356 (100, M^+), 355 (40), 341 (5.1), 339 (6.8), 335 (49), 325 (8), 297 (53), 264 (8.5), 250 (12), 225 (23), 223 (14).

Oxidation–Reduction of 4i and 4j. A.—Mercury(II) acetate (71 mg, 0.22 mmol) was added in small portion over a period of 10 min to a solution of **4i** (10 mg, 0.028 mmol) in glacial acetic acid (9 ml). The mixture was kept at 60° for 10 hr under nitrogen and then filtered. The filtrate was heated to boiling, hydrogen sulfide gas was introduced, the insoluble sulfides were filtered off, and the solvent was evaporated *in vacuo*, giving a yellow oil (**7b**) which was halved.

(1) A suspension of the 3-dehydro compound and a large excess of zinc dust (five to six times the weight of the 3-dehydro compound) in glacial acetic acid was refluxed for 2 hr. The mixture was filtered, the solvent was removed *in vacuo*, and the residue was dissolved in water and made basic with concentrated ammonia. The base was extracted exhaustively with chloroform, and the extract was washed, dried, and evaporated. The residue was separated by preparative tlc [benzene–ethanol (40:10), developed twice, R_f **6a** > **4i**]. It consisted of **4i** and **6a** in the ratio of 3:2.

(2) Sodium borohydride was added gradually to a solution of **7b** acetate in methanol till the starting material disappeared. Analysis of the reaction mixture by tlc [methyl ethyl ketone–hexane–methanol (1.5:3:0.5), R_f **6a** > **4i** or Al_2O_3-G, chloroform–methanol (5.0:0.15), R_f **6a** > **4i**] showed that it consisted mostly of **6a**.

B.—The oxidation was carried out on 10 mg of **4j** by the method described above to **7b**. The material obtained (**7a**) was reduced with sodium borohydride. Analysis of the mixture by tlc [Al_2O_3 G, chloroform–methanol (5.0:0.15)], showed that it consisted of **4j** and **6b** in the ratio of 4:1.

Epimerization of Alloyohimbine (6a) to α-Yohimbine (8b).—Natural alloyohimbine (15 mg) in 3 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen for 4 days. Separation of the mixture by preparative tlc [chloroform–methanol (100:16), R_f **8b** > **6a**] gave 5.6 mg of α-yohimbine (**8b**). The product was shown to be identical in all respects (ir, mass spectrum, tlc spots) with the authentic natural α-yohimbine.

Epimerization of 3-Epi-α-yohimbine (9b) to 3-Epialloyohimbine (4i).—3-Epi-α-yohimbine (**9b**) (1 mg) in 1.5 ml of 2 *N* methanolic sodium methoxide solution was heated at 60° under nitrogen. The isomerization was followed by tlc [chloroform–methanol (5.0:0.5), R_f **4i** > **9b**]. After 80 min the ratio of **9b** and **4i** was 3:2 and in 2 hr **9b** was completely converted to one of the enantiomers of **4i**.

Registry No.—**2**, 40085-19-6; **3**, 40085-20-9; **4a**, 40085-21-0; **4b**, 40085-22-1; **4c**, 40085-23-2; **4d**, 40085-24-3; **4e**, 40085-25-4; **4f**, 40085-26-5; **4g**, 40085-27-6; **4h**, 40085-28-7; **4i**, 40085-29-8; **4j**, 40085-30-1; **5**, 40085-31-2; **6a**, 40085-32-3; **8b**, 131-03-3; **9b**, 483-09-0; 3,4-seco-α-yohimbine, 39990-62-0.

Acknowledgments.—The authors wish to thank the Hungarian Academy of Sciences for financial support; Professor M. Shamma, The Pennsylvania State University, Pennsylvania, and Professor R. Goutarel, Gif-sur-Yvette, France, for providing samples of natural alloyohimbine; Professor M. Anteunis, Gent, Belgium, for the 300-MHz nmr spectra and Dr. P. Kolonits for the 60-MHz nmr spectra; and Dr. J. Tamás for the high-resolution mass spectra.

Synthesis of Yohimbines. II. An Alternative Route to Alloyohimbine Alkaloids

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Received February 13, 1973

Starting from the readily available keto ester **1**, through intermediates **3**, **6a**, **6b**, **6j**, and **6k**, a stereospecific total synthesis of disubstituted alloyohimbanes of type **7** was accomplished. Alloyohimbine (**8m**), α-yohimbine (**8n**), and the other two possible stereoisomers (**8h** and **8i**) were also prepared. In the course of these transformations, the first example of imino ether–enamine tautomerism, neighboring-group participation in the hydrolysis of compounds **6a** and **6b**, and a Knoevenagel condensation under extremely mild experimental conditions were observed and studied.

The route to the synthesis of alkaloids of the alloyohimbine type described in our previous communication[1] utilized a by-product of a catalytic hydrogenation as starting material. Our aim was now to elaborate a high-yield, practical synthesis of alloyohimbine bases.

Condensation of the Keto Ester 1 with Methyl Cyanoacetate and Malononitrile. —The readily available[2] keto ester **1** was the starting material, and the improved mode of preparation of the salt **2** required in its preparation is described in the Experimental Section.

The ketone **1** was condensed with methyl cyanoacetate. It was expected that this reaction would be accompanied by epimerization at C_3, since such a change had been observed earlier in the case of benzo[*a*]-quinolizidine derivatives,[3] and had in fact been used successfully by us in the realization of the stereoselective synthesis of corynantheidine.[4] However, under the experimental conditions (NH_4OAc–HOAc, azeotropic removal of water with benzene) which had proven successful with the analog of **1** possessing a C_3 ethyl substituent, the vinyl lactam **4** was obtained instead of the required cyano ester **3a**. Ring E of this lactam may be opened through acid-catalyzed hydrolysis, and the initial ester **1** can be recovered following esterification. Lactam **4** could also be generated by the reaction of the cyano ester **3a** with ammonium acetate.

Using triethylammonium acetate as catalyst, no vinyl lactam **4** was formed. Rather, the desired cyano ester **3a** was produced in low yield, while the dienamine **5a** formed through oxidation was the main product. The structure assigned to the dienamine **5a** was consistent with the spectral data, and could be supported chemically since mercuric acetate oxidation of **3a** yielded **5a**. The behavior of **5a** is similar in many respects to that of its benzo[*a*]quinolizidine analog prepared and studied earlier.[5] It is a yellow substance, resistant to catalytic hydrogenation. On the basis of the temperature dependence of its nmr spectrum, it must be a mixture of *E* and *Z* isomers. Owing to the reduced energy of activation caused by the extensive conjugation, these two isomers are readily interconvertible,[5] the coalescence of the two indole NH signals occurring at 180°.

After a thorough study of the reaction conditions, we finally succeeded in preparing the desired cyano ester **3a** in good yield by carrying out the reaction in triethylammonium acetate as solvent in the presence of phosphorus pentoxide. Under such conditions the reaction proceeded rapidly at room temperature, and there was no need for azeotropic removal of the water formed.

Reduction of **3a** with sodium borohydride gives **6a** in good yield. The nmr spectrum of this product shows that the methoxyl methyl of the R_1 ester group is split into two peaks which are independent of temperature. This phenomenon is a consequence of the new asymmetric center formed following the reduction.[4] There is no need to separate the diastereoisomers, however, since the new asymmetric center disappears in the course of further reactions.

As an alternative to the condensation of **1** with methyl cyanoacetate, the reaction was performed with malononitrile. The product, **3b**, was similarly easy to reduce to **6b**, while its mercuric acetate oxidation product, **5b**, was the analog of the dienamine **5a**.

The remarkably stable imino ether **6c** could be derived from the dinitrile **6b** using base catalysis in an alcoholic medium. The properties of this base, which include the new imino ether–enamine tautomerism observed in association with it, have been reported elsewhere.[6] In an aprotic solvent, **6c** can be converted with 1 mol of water to the ester **6a**. Alternatively, in dry methanol saturated with hydrogen chloride, the acid amide **6e** is obtained. The latter reaction is so easily controlled that, in the preparation of the ester nitrile **6a** from the dinitrile **6b**, it was found expedient to prepare the amide **6e** first, which was subsequently converted to the ester using the dry methanol–hydrogen chloride treatment. The imino ether to amide conversion is presumably an A_{al} process. This assumption is supported by the fact that in DMF solution **6c** alkylates carboxylic acids, thus, *e.g.*, **6g** to **6a**, at room temperature while converting itself to the acid amide **6e**.

The triester **6f** can be prepared either from the amide **6e** or the ester **6a**. Both ester groups of the ester **6a** hydrolyzed with remarkable ease, by simply

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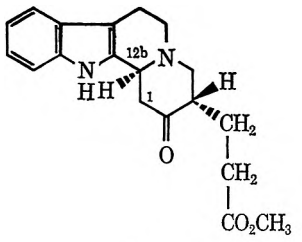
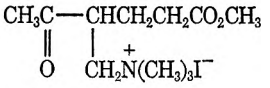
(4) Cs. Szántay and M. Bárczai-Beke, *Chem. Ber.*, **102**, 3963 (1969).

(5) M. Bárczai-Beke, G. Dörnyei, G. Tóth, and Cs. Szántay, *Tetrahedron*, in press.

(6) (a) L. Töke, G. Blaskó, L. Szabó, and Cs. Szántay, *Tetrahedron Lett.*, 2459 (1972). (b) Following our preliminary communication on the imino ether–enamine tautomerization,[6a] Professor H. Ahlbrecht of Giessen, West Germany, was kind enough to draw our attention to some of his still unpublished work relating to the assignments of NH_2 and C=NH proton peaks in the nmr spectra. Further studies on our part initiated by these comments have shown that the spectral assignments for the two functionalities must be contrary to those given by us earlier, so that the ratio of the tautomers should also be reversed.



1



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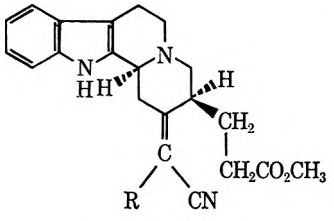

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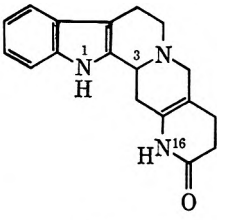

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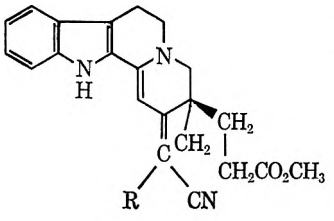

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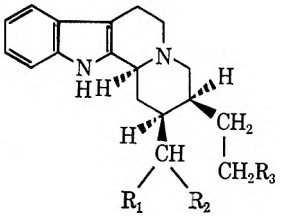
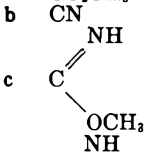
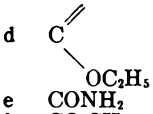


6

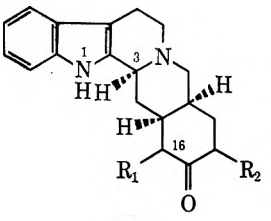
3, 5	R
a	CO_2CH_3
b	CN

6	R_1	R_2	R_3
a	CO_2CH_3	CN	CO_2CH_3
b	CN	CN	CO_2CH_3
c		CN	CO_2CH_3
d		CN	CO_2CH_3
e	$CONH_2$	CN	CO_2CH_3
f	CO_2CH_3	CO_2CH_3	CO_2CH_3
g	CO_2H	CN	CO_2H
h	$CONH_2$	CN	CO_2H
i	H	CN	CO_2H
j	H	CN	CO_2CH_3
k	H	CO_2CH_3	CO_2CH_3

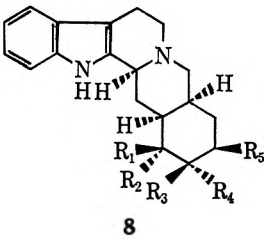
dissolving in alkali at 0° and then acidifying. The precipitate formed is diacid **6g**. This exceedingly rapid hydrolysis could be due to neighboring group participation. A similar behavior is also shown toward alkali by the dinitrile **6b**. However, in this case, the amide **6h** is also present besides the dicarboxylic acid **6g**.

Short boiling of a solution of the diacid **6g** in DMF led, as expected, to decarboxylation and formation of the carboxylic acid nitrile **6i**, which could in turn be converted to the ester nitrile **6j** with diazomethane, or alternatively to the diester **6k** with dry methanol and hydrogen chloride.

Preparation of the Alloyohimbine Skeleton from the Nitrile Ester 6j.—The nitrile ester **6j** can be converted in good yield by potassium *tert*-butoxide in DMSO into the pentacyclic ketone **7a**, which exists as a mixture of keto–enol tautomers both in the solid phase and in solution. From spectral data, the compound must exist in the trans (A_t) conformation. In the allo series, the steric interaction between the C_{21} H, the C_3 H, and the C_{16} substituent, present in the epiallo analogs,[1] is not a factor. There is, therefore, only a minimal difference in energy between an axial and an equatorial C_{16} cyano group in **7a**, so that in an equilibrium mixture both isomers could be present. Accordingly, sodium borohydride reduction of **7a** yielded a 4:1 mixture of the isomeric nitrile alcohols **8a** and **8b**.



7



8

7	R_1	R_2
a	CN	H
b	H	CO_2CH_3
c	H	H
d	CO_2CH_3	H

8	R_1	R_2	R_3	R_4	R_5
a	CN	H	OH	H	H
b	H	CN	OH	H	H
c	CN	H	OAc	H	H
d	H	CN	OAc	H	H
e	H	CN	H	OH	H
f	$CONH_2$	H	OH	H	H
g	H	$CONH_2$	OH	H	H
h	CO_2CH_3	H	OH	H	H
i	H	CO_2CH_3	OH	H	H
j	H	H	OH	H	CO_2CH_3
k	H	H	H	OH	CO_2CH_3
l	H	H	OH	H	CH_2OH
m	H	CO_2CH_3	H	OH	H
n	CO_2CH_3	H	H	OH	H

The spectral characteristics of isomers **8a** and **8b** (Table I) indicate that both exist in the A_t conformation so that the C_{17} OH group can occupy only an axial site. The correctness of this assignment is corroborated by the nmr spectra of the acetylated derivatives **8c** and **8d** (Table I). It can thus be concluded unequivocally that the OH groups in **8a** and **8b** are β, so that attack by borohydride must occur from the convex side of the molecule and is subject to "steric approach control."

TABLE I

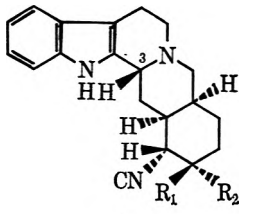
SPECTRAL VALUES

Compd	Nmr,[a] δ: C_{17} proton multiplet	Nmr,[a] δ: C_{17} hydroxyl doublet	Ir,[b] cm^{-1}, Bohlmann bands
8a	3.95	5.05	2815, 2765
8b	3.93	5.15	2810, 2770
8c	5.10		2810, 2760
8d	4.95		2805, 2760

[a] In DMSO-d_6 at 60 MHz. [b] In pyridine.

The above conclusions are also supported by the chemical behavior of the two compounds. Either isomer when dissolved in alcoholic alkali at room temperature yields a nearly 1:1 mixture of **8a** and **8b**. Under such mild conditions only the carbon atom, adjacent to the nitrile group, can be epimerized. It should be mentioned here that **8a** and **8b** must be primary products of the reduction of the ketone **7a** because no epimerization occurs under the conditions of the reduction. Additionally, the ratio of the reduction products remains unchanged when the reaction with sodium borohydride is carried out in acetic acid.

Further confirmation of the steric assignments can be obtained through correlation with the nitrile alcohols **9a** and **9b** of the epiallo series synthesized

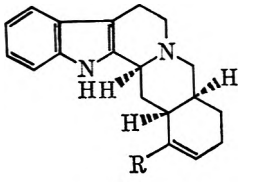


9

9	R_1	R_2
a	OH	H
b	H	OH

earlier.[1] Thus, when the product **9a** was epimerized at C-3 by oxidation with mercuric acetate and subsequent reduction, a product completely identical with **8b** was obtained, proving that in both compounds the C_{17} OH group must be β. On the other hand, similar epimerization of **9b** led to an allo nitrile alcohol which was identical with neither **8a** nor **8b**. For this new nitrile alcohol, structure **8e** can be written.

It will be recalled that the nitrile group in the pentacyclic indole bases could be hydrolyzed in two steps.[1,7] In the first step, treatment of the nitrile with hydrogen peroxide furnished the amide. When the reaction was carried out at room temperature, this transformation occurred at a faster rate than C_{16} isomerization. The unsaturated amide **10b**, which was formed in substan-



10

10	R
a	CN
b	$CONH_2$
c	CO_2CH_3

tial quantities at higher temperature, was present only in trace amounts.

In pyridine solution, the ir spectrum of the amide **8g** shows only weak Bohlmann bands so that the allo-cis (A_{cl}) conformation must predominate. In the A_t conformation both the carboxamide and the hydroxyl groups must be axial, while in the A_{cl} arrangement they are equatorial.

The hydroxy esters **8h** and **8i** can be prepared from the amides using hydrogen chloride in dry methanol. A by-product of this reaction is apo-α-yohimbine. The chromatographic behaviors of both esters **8h** and **8i** differ from that of natural α-yohimbine or alloyohimbine.

The importance of the synthesis of **8h** and **8i** lies primarily in the fact that all the yohimbine isomers with the allo configuration are now available, thus further enhancing our earlier views on the revision of the stereochemistry of alloyohimbine.

The main spectral features of the isomers in question have been summarized in Table II. For clarity's sake, Table II also includes the data for alloyohimbine (**8m**) and α-yohimbine (**8n**) discussed earlier.[1]

(7) L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, **102**, 3248 (1969).

TABLE II

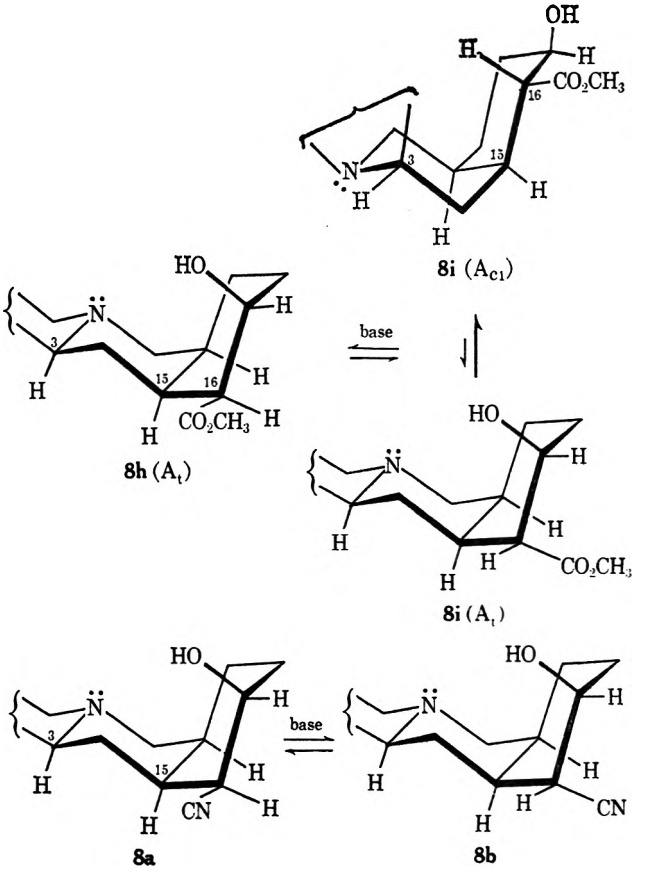
SPECTRAL VALUES

Compd	Nmr, δ: C_{17} proton	Nmr, δ: C_3 proton	Ir,[c] cm^{-1}, Bohlmann bands	Conformation: C_{17} OH	Conformation: C_3 indole ring	Conformation: Skeleton
8h	4.26[a]	3.05	2810, 2760	ax	eq	A_t
8i	3.75[a]	3.95	Very weak	eq	ax	A_{cl}
8m (alloyohimbine)	3.80[b]	3.25	2805, 2760	eq	eq	A_t
8n (α-yohimbine)	3.99[a]	3.15	2805, 2765	eq	eq	A_t

[a] In $CDCl_3$ at 300 MHz. [b] In $CDCl_3$ at 60 MHz. [c] In pyridine.

Epimerization of Yohimbine Isomers.—We have studied the epimerization of yohimbine isomers in 2 *N* methanolic sodium methoxide at room temperature. Under these conditions, only the C_{16} site, adjacent to the carbomethoxy group, can epimerize. Starting with **8h**, its isomer **8i** appeared after a few hours, simultaneously with the elimination product **10c**. Complete equilibration was achieved after about 3 days, with an **8h**:**8i** ratio of about 1:1. Upon further standing, the quantity of **10c** increased. The behavior of the ester alcohols thus bears some similarity to that of the nitrile alcohols **8a** and **8b**, but on the basis of spectral data no full analogy prevails. The transformation **8a** → **8b** occurs between compounds possessing the A_t conformation, and the equilibrium (~1:1) is determined by the small difference in energy between the axial and equatorial positions of the nitrile group (Chart I). It should also be added that the $A_t \rightarrow A_{cl}$ conformational equilibrium also plays an important role (Chart I). Species **8i** is one of those rare sub-

CHART I



stances with the alloyohimbine skeleton whose C/D ring annelation is cis.

Synthesis of the Alloyohimbine Skeleton from the Diester 6k.—The direction of the Dieckmann cyclization of **6k** was predicated on the conditions used as already established earlier[7] in the case of compounds of analogous structures. When the reaction was carried out in hot toluene in the presence of sodium methoxide or sodium hydride, the enolic pentacyclic ketone **7b** was isolated as the sole product. The compound was readily decarboxylated to the known[8] (±)-alloyohimbone (**7c**). Alternatively, sodium borohydride reduction of **7b** yielded alcohols **8j** and **8k** in a 20:1 ratio, together with a small amount of the diol **8l**. Since neither **8j** nor **8k** was identical with any of the previously prepared yohimbine isomers, the ester function must be linked to C_{18}. The steric arrangement of the hydroxyl group in **8j** and **8k** was not extensively investigated. Rather, with the assumption that "steric approach control" is operative, we attributed structure **8j** to the substance formed in larger quantity.

When the cyclization was carried out at room temperature, the isomer **7d**, alloyohimbinone, was isolated in about 30% yield in addition to **7b**. Ketone **7d**, in analogy to **7b**, is also subjected to keto–enol tautomerism, and again leads to (±)-alloyohimbone (**7c**) upon hydrolysis and decarboxylation.

The optically active form of aloyohimbinone (**7d**) is known[9] from the oxidation of α-yohimbine, and it is reported that it exists completely in the enolic form. This statement, however, is valid only in the solid phase, since in pyridine or chloroform solution the keto form predominates by about 80%. Spectral data indicate that **7d** exists both in the solid phase and in solution as the A_t conformer.

Reduction of **7d** with sodium borohydride furnished three hydroxy esters. The main product proved to be identical with the unnatural base **8h**. The second product was (±)-alloyohimbine[1] (**8m**), while the third product was (±)-α-yohimbine (**8n**). The ratio of the alkaloids was **8h**:**8m**:**8n** = 7:3:2.

Taking into consideration our earlier investigations in the normal yohimbane,[7] epialloyohimbane,[1] and berbane series,[10] it can be stated that the structures and relative quantities of the stereoisomeric alcohols obtained from the sodium borohydride reduction of yohimbinones and their analogs containing nitrile are in accordance with the concept of "steric approach control" in the reduction.

Experimental Section

The infrared spectra were determined on Perkin-Elmer 221 and UR-10 spectrometers. Nuclear magnetic resonance spectra were obtained on a Perkin-Elmer R 12 (60 MHz), Varian A-60, and Varian-300 MHz instruments at Gent and are given in δ units downfield from internal tetramethylsilane. Mass spectra were recorded at 70 eV on a AEI-MS-902 double-focusing instrument using direct insertion probe at a temperature of 120–150°. High-resolution mass measurements were accurate to within 2 ppm.

Thin layer chromatography (tlc) was performed on silica gel G, E. Merck AG, unless otherwise noted. Silica gel $PF_{254+366}$ and Al_2O_3 $PF_{254+366}$, E. Merck AG, were used for preparative layer chromatography. Silica gel (0.05–0.2 mm, E. Merck, AG) was used for column chromatography, unless otherwise noted. Anhydrous magnesium sulfate was employed as the drying agent. All reactions utilizing strongly basic reagents were conducted under oxygen-free dry nitrogen atmosphere.

4-Dimethylaminomethyl-5-oxocaproic Acid Methyl Ester Methiodide (2) and 4-Methylene-5-oxocaproic Acid Methyl Ester.[2]—A suspension of 138 g (0.6 mol) of diethyl α-acetylglutarate in 600 ml of 2 *N* sodium hydroxide solution was stirred vigorously for 3 hr at room temperature and the unchanged starting material was extracted with ether (2 × 100 ml). A solution of 61 g (0.75 mol) of diethylamine hydrochloride in 102 ml of 22% aqueous formaldehyde (0.75 mol) was added dropwise with stirring into the aqueous phase obtained above. After the reaction mixture was allowed to stand for 48 hr at room temperature it was acidified to pH 3 with concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The resulting viscous oil, which contained sodium chloride, was dissolved in 100 ml of hot ethanol, and the salt was filtered and washed with ethanol (3 × 50 ml). The combined alcoholic solution was dehydrated by azeotroping with benzene (200 ml). The process was repeated several times with a mixture of benzene–ethanol (2:1) while the water content decreased to 3–8% (checking by Karl–Fischer method). The amount of phosphorus pentoxide necessary for the esterification was calculated by the formula

$$P_2O_5\ (\text{mol}) = \frac{\text{water content (\%)} \times \text{weight of crude material}}{18 \times 100} + \text{mol of starting material}$$

The solution of crude material in 300 ml of methanol was added portionwise to the calculated amount of phosphorus pentoxide in 600 ml of methanol with cooling. After the reaction mixture was allowed to stand at room temperature for 24 hr, the solvent was removed *in vacuo*, and the residue was rendered to pH 3 dissolving in saturated sodium bicarbonate solution and extracted with ether (5 × 200 ml). The combined extracts were washed, dried, evaporated, and distilled to give 27 g (28%) of 4-methylene-5-oxocaproic acid methyl ester, bp 70–72° (2 mm).[2]

The above aqueous solution, which was extracted with ether, was cooled and made alkaline with saturated sodium bicarbonate solution and extracted immediately with ether (5 × 500 ml). The combined extracts were dried and evaporated. The obtained oil (38 g) in 10 ml of dry methanol was treated with methyl iodide (19 ml, 0.3 mol) and allowed to stand overnight. The precipitated crystals were collected and washed with dry ether, giving 50 g (25%) of **2**, mp 118–119°.[2]

15,20-Dehydro-16-azayohimbone (4).—To the solution of 1.25 g (3.82 mmol) of **1** in 300 ml of dry toluene was added 0.8 g (10.4 mmol) of ammonium acetate and 2 ml of glacial acetic acid, and the mixture was refluxed for 4 hr. The reaction was followed by tlc [benzene–methanol (8.5:1.5)], R_f 1 > 4. The cooled solution was neutralized with sodium methoxide, washed with water, and dried, and the solvent was evaporated *in vacuo* under nitrogen. The residue (0.95 g, 84%) was crystallized twice from ethanol to give 0.72 g (64%) of **4**, mp 261–262°.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.41; H, 6.54; N, 14.55.

Ir (KBr) 3370 (lactam NH), 3320 (indole NH), 2815, 2750 (Bohlmann bands), 1665 (lactam C=O), 1630 cm^{-1} (C=C); nmr (DMSO-d_6) δ 8.95 (s, 1, lactam NH), 7.45–6.50 (m, 4, aromatic protons).

Hydrolysis and Subsequent Methylation of 4 to 1.—The solution of 12 mg (4.5×10^{-5} mol) of **4** in 5 ml of 0.005% aqueous HCl was refluxed for 4 hr, the solvent was evaporated *in vacuo*, and the residue was dried by azeotroping with benzene–ethanol. The salt obtained was suspended in 10 ml of methanol and allowed to stand for 30 min with an excess of ethereal diazomethane, tlc, benzene–methanol (8.5:1.5). The residue (12.2 mg, 91%) after removal of the solvent was crystallized from methanol, mp 207–208°. The identity of the material as **1** was established by ir, tlc, and mixture melting point.[2]

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.61; H, 6.79; N, 8.58. Found: C, 69.53; H, 6.86; N, 8.65.

Ir (KBr) 3380 (NH), 1721 (CO_2CH_3), 1710 cm^{-1} (C=O).

Methyl 3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2-ylidenecyanoacetate (3a).—To the solution of 10.4 g (31.7 mmol) of **1** in 42 ml of glacial acetic acid was added 64 ml (460 mmol) of triethylamine, 1.8 g

(8) P. G. Philpott and A. M. Parsons, *J. Chem. Soc.*, 3018 (1958).

(9) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965); J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967).

(10) L. Szabó, K. Honty, I. Tóth, L. Töke, and Cs. Szántay, *Chem. Ber.*, **105**, 3215 (1972); L. Szabó, K. Honty, L. Töke, and Cs. Szántay, *ibid.*, **105**, 3231 (1972).

(12.6 mmol) of phosphorus pentoxide, and 40 ml (450 mmol) of methyl cyanoacetate. The mixture was stirred at 40–50° for 50 hr under dry nitrogen [tlc, benzene–methanol (8:2), R_f **3a** > 1], then diluted with cold chloroform (125 ml) at 0°. The extract was washed with 5% sodium hydroxide (2 × 40 ml) and water (2 × 25 ml), dried, and evaporated *in vacuo*. The residue crystallized from methanol (10 ml) on standing to give 10.2 g (80%) of **3a**. An additional 1.3 g (6.4%) of **3a** oxalate was obtained from the mother liquor with methanolic oxalic acid. A recrystallized sample of **3a** exhibited mp 173–174°.

Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.79; H, 6.18; N, 10.31. Found: C, 67.71; H, 6.10; N, 10.24.

Ir (KBr) 3380 (NH), 2820, 2770 (Bohlmann bands), 2260 (C≡N), 1735 (CO_2CH_3), 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 8.58 (s, 1, NH), 7.60–7.00 (m, 4, aromatic protons), 4.08 (m, 1, C_1 H_{eq}), 3.85 (s, 3, CO_2CH_3 conj), 3.65 (s, 3, CO_2CH_3).

3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12α-hexahydro-2*H*,-6*H*-indolo[2,3-*a*]quinolizin-2-ylidenemalononitrile (3b).—To a stirred solution of 16.3 g (50 mmol) of **1** in 40 ml of glacial acetic acid was added 50 ml (360 mmol) of triethylamine, 4 g (28 mmol) of phosphorus pentoxide, and finally 30 g (450 mmol) of malononitrile. The reaction mixture was allowed to stand at room temperature for 2–3 hr under nitrogen. The progress of the reaction was followed by tlc [benzene–methanol (8:2), R_f **3b** > 1]. The solution was diluted with chloroform (300 ml), the extract was washed thoroughly with 5% sodium hydroxide to remove the acid, and the aqueous layer was reextracted with chloroform (3 × 25 ml). The combined extracts were washed, dried, and evaporated under reduced pressure, giving an oil which was crystallized from methanol (20 ml) on standing (14.9 g, 79.7%). The analytical sample was recrystallized from methanol, mp 158–159°. A further 1.7 g (7.5%) of salt was obtained from the mother liquor with methanolic oxalic acid. The solution of **3b** oxalate (1.7 g, 3.74 mmol) in dioxane (10 ml) was treated with an ethereal solution of diazomethane. After the solvent was evaporated, the residue was crystallized from methanol (4.5 ml) to give 1.19 g of **3b**.

Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.63; H, 6.07; N, 14.92.

Ir (KBr) 3380 (NH), 2855, 2825, 2770 w (Bohlmann bands), 2240, 2250 (C≡N), 1740 (CO_2CH_3), 1605 cm^{-1} (C=C); nmr ($CDCl_3$) δ 8.35 (s, 1, NH), 7.6–7.1 (m, 4, aromatic protons), 3.70 (s, 3, CO_2CH_3).

(*E*,*Z*)-Methyl 3β-(2-Methoxycarbonylethyl)-3,4,7,12-tetrahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2-ylidenecyanoacetate (5a).—A solution of 2.04 g (5 mmol) of **3a** in 20 ml of glacial acetic acid was treated with 4.8 g (15 mmol) of mercury(II) acetate in 20 ml of acetic acid and heated at 100° for 5 min [tlc, chloroform–ether (6:4), R_f **3a** > **5a**]. After cooling the mercury(I) acetate was filtered off, and the solution was neutralized with 40% of sodium hydroxide and extracted with benzene (5 × 150 ml). After removal of the solvent *in vacuo* under nitrogen the residue (1.7 g, 84.7%) was crystallized from methanol, mp 218–219°.

Anal. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.16; H, 5.94; N, 10.45.

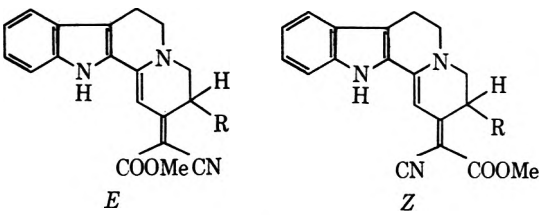
Ir (KBr) 3255 (NH), 2200 (C≡N conj), 1740, 1730 (CO_2CH_3), 1690, 1680 (CO_2CH_3 conj), 1582 cm^{-1} (C=C); nmr ($CDCl_3$) δ 10.27, 9.03 (s, 1, NH), 7.8–7.1 (m, 4, aromatic protons), 6.27 (s, 0.6, C_1H), 3.82 (s, 3, CO_2CH_3 conj), 3.71 (s, 3, CO_2CH_3); nmr ($C_6D_5NO_2$, at 36°) δ 10.40, 10.05 (s, 0.43, 0.57, NH), 7.5–7.0 (m, 4, aromatic protons), 6.43 [s, 0.43, C_1 H (*E*)], 3.84 [s, 0.57, CO_2CH_3 conj (*Z*)], 3.71 [s, broad, 5.43 (0.43, CO_2CH_3 conj (*E*), 3, CO_2CH_3, 2, C_6 H)] (see Chart II); uv (MeOH) λ_{max} 222 nm (log ε 4.54), 254 (4.06), 346 (4.04), 455 (4.66) 481 (4.76).

3β-(2-Methoxycarbonylethyl)-3,4,7,12-tetrahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2-ylidenemalononitrile (5b).—Oxidation of 0.75 g (2.0 mmol) of **3b** with 1.95 g (6.12 mmol) of mercury(II) acetate in 40 ml of glacial acetic acid for 5 min at 100° gave on work-up 0.59 g (78.6%) of yellow crystals. Recrystallization from acetone afforded an analytical sample, mp 205–207°.

Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.42; N, 15.04. Found: C, 70.72; H, 5.56; N, 15.11.

Ir (KBr) 3320 (NH), 2205, 2195 (C≡N conj), 1730 s, 1708 (CO_2CH_3), 1580 cm^{-1} (C=C); nmr (DMSO-d_6) δ 11.9 (s, 1, NH), 7.6–7.1 (m, 4, aromatic protons), 6.15 (s, 1, C_1 H), 3.55 (s, 3, CO_2CH_3); nmr ($C_6D_5NO_2$) δ 10.07 (s, 1, NH), 7.5–7.0 (m, 4, aromatic protons), 6.32 (s, 1, C_1 H), 3.73 (s, 3, CO_2CH_3); uv (MeOH) λ_{max} 221 nm (log ε 4.27), 246 (3.88), 348 (3.98), 448 (4.57), 475 (4.64).

CHART II



R = $CH_2CH_2CO_2CH_3$

Temp, °C	$\Delta\nu_{CO_2CH_3}$ between *E* and *Z* in Hz	Temp, °C	$\Delta\nu_{CO_2CH_3}$ between *E* and *Z* in Hz
36[a]	10.6	119	4.8
63	8.6	138	4.0
82	7.9	155	2.7
100	7.1	T_c = 183	

[a] Determined with a Varian A-60 instrument operated at 60 MHz in $C_6D_5NO_2$.

Methyl 3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2β-ylcyanoacetate (6a).—To a stirred suspension of 10 g (24.5 mmol) of **3a** in 120 ml of methanol was added 3.7 g (98 mmol) of sodium borohydride gradually during 10 hr at 0°. The reduction was followed by tlc [chloroform–diethyl ether (6:4), R_f **3a** > **6a**]. The mixture was acidified to pH 6 with acetic acid, and the precipitate was collected and dried giving 9.21 g (92%) of **6a**. An analytical sample was recrystallized from methanol, mp 171–173°.

Anal. Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.22; H, 6.61; N, 10.04.

Ir (KBr) 3410 (NH), 2800, 2760 (Bohlmann bands), 2250 (C≡N), 1740, 1730 cm^{-1} (CO_2CH_3); nmr ($CDCl_3$) δ 8.15, 7.94 (s, 1, NH), 7.45–6.96 (m, 4, aromatic protons), 3.92, 3.87 (s, 3, CO_2CH_3), 3.68 (s, 3, CO_2CH_3); nmr (DMSO-d_6) δ 10.99, 10.88 (s, 1, NH), 7.15–6.96 (m, 4, aromatic protons), 4.19 (d, 1, *J* = 1.2 Hz, μ-H of methyl cyanoacetate part), 3.92, 3.87 (s, 3, CO_2CH_3), 3.66 (s, 3, CO_2CH_3).

3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,-6*H*-indolo[2,3-*a*]quinolizin-2β-ylmalononitrile (6b).—To a stirred suspension of 6.04 g (16 mmol) of **3b** in 120 ml of methanol was added 2 g (53 mmol) of sodium borohydride gradually at 0° over a 3-hr period [chloroform–diethyl ether (3:2), R_f **3b** > **6b**]. The mixture was acidified to pH 5 with acetic acid, and the precipitate was collected and dried, giving 5.71 g (94%) of **6b**. An analytical sample was crystallized from dioxane–ether, mp 180–182°.

Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.18; H, 6.52; N, 14.48.

Ir (KBr) 3390 (NH), 2820, 2760 (Bohlmann bands), 2255 (C≡N), 1740 cm^{-1} (CO_2CH_3); nmr (DMSO-d_6) δ 10.5 (s, 1, NH), 7.5–6.9 (m, 4, aromatic protons), 3.58 (s, 3, CO_2CH_3).

Methyl Cyano-3β-(2-methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2β-ylacetimidate (6c).—The dinitrile **6b** (2 g, 5.35 mmol) was dissolved in dry methanol (30 ml), and after the addition of 0.10 g (1.85 mmol) of sodium methoxide the solution was refluxed under nitrogen for 1 hr [tlc, benzene–methanol (8:2), R_f **6b** > **6c**]. The resulting crystals were filtered off and washed with methanol (2 × 1 ml), giving 2 g (91.4%) of analytically pure **6c**, mp 214–217°. The material is almost insoluble in common solvents (dioxane, pyridine, DMSO) and it should be stored under vacuum or in a sealed tube.

Anal. Calcd for $C_{23}H_{28}N_4O_3$: C, 67.62; H, 6.91; N, 13.71. Found: C, 67.59; H, 7.02; N, 13.56.

Ir (KBr) 3355 (indole NH), 3295 (NH), 2835, 2810, 2770 (Bohlmann bands), 2250 (C≡N), 1720 (CO_2CH_3), 1670 cm^{-1} (C=N); ir (DMSO) 2190 (C≡N), 1740 (CO_2CH_3), 1675 (C=N), 1660–1630 (NH def), 1600 cm^{-1} (C=C); uv (MeOH) 253 nm (ε 6630), 226 (7200); nmr, see Table III; mass spectrum (70 eV) *m/e* (rel intensity) 408 (18, M^+), 407 (5), 393 (50), 375 (15), 311 (100), 309 (50), 223 (30), 221 (29), 184 (19), 169 (65), 156 (40).

6d was obtained under the same conditions described above, mp 203–205°.

Ir (KBr) 3500–3100 (NH), 2780, 2820 (Bohlmann bands), 2250 (C≡N), 1735 (CO_2CH_3), 1660 cm^{-1} (C=N); ir (DMSO) 2190 (C≡N), 1735 (CO_2CH_3), 1665–1580 cm^{-1} (C=C and C=NH); nmr, see Table IV.

TABLE III

Solvent	Nmr, δ: Indole NH	NH_2[b]	OCH_3	C=NH[b]	Aromatic protons
	10.73 (0.36)[a]	6.65 (0.36)	3.90, 3.95	8.8 (0.72)	7.55–6.95 (4)
DMF-d_7	10.89 (0.28)	6.48 (0.28)	3.80, 3.85		
	11.06 (0.36)		3.63, 3.65		
	11.01	6.63	3.84, 3.87	8.85 (0.30)	7.55–6.97 (4)
DMSO-d_6	11.16	6.54	3.78		
	11.21		3.65		

[a] The sign intensities in parentheses are given in proton units. [b] Assignments for NH_2 and C=NH groups differ from those given in the preliminary communication (ref 6).

TABLE IV

Solvent	Nmr, δ: Indole NH	NH_2[b]	CO_2CH_3	OCH_2CH_3	C=NH[b]	Aromatic protons
DMSO-d_6	10.60	6.41	3.48	3.99 (q, J = 6 Hz)	8.6 (0.30)[a]	7.55–6.95 (m, 4)
	10.65	6.30		4.05 (q, J = 6 Hz)		
	10.80					

[a] The sign intensity in parentheses is given in proton units. [b] Assignments for NH_2 and C=NH groups differ from those given in the preliminary communication (ref 6).

Preparation of 6e from 6c. A.—The solution of 5.3 g (1.3 mmol) of 6c in 20 ml of dry methanol saturated with hydrogen chloride was refluxed for 1 hr, cooled, filtered, and washed to give 4.85 g (87%) of 6e HCl, mp 217°.

B.—When a sample of 6c was allowed to stand under the influence of moisture it was transformed to 6e over a period of some days. The trace of 6c was removed by crystallization from methanol to give 6e, mp 214–215°.

Anal. Calcd for $C_{22}H_{26}N_4O_3$: C, 66.97; H, 6.64; N, 14.20. Found: C, 66.29; H, 6.73; N, 14.42.

Ir (KBr) 3410 (indole NH), 3240–3210 (NH), 2830, 2760 (Bohlmann bands), 2260 (C≡N), 1735 (CO_2CH_3), 1695, 1620 cm^{-1} ($CONH_2$); nmr (DMSO-d_6) δ 11.5 (s, 1, NH), 8.25 (s, 2, NH_2), 7.8–7.1 (m, 4, aromatic protons), 3.67 (s, 3, CO_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 394 (85.8, M^+), 393 (65.3), 379 (1.7), 377 (2), 363 (10), 350 (7.2), 319 (12), 318 (13.7), 311 (100), 309 (27.1), 283 (13.1), 184 (44.6), 170 (41), 169 (48), 156 (38).

Preparation of 6a from 6c.—The mixture of 1 g (2.45 mmol) of 6c in 20 ml of dry dioxane containing 0.5 ml of 10% hydrochloric acid was allowed to stand at room temperature for 30 min [tlc, benzene–methanol (8.5:1.5), R_f 6a > 6c]. The resulting crystals (6a HCl) were filtered off and dissolved in methanol and the 6a free base was obtained by the help of an ethereal solution of diazomethane. Most of the solvent was removed *in vacuo* and the residue was crystallized from methanol, affording 0.45 g (45%) of 6a, mp 171–173°, identical in all respects (ir nmr, tlc spot) with the authentic sample obtained from **32**.

Dimethyl 3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2β-ylmalonate (6f).—To prepare 6f triester it is possible to use as starting material 6a, 6b, 6c, or 6e, respectively. Each of the products was dissolved in dry methanol saturated with hydrogen chloride (50 parts to 1 part of the starting material), refluxed for 1 hr, and then cooled to −5°, hydrogen chloride was introduced, and the reflux was continued. This procedure was repeated while no starting material was detectable on tlc [carbon tetrachloride–methanol (9.0:0.4), R_f 6f > 6a > 6b > 6c > 6e]. Most of the solvent was removed *in vacuo* and the residue was crystallized several times from methanol affording 6f·HCl, mp 205–207°, in an average 50–60% yield.

Anal. Calcd for $C_{24}H_{31}ClN_2O_6$: C, 60.18; H, 6.48; N, 5.85. Found: C, 59.21; H, 6.68; N, 5.97.

Ir (KBr) 3380 (NH), 1745, 1735, 1730 cm^{-1} (CO_2CH_3).

3β-(2-Carboxyethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo-[2,3-*a*]quinolizin-2β-ylcyanoacetic Acid (6g). A.—The solution of 3.3 g (8.08 mmol) of 6a in 40 ml of 15% aqueous sodium hydroxide was allowed to stand at room temperature for 1 hr and then acidified with concentrated hydrochloric acid to pH 4 [tlc, benzene–methanol (8.5:1.5), R_f 6a > 6g]. The precipitated 6g was filtered and washed with dilute hydrochloric acid to give 1.2 g (39%). The mother liquor was evaporated to dryness *in vacuo*, and the residue was treated with DMF (3 × 10 ml). After the solvent was evaporated *in vacuo* (0.6 mm) an additional 1.1 g (35.5%) of material was obtained. The yield was 2.3 g (74.5%). A sample was crystallized from methanol, melted at 214° dec, and was dried *in vacuo* with boiling toluene over phosphorus pentoxide. According its thermoderivatogram the material has a variable amount (*ca.* 1.5–3 mol) of crystal water. The latter cannot be removed without simultaneous decarboxylation, ir (KBr) 3600–2600 (OH, NH polymer association), 2240 (C≡N), 1710 (CO_2H), 1650, 1620 cm^{-1} (CO_2^-).

The material decomposes to 6i in the mass spectrometer and gives the same spectrogram as 6i.

B.—The solution of 0.5 g (1.33 mmol) of 6b in glacial acetic acid (1 ml) was treated with 25% sodium hydroxide solution (10 ml) and allowed to stand at room temperature for 2 hr. After neutralization with concentrated hydrochloric acid to pH 7 and filtering off the resulting crystals, 0.15 g (30%) of 6g was obtained, identical in all respects (ir, melting point, mass spectrum) with the authentic sample obtained from 6a. Methylation of the product with an ethereal solution of diazomethane afforded 6a.

2β-(Cyanocarbamoylmethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionic Acid (6h).—The solution of 0.5 g (1.33 mmol) of 6b in glacial acetic acid (1 ml) was treated with 8 ml of 40% sodium hydroxide. The solid at first precipitated was dissolved after the addition of the whole amount of base. The solution was immediately neutralized with concentrated hydrochloric acid to pH 7 and the crystals separated on cooling were collected to give 0.12 g (24%) of 6h. An analytical sample was crystallized from methanol, mp 225–227°. Treating 6h with an ethereal solution of diazomethane, 6e was obtained.

6h had ir (KBr) 3320 (NH), 2260 (C≡N), 1700–1610 cm^{-1} ($CONH_2$, CO_2H).

2β-Cyanomethyl-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionic Acid (6i).—The solution of 10 g (26.2 mmol) of 6g in 30 ml of dry DMF was heated at 150–160° under nitrogen. The decarboxylation was followed by tlc [isoamyl alcohol–methanol–20% ammonia (5:4:2), R_f 6i > 6g]. The crystals separated on cooling were filtered off and washed with ethanol to give 6.2 g (70%) of 6i. After concentration of the mother liquor to near dryness *in vacuo* under nitrogen, 1.8 g (20.4%) of material was obtained. Crystallization of DMF–methanol afforded white crystals, mp 290–292°.

Ir (KBr) 3600–3050 (OH, NH polymer association), 2265 (C≡N), 1700 (CO_2H), 1630–1550 cm^{-1} (CO_2^-); mass spectrum (70 eV) *m/e* (rel intensity) 337 (95, M^+), 336 (100), 319 (8), 318 (8.4), 297 (27), 269 (18), 211 (9.5), 184 (20), 170 (33), 169 (24), 156 (18).

Methyl 2β-Cyanomethyl-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionate (6j).—The solution of 1 g (2.97 mmol) of 6i in 20 ml of DMF was treated with an excess of an ethereal solution of diazomethane [tlc, benzene–methanol (8.5:1.5), R_f 6j > 6i]. After 1 hr the excess diazomethane was decomposed with acetic acid and the solvent was removed *in vacuo* to give 0.98 g (94%) of 6j. The analytical sample had mp 158–160° from methanol–ether.

Ir (KBr) 3400 (NH), 2810, 2760 (Bohlmann bands), 2250 (C≡N), 1735 cm^{-1} (CO_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 351 (99.4 M^+), 350 (100), 336 (2.6), 320 (11.4), 311 (25.7), 309 (18.2), 283 (16.8), 184 (17.8), 170 (27), 169 (16.4), 156 (12.0).

Methyl 2β-Methoxycarbonylmethyl-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionate (6k).—The solution of 13 g (38.6 mmol) of **6i** in 50 ml of saturated methanolic hydrogen chloride was refluxed for 30 min. After cooling the precipitated **6k** HCl was washed with cold methanol (5 ml), giving 12.1 g (74.5%) of crude material. The solvent was removed *in vacuo*, and the residue was taken up in ice water (20 ml), made basic with solid sodium hydrogen carbonate, and extracted with ether (5 × 30 ml). Evaporation of the solvent gave an additional 2.1 g (14.2%) of **6k**. An analytical specimen prepared from acetone exhibited mp 204°.

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.74; H, 7.34; N, 7.29. Found: C, 68.55; H, 7.31; N, 7.55.

Ir (KBr) 3385 (NH), 2805, 2770 (Bohlmann bands), 1735, 1710 cm^{-1} (CO_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 384 (100, M^+), 383 (95.7), 369 (5.9), 353 (15.3), 311 (12.2), 283 (20), 184 (20), 170 (24.5), 169 (15.2), 156 (11.6).

6k HCl had mp 261–262° from methanol.

Anal. Calcd for $C_{22}H_{29}ClN_2O_4$: C, 62.77; H, 6.94; N, 6.66; Cl, 8.42. Found: C, 62.66; H, 6.84; N, 6.71; Cl, 8.31.

Ir (KBr) 3460 (NH), 3000–2400 (NH^+), 1745 cm^{-1} (CO_2CH_3).

17-Oxoalloyohimban-16-carbonitrile (7a).—A solution of 3.5 g (10 mmol) of **6j** (previously dried *in vacuo* with boiling toluene over phosphorus pentoxide) and 6 g (53 mmol) of sublimed potassium *tert*-butoxide in 8 ml of dry DMSO was allowed to stand at room temperature for 12–16 hr in a carefully dried apparatus under nitrogen [tlc, benzene–methanol (8.5:1.5), R_f **6j** > **7a**]. The dark red solution was acidified with acetic acid to pH 7 and evaporated *in vacuo* (1–2 mm). The residue was treated with chloroform (5 × 50 ml), and the combined extracts were washed, dried, and evaporated to give 2.9 g (91%) of **7a**. Recrystallization from methanol–water gave an analytical sample, mp 228–231° dec.

Ir (KBr) 3450–3280 (OH, NH association), 2810, 2760 (Bohlmann bands), 2255 (C≡N), 2210 (C≡N conj), 1735 (C=O), 1665 cm^{-1} (C=C); ir (pyridine) 2810, 2760 (Bohlmann bands), 2210 (C≡N), 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 319 (91, M^+), 318 (100), 291 (3), 290 (3.9), 237 (8.8), 235 (4.5), 223 (8.8), 221 (9.1), 184 (24.3), 170 (24.5), 169 (27.2), 156 (24.2).

17β-Hydroxyalloyohimban-16β-carbonitrile (8a) and 17β-Hydroxyalloyohimban-16α-carbonitrile (8b).—To a stirred suspension of 0.75 g (2.35 mmol) of **7a** in 2 ml of ethanol was added gradually 0.14 g (3.5 mmol) of sodium borohydride over a 1-hr period. The reduction was followed by tlc [chloroform–methanol (10:1.4), R_f **7a** > **8a** > **8b**]. After stirring at room temperature for 2 hr the starting material was dissolved and the product began to separate, the pH was brought to 7 with acetic acid, and the precipitate was filtered off (0.5 g, a mixture of **8a** and **8b**). The mother liquor was evaporated *in vacuo* to dryness, and the residue was treated with water (1 ml) and filtered. An additional 0.2 g (26%) of **8a** and **8b** was obtained. The mixture of isomers was separated (a) by preparative layer chromatography [silica gel $PF_{254+366}$, chloroform–methanol (100:14), R_f **8a** > **8b**], (b) by column chromatography over silica. Elution with chloroform and with increasing amounts of methanol (1–4%) in chloroform as eluents gave 40 mg of a mixture of nitrile alcohols with unidentified stereostructure and 0.43 g (57%) of **8a**, which upon recrystallization from chloroform–methanol gave colorless crystals, mp 262–263°.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.88; H, 7.16; N, 13.21.

Ir (KBr) 3450–3220 (OH, NH association), 2820, 2770 (Bohlmann bands), 2250 (C≡N), 1000 cm^{-1} (COH); ir (pyridine or acetonitrile) 2815, 2765 cm^{-1} (Bohlmann bands); nmr (DMSO-d_6) δ 10.90 (s, 1, NH), 7.60–6.90 (m, 4, aromatic protons), 5.05 (d, 1, J = 4.0 Hz, C_{17} OH), 3.95 (m, 1, C_{17} H); mass spectrum 70 eV) *m/e* (rel intensity) 321 (73.3, M^+), 320 (100), 304 (2.1), 292 (3.7), 223 (5.4), 184 (10.2), 170 (13), 169 (17.2), 156 (9.3).

Also, 0.11 g (14.5%) of **8b** was obtained. An analytical sample of the latter was crystallized from chloroform–methanol, mp 226–227°.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.65; H, 7.31; N, 13.01.

Ir (KBr) 3550–3200 (OH, NH association), 2820, 2765 (Bohlmann bands), 2245 (C≡N), 1015 cm^{-1} (COH); ir (pyridine) 2810, 2770 cm^{-1} (Bohlmann bands, w); nmr (DMSO-d_6) δ 10.91 (s, 1, NH), 7.60–6.80 (m, 4, aromatic protons), 5.15 (d, broad, 1, C_{17} OH), 3.93 (m, 1, C_{17} H); mass spectrum (70 eV) *m/e* (rel intensity) 321 (87.8, M^+), 320 (100), 304 (3.3), 292 (4.4), 223 (6.3), 184 (12.2), 170 (21), 169 (19.2), 156 (13.8).

Isomerization of 8a to 8b. Alloyohimb-16-ene-16-carbonitrile (10a).—The suspension of 0.80 g (2.4 mmol) of **8a** in 2 *N* methanolic sodium methoxide solution (40 ml) was stirred at room temperature for 48 hr under nitrogen. The isomerization was followed by tlc [chloroform–methanol (10:1.6), R_f **10a** > **8a** > **8b**]. The unchanged starting material (70 mg) was filtered off, and the filtrate was diluted with the mixture of chloroform (100 ml), water (10 ml), and acetic acid (2.5 ml). The aqueous layer was extracted with chloroform (5 × 50 ml), and the combined extracts were washed with water (3 × 10 ml), dried, and evaporated. The resultant mixture of **8a**, **8b**, and **10a** was separated by chromatography as previously described; 70 mg (8.7%) of **10a**, 100 mg (12.5%) of **8a**, and 280 mg (33.7%) of **8b** were obtained.

The analytical sample of **10a** was crystallized from ethanol, mp 234–235°.

Ir (KBr) 3340 (NH), 2800, 2760 (Bohlmann bands), 2220 (C≡N conj), 1630 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 303(100, M^+), 288 (2.1), 275 (2.8), 274 (2.7), 211 (5.0), 210 (3.1), 209 (5.0), 198 (3.8), 197 (4.9), 184 (10), 170 (8.2), 169 (13), 156 (21.4).

17β-Hydroxyalloyohimban-16β-carbonitrile *O*-Acetate (8c).—A mixture of 0.15 g (0.46 mmol) of **8a**, 2 ml of anhydrous pyridine, and 0.9 ml (8.7 mmol) of acetic anhydride was allowed to stand at room temperature for 3 days under nitrogen. The dark solution was diluted with ice water (2 ml) and extracted with chloroform (5 × 10 ml). The combined extracts were washed with water (3 × 5 ml) and dried. After the solvents were evaporated, the product was separated by preparative tlc [silica gel $PF_{254+366}$, methylene chloride–methanol (100:14), R_f **8c** > **8a**]. The yield of **8c** was 70 mg (43.5%); crystallized from ethanol it had mp 213–214° [75 mg (50%) of **8a** was recovered].

Ir (KBr) 3360 (NH), 2180, 2765 (Bohlmann bands, s), 2245 (C≡N), 1745, 1230 cm^{-1} ($OCOCH_3$); ir (pyridine) 2810, 2760 (Bohlmann bands, s); nmr (DMSO-d_6) δ 10.90 (s, 1, NH), 7.40–6.70 (m, 4, aromatic protons), 5.10 (m, 1, C_{17} H), 1.87 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M^+), 362 (108), 320 (5.7), 304 (30), 303 (42), 302 (50), 277 (9.9), 184 (13), 170 (22), 169 (28), 156 (28),

17β-Hydroxyalloyohimban-16α-carbonitrile *O*-Acetate (8d).—A mixture of 0.10 g (0.31 mmol) of **8b**, 3.0 ml of anhydrous pyridine, and 0.1 ml (1.0 mmol) of acetic anhydride was allowed to stand at room temperature for 3 days under nitrogen. The product was purified as described earlier for **8c**, giving 72 mg (64%) of **8d** and 32 mg (32%) of unchanged **8b**. Recrystallization from ethanol gave **8d** as white crystals, mp 166–168°.

Ir (KBr) 3400 (NH), 2810, 2770 (Bohlmann bands, w), 2245 (C≡N), 1725, 1250 cm^{-1} ($OCOCH_3$); ir (pyridine) 2805, 2760 cm^{-1} (Bohlmann bands, w); nmr (DMSO-d_6) δ 10.80 (s, 1, NH), 7.50–6.90 (m, 4, aromatic protons), 4.95 (m, 1, C_{17} H), 2.00 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M^+), 362 (83), 320 (4.7), 304 (32), 303 (24), 302 (33), 184 (9.7), 170 (15.3), 169 (17), 156 (15).

17β-Hydroxyalloyohimban-17β-carboxamide (8f).—To a stirred suspension of 0.12 g (0.37 mmol) of **8a** in a mixture of 1 *N* sodium hydroxide (2 ml) and methanol (4 ml), 30% hydrogen peroxide was added dropwise keeping its concentration as low as possible to avoid the formation of *N*-oxide. The stirring was continued for 50–60 hr and the reaction was followed by tlc [chloroform–methanol (10:1.4), R_f **8a** > **8f**]. Sodium borohydride was added to the solution to decompose the excess hydrogen peroxide, and the white precipitate was collected, washed with water, and dried, giving 94 mg (74%) of white solid. An additional 16 mg (12.6%) of **8f** was obtained from the evaporated mother liquor by preparative tlc (Al_2O_3 $PF_{254+366}$, chloroform–methanol (100:10). Recrystallization from 70% ethanol gave an analytical sample, mp 195° dec.

Ir (KBr) 3350–3150 (OH, NH), 2800, 2760 (Bohlmann bands, s), 1650, 1600 ($CONH_2$), 1010 cm^{-1} (COH); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M^+), 338 (70), 337 (15), 321 (79), 320 (53), 295 (14), 277 (15), 223 (16), 221 (13), 209 (20), 197 (16), 195 (12), 184 (53), 170 (24), 169 (34), 156 (34).

17β-Hydroxyalloyohimban-16α-carboxamide (8g).—To the stirred suspension of 0.12 g (0.37 mmol) of **8b** in a mixture of 1 *N* sodium hydroxide (1 ml) and methanol (2 ml), 30% hydrogen peroxide was added drop by drop to maintain the concentration of the reagent as low as possible (checking with potassium iodine–starch paper). The reaction was followed by tlc [Al_2O_3 G, chloro-

form–methanol (10:0.5), R_f **8b** > **8g**]. After 15–20 hr of stirring the excess hydrogen peroxide was decomposed with sodium borohydride and the solvent was removed *in vacuo*. The residue was taken up in methanol and purified by preparative tlc [Al_2O_3 $PF_{254+366}$, chloroform–methanol (100:14)] to yield 0.10 g (79%) of **8g**. An analytical sample was crystallized from 70% ethanol, mp 195° dec.

Ir (KBr) 3550–3200 (OH, NH), 2820, 2760 (Bohlmann bands, w), 1670, 1630 ($CONH_2$), 1015 cm^{-1} (COH); ir (pyridine) 2800, 2750 cm^{-1} (Bolhmann bands, w); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M^+), 338 (70), 337 (10), 321 (36), 320 (28), 295 (10.5), 277 (7.6), 223 (10.6), 221 (10.6), 209 (10), 197 (9.3), 184 (25), 170 (20), 169 (22), 156 (24).

Oxidation–Reduction on 9a and 9b. A.—Mercury(II) acetate (67 mg, 0.21 mmol) was added in small portions over a period of 10 min to a solution of **9a**[1] (11.7 mg, 0.036 mmol) in glacial acetic acid (3 ml). The mixture was kept at 60° for 8 hr under nitrogen and then filtered. The filtrate was heated to boiling, hydrogen sulfide gas was introduced, the insoluble sulfides were filtered off, and the solvent was evaporated *in vacuo*. The residue was taken up in methanol (1 ml), reduced with an excess of sodium borohydride, and subjected to preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (50:8), R_f **9a** > **8b**]. The identity of the material obtained (3 mg) as **8b** was established by ir, mass spectrum, and tlc [Al_2O_3 G, chloroform–methanol (5.0:0.15), R_f **8a** > **8b** > **9a** > **9b**].

B.—The oxidation was carried out of 30 mg (0.091 mmol) of **9b** and 170 mg (0.53 mmol) of mercury(II) acetate by the method described above to **9a**. The material obtained was reduced with sodium borohydride. After separation of the mixture by preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (50:8), R_f **8e** > **9b**] 4 mg of **8e** was obtained, mp 268–270° dec.

Ir (KBr) 3410–3370 (OH, NH), 2820, 2760 (Bohlmann bands), 2235 cm^{-1} (C≡N); ir (pyridine) 2805, 2760 (Bohlmann bands), 2245 cm^{-1} (C≡N); mass spectrum (70 eV) *m/e* (rel intensity) 321 (90, M^+), 320 (100), 306 (1.6), 293 (2.2), 292 (3.0), 184 (5), 170 (22), 169 (14), 156 (8).

Alloyohimb-16-ene-16-carboxamide (10b).—The solution of 50 mg (0.44 mmol) of **8f** (or **8g**) in 10 ml of 0.5 *N* sodium hydroxide containing 20 ml of dioxane was refluxed for 12 hr [tlc, Al_2O_3 G, chloroform–methanol (10:0.5), R_f **10b** > **8f** > **8g**]. After cooling the solution was neutralized with concentrated hydrochloric acid and evaporated to dryness. The residue was crystallized from ethanol–water to give 30 mg (63.5%) of **10b**: mp 166–168°; mass spectrum (70 eV) *m/e* (rel intensity) 321 (100, M^+), 320 (65), 277 (9.4), 197 (9.4), 184 (34), 170 (8), 169 (18), 156 (30).

Methyl 17β-Hydroxyalloyohimban-16β-carboxylate (8h).—A solution of 90 mg (0.26 mmol) of **8f** in 20 ml of methanol saturated with hydrogen chloride was refluxed for 12 hr under nitrogen [tlc, chloroform–methanol (10:1.4), R_f **8h** > acid]. The cooled solution was neutralized with sodium methoxide, filtered, and evaporated *in vacuo*, yielding an oil which was purified by preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (100:15), R_f **8h** > **8f**] to give 60 mg (64%) of **8h**. An analytical sample was obtained by crystallization from methanol, mp 195–197°.

Ir (KBr) 3450–3260 (OH, NH), 2805, 2760 (Bohlmann bands, s), 1735 (CO_2CH_3), 1020 cm^{-1} (COH); ir ($CHCl_3$) 3550–3460 (OH, NH), 3480 (NH), 2810, 2760 (Bohlmann bands, s), 1020 cm^{-1} (COH); nmr ($CDCl_3$, 300 MHz) δ 7.76 (s, 1, NH), 7.42 (d, 1, C_9 H),[11] 7.27 (d, 1, C_{12} H), 7.12–7.01 (m, 2, C_{10} and C_{11} H), 4.26 (s, 1, C_{17} H), 3.82 (s, 3, CO_2CH_3), 3.05 (m, 1, C_3 H);[12] mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (98), 352 (7), 339 (5.8), 337 (2), 336 (1.3), 335 (2.2), 323 (4.5), 295 (2.8), 279 (1.3), 225 (3.5), 224 (7.5), 223 (5.5), 221 (3.5), 184 (8.5), 170 (9), 169 (12), 156 (7.5).

Methyl 17β-Hydroxyalloyohimban-16α-carboxylate (8i).—The reaction was carried out by the method described for **8h** starting from 60 mg (0.17 mmol) of **8g** in 40 ml of methanol saturated with hydrogen chloride, over a period of 30 hr reflux. Similar work-up gave 38 mg (61%) of **8i**. An analytical specimen was prepared from methanol, mp 223–224°.

Ir ($CDCl_3$) 3480–3350 (OH, NH), 3480 (NH), 2760, 2801 (Bohlmann bands, very weak), 1725 (CO_2CH_3), 1025 cm^{-1} (COH); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (98), 339 (5.5), 337 (4.1), 336 (5.3), 335 (5.9), 321 (9.5), 320 (8.6), 305 (1.9), 295 (2), 293 (1.4); nmr (DMSO-d_6) 10.65 (s, 1, NH), 7.4–6.8 (m, 4, aromatic protons), 4.61 (s, 1, OH), 3.97 (m, 1, C_{17} H), 3.60 (s, 3, CO_2CH_3).

Methyl 17-Oxoalloyohimban-16-carboxylate (7d) [(±)-Alloyohimbinone], Methyl 17-Oxoalloyohimban-18-carboxylate (7b), and (±)-Alloyohimbone (7c).—A solution of 1.6 g (4.16 mmol) of **6k** (previously dried *in vacuo* with boiling benzene over phosphorus pentoxide) and 3.0 g (26.8 mmol) of sublimed potassium *tert*-butoxide in 15 ml of dry DMSO was allowed to stand at room temperature in a carefully dried apparatus under nitrogen. After completion of the reaction [about 1 week, tlc chloroform–methanol (10:1.5), R_f **6k** > **7b** > **7d** > **7c**] the pH was brought to 7 with acetic acid and the solvent was removed *in vacuo* (0.5–1 mm) under nitrogen. The residue was triturated with chloroform (5 × 60 ml) and filtered, and the combined extracts were washed with water (2 × 10 ml), dried, and evaporated, giving an amorphous powder which was subjected to preparative tlc [silica gel $PF_{254+366}$, hexane–ethyl methyl ketone–acetone (60:30:10), R_f **7b** > **7d** > **7c**]. When the mixture was separated 0.52 g (36%) of **7b**, 0.18 g (15%) of **7c**, and 0.45 g (30%) of **7d** were obtained.

7b, mp from methanol 276–278°, had ir (KBr) 3400 (NH), 2820, 2775 (Bohlmann bands), 1740 (CO_2CH_3), 1720 cm^{-1} (C=O); ir ($CHCl_3$) 3400 (NH), 2820, 2770 (Bohlmann bands), 1740 (CO_2CH_3, s), 1720 (C=O, s), 1670, 1630 cm^{-1} (enolic β-keto ester, m); ir (pyridine) 1750 (CO_2CH_3, w), 1720 (C=O, w), 1680–1620 cm^{-1} (enolic β-keto ester, s); mass spectrum (70 eV) *m/e* (rel intensity) 352 (100, M^+), 351 (46.8), 335 (6.8), 321 (12.6), 320 (30), 319 (42.8), 293 (37.4), 291 (14.3), 235 (7.4), 223 (10.1), 221 (15), 184 (15.6), 170 (18.9), 169 (22.4), 156 (17.6).

7c, mp from methanol 265–267°, had ir (KBr) 2820, 2760 (Bohlmann bands), 1705 (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 294 (91, M^+), 293 (100), 279 (1.3), 277 (1.5), 265 (2.2), 235 (6.1), 223 (7.1), 211 (6.1), 184 (6.1), 170 (13.8), 169 (18.3), 156 (11.2).

7d, mp 192–193°, had ir ($CDCl_3$) 3480 (NH), 2810, 2770, 2760 (Bohlmann bands), 1750 (CO_2CH_3, shoulder), 1720 (C=O, m), 1660, 1620 cm^{-1} (enolic β-keto ester, m); mass spectrum (70 eV) *m/e* (rel intensity) 352 (100, M^+), 351 (36), 337 (5), 335 (3.4), 321 (18), 320 (66), 319 (70), 293 (34), 291 (5.8), 235 (5.4), 223 (8), 221 (10), 184 (15), 170 (14.5), 169 (23), 156 (30).

Preparation of 7c from 7b.—The solution of 0.15 g (0.42 mmol) of **7b** in 20 ml of hydrochloric acid containing 5 ml of dioxane was refluxed for 3 hr, cooled, and rendered alkaline with 40% sodium hydroxide. The resulting solid was filtered off to give 88 mg (72%) of **7c**, mp 265–267°.[8]

Methyl 17β-Hydroxyalloyohimban-18β-carboxylate (8j), Methyl 17α-Hydroxyalloyohimban-18β-carboxylate (8k), and 17β-Hydroxy-18β-hydroxymethylalloyohimban (8l).—The stirred solution of 0.4 g (1.14 mmol) of **7b** in 15 ml of methanol–DMF (2:1) was treated with sodium borohydride (0.3 g, 6.9 mmol) in small portions at 0°. After a total reaction time of 6 hr [tlc, chloroform–methanol (10:1.5), R_f **7b** > **8j** > **8k** > **8l**] the solution was neutralized with acetic acid and the solvent was removed *in vacuo*. The residue was triturated with chloroform (5 × 50 ml), filtered, washed with water (2 × 10 ml), dried, and concentrated to give a solid (0.3 g, 74%) which was submitted to preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (100:15)]; 168 mg (42%) of **8j**, 8 mg (2%) of **8k**, and 18 mg (5%) of **8l** were obtained.

8j had mp 143–145°; mass spectrum (70 eV) (rel intensity) 354 (100, M^+), 353 (90), 339 (4.3), 335 (1.2), 323 (5.8), 295 (2.1), 293 (1.0), 223 (3.3), 221 (4.1), 184 (6.4), 170 (8.1), 169 (12), 156 (7.8), 144 (6.5); ir (KBr) 3550–3150 (OH, NH), 2810, 2760 (Bohlmann bands), 1735 (CO_2CH_3), 1045 cm^{-1} (COH).

8k had mp 164–167°; mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 339 (5.3), 325 (3.1), 323 (6), 184 (15), 170 (28), 169 (37), 156 (20).

8l had mp 192–194°; ir (KBr) 3520–3170 (OH, NH), 1040 cm^{-1} (COH); nmr (DMSO-d_6) δ 10.65 (s, 1, NH), 7.40–6.80 (m, 4, aromatic protons), 4.11 (d, 2, CH_2OH), 3.86 (m, 1, C_{17} OH); mass spectrum (70 eV) *m/e* (rel intensity) 326 (91, M^+), 325 (100), 311 (1.3), 309 (2.6), 307 (3.7), 295 (3.2), 253 (3.3), 223 (3), 221 (6.7), 211 (5.7), 197 (6.3), 184 (11), 169 (36), 156 (15).

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(12) L. Bartlett, N. J. Dastoor, J. Hrbek, W. Klyne, and G. Snatzke, *Helv. Chim. Acta*, **54**, 1238 (1971).

Methyl 17β-Hydroxyalloyohimban-16β-carboxylate (8h), (±)-Alloyohimbine (8m) and (±)-α-Yohimbine (8n) from 7d.—A solution of 0.12 g (0.34 mmol) of **7d** in 10 ml of methanol was reduced with 0.2 g (5.3 mmol) of sodium borohydride over a 5-hr period at 0° [tlc, chloroform–methanol (10:1.5), R_f **7d** > **8n** > **8m** > **8h**]. After neutralization with acetic acid, most of the solvent was removed *in vacuo* and the product was extracted with chloroform (5 × 50 ml). The extracts were combined, washed with water (2 × 10 ml), dried, and evaporated and the resulting mixture of isomers (96 mg, 90%) was separated by (1) preparative tlc [Al_2O_3 G (type E), hexane–ethyl methyl ketone (60:40), R_f **8h** > **8n** ~ **8m**, and then silica gel $PF_{254+366}$, chloroform–methanol (100:15), R_f **8n** > **8m**]; (2) column chromatography over alumina (Brockmann, activity II–III), elution with hexane–ethyl methyl ketone (90:10) and with increasing amount of ethyl methyl ketone (12–20%) as eluents. In another reduction run exactly as above, starting from 0.16 g of **7c**, 32 mg (20%) of **8h**, 10 mg (6%) of **8n**, and 14 mg (9%) of **8m** were obtained.

8h was identical in all respects (ir, mass spectrum, tlc spot) with an authentic sample obtained from **8f**.

8m had mp 136–137° (from ethyl acetate following ether); by mixture melting point, ir, nmr, and tlc spot, **8m** was identical with an authentic sample of (±)-alloyohimbine obtained from **9b**.[1]

8n had ir ($CHCl_3$) identical with that of natural α-yohimbine, 3570 (OH), 3480 (NH), 2805, 2765 (Bohlmann bands), 1730 (CO_2CH_3), 1055 cm^{-1} (COH); nmr ($CDCl_3$ at 300 M-z) δ 7.75 (s, 1, NH), 7.44 (d, 1, C_9 H),[11] 7.28 (d, 1, C_{12} H), 7.15–7.02 (m, 2, C_{10}, C_{11} H), 3.99 (d of t, 1, C_{17} H, J = 26 Hz), 3.84 (s, 3, CO_2CH_3), 3.15 (m, 1, C_3 H);[12] mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (88), 339 (4.8), 337 (1.6), 335 (1.8), 323 (4.8), 321 (2.9), 320 (2), 295 (5.1), 293 (3.1), 226 (8), 224 (13), 223 (5.6), 221 (5.8), 184 (9.7), 170 (11), 169 (12), 156 (8).

Epimerization of Alloyohimine Isomers. Preparation of 8i (and 10c) from 8h.—**8h** (28 mg, 7.9 × 10^{-1} mmol) in 1 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen for 3–4 days. Separation of the mixture by preparative tlc [Al_2O_3 G (type E), hexane–ethyl methyl ketone (60:40), R_f **10c** > **8h** > **8i**] gave 5.5 mg (20%) of **10c**, 5.0 mg (18%) of **8h**, and 11.8 mg (42%) of **8i**.

10c had mp 195–197°, ir (KBr) 3350 (NH), 1700 (CO_2CH_3 conj), 1640 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 336 (100, M^+), 335 (99), 321 (23), 206 (15), 197 (11), 191 (12), 184 (17), 169 (14), 165 (26).[12]

8i was identical in all respects with an authentic sample obtained from **8g**.

Preparation of (±)-α-Yohimbine (8n) from (±)-Alloyohimbine (8m).—**8m** (30 mg, 8.1 × 10^{-2} mmol) in 1 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen. The progress of the epimerization was followed by tlc [chloroform–methanol (10:1.5), R_f **8n** > **8m**]. After 3–4 days the solution was neutralized with acetic acid, evaporated to dryness, and triturated with chloroform (3 × 2 ml). After the solvent was evaporated, 17.3 mg (58%) of **8n** was obtained, identical with the sample obtained from **7d**.

Thin Layer Chromatographic Behavior of Hydroxy Esters with Alloyohimbane Skeleton.—Al_2O_3 G (Type E), hexane–ethyl methyl ketone (6:4), showed R_f **8h** > **8j** > **8n** > **8i** > **8m** > **8k**; silica gel G, hexane–ethyl methyl ketone–methanol (6:3:1) showed R_f **8n** > **8m** > **8h** > **8i** > **8j** > **8k**.

Registry No.—**1**, 40087-90-9; **2**, 2107-58-6; 2 free base, 2107-57-5; **3a**, 40087-94-3; **3b**, 40087-91-0; **3b** oxalate, 40087-92-1; **4**, 40087-93-2; (*Z*)-**5a**, 40087-95-4; (*E*)-**5a**, 40087-96-5; **5b**, 40087-97-6; **6a**, 39032-75-2; **6b**, 39032-72-9; **6c**, 39032-73-0; **6d**, 39032-74-1; **6e**, 39032-76-3; **6e** HCl, 40037-02-3; **6f** HCl, 40037-03-4; **6g**, 40088-02-6; **6h**, 40088-03-7; **6i**, 40088-04-8; **6j**, 40085-19-6; **6k**, 40088-06-0; **6k** HCl, 40088-07-1; **7a**, 40088-08-2; **7b**, 40088-09-3; **7c**, 40088-10-6; **7d**, 40088-11-7; **8a**, 40088-12-8; **8b**, 40088-13-9; **8c**, 40088-14-0; **8d**, 40088-15-1; **8e**, 40088-16-2; **8f**, 40088-17-3; **8g**, 40088-18-4; **8h**, 40088-19-5; **8i**, 40088-20-8; **8j**, 40088-21-9; **8k**, 40088-22-0; **8l**, 40088-23-1; **8m**, 40085-32-3; **8n**, 40088-25-3; **9a**, 40085-22-1; **9b**, 40085-21-0; **10a**, 40088-28-6; **10b**, 40088-29-7; **10c**, 40088-30-0; diethyl α-acetylglutarate, 1501-06-0; diethylamine hydrochloride, 660-68-4; methyl iodide, 74-88-4; ammonium acetate, 631-61-8; acetic acid, 64-19-7; triethylamine, 121-44-8; phosphorus pentoxide, 1314-56-3; methyl cyanoacetate, 105-34-0; malononitrile, 109-77-3; sodium borohydride, 16940-66-2; sodium methoxide, 124-41-4; potassium *tert*-butoxide, 865-47-4.

Acknowledgments.—We thank the Hungarian Academy of Sciences for financial support of this work, and Drs. P. Kolonits and P. Biacs for the ir and nmr spectra.

Heterocyclic Amino Sugar Derivatives. VI. Stabilization of a Reactive Intermediate by Steric Hindrance. Mechanism of 3,6-Anhydro Sugar Formation[1]

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Received December 28, 1972

Circumstantial evidence was obtained that 3,6-anhydro-2-benzamido-2-deoxy-β-D-glucopyranosides are formed from 2-benzamido-2-deoxy-3-*O*-mesyl-β-D-glucopyranosides *via* the 3,4 epoxide, and *not via* an oxazoline intermediate. For the synthesis of benzyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside from benzyl 2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside the order of ring closures of the carbonyl and anhydro rings was determined. An intermediate with the 3,6-anhydro structure was isolated. This intermediate was then changed to the 2-*N*,4-*O*-carbonyl compound.

Two procedures are currently available for the synthesis of 3,6-anhydro derivatives of 2-amino-2-deoxy-β-D-glucopyranosides.

Foster, Stacey, and Vardheim[2] used methyl 2-benzyloxycarbonylamino-2-deoxy-6-*O*-tosyl-β-D-glucopyranoside (I) in reaction with base to form methyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside (II).[2] Under these conditions no inversion occurred at C_3. The tosyl group at C_6 was readily displaced and the 3,6-anhydro ring was unequivocally formed, the formation of other rings being sterically impossible. In the second procedure, Reckendorf and Bonner used methyl 2-benzamido-2-

(1) A preliminary communication was presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstract Carb 000. Taken from the doctoral thesis of C. A. Johnson, University of the Pacific, 1971. This work was partially supported by Grant No. GP 12222 of the National Science Foundation. Part V: F. R. Seymour and P. H. Gross, *J. Org. Chem.*, **36**, 1085 (1971).

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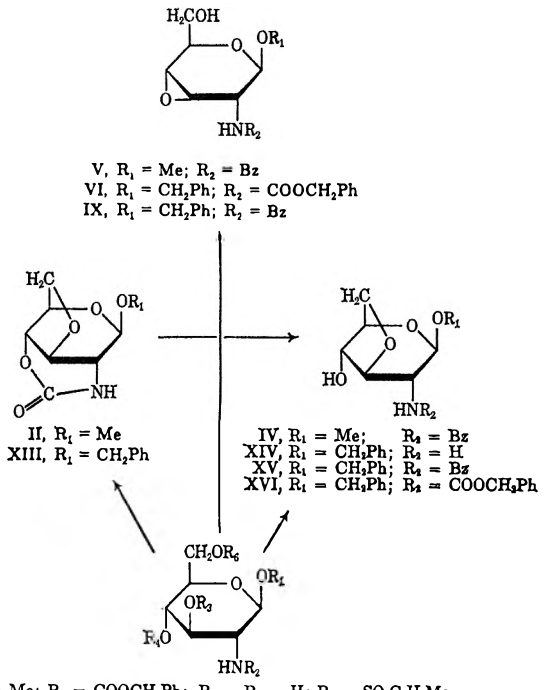

V, R_1 = Me; R_2 = Bz
VI, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$
IX, R_1 = CH_2Ph; R_2 = Bz

II, R_1 = Me
XIII, R_1 = CH_2Ph

IV, R_1 = Me; R_3 = Bz
XIV, R_1 = CH_2Ph; R_3 = H
XV, R_1 = CH_2Ph; R_3 = Bz
XVI, R_1 = CH_2Ph; R_3 = $COOCH_2Ph$

I, R_1 = Me; R_2 = $COOCH_2Ph$; R_3 = R_4 = H; R_6 = $SO_2C_6H_4Me$
III, R_1 = Me; R_2 = Bz; R_3 = SO_2Me; R_4 = R_6 = H
VII, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = SO_2Me; R_4 = R_6 = H
VIII, R_1 = CH_2Ph; R_2 = Bz; R_3 = SO_2Me; R_4 = R_6 = H
X, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = Ac; R_4 = R_6 = H
XI, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = Ac; R_4 = H; R_6 = $SO_2C_6H_4Me$
XII, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = Ac; R_4 = R_6 = $SO_2C_6H_4Me$
XVII, R_1 = CH_2Ph; R_2 = $COOCH_2Ph$; R_3 = R_4 = H; R_6 = $SO_2C_6H_4Me$

deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (III) as starting material for the preparation of a 3,6-anhydro derivative (IV).[3] In this case there are other possible products. The benzamido group at C_2 could attack at C_3 to form either an oxazoline or an epimine derivative of the allo configuration. The 3,6-anhydro derivative IV which Reckendorf and Bonner obtained in fact was assumed to result from a second inversion at C_3 by attack of the C_6 hydroxyl on an intermediate oxazoline.[3] Also, the OH group at C_4 could attack with inversion at C_3 to form a 3,4-anhydro derivative (V) of the allo configuration. The similar 3,4-anhydro sugar VI was formed[4] when benzyl 2-benzyloxycarbonylamino-2-deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (VII)[5] or its 4,6-di-*O*-acetyl derivative[5] were treated with base. At the time when these experiments were carried out, it was already considered possible that such 3,4-anhydro sugars may rearrange to 3,6-anhydro sugars.[6] Similarly, the 3,4-anhydro sugar V, instead of an oxazoline, could have been[7] the actual intermediate in the 3,6-anhydro sugar synthesis by Reckendorf and Bonner.[3]

Two explanations appear possible for the difference in results obtained by Reckendorf and Bonner with the methanesulfonate III and by this laboratory with the methanesulfonate VII. First, benzamido groups are known to give better anchimeric assistance as compared to benzyloxycarbonylamino groups, and this may explain 3,6-anhydro sugar formation *via* the oxazoline.[3]

Secondly, there exists recent evidence[8] that arrangements of large syn-diaxial groups are thermodynamically unfavorable structures. The bulky benzyl glycoside in VI may have prevented or slowed down the rearrangement of the 3,4-anhydro to the 3,6-anhydro sugar.

If the second explanation is true, it should be possible to ascertain the nature of the intermediate in the reaction of III to give IV with alkali, by replacing only the methyl glycoside by the bulkier benzyl glycoside (VIII). The formation of either the 3,4-anhydro sugar IX or an oxazoline intermediate should then still be possible in the C1 conformation.[9] However, the bulkier benzyl glycoside in VIII would make attainment of the 1C conformation in the transition state leading to XV less favorable, and whatever would be the "intermediate," 3,4-anhydro sugar or oxazoline, could be isolated as end product.

Following the procedures of Reckendorf and Bonner,[3] benzyl 2-benzamido-2-deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (VIII)[9] was treated with $NaOCH_3$ to give benzyl 3,4-anhydro-2-benzamido-2-deoxy-β-D-allopyranoside (IX). Compound IX decomposed in methanolic aqueous KOH at room temperature. The 3,6-anhydro derivative XV, prepared by the unequivocal procedure to be described below, was stable under these conditions. The ir spectra of IX and XV differed. The ir spectrum of IX had absorptions at 1638 and 1536 cm^{-1}, ascribed to an amide group. This indicated that IX was not an epimine or an oxazoline derivative.

It is thus found here that the formation of 3,6-anhydro sugars from a cis configuration of methanesulfonyl and hydroxymethyl groups follows a similar mechanistic pattern as the formation of 1,6-anhydro sugars from a cis configuration of negative leaving group at the glycosidic carbon and the hydroxymethyl group at C-5, where the intermediate was shown to be a 1,2 epoxide.[10] Studies with molecular models show that, more so than the normal C1 conformation of an oxazoline intermediate, the C1 half chair of epoxides lends itself to an easy switch into the 1C half-chair conformation, and an axial back-side attack of the hydroxymethyl group in accordance with the Fürst-Plattner rule.[11] Also, the anomeric effect[12] should favor half-chair inversion for a β-glycoside. By contrast, axial back-side attack in a normal 1C conformation is seen to be sterically hindered by axial hydrogen. For nonnitrogenous sugars, conversion of 3,4-anhydroglucopyranoside into 3,6-anhydroglucopyranoside was first suggested by Ohle and Wilcke.[13] The technique of stabilization by steric hindrance of a reactive intermediate that precedes a reaction step involving conformational change may be applied to other investigations of complex neighboring group reactions in the cyclohexane or carbohydrate series.

Following the experimental procedure of Foster, *et al.*,[2] the tosylation of benzyl 3-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranoside[5] (X) gave benzyl 3-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XI). Some

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of the 4,6-di-*O*-tosyl derivative (XII) was also formed. The reaction of XI with methanolic aqueous KOH gave the carbonyl compound benzyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside (XIII). Especially characteristic for this structure was the ir absorption for the ring carbonyl amide at 3322 (NH) and 1722 cm^{-1} (C=O) and the absence of the amide II band.

Compound XIII was heated in aqueous methanolic KOH to give benzyl 2-amino-3,6-anhydro-2-deoxy-β-D-glucopyranoside (XIV). Treatment of XIV with benzoyl chloride gave the *N*-benzoyl derivative XV. Similarly, treatment of XIV with carbobenzoxy chloride gave XVI.

A more direct route for the preparation of XVI was also developed. This route led to the resolution of a mechanistic question in the preparation of the carbonyl compound XIII. For the synthesis of the methyl glycoside II by Foster, *et al.*,[2] it was assumed that the 3,6-anhydro ring was closed before the formation of the 2,4-carbonyl ring. For compound XIII this was proven as follows. Benzyl 2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XVII) was obtained from the 3-*O*-acetyl derivative XI and methanolic aqueous KOH at room temperature. Deacetylation occurs easily under these conditions and XVII crystallized immediately before the 3,6-anhydro ring could be formed. Compound XVII left for 3 days in methanolic aqueous KOH at room temperature gave the benzyloxycarbonylamino-3,6-anhydro derivative XVI. When XVI was kept longer in the methanolic aqueous KOH, compound XIII was formed.

Experimental Section

Melting points were taken in a Thomas-Hoover melting point apparatus Model No. 6404H. All melting points reported herein are uncorrected. Optical rotations were measured at the sodium D line with an O. C. Rudolph and Sons Inc., Model No. 956 polarimeter. Ir spectra were recorded with a Perkin-Elmer spectrophotometer (Model 337) using the KBr pellet technique. The homogeneity of all compounds synthesized was determined by thin layer chromatography using a mixture of two parts Merck silica gel G with one part Merck silica gel GF_{254}, the plates being activated by heating at 120° for 2 hr. The plates were developed with chloroform containing sufficient ethanol to produce R_f values between 0.2 and 0.7. The compounds were detected by extinction of the ultraviolet fluorescence of a zinc–silicate indicator and also by subsequent spraying with sulfuric acid (10%)–methanol and heating for about 15 min at 120°. The preparative tlc separations were made on Merck precoated silica gel plates, F_{254}, 2 mm thick. The microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Engelskirchen, West Germany.

Benzyl 3,4-Anhydro-2-benzamido-2-deoxy-β-D-allopyranoside (IX).—Benzyl 2-benzamido-2-deoxy-3-*O*-methanesulfonyl-β-D-glucopyranoside (VIII)[9] (0.5 g, 0.0011 mol) was dissolved in methanol (10 ml) containing sodium methoxide (0.0013 mol) and left overnight at room temperature. The solution was poured into water. The precipitate was filtered, washed with water, and recrystallized from methanol–water to give 0.29 g (74%): mp 183–185°; $[\alpha]^{25}D$ 142.8° (*c* 1, $CHCl_3$); $\bar{\nu}_{max}$ 3261 (NH), 1638, 1536 (amide C=O), 746, 695 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.59; H, 5.96; N, 3.95. Found: C, 67.44; H, 592; N, 3.89.

Benzyl 3-*O*-Acetyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XI).—Benzyl 3-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranoside (X)[5] (5 g, 0.011 mol) was dissolved in pyridine (25 ml) and the solution was cooled to 0° in an ice bath. *p*-Toluenesulfonyl chloride (4 g) in pyridine (12 ml) was added over a 20-min period. The solution was left at room temperature for 36 hr and poured into ice water (100 ml). The resulting oil was separated and dissolved in hot ethanol. At 0° the 4,6-di-*O*-tosyl derivative XII precipitated and was filtered off. The filtrate was concentrated, and the resulting precipitate was recrystallized from chloroform and diisopropyl ether to give 3.25 g (49%): mp 117–118°; $[\alpha]^{25}D$ 25° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3300 (NH), 1736 (ester C=O), 1682, 1555, 1512 (amide C=O), 1350 (SO_2), 744, 696 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{30}H_{33}NO_{10}S$ (599.63): C, 60.09; H, 5.54; N, 2.33; S, 5.35. Found: C, 60.43; H, 5.54; N, 2.39; S, 5.29.

Benzyl 3-*O*-Acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-di-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XII).—The 4,6-di-*O*-tosyl derivative XII, which was separated in the preparation of XI, was recrystallized from ethanol to give 0.97 g (11%): mp 158–159°; $[\alpha]^{25}D$ −8.5° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3397 (NH), 1755 (ester C=O), 1695, 1522 (amide C=O), 1265 (SO_2), 737, 697 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{37}H_{39}NO_{12}S_2$ (753.82): C, 58.96; H, 5.22; N, 1.86; S, 8.51. Found: C, 59.24; H, 5.03; N, 1.88; S, 8.52.

Benzyl 2-Amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside (XIII). Following the procedures of Foster, *et al.*,[2] for the preparation of methyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy-β-D-glucopyranoside, compound XI (2 g, 0.0033 mol) was dissolved in ethanol (20 ml), and 1 *N* potassium hydroxide (10 ml) was added. The solution was refluxed for 30 min and then cooled. The precipitate was filtered off and washed in ethanol to give 0.53 g (58%): mp 235–236°; $[\alpha]^{25}D$ −172° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3322 (NH), 1722 (C=O), 754, 704 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{14}H_{15}O_5N$ (277.27): C, 60.63; H, 5.45; N, 5.05. Found: C, 60.83; H, 5.24; N, 5.07.

Benzyl 2-Amino-3,6-anhydro-2-deoxy-β-D-glucopyranoside (XIV).—Compound XIII (0.4 g, 0.0014 mol) was dissolved in methanol (10 ml), and potassium hydroxide (2.17 g) in water (3 ml) was added. The solution was heated at 70° for 15 hr and evaporated *in vacuo*. The residue was crystallized from water to give 0.16 g (49%): mp 172–173°; $[\alpha]^{25}D$ −149.5° (*c* 1, CH_3OH); $\bar{\nu}_{max}$ 3301 (NH), 737, 692 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{13}H_{17}NO_4$ (251.28): C, 62.12; H, 6.82; N, 5.59. Found: C, 62.22; H, 6.82; N, 5.61.

Benzyl 3,6-Anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XV).—Compound XIV (0.2 g, 0.0008 mol) was dissolved in ethylene dichloride (10 ml) and added to 2.5% aqueous sodium bicarbonate (4 ml). Benzoyl chloride (0.1 ml) was added and the mixture was vibrated overnight. The ethylene dichloride layer was evaporated *in vacuo* and the product was recrystallized from ethanol and chloroform to give 0.18 g (63%): mp 184–185°; $[\alpha]^{25}D$ −156° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3238 (NH), 1633, 1522 (amide C=O), 740, 690 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.58; H, 5.96; N, 3.95. Found: C, 67.71; H, 5.96; N, 3.84.

Benzyl 3,6-Anhydro-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranoside (XVI).—Compound XIV (0.05 g, 0.0002 mol) was dissolved in ethylene dichloride (10 ml) and added to 2.5% aqueous sodium bicarbonate (3 ml). Carbobenzoxy chloride (0.036 g) was added and the mixture was vibrated overnight. The ethylene dichloride layer was separated and evaporated *in vacuo* at room temperature, and the resulting oil solidified with addition of diisopropyl ether to give 0.04 g (52%): mp 147–148°; $[\alpha]^{25}D$ −98° (*c* 1, $CHCl_3$); $\bar{\nu}_{max}$ 3360 (NH), 1677, 1511 (amide C=O), 744, 696 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.42): C, 65.44; H, 6.02; N, 3.64. Found: C, 65.11; H, 6.02; N, 3.56.

Benzyl 2-Benzyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranoside (XVII).—Compound XI (3.5 g, 0.0058 mol) was dissolved in methanol (30 ml) at room temperature, and potassium hydroxide (1 g) in water (20 ml) was added. Precipitation occurred almost immediately and the precipitate was filtered off and washed with a mixture of water and methanol (1:1). The product was recrystallized from 2-propanol to give 2.2 g (63%): mp 149–150°; $[\alpha]^{25}D$ −16° (*c* 1, pyridine); $\bar{\nu}_{max}$ 3416 (NH) 1688, 1525 (amide C=O), 1360 (SO_2), 737, 693 cm^{-1} (C_6H)$_5$.

Anal. Calcd for $C_{28}H_{31}NO_9S$ (577.60); C, 60.21; H, 5.60; N, 2.51; S, 5.76. Found: C, 59.86; H, 5.22; N, 2.70; S, 5.81.

The filtrate from the above reaction was left at room temperature for 3 days and precipitation occurred. The precipitate

was filtered and recrystallized from toluene to give 0.16 g, mp 147–148°. It was homogenous on tlc and had physical constants and an ir spectrum identical with those of compound XVI.

Further precipitation from the filtrate from the above reaction gave mixtures of XVI and XIV as shown by tlc.

Registry No.—VIII, 24718-05-6; IX, 39533-58-9; X, 10512-69-3; XI, 39533-60-3; XII, 39533-61-4; XIII, 39599-19-4; XIV, 39533-62-5; XV, 39533-63-6; XVI, 39533-64-7; XVII, 39533-65-8; *p*-toluenesulfonyl chloride, 98-59-9.

A Condensed Methyl Reductic Acid from Hydrolysis of Amino-hexose-reductones

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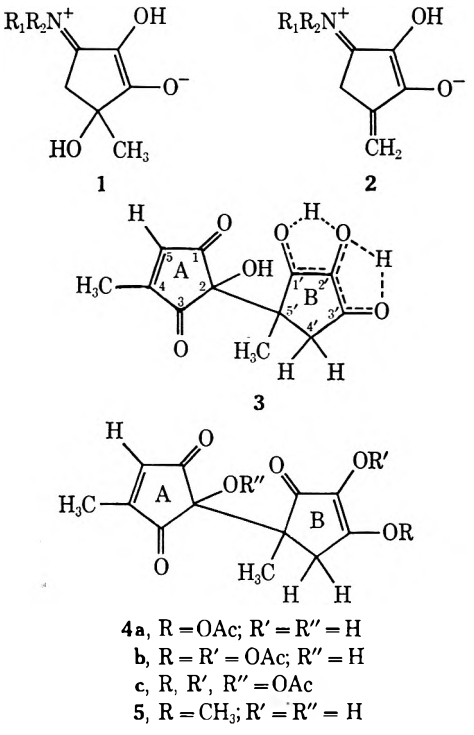
Received November 9, 1972

Dilute mineral acid hydrolyzes the amino group of hexose-reductones to yield 26% of a new yellow reductone, 2-hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione. The structure is assigned from ultraviolet, infrared, mass spectral, and proton magnetic resonance data. Chemical evidence supporting the condensed methyl reductic acid structure was obtained from periodate and hydrogen peroxide oxidations; 2-methyl-(*Z*)-butenedioic acid and 2-carboxy-2-methylbutanedioic acids were identified. Reduction of the yellow reductone and acetylation of the mixture produce the diacetate of methyl reductic acid, the di- and triacetates of unreacted yellow reductone, and the mixed acetates of the partially reduced parent material. These products were also identified by spectral techniques and confirmed by comparisons with data from authentic compounds whenever possible.

The hydroxy- and amino-substituted methyl reductic acids (**1**), trivially named amino-hexose-reductones, have been prepared from aldo- and ketohexoses in reactions with various secondary amine salts.[2-5] Dehydration of **1** by dehydrohalogenation yields **2**.[3,4] The mechanism of formation of piperidino-hexose-reductone has been determined.[6,7] Although both **1** and **2** are excellent antioxidants in animal fats and vegetable oils,[8] most of the different amino derivatives of **1** and **2** are toxic to small animals.[9,10]

To eliminate the toxicity and retain the antioxidant properties, removal of the amino group by acid hydrolysis was tried; however, no simple hexose-reductone was isolated. Instead, hydrolysis condensed the C_6 methyl reductic acid radicals to C_{12}, C_{22}, and higher compounds. The major product after hydrolysis of either **1** or **2** (R_1, R_2 = C_5H_{10} or $C_2H_4OC_2H_4$; $R_1 = R_2 = C_6H_5CH_2$) in 2 or 4 *N* hydrochloric acid at 25° was a new, yellow, crystalline, nonnitrogenous reductone, 2-hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione (**3**). This reductone did not induce the neurological effects that were observed for various amino derivatives of **1**, and lethal dosages were much higher than those of amino derivatives of **2**.[11]

Elemental analysis of **3** furnished the formula $C_{12}H_{12}O_6 \cdot H_2O$, and this composition was confirmed by mass spectrometry (*m/e* 252.0660, M·+). Ir analysis



1 **2** **3**

4a, R = OAc; R′ = R″ = H
b, R = R′ = OAc; R″ = H
c, R, R′, R″ = OAc
5, R = CH_3; R′ = R″ = H

(KBr disk) of **3** indicated several H-bonded hydroxyl groups (3500–3250 cm^{-1}). The yellow reductone **3** forms a monoacetate **4a** and, since the diacetate **4b** still exhibited a broad absorption at 3410 cm^{-1}, a third hydroxyl group was evident. Isolation of the triacetate **4c** confirmed the number of free hydroxyls. The important absorptions at 1748, 1706, and 1607 cm^{-1} were difficult to assign with certainty. The weaker 1748-cm^{-1} absorption is not congruent with an ene-1,3-dione, other reductone systems, an overtone, or a Fermi resonance assignment. Hesse, *et al.*,[12,13] presented solid-state ir spectra for methyl reductic acid and a tetramethyl, six-membered ring reductone, which

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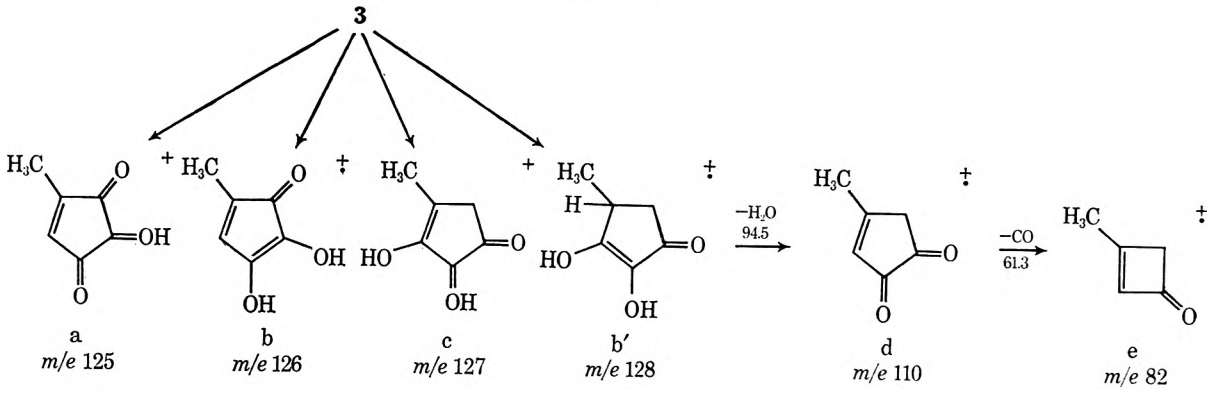
SCHEME I



revealed weak absorptions at 1710 and 1730–1745 cm^{-1}, respectively, and left those frequencies unassigned. The 1710–1745- and the 1748-cm^{-1} absorptions may indicate that the reductones and crystalline **3** contain, in small amounts, an unenolized ane-1,3-dione B ring structural contributor.[14] The strong, broad absorption at 1706 cm^{-1} was assigned to both carbonyls of the five-membered, ene-1,3-dione ring,[15–17] and the one of the reductone moiety.[12,14,18] The strongest absorption at 1607 cm^{-1}, also broadened, was assigned to the carbonyl-conjugated double bonds of both rings.[12,14,16–18]

Further evidence for the 2,3-dihydroxy-2-enone reductone moiety was indicated by the strong reducing action of **3** with 2,6-dichloroindophenol (Tillmans' reagent) and methylene blue in acid solution. Ferric chloride produced a temporarily blue solution indicative of the enolic hydroxyl function. In our earlier study with disubstituted enones,[19] absorptions in the 1800–1600-cm^{-1} region were similar. Monomethylation of **3** with diazomethane or methanol–hydrogen chloride yields **5**, and **5** fails to reduce Tillmans' reagent. Preferential alkylation would occur at the more acidic 3′-hydroxy group in agreement with the alkylation results of methyl reductic acid[12] and the methylation of 2,3-dihydroxy-4,4,6 6-tetramethyl-2-cyclohexenone.[13] A change in the ir absorptions in the 3500–3200- and 2750–2510-cm^{-1} regions indicated that chelation was greatly disrupted.

The uv spectrum of **3** in 95% ethanol provided two maxima at 234 nm (ϵ 12,600) and 268 (7068) which represent two separate conjugated systems. These maxima are consistent with reported literature values for the proposed chromophores.[12,20–22]

Examination of **3** by pmr in dimethyl sulfoxide-d_6 (DMSO-d_6) provided evidence for an uncoupled, aliphatic methyl group (singlet, δ 1.16), one vinyl methyl group (δ 1.98) coupled to a vinyl proton (δ 6.94), and a geminal methylene quartet (δ_A 3.15, δ_B 1.84, J_{AB} = −18 Hz). The negative AB coupling constant agrees with the values reported for methylene protons α to carbonyl groups.[23,24] Irradiation of each doublet of the AB quartet allows the individual frequency assignments. Three hydroxyl protons were present as broad resonances at δ 8.10, 6.10, and 3.39. The vinyl proton resonance collapsed to a singlet when the methyl protons at δ 1.98 were irradiated. Acetyl or methyl substitution, **4a** and **5**, produces no change in the basic pmr spectral pattern of **3**. The acetyl group (δ 2.01 in $CDCl_3$) is assigned to the 3′ position because this derivative failed to reduce Tillmans' reagent, and previously examined α-acetoxy methyl groups in α,β-unsaturated cyclopentanes and cyclohexanes in chloroform-*d* were shielded more and displaced to a lower field near δ 2.2.[25]

Low- and high-resolution mass spectra were analyzed for **3**, its monomethyl ether (**5**), and the monoacetyl derivative (**4a**). The composition of each fragment from **3** shown in Scheme I is verified by high-resolution analysis. The intensity of the fragments at *m/e* 125–128 indicates the relative ease of cleavage of the 2–5′ bond, and the splitting results in two fundamental ions each representing one ring of the proposed structure. The formation of fragment b, *m/e* 126, arises *via* a hydrogen transfer, most likely through a McLafferty rearrangement,[26] and may involve both the 5′-methyl and 4′-methylene protons on the methyl reductic acid moiety. Fragment d, *m/e* 110, was shown to be produced from b′ (formed with a proton transfer) by a metastable ion, and then d expels CO to form e, *m/e* 82. The pattern of *m/e* 128 → 110 → 82 is also observed in the fragmentation of the mono- and diacetates of methyl reductic acid after the loss of one and two molecules of ketene. This ketene expulsion process agrees with results by Biemann, *et al.*[27] Fragments at *m/e* 237 (f), 224 (g), and 234 (h) arise, respectively, from loss of a methyl radical (C-5′ most likely), carbon monoxide, and water.

The fragmentation of **5** (Scheme II) produces high-intensity peaks at *m/e* 140, 141, and 142 that represent fragments i, j, and k. As in the fragmentation pattern

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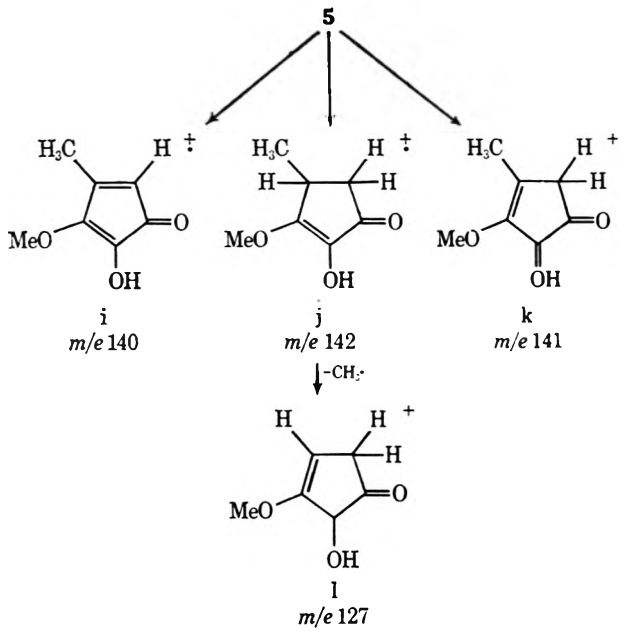
(21) A. A. Kiang, H. H. Lee, and K. Y. Sim, *J. Chem. Soc.*, 4328 (1962).
(22) A. J. Birch and R. J. English, *ibid.*, 3805 (1957).
(23) T. Takahashi, *Tetrahedron Lett.*, **No. 11**, 565 (1964).
(24) C. H. DePuy, C. E. Lyons, and L. B. Rodewald, *J. Chem. Eng. Data*, **11**, 102 (1966).
(25) α-Acetyl methyl proton resonances in α,α'-diacetoxydihydro-γ-pyrone, methyl cyclopentenolone acetate, dihydromaltol acetate, and maltol acetate are 2.20, 2.22, 2.21, and 2.30.
(26) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectroscopy of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 155.
(27) K. Biemann, D. C. DeJongh, and H. K. Schones, *J. Amer. Chem. Soc.*, **85**, 2289 (1963).

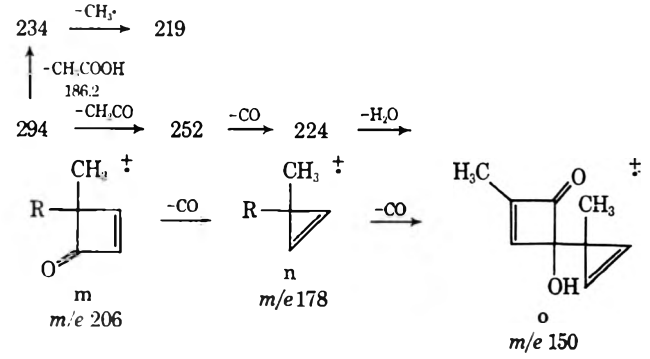
SCHEME II



of **3**, the loss of a methyl radical, *m/e* 251, and CO, *m/e* 238, are present in the mass spectrum of **5**; however, since no $M \cdot^+ - 18$ ion is observed, water expulsion during ionization of **3** evidently arises from the dihydroxyenone portion of the molecule. Ions at *m/e* 125 (a), 126 (b), and 127 (c) are still present at reduced intensities. All are assumed to originate by loss of $CH_3 \cdot$ from ions i, j, and k since l, *m/e* 127, originates from k as shown by the metastable peak at 113.5.

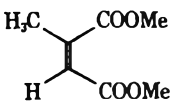
The mass spectral pattern of the monoacetate **4a** is somewhat more complicated owing to this modifying group; new decomposition paths became available. The new fragments, *m/e* 219, 206, 178, and 150, are rationalized in Scheme III, which brings all the more

SCHEME III

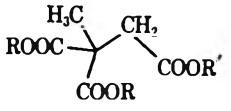


significant mass spectral data for the parent compound and its two derivatives into agreement.

Further information to support the assigned structure came from oxidation and reduction of **3**. Periodate treatment of **3** furnishes chemical evidence for the 1,3-enedione structural unit in the A ring. A dibasic acid, isolated after periodate treatment of **3** as its methyl ester, is identified as **6** (81% yield of free acid) by comparative glc and mass spectral analyses with authentic dimethyl citraconate. The mass spectrum is straightforward, does not contain any skeletal rearrangements, and is in agreement with the work of Bowie, *et al.*,[28] on malates.



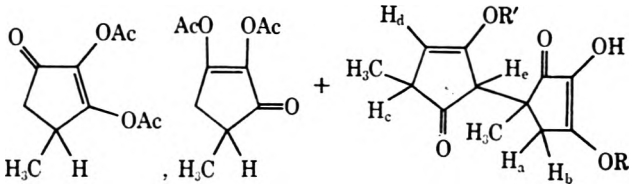
6



7, R, R′ = H
8. R, R′ = CH_3

A second polybasic acid, **7**, was isolated in 43% yield (50% overall) after hydrogen peroxide treatment of **3** and arises from ring B plus C-2 of ring A. Pmr of compound **8**, the trimethyl ester of **7**, reveals the *C*-methyl protons at δ 1.53, two equivalent methyl ester groups (R, δ 3.76), and a third group (R′) displaced further upfield (δ 3.65); a 3:2 ratio of methyl-methylene protons is also demonstrated. No molecular ion is observed in the mass spectrum of **8**; the highest mass is at *m/e* 187. The structure of compound **8** was confirmed by comparison with an authentic sample.

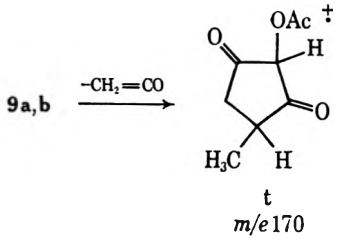
Partial hydrogenation of **3**, with isolation of the reduced products as their acetate derivatives, also supports the assigned structure. Three products, **9** (37.7%), **10** (5.7%), and **11** (6.6%), are assigned structures based on spectral data; **9** is identical with a synthetic product. Analyses of **9** by glc and tlc indicate this material to be homogeneous, but pmr shows **9** to be a mixture of the two isomers **9a** and **9b**.



9a,b

10, R = R′ = OAc
11, R = H; R′ = OAc

Analogous isomers are indicated for the mono-*O*-methyl ethers of methyl reductic acid.[12] Mass spectrometry of the mixture **9** shows that the first fragmentation of each isomer, **a** and **b**, produces a common ion **t**, *m/e* 170, which is responsible for the remaining fragmentation pattern; *viz.* below.



The ir, pmr, and mass spectral data from the isolated product agree with spectral information obtained from an authentic sample of **9**. Structure **10** is assigned primarily from pmr and mass spectral information. Mass spectrometry establishes a formula of $C_{16}H_{18}O_7$ ($M \cdot^+$ 322), a diacetate by pmr; the loss of two ketene units ($m \cdot^+ - 42 - 42$) in the fragmentation of **10** supports the diacetate assignment and also shows these functional groups to be attached to double bonds. The pmr spectrum of **10** indicates that the

(28) J. H. Bowie, D. H. Williams, P. Madsen, G. Schroll, and S.-C. Lawesson, *Tetrahedron*, **23**, 305 (1967).

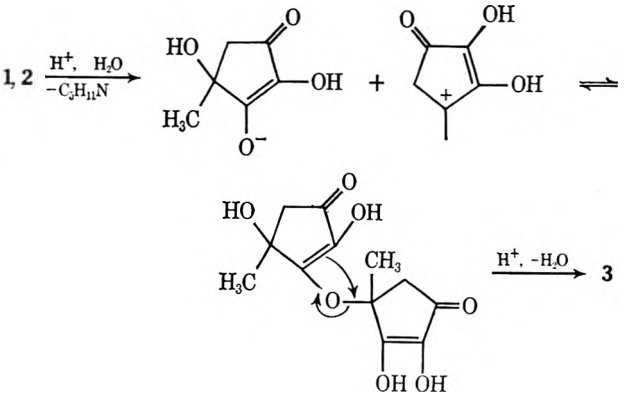
ring A methyl group is involved in a six-spin system (shown by decoupling experiments) including the methyl group (δ 1.18, J_{CH_3,H_c} = 6.7 Hz), H_c (δ 2.85, multiplet,) and H_d (δ 4.70, J_{H_c,H_d} = 4.8 Hz, finely split quartet). Two resonances at δ 2.15 and 2.27 (one-half proton each) are assigned to proton H_e; irradiation indicates long-range coupling between H_c and H_e protons, as should occur in the planar, modified A ring.[29] The chemical shifts of H_e (at 2.15 and 2.27) on the diastereotopic muclei arising from the C-2 chiral carbon atom,[30] along with the lack of optical activity, indicate that **10** (also **11**) exists as a racemic modification. Homoallylic coupling of H_e, H_c supports structure **10**.[31] Further irradiation at δ 2.85 converts the finely split doublet of the vinyl proton into a broadened singlet and produces a broadened, methyl group singlet at δ 1.18. The complicated six-spin interaction lends itself to only a partial solution by first-order analysis, and the parameters indicate a $CH_3CHRCH{=}CROAc$ relationship. The geminal protons (H_A, H_B) are still present at δ 2.86 and 3.15 (J_{H_A,H_B} = −18 Hz) along with two acetyl methyl groups at δ 2.10 and 2.22.

The ir spectrum of **10** supports the five-membered ketone, vinyl acetate, bonded hydroxyl, and a substituted α,β-enone assignment. Other spectral information (pmr, mass spectrum) shows product **11** to be similar to **10**, except that this derivative has only a single acetate group. The pmr data are in concert with that of **10**: acetyl methyl δ 2.22; aliphatic methyl δ 1.36; aliphatic methyl δ 1.16 (J_{CH_3,H_c} = 6.4 Hz), a broadened singlet upon irradiation of H_c; geminal methylene protons, δ 2.52 and 2.96 (J_{H_A,H_B} = −18.7 Hz); vinyl proton at δ 4.63; methine proton at δ 2.02 and 2.12 (one proton); methine proton at δ 2.87 (multiplet). Three different irradiations show C-2, C-4, and C-5 protons plus methyl protons to be involved in a six-spin interaction. High-resolution mass spectrometry fixes the formula at $C_{14}H_{16}O_6$ and shows the material to contain a vinyl acetate moiety ($M\cdot^+ - 42$). A positive reduction test with Tillmans' reagent supports the placement of the acetate group in the modified A ring.

In effect, reduction of the double bond in the A ring of the yellow reductone occurs along with either one of the carbonyl groups and yields a product which should be easily dehydrated (loss of the tertiary hydroxyl group) during the anhydrous acetylation. Finally, enolization and acetylation gives compounds **10** and **11**. The reduction sequence agrees with early information on the reduction of 4-cyclopentene-1,3-dione[20] and its 2,2-dimethyl derivative.[32] Also, products **4b** (23.8%) and **4c** (11.6%) are isolated from the reduced, acetylated mixture by fractional crystallization of the solid that initially crystallizes from the reaction mixture.

Initially, a vinyl–allyl ether linkage between the two rings in **3** was proposed because of the *m/e* fragments a and b. This assignment was discarded because vinyl ethers are readily hydrolyzed in acidic media.[33–35] Nevertheless, the vinyl ether is involved in a logical explanation for formation of the yellow reductone (Scheme IV). After hydrolysis and carbonium ion formation in the strongly acidic medium, a labile and reversible ether bond forms. The vinyl–allyl ether is short lived and the methyl reductic acid double bond enhances (anchiomeric assistance) rearrangement to the final product in a 1,3-intramolecular shift. This phenomenon of the reductone double bond assistance probably promotes the σ bond (C-2–C-5′) cleavage that takes place during the hydrogenation of **3**. The lack of optical activity in compound **3**, which contains two chiral centers, indicates a racemic modification and nonstereospecificity in the overall reaction (Scheme IV). Also, hydrolysis of **2** results in **3**, and it is likely that both reactions proceed *via* the same intermediate.

SCHEME IV



Experimental Section

General.—Melting points were recorded on a Thomas-Hoover Unimelt[36] apparatus and are uncorrected. Ir spectra were obtained with a Perkin-Elmer Model 612 spectrophotometer from potassium bromide disks or solutions in chloroform. The mass spectra were determined with a Nuclide 12-90-DF double-focusing spectrometer at 70 eV and either a direct or heated inlet (approximately 160°) was used. The pmr spectra were recorded with a Varian HA-100 instrument, and various sweep widths (50, 100, 500 Hz) were employed in coupling constant evaluations. Me_4Si served as an internal standard. The uv spectrum was measured on a Cary Model 60 recording photometer from 95% ethanol solutions. Optical rotations were measured on a Beckman automatic recording polarimeter Model 1169 from absolute ethanol solutions. Tillmans' reagent is a slightly basic, dilute solution of 2,6-dichloroindophenol.

Yellow Reductone (3), 2-Hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione.—Piperidino-hexose-reductone (**1**, 143.5 g)[2-5] was added to 273 ml of 4 *N* hydrochloric acid. Upon dissolution, the mixture turned orange-red. The head space was filled with nitrogen and the stoppered flask was stored in the dark for 12 days. At the end of this period, the yellow, crystalline precipitate was removed and recrystallized from hot water (cooling to room temperature). After 24 hr, 48.4 g precipitated (26.3%) and had mp 153–156° (drying over calcium chloride at 26° for 12 hr at 0.1 Torr); $[\alpha]^{26}D$ −0.01 (0.7 g/100 ml ethanol). Compound **3** may

(29) M. Barfield and D. M. Grant, *Advan. Magn. Resonance*, **1**, 189 (1965).

(30) J. F. Stoddart, "Stereochemistry of Carbohydrates," Wiley-Interscience, New York, N. Y., 1971, Chapter 2.

(31) C. M. Cimarusti and J. Wolinsky, *J. Org. Chem.*, **31**, 4118 (1966), and references cited therein.

(32) W. C. Agosta and A. B. Smith, III, *ibid.*, **35**, 3856 (1970).

(33) P. Paul, *Bull. Soc. Chim. Fr.*, **1**, 971 (1934).

(34) A. Skrabel and R. Skrabel, *Z. Phys. Chem.*, **A181**, 449 (1938).

(35) T. Okuyama, T. Fueno, H. Nakatsuji, and J. Furukawa, *J. Amer. Chem. Soc.*, **89**, 5826 (1967).

(36) Mention of companies or products by name does not imply their endorsement by the U. S. Department of Agriculture over others not cited.

also be prepared from morpholino- (in similar yields) and *N,N*-dibenzylamino- (in 10% yield) hexose-reductones.

Anal. Calcd for $C_{12}H_{12}O_6 \cdot H_2O$: C, 53.33; H, 5.22; neut equiv, 270. Found: C, 53.41; H, 5.45; neut equiv, 279.

Ir (KBr disk) 3560 (br), 3470 (br), 3350 (br), 3250 (br), 2990, 2750–2510 (v br), 1748 (m), 1706 (vs), 1607 (br, vs), 1418, 1379, 980, 898 cm^{-1}.

Pmr (DMSO-d_6) δ 1.16 (3 H) aliphatic methyl; 1.98 (3 H) vinyl methyl; 3.15 (1 H_A) and 1.84 (1 H_B), $J_{H_AH_B} = -18$ Hz; 8.10 (1 OH), 6.10 (1 OH), and 3.39 (1 OH), broad, hydroxyl protons; 6.94 (1 H) vinyl proton, $J_{CH_3,H} = 1.3$ Hz.

Mass spectrum *m/e* (rel intensity) 252 (50), 237 (2), 234 (1), 224 (17), 167 (6), 128 (98), 127 (84), 126 (100), 125 (29), 110 (76), 82 (16), 68 (37).

Uv $\lambda_{max}^{95\% EtOH}$ 234 nm (ϵ 12,600), 268 (7068).

Acetylation of 3 (4a).—One gram of **3** was dissolved with warming in 6 ml of acetic anhydride. Acetyl chloride (6 drops) and pyridine (6 drops) were added and the solution was refluxed for 2 hr. After cooling, the solution was concentrated *in vacuo* and the resulting residue was crystallized from methanol–water (90 mg). After two crystallizations the melting point was 194–196° dec.

Ir (KBr disk) 3430, 3080, 1780 (w), 1760, 1665, 1650, 1610 cm^{-1}.

Pmr (acetone-d_6) δ 1.30 (3 H), aliphatic methyl; 2.01 (3 H), vinyl methyl; 2.03 (3 H), acetyl methyl; 3.16 (1 H_A), 2.06 (1 H_B), $J_{H_A,H_B} = -18$ Hz); 6.84 (1 H), vinyl proton, $J_{CH_3,H} = 1.6$ Hz.

Mass spectrum *m/e* (rel intensity) 294 (64), 252 (19), 234 (18), 224 (3), 206 (28), 192 (11), 178 (15), 177 (13), 128 (64), 127 (64), 126 (83), 125 (18), 110 (26), 69 (17), 43 (100).

Acetylation of 3 (4b).—Yellow reductone **3** (100 mg) was dissolved with warming in 10 ml of acetic anhydride containing 40 mg of anhydrous sodium acetate. The mixture was heated on a steam bath for 2 hr. After cooling, the mixture was poured onto 100 ml of ice and the solution was then neutralized with sodium bicarbonate. After standing for 30 min, a white precipitate formed, 20 mg, mp 258°. Extraction of the aqueous phase with chloroform and the subsequent work-up yielded, after recrystallization from ethanol–water, an additional 50 mg of product.

Ir (KBr disk) 3430, 3080, 2990, 2830, 1775, 1760, 1735, 1708, 1650, 1610 cm^{-1}.

Pmr (DMSO-d_6) δ 1.31 (3 H), aliphatic methyl protons; 2.02 (3 H), vinyl methyl protons, doublet; 2.16 and 2.17 (6 H), acetyl methyl protons; 2.47 and 3.34 (2 H), geminal protons, $J_{H_A,H_B} = -18$ Hz; 6.55 (1 H) vinyl proton, quartet, $J_{CH_3,H} = 1.6$ Hz.

Mass spectrum *m/e* (rel intensity) 336 (65), 318 (4), 308 (4), 300 (12), 294 (22), 276 (26), 266 (10), 252 (2), 248 (24), 234 (100), 224 (42), 219 (40), 216 (24), 206 (76), 201 (7), 178 (27), 165 (6), 150 (8), 149 (10), 128 (5), 127 (27), 126 (23), 125 (6), 110 (13), 69 (3).

Monomethyl Ether 5. A. Prepared with Diazomethane.—An ethereal solution of 9 mmol of diazomethane was added in three portions to 0.840 g (3 mmol) of **3** in 10 ml of methanol. The resulting solution was allowed to stand at room temperature for 24 hr (after 1.5 hr a slight precipitate formed), the solvent was removed with a stream of nitrogen, and the residue was taken up in 4 ml of methanol. Ether (50 ml) was added and the solution was cooled; 400 mg of product was obtained, mp 198–200°. Tlc on silica gel (Brinkmann, precoated silica gel F-254, 0.25 mm) using benzene–acetone–methanol (20:10:5) showed this material to be a mixture. The mixture was chromatographed on a 70-g silica gel column (Baker, chromatographic grade). The column was developed with the same solvent system. Those fractions that contained only the fastest moving component were combined, and the product was isolated by solvent evaporation. The residues were combined and crystallized from methanol–ether, 200 mg, mp 229–230°. Tlc showed this product to be homogeneous.

Ir (KBr disk) 3410, 3230, 3060, 3000, 2982, 1738, 1695, 1610, 1580, 1468, 1400, 915, 905 cm^{-1}.

Pmr (DMSO-d_6) δ 1.17 (3 H), aliphatic methyl protons; 1.95 (3 H), vinyl methyl protons; 2.10 and 3.33 (2 H), geminal protons, $J_{H_A,H_B} = -18$ Hz; 3.25 and 3.27 (2 H), hydroxyl protons; 3.90 (3 H), *O*-methyl protons; 6.98 (1 H) vinyl proton, $J_{CH_3,H} = 1.5$ Hz.

Mass spectrum *m/e* (rel intensity) 266 (74), 251 (6), 238 (17), 234 (18), 224 (3), 206 (2), 178 (2), 142 (100), 141 (44), 140 (33), 127 (62), 126 (11), 125 (9), 124 (19), 114 (17), 110 (19), 69 (36).

B. Prepared with Methanol–Hydrogen Chloride.—To 20 ml of a solution of anhydrous HCl in methanol (prepared from acetyl chloride–methanol) **3** (0.4 g) was added. The solution stood at room temperature for 18 hr, and then the solvent was removed *in vacuo*. The residue was crystallized twice from methanol–ether, 380 mg, mp 227–229°. Tlc on silica gel with either the above solvent system or ethyl acetate indicated the product to be homogeneous. A mixture melting point determination, with the previously prepared *O*-methyl ether, gave no depression. Pmr data in DMSO-d_6 were identical with that of the above monomethyl ether.

Oxidation of 3 with Sodium Periodate (6, 8).[37]—Yellow reductone **3** (2.52 g in 50 ml of water) was treated with three portions of sodium periodate (12.83 g in 100 ml of water). The first 30-ml addition changed the solution to a light yellow; some free iodine was liberated. Hydrochloric acid (0.1 *N*) was added to bring the pH of the solution to 3. The stoppered flask was protected from light, and the mixture was stirred overnight. The colorless reaction mixture was continuously extracted with ether for 5 hr and the resulting extract was dried with sodium sulfate. After filtration and solvent removal, 1.49 g of residue was isolated.

A portion of this residue was methylated with excess diazomethane in methanol–ether; glc analysis (6 ft × 0.25 in., 15% SE-30 on 80–100 UPh) indicated that the sample contained **6** (85%) and a lesser quantity of **8** (10%). Another portion was treated for 1 hr on a steam bath with 25 ml of water containing 2 ml of 30% hydrogen peroxide. The products were isolated by solvent extraction in the usual manner and methylated with diazomethane. Glc analysis showed this mixture to consist of 6:8:unknown in a 65:22:13 ratio [diethyl 2-methylmalonate (DEMM) was used as an internal standard]. Total yields of free acids: citraconic, 81%; **7**, 6%.

A further portion of the methylated mixture was separated by preparative glc on a 6 ft × 0.25 in., 15% SE-30 on 80–100 UPh column. The material corresponding to **6** was isolated and subjected to ir and mass spectral analyses.

Ir ($CHCl_3$) 3010, 2955, 2850, 1665, 1445, 1435, 1372, 1360, 1280, 1168, 1125, 1040 cm^{-1}.

Mass spectrum *m/e* (rel intensity) 158 (4), 144 (2), 129 (2), 128 (8), 127 (100), 100 (2), 99 (20), 64 (5), 63 (6), 59 (22).

Hydrogen Peroxide Oxidation of 3 (6, 7, and 8).—Yellow reductone (5.0 g) was dissolved in 100 ml of water, and three 8-ml portions of 30% hydrogen peroxide were added to the stirred, heated (90°) solution. After 1.5 hr, the solution was cooled and 40 g of lead acetate trihydrate was added. This turbid mixture was allowed to stand for 24 hr, and the precipitate was isolated, dried, ground into a fine powder, and suspended in 75 ml of water. Excess hydrogen sulfide was passed into the solution for 30 min; after the lead sulfide was removed, the filtrate was concentrated to a thick syrup *in vacuo*. When the oil (3.0 g) was treated with ethyl acetate, 1.5 g (43%) of crystalline **7** was produced.

The ethyl acetate mother liquor was concentrated and a portion of the residue was treated with diazomethane. This mixture was analyzed by glc with DEMM as an internal standard. The mixture contained 19% **8** (dimethyl 2-carboxymethyl-2-methylbutanedioate) and 2% **6** [dimethyl 2-methyl-(*Z*)-butenedioate].

A portion of compound **7** dissolved in ether–methanol was treated with excess diazomethane. The solvent was removed with a stream of nitrogen and a portion of the methylated product was examined on the 15% SE-30 column that was programmed at 80°, 4°/min to 200°. The ester **8** was homogeneous, retention time 11 min (relative to DEMM).

Ir ($CHCl_3$) 2962, 2850, 1731, 1458, 1439, 1370, 1169, 1115 cm^{-1}.

Pmr (CDCl) δ 1.53 (3 H), aliphatic methyl protons; 2.92 (2 H), methylene protons; 3.65 (3 H) and 3.76 (6 H), *O*-methyl protons.

Mass spectrum *m/e* (rel intensity) no parent ion, 187 (53), 159 (28), 145 (11), 131 (9), 127 (100), 115 (67), 99 (27), 69 (41), 59 (49).

Hydrogenation of 3 (4a, 4b, 9a, 9b, 10, and 11).—After the yellow reductone **3** (3 g) was dissolved in 40 ml of 95% ethanol, 0.2 g of 10% Pd/C in 40 ml of ethanol was added, and the final volume was brought to 100 ml with ethanol. The mixture was hydrogenated at 3.1 atm and room temperature for 2 hr. The

(37) M. L. Wolfrom and J. M. Bobbitt, *J. Amer. Chem. Soc.*, **78**, 2489 (1956).

solution was filtered through Celite and concentrated. The resulting thin syrup (3.0 g) was added to 50 ml of chloroform containing 16 ml of acetic anhydride and 80 mg of anhydrous sodium acetate. The mixture was refluxed for 3 hr and, after cooling, poured into 200 ml of ice. The aqueous mixture was stirred for 1.5 hr and was then extracted three times with 25 ml of chloroform. The combined organic phase was dried over calcium chloride. Filtration and solvent removal produced a light oil (3.10 g). The oil was distilled at 0.1 Torr: fraction 1, 140–160°, 1.0 g; fraction 2, 160–180°, 2.0 g.

Fraction 1 (1.0 g) was examined by glc on the SE-30 column and shown to be 95% pure; retention time 26.8 min, programmed from 80° at 4°/min and a flow rate of 56 ml He/min. A portion of this material was purified by preparative glc (50 mg of 9).

Ir ($CHCl_3$) 2970, 2925, 2870, 1778, 1717, 1660, 1450, 1425, 1408, 1369, 1330, 1172, 1155 cm^{-1}.

Pmr ($CDCl_3$) δ 1.18 and 1.27 (3 H), doublet of doublets representing two different methyl group protons; 3.02–4.00 (3 H), methylene protons, multiplet; 2.21, 2.24, 2.26, and 2.28 (6 H), representing two acetyl methyl groups per isomer of the two diacetates present.

Mass spectrum *m/e* (rel intensity) 212 (6), 170 (22), 128 (68), 113 (7), 110 (3), 100 (4), 85 (4), 69 (3), 43 (100).

A 1.0-g portion of fraction 2 was dissolved in ethyl acetate–methanol and stirred at −15°. After 3 days, a white, crystalline precipitate formed, 0.174 g, mp 246–250° dec (**4c**).

Ir (KBr disk) 2810–2740 (br), 1782, 1778, 1740, 1655, 1615, 1425, 1370, 1235, 1190, 1170, 1145, 1098 cm^{-1}.

Pmr (DMSO-d_6) δ 1.27 (3 H), aliphatic methyl protons; 1.90 (3 H), aliphatic acetyl methyl protons; 2.09 (3 H), vinyl acetyl methyl protons; 2.11 (3 H), vinyl acetyl methyl protons; 1.98 (3 H), vinyl methyl protons; 2.15 and 2.28 (2 H), J_{AB} = −18 Hz, geminal, methylene protons; 7.02 (1 H), vinyl proton (quartet).

Mass spectrum *m/e* (rel intensity) 378 (11), 336 (59), 294 (49), 276 (6), 266 (10), 252 (54), 234 (85), 224 (32), 206 (28), 192 (7), 178 (9), 170 (13), 169 (14), 150 (8), 129 (8), 128 (61), 127 (44), 126 (63), 125 (10), 110 (10), 69 (16), 43 (100).

Compound **4b** was isolated by careful concentration of the mother liquors resulting from the retreatment of the difficulty soluble residue (0.475 g). The mass and ir spectra were superimposable on those from previously prepared **4b**.

The remainder of the residue soluble in the original supernatant (over **4c**) was applied to a small amount of silica gel (<2.0 g). The mixture, after solvent removal, was placed on a silica gel dry-packed column (42 g of Baker chromatographic grade containing 10% water by weight). The column was developed and eluted with chloroform; 5-ml samples were taken. Fractions 25–37 contained 200 mg of **10**, $[\alpha]^{25}D$ −0.02° (c 1.0, ethanol), and fractions 50–70 yielded 250 mg of **10** and **11**. Fractions 50–70 were combined and the resulting residue was applied to a 2-mm silica gel preparative plate (Brinkmann) which was then developed three times with benzene–ethyl acetate (3:1). Each zone corresponding to **10** and **11** was removed and extracted with ethyl acetate: 20 mg **10**, 220 mg **11**.

Spectra of 10.—Ir ($CHCl_3$) 3400 (v br), 2975, 2930, 2878, 1772 (br), 1695, 1668, 1445, 1372, 1368, 975, 955 cm^{-1}.

Pmr ($CDCl_3$) δ 1.18 (3 H), aliphatic methyl protons, doublet J_{Me,H_c} = 6.7 Hz; 1.30 (3 H), aliphatic methyl protons; 2.10 and 2.22 (6 H), acetyl methyl groups; 2.27 and 2.15 (1 H), methine proton H_c; 2.86 and 3.15 (2 H), geminal protons, J_{H_A,H_B} = −18 Hz; 4.70 (1 H), vinyl proton (H_d) finely split doublet; 2.85 (1 H_c), multiplet, J_{H_c,H_d} = 4.8 Hz.

Mass spectrum *m/e* (rel intensity) 322 (3), 280 (83), 238 (5), 220 (22), 192 (32), 172 (100), 164 (21), 161 (23), 148 (32), 133 (10), 110 (5), 86 (5), 69 (6), 43 (100).

Spectra of 11.—Ir ($CHCl_3$) 2980, 2940, 2918, 2860, 1750 (br), 1602 (br), 1489, 1440, 1390, 1372, 1300, 942, 905 cm^{-1}.

Pmr ($CDCl_3$) δ 1.16 (3 H), aliphatic methyl, J_{CH_3,H_c} = 6.4 Hz; 1.36 (3 H), aliphatic methyl group; 2.22 (3 H), acetyl methyl protons; 2.52 and 2.96 (2 H), geminal methylene protons, J_{H_A,H_B} = −18.6 Hz; 2.02 and 2.12 (1 H), methine proton H_c; 2.87 (1 H_c), methine proton, multiplet; 4.63 (1 H_d), vinyl proton, finely split doublet, J_{H_c,H_d} = 4.4 Hz.

Mass spectrum *m/e* (rel intensity) 280 (18), 238 (53), 220 (18), 192 (6), 164 (3), 148 (2), 124 (8), 123 (8), 43 (100).

2-Carboxy-2-methylbutanedioic Acid.—This compound was prepared according to a modified, previously established procedure.[38] Sodium (2.3 g) was dissolved in absolute ethanol, and diethyl 2-methylmalonate (17.4 g) was added to the solution over 30 min. Ethyl chloroacetate (12.62 g) was added to the sodium salt over a 40-min period, and the final mixture was refluxed for 4 hr. The reaction was cooled and most of the alcohol was removed *in vacuo;* the residue was added to water and the new mixture was extracted with ether. The combined ether extract was dried over calcium sulfate, filtered, and then reduced to a light oil by solvent evaporation; distillation at 150° and 18 Torr produced 10 g of ester (38%).

The ethyl ester (5 g) was saponified with 10% potassium hydroxide (100 ml). Extraction of the cooled, acidified solution with ether produced (after the usual work-up) 4.5 g of tricarboxylic acid, mp 174° (lit. mp 176°).

Dimethyl 2-Carbomethoxybutanedioate.—The free acid (1.0 g) was dissolved in a small amount of methanol, and an excess of diazomethane (in ether) was added in two portions. The solvent was removed after 1 hr with a stream of nitrogen and the product was distilled at 15 Torr. The product was homogeneous (glc on 15% SE-30 column), and the spectral data of this ester were identical with those of **8**.

Dimethyl 2-Methyl-(*Z*)-butenedioate (Dimethyl Citraconate).—An authentic sample of acid (1.0 g) was methylated with an excess of diazomethane in methanol–ether. Solvent removal produced the desired product, 1.20 g. The ir, pmr, and mass spectral analyses of this compound were identical with those of **6**.

2,3-Diacetoxy-4-methyl-2-cyclopentenone and 2,3-Diacetoxy-5-methyl-2-cyclopentenone.—An attempt to prepare methyl reductic acid by the procedure of Hesse and Breig[39] met with limited success. A slight modification allowed isolation of the diacetate derivative of methyl reductic acid. The residue from the hydrolysis of the monohalocyclopentenolone was distilled and the fraction of bp 160–170° (0.1 mm) was isolated. This material was added to 25 ml of chloroform, 4 ml of acetic anhydride, and 60 mg of sodium acetate. The mixture was refluxed for 4 hr and, after cooling, poured into ice water. After stirring for 2 hr, the organic phase was removed and the aqueous portion was extracted with chloroform three times. Combination of all organic phases yielded 8% of the diacetate after drying and filtration. The isolate did not crystallize on standing in the cold. Glc (SE-30 column) and tlc (silica gel, benzene–ethyl acetate solvent systems) showed this material to be homogeneous. However, pmr information indicated this product to be a mixture of 2,3-diacetoxy-4-methyl-2-cyclopentenone and 2,3-diacetoxy-5-methyl-2-cyclopentenone. The two isomer isolates agreed with the work of Hesse, *et al.*,[12] on the monoalkyl ether derivatives of methyl reductic acid.

Ir ($CHCl_3$) 2970, 1785, 1722, 1665, 1372, 1335, 1190, 1165, 1000 cm^{-1}.

Pmr ($CDCl_3$) δ 1.24 (3 H), doublet, superimposition of two methyl group protons; 2.21, 2.22, 2.24, and 2.26 (6 H), acetyl methyl protons; 3.00–4.30 (3 H), multiplet, methine and methylene protons.

Mass spectrum *m/e* (rel intensity) 212 (2), 170 (22), 128 (68), 113 (8), 110 (2), 100 (4), 85 (4), 69 (3), 43 (100).

Registry No.—**1** (R_1R_2N = piperidino), 39994-32-6; **1** (R_1R_2N = morpholino), 39994-33-7; **1** (R_1 = R_2 = benzyl), 39994-34-8; **3**, 39994-35-9; **4a**, 39994-36-0; **4b**, 39994-37-1; **4c**, 40081-61-6; **5**, 39994-38-2; **6**, 617-54-9; **7**, 39994-39-3; **8**, 39994-40-6; **9a**, 39994-41-7; **9b**, 39994-42-8; **10**, 39994-43-9; **11**, 39994-44-0; diethyl 2-carboethoxy-2-methylbutanedioate, 39994-45-1.

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The Rates of Racemization and Peptide Bond Formation of Glutamic and Aspartic Acid Active Esters[1]

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Received January 18, 1972

Racemization and coupling rate constants of several *N*-carbobenzoxy-γ-methyl-L-glutamic acid and *N*-carbobenzoxy-β-methyl-L-aspartic acid active esters have been determined. The order of magnitude of coupling rate constants for both amino acid esters is comparable to that reported for the corresponding cysteine active esters. However, significant differences are observed for the racemization rates. The importance of the ratio of coupling to racemization rate constants is discussed.

It has been previously reported that racemization of *N*-carbobenzoxy-*S*-benzyl-L-cysteine active esters in organic solvents and in the presence of triethylamine occurs through α-hydrogen abstraction and proceeds with unusual facility.[2-4] It was also reported that the racemization for *N*-carbobenzoxy-*S*-benzyl-L-cysteine pentachlorophenyl ester and *N*-carbobenzoxy-L-phenylalanine pentachlorophenyl ester in a nonpolar solvent proceeds *via* isoracemization.[5,6] In addition the rate of coupling of the cysteine active ester derivatives with L-valine methyl ester was investigated.[3,4] From these data an important conclusion was drawn, that a fast coupling active ester which racemizes relatively slowly is probably the best choice for the synthesis of peptides and sequential polypeptides. Numerically this can be best expressed by the ratio of the rate constants of coupling (k_c) to racemization (k_{rac}); the larger this number, the smaller the racemization to be expected during coupling.

The fast racemization of the commonly used active esters of *N*-carbobenzoxy-*S*-benzylcysteine, as well as the reports of Anderson,[7] Liberek,[8] and others that several amino acid active ester derivatives racemize in the presence of a tertiary base, led us to study the effect of the side chain of amino acids on the rates of racemization and coupling. The results with glutamic and aspartic acids are reported in this paper.

Rates of Racemization of *N*-Carbobenzoxy-γ-methyl-L-glutamic and *N*-Carbobenzoxy-β-methyl-L-aspartic Acid Active Esters.—The racemization of several frequently used active esters of glutamic and aspartic acids was studied in tetrahydrofuran solution in the presence of triethylamine under the conditions described for cysteine active ester derivatives.[4] The results are given in Table I,[9] which contains the pseudo-first-order as well as the second-order racemization rate constants. These values were shown to be true second-order rate constants by carrying out experiments at 1, 7, and 35 equiv of triethylamine/mol of ester.

TABLE I

RACEMIZATION RATE CONSTANTS FOR THE REACTION OF *N*-CARBOBENZOXY-γ-METHYL-L-GLUTAMIC AND *N*-CARBOBENZOXY-β-METHYL-L-ASPARTIC ACID ACTIVE ESTERS WITH TRIETHYLAMINE[a-e]

R of Z–Glu(OMe)–R	$k_{rac} \times 10^6$, sec^{-1}	$k_{rac} \times 10^6$, M^{-1} sec^{-1}
OSu[d]	16.1 ± 2.5	45.0 ± 7.1
OPFP[d]	11.5 ± 1.1	32.2 ± 3.2
OTCP[c](2,4,5)	2.12 ± 0.01	5.93 ± 0.03
ONP[c]	1.08 ± 0.09	3.03 ± 0.27
OPCP[c]	0.701 ± 0.01	1.96 ± 0.04
R of Z–Asp(OMe)–R		
OPFP[c]	87.0 ± 3.2	244 ± 8.9
OTCP[c](2,4,5)	12.6 ± 0.1	35.3 ± 0.27
ONP[c]	9.65 ± 0.8	27.0 ± 2.20
OPCP[c]	6.29 ± 0.33	17.6 ± 0.92

[a] 23 ± 1°, in tetrahydrofuran. [b] The concentration of triethylamine was 0.35 *M*; the concentration of active ester was 0.05 *M*. [c] The average of two experiments. [d] The average of four experiments. [e] The average of five experiments. [f] The OSu ester was not isolated in pure form.

Comparing the second-order racemization rate constant of glutamic and aspartic acid active esters with that of the cysteine active esters, it becomes evident that glutamic acid active esters racemize about 50–100 times and the aspartic acid active esters about 13–23 times slower than the corresponding cysteine active esters. It can be seen that the rate of racemization for both glutamic and aspartic acid active esters decreases in the order OPFP > OTCP > ONP > OPCP. Furthermore, this order is the same as that for the corresponding cysteine active esters,[4] with the exception of *p*-nitrophenyl and pentachlorophenyl esters, which racemize at the same rate in the case of cysteine.

Rates of Coupling of *N*-Carbobenzoxy-γ-methyl-L-glutamic Acid and *N*-Carbobenzoxy-β-methyl-L-aspartic Acid Active Esters with L-Valine Methyl Ester.—The rate of coupling was studied for these amino acid active esters with equimolar amounts of L-valine methyl ester in tetrahydrofuran. The dipeptide coupling products from each active ester were isolated and characterized. The second-order coupling rate constants are given in Table II together with the 99% reaction time. These rate constants were determined by following the disappearance of the active ester

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(9) The following abbreviations have been used: Z = carbobenzoxy; Me = methyl; OSu = *N*-hydroxysuccinimidyl; OPFP = pentafluorophenyl; OTCP(2,4,5) = 2,4,5-trichlorophenyl; OPCP = pentachlorophenyl; ONP = *p*-nitrophenyl.

TABLE II

SECOND-ORDER COUPLING RATE CONSTANTS FOR THE REACTION OF *N*-CARBOBENZOXY-γ-METHYL-L-GLUTAMIC AND *N*-CARBOBENZOXY-β-METHYL-L-ASPARTIC ACID ACTIVE ESTERS WITH VALINE METHYL ESTER[a,b]

R of Z-Glu-R / OMe	$k_c \times 10^2$, M^{-1} sec^{-1}	99% reaction time, hr; active ester concentration 0.13 *M*	0.01 *M*
OPFP[d]	11.6 ± 2.2	1.82	24
OSu[e]	2.70 ± 0.67	7.85	102
OPCP[d]	0.164 ± 0.02	129	1680
OTCP[c](2,4,5)	0.100 ± 0.06	212	2750
ONP[c]	0.045 ± 0.008	470	6110
R of Z-Asp-R / OMe	$k_c \times 10^2$, M^{-1} sec^{-1}	99% reaction time, hr; active ester concentration 0.13 *M*	0.01 *M*
OPFP[c]	14.7 ± 0.9	1.44	19
OPCP[c]	0.737 ± 0.07	28.6	372
OTCP[c](2,4,5)	0.262 ± 0.01	80.8	1050
ONP[c]	0.072 ± 0.008	295	3830

[a] 23° ± 1, in tetrahydrofuran. [b] The concentration of the active ester and valine methyl ester was 0.13 *M*. [c] The average of two experiments. [d] The average of three experiments. [e] The average of five experiments.

carbonyl absorption peak in the infrared region between 5 and 6 μ.

The data presented in this table show that the order of magnitude of the rate constants for both amino acid active esters is comparable with that reported for the corresponding cysteine active esters.[4] In contrast to racemization, the side chain of the amino acid has no significant effect on the rate of coupling. The rate of coupling for all three amino acids investigated decreases with decreasing electron-withdrawing ability of the active ester groups in the following order: pentafluorophenyl > *N*-hydroxysuccimimide > pentachlorophenyl > 2,4,5-trichlorophenyl > *p*-nitrophenyl.

Conclusion

Significance of the Ratio of Coupling and Racemization Rate Constants.—Comparison of the data presented in Tables I and II shows that the decreasing order of the racemization rate constants for the previously discussed active esters is not the same as the decreasing order of the coupling rate constants; this indicates that *the "activity" of an ester is not strictly parallel with its ability to racemize.* This is clearly indicated by the ratio of coupling to racemization rate constants, which is presented in Table III. For the conditions studied these ratios are considered to be important figures, since these numbers indicate the relative extent of racemization which can be expected during coupling by the α-hydrogen abstraction mechanism. The larger this number the smaller the amount of racemization to be expected during coupling. In Table II the times for 99% completion of coupling reactions are also given at two different concentrations of the active esters with 1 equiv of valine methyl ester. The 99% reaction times were calculated using the equation given in the Experimental Section. As the equation indicates, the 99% reaction time is inversely proportional to the initial concentration of the active ester; hence the amount of racemization in concentrated solution should be less extensive.

It is apparent from these data that the extent of racemization by α-hydrogen abstraction expected during coupling increases in the following order: pentafluorophenyl < pentachlorophenyl < *N*-hydroxysuccinimide < 2,4,5-trichlorophenyl < *p*-nitrophenyl esters. This order corresponds to that previously reported for the cysteine active esters.[4]

TABLE III

RATIO OF COUPLING TO RACEMIZATION RATE CONSTANTS[a]

R of Z-Glu-R / OMe	k_c/k_{rac}
OPFP	3590
OPCP	835
OSu	600
OTCP(2,4,5)	170
ONP	150
R of Z-Asp-R / OMe	k_c/k_{rac}
OPFP	1210
OPCP	840
OTCP(2,4,5)	150
ONP	55

[a] In this paper the simple ratio of coupling to second-order racemization rate constants, given in Table I and II, is used. In our previous paper[4] for the calculations of the ratios $^1/_2 k_{rac}$ (k_2) was used.

The influence of the side chain of the amino acid on the extent of racemization during coupling of the above active esters is reflected by the magnitude of k_c/k_{rac}. The decreasing order of k_c/k_{rac} for the three amino acids investigated so far is glutamic acid > aspartic acid > cysteine. For glutamic acid active ester derivatives the ratios are very large and therefore the choice of active ester is not so critical as for cysteine active ester derivatives.

Experimental Section

All melting points are uncorrected and were determined in a Thomas-Hoover melting point apparatus. The kinetics of racemization were studied on a Rudolph photoelectric polarimeter, Model 200S-340-80Q3. Coupling kinetics were studied using a Beckman Model IR-8 spectrophotometer. All kinetic studies were done in a constant-temperature room (23 ± 1°).

Solvents and Reagents.—Gc spectrograde tetrahydrofuran was stored over molecular sieves. Gc Spectrograde triethylamine was stored over sodium. The valine methyl ester was freshly distilled under vacuum.

Preparation of *N*-Carbobenzoxy-γ-methyl-L-glutamic Acid Pentafluorophenyl Ester.—1-Cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate (12.71 g, 30 mmol) and pentafluorophenol (5.52 g, 30 mmol) were dissolved in 200 ml of methylene chloride at room temperature. The solution was cooled at 0° and 8.85 g (30 mmol) of *N*-carbobenzoxy-γ-methyl-L-glutamic acid was added. The reaction mixture was stirred at 0° for 4 hr, washed with 5% sodium bicarbonate, 1 *N* hydrochloric acid, and water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The yellow oil solidified on trituration with hexane at −20°. It was recrystallized from ether–pentane: yield 8.75 g (63%); mp 59–60°; $[\alpha]^{22}D$ −17.4° (c 2.02, ethyl acetate). The infrared spectrum showed the characteristic active ester peak at 5.6 μ (KBr). *Anal.* Calcd for $C_{20}H_{16}NO_6F_5$: C, 52.27; H, 3.48; N, 3.02; F, 20.50. Found: C, 52.06; H, 3.57; N, 3.24; F, 20.31.

The above procedure was used for the preparation of the other active esters described below.

***N*-Carbobenzoxy-γ-methyl-L-glutamic Acid Pentachlorophenyl Esters.**—The crude yellow oily ester was triturated with absolute ethanol, giving a white solid, mp 110–113°, yield 10.2 g (81%). It was recrystallized from hot absolute ethanol: mp 120–121°; $[\alpha]^{22}D$ −15.4° (c 2.01, ethyl acetate); ir (KBr) 5.6 μ (active ester). *Anal.* Calcd for $C_{20}H_{16}NO_6Cl_5$: C, 44.39; H, 3.00;

N, 2.57; Cl, 32.49. Found: C, 44.15; H, 2.89; N, 2.76; Cl, 32.74.

N-Carbobenzoxy-γ-methyl-L-glutamic Acid *N*-Hydroxysuccinimide Ester.—The crude oil was crystallized from hot absolute ethanol and recrystallized twice from the same solvent: yield 8.5 g (70%); mp 107–108°; $[\alpha]^{22}D$ −24.0° (*c* 2, dioxane); ir (KBr) 5.5 μ (active ester). [This ester was prepared by a different method described by Anderson,[10] mp 107–108°, $[\alpha]^{22}D$ −23.3° (*c* 2, dioxane)].

N-Carbobenzoxy-γ-methyl-L-glutamic Acid 2,4,5-Trichlorophenyl Ester.—The crude oil was crystallized from hot absolute ethanol and recrystallized twice from the same solvent: yield 10.5 g (70%); mp 122–123°; $[\alpha]^{22.5}D$ −26.0° (*c* 2, dimethylformamide); ir (KBr) 5.6 μ (active ester). [This ester was prepared by a different method described by Pless and Boissonnas,[11] mp 123°, $[\alpha]^{22}D$ −26.0° (*c* 2, dimethylformamide)].

N-Carbobenzoxy-γ-methyl-L-glutamic Acid *p*-Nitrophenyl Ester.—The crude oil was crystallized from hot absolute ethanol and recrystallized twice from the same solvent: yield 9.6 g (80%); mp 107–108°; $[\alpha]^{22}D$ −32.3° (*c* 1, 95% acetic acid); ir (KBr) 5.6 μ (active ester). [This ester was prepared by a different method described by Klieger and Gibian,[12] mp 107–108°, $[\alpha]^{22}D$ −32.7° (*c* 1, 95% acetic acid)].

N-Carbobenzoxy-β-methyl-L-aspartic Acid Pentafluorophenyl Ester.—The crude oil was crystallized from hot absolute ethanol and recrystallized from the same solvent: yield 10.8 g (80%); mp 80–81°; $[\alpha]^{23}D$ −20.5° (*c* 2, tetrahydrofuran); ir (KBr) 5.6 μ (active ester). *Anal.* Calcd for $C_{19}H_{14}NO_6F_5$: C, 51.02; H, 3.16; N, 3.13; F, 21.24. Found: C, 51.30; H, 3.41; N, 3.27; F, 20.94.

N-Carbobenzoxy-β-methyl-L-aspartic Acid Pentachlorophenyl Ester.—The crude solid was recrystallized twice from hot absolute ethanol to give white crystals: yield 11.5 g (85%); mp 134–135°; $[\alpha]^{22}D$ −23.0° (*c* 2, tetrahydrofuran); ir (KBr) 5.6 μ (active ester). *Anal.* Calcd for $C_{19}H_{14}NO_6Cl_5$: C, 43.59; H, 2.66; N, 2.64; Cl, 33.45. Found: C, 43.46; H, 2.61; N, 2.89; Cl, 33.15.

N-Carbobenzoxy-β-methyl-L-aspartic Acid 2,4,5-Trichlorophenyl Ester.—The crude oil was crystallized from hot 2-propanol and recrystallized from the same solvent: yield 8.1 g (60%); mp 97–98°; $[\alpha]^{22}D$ −34.0° (*c* 2, tetrahydrofuran); ir (KBr) 5.6 μ (active ester). *Anal.* Calcd for $C_{19}H_{16}NO_6Cl_3$: C, 49.54; H, 3.50; N, 3.04; Cl, 23.09. Found: C, 49.66; H, 3.74; N, 3.15; Cl, 22.84.

N-Carbobenzoxy-β-methyl-L-aspartic Acid *p*-Nitrophenyl Ester.—The crude oil was crystallized from chloroform–hexane and recrystallized from the same solvent: yield 7.3 g (60%); mp 105–106°; $[\alpha]^{22}D$ −43.5° (*c* 2, dimethylformamide); ir (KBr) 5.6 μ (active ester). [This ester was prepared by a different method and described by Goodman and Boardman,[13] mp 105–106°, $[\alpha]^{25}D$ −43.7° (*c* 2, dimethylformamide)].

Aminolysis Rate Studies on Active Esters.—Calibration curves of the esters were obtained by measuring the net absorbancies of the active ester peak by the base-line method.[14] A tetrahydrofuran solution which was 0.13 *M* in active ester and 0.13 *M* in valine methyl ester[15] was used to study the aminolysis of all esters. The reactions were followed using a double-beam infrared spectrometer by monitoring the disappearance of the active ester carbonyl band in the 5.6-μ region. A sealed 0.1-mm BaF_2 cell was used for the solutions; a matched BaF_2 cell containing the solvent was in the reference beam. Conformance to Beer's law was checked for all esters studied throughout the pertinent concentration ranges.

For the slower reactions, the spectrum between 5 and 6 μ was scanned periodically throughout the reaction. At least ten data points were taken for each run.

For the faster reactions, the spectrometer was set on the absorbance maximum of the active ester carbonyl peak and the pen excursion at this wavelength was monitored as a function of time.[4] In all cases, the initial reading was taken within 20 sec of mixing. Using this technique, a minimum of ten data points were obtained for each run. The 99% reaction time was calculated using the equation $t_{99\%} = 99/k_c C_E^0$, where k_c = coupling rate constant, C_E^0 = initial ester concentration, and $t_{99\%}$ = time when the coupling reaction is 99% complete. This equation is valid only for the case where the initial concentration of the ester and the amine are identical.

For each active ester when the reaction time reached 90–95% completion the *N*-carbobenzoxy-β-methyl-L-aspartyl-L-valine methyl ester and *N*-carbobenzoxy-γ-methyl-L-glutamyl-L-valine methyl ester dipeptides were isolated and characterized. A typical procedure for the isolation of the dipeptides is illustrated by the preparation of *N*-carbobenzoxy-β-methyl-L-aspartyl-L-valine methyl ester.

N-Carbobenzoxy-β-methyl-L-aspartyl-L-valine Methyl Ester.—A 280-mg portion of *N*-carbobenzoxy-β-methylaspartic acid pentachlorophenyl ester (70 mg/ml, 0.13 *M*) and 68 mg of valine methyl ester (17 mg/ml, 0.13 *M*) were dissolved in 4 ml of tetrahydrofuran. After 14 hr the solvent was removed under vacuum and the residue was triturated with pentane–ether (9:1) to remove the phenol. After standing, the crystalline dipeptide was filtered, washed with pentane–ether (9:1), and dried at 35° over P_2O_5 under vacuum, yield 394 mg (94.6%), mp 72–74°. The crystalline material was dissolved in a minimum amount of hot ether and filtered and then pentane was added to slight turbidity. The recrystallized dipeptide was filtered, washed with pentane–ether (9:1), and dried under vacuum over P_2O_5 for 1 hr: yield 250 mg (64%); mp 73–75°; $[\alpha]^{24}D$ −15.2° (*c* 2, tetrahydrofuran). *Anal.* Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.65; N, 7.10. Found: C, 57.62; H, 6.72; N, 6.93.

N-Carbobenzoxy-γ-methyl-L-glutamyl-L-valine Methyl Ester.—This dipeptide was prepared from *N*-carbobenzoxy-γ-methyl-L-glutamic acid 2,4,5-trichlorophenyl ester and used for analysis. *Anal.* Calcd for $C_{20}H_{28}N_2O_7$: C, 58.82; H, 6.91; N, 6.86. Found: C, 58.60; H, 6.94; N, 6.97.

The procedures used for the coupling of the remaining active esters with valine methyl ester are the same as that described above for *N*-carbobenzoxy-β-methyl-L-aspartyl-L-valine methyl ester. The coupling results for these esters are described in Table IV. All compounds which were not analyzed gave iden-

TABLE IV

RESULTS OF THE COUPLING OF GLUTAMIC AND ASPARTIC ACID ACTIVE ESTER DERIVATIVES WITH VALINE METHYL ESTER[a]

		Dipeptide			
Registry no.	Active ester	Yield, mg (%)	Mp, °C, crude	Mp, °C,[b] recrystd	$[\alpha]^{22}D$, deg (*c* 1, THF)
39993-89-0	Z-Asp(OMe)-OPCP	394 (94)	72–74[c]	73–75	−15.2
39993-91-4	Z-Asp(OMe)-OTCP(2,4,5)	215 (89)	72–73	73–75	−15.0
39993-92-5	Z-Asp(OMe)-OPFP	252 (98)	74–75		−15.1
3330-39-0	Z-Asp(OMe)-ONP	88 (82)	73–75	74–75	−14.8
25613-46-1	Z-Glu(OMe)-OPCP	200 (76)	87–88[d]	89–91	−7.0
39993-96-9	Z-Glu(OMe)-OTCP(2,4,5)	150 (71)	91–92	91–92	−7.5
39993-97-0	Z-Glu(OMe)-OPFP	125 (60)	88–89	89–90	−7.0
5672-80-0	Z-Glu(OMe)-ONP	76 (50)	89–90	90–91	−7.0
39538-31-3	Z-Glu(OMe)-OSu	148 (93)	87–88	89–90	−6.5

[a] The concentration of each active ester and the valine methyl ester was 0.13 *M* in tetrahydrofuran. [b] The recrystallization of all dipeptides was carried out as described for the preparation of Z-(OMe)-Asp-Val-OMe. [c] Registry no., 39993-90-3. [d] Registry no., 4823-98-7.

(10) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **86**, 1839 (1964).

(11) J. Pless and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1609 (1965).

(12) E. Klieger and H. Gibian, *Justus Liebigs Ann. Chem.*, **655**, 195 (1962).

(13) M. Goodman and F. Boardman, *J. Amer. Chem. Soc.*, **85**, 2483 (1963).

(14) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 210.

(15) R. Schwyzer, B. Iselin, H. Kappeler, B. Riniker, W. Rittel, and H. Zuber, *Helv. Chim. Acta*, **41**, 1273 (1958).

tical ir spectra with those of the analyzed dipeptides in both series.

Racemization Rate Studies on Active Esters.—The racemization rate studies were carried out in tetrahydrofuran solution with active ester concentrations of 0.05 *M* and 1, 7, and 35 equiv of triethylamine at 23 ± 1°. The preparation and storage of all solutions for the rate studies using 7 equiv of triethylamine were carried out in a glove bag under a dry nitrogen atmosphere. The racemization experiments with 1 and 35 equiv of triethylamine were performed using anhydrous solutions in the open atmosphere. All kinetics were followed at 589 nm. The first observed rotations were taken within 5 min of mixing the reagents. The pseudo-first-order data for the 7 equiv of triethylamine were plotted and found to be linear up to 90% racemization for all the esters. The second-order rate constants listed in Table I were obtained by dividing the pseudo-first-order rate constants by the triethylamine concentration. An unweighted linear least-squares computer program was routinely used to evaluate all kinetic data.

The second-order racemization rate constants for 1 and 35 equiv of triethylamine were calculated from the initial rates and were identical within experimental error with those obtained from the racemization with 7 equiv of triethylamine.

For the experiments with 1 and 35 equiv of triethylamine, after 95% reaction time the tetrahydrofuran solutions were evaporated under vacuum and the residues were used for racemate identification. The racemized active esters were analyzed using infrared spectroscopy and thin layer chromatography. The residue from the 1-equiv experiments was compared in chloroform solution with the pure L isomer; in all cases the ir spectra of the DL isomers were essentially identical with that of the L isomer. A thin layer chromatogram ($CHCl_3$–MeOH, 9:1) showed the DL compound and a very small amount of phenol which may have resulted from the hydrolysis of the active esters during the course of the experiments. In the case of 35 equiv of triethylamine experiments the thin layer chromatograms indicated more extensive hydrolysis. The extent of hydrolysis seems to be parallel with the reactivity of the ester. This was supported by infrared spectra, which showed the free carboxyl group absorptions.

One racemized active ester from each series was isolated, recrystallized, and characterized by elemental analysis.

Racemized *N*-Carbobenzoxy-γ-methylglutamic Acid Pentachlorophenyl Ester.—The residue from the racemization experiment with 35 equiv of triethylamine was triturated with ether and filtered, mp 118–120°. After two recrystallizations from methanol the compound was dried over P_2O_5 under vacuum at 75° for 2 hr, mp 119–120°, $[\alpha]^{23}D$ 0.00 (*c* 2, ethyl acetate). *Anal.* Calcd for $C_{20}H_{16}NO_6Cl_5$: C, 44.19; H, 2.97. Found: C, 43.70; H, 2.97.

Racemized *N*-Carbobenzoxy-β-methylaspartic Acid Pentachlorophenyl Ester.—This ester was isolated similarly to the glutamic acid active ester which is described above. The crude compound, mp 125–126°, was recrystallized from methanol–water and a second time from methanol–ether, mp 122–124°, $[\alpha]^{23}D$ −0.9 (*c* 2, tetrahydrofuran). *Anal.* Calcd for $C_{19}H_{14}NO_6Cl_5$: C, 43.09; H, 2.66. Found: C, 42.71; H, 2.78.

Registry No.—*N*-Carbobenzoxy-γ-methyl-L-glutamic acid, 4652-65-7; *N*-carbobenzoxy-β-methyl-L-aspartic acid, 3160-47-2; triethylamine, 121-44-8; valine methyl ester, 4070-48-8; 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate, 4641-47-8; pentafluorophenol, 771-61-9; *N*-carbobenzoxy-γ-methylglutamic acid pentachlorophenyl ester racemate, 39994-03-1; *N*-carbobenzoxy-β-methylaspartic acid pentachlorophenyl ester racemate, 39994-04-2.

Acknowledgment.—This work was supported by Grant No. GM-08795 from the National Institutes of Health.

Reactions of *tert*-Butyl Trimethylsilyl Carbonate and of Bistrialkylsilyl Carbonates with Amino Acids. Carbon-13 Chemical Shifts in Carbonates and Silyl Carbonate Derivatives

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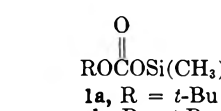
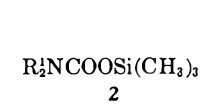
Received February 1, 1972

A number of bistrialkylsilyl carbonates, $R_3SiOC(=O)OSiR_3'$, have been prepared. The recently described *tert*-butyl trimethylsilyl carbonate (1a) has been shown to react with α-amino acid esters to form the corresponding silylurethanes, $RC(NHCOOR')HCOOR''$, where $R' = Si(CH_3)_3$. Under more drastic conditions, the completely silylated amino acid derivatives are formed. All of the silylated derivatives are hydrolyzed by moist ether to the parent amino acids or esters; with L-tyrosine, complete silylation followed by hydrolysis with moist ether regenerates the L-tyrosine, with no evidence of racemization. Bistriethylsilyl carbonate (**3c**) and *tert*-butyl triethylsilyl carbonate (**1b**) yield the same silylurethane from glycine ethyl ester. ^{13}C chemical shifts have been measured, and assignments of chemical shifts to specific types of carbon have been made for a series of carbonate esters, di- and tricarbonates, silyl carbonates, and *t*-BOC and other urethanes derived from glycine ethyl ester. As the number of carbonate groups in the molecule increases, the chemical shifts of the carbonyl carbons move to higher field. The presence of sulfur (in place of oxygen) next to the carbonyl carbon moves its chemical shift downfield ~16–18 ppm. Other regularities are noted.

Recently[1] we described the preparation of *tert*-butyl trimethylsilyl carbonate (**1a**) and related compounds;



1a, R = *t*-Bu
b, R = *t*-Bu, $Si(C_2H_5)_3$ instead of $Si(CH_3)_3$



2

it was shown that amines attacked **1a** to form the corresponding silylurethanes, $R_2^1NCOOSi(CH_3)_3$, rather than the carbon urethanes (*t*-BOC derivatives), $R_2NCOOC(CH_3)_3$. Acid chlorides, however, attacked **1a** to form anhydrides, such as $ROC(=O)OC(=O)R^1$ (R = *t*-Bu, $R^1 = CH_3$ or OC_2H_5), presumably with the elimination of $ClSi(CH_3)_3$.

The present paper describes the reaction of **1a** with amino acids or their esters to form silylated derivatives analogous[2] to **2**. In a companion study in this labora-

(1) Y. Yamamoto and D. S. Tarbell, *J. Org. Chem.*, **36**, 2954 (1971).

(2) Similar silylated derivatives of amino acids, prepared in other ways, have been reported by H. R. Kricheldorf, *Synthesis*, 259 (1970); *Justus Liebigs Ann. Chem.*, **748**, 101 (1971); and earlier papers. Silylation of several amino acids by bis(trimethylsilyl)trifluoroacetamide for vpc analysis is reported by K. Bergstrom and J. Gurtler, *Acta Chem. Scand.*, **25**, 175 (1971), and references cited therein.

TABLE I

BISTRIALKYLSILYL CARBONATES, $RSiOC(=O)OSiR^1$

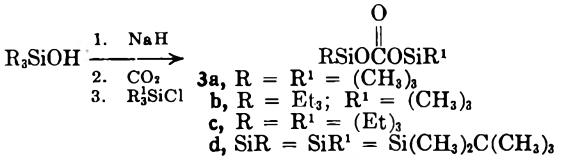
Compd[a]	Bp, °C (mm)	Yield, %	Ir, C=O (neat), cm^{-1}	Nmr (CCl_4), ppm
3b, R = $(CH_3)_3$; R^1 = $(C_2H_5)_3$	79–82 (3)	81	1705 1740	0.28 (s) 0.5–1.4 (m, A_3B_2)
3c, R = R^1 = $(C_2H_5)_3$	86–87 (1)	63	1705 1740	0.5–1.25 (m, A_2B_3)
3a, R = R^1 = $(CH_3)_3$	mp 26–30		1705, 1740 in CCl_4	0.28 (s)
3d, SiR = SiR^1 = $Si(CH_3)_2C(CH_3)_3$	90 (3), mp 60–63		1705 1735	0.25 (s), 0.93 (s) ratio 2:3

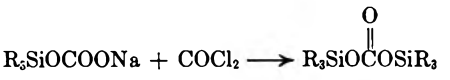
[a] All compounds showed C and H analyses within 0.4% of calculated values, except for R = R^1 = $(CH_3)_3$, which, in spite of several trials, showed carbon 0.5% away.

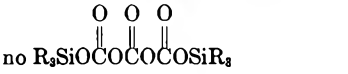
tory, it has been found that the recently available[3] di-*tert*-butyl dicarbonates react smoothly with amino acid esters to form the corresponding urethanes, $R^1CH(NHCOOR)COOEt$ or $R^1CH(NHCOSR)COOEt$ (R = *t*-Bu).[4]

We have also prepared some bistrialkylsilyl carbonates **3**, as shown in Table I, and have examined one of them as a silylating agent.

Compounds in Table I were prepared as follows.







The action of the *tert*-butyl trialkylsilyl carbonates (**1a**, **1b**) and of the bistriethylsilyl carbonate **3c** on several amino acids and amino acid esters yielded the results shown in Table II. The free tyrosine was insoluble in the silyl carbonate; heating at 100° gave gradual reaction and solution, leading to the completely silylated derivative[2] of tyrosine. Glycine ethyl ester was very readily silylated, once on nitrogen, to form the urethane analog, $N(CH_2COOEt)HCOOSi(CH_3)_3$, under mild conditions with a trace of tertiary base; the ethyl ester group and the NH group are unaltered by this treatment.

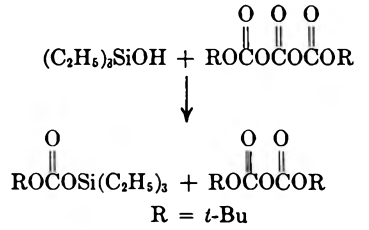
The reaction of *tert*-butyl trimethylsilyl carbonate with 4-hydroxy-L-proline showed that an alcohol group could be silylated as easily as a phenolic OH.

The reactions with valine and serine show the low reactivity of the hydrogen on the carbamate nitrogen or perhaps the sensitivity of the N–Si bond formed. In the case of valine no silylation of the nitrogen was observed. It is unlikely that it was decomposed on heating, since the tyrosine compound survived distillation at a much higher temperature. It is unlikely that only the N–Si bond would be completely hydrolyzed and none of the other positions affected, particularly since every precaution was taken to avoid exposure to water. The nmr of the serine derivative suggested that about 25% of the compound was not substituted on the N–H. This may have been due to fast hydrolysis or incomplete reaction.

The reason for the unreactivity of the valine NH is not evident. It might be due to the increased steric hindrance of the isopropyl group.

The completely silylated compounds were hydrolyzed very rapidly, even by shaking with moist ether at room temperature. The silylated derivative prepared from L-tyrosine was hydrolyzed in this way to regenerate tyrosine of rotation identical with that of starting material, and therefore no racemization had occurred during silylation or hydrolysis.

Treating triethylsilanol with di-*tert*-butyl tricarbonate led to the mixture shown below, as indicated by ir and nmr spectra. Attempts to convert triethylsilano



to the corresponding tricarbonate, $R_3SiOCOOCOO-COOSiR_3$, by sodium hydride, CO_2, and $COCl_2$, in the usual way[3] gave a mixture, probably containing some of the tricarbonate, and more of the *tert*-butyl trialkylsilyl monocarbonate, as judged from the ir.

^{13}C Nmr Chemical Shifts in Mono-, Di-, and Tricarbonates and in Silyl Carbonates.—The availability of samples of fairly complete series of these compounds, resulting from this and earlier work in this laboratory,[1,3] allowed the determination of the ^{13}C chemical shifts of the carbons, including the carbonyl carbons in varied environments. The results are shown in Table III; because not all of the compounds measured are described in the present paper, the structural formulas in the tables are numbered with Roman numerals to facilitate discussion of the trends observed.

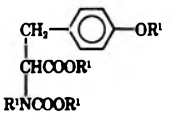
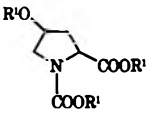
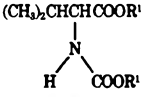
Discussion of ^{13}C Chemical Shifts.—The carbonate carbonyls absorb at the high-field end of the carbonyl region of the ^{13}C nmr spectrum. As the number of carbonate groups in the molecule increases, the chemical shifts of the carbonyl carbons move to higher field (compounds I, III, and VI, carbons c and d). The presence of sulfur in place of oxygen next to the carbonyl carbon drives its chemical shift downfield about 16–18 ppm (compounds IV, V, VII, and X, carbon c); however, the chemical shift of a carbonyl carbon one position removed from the sulfur (compounds IV, VII, and X, carbon d) moves slightly upfield. A nitrogen in place of the oxygen (compound XV,

(3) C. S. Dean, D. S. Tarbell, and A. W. Friederang, *J. Org. Chem.*, **35**, 3393 (1970).

(4) D. S. Tarbell, Y. Yamamoto, and B. M. Pope, *Proc. Nat. Acad. Sci. U. S.*, **69**, 730 (1972).

Table II

Reactions of Silyl Carbonates with Amino Acids

Silylating agent (R = *t*-Bu)	Amino acid	Registry no.	Condition	Product,[c] R¹ = $Si(CH_3)_3$	Registry no.	Yield, %	Ir, C=O (neat), cm^{-1}
$ROCOOSi(CH_3)_3$	Gly	56-40-6	*a*	CH_2COOR^1 *d* R^1NCOOR^1	27762-05-6	89	1735, 1690
$ROCOOSi(CH_3)_3$	Tyr	60-18-4	*a*		40088-31-1	63	1730, 1690
$ROCOOSi(CH_3)_3$	Hypro	51-35-4	*a*		40088-32-2	78	1725, 1690
$ROCOOSi(CH_3)_3$	Val	72-18-4	*a*		40088-33-3	66	1680–1710 (broad)
$ROCOOSi(CH_3)_3$	Ser	56-45-1	*a*	$R^1OCH_2CHCOOR^1$ *e* N R^1 $COOR^1$	40088-34-4	72	1685–1720 (broad)
$ROCOOSi(CH_3)_3$	Gly OEt	459-73-4	*b*	$CH_2COOC_2H_5$ $NHCOOR^1$	39982-07-5	82	3380 (NH), 1740–1760, 1680–1720
$ROCOOSi(C_2H_5)_3$	Gly OEt		*b*	$CH_2COOC_2H_5$ $NHCOOSi(C_2H_5)_3$	39982-08-6	84	3370 (NH), 1745, 1690
$(C_2H_5)_3SiOCOOSi(C_2H_5)_3$	Gly OEt		*b*	$CH_2COOC_2H_5$ $NHCOOSi(C_2H_5)_3$		84	3370 (NH), 1745, 1690

[a] Heated at 100° for *ca.* 16 hr. [b] Treated with a trace of Et_3N in ether at reflux or room temperature for 30 min. [c] Compounds were purified by distillation and showed satisfactory C and H analyses. The nmr spectra were in agreement with the expected values, and showed expected splitting patterns. [d] This compound was reported, along with some analogs, by H. R. Kricheldorf, *Synthesis*, 259 (1970), prepared by a different method. [e] The analogous DL-serine compound has been reported by H. R. Kricheldorf, ref *d* above.

carbon e) also drives the chemical shift to lower field. A carbonyl carbon with a nitrogen and a sulfur attached (compound XVI, carbon e) has a chemical shift in the same region as that with sulfur and oxygen attached. However, replacement of the *tert*-butyl groups with trialkylsilyl groups (compounds XII, carbon d, and XIII, carbon e) has only a very minor effect upon the chemical shift of the carbonyl carbon. Maciel[5] attributes the shifts to higher field upon attachment of more electronegative groups to the carbonyl carbon to a change in the π bond polarity of the carbonyl group owing to withdrawal of electrons from the carbonyl oxygen.

The chemical shifts of the *tert*-butyl carbons do not yield any unexpected results. The central carbon attached to oxygen is more deshielded than that attached to sulfur, as would be expected from the electronegativities of the two atoms. The outer carbons are rather insensitive to the structure of the rest of the molecule.

Experimental Section[6]

***tert*-Butyl triethylsilyl carbonate (1b)** was prepared from potassium *tert*-butylcarbonate and triethylchlorosilane by the method described earlier for the trimethylsilyl compound[1] **1a**, in 58% yield: bp 62–64° (1 mm); ir (CCl_4) 1755, 1720 cm^{-1} (C=O); nmr (CCl_4) 1.43 (s, 9 H), 0.6–1.35 ppm (m, 5 H, C_2H_5).

Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.60; H, 10.21.

Triethylsilyl Trimethylsilyl Carbonate (3b).—A 50% dispersion of sodium hydride (0.55 g) was washed with three 10-ml portions of THF and suspended in 30 ml of THF. To the suspension was added dropwise a solution of triethylsilanol[7] (1.38 g) in THF (20 ml) with stirring at room temperature; stirring was continued for an additional 45 min. Dry CO_2 gas was then passed for 30 min into the mixture, cooled with an ice–salt bath. A solution of chlorotrimethylsilane (1.09 g) in THF (15 ml) was added dropwise. Stirring and cooling were continued for 30 min more. An insoluble material was filtered off. The solvent was removed at room temperature, and distillation of the residual liquid gave a colorless liquid (2 g, 81%), bp 79–82° (3 mm).

Anal. Calcd for $C_{10}H_{24}O_3Si_2$: C, 48.34; H, 9.74. Found: C, 48.64; H, 9.72.

The other compounds in Table I were prepared by similar procedures. The bistrimethylsilyl carbonate decomposed on attempted distillation.

Complete Silylation of Tyrosine (Table II, Method A).—A mixture of 2.9 g (0.015 mol) of *tert*-butyl trimethylsilyl carbonate (1a) and 0.45 g (0.0025 mol) of L-tyrosine (99+%, Aldrich, used without purification) was heated at 90–100° (bath temperature) for 16 hr with stirring. Distillation of the reaction mixture gave a colorless, viscous liquid, bp 146–150° (0.3 mm), 0.8 g (63% based on tyrosine). Its properties were ir (liquid film) 1730, 1690 cm^{-1} (C=O); nmr (CCl_4) singlets of $Si(CH_3)_3$ groups at 0.11, 0.35, 0.38, and 0.41, a multiplet of $-CHCH_T-$ at 2.7–3.9, and four aromatic protons at 6.7–7.16 ppm.

Anal. Calcd for $C_{22}H_{43}O_5NSi_4$: C, 51.42; H, 8.43; N, 2.72. Found: C, 51.77; H, 8.63; N, 2.97.

Hydrolysis of silylated tyrosine was carried out by dissolving 0.75 g of the silylated compound in 30 ml of moist ether and stirring for 30 min at room temperature. The solvent was evaporated and the residue was dried at reduced pressure by an aspirator. The residual solid (0.3 g) was dissolved in 5 ml of 1 *N* HCl, and the insoluble material (possibly a polymer of silicone compound) was removed by filtration. The clear layer was

(5) G. E. Maciel, *J. Chem. Phys.*, **42**, 2746 (1965).

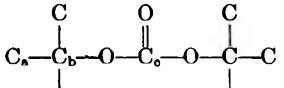
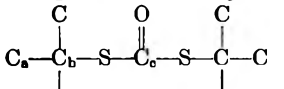
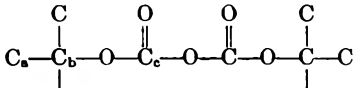
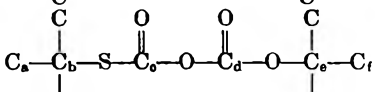
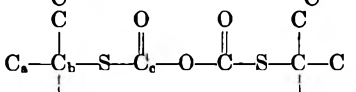
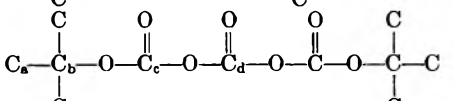
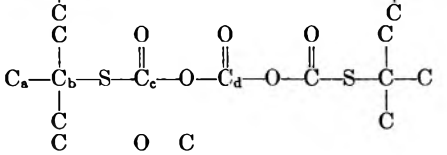
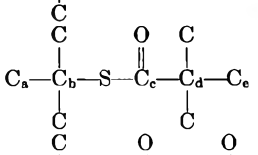
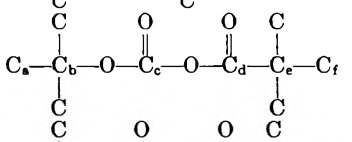
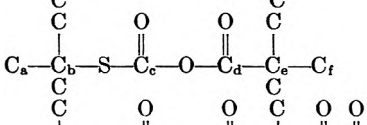
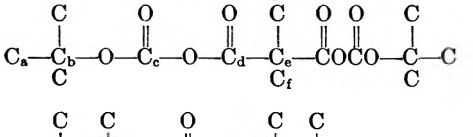
(6) Instrumentation was as reported in earlier studies;[3] microanalyses were by Galbraith Laboratories.

(7) L. H. Sommer and L. J. Tyler, *J. Amer. Chem. Soc.*, **76**, 1030 (1954).

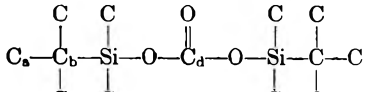
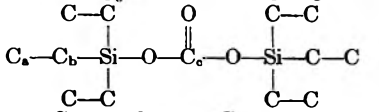
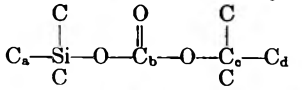
TABLE III

CHEMICAL SHIFTS OF ^{13}C FROM CS_2

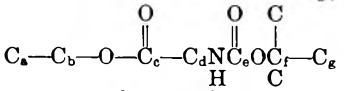
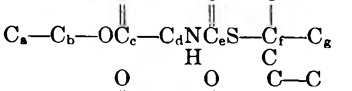
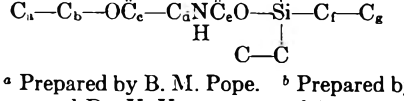
A. Carbonates, Esters, and Carbonic Anhydrides

Compd	No.	C_a	C_b	C_c	C_d	C_e	C_f	
	I	164.9	113.2	40.4				
	II	162.4	142.5	3.9				
	III[a]	164.8	108.0	45.8				
	IV[c]	163.0	144.5	28.3	46.6	107.7	165.2	
	V	163.5	144.0	28.8				
	VI[a]	165.5	105.7	48.1	49.0			
	VII	163.2	142.3	30.2	50.7			
	VIII[b]	162.2	145.5 or 146.0	−12.5	145.5 or 146.0	164.6		
	IX[b]	165.0 or 165.8	108.2	44.7	16.5	157.4	165.0 or 165.8	
	X[b]	162.9	144.2	28.4	20.5	152.5	165.8	
	XI[c]	165.2	107.2	46.8	26.1	141.9	171.2	

B. Silyl Carbonates

	XII	166.8	174.6	197.2	41.4			
	XIII	186.2	188.0	41.4				
	XIV	191.5	41.8	112.0	163.2			

C. *t*-BOC and Other *N*-Acyl Derivatives of Glycine Ethyl Ester

	XV[d]	178.7	132.0	22.7	150.0	37.1	115.6	162.5
	XVI[d]	178.8	131.7	23.7	150.5	25.5	145.3	162.0
	XVII[d]	178.7	131.9	22.9	149.7	37.6	187.8	186.1

[a] Prepared by B. M. Pope. [b] Prepared by R. L. Stanley. [c] Prepared by Dr. Y. Yamamoto, unpublished work. [d] Prepared by B. M. Pope and Dr. Y. Yamamoto, ref 4.

neutralized with 10% $NaHCO_3$. The precipitate formed was taken up by filtration, washed with a small amount of cold water, and dried over P_2O_5 at 56° *in vacuo;* 0.15 g of colorless solid, which decomposed at 309–312°, was obtained. Its optical rotation was $[\alpha]^{25}D$ −9.8° (*c* 4, 1 *N* HCl). L-Tyrosine used as starting material decomposed at 310–312° and its optical rotation was $[\alpha]^{25}D$ −10.0° (c 4, 1 *N* HCl).

The completely silylated glycine was likewise hydrolyzed to glycine, identified as hippuric acid.

Action of *tert*-Butyl Trimethylsilyl Carbonate with Glycine Ethyl Ester. Method B.—A solution of 2.8 g (0.0147 mol) of *tert*-butyl trimethylsilyl carbonate (1a), 1.5 g (0.0147 mol) of glycine ethyl ester, and 3 drops of Et_3N in 30 ml of dry ether was refluxed for 30 min. The reaction mixture was evaporated at reduced pressure by an aspirator and distilled. A colorless liquid, bp 86–87° (0.6 mm), 2.6 g (82%), was obtained with the following properties: ir (liquid film) 3380 (NH, broad), 1740–1760 (C=O), 1680–1720 cm^{-1} (C=O, broad); nmr (CCl_4) 0.28 [s, $Si(CH_3)_3$], 1.29 (t, $-CH_2CH_3$, J = 7.5 Hz), 4.17 (q, $-CH_2CH_3$, J = 7.5 Hz), 3.8 (d, NCH_2C, J = 6 Hz), 5.7 ppm (broad, NH). The ratios of protons were correct.

Anal. Calcd for $C_8H_{17}O_4NSi$: C, 43.81; H, 7.81; N, 6.39. Found: C, 44.03; H, 7.74; N, 6.33.

Hydrolysis of *N*-Trimethylsiloxycarbonyl Glycine Ethyl Ester to Glycine Ethyl Ester.—To a solution of 1.5 g of *N*-trimethylsiloxycarbonyl glycine ethyl ester in 20 ml of ether was added 0.5 ml of water with stirring at room temperature. Subsequently $MgSO_4$ was added, filtered off, and washed well with ether. The filtrate was combined with washings and evaporated. Distillation of the residual-liquid gave 0.5 g (83%) of glycine ethyl ester, bp 46–48° (10 mm), of which the ir spectrum (liquid film) and the nmr spectrum were identical in all respects with those of an authentic sample.

It was confirmed that the filtrate contained hexamethyldisiloxane, $(CH_3)_3SiOSi(CH_3)_3$, by vpc.

Action of *tert*-Butyl Trimethylsilyl Carbonate with L-4-Hydroxyproline (Method A).—A mixture of 2.9 g (0.015 mol) of *tert*-butyl trimethylsilyl carbonate and 0.3277 g (0.0025 mol) of L-4-hydroxyproline was treated as in the tyrosine case. Distillation gave a colorless liquid, bp 111° (0.1 mm), 0.7595 g (78%), with the following properties: ir (liquid film) 1690 and 1725 cm^{-1} (C=O, broad); nmr ($CDCl_3$) 0.12 (s, 9 H), 0.27 and 0.29 (two s, 9 H) and 0.30 (s, 9 H) [$Si(CH_3)_3$], 2.16 (m, 2 H ring protons, 3 position), 3.62 (m, 2 H ring protons, 5 position), 4.5 ppm (m, 2 H, ring protons, 2 and 4 positions).

Anal. Calcd for $C_{15}H_{33}NO_5Si_3$: C, 46.00; H, 8.49. Found: C, 45.84; H, 8.33.

Action of *tert*-Butyl Trimethyl Carbonate with L-Valine (Method A).—A mixture of 2.9 g (0.015 mol) of *tert*-butyl trimethylsilyl carbonate and 0.2907 g (0.00248 mol) of L-valine was treated as in the tyrosine case. Distillation gave a colorless liquid, bp 90° (1.2 mm), 0.4982 g (66%), with the following properties: ir (liquid film) 3330 (NH, broad), 1680–1710 cm^{-1} (C=O, broad); nmr ($CDCl_3$) 0.26 (s, 9 H), 0.28 (s, 9 H) [$Si(CH_3)_3$], 0.94 (d, 3 H, J = 7 Hz), 1.01 [d, 3 H, J = 7 Hz, $CH(CH_3)_2$], 2.10 [m, 1 H, $CH(CH_3)_2$], 4.28 (pair of d, 1 H, J = 4 and 9 Hz, α proton), 5.34 ppm (d, 1 H, J = 9 Hz, NH).

Anal. Calcd for $C_{12}H_{27}NO_4Si_2$: C, 47.18; H, 8.91. Found: C, 47.13; H, 8.89.

Action of *tert*-Butyl Trimethylsilyl Carbonate with L-Serine (Method A).—A mixture of 2.9 g (0.015 mol) of *tert*-butyl trimethylsilyl carbonate and 0.2621 g (0.0025 mol) of L-serine was treated as in the tyrosine case. Distillation gave a colorless liquid, bp 117° (0.5 mm), 0.7835 g (72%), with the following properties: ir (liquid film) 3440 (NH, weak), 1685–1720 cm^{-1} (C=O, broad); nmr ($CDCl_3$) 0.08 (s, 9 H), 0.23, 0.24, 0.26, and 0.30 (all s, 27 H) [$Si(CH_3)_3$], 4.06 (m, 3 H, α and β protons), 5.68 (d, J = 9 Hz, 1/4 H, NH).

Anal. Calcd for $C_{16}H_{39}NO_5Si_4$: C, 43.90; H, 8.98. Found: C, 43.60; H, 8.67.

Determination of ^{13}C Chemical Shifts.—The nmr spectra were taken on a Varian XL-100-15 spectrometer locked on deuteriobenzene. Except where the diluteness of the solution required accumulation, all of the spectra were single scan spectra taken with heteronoise decoupling of the protons. All of the spectra were taken in perdeuteriobenzene solution. The concentrations depended upon the availability of the compounds and their solubility in benzene. The chemical shifts were measured from deuteriobenzene and converted to parts per million from carbon disulfide by the equation[8]

$$S_{benzene} - S_{CS_2} = 65.0 \text{ ppm}$$

Assignments were made by comparison of spectra in the above series, along with data from the literature.

Registry No.—**1a,** 30882-87-2; **1b,** 39981-88-9; **3a,** 39981-89-0; **3b,** 39981-90-3; **3c,** 37170-06-2; **3d,** 39981-92-5; I, 34619-03-9; II, 16118-32-4; III, 24424-99-5; IV, 39981-96-9; V, 22085-40-1; VI, 24424-95-1; VII, 22085-39-8; VIII, 28058-96-0; IX, 39982-01-9; X, 28058-95-9; XI, 39982-03-1; XII, 14719-37-0; XVI, 37787-80-7; XVII, 39982-08-6; potassium *tert*-butyl carbonate, 39982-09-7; triethylchlorosilane, 994-30-9; triethylsilanol, 597-52-4; chlorotrimethylsilane, 75-77-4.

(8) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1966, p 1003.

Stereoselective Organometallic Alkylation Reactions. II. Organomagnesium and Organoaluminum Addition to Ketones Having Varied Steric Requirements. A New Concept of Stereochemical Control[1]

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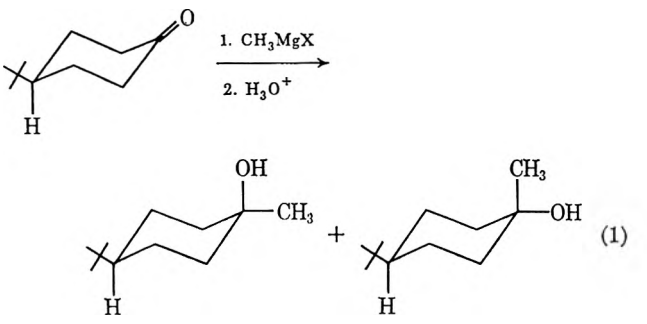
Received November 14, 1972

The stereochemistry of organoaluminum and organomagnesium addition to several ketones has been investigated. Alkylation occurred from the least hindered side of the molecule in all cases studied with organoaluminum and organomagnesium compounds in diethyl ether as well as with organoaluminum compounds in a 1:1 reactant ratio in benzene. However, when the organoaluminum compound to ketone ratio was 2:1 or greater in benzene solvent, a significant and often predominant percentage of the product resulted *via* alkylation from the most hindered side of 2-methylcyclopentanone, 4-*tert*-butylcyclohexanone, and 3,3,5-trimethylcyclohexanone. We conclude that the reversal of stereochemistry in these cases is due neither to the fundamental nature of four- and six-center transition states nor to a conformational change in the complexed ketone but to a compression of the complexed carbonyl group in a six-center transition state against the 2,6-diequatorial hydrogens in the cyclohexanone cases and against the 2-methyl group in the 2-methylcyclopentanone case. In those ketones in which product ratios are dependent on reactant ratios, the "compression effect" opposes the "steric approach factor." When the organoaluminum compound to ketone ratio is 2:1 or greater in benzene solvent, results with norcamphor, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone are nearly identical with those found with a 1:1 reactant ratio. In these ketones the "compression effect" is either nonexistant owing to equivalent substituents on carbon atoms adjacent to the carbonyl or reinforces the "steric approach factor." Further evidence against a conformational change from the chair form of 4-*tert*-butylcyclohexanone to the half-chair of the ketone–aluminum alkyl complex to explain the change in stereochemistry is provided by a nmr analysis of the spectra of 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3 and the corresponding complex with $AlCl_3$. Both spectra indicate clearly the presence of axial and equatorial hydrogens in the 2,6 positions indicating that the complex is not in the half-chair conformation. The concepts of "steric approach control" and "torsional strain" do not provide a satisfactory explanation for the observed stereochemistry; however, the proposed "compression effect" does provide a satisfactory explanation of the observed stereochemistry in this study as well as all other studies involving organometallic alkylation reactions with which we are familiar.

Early concepts concerning factors involved in the stereochemistry of reduction of cyclic ketones were formulated by Dauben.[2] "Steric approach control" assumed an early, reactant-like transition state in which the entering group approached the least hindered side of the ketone. "Product development control" assumed a late, product-like transition state in which the observed stereochemistry reflected the stability of the products. In the absence of significant steric factors involving the attacking reagent on the substrate, "product development control" determined the observed stereochemistry.

Competitive rate experiments involving reduction of several cyclohexanones have demonstrated that the rate of axial attack is greatly reduced when the axial hydrogen at C-3 and/or C-5 is replaced by an axial methyl group, whereas the rate of equatorial attack remains essentially constant.[3] Thus, factors other than "product development control" appear to influence stereochemistry.

One of the first comprehensive studies concerning the steric course of alkylation of cyclic ketones by organometallic compounds was reported by Houlihan.[4] Methyl Grignard reagents were allowed to react with 4-*tert*-butylcyclohexanone in diethyl ether to yield the 4-*tert*-butyl-1-methylcyclohexanols (eq 1). With all reagents studied the axial alcohol was always formed in 50% or greater yield. Thus, attack was found to occur predominantly at the least hindered side of the carbonyl group, the equatorial side.



(1)

axial alcohol equatorial alcohol

Chérest and Felkin[5] considered the stereoselectivity of alkylation of cyclohexanones (chair conformation) to be influenced by two factors: (1) the steric strain of the incoming group with the 3,5-axial substituents and (2) the torsional strain (single bond repulsion) of the incoming group with the 2,6-axial substituents. The two effects oppose each other; steric strain hinders axial attack whereas torsional strain hinders equatorial attack. The actual stereochemistry of alkylation depends upon which effect is greater in a particular case. They suggest that for a cyclohexanone derivative with no axial substituent larger than hydrogen small entering groups (hydride) are opposed more strongly by torsional strain and therefore attack occurs predominantly from the axial side, whereas larger groups (methyl, ethyl, etc.) are opposed more strongly by steric strain and attack occurs predominantly from the equatorial side.[6] If the cyclohexanone contains one or more large axial substituents (methyl, ethyl, etc.) at the 3 or 5 positions, steric strain is highly important regardless of the size of the incoming group.

(1) We are indebted to the National Science Foundation (Grant No. GP-31550X) for partial support of this work.

(2) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(3) E. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1960).

(4) W. J. Houlihan, *J. Org. Chem.*, **27**, 3860 (1962).

(5) M. Chérest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).

(6) (a) M. Chérest, H. Felkin, and C. Frajerman, *ibid.*, 379 (1971); (b) M. Chérest and H. Felkin, *ibid.*, 383 (1971).

An apparent exception to the Chérest and Felkin concept[5,6] occurs when trimethylaluminum is allowed to alkylate 4-*tert*-butylcyclohexanone in 2:1 ratio in hydrocarbon solvent.[7] Reaction of 4-*tert*-butylcyclohexanone with 1 equiv of $(CH_3)_3Al$ in benzene solvent gives predominantly equatorial attack (~70%) as predicted, but reaction with 2 or more equiv of trimethylaluminum gives predominantly axial attack (~90%).

Earlier we reported[8] that the reaction of $(CH_3)_3Al$ and benzophenone in a 1:1 ratio results in a transition state describing the rate-determining step as containing one molecule of $(CH_3)_3Al$ and one molecule of ketone. The reaction occurs through the formation of a complex followed by formation of a four-center transition state. On the other hand, when $(CH_3)_3Al$ and benzophenone were allowed to react in a 2:1 or greater ratio, it was found that the transition state describing the rate-determining step contains two molecules of $(CH_3)_3Al$ and one molecule of ketone. The mechanism of this reaction is envisioned as attack of a molecule of $(CH_3)_3Al$ on the 1:1 complex, possibly *via* a six-center transition state, to form the product. In light of the fact that two different mechanisms are operating in these two cases,[8] it is not surprising to find a difference in the stereochemistry; however, such a dramatic change in the stereochemistry was surprising.

Close scrutiny of molecular models depicting four- and six-center transition states do not readily reveal the reason for the unusual stereochemistry found in the reaction of $(CH_3)_3Al$ and 4-*tert*-butylcyclohexanone in hydrocarbon solvent. From a steric point of view, axial attack on a chair conformation should be hindered by the 3 and 5 axial substituents regardless of whether the transition state is four or six center. It is conceivable that cyclohexanones complexed to aluminum alkyls exist in conformations other than chairs, or other factors, not yet considered, might be important. In order to resolve the speculation surrounding this unusual stereochemical observation, a comprehensive study of the reaction of aluminum alkyls and aryls with several ketones was undertaken. In most cases the organomagnesium compounds with corresponding alkyl or aryl groups were also studied for comparison purposes. In addition, an nmr study of 4-*tert*-butylcyclohexanone and 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3 (axial 3-D) and their aluminum chloride complexes was undertaken in order to obtain evidence for the preferred conformation of these species in solution.

Experimental Section

Materials.—Trimethylaluminum and triethylaluminum were obtained from Texas Alkyls, Inc., and distilled through a 1-ft glass helix packed column prior to use. Triphenylaluminum was prepared and purified by the method of Eisch,[9] mp 240–241° (lit.[9] mp 240–242°). Grignard reagents were prepared by methods reported in detail elsewhere.[10]

2-Methylcyclopentanone, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone, obtained from Chemical Samples Co., were dried over activated 4-A molecular sieve prior to use. 3,3,5-Trimethylcyclohexanone, obtained from Chemical Samples Co., was distilled under nitrogen prior to use. Norcamphor (Aldrich Chemical Co.) and 4-*tert*-butylcyclohexanone (Frinton Lab.) were sublimed prior to use. Analysis of all ketones by glpc showed each of them to be at least 98% pure.

Fisher reagent grade anhydrous aluminum chloride was sublimed under nitrogen at 200°.

4-*tert*-Butylcyclohexanone-*cis*-3,5,5-d_3 (axial 3-D) was obtained from 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3 oxime[11] by cleavage with sodium bisulfite followed by hydrolysis with dilute HCl.[12] The reaction progress was followed by glpc.

Fisher certified anhydrous diethyl ether was distilled from $LiAlH_4$ prior to use. Fisher certified thiophene-free benzene was distilled from $NaAlH_4$ prior to use.

Apparatus and Procedure.—A Varian A-60D, 60 MHz spectrometer was used for recording nuclear magnetic resonance spectra. An F & M Model 720 gas chromatograph was used to identify all reaction products. Transfers of materials used in this study were performed in a glove box described elsewhere[13] or were transferred in Schlenk tubes under a blanket of high-purity nitrogen.

Calibrated syringes equipped with stainless steel needles were usef for transfer of reagents. Deliveries could be reproduced to better than ±0.5%.

Solutions of ketones were prepared by weighing out a known amount of ketone in a calibrated volumetric flask and diluting to the mark with an appropriate solvent.

Solutions of organoaluminum compounds and Grignard reagents were prepared by diluting known amounts of the standard reagents with an appropriate solvent. In the case of Grignard reagents, magnesium analysis was carried out by EDTA titration of a hydrolyzed aliquot at pH 10 using Eriochrome Black T as an indicator. The concentrations of organoaluminum solutions were determined by hydrolysis of an aliquot followed by aluminum analysis which was carried out by EDTA–zinc acetate titration at pH 4 using dithizone as an indicator.

Reactions.—All reactions were carried out on a vacuum manifold equipped with three-way glass stopcocks attached to 24/40 inner joints. Round-bottom flasks equipped with 24/40 outer joints were attached to the manifold and the system was evacuated, flamed, and refilled with nitrogen three times prior to use.

In the case where a 1:1 ratio of organoaluminum compound to ketone in benzene was desired, an appropriate amount of ketone was added to the flask under nitrogen flush followed by injection of the correct amount of organoaluminum reagent. This mode of addition ensured that at no time was the organoaluminum compound in excess. In all other cases, ketone was added to the organometallic compounds. Mixing was accomplished *via* rapid stirring with a Teflon stirring bar.

Product Analysis.—Products were analyzed by glpc where separations were possible and by nmr spectroscopy in other cases. In those cases where glpc was employed, reaction mixtures were hydrolyzed with distilled water. After an appropriate internal standard was added and the metallic salts had separated from the organic layer, a sample of the supernatant layer was withdrawn for analysis. The following conditions were employed for product analysis by glpc. For trimethylaluminum addition to 4-*tert*-butylcyclohexanone, a 10 ft × 0.25 in. column of 20% SAIB on Chromosorb W at 182° (flow 60 ml/min) gave the following retention times for ketone, axial alcohol, and equatorial alcohol: 11.3, 8.7, and 10.7 min. For trimethylaluminum addition to 3,3,5-trimethylcyclohexanone, the same column and conditions gave retention times of 5.0, 4.3, and 6.0 min for the ketone, axial alcohol, and equatorial alcohol, respectively. For trimethylaluminum addition to 2-methylcyclopentanone, a 15-ft column of 10% diglycerol on Chromosorb W at 80° gave 5.4, 7, and 12.4 min for ketone, *trans*-1,2-dimethylcyclopentanol, and *cis*-1,2-dimethylcyclopentanol, respectively. For triethylaluminum addition to 4-*tert*-butylcyclohexanone, a column of 20% SAIB on 5 Chromosorb W at 150° (flow 60 ml/min) gave the following retention times for ketone, axial alcohol (alkyla-

(7) (a) E. C. Ashby and S. H. Yu, *J. Chem. Soc. D*, 351 (1971); (b) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37**, 1918 (1972); (c) J. L. Namy and H. Normant, *C. R. Acad. Sci. Ser. C*, **272**, 1334 (1971).

(8) E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Amer. Chem. Soc.*, **90**, 5183 (1968).

(9) J. J. Eisch and W. Kaska, *ibid.*, **88**, 2976 (1966).

(10) (a) F. W. Walker and E. C. Ashby, *ibid.*, **91**, 3845 (1969); (b) E. C. Ashby, J. Laemmle, and H. M. Neumann, *ibid.*, **94**, 5421 (1972).

(11) We are indebted to Professor A. C. Huitric, College of Pharmacy, University of Washington, for a generous gift of 0.8 g of 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3 oxime.

(12) S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, **31**, 3446 (1966).

(13) T. L. Brown, D. W. Dickerhoof, D. A. Bafus, and G. L. Morgan, *Rev. Sci. Instrum.*, **33**, 491 (1962).

tion), equatorial alcohol (alkylation), axial alcohol (reduction), and equatorial alcohol (reduction): 30, 39, 45, 27.7, and 32.2 min. For triethylaluminum addition to 3,3,5-trimethylcyclohexanone, the same column at 155° gave retention times of 9.6, 13.3, 18, 10.4, and 12.3 min for ketone, axial alcohol (alkylation), equatorial alcohol (alkylation), axial alcohol (reduction), and equatorial alcohol (reduction), respectively.

The isomeric alcohols resulting from the methylation of norcamphor, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone could not be separated by glpc. In addition, the isomeric alcohols resulting from the phenylation of all ketones studied could not be determined by glpc owing to dehydration. Thus, the isomer ratios in these cases were determined by nmr analysis.

Several known mixtures of authentic samples of the methylnorborneols were prepared. The peak heights of the methyl singlets of the exo alcohol (73 Hz) and endo alcohol (74 Hz) in benzene were related to their concentrations. Reaction mixtures involving norcamphor were analyzed by comparing the nmr spectra in benzene to those of the authentic mixtures.

The isomer ratios in the case of the methylation of 3-methylcyclopentanone and *cis*-3,4-dimethylcyclopentanone and in the phenylation of all ketones was determined by nmr spectroscopy utilizing the peak areas of the hydroxyl protons of the alcohols in DMSO-d_6. In these cases work-up of reaction mixtures was carried out as follows. When benzene was employed as a solvent, the reaction solution was subjected to vacuum until all benzene had been removed. Wet ether was then added to the carbinolate in order to effect hydrolysis. The solution was then transferred to a separatory funnel and the aluminum salts were removed by repeated washings with distilled water. The ether layer was separated and allowed to evaporate and DMSO-d_6 was added to the sample. The sample was then dried over Linde 4A molecular sieve and transferred to a nmr tube. The purpose of this treatment was twofold. First, no acids were used in the work-up in order to minimize dehydration and equilibration and no evidence of either was found. Secondly, only the carbinolate was subjected to vacuum to remove solvent, thus lessening the possibility of stripping out a portion of the desired alcohols. Addition of benzaldehyde to the sample as an internal nmr standard demonstrated that this method was satisfactory with all ketones and 100% recovery was realized. In those cases where ether was employed as a solvent, the work-up was identical except that the solution was hydrolyzed directly with distilled water.

The assignment of each alcohol hydroxyl peak to a particular isomer was based on numerous reports in the literature concerning their chemical shifts in DMSO and in DMSO-d_6.[14] For the reaction of trimethylaluminum and 3-methylcyclopentanone the chemical shifts for the hydroxyl protons are τ 5.82 for *trans*-1,3-dimethylcyclopentanol and 5.90 for *cis*-1,3-dimethylcyclopentanol. For the methylation of *cis*-3,4-dimethylcyclohexanone, the chemical shifts are τ 5.8 for *trans*-1-methyl-*cis*-3,4-dimethylcyclopentanol and 5.97 for *cis*-1,3,4-trimethylcyclopentanol. In the case of the phenylation of 4-*tert*-butylcyclohexanone, the chemical shifts are τ 5.44 and 5.27 for the axial and equatorial hydroxyl protons, respectively. In the case of phenylation of 3,3,5-trimethylcyclohexanone, a single hydroxyl resonance was observed at τ 5.5 for the axial alcohol. No other hydroxyl peak was observed in any run. In the case of the phenylation of 2-methylcyclopentanone, the chemical shifts of the hydroxyl protons are τ 5.52 for *trans*-1-phenyl-2-methylcyclopentanol and 5.23 for *cis*-1-phenyl-2-methylcyclopentanol. In the case of the phenylation of 3-methylcyclopentanone, the chemical shifts of the hydroxyl protons are τ 5.23 for *trans*-1-phenyl-3-methylcyclopentanol and 5.25 for *cis*-1-phenyl-3-methylcyclopentanol. In the case of the phenylation of *cis*-3,4-dimethylcyclopentanone, the chemical shifts for the hydroxyl protons are τ 5.14 for *trans*-1-phenyl-*cis*-3,4-dimethylcyclopentanol and 5.22 for *cis*-1-phenyl-3,4-dimethylcyclopentanol.

In all cases involving reaction of trimethyl- and triphenylaluminum in a 2:1 ratio in benzene and the corresponding Grignard reagents with ketones in all ratios in ether, 100% yield of alcohols formed by addition was realized. In the cases involving triethylaluminum reaction with ketones, both alkylation and reduction were observed. When organoaluminum compounds were allowed to react with ketones in 1:1 ratio in benzene or in diethyl ether, reaction rates were much slower, resulting in conversion to alcohol product from 50 to 100% depending on the individual cases with the remaining material being unreacted ketone. Thus, no products other than those arising from normal alkylation were observed except in the case of triethylaluminum–ketone reaction, which produced some reduction product.

Ketone–$AlCl_3$ Complexes.—Solutions of 4-*tert*-butylcyclohexanone–aluminum chloride complex and 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3 (axial 3-D)–aluminum chloride complex were prepared by adding an appropriate amount of ketone solution in benzene to a weighed amount of $AlCl_3$ in a 1-ml volumetric flask and diluting to the mark with benzene. All the $AlCl_3$ dissolved to give solutions 1 *M* in complex. The formation of complex was verified by the fact that solubility of $AlCl_3$ in the benzene–ketone solution greatly exceeded the solubility of $AlCl_3$ in benzene as determined in this study and reported elsewhere.[15] Solutions of 4-*tert*-butylcyclohexanone–aluminum chloride in benzene were initially colorless but turned yellow over a period of time. This color is possibly due to formation of small amounts of condensation products.[16] However, a 1.2 *M* solution of 4-*tert*-butylcyclohexanone–aluminum chloride in benzene at room temperature was sampled over a period of time by glpc. The peak area of the ketone remained the same for equal sample injections after 1 week and no other peaks were detected. Thus the concentration of condensation products formed must be very small. Nevertheless, as an added precaution, samples employed in the nmr study were stored in sealed nmr tubes and were kept frozen at all times except when actual spectra were being taken.

Results and Discussion

Table I illustrates the reaction of several organoaluminum compounds with 4-*tert*-butylcyclohexanone.

TABLE I

REACTION OF ORGANOALUMINUM COMPOUNDS WITH 4-*tert*-BUTYLCYCLOHEXANONE

AlR_3	Solvent	Initial $[AlR_3]$, *M*	Ratio of AlR_3/ ketone	% axial[a] alcohol	% equatorial[a] alcohol
$(CH_3)_3Al$	Benzene	0.28	0.5	80	20
		0.37	1.0	76	24
		0.41	1.5	53	47
		0.45	2.0	17	83
		0.48	3.0	12	88
$(C_2H_5)_3Al$[b]	Benzene	0.43	1.0	88	12
		0.54	2.0	17	83
		0.62	4.0	14	86
$(C_6H_5)_3Al$	Benzene	0.074	1.0	51	49
		0.077	2.0	27	73
		0.078	4.0	8	92
$(CH_3)_3Al$	Diethyl ether	0.33	1.0	85	15
		0.42	3.0	87	13
$(C_2H_5)_3Al$[b]	Diethyl ether	0.27	1.0	88	12
		0.33	3.0	88	12
$(C_6H_5)_3Al$	Diethyl ether	0.17	1.0	44	56
		0.19	3.0	44	56

[a] Normalized as per cent axial alcohol + per cent equatorial alcohol = 100%. [b] Reaction gives some reduction product with the equatorial alcohol predominating (~78%) in all cases.

It may be noted that in the reaction of $(CH_3)_3Al$ and $(C_2H_5)_3Al$ in benzene solvent the predominant isomer formed is the axial alcohol when the organoaluminum compound to ketone ratio is 1:1 or less. The same

(14) (a) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); (b) R. J. Ouellette, *ibid.*, **86**, 4378 (1964); (c) G. D. Meakins, R. K. Percy, E. E. Richards, and R. N. Young, *J. Chem. Soc. C*, 1106 (1968); (d) J. Battioni, W. Chodkiewicz, and P. Cadiot, *C. R. Acad. Sci., Ser. C*, **264**, 991 (1967); (e) J. Battioni, M. Chapman, and W. Chodkiewicz, *Bull. Soc. Chim. Fr.*, 976 (1969); (f) J. Battioni and W. Chodkiewicz, *ibid.*, 981 (1969); (g) *ibid.*, 1824 (1971).

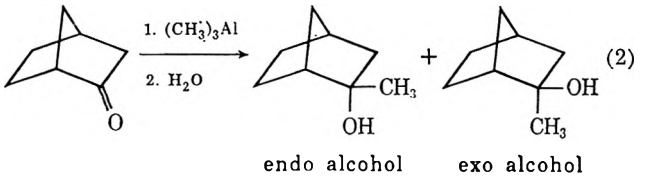
(15) (a) B. Menschutkin, *J. Russ. Phys. Chem. Soc.*, **41**, 1089 (1909); (b) L. Bruner, *Z. Phys. Chem.*, **41**, 333 (1902).

(16) (a) J. G. Pereira, *Chemiker 2*, **33**, R406 (1909); (b) E. Louis, *C. R. Acad. Sci.*, **95**, 602 (1882); (c) C. Courtot and V. Ouperoff, *ibid.*, **191**, 416 (1930).

is true for these compounds in diethyl ether at all reactant ratios. These reactions are believed to involve four-center transition states[8,17] and a reasonable explanation of the stereochemistry of the products is that the organometallic reagent attacks at the least hindered (equatorial) side of the chair conformation of the ketone. When the ratio of $(CH_3)_3Al$ or $(C_2H_5)_3Al$ to ketone is 2:1 or greater in benzene solvent, the predominant product is the equatorial alcohol arising from attack at the more hindered (axial) side of the chair conformation of the molecule. On the other hand, triphenylaluminum presents a slightly different picture. As in the case of $(CH_3)_3Al$ and $(C_2H_5)_3Al$ the ratio of product alcohol from triphenylaluminum is essentially the same in 1:1 reactant ratio in benzene and all ratios in ether. However, the initial ratio of alcohols is about 50:50 when the $(C_6H_5)_3Al$ to ketone ratio is 1:1 followed by the usual change involving predominant axial attack. Thus the reaction of $(C_6H_5)_3Al$ with ketone in benzene in 1:1 ratio and in ether in all ratios appears to have little preference for attack at either the axial or equatorial position. However, the significant point is that the ratio changes in favor of axial attack as the $(C_6H_5)_3Al$ to ketone ratio in benzene is increased from 1:1 to 2:1 or greater.

Considerations Involving an Early Transition State. Steric Approach Control *vs.* Compression Effect.—Assuming an early transition state, three possibilities were considered as explanations of the unusual stereochemistry observed in the reactions of excess organoaluminum compounds with 4-*tert*-butylcyclohexanone in benzene solvent. First, it was considered that the reversal in stereochemistry may be inherent in the change from a four- to a six-center transition state. That is, a six-center transition state may always lead to alkylation of a substrate from the opposite side when compared to a four-centered transition state. Alternatively, it was considered possible that the 4-*tert*-butylcyclohexanone–AlR_3 complex might exist in a conformation other than a chair (*e.g.*, boat or half chair), thus rendering the axial side the least hindered side in a six-center transition state. Finally, it was considered possible that some other, heretofore unknown factor might have given the observed result.

In order to obtain information as to whether a change in product isomer ratio will always occur when a ketone is subjected to alkylation *via* a four- or six-center transition state, the reaction of trimethylaluminum with norcamphor in benzene was examined (eq 2). Since



endo alcohol exo alcohol (2)

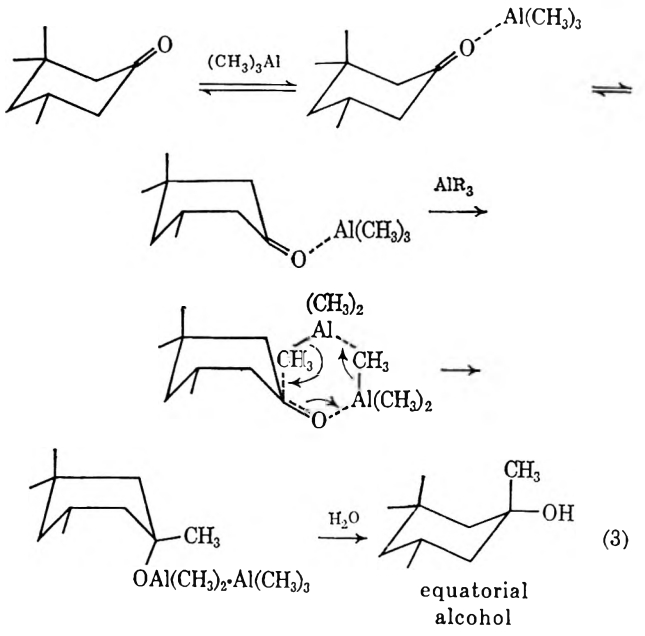
norcamphor is a rigid bicyclic ketone, the possibility of a conformational change in which the endo side becomes the least hindered side is eliminated. The results show that alkylation of norcamphor in benzene by trimethylaluminum over a $(CH_3)_3Al$:ketone ratio of 0.5–4 produced on hydrolysis 95% of the endo alcohol regardless of the R_3Al:ketone ratio. These results can be easily explained by noting that attack occurs primarily from the least hindered side of the molecule, *i.e.*, the exo side. They also show that a reversal in stereochemistry does not occur in all systems when the mechanism of alkylation changes from a four-center to a six-center transition state.

The results with the rigid norcamphor molecule suggested further study concerning the possibility that the reversal in stereochemistry found with 4-*tert*-butylcyclohexanone and excess $(CH_3)_3Al$ in benzene may be due to the fact that the complexed ketone exists in a nonchair conformation (boat or half chair). A boat conformation transition state has been used to explain the large percentage of axial attack on 3,3,5-trimethylcyclohexanone by various aluminohydrides.[18] If the 4-*tert*-butylcyclohexanone–AlR_3 complex exists in a boat conformation, the side of the molecule which is most hindered in the chair conformation becomes the least hindered in the boat conformation. Although attack on the boat conformation of the complex is from the least hindered side, after alkylation the boat flips back to the chair conformation, exhibiting the methyl group axial as if the chair conformation of the complex had been attacked from the most hindered side. Two factors that argue against this conformational change are the following: (1) the boat conformation is a higher energy conformation than the chair (thus the rate of reaction of the boat conformation would have to be hundreds of times faster than that of the chair conformation) and (2) if the transition state resembles the product to any extent, it should be of higher energy owing to the bulk of the resulting $-OAl(CH_3)_2 \cdot Al(CH_3)_3$ groups interacting with the endo hydrogens and the flagpole hydrogen. In order to obtain more evidence concerning this point, the stereochemistry of the reactions of trimethyl- and triphenylaluminum with 3,3,5-trimethylcyclohexanone was studied. It has been pointed out that the 3-axial methyl group destabilizes the chair conformation such that 3,3,5-trimethylcyclohexanone and its AlR_3 complex should exist in flexible conformations to a greater extent than 4-*tert*-butylcyclohexanone.[18] It should be noted that, owing to the steric requirement of the 3-axial methyl group, if attack in the 2:1 case occurs *via* the chair conformation of the complex, the extent of axial attack should be much less than in a similar reaction with 4-*tert*-butylcyclohexanone. However, if attack occurs through the boat conformation of the complexed ketone, then the percentage of axial attack for 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone should be comparable since the steric factors would be nearly equal (eq 3).

The results, shown in Table II, demonstrate that the percentage of axial attack is much smaller than that found with 4-*tert*-butylcyclohexanone. For example, in all cases involving the reaction of excess $(CH_3)_3Al$ or $(C_2H_5)_3Al$ with 4-*tert*-butylcyclohexanone in benzene, the equatorial alcohol is the major product whereas in the case of 3,3,5-trimethylcyclohexanone it is never the major product. In the case of arylation involving triphenylaluminum, 4-*tert*-butylcyclohexanone gives 92% axial attack at 4:1 ratio whereas the results with 3,3,5-trimethylcyclohexanone show no axial attack at any ratio. In addition, the reaction

(17) E. C. Ashby and J. Laemmle, *J. Org. Chem.*, **33**, 3389 (1968).

(18) S. R. Landor and J. P. Regan, *J. Chem. Soc. C*, 1159 (1967).



(3)

TABLE II

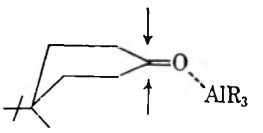
REACTION OF ORGANOALUMINUM COMPOUNDS WITH 3,3,5-TRIMETHYLCYCLOHEXANONE IN BENZENE

AlR_3	Initial $[AlR_3]$, M	Ratio of AlR_3/ ketone	% axial[a] alcohol	% equatorial[a] alcohol
$(CH_3)_3Al$	0.60	1.0	100	0
	0.74	2.0	81	19
	1.55	4.0	60	40
$(C_2H_5)_3Al$[b]	0.42	1.0	100	0
	0.53	2.0	89	11
	0.62	4.0	78	22
$(C_6H_5)_3Al$	0.073	1.0	100	0
	0.076	2.0	100	0
	0.078	4.0	100	0

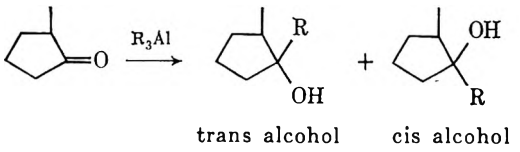
[a] Normalized as per cent axial alcohol + per cent equatorial alcohol = 100%. [b] Reaction gives some reduction product with the axial alcohol predominating (~70–75%) in all cases.

of $(CH_3)_3Al$, $(C_2H_5)_3Al$, and $(C_6H_5)_3Al$ with 3,3,5-trimethylcyclohexanone in diethyl ether gave 100% equatorial attack regardless of the ratio of R_3Al to ketone. Thus, in order for the steric requirement of the 3 axial methyl group to be important, it is unlikely that attack on 3,3,5-trimethylcyclohexanone would occur through the boat conformation of the ketone–AlR_3 complex.

Although reaction of excess $(CH_3)_3Al$ with cyclohexanones does not appear to occur through the boat conformation of the complexed ketone, other conformations with lower energy requirements cannot be immediately overruled. For example, it is possible that a significant percentage of the 4-*tert*-butylcyclohexanone–AlR_3 complex might exist in a half-chair conformation. Top-side attack on the complex in this



conformation by a second organoaluminum molecule would be somewhat favored owing to the steric effect of the flagpole hydrogen on C-4, although it does not seem reasonable that attack from this direction is so favorable as to result in 90% attack from this side. Top-side attack would, of course, produce equatorial alcohol. In order to pursue this possibility further, the reaction of 2-methylcyclopentanone with Grignard reagents and aluminum alkyls were investigated (eq 4). The alkylation of this ketone was reported



(4)

to result in 60–70% trans attack (giving cis alcohol) in the case of Grignard reagent alkylation,[14d,g] thereby demonstrating a much smaller steric requirement than for norcamphor. Although the 2-methylcyclopentanone ring can pucker to some extent, it cannot undergo conformational distortions so servere that the side of the ring possessing the methyl group (cis side) is the least hindered Therefore, if the reason for the reversal of stereochemistry observed with the cyclohexanone systems is due to conformational changes which render the axial side of the chair conformation of the complexed ketone the least hindered side, then little or no change in stereochemistry with reactant ratio in the case of organoaluminum alkylation of 2-methylcyclopentanone in benzene should be observed since such a conformational change is not possible. The results are shown in Table III.

TABLE III

REACTION OF ORGANOALUMINUM COMPOUNDS AND GRIGNARD REAGENTS WITH 2-METHYLCYCLOPENTANONE

RM	Solvent	Initial [RM], M	Ratio of RM/ ketone	% cis[a] alcohol	% trans[a] alcohol
$(CH_3)_3Al$	Benzene	0.1	1.0	60	40
		0.2	2.0	23	77
		0.4	4.0	22	78
$(C_6H_5)_3Al$		0.076	1.0	100	0
		0.076	2.0	94	6
		0.076	4.1	84	16
CH_3MgBr	Diethyl ether	0.88	8.8	60	40
C_6H_5MgBr	Diethyl ether	0.34	4.0	100	0

[a] Normalized as per cent cis alcohol + per cent trans alcohol = 100%.

It should be noted that, when Grignard reagents and trimethylaluminum react with 2-methylcyclohexanone in 1:1 ratio, attack trans to the 2-methyl group takes place, producing the cis alcohols as the predominant product. These reagents are known to alkylate ketones *via* a four-center transition state[8,10b] and the stereochemistry observed can readily be explained by noting that attack occurs preferentially at the least hindered side of the molecule. In the case of $(CH_3)_3Al$ alkylation in a 2:1 or greater ratio in benzene, a much larger percentage of cis attack is observed, producing the trans alcohol. Even in the case of $(C_6H_5)_3Al$, more cis attack is observed when the R_3Al:ketone ratio is varied from 1:1 to 4:1. Thus a significant increase in the amount of attack from the most hindered side of the molecule is ob-

served when the R_3Al:ketone ratio is 2:1 compared to when the ratio is 1:1.

The results presented thus far indicate that the reversal in stereochemistry observed in the organoaluminum ketone systems in benzene is due neither to a fundamental occurrence inherent in the nature of a six-center transition state nor to conformational changes in the complexed ketone but to a factor not previously described. The concept of "steric approach control" satisfactorily explains the results of the AlR_3–ketone reactions in 1:1 ratio in benzene as well as Grignard reagent and AlR_3 reactions in ether in all ratios owing to the fact that simple bimolecular reactions should be controlled by steric factors. However, both the concepts of "steric approach control" and "torsional strain" are inadequate to explain the results of the AlR_3–ketone reaction in benzene in 2:1 or greater ratios.

The following explanation satisfies the stereochemistry observed with each ketone. Figure 1 represents the various orientations of the carbonyl oxygen to substituents on adjacent carbon atoms for each ketone studied. (It should be noted that Figure 1 indicates the cyclohexanones to be in perfect chair conformations and the cyclopentanones to be planar. While this may not be exactly the case, it is a reasonable approximation.) Calculations by Allinger[19a] and Fournier[19b] give the dihedral angle H_{eq}–C–C–O in cyclohexanones as 3.3 and 5.6°, respectively. The dihedral angle H_{eq}–C–C–O···AlR_3 in the cyclohexanone–AlR_3 complex would be expected to be as large as or larger than in the uncomplexed ketone owing to the steric interaction of the complexed carbonyl with the 2,6-diequatorial hydrogens Figure 1A illustrates the angle between the carbonyl oxygen and the hydrogens on adjacent carbons for the 4-*tert*-butylcyclohexanone–AlR_3 complex. It can be seen that equatorial attack by a second molecule of R_3Al compresses the complexed carbonyl against the equatorial hydrogens in the transition state. On the other hand, axial attack leads to a staggered arrangement between the complexed carbonyl and hydrogens on adjacent carbon atoms. Thus, in the case of the cyclohexanones, this "compression effect" favors attack from the more hindered side of the molecule in the 2:1 R_3Al:ketone ratio. This same effect explains the stereochemistry observed with the other ketones. In the case of 2-methylcyclopentanone, Figure 1B shows the orientation between the carbonyl oxygen and the substituents on the 2 carbon atom and Figure 1C shows the orientation between the carbonyl oxygen and the substituents on the 5 carbon atom. Trans attack by a second organoaluminum molecule compresses the complexed carbonyl into a methyl group and a hydrogen in the transition state, whereas cis attack compresses the complexed carbonyl between two hydrogens. Thus, the "compression effect" favors attack by a second molecule of organoaluminum compound from the most hindered side of the ketone, the cis side.

In the above cases the "compression effect" and the "steric approach factor" oppose each other. Thus, a reversal of stereochemistry is anticipated where the ratio of organoaluminum compound to ketone is increased from 1:1 to 2:1. Norcamphor represents a different case. Figure 1C represents the orientation of the carbonyl group of norcamphor with the hydrogens on the 3 carbon atom. It can be seen that the complexed carbonyl will be compressed against the exo or endo hydrogens equally regardless of whether exo or endo attack occurs. Endo attack on norcamphor will compess the complexed carbonyl against the hydrogen on the 1 carbon atom, however, whereas exo attack does not (Figure 1D). Thus, in the case of norcamphor, the "steric approach factor" and the "compression effect" operate in the same direction. Thus, it is anticipated that exo attack to give endo alcohol will be highly favored regardless of the R_3Al:ketone ratio, and a reversal in stereochemistry will not be observed. This prediction was justified when 95% endo alcohol was observed in the reaction of $(CH_3)_3Al$ with norcamphor in benzene in ratios varying from 0.5 to 4.

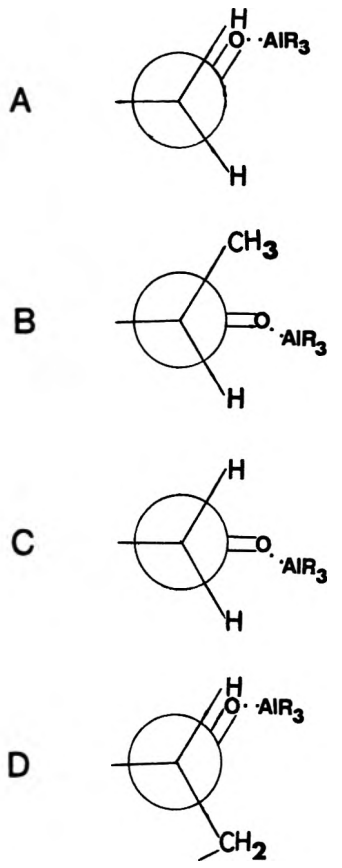
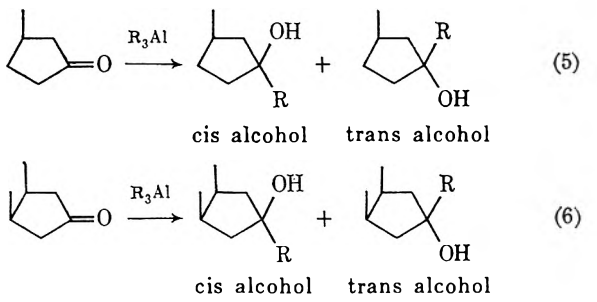


Figure 1.—Orientation of the complexed carbonyl oxygen to substituents on adjacent carbon atoms for (A) 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone; (B) 2-methylcyclopentanone; (C) norcamphor, 2-methylcyclopentanone, 3-methylcyclopentanone, *cis*-3,4-dimethylcyclopentanone; (D) norcamphor.

Further evidence supporting our conclusions was obtained from a study of organoaluminum compounds and Grignard reagents with 3-methylcyclopentanone and *cis*-3,4-dimethylcyclopentanone (eq 5, 6). Figure 1C represents the orientation between the complexed carbonyl oxygen and the hydrogens on adjacent carbons for these ketones. Attack on these molecules from either side by a second organoaluminum molecule compresses the complexed carbonyl oxygen against nearly equivalent hydrogens. Thus, unlike previous

(19) (a) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972); (b) J. Fournier and B. Waegell, *ibid.*, **26**, 3195 (1970).



examples, complexes involving these ketones exhibit little net "compression effect" and the stereochemistry will be controlled by other factors. The results are illustrated in Tables IV and V. It should be noted

TABLE IV

REACTION OF ORGANOALUMINUM COMPOUNDS AND GRIGNARD REAGENTS WITH 3-METHYLCYCLOPENTANONE

RM	Solvent	Initial [RM], M	Ratio of RM/ ketone	% cis[a] alcohol	% trans[a] alcohol
$(CH_3)_3Al$	Benzene	0.40	1.0	61	39
		0.20	2.0	57	43
		0.40	4.0	56	44
$(C_6H_5)_3Al$	Benzene	0.076	1.0	58	42
		0.076	2.0	63	37
CH_3MgBr	Diethyl ether	0.88	8.8	58	42
C_6H_5MgBr	Diethyl ether	0.34	4.0	58	42

[a] Normalized as per cent cis alcohol + per cent trans alcohol = 100%.

TABLE V

REACTION OF ORGANOALUMINUM COMPOUNDS AND GRIGNARD REAGENTS WITH *cis*-3,4-DIMETHYLCYCLOPENTANONE

RM	Solvent	Initial [RM], M	Ratio of RM/ ketone	% cis[a] alcohol	% trans[a] alcohol
$(CH_3)_3Al$	Benzene	0.40	1.0	92	8
		0.20	2.0	91	9
		0.40	4.0	90	10
$(C_6H_5)_3Al$	Benzene	0.078	1.0	91	9
		0.078	2.0	100	0
CH_3MgBr	Diethyl ether	0.88	8.8	92	8
C_6H_5MgBr	Diethyl ether	0.34	4.0	92	8

[a] Normalized as per cent cis alcohol + per cent trans alcohol = 100%.

that the product isomer ratio remains essentially the same with both ketones regardless of the ratio of organoaluminum compound to ketone. These results are consistent with our arguments concerning the existence of a "compression effect" and also reinforce our previous suggestion that a change in transition state (four- to six-center) in itself does not result in such a change in stereochemistry.

The "compression effect" proposed here is similar to effects proposed by other workers to explain the fact that diborane attacks 4-*tert*-butylcyclohexanone preferentially from the axial side.[20] However, this viewpoint is not held by most workers, for the following reasons. Microwave and nmr studies have shown that in the case of acetaldehyde the preferred conformation is one in which a hydrogen atom eclipses the carbonyl group and that propionaldehyde exists mainly in the conformation in which a methyl group is eclipsed by the double bond.[21] In 4-*tert*-butylcyclohexanone the carbonyl group is almost eclipsed by the 2,6-equatorial hydrogens (Figure 1A) and complete eclipsing in an early transition state may even be favorable. "Torsional strain" and "eclipsing" in the sense used by Chérest and Felkin imply a repulsion between single bonds.[5] As noted above,[21] the forces between single and double bonds appear to be attractive. *Since ultraviolet studies of benzophenone–$Al(CH_3)_3$ complex indicate that the double bond remains intact, we believe that the effect described in this paper is a steric effect. The effective bulk of the carbonyl group is increased to such an extent by complexation with an organoaluminum compound that severe interactions with groups on adjacent carbons can occur in the transition state. Hence we choose to call this effect a "compression effect" as opposed to an "eclipsing effect" or "torsional effect" which, as previously stated, denotes single bond repulsion.*

One interesting factor concerning the addition of organoaluminum compounds to ketones in a 2:1 or greater reactant ratio should be pointed out. In those cases where a reversal of stereochemistry occurs, ketones exhibiting relatively small steric requirements (4-*tert*-butylcyclohexanone, 2-methylcyclopentanone), show no tendency to yield a further significant change in isomer ratio as the reactant ratio is increased from 2:1 to higher ratios, if the organoaluminum compound also possesses a small entering group (methyl, ethyl). However, the isomer ratio continues to change with reactant ratio beyond 2:1 with these same ketones when the organoaluminum compound possesses a large entering group (phenyl) (Tables I, III). On the other hand, the product ratio continues to change with reactant ratio beyond 2:1 for those ketones exhibiting a relatively large steric requirement (3,3,5-trimethylcyclohexanone) regardless of the size of the entering group (Table II). The reason for this difference is found in the relative rates at which organoaluminum compounds react with ketones by the two mechanisms. In the one case, the rate-controlling step is the rearrangement of an organoaluminum–ketone complex (eq 7) and the other is the reaction of complex with a

$$C \longrightarrow P \qquad (7)$$

second molecule of organoaluminum compound (eq 8).[8] It should be noted that rearrangement of com-

$$C + A \longrightarrow P \qquad (8)$$

plex (eq 7) is a first-order process and is independent of the reactant ratio beyond 1:1. Attack on the complex by a second organoaluminum molecule is a second-order process in which the rate of reaction increases as the ratio of organoaluminum compound to ketone increases.

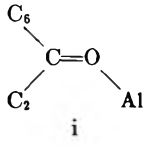
In those cases in which the isomer ratio does not increase significantly beyond a 2:1 reactant ratio, almost all reactions proceed through an attack on the complex at a 2:1 reactant ratio. Thus, the isomer ratio observed is that produced solely by reaction *via* eq 8 at 2:1 and greater reactant ratios. On the

(20) J. Klein and D. Lichtenberg, *J. Org. Chem.*, **35**, 2654 (1970).

(21) (a) R. W. Klib, C. C. Lin, and E. B. Wilson, *J. Chem. Phys.*, **26**, 1695 (1957); (b) R. J. Abraham and J. A. Pople, *Mol. Phys.*, **3**, 609 (1960).

other hand, in those cases where the isomer ratio changes significantly with reactant ratio beyond 2:1, the relative rates of reaction *via* both paths are comparable. Thus, the isomer ratio observed is that due to reaction *via* both mechanisms. As the ratio of organoaluminum compound to ketone is increased beyond 2:1, the rate of product formation through rearrangement of complex remains unchanged but the rate of product formation *via* attack on complex is increased. Hence more product resulting from attack at the most hindered side of the ketone is observed. It should be noted that this effect occurs with ketones having large steric requirements or organoaluminum compounds having large entering groups. This is due to the fact that, as noted before, the "steric approach factor" and the "compression effect" oppose each other. Thus, in those cases with a large "steric approach factor," reaction *via* attack on complexes where the "compression effect" operates will be slowed down relative to rearrangement of complex.

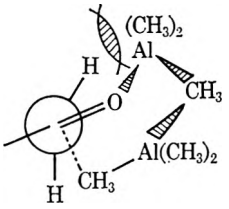
The reason a "compression effect" is observed in the case of a six-center transition state but not in the case of a four-center transition state is the spatial arrangement of the atoms in each case.[22] In the 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$ complex, for example, the unit i lies in a plane. Attack on this complex by



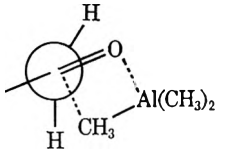
i

another molecule of $(CH_3)_3Al$ leads to a six-center transition state in which the attacking species is perpendicular to the plane of the carbonyl group. Compression then occurs between the complexed carbonyl and the groups on C_2 and C_6 which lie on the opposite side of the carbonyl from the entering $(CH_3)_3Al$. The compression effect is then due to the $Al(CH_3)_3$ originally complexed to the carbonyl and not to the attacking $(CH_3)_3Al$ (transition state A).

In a four-center transition state, the $(CH_3)_3Al$ molecule lies perpendicular to the plane of the carbonyl group. Since the $(CH_3)_3Al$ is on the opposite



transition state A



transition state B

side of the carbonyl group from the groups on C-2 and C-6 which the carbonyl must eclipse in the transition state, no compression involving the $Al(CH_3)_2$ unit will occur in an early transition state (transition state B). Steric approach control should then determine the isomer ratio.

Considerations Involving a Late Transition State. Product Development Control.—The discussion to this point has assumed an early, reactant-like transition

(22) For a detailed discussion of the nature of the transition state in $(CH_3)_3Al$ alkylation of benzophenone see H. M. Neuman, J. Laemmle, and E. C. Ashby, *J. Amer. Chem. Soc.*, **95**, 2597 (1973).

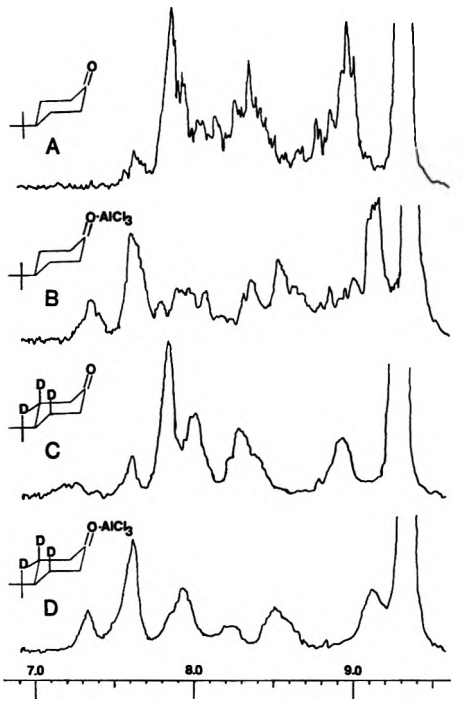


Figure 2.—60-MHz nuclear magnetic resonance spectra for 1 *M* benzene solutions of (A) 4-*tert*-butylcyclohexanone, (B) 4-*tert*-butylcyclohexanone–$AlCl_3$ complex; (C) 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3; (D) 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3–$AlCl_3$ complex.

state in the reaction of $(CH_3)_3Al$ with ketones in 2:1 ratio. The possibility of a late, product-like transition state should also be considered. If a late transition state occurs, the stereochemistry could be determined by the position of the large $OAlR_2 \cdot AlR_3$ group in the product. This group will tend to occupy the least hindered position in the product, *i.e.*, equatorial in the case of alkylation of 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone, exo in alkylation of norcamphor, and trans in alkylation of 2-methylcyclopentanone, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone. The entering group would then occupy the remaining position, *i.e.*, axial in alkylation of 4-*tert*-butylcyclohexanone and 3,3,5-trimethylhexanone, endo in alkylation of norcamphor, and cis in alkylation of 2-methylcyclopentanone, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone.

If product development control determined the observed isomer ratio in the reaction of $(CH_3)_3Al$ with ketones in 2:1 ratio, then all ketones would show an increase in attack from the more hindered side when compared to 1:1 reactant ratio. While a change in isomer ratio with reactant ratio does occur in R_3Al alkylation involving 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and 2-methylcyclopentanone, it does not occur in R_3Al alkylation involving norcamphor, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone. Therefore the final position of the $OAlR_2 \cdot AlR_3$ group is not a factor in the determination of the isomer ratio of the reactions reported herein and thus product development control cannot explain the observed stereochemistry in these reactions.

Nmr Evidence for the Chair Conformation of the Complex.—The importance of knowing the preferred conformation of cyclohexanones and their aluminum alkyl complexes in stereoalkylation has already been

pointed out. In this connection an nmr study involving 4-*tert*-butylcyclohexanone and 4-*tert*-butylcyclohexanone-*cis*-3,5,5-d_3 (axial 3D) and their $AlCl_3$ complexes was undertaken. Figure 2 illustrates the 60-MHz nmr spectra of the ketones and their $AlCl_3$ complexes as 1 *M* solutions in benzene (τ 2.73). The low-field doublets of the trideuterated ketone (τ 7.69, J_{gem} = −13.4 Hz) and complex (τ 7.42, J_{gem} = −17.0 Hz) are assigned to equatorial protons on C-2 and C-6. The assignments are based on the following facts: (1) the signals integrate to two protons in each case, (2) the signals appear basically as doublets in the nondeuterated compounds,[23a] (3) the widths of the signals are relatively narrow owing to axial–equatorial H–D vicinal coupling constants,[23b] and (4) the relatively large shift of these protons in going from ketone to complex. The high-field doublets of the trideuterated ketone (τ 8.14, J_{gem} = −13.4 Hz)[24] and complex (τ 8.10, J_{gem} = −17.0 Hz) are assigned to the axial protons on C-2 and C-6. These assignments are based on the following facts: (1) the signals intergrate to two protons in each case, (2) the signals give a complex splitting pattern in the nondeuterated compounds,[23a] (3) the widths of the signals are relatively broad owing to axial–axial H–D vicinal coupling constants,[23b] and (4) the relatively slight shift of these protons in going from ketone to complex.

The nmr spectra of ketone and ketone–$AlCl_3$ show nonflexible conformations displaying axial and equatorial protons on C-2 and C-6. The spectra are consistent with a very high population of the chair form of the ketone and ketone–$AlCl_3$. The spectra do not rule out the possibility of an equilibrium between the chair conformation and certain nonchair conformations, where the equilibrium is in the direction of a high predominance of the chair form. Unfortunately, the spectra do not allow predictions regarding detectable limits of nonchair conformers.

(23) (a) W. F. Trager and A. C. Huitric, *Tetrahedron Lett.*, 825 (1966); (b) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

(24) A JEOL H4 100 spectrometer was used to obtain 100-MHz nmr spectra for all samples. In this case a distinct doublet at τ 8.14 was observed.

Registry No.—$(CH_3)_3Al$, 75-24-1; $(C_2H_5)_3Al$, 97-93-8; $(C_6H_5)_3Al$, 841-76-9; CH_3MgBr, 75-16-1; C_6H_5MgBr, 100-58-3; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; 2-methylcyclopentanone, 1120-72-5; 3-methylcyclopentanone, 1757-42-2; *cis*-3,4-dimethylcyclopentanone, 19550-72-2.

Acknowledgment.—We are grateful to Dr. A. C. Huitric for helpful comments concerning the interpretation of the nmr spectra shown in Figure 2.

Reaction of Alkali Metal Diphenylmethides with 1,1-Dichloroalkanes. Conjugate Addition to 1,1-Diphenylalkenes

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Received February 8, 1973

The reaction of sodium diphenylmethide (1′) with methylene chloride was previously considered to proceed by a twofold alkylation to give 1,1,3,3-tetraphenylpropane (**3**). The reaction is shown to proceed by a single alkylation to give diphenylethyl chloride, which is dehydrohalogenated to diphenylethylene. Conjugate addition of 1′ to the latter olefin, followed by neutralization, gives **3**. Conjugate addition of 1′ to other 1,1-diphenylalkenes is not observed. Alkali triphenylmethides react similarly with methylene chloride, except that elimination is not possible, and the monoalkylation product does not react further.

Previously, sodium diphenylmethide in liquid ammonia was shown to react with α,ω-dihaloalkanes including methylene chloride and ethylene chloride, to give the tetraphenylalkanes corresponding to twofold alkylation of the halide by the anion, although the triphenylmethide ion reacted but once with methylene chloride to give triphenylethyl chloride.[2]

Subsequently, sodium and potassium diphenylmethide were shown to undergo quite different reactions with chloroform (proton abstraction) and carbon tetrachloride (displacement on halogen).[3] Also, methylene iodide was shown to iodinate certain organometallic compounds,[4] and ethylene bromide and iodide were shown to react with 1′ differently than did the chloride.[5] It thus seemed important to reexamine the reaction of the alkali diphenylmethides with the methylene halides.

When potassium diphenylmethide (1′) was treated with 0.5 molar equiv of methylene chloride, the orange color, as previously noted,[2] was not discharged, but a substantial excess of halide did discharge the color. Work-up of this reaction mixture gave almost none of the expected tetraphenylpropane (**3**), but gave 1-chloro-2,2,4,4-tetraphenylbutane (**4**), in 40% conversion. Gas chromatography indicated a small amount of tetraphenylpropane (about 15%), but showed a 35% recovery of diphenylmethane (**1**). Three mechanisms were considered to explain these results; path C, Scheme I, was shown to be correct.

When hydrocarbon **3** was treated with ammoniacal potassium amide, a red color indicative of an anion was observed, but, when the color was discharged by methylene chloride, starting material was largely recovered, indicating a slight extent of ionization. This rules out path A, Scheme I, since diphenylmethide must be an even weaker base than amide ion. Path B, Scheme I,

(1) NSF Undergraduate Research Participant, summer, 1971.

(2) C. R. Hauser, C. F. Hauser, and P. J. Hamrick, *J. Org. Chem.*, **24**, 397 (1959).

(3) C. R. Hauser, W. G. Kofron, W. R. Dunnavant, and W. F. Owens, *J. Org. Chem.*, **26**, 2627 (1961).

(4) R. L. Gay, T. F. Crimmins, and C. R. Hauser, *Chem. Ind. (London)*, 1635 (1966).

(5) W. G. Kofron and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 4126 (1968).

SCHEME I

Path A $2 + 1' \longrightarrow 3$; $3 + 1' \longrightarrow 3'$; $3' + CH_2Cl_2 \longrightarrow 4$

Path B $2 + 1' \longrightarrow 2'$; $2' + 2 \longrightarrow 4$

Path C $2 + 1' \longrightarrow (2') \longrightarrow 5$; $5 + 1' \longrightarrow 3'$; $3' + CH_2Cl_2 \longrightarrow 4$; or $3' + NH_4^+ \longrightarrow 3$

Overall: $3\ 1' + CH_2Cl_2 \xrightarrow{NH_4^+} 3 + 1$

$2\ 1' + CH_2Cl_2 \xrightarrow{NH_4^+} {}^1/_3\ 4 + {}^1/_3\ 3 + {}^2/_3\ 1$

$(C_6H_5)_2CH_2 \xrightarrow{NH_2^-} (C_6H_5)_2\bar{C}H \xrightarrow{CH_2Cl_2} (C_6H_5)_2CHCH_2Cl$

1 1′ 2

$(C_6H_5)_2\bar{C}CH_2Cl$

2′

$(C_6H_5)_2CHCH_2CH(C_6H_5)_2$ $(C_6H_5)_2CHCH_2\bar{C}(C_6H_5)_2$

3 3′

$(C_6H_5)_2CHCH_2C(C_6H_5)_2CH_2Cl$ $(C_6H_5)_2C{=}CH_2$

4 5

appeared unlikely, since the β-halo anion (2′) would probably eliminate halide; in agreement with this, treatment of 2 with 1 molar equiv of 1′ gave both 3 (51%) and 5 (47%). Treatment of 5 with 1′ did result in a change in color from orange (1′) to red (other alkyldiphenylmethide ions have colors more red than 1′), and treatment of this mixture with methylene chloride resulted in a 62% yield of 4. When this experiment was repeated, but with methylene chloride omitted and the adduct neutralized with ammonium chloride, 3 was obtained in 52% yield. If Scheme I's path C is correct, then formation of 3 must also involve an intermediate dehydrohalogenation of 2 to 5. The stoichiometry of this pathway would then be a 3:1 ratio of 1′ to methylene chloride, and not 2:1 as previously assumed. Reexamination of the original report suggests no disagreement with this stoichiometry, even though the reported yield of 3 was 72% (67% would be the maximum by Scheme I). If ${}^1/_2$ molar equiv of methylene chloride is used, ${}^1/_3$ molar equiv will react to form 3′, leaving ${}^1/_6$ molar equiv of methylene chloride to alkylate 3′ to give 4. The remainder of the 3′ imparts the observed color to the solution and is converted to 3 upon work-up. While only 67% of 1 is converted to solid products (3 and 4), the molecular weight of 4 is increased 14% over 3; thus the total amount of solid would give an apparent yield of approximately 72%. The chloro compound (4) is more soluble than 3, and on recrystallization pure 3 is obtained. When the alkylation of 1′ was carried out with ${}^1/_3$ molar equiv of methylene chloride, followed by neutralization with ammonium chloride after 20 min, 3 was obtained in 61% yield (41% conversion).

A similar conjugate addition of 1′ has been observed with 1,1-dichloro-2,2-diphenylethylene.[6] This suggests that such a reaction might be a convenient route to 2-alkyl-1,1,3,3-tetraphenylpropanes, since 1,1-diphenylalkenes are readily available from benzophenone, and since 1,1-dichloroalkanes other than methylene chloride are not alkylated by 1′.[5] However, several 1,1-diphenylalkenes failed to react with 1′ to give adducts. Apparently the alkene is deprotonated by 1′ to form an allylic anion, which does not react further with 1′, and on work-up the starting materials are recovered. The formation of the anion from 1,1-diphenylpropene with potassium amide was demonstrated by carbonation to give 4,4-diphenyl-3-butenoic acid (eq 1). Thus the

$$(C_6H_5)_2C{=}CHCH_3 \xrightarrow{NH_2^-} (C_6H_5)_2C{=}C\bar{H}CH_2 \xrightarrow{CO_2,\,H^+} (C_6H_5)_2C{=}CHCH_2COOH \quad (1)$$

conjugate addition of 1′ is only observed with alkenes such as 5, which do not have allylic protons.

The original report suggests that sodium triphenylmethide undergoes reaction with methylene chloride to give 1,1,1-triphenyl-2-chloroethane.[2] This halide and the analogous bromide were prepared from the methylene halide and sodium triphenylmethide.[7,8] The chloride was shown to be thermally unstable, rearranging to triphenylethylene with loss of hydrogen chloride,[7] and, when converted with sodium to the 1,1,1-triphenylethyl anion, undergoing rearrangement to 1,1,2-triphenylethane.[8] When the alkylation of potassium triphenylmethide with methylene chloride was carried out in liquid ammonia, triphenylethyl chloride could be obtained in 52% yield, even though the halide was added to the anion solution. In fact, the halide was not dehydrohalogenated and was recovered even when refluxed in ether with 1 equiv of potassium triphenylmethide, or when stirred at room temperature in ether with 1 equiv of potassium amide.

Experimental Section

Reactions of Potassium Diphenylmethide and Methylene Chloride. A. General Procedure.—Potassium diphenylmethide was prepared in liquid ammonia as previously described.[5] Unless otherwise indicated, methylene chloride in ether was added to the anion solution. A general procedure is described in detail; the other reactions were similar, and the yields are summarized in Table I.

TABLE I

REACTIONS OF 1′ WITH METHYLENE CHLORIDE[a]

Mole ratio of 1′:CH_2Cl_2	Product (conversion, %) [yield, %][c]
2	1 (31)[93]
	3 (28)[85]
	4 (28)[85]
	5 (5.3)
3	1 (20)[60]
	3 (41)[61]
	4 (1)
	5 (trace)
0.1[b]	1 (18)
	5 (18)
	2 (47)

[a] The potassium salt was used; results were similar whenever reactions were repeated with the sodium salt. [b] Inverse addition. [c] The conversion is the amount of 1′ converted to the indicated product; the yield is that based on the overall stoichiometry of Scheme I.

B. Reaction of Potassium Diphenylmethide with 0.5 Molar Equiv of Methylene Chloride.—To 0.1 mol of potassium diphenylmethide was added 4.25 g (0.05 mol) of methylene chloride. After 20 min the color was discharged by the addition of ammonium chloride, the ammonia was evaporated, and the residue was stirred with ether and water. The ethereal solution was separated, washed with dilute hydrochloric acid, water, and brine, dried over magnesium sulfate, and evaporated. The

(6) F. B. Kirby, W. G. Kofron, and C. R. Hauser, *J. Org. Chem.*, **28**, 2176 (1963).

(7) J. C. Charlton, I. Dostrovsky, and E. D. Hughes, *Nature (London)*, **167**, 987 (1951).

(8) E. Grovenstein, *J. Amer. Chem. Soc.*, **79**, 4985 (1957).

residue was stirred with hexane and filtered. The solid (6.75 g) was recrystallized from hexane to give 5.6 g (28% conversion of anion) of 1-chloro-2,2,4,4-tetraphenylbutane, mp 121–122°.

Anal. Calcd for $C_{28}H_{25}Cl$: Cl, 8.93. Found: Cl, 9.06.

The hexane filtrate was evaporated and the residual oil was distilled at 2 mm to give 5.2 g (31% recovery) of diphenylmethane, bp 89–96°. The still pot residue was crystallized in hexane and recrystallized from methanol to give 5.1 g (28% conversion) of 1,1,3,3-tetraphenylpropane, mp 139.5–141.5°. Diphenylethylene was detected in the combined mother liquors by gas chromatography (estimated 0.95 g, 5.3% conversion).

Reaction of Potassium Diphenylmethide with 1,1-Diphenylethylene.—To a solution of 0.05 mol of potassium diphenylmethide in 120 ml of liquid ammonia was added an ethereal solution of 9 g (0.05 mol) of 1,1-diphenylethylene. The dark red solution was stirred for 20 min and 3 g of ammonium chloride was added. The ammonia was evaporated and the residue was stirred with ether and water. The ethereal solution was separated, washed, dried, and evaporated to give 17.4 g of solid. Recrystallization from ethanol and hexane gave 9 g (52%) of tetraphenylpropane, mp 139–140°. Another 5.4 g of lower melting product was obtained from the mother liquor. In another experiment, 5.4 g (0.03 mol) of 1,1-diphenylethylene in ether was added to 0.03 mol of potassium diphenylmethide, and the deep red solution was stirred for 30 min. An ethereal solution of 2.6 g (0.03 mol) of methylene chloride was added. The color was slowly (25 min) discharged. Work-up as above gave 7.4 g (62%) of tetraphenylchlorobutane, 2.3 g (22%) of tetraphenylpropane, and 15% each of diphenylmethane and diphenylethylene.

Reaction of 1,1-Diphenyl-1-propene with Potassium Amide.—To a solution of 0.025 mol of potassium amide in 100 ml of liquid ammonia was added an ethereal solution of 4.85 g (0.025 mol) of 1,1-diphenyl-1-propene. The ammonia was replaced with ether, and the deep red solution was poured onto Dry Ice. Water was added and the aqueous layer was separated and acidified. The solid was recrystallized from carbon tetrachloride to give 3 g (50%) of 4,4-diphenyl-3-butenoic acid, mp and mmp 118–119°.[9]

Reaction of Potassium Triphenylmethide with Methylene Chloride—To a solution of 0.025 mol of potassium triphenylmethide, prepared from 0.025 mol of potassium amide and 6.1 g (0.025 mol) of triphenylmethane in liquid ammonia, was added 2.4 g (0.028 mol) of methylene chloride. The color was not discharged after 40 min. Ammonium chloride was added to discharge the color and the ammonia was evaporated. The residue was stirred with ether and water and the ethereal layer was separated, dried over magnesium sulfate, and evaporated. The residue was recrystallized from methylene chloride–ethanol to give 3.8 g (52%) of 1-chloro-2,2,2-triphenylethane, mp 99–100°. The experiment was repeated, except that after the methylene chloride had been added and the solution stirred for 20 min an ammoniacal solution of 0.025 mol of potassium amide was added, and the mixture was stirred until the ammonia had evaporated (about 1.5 hr). Work-up as above afforded only triphenylethyl chloride (53%), and triphenylethylene could not be detected.

Registry No. —**1**, 101-81-5; **1′**, 10060-17-0; **3**, 36171-50-3; **4**, 40139-28-4; **5**, 530-48-3; methylene chloride, 75-09-2; 1,1-diphenyl-1-propene, 778-66-5; potassium amide, 17242-52-3; 4,4-diphenyl-3-butenoic acid, 7498-88-6; potassium triphenylmethide, 1528-27-4; 1-chloro-2,2,2-triphenylethane, 33885-01-7.

(9) W. S. Johnson, J. W. Petersen, and W. P. Schneider, *J. Amer. Chem. Soc.*, **69**, 74 (1947).

Kinetic Isotope Effects in the Oxidation of Alcohols by Silver Carbonate

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Received February 5, 1973

The kinetic isotope effect resulting from the silver carbonate oxidation of a variety of alcohols has been determined by a convenient double labeling technique which may be utilized for similar determinations in other systems. The method is especially suitable to systems where reproducible direct kinetic measurements are not possible. The theory strengths and limitations of the method are discussed and its validity is experimentally verified.

The importance of kinetic isotope effects in the study of organic reaction mechanisms is well known and has been extensively reviewed.[1] Frequently the mere existence or absence of a kinetic isotope effect is a sufficient clue for the differentiation among many theoretically plausible mechanistic alternatives.

The study of kinetic isotope effects is also useful in establishing the magnitude of errors involved in tracer experiments and in providing experimental verification of theoretical calculations regarding the nature of the transition states in various types of bond-breaking processes.

The above applications as well as the general methods for evaluating kinetic isotope effects have been elegantly discussed and reviewed by Raaen and his coauthors.[2]

However, kinetic isotope effects in chemical reactions are frequently difficult to measure because of the problems involved in obtaining sufficiently reproducible direct kinetic data on individual isotopic species. This difficulty is particularly evident in heterogeneous reaction systems, where it may prove impossible to maintain even an approximate control over all the significant reaction variables.

Frustration over attempts to obtain such direct kinetic data for the oxidation of alcohols by silver carbonate on Celite,[3] a combination known as Fetizon's reagent,[4] led us to utilize a double isotopic labeling technique which permits different isotopic species to be studied in a single reaction mixture and the determination of the kinetic isotope effect without a concurrent determination of the kinetics of the reaction.

It must be emphasized that theoretical treatments relating kinetic isotope effects to the isotopic composition of reactants and products have been previously described.[5] Also the use of one isotope as a

(1) C. J. Collins and N. S. Bowman, "Isotope Effects in Chemical Reactions," ACS Monograph 167, Van Nostrand-Reinhold, Princeton, N. J., 1970.

(2) V. F. Raaen, G. A. Ropp, and H. R. Raaen, "Carbon 14," McGraw-Hill, New York, N. Y., 1968, pp 47–83.

(3) F. J. Kakis, "On the Mechanism of the Oxidation of Alcohols by Silver Carbonate," 7th Western Regional Meeting of the American Chemical Society, Anaheim, Calif., Oct 1971.

(4) M. Fetizon and M. Golfier, *C. R. Acad. Sci., Ser. C*, **276**, 900 (1968).

(5) J. Ying-Peh Tong and P. E. Yankwich, *J. Phys. Chem.*, **61**, 540 (1957).

tracer for another is well known.[6-7] Thus no originality in this respect is either claimed or intended.

We have utilized these concepts, integrated them into a single, coherent, and generally applicable procedure, critically examined its strengths and limitations, and shown experimentally that it can yield reproducible kinetic isotope data in a system where direct kinetic measurements were found to be difficult to obtain.

Theory.—Consider a mixture of two isotopically distinct reactants A and B, and assume A additionally to be labeled in a manner not affecting its kinetic properties in the reaction to be studied. Let the reaction mixture originally contain mole fractions x_a and x_b of A and B, respectively, and let Q_0 be the initial specific radioactivity (per mole) of pure A. After the reaction has been allowed to proceed for an unknown amount and for an arbitrary time interval, let the unreacted reactant mixture then have molar specific activity Q_r and the mixture of products Q_p. The above-described information suffices to determine the ratio of the reaction rate constants for A and B.

The analysis is based on the assumption that the numbers of moles of A and B, n_a and n_b, respectively, are governed by rate equations of the general forms

$$\frac{-dn_a}{dt} = k_a n_a f(n_a + n_b) \tag{1a}$$

$$\frac{-dn_b}{dt} = k_b n_b f(n_a + n_b) \tag{1b}$$

where k_a and k_b are the rate constants for reaction of isotopic species A and B, and $f(n_a + n_b)$ is a function containing the remainder of the expression for the rate. This function may depend upon time, upon the concentrations of other species (and therefore upon the extent of reaction and ultimately upon $n_a + n_b$), and upon various other factors, but it is specifically assumed that the same function occurs in the rates for both isotopic species. It is further assumed that the difference in rate among isotopically substituted reactants is first order in the reactant concentration, although the overall rate may be of higher order. This assumption avoids the necessity for considering processes in which several isotopic molecules are involved in rate-determining reaction steps.

Combining eq 1a and 1b, we may find

$$\frac{dn_a}{k_a n_a} = \frac{dn_b}{k_b n_b} \tag{2}$$

and therefore, at any time,

$$\frac{n_a}{n_a^0} = \left(\frac{n_b}{n_b^0}\right)^K \tag{3}$$

where $K = k_a/k_b$ and n_a^0 and n_b^0 are the initial numbers of moles of A and B. The rate-constant ratio K characterizes the isotope effect.

We now wish to relate the activity data to the isotope effect. Using the fact that the specific activity of pure A is Q_0, we see that the reactant activity value Q_r implies that the mole fraction of A in the unreacted sample is Q_r/Q_0, so

$$\frac{n_a}{n_a + n_b} = \frac{Q_r}{Q_0} \tag{4}$$

Similarly, noting that $n_a^0 - n_a$ and $n_b^0 - n_b$ are the numbers of moles of A and B converted to products, that activity value Q_p yields

$$\frac{n_a^0 - n_a}{(n_a^0 - n_a) + (n_b^0 - n_b)} = \frac{Q_p}{Q_0} \tag{5}$$

Equations 4 and 5 may now be combined with eq 3 and solved for K, giving

$$K = 1 + \frac{\log\left[\dfrac{x_b Q_r}{x_a(Q_0 - Q_r)}\right]}{\log\left[\left(\dfrac{Q_0 - Q_r}{Q_p - Q_r}\right)\left(\dfrac{Q_p - x_a Q_0}{x_b Q_0}\right)\right]} \tag{6}$$

Scope and Limitations.—While eq 6 is valid over the entire course of an isotopically mixed reaction, it should be pointed out that the last term on its right-hand side approaches an indeterminate form of the type 0/0 if Q_p and Q_r are determined in the very first stages of a reaction or if the isotope effect is very small. In both these cases the experimental data can still provide a good determination of the isotope effect but precision will be required in carrying out the numerical evaluation. Also it may be necessary to introduce corrections to compensate for the apparent lagging of the heavy isotope.[8] If a reaction proceeds so slowly that it is practical to study the initial rate, eq 6 reduces to the simple form

$$K = \frac{x_b}{x_a}\left(\frac{Q_p}{Q_0 - Q_p}\right) \tag{7}$$

If, on the other hand, Q_p and Q_r are determined very late in the course of a reaction, the last term of eq 6 approaches an indeterminate form of the type ∞/∞, with physical significance that as the reaction moves toward completion we lose all information about the isotope effect except its direction.

An examination of the foregoing equations suggests that the most precise results will be obtained when the activities of unreacted mateial, Q_r, and product, Q_p, differ as much as possible. This situation can be best achieved by having the more rapidly reacting isotopic species initially present in small concentration, and making assays as early as practical in the reaction course.

The described technique is applicable when the reactant under study is available as an isotopic mixture of known composition, and when one of the isotopic species has an additional labeling lacking in the other.

The second label must be sufficiently removed from the reactive site so that it is in no way involved in the rate-determining process. Its presence is merely a convenient means for monitoring the reaction. Although in our experiments we have used a radioactive element as the second label, this is not a limitation of the method. Any isotope can be used as a tracer, the choice being limited only by the available means for establishing the isotopic composition of the reaction mixtures.

If the object is to measure highly precise or very small kinetic isotope effects and traditional direct kinetic measurements are possible, then obviously this will not be the method of choice. However,

(6) V. F. Raeen, T. K. Dunham, D. D. Thompson, and C. J. Collins, *J. Amer. Chem. Soc.*, **85**, 3497 (1963).

(7) D. E. Schmidt, Jr., W. G. Nigh, C. Tanzer, and J. H. Richards, *J. Amer. Chem. Soc.*, **91**, 5849 (1969).

(8) For an extensive discussion *cf.* C. J. Collins and M. H. Lietzke, *J. Amer. Chem. Soc.*, **81**, 5379 (1959).

in some instances this may be the only way to obtain information about kinetic isotope effects.

Thus, we consider the above method as particularly advantageous when reproducible conditions cannot be maintained for different reacting samples, when the significant factors governing the reaction are uncontrollably varying with time, and even when the act of removing an aliquot sample for analysis causes an unknown disturbance in the reacting system.

The double labeling also permits analysis to be based on sampling of the reaction system and avoids the necessity of quantitative isolation of the various components in the reaction mixtures. Finally this method can be used as an independent check of kinetic isotope effect data obtained by the conventional methods.

Application, Results, and Discussion

The oxidation of alcohols by silver carbonate precipitated on Celite[4] is a heterogeneous reaction which takes place under neutral conditions and involves the simple reflux of the oxidizing agent with a solution of the alcohol. For the past 2 years we have been investigating the mechanism of this reaction.[3] During the course of this investigation we have decided to measure the primary and secondary deuterium isotope effect; however, we discovered that it was very difficult to obtain reproducible data from straightforward kinetic determinations. In the first place the reaction showed induction periods of varying times. Furthermore, considerable variation in the extent of oxidation was at times observed even on identically prepared samples maintained at the same constant temperature for the same amount of time. These discrepancies can arise from a variety of factors which are difficult to control, such as the mesh distribution or state of aggregation of the solid oxidizing agent, the rate of stirring and reflux, etc. In view of this, it became apparent that the only valid comparison of the rate of oxidation of the protium and deuterium-labeled alcohols would be one involving the simultaneous oxidation of a mixture of the two in the same vessel. Only in this way can one be assured that the conditions were identical. To this end mixtures of nonradioactive deuterated alcohols and radioactive (C-14 labeled) protium alcohols of known specific activity were simultaneously oxidized.

The choice of the particular substrates used was dictated by their availability. Some of the immediate precursor ketones of the alcohols used were on hand from a previous study.[9] Other samples were privately supplied.[10] In each case the ketones were first reduced to the corresponding alcohols by either lithium hydride or lithium aluminum deuteride as follows.

$$R^{14}CR_1(=O) \xrightarrow{LiAlH_4} R^{14}CHR_1(OH) \quad \text{A}$$

$$RCR_1(=O) \xrightarrow{LiAlD_4} RCDR_1(OH) \quad \text{B}$$

R = alkyl or aryl

After suitable purification alcohol A was assayed for ^{14}C and its specific activity Q_0 was determined. Alcohol B was examined by nmr to ensure that it had been completely deuterated. Subsequently a mixture of A and B was prepared and homogenized by dissolving both in a suitable solvent, which was then evaporated to recover the crystals. The crystals were then dried and the mixture was assayed for radioactivity. From the known specific activity Q_0 of pure A and that of the mixture Q_m the mole fractions x_a and x_b were calculated as follows.

$$x_a = \frac{Q_m}{Q_0} \text{ and } x_b = 1 - x_a$$

The mixtures of A and B were then partially oxidized.

$$R^{14}CHR_1(OH) + RCDR_1(OH) \xrightarrow[\text{benzene or heptane}]{Ag_2CO_3/\text{Celite}} R^{14}CR_1(=O) + RCR_1(=O)$$

At the end of the oxidation the reaction mixtures contained ketonic products and unreacted alcohols. These were separated by thin layer chromatography and purified. The specific activities of the pure unreacted starting material Q_r and of the pure product Q_p were then determined by ^{14}C assays. Substitution of all this data into eq 6 permitted the calculation of the kinetic isotope effect.[11]

Thirteen different alcohols were tested by this method. Each oxidation was performed in triplicate, the reported values being the average of these determinations.

The experimental data and the calculated results are summarized in Table I. Retaining only two significant figures, we find an average value for K of 3.0 ± 0.1. The only other information on the deuterium isotope effect in the silver carbonate oxidation of alcohols comes from the work of Eckert, *et al.*,[12] who studied the oxidation of norbornanols by gas chromatography. They report an isotope effect between 3 and 4. Thus we conclude that the described technique can afford reliable kinetic isotope effect data within the limitations discussed.

Experimental Section

General.—Melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A or T-60 spectrometer, with tetramethylsilane as an internal standard. Infrared spectral data were recorded on a Beckman IR-5A spectrophotometer. Radioactivity levels of the various carbon-14 labeled compounds were determined by dry combustion of the samples to carbon dioxide, which was collected in an ionization chamber and assayed in the usual way[13] using a Cary Model 31 vibrating-reed electrometer. All the deuterated alcohols were obtained from the corresponding ketones by lithium aluminum deuteride reduction. The procedure used in each case was identical with that described below for the synthesis of deuterated 1,2,2-triphenylethanol. All of the carbon-14 labeled protium alcohols were similarly obtained from their carbon-14 labeled ketone precursors[9,10] by lithium aluminum hydride reduction. The silver carbonate oxidations of the various samples followed a procedure exactly analogous to that described below for the oxidation of 1,2,2-triphenylethanol.

(9) F. J. Kakis, D. Brase, and A. Oshima, *J. Org. Chem.*, **36**, 4117 (1971).

(10) We are indebted to Dr. C. J. Rossi for supplying us with some of the radioactive samples and for performing some of the assays.

(11) To facilitate the computations a simple program was written in basic Fortran. K was then calculated with the aid of a National Cash Register CENTURY 100 computer. This program is available from the author upon request.

(12) M. Eckert-Maksic, Lj. Tusek, and D. E. Sunko, *Croat. Chim. Acta*, **43**, 79 (1971).

(13) V. F. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

TABLE I

ALCOHOLS OXIDIZED, RADIOACTIVITY DATA, AND CALCULATED RESULTS

Compd[a]	x_a	x_b	Q_0, mCi/mol[b]	Q_r, mCi/mol[b]	Q_p, mCi/mol[b]	K (K_H/K_D)
1,2,2-Triphenylethanol[c]	0.5056	0.4944	4.755	1.623	3.304	3.0
1,2,2-Tri-*p*-anisylethanol[c]	0.3279	0.6721	8.013	1.832	4.393	3.1
1,2,2-Tri-*p*-tolylethanol[c]	0.4358	0.5642	7.837	2.176	4.927	3.0
1,2-Diphenylethanol[d]	0.2795	0.7205	8.276	1.791	4.077	2.9
1,3-Diphenyl-2-propanol[c]	0.4478	0.5522	6.055	2.367	4.188	3.1
Benzhydrol[d]	0.3569	0.6431	7.537	2.018	4.296	2.9
Di-*o*-tolylmethanol[d]	0.3027	0.6973	8.210	1.952	4.461	3.2
Di-*p*-tolylmethanol[d]	0.2868	0.7132	7.976	1.897	4.231	3.2
1-Phenyldodecanol[d]	0.4680	0.5320	5.932	2.296	4.056	2.9
Phenyl-*p*-tolylcarbinol[d]	0.3645	0.6355	7.562	1.997	4.506	3.2
1,3-Diphenyl-1-propanol[d]	0.4063	0.5937	8.105	1.699	4.689	3.0
1,2-Diphenyl-1-decanol[d]	0.4271	0.5729	4.972	1.832	3.259	2.9
1-Phenyl-2,2-di-*p*-tolylethanol[d]	0.3723	0.6277	6.979	1.974	4.267	3.2

[a] Registry numbers for deuterated (^{14}C) form: 39994-06-4 (39994-07-5), 39994-08-6 (39994-09-7), 39994-10-0 (39994-11-1), 39994-12-2 (39994-13-3), 39994-14-4 (39994-15-5), 17498-07-6 (39994-17-7), 39994-18-8 ((39994-19-9), 39994-20-2 (39994-21-3), 39994-22-4 (39994-23-5), 39994-24-6 (39994-25-7), 39994-26-8 (39994-27-9), 39994-28-0 (39994-29-1), 39994-30-4 (39994-31-5). [b] The values shown are the average of three assays. The maximum deviation observed in these measurements was less than 1%. [c] Labeled on the β carbon. [d] Ring labeled.

Deuterated 1,2,2-Triphenylethanol [$Ph_2CHC(OH)DPh$] (B).—A magnetically stirred suspension of excess lithium aluminum deuteride (3 g) in anhydrous ether (200 ml) was treated gradually with a solution of analytically pure (mp 139–140°) phenylbenzhydryl ketone (2.72 g, 0.01 mol) in anhydrous ether. Solution of the ketone in the ether was achieved by equipping the flask with a Soxhlet extractor and placing the ketone crystals in an extraction thimble.

The mixture was continually stirred and refluxed gently with a hot water bath over a period of 4 hr, after which it was cooled in a Dry Ice–isopropyl alcohol bath. The decomposition of the complex and the destruction of the excess hydride was accomplished by the cautious successive addition of water (3 ml), 15% sodium hydroxide solution (3 ml), and again water (9 ml). This procedure gave a white, crystalline precipitate of inorganic salts which was filtered in a cintered glass filter funnel and washed with ether. The organic phase was dried over anhydrous magnesium and sodium sulfates. On evaporation of the solvents, a viscous oil was obtained which was crystallized by triturating with a few milliliters of hot hexane. After two recrystallizations from hexane a pure sample (mp 81–82°) of deuterated 1,2,2-triphenylethanol was obtained. The yield was quantitative. The identity and isotopic purity of the product were confirmed by infrared and nmr spectroscopy.

Carbon-14 Labeled 1,2,2-Triphenylethanol [$Ph_2{}^{14}CHC(OH)HPh$] (A).—This compound was prepared from carbon-14 labeled phenylbenzhydryl ketone[9] by lithium aluminum hydride reduction. The procedure used was identical with the one described above.

Partial Oxidation of a Mixture of $Ph_2{}^{14}CHC(OH)HPh$ (A) and $Ph_2CHC(OH)DPh$ (B).—A sample (0.99500 g) of radioactive (4.755 mCi/mol) protium alcohol A was mixed with a sample (0.99495 g) of the deuterated alcohol B. The mixture was then dissolved in spectral grade chloroform to homogenize the samples. The chloroform was subsequently removed by rotatory evaporation and the crystals were dried under vacuum over phosphorus pentoxide. The mixture was then assayed for carbon-14 and found to have a specific activity of 2.404 mCi/mol. From this data the exact mole fractions of A (x_a = 0.5056) and B (x_b = 0.4944) were calculated.

A portion of this mixture (552.5 mg, *ca.* 0.002 mol) was added to a suspension of predried silver carbonate–Celite reagent[4] (638 mg, *ca.* 0.0011 mol) in anhydrous benzene (50 ml). After refluxing for several hours the reaction was stopped, the solids were filtered off, and the benzene was evaporated. The residue consisting of unreacted alcohols and phenylbenzhydryl ketone was chromatographed on thin layer plates coated with fluorescent silica and eluted with benzene. This afforded a good separation of the alcohols from the ketone. The individual samples were then isolated and purified, the alcohols by successive recrystallizations from hexane and the ketone by sublimation followed by recrystallization from methanol. The pure samples were then assayed for carbon-14 and the specific activities of the unreacted alcohols (Q_r = 1.623 mCi/mol) and of the products (Q_p = 3.304 mCi/mol) were determined. When all of the above data were substituted into eq 6, the calculated value for K was 3.0114. Repetitive oxidations of the same mixture gave similar results.

Registry No.—Ag_2CO_3, 534-16-7.

Acknowledgments.—The generous support of this study by a grant from the Research Corporation is gratefully acknowledged. The author also wishes to acknowledge helpful discussions with Dr. F. E. Harris whose participation was supported in part by NSF Grant GP-31373X.

Reactions of Isopropenyl Stearate with Diethyl Malonate, Acetoacetic Ester, and Related Keto Esters. Enol Esters. XVII[1]

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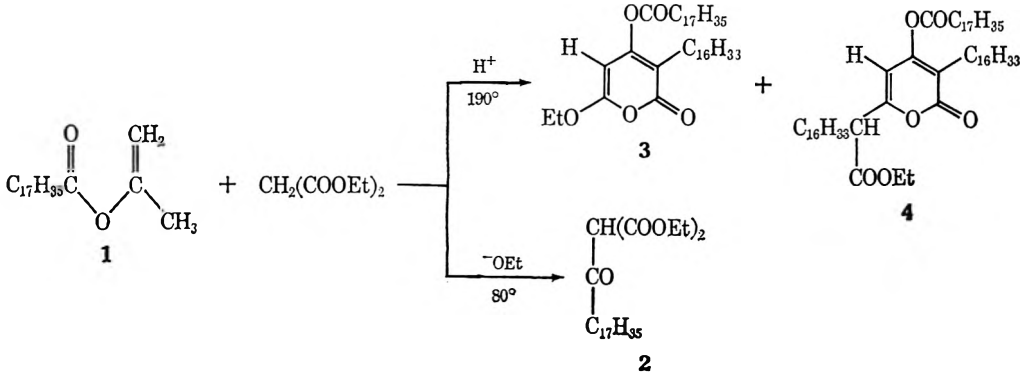
Received February 23, 1973

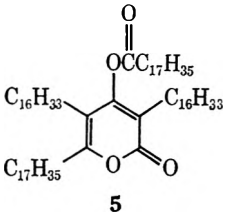
The major product from the acid-catalyzed reaction of isopropenyl stearate with diethyl malonate is identified as the α-pyrone, 6-ethoxy-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one. Alcoholysis of the 6-alkoxy α-pyrone proceeds unusually easily without requiring catalysis. Acetoacetic ester and 3-oxoglutarate esters react analogously with isopropenyl stearate to form α-pyrones.

Isopropenyl esters of long-chain fatty acids are versatile acylation agents for the convenient preparation of a wide variety of O-, N-, S-, and C-acylated products.[3a-e] We had examined the base-catalyzed C-acylation of diethyl malonate using isopropenyl stearate (1) as a probe reagent and obtained the expected product, 2-stearoyl diethyl malonate[3d] (2).



At the temperature of the refluxing diethyl malonate solution and under conditions of acidic catalysis, however, a totally different substance was formed. We have been aware for some time[3e] that our previously assigned β-diketone structure[3f] for the latter substance was incorrect. The present paper deals with the elucidation of the structure of the major product of the acid-catalyzed reaction as a 6-ethoxy α-pyrone, namely, **3**. We have also detected traces of a minor α-pyrone companion product **4**. The synthesis and elucidation of the structure of product **4** materially aided the establishment of the correct structure of the major product **3**.

The ease of obtaining the reaction product **3** contrasted markedly with the difficulty of correctly assigning its structure. Technical difficulties hindering the solution of the problem included the facts that the ir spectra of very different structures have similar appearances because of the overpowering effect of the lengthy alkyl groups present. Similar considerations apply to the nmr, uv, and mass spectra; glc analysis is also precluded by the high molecular weight of the compounds, a feature also hindering mass spectral molecular ion determinations. In addition, melting points in this series tend to be deceptively similar; for example, the 6-ethoxy α-pyrone **3**, the 6-methyl α-pyrone **12**, and the hexadecylketene tetramer (3,5-dihexadecyl-6-heptadecyl-4-stearoyloxy-2*H*-pyran-2-one, **5**)[4,5] all melt at 76° and do not depress on admixture.



The carbon and hydrogen compositions given by elemental analyses are not very helpful in this series of compounds, nor is the attempted simplification of the problem by using a lower molecular weight enol ester reactant. For example, the reaction of isopropenyl octanoate with diethyl malonate gave a complex product mixture complicating rather than simplifying the structural elucidations.

In support of the α-pyrone structure **3** for the principal product from the reaction of **1** and diethyl malonate we observed the molecular ion $C_{41}H_{74}O_6$, 646.5516 mass units[6] in the high-resolution mass spectrum. The ir spectrum showed enol ester absorption bands (1771 cm^{-1}), lactone carbonyl bands (1740 cm^{-1}), and a double-bond function (1640 cm^{-1}). The nmr spectrum (unaffected by attempted D_2O exchange) consisted of a singlet (1 H) at 5.30 ppm for

(1) Previous papers in this series: E. S. Rothman, S. S. Hecht, P. E. Pfeffer, and L. Silbert, *J. Org. Chem.*, **37**, 3551 (1972); E. S. Rothman, G. G. Moore, J. M. Chirinko, and S. Serota, *J. Amer. Oil Chem. Soc.*, **49**, 376 (1972).

(2) Agricultural Research Service, U. S. Department of Agriculture.

(3) (a) E. S. Rothman, S. Serota, and D. Swern, *J. Org. Chem.*, **29**, 646 (1964); (b) E. S. Rothman, G. G. Moore, and S. Serota, *ibid.*, **34**, 2486 (1969); (c) E. S. Rothman and G. G. Moore, *Tetrahedron Lett.*, 2553 (1969); (d) *J. Org. Chem.*, **35**, 2351 (1970); (e) *Tetrahedron Lett.*, 1065 (1971); (f) E. S. Rothman, *J. Org. Chem.*, **31**, 628 (1966).

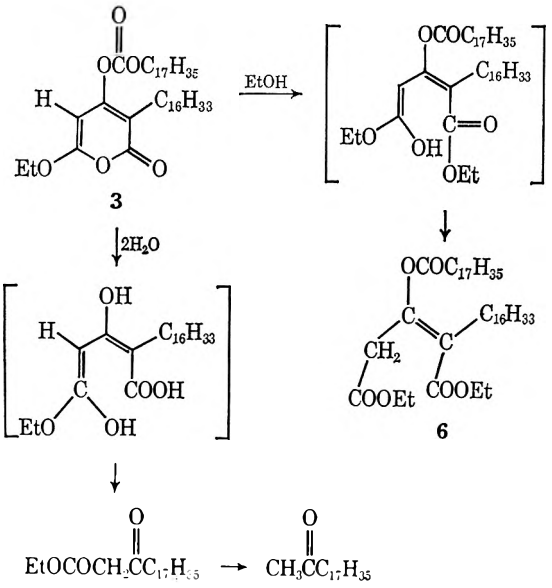
(4) E. S. Rothman, *J. Amer. Oil Chem. Soc.*, **45**, 189 (1968).

(5) In U. S. Patent 3,567,748 (March 2, 1971) it may now be established that the "unknown substance" in example 1 is the 6-ethoxy α-pyrone **3** and the compound in example 2 is the hexadecylketene α-pyrone tetramer **5**.

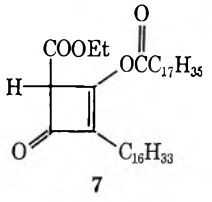
(6) The less precise method of molecular weight determination by thermistor technique gave a value of 714 g/mol.

the ring proton,[7] a quartet (2 H) at 4.25 ppm for ethoxy methylene protons, two overlapping triplets (2 H each) at 2.58 and 2.32 ppm, and the methylene envelope (1.8–0.8 ppm) corresponding to the remaining protons. The uv absorption maximum at 315 nm was in agreement with the α-pyrone structure assignment. The alternative γ-pyrone isomer was ruled out, since such structures absorb in the 250-nm range.[8]

A characteristic property of the alkoxy pyrone **3** is its facile, uncatalyzed reaction with 1 equiv of ethanol to form diethyl 2-hexadecyl-3-stearoyloxy-2-pentenedioate (**6**). Hydrolyses of **3** under controlled conditions enabled the isolation of stearoylacetic ester and of methyl heptadecyl ketone as shown in the following equation.

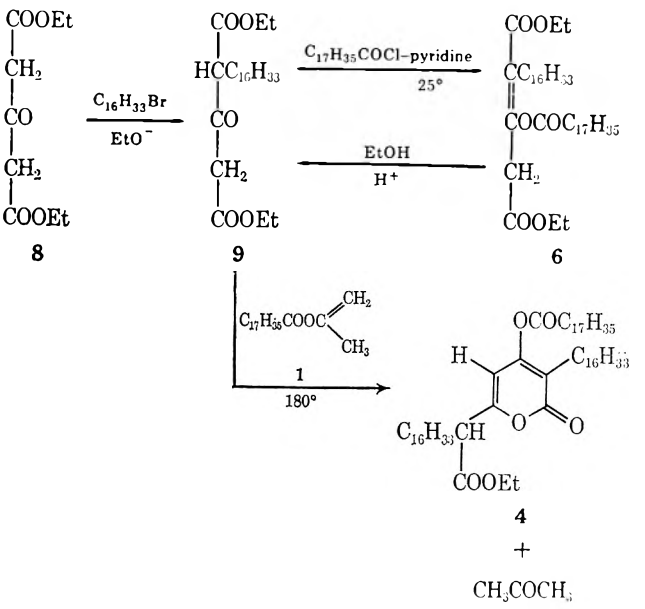


An alternative cyclobutenone structure **7** was considered and rejected. Although such a structure would



be expected to give **6** by an easy ring-opening reaction, cyclobutenones are reported to absorb near 250 nm[9] and not in the 315-nm region as we observed for **3**.

Since our conclusion on structure **3** rests directly on the correctness of the structure assignment **6** for the ring-opened product, we confirmed the latter structure by an independent synthesis. Alkylation of diethyl 3-oxoglutarate[10] (**8**) with hexadecyl bromide gave diethyl 2-hexadecyl-3-oxoglutarate (**9**). The latter was acylated with stearoyl chloride in pyridine to give a compound identical with the ring-opened product **6**. We were also able to hydrolyze selectively the enol ester–diester **6** to the diester **9**. Significantly, if the acylation of diester **9** was carried out, not with stearoyl chloride–pyridine, but rather with isopropenyl stearate (**1**) at elevated temperatures (conditions such as we routinely use to stearoylate substrate materials[3a]), we obtained good yields (as the sole product) of the α-pyrone **4**, "the companion substance." These interrelationships are clarified by the following sequence of equations.



Spectral data supporting the structure assignment **6** for the ring-opened product include the observation of the molecular ion $C_{43}H_{80}O_6$ (*m/e* 692.5970) in the high-resolution mass spectrum; bands in the ir spectrum at 1760 cm^{-1} attributable to enol ester carbonyl and at 1745 (saturated ester) and at 1629 cm^{-1} corresponding to olefinic unsaturation; and the nmr, which displays two overlapping quartets (4 H) at 4.17 and 4.12 ppm (CH_3CH_2O–), a singlet (2 H) at 3.72 ppm (C=CCH_2–COOEt–), overlapping triplets at 2.40 ppm (unlike pairs of α-CH_2 side chain units), and the usual methylene group envelope from 1.70 to 0.90 ppm. The ultraviolet spectrum shows only weak absorption at 220 nm.

The high-temperature transformation of the alkylated oxoglutarate **9** to the "companion pyrone" **4** deserves further comment. The structure proof of **4** includes observation of the molecular ion at *m/e* 912 (supported by the approximate value of 908 g/m determined by the thermistor method); the nmr spectrum shows a singlet at 6.13 ppm (ring proton), a quartet (2 H) at 4.24 ppm (CH_3CH_2OCO–), a triplet (1 H) at 3.45 ppm ($C_{16}H_{33}CHCOOEt$), and the composite absorption due to three lengthy alkyl chains. The ir spectrum has bands corresponding to enol ester, saturated ester, and the olefin function. The uv maximum at 297 nm is also in accord with the α-pyrone structure. Hydrolysis of **4** gave the carboxylic acid **10** with retention of the α-pyrone ring structure.[11] Analogously, for purposes of comparison, we used diethyl 3-oxoglutarate in reaction with **1** to prepare **11**. The carbethoxymethylene pyrone **11**, which resembles the "companion substance" **4** structurally in every way, except for the absence of the hexadecyl group from the

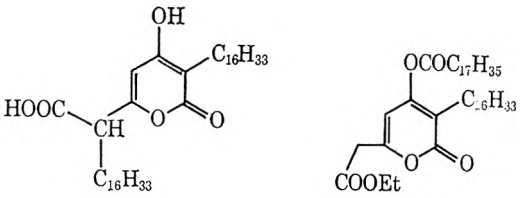
(7) This chemical shift of 5.30 ppm is almost 1 ppm further upfield than that observed for the 5 H in pyrones such as **4** where there is 6-alkyl instead of 6-ethoxy functionality. For nmr spectra of other 6-alkoxy α-pyrones, see A. Corbella, P. Garibaldi, G. Jommi, and G. Russo, *Gazz. Chim. Ital.*, **98**, 1096 (1968), and of ring protons in 6-alkylated cases, E. E. Kilbourn and M. C. Seidel, *J. Org. Chem.*, **37**, 1145 (1972).

(8) J. A. Berson, *J. Amer. Chem. Soc.*, **75**, 3521 (1953).

(9) R. B. Woodward and G. Small, Jr., *ibid.*, **72**, 1297 (1950).

(10) "Organic Syntheses," Collect. Vol. I, 2nd ed, H. Gilman and A. H. Blatt, Ed., Wiley, New York, N. Y., 1944, p 237.

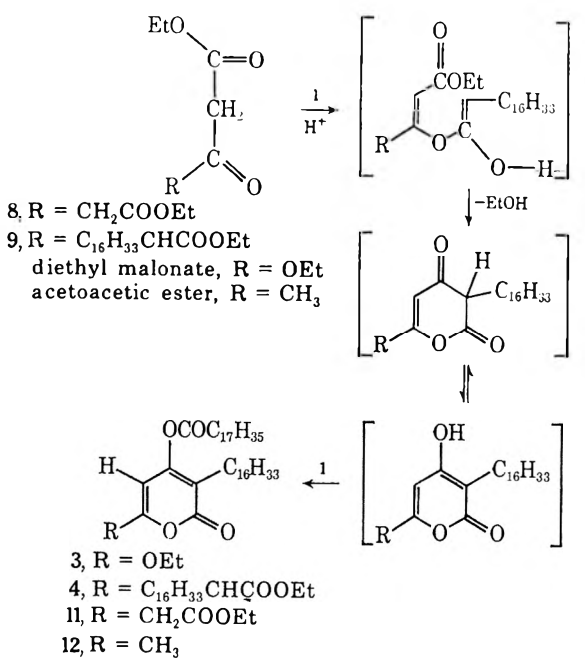
(11) 6-Alkyl pyrones are far more resistant to attempted ring opening than are the highly sensitive 6-alkoxy pyrones.



10 11

C-6 side-chain position, had the expected spectral properties (see Experimental Section).

The reaction of the 3-oxoglutarate **8** (or of the alkylated 3-oxoglutarate **9**) with isopropenyl stearate may be described in the scheme below as a sequence of steps involving an O-acylation, followed by the intramolecular C-acylation ring closure step, and, finally, enol O-acylation. Such a sequence also is in accord with the formation of the pyrone **3** from diethyl malonate and isopropenyl stearate, and also served to predict correctly formation of the pyrone product **12** from the reaction of acetoacetic ester with isopropenyl stearate.[12]



8, R = CH_2COOEt
9, R = $C_{16}H_{33}CHCOOEt$
diethyl malonate, R = OEt
acetoacetic ester, R = CH_3

3, R = OEt
4, R = $C_{16}H_{33}CHCOOEt$
11, R = CH_2COOEt
12, R = CH_3

In the initial O-acylation step, effected by means of isopropenyl stearate, reaction is probably favored by the irreversible elimination of acetone. In agreement with this view, we have found that *ethyl* stearate does *not* react with diethyl malonate under the same conditions.

The reactive 6-alkoxy pyrone system has received only scant attention in the literature. The single preparative procedure utilized by several researchers[13] uses fuming sulfuric acid to effect ring closure of "acetone dicarboxylic acid esters" to give low yields of mixtures of 2- and 6-alkoxy α-pyrones.

(12) The formation of the companion substance **4** in the reaction of isopropenyl stearate with diethyl malonate may result from the ethanolysis of **3** to **6** and then to **9** followed by reaction with isopropenyl stearate as shown in the generalized reaction scheme.

(13) G. Schroeter and C. Stassen, *Ber.*, **40**, 1604 (1907); G. Schroeter, H. Kesseler, O. Liesche, and R. F. Mueller, *ibid.*, **49**, 2697 (1916); G. Schroeter, *ibid.*, **59B**, 973 (1926).

Experimental Section

Melting points were determined on the Kofler stage but are otherwise uncorrected. Infrared spectra were recorded on a Perkin-Elmer[14] Model 457 grating instrument.

6-Ethoxy-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (3).—Isopropenyl stearate[15] (8.03 g, 0.0248 mol), diethyl malonate (10 ml, 0.066 mol), and *p*-toluenesulfonic acid (0.1 g) were heated at the boiling temperature until acetone evolution ceased[3f] (30–40 min). On cooling to 25°, a crystalline product separated and was collected, washed with hexane, and recrystallized from hexane (yield 70%): mp 76.0–76.7°; ir (CS_2) 1771 (enol ester), 1740 (lactone), and 1640 (C=C), characteristic doublet at 1111 and 1128 cm^{-1}; uv max (C_2H_5OH) 227 nm (ϵ 5800), 315 (8700); nmr ($DCCl_3$) δ 5.32 (s, 1, ring proton), 4.25 (q, 2, ethyl), two unresolved triplets centered at 2.32 and 2.58 ppm (α-acyl protons and alkyl ring-adjacent methylene protons); mass spectrum *m/e* (rel intensity) 646 (28, molecular ion), 380 (100), 284 (27), 267 (33), 222 (25), and 169 (18).

Anal. Calcd for $C_{41}H_{74}O_5$: C, 76.11; H, 11.53. Found: C, 76.19; H, 11.72.

Diethyl 2-Hexadecyl-3-stearoyloxy-2-pentenedioate (6). Procedure A.—A sample of **3** (100 mg) was heated in 10 ml of C_2H_5OH on the steam bath for 20 min without catalyst. On evaporation of the solvent a residue of crystalline **6**, mp 33–34°, was obtained identical in ir with an authentic specimen.

Procedure B.—Attempted purification of **3** by slow partition chromatography on silica gel (10 g impregnated with 4 ml of C_2H_5OH) (98% CH_2Cl_2/2% C_2H_5OH moving phase) gave pure **6** quantitatively: mp 48°; ir (CS_2) 1760 (enol ester C=O), 1745 (saturated ester C=O), 1716 (α,β-unsaturated ester C=O), 1629 (C=C), and 1112 cm^{-1} (prominent peak); nmr ($CDCl_3$) δ 3.75 (s, 2), overlapping quartets centered at 4.20 and 4.43 (4), 2.0–2.7 ppm (4); uv max (C_2H_5OH) 222 nm (ϵ 10,250); mass spectrum *m/e* (rel intensity) 692 (8, molecular ion), 426 (80), 381 (70), 362 (100), 267 (70).

Procedure C.—Diethyl 3-oxoglutarate[10] (19 g, 0.062 mol) in 60 ml of dry C_2H_5OH containing 2 g of dissolved sodium, 2 g of sodium iodide, and 11.5 g (0.062 mol) of hexadecyl bromide was refluxed for 7 hr and let stand overnight. The mixture was acidified (dilute HCl), extracted with ether, and dried (Na_2SO_4). After removal of solvent, the product was purified by chromatography on silica gel. The product, eluted with CH_2Cl_2, after recrystallization from pentane, melted at 48.0–48.2° (lit. mp 47–48°),[16] yield 10 g of diethyl 2-hexadecyl-3-oxoglutarate. The alkylated glutarate (0.21 g, 0.5 mmol) in 1 ml of dry pyridine was added to a cold solution of stearoyl chloride (160 mg) in 2 ml of pyridine and the mixture was then stirred at room temperature for 3.5 hr. After dilution with water, acidification (HCl), extraction (CH_2Cl_2), and drying (Na_2SO_4), the product showed the same infrared spectrum as **6** prepared from **3**. Purification was effected by chromatography on silica gel (note: Florisil is destructive) to give a product, mp 47–48°, identical with **6** described in procedures A and B above (and different from 2-hexadecyl 3-oxoglutarate coincidentally melting at the same temperature). The analytical sample crystallized from pentane retained one molecule of (clathrated?) pentane removable by a single recrystallization from carbon tetrachloride.

Anal. Calcd for $C_{43}H_{80}O_6$: C, 74.51; H, 11.64. Found: C, 74.57; H, 11.72.

Selective Ethanolysis of 6 to Diethyl 2-Hexadecyl-3-oxoglutarate (9).—To a sample of **6** (114 mg) in 10 ml of absolute ethanol was added 1 drop of concentrated sulfuric acid. The mixture was stirred and refluxed for 16 hr, poured into 25 ml of water, and extracted with ether to give, after solvent removal, 90 mg of residue. Crystallization from pentane gave 30 mg of starting material. The mother liquor fraction gave 59 mg of diethyl 2-hexadecyl-3-oxoglutarate, mp 43–45°, identical in ir and tlc R_f value with an authentic specimen.

Ethanolysis of 3 to Ethyl Stearoylacetate.—A sample of **3** (0.25 g) was refluxed for 2.5 hr with sodium ethoxide (from 0.06 g of Na) in 20 ml of absolute ethanol. After acidification (HCl), extraction (CH_2Cl_2), drying the organic layer, and removal of solvent, the residue was chromatographed on Florisil to give

(14) Reference to brand or firm name does not constitute endorsement by the U. S. Department of Agriculture over others of a similar nature not mentioned.

(15) E. S. Rothman and S. Serota, *J. Amer. Oil Chem. Soc.*, **48**, 373 (1971).

(16) E. Graf and K. C. Liu, *Arch. Pharm. (Weinheim)*, **300** (1), 348 (1967).

ethyl stearate, methyl heptadecyl ketone, and ethyl stearoylacetate, identical in ir and melting point with an authentic sample.[17]

Hydrolysis (Complete) of 3 to Methyl Heptadecyl Ketone.—A solution of **3** (0.14 g) in 9 ml of methanol and 1 ml of water containing 0.36 g of sodium hydroxide was refluxed for 2.3 hr, cooled, acidified (HCl), extracted into methylene chloride, and dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by chromatography on silica gel. The 70% CH_2Cl_2–30% pentane eluate gave quadrilateral crystals, 30 mg, from cold methanol, identical in ir, glc retention time, and mass spectrum (molecular ion 282 g/m) with an authentic specimen. Stearic acid, 60 mg, mp 69–70°, was found in the later eluates.

6-(α-Carbethoxyheptadecyl)-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (4).—Diethyl 2 hexadecyl-3-oxoglutarate (9) (2.3 g, 5.4 mmol) and isopropenyl stearate (3.2 g, 0.01 mol) were heated with 5 mg of *p*-toluenesulfonic acid to 190° for 25 min, during which time acetone was evolved. Chromatography of the cooled reaction mixture on Florisil using warm 5% CH_2Cl_2–95% hexane as the eluting agent (to prevent crystallization on the column) gave a good yield of **4** in the earliest cuts. Recrystallization from hexane gave the analytical sample, mp 71–72°, identical in ir, nmr, and melting point with a sample laboriously isolated from mother liquors from the isopropenyl stearate–diethyl malonate reaction mixture described above. The product showed the following spectra: nmr ($CDCl_3$) δ 6.15 (s, 1), 4.23 (q, 2), 3.45 (t, 1), 2.5 (two overlapping α-methylene triplets); ir (CS_2) 1770 (enol ester C=O), 1730 (lactone C=O), 1648 (C=C), 1109 cm^{-1} (characteristic peak); mass spectrum *m/e* (rel intensity) 912 (1, molecular ion), 647 (13), 646 (20), 629 (10), 602 (16), 435 (16), 435 (6), 422 (6), 336 (100) ($C_{21}H_{36}O_3$), 112 (25); uv max (C_2H_5OH) 210 nm (ε 9000), 300 (10,300).

Anal. Calcd for $C_{59}H_{108}O_6$: C, 77.57; H, 11.92. Found: C, 77.88; H, 12.16.

6-(α-Carboxyheptadecyl)-3-hexadecyl-4-hydroxy-2*H*-pyran-2-one. Hydrolysis of 4 to 10.—A sample of **4** (0.1 g) in 6 ml of ethanol containing 0.17 g of potassium hydroxide was refluxed for 3 hr and let stand for 24 hr. After acidification (HCl), extraction (CH_2Cl_2), drying (Na_2SO_4), and solvent evaporation, the residue was chromatographed on silica gel. Elution with methylene chloride removed impurities. Elution with ether gave the product acid, mp 109–110°, unchanged by recrystallization from pentane: uv max (C_2H_5OH) 210 nm (ε 12,900), 292 (9000); ir ($CHCl_3$) broad band 3450–2400 (OH), broad band 1660–1710 (C=O), 1582 cm^{-1}.

Anal. Calcd for $C_{39}H_{70}O_5$: C, 75.68; H, 11.40. Found: C, 75.59; H, 11.29.

6-Carbethoxymethylene-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (11).—A mixture of diethyl 3-ketoglutarate (8) (2.0 g, 0.01 mol), isopropenyl stearate (4.5 g, 0.013 mol), and *p*-toluenesulfonic acid (160 mg) was heated at 160° for 23 min. After cooling, the mixture was dissolved in pentane and cooled to deposit 1.05 g of the α-pyrone **11**. One pass through a short column of Florisil using 25% methylene chloride in pentane as eluting agent gave, after isolation and recrystallization, analytically pure material: mp 72–73°; nmr ($CDCl_3$) δ 6.3 (s, 1), 4.35 (q, 2), 3.61 (s, 2); ir (CS_2) 1770, 1730, 1648, 1109 cm^{-1}; mass spectrum *m/e* (rel intensity) 688 (0.5, molecular ion), 422 (25), 335 (6), 211 (100), 165 (50).

Anal. Calcd for $C_{43}H_{76}O_6$: C, 74.95; H, 11.12. Found: C, 75.13; H, 11.41.

Reaction of Ethyl Acetoacetate with Isopropenyl Stearate. 6-Methyl-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (12).—Isopropenyl stearate (30 g, 0.094 mol) and dry ethyl acetoacetate (37 g, 0.26 mol) were refluxed with 0.05 g of *p*-toluenesulfonic acid for 0.5 hr. Pentane was added to the product and the mixture was cooled in a freezer and then filtered cold. The precipitate and the filtrate were separately chromatographed on silica gel. Elution of the precipitate fraction with pentane containing methylene chloride gave stearic anhydride, ethyl stearate, and **12** (14.6 g, 25%), which melted at 75–76° after recrystallization from pentane: ir (CS_2) 1770, 1729, 1651, 1109 cm^{-1}; nmr ($CDCl_3$) δ 5.98 (s, 1), 2.6 (two overlapping triplets, 4), 2.22 (s, 3), 1.9–0.7 (m, 64); uv max (C_2H_5OH) 292 nm (ε 7000).

Anal. Calcd for $C_{40}H_{72}O_4$: C, 77.86; H, 11.76. Found: C, 78.28; H, 11.87.

The filtrate fraction was eluted with pentane and methylene chloride to give ethyl stearate and 6.0 g (17%) of the enol stearate of ethyl acetoacetate (ethyl 3-stearoyloxy-2-butenoic acid): mp 42.7–43.4°; ir (CS_2) 1768, 1729, 1670, 1220, 1144, 1108, 1055 cm^{-1}; nmr ($CDCl_3$) 5.68 (s, 1), 4.22 (q, 2), 2.58 (t, 2), 2.07 (s, 3), 1.9–0.7 (m, 36); uv max (C_2H_5OH) 218 nm (ε 9000).

Anal. Calcd for $C_{24}H_{44}O_4$: C, 72.68; H, 11.18. Found: C, 72.42; H, 11.28.

Registry No.—**3**, 40317-84-8; **4**, 40110-40-5; **6**, 40110-41-6; **8**, 105-50-0; **9**, 14251-08-2; **10**, 40110-44-9; **11**, 40110-45-0; **12**, 40110-46-1; isopropenyl stearate, 6136-89-6; diethyl malonate, 105-53-3; hexadecyl bromide, 111-82-3; stearoyl chloride, 112-76-5; ethyl acetoacetate, 141-97-9; ethyl 3-stearoyloxy-2-butenoic acid, 40110-47-2.

Acknowledgment.—The authors are grateful to Dr. Charles Hignite of the Massachusetts Institute of Technology and Mr. Calvin Dooley for mass spectrographic data on unusually difficult compounds; to Mrs. A. Kravitz and L. Scroggins for elemental analyses; and to Mr. J. M. Chirinko for technical assistance.

(17) F. Bergel, A. Jacob, A. R. Todd, and T. S. Work, *J. Chem. Soc.*, 1375 (1938).

Notes

The Effect of Substituents on the Carbonyl and Acetylene Stretching Frequencies of Phenylbenzoylacetylenes

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Received March 9, 1972

The efficacy of the carbon–carbon triple bond as a unit which transmits substituent effects has been previously studied by measurement of the ionization constants of phenylpropiolic acids,[1] of rates of esterification of phenylpropiolic acids,[1] and of rates of hydrolysis of phenylpropiolic esters.[2] Comparison of ρ values obtained from ionization of *trans*-cinnamic and phenylpropiolic acids showed no difference between the two systems, *i.e.*, ρ = 0.43 and 0.42, respectively.[3,4] The ρ values obtained from esterification rates of *trans*-cinnamic and phenylpropiolic acids with diphenyldiazomethane were 0.42 and 0.33, respectively,[3] and the ρ values obtained from alkaline hydrolysis of the ethyl *trans*-cinnamates and phenylpropiolates were 1.31[5] and 1.10.[2] Thus it appears in aryl-substituted acetylenes, in spite of an earlier report to the contrary,[6] that the acetylene link transmits electronic effects somewhat less effectively than the ethylene unit. Results of studies on propiolic acids with the substituents directly attached to the triple bond led to the same conclusion.[7] Nevertheless, it seems desirable to test the effectiveness of the acetylene unit to transmit electronic effects by an independent probe, particularly one which in contrast to the previous studies on the arylacetylenes does not involve fully charged intermediates. In view of this and our continuing interest[8] in the effect of substituents on the carbonyl stretching frequency (C=O) of aryl ketones we have measured the C=O of a series of 4-substituted phenylbenzoylacetylenes.

The carbon–carbon triple bond stretching frequency ($\nu_{C\equiv C}$) is generally regarded to be relatively insensitive to substituent effects.[9] The $\nu_{C\equiv C}$ for substituted phenylacetylenes has been reported to show only a very qualitative correlation with the donating–withdrawing ability of the substituent.[10] Correlations between the intensity of the carbon–carbon triple bond stretch and σ^+ have been reported;[11] however, it seems that a correlation of $\nu_{C\equiv C}$ by the Hammett expression has not appeared. It is, therefore, of particular further interest to carefully measure the triple bond stretching frequency of the phenylbenzoylacetylenes under investigation and treat the results with the Hammett expression.

The phenylbenzoylacetylenes were prepared by the method of Bickel,[12] which involves addition of bromine to the chalcone, dehydrohalogenation by NaOAc–HOAc of the resulting chalcone dibromide to produce the corresponding α-bromochalcone, and finally KOH dehydrohalogenation of the latter to yield the desired acetylene. In our hands the final step gave erratic yields for most compounds and failed completely with certain compounds which were substituted with electron donors.

The 4-substituted phenylbenzoylacetylenes employed in this investigation and their stretching frequencies values, which were determined in carbon tetrachloride solution, are listed in Table I. The $\nu_{C=O}$ values were correlated employing σ^+ values obtained from the review of Ritchie and Sager.[13] Table II contains the results of a statistical analysis of the correlations carried out according to the approach of Jaffe.[14] The correlation between σ^+ and $\nu_{C=O}$ is only fair, r = 0.966.

A comparison of the ρ value obtained from the

Table I

Phenylbenzoylacetylenes Stretching Frequencies

Compd	Substituent	$\nu_{C=O}$	$\nu_{C\equiv C}$
1	4-CH_3O	1645.0	2196.0
2	4-F	1649.7	2200.0
3	4-H	1649.2	2202.0
4	4-Cl	1650.5	2201.3
5	4-Br	1650.0	2202.0
6	3,4-DiCl	1650.7	2206.2
7	4-NO_2	1653.8	2207.0

Table II

Results of Statistical Treatment Using σ^+ Constants[a,b]

	n	ρ	s	i	c
$\nu_{C=O}$	7	5.10	0.74	1649.3	0.966
$\nu_{C\equiv C}$	7	7.39	0.83	2201.3	0.979

[a] See ref 8c. [b] n = number of points; ρ = slope as determined by the method of least squares; s = standard deviation; i = intercept; c = correlation coefficient.

(1) I. J. Solomon and R. Filler, *J. Amer. Chem. Soc.*, **85**, 3492 (1963).
(2) R. Fuchs, *J. Org. Chem.*, **28**, 3209 (1963).
(3) K. Bowden and D. C. Parkin, *Can. J. Chem.*, **46**, 3909 (1968).
(4) This conclusion is questionable since the ionization of the cinnamic acids was measured in water and the propiolic acids ionization was measured in 50% ethanol.
(5) J. J. Bloomfield and R. Fuchs, *J. Org. Chem.*, **26**, 2991 (1961).
(6) J. D. Roberts and R. A. Carboni, *J. Amer. Chem. Soc.*, **77**, 5554 (1955).
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(8) (a) W. F. Winecoff, III, and D. W. Boykin, Jr., *J. Org. Chem.*, **37**, 674 (1972); (b) P. J. Duke and D. W. Boykin, Jr., *ibid.*, **37**, 1436 (1972); (c) N. L. Silver and D. W. Boykin, Jr., *ibid.*, **35**, 759 (1970); (d) A. Pérjessy, D. W. Boykin, Jr., L. Fišera, Krutošíkova, and J. Kováč, *ibid.*, in press.
(9) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, London, 1968, p 77.
(10) A. D. Allen and C. D. Cook, *Can. J. Chem.*, **41**, 1084 (1963).
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phenylbenzoylacetylene series (ρ 5.10) with those obtained from $\nu_{C=O,s\text{-}cis}$ (ρ 5.62) and $\nu_{C=O,s\text{-}trans}$ (ρ 7.20) of chalcone[8c,15] shows that transmission *via* the carbon–carbon triple bond to the carbonyl group is as effective as that through the double bond with the carbonyl group in the s-cis conformation and is somewhat less efficient than that through the double bond with the carbonyl group in the s-trans conformation. Thus it would appear that, in spite of the low polarizability[16] of the carbon–carbon triple bond, it functions well as a transmitting unit, albeit not quite so effectively as the carbon–carbon double bond.

The stretching frequencies for the carbon–carbon triple bond are correlated reasonably well with σ^+ values; r = 0.979 (Table II). This apparently constitutes the first reported case of a quantitative correlation of carbon–carbon triple bond stretching frequencies by the Hammett expression. It is of interest to note that the correlations between $\nu_{C\equiv C}$ and σ or σ^0 are significantly poorer than with σ^+. This is in contrast to the correlation of the carbon–nitrogen bond stretch for benzonitriles, which has been found to be better correlated by σ.[17] This result suggests that during the carbon–carbon triple-bond stretch a partial positive change is generated on the benzyl type carbon analogous to that for the carbonyl stretch. In this case this result may be a consequence of the fact that the triple bond is part of an α,β-unsaturated ketone system. Comparison of the magnitude of the ρ value (7.39) obtained from the carbon–carbon triple-bond data with that obtained from benzonitriles[17] for the carbon–nitrogen triple bond (ρ 5.4) indicates, in contrast to previous suggestions, that $\nu_{C\equiv C}$ is relatively sensitive to substituent effects. Additional sets of $\nu_{C\equiv C}$ and $\nu_{C\equiv N}$ data must be collected before the questions of the relative sensitivity of these stretches to substituents and of the best choice of σ constants to assess this sensitivity can be answered with a reasonable degree of confidence.

Experimental Section

Infrared Frequencies.—The ir stretching frequencies were determined using a Beckman IR-12 spectrometer operated in the expanded scale mode at scan rates of 8 cm^{-1}/min, chart speeds of 1 in./min, and period setting of 8 (see ref 8c for comments on error). The instrument was calibrated as previously described;[8c] see also ref 8c for comments about errors. The spectra were taken on *ca.* 5% solutions in spectral grade carbon tetrachloride at 35 ± 4° in a matched set of KBr cells of path length of 0.05 mm. The frequencies were taken as the point of half-band height at half-band width. The values shown in Table I are the average of six different scans taken on two different days, all of which gave frequencies which were within 0.3 cm^{-1} of one another.

Phenylbenzoylacetylenes.—The method used to prepare the phenylbenzoylacetylenes is essentially as described by Bickel[12] and modified by Lutz and Black.[18] In a typical reaction sequence 6.0 g of Br_2 was added dropwise to 10.0 g of 4-bromochalcone in 200 ml of HOAc at 50–60°. After addition was complete the solution was heated to reflux, 4.0 g of Na_2CO_3 was cautiously added, and refluxing was continued for 3 hr. The solution was poured into H_2O and extracted with Et_2O. The organic layer was washed (H_2O), dried ($CaSO_4$), and evaporated. The oily α-bromochalcone was used directly in the next reaction by dissolving it in 50 ml of acetone, adding to it 30 ml of H_2O, and heating to reflux. To the refluxing solution was added dropwise during *ca.* 20 min a solution of 4.0 g of KOH in 20 ml of H_2O. The reaction mixture was allowed to reflux for an additional 20 min, then it was poured into H_2O, extracted (Et_2O), dried ($CaSO_4$), and evaporated. The black residue obtained was purified by column chromatography over alumina employing benzene–low-boiling petroleum ether mixtures as the eluent. The final dehydrohalogenation step failed for 4-methyl- and 4-dimethylamino-α-bromochalcone.

Table III contains melting points obtained with a Thomas-Hoover Uni-Melt and they are uncorrected. Also included in Table III are the uv data obtained on the phenylbenzoylacetylenes in *ca.* 10^{-5} *M* absolute ethanol solutions using a Beckman Acta-V spectrometer. Analyses were obtained by Atlantic Microlab, Atlanta, Ga.

TABLE III
PHENYLBENZOYLACETYLENES[a]

Compd	Mp, °C	$\lambda \times 10^{-3}$, cm^{-1}	($\epsilon \times 10^{-3}$)
1	81–82 (82.5–83.5)[b]	30.6	(23.7)
		38.0	(17.6)
		40.8	(16.5)
2	79–79.5	33.1	(15.4)
		34.7	(15.5)
		37.1	(18.7)
		45.2	(18.8)
3	48–49.5 (49–50)[c]	33.3	(17.7)
		34.8	(17.8)
		36.9	(15.7)
		45.2	(14.0)
4	101–102	32.5	(23.0)
		34.2	(21.3)
		36.6	(16.0)
		43.8	(14.5)
5	117–118	32.4	(36.1)
		34.1	(34.0)
		37.4	(28.4)
		44.2	(21.6)
6	113–114	32.6	(19.4)
		34.8	(22.5)
		43.0	(14.9)
7	148–148.5	33.8	(26.6)

[a] All compounds except 1 and 3 were analyzed for C, H, and all results were within ±0.3 of theory. [b] Literature melting point in parenthesis; see ref 18. [c] C. Dufraisse, *Ann. Chim. (Paris)*, **17**, 133 (1922).

Registry No.—1, 20442-66-4; 2, 39833-45-9; 3, 7338-94-5; 4, 29776-35-0; 5, 39833-48-2; 6, 39900-69-1; 7, 39833-49-3.

Acknowledgments.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We wish to thank Professor R. E. Lutz for samples of 1 and 3. We thank M. E. Estes and R. W. Woodard for technical assistance.

(15) These values for ρ were obtained by taking $\nu_{C=O}$ data for 4-$(CH_3)_2N$-, 4-NH_2-, 4-CH_3O-, 4-CH_3-, 4-H-, 4-F-, 4-Cl-, 3-Cl, 4-CN, and 3-NO_2 chalcones from A. Perjessy, *Chem. Zvesti*, **23**, 343 (1969), and treating the data with σ^+ by our statistical method.

(16) (a) A. D. Walsh, *Quart. Rev., Chem. Soc.*, **2**, 78 (1948); (b) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3454 (1953); (c) H. Sinn, *Z. Electrochem.*, **61**, 989 (1961).

(17) (a) C. N. R. Rao and R. Venkataraghavan, *Can. J. Chem.*, **39**, 1757 (1961). (b) Using our statistical treatment on the $\nu_{C\equiv N}$ values obtained in CCl_4 on benzonitriles reported by M. R. Mander and H. W. Thompson, *Trans. Faraday Soc.*, **53**, 1402 (1957), the correlation coefficient with σ was 0.966 and with σ^+ was 0.943. The substituted benzonitriles were 4-OH, 4-CH_3O, 4-CH_3, 3-CH_3, 4-H, 4-Cl, 4-CN, 3-NO_2, and 4-NO_2.

(18) W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **77**, 5134 (1955).

Cleavage of the *N*-Carbobenzyloxy Group in Neutral and Basic Media. Neighboring-Group Participation of the Carbamate Moiety

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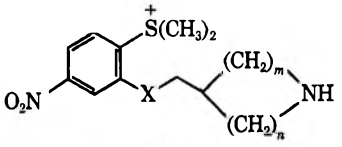
Received February 7, 1973

In the course of continuing our kinetic investigations of nonenzymic transmethylation reactions,[1] we wished to synthesize several compounds of type **1**. A proposed synthesis of these molecules involved a Wittig condensation of 2-methylthio-5-nitrobenzaldehyde[2] with the appropriate phosphonium salt to give an amino-protected olefin precursor of **1**, X = CH_2. Alternatively, condensation of 2-methylthio-5-nitrophenol with an appropriate halide should give the protected ether precursor of **1**, X = O. Our synthetic studies have revealed that the carbobenzyloxy (Cbz) group in certain *N*-Cbz precursors of **1** readily undergoes cleavage of the benzyl moiety. The Cbz residue is generally thought to be stable to neutral and basic conditions, and is one of the most widely used amino protecting groups.[3] The labilization of this group under the conditions described herein places specific limitations on the utility of this group in the synthesis of polyfunctional molecules.

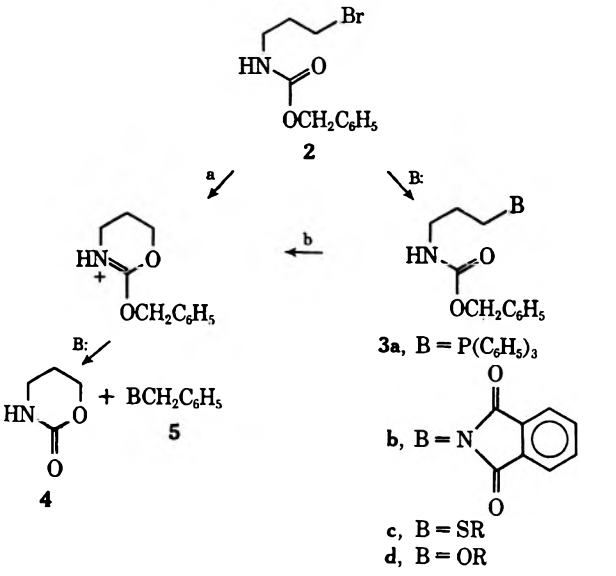


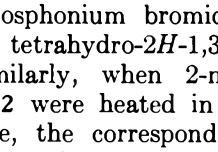
1

X = CH_2, O
$m + n$ = 1, 3, 4

When a solution of triphenylphosphine and 3-(*N*-Cbz)amino-1-bromopropane (**2**)[4] in nitromethane was heated overnight, only 30% of the desired phosphonium salt, **3a**, was isolated; the major products were benzyltriphenylphosphonium bromide (**5a**)[5] and the cyclic carbamate, tetrahydro-2*H*-1,3-oxazin-2-one (**4**)[6] (Scheme I). Similarly, when 2-methylthio-5-nitrophenol (**6a**) and **2** were heated in DMF containing sodium methoxide, the corresponding benzyl ether, **6b**, was formed in good yield, and none of the desired ether, **6c**, was obtained. Compound **2** was subjected to the conditions described above, but in the absence of either triphenylphosphine or **6a**. Analysis of the reaction mixture by tlc indicated the presence of benzyl bromide as well as unreacted **2**. These results show that formation of **4** or **5** may occur *via* path a from **2**, but do not rule out path b. It is important to note that the ratio of desired substitution product, **3**, to rearranged products, **4** and **5**, apparently depends on the nucleophile employed in the reaction. Thus, treatment of **2** with nucleophiles such as potassium phthalimide,[4] thiolate anions,[7] or certain oxy anions[8] gave **3b**, **3c**, or **3d**, respectively, as the only products isolated. This is to be compared with the results obtained in the present work, whereby reaction of **2** and triphenylphosphine led to a mixture of products, and only **6b** was obtained on treatment of **2** with **6a**.

SCHEME I



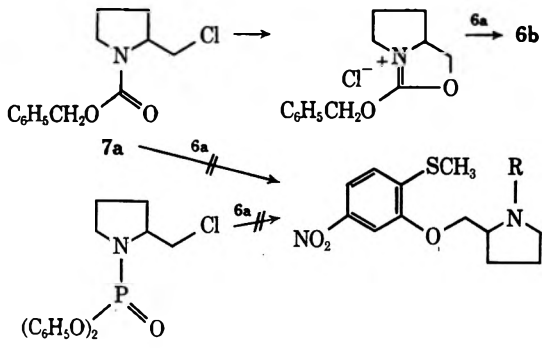


6a, R = H
b, R = CH_2Ph
c, R = $(CH_2)_3NHCbz$
d, R = $(CH_2)_3CH_3$

The cyclization reaction of Scheme I is not a unique property of **2**. This can be shown by the results obtained when we attempted to synthesize compounds of type **1** which incorporated the cyclic secondary amines pyrrolidine or piperidine in the side chain ortho to the SCH_3 group. Heating a methanolic solution of α-(chloromethyl)-*N*-Cbz-pyrrolidine (**7a**) and **6a** with sodium methoxide gave only the benzyl ether **6b**; none of the desired ether precursor of **1** was obtained (Scheme II). In order to avoid the undesired cyclization reaction, the Cbz group of **7a** was replaced by a phosphoramidate group (**7b**). No reaction was observed to occur between **6a** and **7b**; only unreacted starting materials were detected on tlc. Similarly, when β-(chloromethyl)-*N*-Cbz-pyrrolidine was used in place of the α isomer, **7a**, no reaction with **6a** was observed, even in the presence of potassium iodide. These results indicate that displacement of chloride ion by **6a** from either α- or β-(chloromethyl)pyrrolidine is not readily accomplished. However, when intramolecular participation by the Cbz group is possible, as in **7a**, the chloride ion is readily displaced and sub-

(1) J. K. Coward and W. D. Sweet, *J. Org. Chem.*, **36**, 2337 (1971).
(2) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 2425 (1927).
(3) R. A. Boissonnas, *Advan. Org. Chem.*, **3**, 159 (1963).
(4) B. R. Baker and J. K. Coward, *J. Heterocycl. Chem.*, **4**, 202 (1967).
(5) F. Ramirez, O. P. Madan, and C. R. Smith, *Tetrahedron*, **22**, 567 (1966).
(6) (a) E. Dyer and H. Scott, *J. Amer. Chem. Soc.*, **79**, 672 (1957). (b) W. Hechelhammer and M. Coenen, German Patent 839,037 (1957); *Chem. Abstr.*, **51**, 14823e (1957).
(7) J. K. Coward and W. D. Sweet, *J. Med. Chem.*, **15**, 381 (1972).
(8) (a) Only **3d** (R = p-$CH_2SC_6H_4$) was isolated on treatment of **2** with p-(methylthio)phenol in refluxing ethanolic NaOMe for 6 hr: mp 75–76°. *Anal.* Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.40; N, 4.22. Found: C, 65.34; H, 6.58; N, 4.42. (b) B. R. Baker and E. E. Janson, *J. Med. Chem.*, **12**, 672 (1969), prepared **3d** (R = 2-Cl, 4-$NO_2C_6H_3$) in 37% yield by treating **2** with 2-chloro-4-nitrophenol in DMF and K_2CO_3 at 85° for 36 hr.

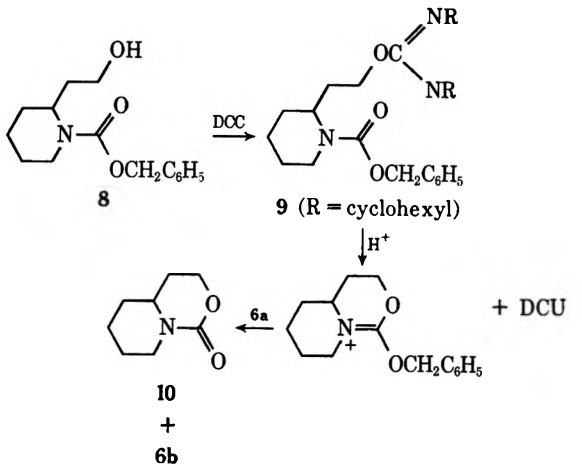
SCHEME II



sequent attack by **6a** on the bicyclic intermediate yields the benzyl ether, **6b**. By contrast, *n*-butyl chloride reacts with **6a** to give **6d** in good yield.

With the above data available, we decided to investigate the coupling of **6a** with alcohols, using dicyclohexylcarbodiimide (DCC) as the condensing agent.[9] Using this method, benzyl alcohol and **6a** were readily condensed to give **6b**. When α-(2-hydroxyethyl)-*N*-Cbz-piperidine (**8**) and **6a** were heated for 24 hr at 110° in the presence of DCC, only the benzyl ether **6b** was isolated, again indicating labilization of the Cbz group (Scheme III). This probably occurs *via* anchi-

SCHEME III

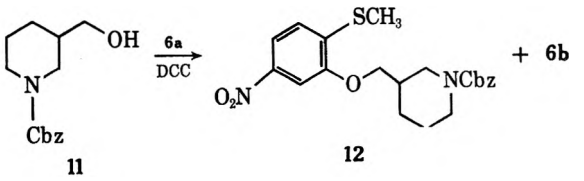


meric assistance in the alkylpseudourea intermediate **9**. Direct cyclization[10] of hydroxyalkyl carbamate **8** to give **10** and benzyl alcohol was ruled out by the following data. Compound **8** was subjected to the conditions described above, except in the absence of DCC and **6a**. No benzyl alcohol was detected by tlc analysis; only unreacted **8** was present in the reaction mixture. When the DCC coupling reaction was carried out using **6a** and β-(hydroxymethyl)-*N*-Cbz-piperidine (**11**), the desired ether precursor was obtained as the major product, together with a small amount of benzyl ether **6b** (Scheme IV). Presumably, the difficulty in formation of the bicyclic carbamate[11] involved in labilization of the Cbz group in the β isomer precludes formation of **6b** as the major product, and this forces formation of the desired ether, **12**.

Participation of the amide group in many solvolysis

(9) F. L. Bach, *J. Org. Chem.*, **30**, 1300 (1965).
(10) E. Dyer and R. E. Read, *ibid.*, **24**, 1789 (1959).
(11) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **80**, 6412 (1958).

SCHEME IV



reactions is a well-established fact.[12] However, there are very few examples of similar participation of the carbamate group. The cyclization of carbamates of γ-aminoalkyl alcohols[9] and β-aminoalkyl halides[13] has been known for some time, and occurs at elevated temperatures under high vacuum. More closely related to the present work is the report of Ginsberg and Wilson,[14] who failed to observe any oxazoline formation from *N*-Cbz-*O*-tosylethanolamine in hot alcoholic sodium methoxide. The study described herein has shown that the Cbz group can be labilized *via* its participation in the displacement of a suitably positioned leaving group to give an incipient benzyl carbonium ion as shown in Schemes I–III.

Experimental Section[15]

***N*-Cbz-3-aminoprop-1-yltriphenylphosphonium Bromide (3a).**—The *N*-Cbz protected 3-amino-1-bromopropane[4] (11.55 g, 42.5 mmol) was dissolved in 50 ml of nitromethane, and 10.5 g (40 mmol) of triphenylphosphine was added in one portion. This mixture was heated overnight at reflux temperature, after which the resulting orange solution was allowed to cool slowly to ambient temperature. The white crystals which separated on cooling were collected by filtration, yielding 10.0 g (58%) of triphenylbenzylphosphonium bromide (**5a**); a small portion was recrystallized from $CHCl_3$–ether to give a white solid, mp 289–294° (lit.[5] mp 290–291°). The nitromethane filtrate was concentrated *in vacuo*, the oily residue was triturated with EtOAc, and the insoluble solid was collected by filtration to give 6.5 g (30%) of **3a**, an off-white material, mp 159–162°. Recrystallization of a small portion from ethanol–ether gave white crystals, mp 170–175°.

Anal. Calcd for $C_{29}H_{29}BrNO_2P$: C, 65.17; H, 5.46; N, 2.62. Found: C, 64.97; H, 5.25; N, 2.39.

The ethyl acetate filtrate was concentrated *in vacuo* to give 2.8 g of a yellow-orange oily residue. Distillation of this material gave 1.72 g (43%) of **4**, bp 150–153° (1.3 mm) [lit.[6b] bp 130–135° (0.4 mm)].

2-Methylthio-5-nitrophenol (6a).—2-Amino-5-nitrophenol was diazotized and converted to the ethyl xanthate ester by conventional procedures.[16] The moist xanthate was treated with ethylenediamine at 30° under N_2 according to the method of Mori and Nakamura.[17] After 3 hr the basic solution was added to concentrated H_2SO_4 and the precipitate was filtered. The weight of crude 2-mercapto-5-nitrophenol amounted to about 52% yield from the nitroamino phenol.

The crude mercaptophenol (9 g, 53 mmol) was stirred overnight at room temperature with NaOMe (2.86 g, 53 mmol) in 100 ml of methanol and 15 g (110 mmol) of methyl iodide. The resulting solution was concentrated and the residue was triturated with hot benzene. Evaporation of the benzene supernatant left 4.7 g of an orange solid. Recrystallization from CCl_4 and

(12) T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, p 187.
(13) E. Katchalski and D. Ben Ishai, *J. Org. Chem.*, **15**, 1067 (1950).
(14) S. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.*, **86**, 4716 (1964).
(15) All melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were recorded on a Varian A-60 or a Jeol minimar spectrometer. Tlc were run on Eastman chromatograms 6060 (silica gel with fluorescent indicator). Spots were detected by visual examination under uv light or iodine. All purified compounds were homogeneous by tlc and had the expected spectral characteristics.
(16) D. S. Tarbell and D. K. Fukushima, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 809.
(17) K. Mori and Y. Nakamura, *J. Org. Chem.*, **34**, 4170 (1969).

final purification by sublimation gave 2.7 g (28%) of a yellow solid, mp 130–140° (lit.[3] mp 146–147°). This material was suitable for further transformations.

Benzyl (2-Methylthio-5-nitro)phenyl Ether (6b). A. By Condensation of 6a with 2.—The sodium salt of **6a** was prepared from 185 mg (1 mmol) of **6a** and 2 ml of a 0.5 *M* methanolic sodium methoxide solution. Methanol was evaporated and bromide **2a** (272 mg, 1 mmol) dissolved in 3 ml of DMF was added. The mixture was heated at 75° for 15 hr, poured into ice water, and extracted with methylene chloride. The organic phase was washed consecutively with 1 *N* NaOH, water, and saturated NaCl solution. Methylene chloride was evaporated and the residue was chromatographed on a silica gel column with benzene as the eluent. A yellow solid weighing 137 mg (50%) was obtained: mp 101–103°; ir (CCl_4) 1520, 1338 (NO_2), 1243, 1065 cm^{-1} (C=COC); nmr (CCl_4) δ 2.4 (s, 3 H, SCH_3), 5.1 (s, 2 H, OCH_2Ar), 7.35 (m, 8, Ar H).

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.08; H, 4.76; N, 5.09. Found: C, 60.84; H, 4.85; N, 5.31.

B. By Condensation of 6a with 7a.—Methylthio ether **6a** (185 mg, 1 mmol) was dissolved in 2 ml of a 0.5 *M* methanolic sodium methoxide solution and mixed with pyrrolidine **7a**[18] (254 mg, 1 mmol) in 1 ml of methanol. The mixture was refluxed for 8 hr and then allowed to stand overnight at room temperature. Methanol was evaporated, and the residue was extracted between 1 *N* NaOH and ether. The organic solution was dried and ether was removed. Chromatography of the residue as above gave a yellow solid. Its nmr and ir were identical with those of the sample obtained *via* method A.

C. By Condensation of 6a with 8.—A mixture of **8**[20] (132 mg, 0.5 mmol), 114 mg (0.55 mmol) of DCC, and 93 mg (0.5 mmol) of **6a** was heated in a flask purged with Ar at 110°. After 24 hr, the contents were washed with acetone and filtered. The filtrate was concentrated and the residue was extracted between CCl_4 and 1 *N* KOH. The organic phase was dried with saturated NaCl solution and then anhydrous $MgSO_4$. The residue left from evaporation of CCl_4 was triturated with petroleum ether (bp 30–60°). A yellow solid weighing 86 mg (62%) was obtained when the petroleum ether was removed. The solid had the same ir and nmr spectrum as the sample obtained *via* method A.

D. By Condensation of 6a with Benzyl Alcohol.—A mixture of benzyl alcohol (130 mg, 1.2 mmol), methylthio ether **6a** (185 mg, 1 mmol), and DCC (227 mg, 1.1 mmol) was heated at 105° for 81 hr under Ar. The contents were washed with CCl_4 and filtered. The filtrate was washed with 1 *N* KOH. The organic layer was dried and concentrated. A residue weighing 250 mg (91%) was obtained. Its spectral properties were identical with those of the sample obtained by method A.

***n*-Butyl (2-Methylthio-5-nitro)phenyl Ether (6d).**—A solution containing methylthiophenol **6a** (185 mg, 1 mmol) and 2 ml of 0.5 *M* methanolic NaOMe was evaporated to dryness. Then 3 ml of DMF was added, followed by 0.2 ml (177 mg, 1.9 mmol) of *n*-butyl chloride and a pinch of powdered potassium iodide. The mixture was heated at 62° for 12 hr, and then poured into a 1 *N* NaOH solution. The precipitate was filtered and sucked dry. The crude residue (**6d**) weighed 110 mg (45% yield), and gave only one major spot on tlc. Treatment of this material with methyl iodide and $AgClO_4$ gave the dimethylsulfonium salt, mp 123–127°.

Anal. Calcd for $C_{12}H_{18}NClO_7S$: C, 40.6; H, 5.07; N, 3.95. Found: C, 40.36; H, 5.11; N, 3.96.

***N*-Cbz-β-piperidinomethyl (2-Methylthio-5-nitro)phenyl Ether (12).**—A mixture of β-(hydroxymethyl)-*N*-Cbz-piperidine (**11**)[21] (125 mg, 0.50 mmol), DCC (114 mg, 0.55 mmol), and **6a** (93 mg, 0.5 mmol) was heated at 110° in a flask purged with Ar. After 24 hr, the contents were washed with acetone and filtered. The filtrate was worked up as desdribed for **6b** (method C). The residue was chromatographed on a preparative tlc plate (silica gel with fluorescent indicator, benzene–ethyl acetate, 20:1, as eluent). Two yellow bands were extruded. One had the same R_f and nmr spectrum as **6b**. The other slower migrating band, obtained as a thick oil, weighed 107 mg (51.5%): ir ($CHCl_3$) 1685 (C=O), 1510, 1334 (NO_2), 1240, 1065 cm^{-1} (C=COC); nmr ($CDCl_3$) δ 1.7 (m, 4 H, ring H), 2.42 (s, 3 H, SCH_3), 3.0 (m, 3 H, ring H), 3.98 (d, J = 5 Hz, 2 H, OCH_2–), 4.3 (m, 2 H, CHNCH), 5.14 (s, 2 H, CH_2Ar), 2.5 (m, 8 H, ArH).

This *N*-Cbz ether (**12**) was methylated with CH_3I and $AgClO_4$ in CH_2Cl_2 and the resulting sulfonium compound was treated with 70% $HClO_4$ to cleave the Cbz group. The diperchlorate ammoniosulfonium salt (**1**, X = O, m = 1, n = 3) was recrystallized from absolute ethanol, mp 182–185°.

Anal. Calcd for $C_{14}H_{22}Cl_2N_2O_{11}S$: C, 33.8; H, 4.43; N, 5.64. Found: C, 34.01; H, 4.47; N, 5.61.

Registry No.—**1** (X = O, m = 1, n = 3) diperchlorate, 39945-31-8; **2a**, 39945-54-5; **3a** bromide, 39945-55-6; **5a** bromide, 1449-46-3; **6a**, 772-42-9; **6a** Na salt, 39945-45-4; **6b**, 39945-46-5; **6d**, 39945-47-6; **6d** dimethylsulfonium perchlorate salt, 39945-48-7; **7a**, 39945-49-8; **8**, 39945-50-1; **11**, 39945-51-2; **12**, 39945-52-3; 3-amino-1-bromopropane, 18370-81-5; triphenylphosphine, 603-35-0; benzyl alcohol, 100-51-6.

Acknowledgment.—This work was supported by grants from the National Cancer Institute (CA 10,748) and the National Institute of Mental Health (MH 18,038). R. L. is a Postdoctoral Fellow supported by USPHS Training Grant GM 0059.

(18) Prepared from α-(chloromethyl)pyrrolidine hydrochloride[19] and CbzCl.

(19) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 982 (1963).

(20) Prepared from commercially available α-(2-hydroxyethyl)piperidine and CbzCl.

(21) Prepared from commercially available β-(hydroxymethyl)piperidine and CbzCl.

An Improved Synthesis of Alkyl-Substituted 1,2-Dithiolium Salts

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Received January 26, 1973

Although there are several convenient routes to aryl-substituted[1-4] 1,2-dithiolium ions (**3**) only two general methods have been published for the preparation of the important alkyl-substituted 1,2-dithiolium ions. Both methods depend on the action of the –S–S– group of either H_2S_x ($x \geq 2$)[5] or Ac–S–S–Ac[6] on the parent β-dicarbonyl compound.

In the present work, based on earlier experiments in these laboratories,[7,8] the combined action of a halogen and hydrogen sulfide on the appropriate β-dicarbonyls readily yields the corresponding 1,2-dithiolium salts (eq 1). The method requires only readily available starting materials, and, fort he 3,5-dimethyl-1,2-dithiolium ion at least, much improved yields are obtained.

With iodine as oxidant, the reaction proceeds smoothly *via* two steps. Firstly, the 1,2-dithiolium ion formed in the oxidizing medium usually separates

(1) H. Prinzbach and E. Futterer, *Advan. Heterocycl. Chem.*, **7**, 39 (1966).

(2) H. Behringer and A. Grimm, *Justus Liebigs Ann. Chem.*, **682**, 188 (1965).

(3) J. P. Guemas and H Quiniou, *C. R. Acad. Sci., Ser. C*, 1805 (1969).

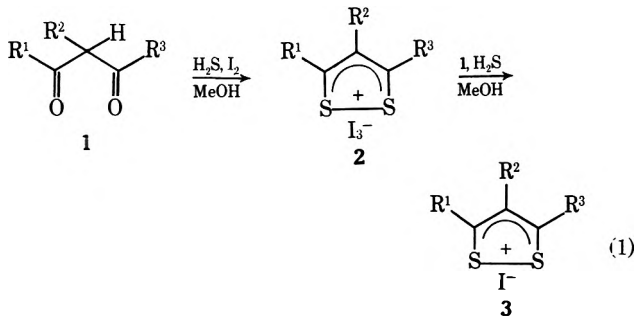
(4) E. Klingsberg, *J. Amer. Chem. Soc.*, **83**, 2934 (1961).

(5) M. Schmidt and H. Schulz, *Chem. Ber.*, **101**, 277 (1968).

(6) H. Hartmann, K. Fabian, B. Bartho, and J. Faust, *J. Prakt. Chem.*, **312**, 1197 (1970).

(7) G. A. Heath, R. L. Martin, and I. M. Stewart, *Chem. Commun.*, 54 (1969).

(8) G. A. Heath, R. L. Martin, and I. M. Stewart, *Aust. J. Chem.*, **22**, 83 (1969).



a, $R^1 = R^3 = Me$; $R^2 = H$
b, $R^1 = Me$; $R^2 = H$; $R^3 = C_6H_5$
c, $R^1 = R^2 = R^3 = Me$
d, $R^1 = R^2 = R^3 = H$

as its triiodide salt (2). This intermediate has been characterized by analysis for the 3,5-dimethyl-1,2-dithiolium ion (**2a**) only, but appears to form with the other 1,2-dithiolium ions studied. Further reaction with H_2S results in complete conversion of this intermediate to the iodide salt (**3a–c**). Bromine has been successfully used as oxidant to form the 3,5-dimethyl-1,2-dithiolium bromide (**4**). No attempt has been made to utilize chlorine as the oxidant.

Two further cations prepared in this work, *viz.*, the 3,4,5-trimethyl- (**3c**) and 3-methyl-5-phenyl-1,2-dithiolium ions (**3b**), suggest that the method may be widely applicable for the preparation of trisubstituted and aryl-substituted cations. The parent compound, 1,2-dithiolium iodide (**3d**), is not obtained from this reaction utilizing malondialdehyde tetraethyl acetal as the "β-dicarbonyl." However, this dithiolium salt has been obtained in reasonable yield from the same reaction in the presence of anhydrous HCl.[9]

Experimental Section

H_2S gas was dried by passage through anhydrous $CaCl_2$ towers. Nmr spectra were obtained at 100 MHz on approximately 0.5 *M* solutions of the salts in trifluoroacetic acid. All chemical shift values (δ, parts per million) are reported relative to internal TMS.

3,5-Dimethyl-1,2-dithiolium Iodide (3a). Method A.—Iodine (25 g) was dissolved in MeOH (AR, 150 ml) containing acetylacetone (10 g), and H_2S was passed through the stirred mixture at room temperature. The ensuing reaction was quite exothermic although cooling was not utilized. Large yellow-green crystals of the triiodide separated initially, but on continued treatment with H_2S they dissolved and were replaced by the dithiolium iodide. The crude product was collected, washed with MeOH, CS_2, and Et_2O, and recrystallized from glacial acetic acid (12 g), mp 148–150° (reported[6] mp 146–150°), nmr CH_3, 3.12 (6), H, 8.21 (1).

Anal. Calcd for $C_5H_7IS_2$: C, 23.3; H, 2.7; I, 49.2; S, 24.8. Found: C, 23.1; H, 2.8; I, 49.3; S, 24.8.

Method B.—H_2S was bubbled into a vigorously stirred solution of acetylacetone (50 g) and iodine (100 g) in MeOH (200 ml). After 2 hr the triiodide salt had crystallized out. The reaction mixture was brought to reflux and H_2S was passed for a further 2 hr. At this stage, the hot solution was decanted from the sulfur (~5 g) and diethyl ether (500 ml) was added. On cooling the solution deposited 60 g of the pure crystalline, yellow iodide salt, yield 60%.

Anal. Calcd for $C_5H_7IS_2$: C, 23.3; H, 2.7; I, 49.2; S, 24.8. Found: C, 23.5; H, 2.7; I, 48.8; S, 24.7.

3,5-Dimethyl-1,2-dithiolium Triiodide (2a).—A sample of the 3,5-dimethyl-1,2-dithiolium triiodide intermediate formed in the preparation of the iodide salt was isolated and twice recrystallized from MeOH, mp 118–120° (reported[6] mp 118–125°), nmr CH_3, 3.12 (6), H, 8.19 (1).

Anal. Calcd for $C_5H_7I_3S_2$: C, 11.7; H, 1.4; I, 74.4; S, 12.5. Found: C, 12.0; H, 1.4; I, 72.9; S, 11.9.

3,5-Dimethyl-1,2-dithiolium Bromide (4a).—Acetylacetone (6 ml) was carefully added to a solution of bromine (24 g) in methanol (100 ml) at 0°. H_2S was bubbled into this vigorously stirred mixture. After 5 min the remainder of the acetylacetone (9 ml) was added, almost completely discharging the color of the bromine. H_2S was bubbled into the solution at room temperature until the solution turned deep red (~4 hr). Stirring was continued overnight. The solution was separated from a small quantity of sulfur, and diethyl ether (300 ml) was slowly added with stirring. The crystals were collected and washed. The compound was recrystallized by dissolving the crude product in a quantity of warm methanol, filtering, and adding a fourfold excess of diethyl ether. On cooling, the solution deposited crystals (8 g, 25%) which were collected, washed, and dried, mp slowly decomposes above 160°, nmr CH_3, 3.12 (6), H, 8.19 (1).

Anal. Calcd for $C_5H_7BrS_2$: C, 28.5; H, 3.4; Br, 37.8; S, 30.4. Found: C, 28.5; H, 3.4; Br, 38.0; S, 30.6.

3-Methyl-5-phenyl-1,2-dithiolium Iodide (3b).—A solution of benzoylacetone (40 g) and iodine (51 g) in MeOH (150 ml) was stirred vigorously while H_2S was passed through at room temperature. Initially, sulfur was deposited and finally the dithiolium iodide crystallized from the solution. Addition of diethyl ether to the reaction mixture led to further recrystallization of the required compound, which was twice recrystallized from methanol (16 g), mp 127–132°, nmr CH_3, 3.18 (3), C_6H_5, 7.5–8.1 (5), H, 8.58 (1).

Anal. Calcd for $C_{10}H_9IS_2$: C, 37.6; H, 2.8; I, 39.7; S, 20.0. Found: C, 37.7; H, 2.9; I, 39.7; S, 20.2.

3,4,5-Trimethyl-1,2-dithiolium Iodide (3c).—H_2S was bubbled into a methanolic solution (150 ml) of α-methylacetylacetone (19 g) and iodine (46 g) for approximately 0.5 hr, when large crystals separated (presumed to be 3,4,5-trimethyl-1,2-dithiolium triiodide). On continued bubbling of H_2S (~2 hr) the large crystals were replaced by smaller yellow crystals. When the red coloration of the iodine was completely discharged the product was collected, washed, and recrystallized from MeOH as pale yellow crystals (15 g), mp 217–218°, nmr 3-CH_3 and 5-CH_3, 3.00 (6), 4-CH_3, 2.52 (3).

Anal. Calcd for $C_6H_9IS_2$: C, 26.5; H, 3.3; I, 46.6; S, 23.6. Found: C, 26.4; H, 3.3; I, 46.8; S, 23.7.

Registry No.—**1a**, 123-54-6; **1b**, 93-91-4; **1c**, 815-57-6; **2a**, 22372-84-5; **3a**, 22251-86-1; **3b**, 37344-00-6; **3c**, 39703-73-6; **4a**, 20365-60-0; iodine, 7553-56-2; bromine, 7726-95-6.

Acknowledgment.—One of the authors (A. R. H.) wishes to thank the CSIRO for a Postgraduate Studentship.

(9) G. A. Heath, A. R. Hendrickson, R. L. Martin, and A. F. Masters, unpublished results.

Comparisons of the Reactions of Chlorine and Alkyl Hypochlorites with Aromatics in Nitromethane

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Received November 7, 1972

A few years ago Norman and Harvey[2] investigated the reactions of *tert*-butyl hypochlorite with several aromatic hydrocarbons. They found that these reac-

(1) Bethany Nazarene College.
(2) D. R. Harvey and R. O. C. Norman, *J. Chem. Soc.*, 3604 (1961).

tions were very slow[3] and that the hypochlorite and chlorine gave nearly identical ratios of aromatic substitution products. On the basis of their observations, these researchers came to the conclusion that *tert*-butyl hypochlorite reacts by initially decomposing to atomic chlorine. The chlorine radicals can then react directly with the aromatics (toluene to give benzyl chloride) or combine to form molecular chlorine which subsequently reacts with the aromatic (anisole).[4]

We have recently reported[5] that there are significant differences between the reactions of alkyl hypochlorites with aromatics in nitromethane and in the other solvents.[2] In nitromethane the reactions are far more rapid, and in certain cases there is a competition between chlorination of the aromatic and nitromethane[6] (formation of chloronitromethane). We have continued to study both of these reactions and wish to present information here on the aromatic substitution reaction.

Results and Discussion

The data in Table I indicate that all three hypochlorites give significantly different ratios of substitution

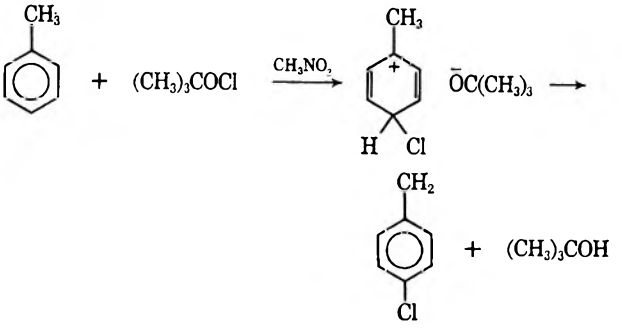
TABLE I

CHLORINATION OF AROMATICS WITH HYPOCHLORITES AND CHLORINE

Aromatic	Chlorinating agent	Orientation 2	Orientation 4
Toluene	DEMC hypochlorite[a]	32	68
Toluene	*tert*-Butyl hypochlorite	32	68
Toluene	Methyl hypochlorite	34	66
Toluene	Chlorine	45	55
m-Xylene	DEMC hypochlorite	11	89
m-Xylene	*tert*-Butyl hypochlorite	10	90
m-Xylene	Methyl hypochlorite	12	88
m-Xylene	Chlorine	18	82
Anisole	*tert*-Butyl hypochlorite	8	92
Anisole	Methyl hypochlorite	8	92
Anisole	Chlorine	10	90

[a] DEMC hypochlorite equals diethylmethylcarbinyl hypochlorite.

products with toluene and *m*-xylene than chlorine does. These results suggest that the hypochlorites and chlorine do not involve the same chlorinating agent, and that there is a direct reaction between the hypochlorite and the aromatic. The probable reaction pathway for *tert*-butyl hypochlorite is illustrated in the following equations with toluene (showing para attack).



Since the reactions of the hypochlorites with toluene and *m*-xylene are relatively slow in comparison to those with chlorine (see Table II), the preference for the 4

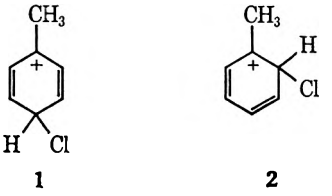
TABLE II

RELATIVE REACTIVITIES OF CHLORINE AND HYPOCHLORITES WITH SEVERAL AROMATICS

Aromatic	Relative reactivities[a] *t*-BuOCl	MeOCl	Cl_2
Toluene	1.00	2.24	47.6
p-Xylene	1.48	2.75	296
o-Xylene	2.42	4.05	405
m-Xylene	2.81	32.9	*b*
Naphthalene	15.8	5497	*b*
Anisole	115	*b*	*b*

[a] See the Experimental Section for a discussion of the procedure for determining the relative rates. [b] Reactions were too rapid to be followed under our reaction conditions.

position probably results from the greater stability of resonance structure **1** compared to **2** (illustrated with



1 **2**

toluene).[7] Anisole, on the other hand, reacts extremely rapidly with the hypochlorites and with chlorine. In this case, since the transition state is reactant-like, the substitution ratio should be a reflection of the relative electron densities in the 2 and 4 positions in the ground state, and should result in the attack occurring primarily at the 4 position.[8]

We anticipated that the bulky hypochlorites (*tert*-butyl and diethylmethylcarbinyl) when compared to

(3) The reactions in carbon tetrachloride, dioxane, acetonitrile, and *tert*-butyl alcohol took approximately 2 days; reactions in acid solution were considerably more rapid (15 min). Nitromethane was not employed as a solvent.

(4) Chlorinations in acid solution with *tert*-butyl hypochlorite were assumed to involve the chlorinium ion intermediate.

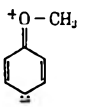
(5) V. L. Heasley, G. E. Heasley, M. R. McConnell, K. A. Martin, D. M. Ingle, and P. D. Davis, *Tetrahedron Lett.*, 4819 (1971).

(6) As described earlier,[5] the presence of the aromatic is essential as a catalyst in the reaction of the hypochlorite with nitromethane. The extent of chlorination of nitromethane varies with the particular aromatic, as described in the Experimental Section.

We are continuing to investigate this complex reaction. Preliminary work suggests that in the case of the xylenes the ratio of chloronitromethane to chloroaromatic is influenced by the presence of traces of acid, base, and water in the solvent. We are assuming that the ratios of chloroaromatics are not affected by the competing reaction between the hypochlorites and nitromethane.

(7) Norman and Radda [*J. Chem. Soc.*, 3610 (1961)] present a detailed discussion on the comparison of the transition states of slow and rapid aromatic substitution reactions. In our case, since the reactions of the hypochlorites with toluene and *m*-xylene are much slower than those wtih chlorine, these reactions (hypochlorites) involve a product-like (cyclohexadienyl intermediate) transition state; **1** makes a greater contribution to this transition state than **2**. Since chlorine reacts extremely rapidly with these aromatics in nitromethane, the transition state should be reactant-like, and hence influenced primarily by the relative electron densities in the ground state. Therefore, since the electron densities are significant in the 2 position in the ground state in the cases of toluene and *m*-xylene because of the inductive effects of the methyl groups, considerable attack occurs at the 2 position.

(8) With anisole the electron density in the ground state is decreased in the 2 position by the inductive effect of the oxygen, and is increased in the 4 position by the following resonance structure.



methyl hypochlorites might show preference for the less hindered 4 position in *m*-xylene. Apparently this is not the case.[9] (All of the substitution products from *m*-xylene and the hypochlorites are within experimental error of each other.)

The relative rate data (Table II) provide additional proof for the fact that the hypochlorites are not reacting *via* chlorine. If chlorine were involved, all of the aromatics should react at the same rate, since the rate-limiting step would certainly be the decomposition of the hypochlorites, as illustrated in the following equations.

$$\mathrm{ROCl} \xrightarrow[\text{slow}]{} \mathrm{Cl{\cdot}(Cl_2)} \xrightarrow[\text{fast}]{\mathrm{ArH}} \text{product}$$

The rates of reaction do fall in the expected order if the basicities of the leaving anions (Cl^-, OCH_3^-, and O-*t*-Bu^-) and the reactivities of the aromatics are considered, and if the suggestion of a direct reaction between the hypochlorites and the aromatics is accepted.

Experimental Section

Materials.—All solvents and reagents were obtained commercially in high purity unless otherwise indicated. The hypochlorites were prepared as described by Walling and McGuinness.[10] Their structures were confirmed by ir and uv analysis. A detailed discussion of the synthesis and physical properties of 2-chloro-1,3-dimethylbenzene and 4-chloro-1,3-dimethylbenzene has been reported.[11]

Reaction Conditions.—To a well-stirred solution of nitromethane (n = 0.98) and the aromatic (n = 0.02) in an ice bath was added instantly a dichloromethane–hypochlorite (or chlorine) solution. (Final volume was about 28 ml.) Sufficient halogenating agent was added to react with approximately 30% of the aromatic. The molarities of the dichloromethane–halogenating agent solutions in the cases of toluene and *m*-xylene were, respectively, 1.40 and 1.00. Our studies indicate that the molarity of the halogenating agent solution seemed to have no effect on the substitution ratio.

Yields.—The yields of chloroanisoles with chlorine, methyl hypochlorite, and *tert*-butyl hypochlorite were, respectively, 96, 77, and 73%. The vpc analysis procedure (ortho and para isomers were resolved) has been previously described.[12]

Toluene reacted with the halogenating agents (listed as with anisole) to give the following yields of chlorotoluenes, respectively, 58, 51, and 54%. (The yield of chlorotoluenes with diethylmethylcarbinyl hypochlorite was not determined.) Traces of chloronitromethane were formed in the cases of anisole and toluene with the hypochlorites.[6] The yields of the chlorotoluenes were determined by vpc analysis (isomers were unresolved) under the following conditions: column temperature, composition and dimensions, 67°, 1.5% dinonyl phthalate on 60–80 mesh Chromosorb W, and 4 ft × 0.25 in. The retention times of the chlorotoluenes and the internal standard (*p*-chlorobromobenzene) were, respectively, 5.4 and 9.5 min at a flow rate (He) of 60 ml/min.

m-Xylene reacted with chlorine, methyl, *tert*-butyl, and diethylmethylcarbinyl hypochlorites to give the following yields of chloro *m*-xylenes, respectively, 83, 51, 38, and 31%. (The yields of chloronitromethane with the hypochlorites are, respectively, 5, 55, and 38%). The yields of chloro-*m*-xylenes were determined by vpc analysis (peaks were unresolved) under the following conditions: column temperature, composition and dimensions, 67°, 15% diethylene glycol succinate on 60–80 mesh Chromosorb W, and 5 ft × 0.25 in. The retention times of the chloro-*m*-xylenes and the internal standard (*p*-chlorobromobenzene) were, respectively, 5.4 and 9.5 min, at a flow rate (He) of 60 ml/min.

Determination of Substitution Ratios—The ratios of 2- and 4-chlorotoluenes were determined by an ir analysis procedure which has been described previously,[11] and by vpc analysis. The accuracy of the vpc analysis procedure was confirmed by repeated analysis of mixtures of chlorotoluenes of known composition. The ir and vpc analyses were in very close agreement (1–3%). The vpc analysis conditions for determination of the substitution ratio for the chlorotoluenes are as follows: column temperature, composition and dimensions, 39°, 1.5% dinonyl phthalate on 80–100 mesh Chromosorb W, and 8 ft × 0.125 in. The retention times for 2- and 4-chlorotoluene are, respectively, 13.5 and 15.1 min.

The substitution ratios for the 2-chloro- and 4-chloro-1,3-dimethylbenzenes were determined by ir analysis, as described previously,[11] with the exception that we isolated the individual chloro-*m*-xylenes by preparative gas chromatography. Since *m*-xylene interferes with the ir analysis, we confirmed by vpc analysis that each collected sample contained none of the starting aromatic.

The data on the substitution ratios (Table I) are accurate to ±2%.

Relative Rate Determinations.[13]—The relative rates of reaction of the hypochlorites and chlorine with the aromatics (Table II) were determined in the following manner. To a stirred solution (20 ml) of nitromethane (n = 0.98) and the appropriate aromatic (n = 0.02) at 0–0.5° was added instantly 2 ml of a 1.25 *M* solution of the halogenating agent in dichloromethane. Periodically, samples were removed and titrated iodometrically. The half-life for each aromatic was determined graphically.

The reciprocal of each half-life (in seconds) was then calculated and made relative to the value for *tert*-butyl hypochlorite and toluene. (Half-life of these reactants was 19,500 sec.)

Studies on the Decomposition of the Hypochlorites.—We determined that the hypochlorites do not decompose to chlorine in nitromethane by the following procedure. Methyl and *tert*-butyl hypochlorite were allowed to stand in nitromethane for 12 hr at ice-bath temperatures. 1-Hexene was then added to these hypochlorite–nitromethane solutions. Only traces of 1,2-dichlorohexane were formed in either case; chloronitromethane was the product. Previous studies of ours[6] have shown that alkyl hypochlorites and 1-hexene in nitromethane gives chloronitromethane; chlorine, 1-hexene, and nitromethane give 1,2-dichlorohexane.

Comparisons of Our Substitution Ratios with Those of Previous Studies.—Stock and Hinoe[14] reported the following product composition (%) for the chlorination of toluene in nitromethane: 2-chlorotoluene (34) and 4-chlorotoluene (66). Using their exact conditions we were unable to obtain their result, although we repeated the reaction several times. In fact, we found that the product composition was not influenced by the method of addition of chlorine, or whether the chloride was dissolved in nitromethane, dichloromethane, or carbon tetrachloride. In all cases we obtained the composition reported in Table I.

Apparently the chlorinations of anisole of *m*-xylene in nitromethane have not been investigated; the chlorination of anisole in 2-nitropropane has been reported[14] to give less than 1% of the ortho isomer.

There have been no previous studies on the reactions of alkyl hypochlorites with aromatics in nitromethane.

Registry No.—Toluene, 108-88-3; *m*-xylene, 108-38-3; anisole, 100-66-3; diethylmethylcarbinyl hypo-

(9) It is conceivable that the "active" chlorinating agent in these reactions is the product of a reaction between the hypochlorites and nitromethane, as shown in the following equation.

$$\mathrm{ROCl} + \mathrm{CH_3NO_2} \rightleftharpoons \mathrm{ClO\overset{O}{\overset{\|}{N}}CH_2(OR^-)}^{+}$$

This seems doubtful, however, in the light of the reactivities in Table II. Also, we have carried out ir studies on *t*-BuOCl–CH_3NO_2 solutions and have observed that there were no detectable decreases in the *t*-BuOCl absorption bands, nor were any "new" bands formed. We recognize that this does not rule out the possibility of the existence of a trace amount (in equilibrium) of another halogenating agent, but it makes it very unlikely.

(10) C. Walling and J. A. McGuinness, *J. Amer. Chem. Soc.*, **91**, 2053 (1969).

(11) H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.*, **79**, 5175 (1957).

(12) F. S. Broun and L. P. Hager, *J. Amer. Chem. Soc.*, **89**, 719 (1967).

(13) The relative rate data indicate how rapidly the halogenating agent is consumed. In certain cases there is concomitant chlorination of the solvent (chloronitromethane formation) and the aromatic. The reaction of the halogenating agent and the solvent becomes significant in the following cases (% chloronitromethane): methyl hypochlorite and naphthalene (100); *tert*-butyl hypochlorite with naphthalene (100); *m*-xylene (55); *o*- and *p*-xylene (*ca.* 25%).

(14) L. M. Stock and A. Hinoe, *Tetrahedron Lett.*, **No. 13**, 9 (1960).

chlorite, 39835-22-8; *tert*-butyl hypochlorite, 507-40-4; methyl hypochlorite, 593-78-2; chlorine, 7782-50-5; *p*-xylene, 106-42-3; *o*-xylene, 95-47-6; naphthalene, 91-20-3.

Acknowledgment.—Support for this work was provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the Union Oil Co. of California Foundation, Brea, Calif.

Preparation and Characterization of Dichlorocyclopentadienylborane and Attempted Preparation of 1-Chloro-2,3,4,5,6-pentacarba-*nido*-hexaborane Cation

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Received December 27, 1972

The properties and structure of dialkylcyclopentadienylboranes have been reported by Grundke and Paetzold.[1] We wish to report a dichloro analog which appears to differ significantly in stability and acidity from the alkyl systems, but whose boron-11 and proton nmr spectra are sufficiently comparable to allow similar structural conclusions to be made. Because the formal loss of Cl^- from this compound would result in the possible formation of a *B*-chloro derivative of the hypothetical *nido*-$C_5BH_6^+$ ion, attempts were made to effect this conversion.

Experimental Section

Materials.—Sodium cyclopentadienide was obtained from the Eastman Chemical Co. as an 18% solution in tetrahydrofuran. The solvent was removed under reduced pressure. Boron trichloride, Matheson Co., was fractionated through −130° traps to remove HCl, and butyllithium in hexane was obtained from the Foote Mineral Co. Aluminum chloride was freshly sublimed. Most experimental procedures were carried out using conventional vacuum techniques.

Dichlorocyclopentadienylborane.—Since the reaction of boron trichloride and its vapor with cyclopentadienide was found to be highly exothermic, NaC_5H_5 was added as a powder to liquid BCl_3 previously cooled to −78°. This was accomplished by pulverizing the salt, freed from its solvent, tetrahydrofuran, under an inert atmosphere, and transferral of the powder to a rotatable side arm attached to the reactor vessel. Then sodium cyclopentadienide (75.9 mmol) was slowly added with stirring to 40 ml of boron trichloride maintained at −78°. The temperature was raised over a period of a few hours to 0° after which the reaction was allowed to continue for 3 hr more. The volatile components were removed at reduced temperature and pressure and fractionated through traps at −78° and −190°. When all the liquid BCl_3 had been removed from the reaction vessel, the insoluble brown solid residue remaining was gradually warmed to room temperature, and then, over a period of several hours, heated to ~300° while the volatiles were continued to be pumped through the cold traps. Approximately 0.3–0.4 ml of the product $C_5H_5BCl_2$ was retained in the −78° trap as a solid. Dichlorocyclopentadienylborane was a colorless liquid which darkened noticeably within an hour at room temperature. It had a vapor pressure of ~3 mm at 25°. The ^{11}B nmr spectrum was a singlet at about δ −47 ppm (neat) ($BF_3 \cdot OEt_2$, δ 0) which tended to broaden considerably at temperatures below −30°. In methylene chloride the chemical shift was −51 ppm. The proton spectrum exhibited four peaks with no observable fine structure in an apparent 1:1:1:2 ratio at τ 2.36, 3.14, 3.36, and 6.68, respectively, for the neat material. In chloroform the values were τ 2.16, 2.94, 3.17, and 6.66. The ^{11}B signals were observed to decrease in intensity after 5 min at room temperature with no new resonances appearing. The proton spectrum revealed a total decomposition of $C_5H_5BCl_2$ after 1 hr at 25° as evidenced by the loss of all olefinic signals and a growth in peaks at higher field attributed to hydrogen on saturated carbons.

The mass spectrum of the pure $C_5H_5BCl_2$ exhibited major peak envelopes at *m/e* 143–150 and 108–113 as well as a number of other peaks at lower masses. The parent region intensities were *m/e* 150 (rel intensity 9.4), 149 (3.3), 148 (62.0), 147 (20.7), 146 (100.0), 145 (31.5), 144 (17.7), and 143 (4.0). This corresponds to the monoisotopic species: at *m/e* 146, $^{12}C_5{}^1H_5{}^{10}B^{35}Cl_2$ (relative intensity 100.0); *m/e* 145, $^{12}C_5{}^1H_4{}^{10}B^{35}Cl_2$ (8.3); *m/e* 144, $^{12}C_5{}^1H_3{}^{10}B^{35}Cl_2$ (18.5).

Reaction of $C_5H_5BCl_2$ with Butyllithium.—About 0.11 mol of butyllithium in hexane was syringed into a dry 5-mm nmr tube, cooled to −196° and the system evacuated. Approximately 0.1 mmol of $C_5H_5BCl_2$ was then condensed into the tube. The ^{11}B nmr spectrum was obtained of the mixture at increasing temperature starting at −40°. Little change was observed in the chemical shift or appearance of the single peak even after standing at room temperature several days, the resonances appearing at about −49 ± 1.5 ppm depending on the temperature. The ^1H nmr spectrum at 25° showed only two doublets of approximately the same intensity appearing at τ 2.82 and 3.29 (J = 2.2 Hz and 1.9 Hz, respectively) which suggest the presence of olefinic hydrogens. The nmr sample was opened and the contents were fractionated to remove hexane. The only volatile product was butane.

Reaction of $C_5H_5BCl_2$ with Al_2Cl_6.—When dichlorocyclopentadienylborane was treated with aluminum chloride in either methylene chloride or chloroform, rapid and total decomposition of the borane to a dark brown sludge was the only reaction observed. This process, which was followed by ^1H nmr and ^{11}B nmr, was essentially complete in less than 1 hr at 25° as revealed by the loss of olefinic signals in the proton spectrum and the boron singlet in the boron spectrum. The decomposition of $C_5H_5BCl_2$ under these conditions appeared to be more rapid than in CH_2Cl_2 or neat in the absence of Al_2Cl_6.

Discussion

The reported preparative method of the reaction of a Lewis base adduct of a halodialkylborane with cyclopentadienide ion and subsequent treatment with a Lewis acid[1] was unsuccessful when boron trichloride was used in place of the halodialkylborane. However, low yields of dichlorocyclopentadienylborane are obtainable from the reaction of sodium cyclopentadienide directly with boron trichloride, the latter reactant also serving as solvent. This reaction is not without complications and these are commented upon.

The reaction between NaC_5H_5 and BCl_3 may be reasonably expected to produce $C_5H_5BCl_2$ and NaCl. However, when the reactants are carefully mixed, the only product isolated is a brown boron trichloride insoluble solid that shows no evidence of $C_5H_5BCl_2$.

$$NaC_5H_6 + BCl_3 \xrightarrow{0^\circ} \not\rightarrow C_5H_5BCl_2 + NaCl$$

The presence of this insoluble solid in the boron trichloride solution, coupled with the absence of a volatile product even near ambient temperature suggests that the initial substance may be $Na^+C_5H_5BCl_3^-$. This adduct appears quite stable at temperatures to 100°, but begins to decompose when heated at 150 to 250°.

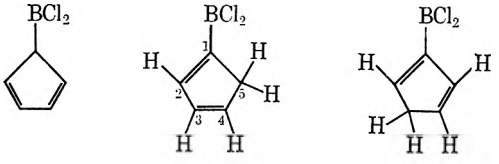
(1) H. Grundke and P. I. Paetzold, *Chem. Ber.*, **104**, 1136 (1971).

In this temperature range $C_5H_5BCl_2$ is produced suggesting that the following reaction occurs.

$$Na^+C_5H_5BCl_3^- \xrightarrow{250^\circ} C_5H_5BCl_2 + \text{nonvolatile residue (NaCl + ?)}$$

As described in the Experimental Section, dichlorocyclopentadienylborane is a compound of limited stability, and when treated with Al_2Cl_6 its rate of decomposition is noticeably enhanced. Since it has been reported that there is a parallel relationship between the rate of dimerization of diethylcyclopentadienylborane in the presence of Al_2Cl_6 and the rate of its dimerization in the absence of Al_2Cl_6,[1] it is possible that a similar phenomenon is operative in the dichloro compound. In this case, however, a pathway for decomposition may be available through formation of a dimer of low stability. No evidence was found to indicate the removal by Al_2Cl_6 of Cl^- from $C_5H_5BCl_2$ to form the cation $C_5H_5BCl^+$ which is potentially a *B*-chloro derivative of $C_5BH_6^+$ and isoelectronic with the boron hydride B_6H_{10} and the nido carborane series $C_nB_{6-n}H_{10-n}$.[2]

The singlet observed in the ^{11}B nmr spectrum at -47 ppm places the boron of $C_5H_5BCl_2$ in the general region of trigonal dichlorinated alkylboranes.[3] Such a molecule is therefore consistent with a cyclopentadienyl group σ bonded to boron. The remaining structural question centers about the location of the double bonds in the ring. The following possibilities may be considered.



I II III

Since the proton nmr spectrum reveals three hydrogens of an apparent olefinic nature at τ 2.36, 3.14, and 3.36, and what appears to be two methylene hydrogens at τ 6.86, structure I can be eliminated. Distinguishing between II and III presents a problem since each could conceivably have three nonequivalent olefinic hydrogens which correspond to the three resonances in the vinyl region of the spectrum. To determine the correct structure solely on the basis of proton types in the pmr, therefore, becomes speculative at this time. However, if one postulates a not insignificant amount of electron delocalization from the cyclopentadienyl ring into the p_z orbital on the boron, perhaps the more highly conjugated structure II is energetically favored, should both isomers be kinetically accessible to a comparable extent during the reaction.

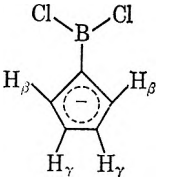
On the assumption that the compound has the double bonds placed as in structure II, the pmr spectrum may be assigned by a combination of resonance and inductive effects. This, and also by drawing analogies to pmr spectra of alkyl and alkyenyl derivatives of trigonal boranes,[1,4,5] the vinyl resonances at τ 2.36, 3.14, and 3.36 are assigned to H-2, H-3, and H-4, respectively.

Grundke and Paetzold[1] attempted the reaction of diethylcyclopentadienylborane with various strong bases in an examination of its Brønsted acidity. Breaking of the B–C (cyclopentadienyl) bond was reported to be the essential feature of the reactions and no deprotonation was observed. However, in the case of dichlorocyclopentadienylborane strong evidence is obtained for the presence of $C_5H_4BCl_2^-$ as a butyllithium reaction product. Thus, butane is recovered, having been produced by the apparent removal of a methylene proton by $C_4H_9^-$ according to the reaction

$$C_5H_5BCl_2 + C_4H_9^- \longrightarrow C_5H_4BCl_2^- + C_4H_{10}$$

This behavior, which differs from that of the ethyl derivative, may be rationalized on the basis of the greater electronegativity of the chlorine atoms as compared to the ethyl groups. This would presumably lead to an increase in the positive character of the cyclopentadienyl ring, therefore allowing a proton to be more easily removed.

The two olefinic multiplets of similar intensity in $C_5H_4BCl_2^-$ appear at higher fields than the signals attributed to the olefin hydrogens of $C_5H_5BCl_2$, which is a factor consistent with the negative charge on the ion and the predictable increase in shielding of the ring protons. Since the C_5H_4 ring in $C_5H_4BCl_2^-$ probably has some aromatic character, the proton environment would tend to be more uniform than in the neutral species. However, inductive action by the boron attached chlorine atoms may affect the β protons more than the γ protons, lowering the field of the former relative to the latter. Based on this premise the nmr signal at τ 2.82 may be assigned to the β hydrogens and the peak at τ 3.29 attributed to the γ hydrogens.



Deprotonation of dichlorocyclopentadienylborane does not appear to significantly affect the chemical shift of the boron atom. However, the increase in stability of the anion over the neutral molecule may reflect the reluctance of two negatively charged ions to approach each other and initiate decomposition through a dimerization mechanism.

Registry No.—Sodium cyclopentadienide, 4984-82-1; dichlorocyclopentadienylborane, 39839-30-0; butyllithium, 109-72-8; $AlCl_3$, 7446-70-0; $C_5H_4BCl_2^-$, 39839-31-1; BCl_3, 10294-34-5.

Acknowledgment.—This project was supported, in part, by the Office of Naval Research.

(2) R. N. Grimes, "Carboranes," Academic Press, New York, N. Y., 1970.

(3) G. R. Eaton and W. N. Lipscomb, "NMR Studies of Boron Hydrides and Related Compounds," W. A. Benjamin, New York, N. Y., 1969.

(4) C. D. Good and D. M. Ritter, *J. Amer. Chem. Soc.*, **84**, 1162 (1962).

(5) H. Nöth and H. Vahrenkamp, *J. Organometal. Chem.*, **12**, 23 (1968).

Amphetamine. Specific Labeling and Solution Conformation

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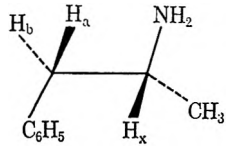
Received December 27, 1972

In connection with other work[1] it became necessary to determine the solution conformation of amphetamine (**1**). The conformation population analysis of **1** required



1

specific deuterium labeling of H_a and H_b of the ABX (methyl decoupled) spin system, affording previously unreported specifically deuterated amphetamine which is of potential utility in biochemical mechanistic investigations.

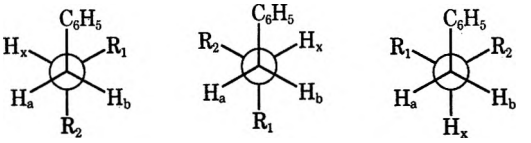
The identities of H_a and H_b were established as indicated in Chart I. The previously assigned configuration of 2-methylcinnamic acid (**2**)[2] was confirmed by europium-induced shift studies[3] of the diastereomeric ethyl 2-methylcinnamates. Conversion of **2** to the corresponding ester with subsequent photochemical isomerization[4] afforded the mixture of esters (*E*)- and (*Z*)-**3**. Granted that the most basic site in the ester is the carbonyl oxygen and that coordination of $Eu(fod)_3$ will occur at the carbonyl oxygen, it should be expected that the vinylic hydrogen of (*E*)-**3** should suffer the greater paramagnetic shift of the pair of diastereomers.[5] The ester prepared directly from **2** exhibited a slope of shift *vs.* mol $Eu(fod)_3$/mol ester 2.1 times that exhibited by the photochemical isomerization product. Thus, the ester produced directly from **2** is (*E*)-**3** and the configuration of **2** is firmly[2] established as *E*.

Exchange of the acidic proton of (*E*)-**2** with subsequent catalytic deuteration afforded the enantiomers (2*R*,3*S*)- and (2*S*,3*R*)-2,3-dideuterio-2-methylcinnamic acid (**4a** and **4b**, respectively). Nonspecific deuteration of (*E*)-**2** would produce the 2*R*,3*R* and 2*S*,3*S* diastereomers of **4** in addition to the predicted 2*R*,3*S* and 2*S*,3*R* enantiomers produced by cis deuteration of **2**. The production of diastereomers, resulting from nonspecific (cis and trans) deuteration, is not experimentally observed; **4** exhibits a single-proton resonance in the ABX region of the spectrum, not the doubled resonances (H_a and H_b) expected from a mixture of diastereomers.[6]

Hoffmann rearrangement of the amides of **4a** and **4b** produces (1*R*,2*R*)- and (1*S*,2*S*)-1,2-dideuterio-1-phenyl-2-propylamine (**5a** and **5b**, respectively), *i.e.*, with retention of configuration at C-2.[7] Thus, the single-proton resonance observed in the ABX region of the nmr spectrum of **5** is identified as H_b in **1**.

The coupling constants and conformer populations of amphetamine are reported in Table I. The conformer

TABLE I
NMR PARAMETERS AND POPULATIONS[a]



a b c

					Mole fraction[b]		
R_1	R_2	Solvent	J_{ax}	J_{bx}	n_a	n_b	n_c
CH_3	NH_2	$CDCl_3$	8.31	5.84	0.29	0.52	0.19
CO_2^-	NH_3^+	D_2O	8.02[c]	5.10	0.23	0.50	0.27
CO_2^-	NH_2	D_2O	7.52[c]	5.43	0.25	0.47	0.28

[a] 0.5 *M* solution in the given solvent, temperature 18°. [b] Calculated assuming $J_t = 13.6$ and $J_g = 2.6$ Hz (see text). [c] Reference 9.

populations were calculated from the equations

$$J_{ax} = n_a J_g + n_b J_t + n_c J_g$$

$$J_{bx} = n_a J_t + n_b J_g + n_c J_g$$

$$1 = n_a + n_b + n_c$$

assuming $J_t = 13.6$ and $J_g = 2.6$ Hz. These values have been employed in the determination of the conformer populations of amino acids and have both theoretical[8] and experimental[9] support. Granted that a large electronegativity correction on J_g and J_t does not result upon changing a single group (CO_2H in amino acids to CH_3 in amphetamine), these values appear reasonable for amphetamine as well.[10,11]

Granted also that the values of J_t and J_g for amphetamine and phenylalanine are approximately equal,[12] the conformer population of **1** should closely parallel that previously observed[9] for phenylalanine (Table I). In all cases that conformer is preferred in which phenyl and methyl or carboxyl are anti and phenyl and amino are gauche. On the basis of steric interactions alone it should be expected that conformer

(1) J. Jacobus, *Biochemistry*, **10**, 161 (1971).

(2) On the basis of ultraviolet[3] and equilibration[4] data the assignment of configuration *E* to the 81° melting isomer would appear to be correct.

(3) A. Mangini and F. Montanari, *Gazz. Chim. Ital.*, **88**, 1081 (1958).

(4) C. Sandris, *Tetrahedron*, **24**, 3569 (1968).

(5) The utilization of shift reagents has recently been reviewed: see R. von Ammon and R. D. Fischer, *Angew. Chem.*, **84**, 737 (1972).

(6) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

(7) C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939).

(8) K. G. R. Pachler, *Spectrochim. Acta*, **19**, 2085 (1963); **20**, 581 (1964).

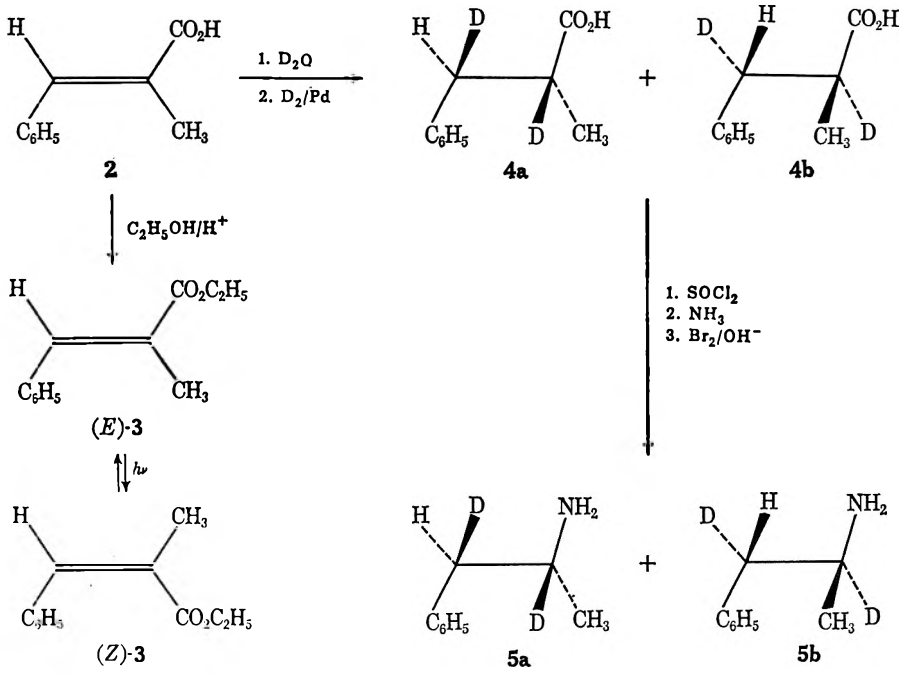
(9) J. R. Cavanaugh, *J. Amer. Chem. Soc.*, **89**, 1558 (1967); **90**, 4533 (1968).

(10) The group electronegativities of CH_3 and CO_2H are 2.30 and 2.85, respectively (P. R. Wells, "Progress in Physical Organic Chemistry," Vol. 6, Interscience, New York, N. Y., 1968, p 111 ff). This change should amount to a ca. 0.04 Hz change in J_t and J_g.[11]

(11) *Cf.* A. A. Bothner-By, "Advances in Magnetic Resonance," Vol. 1, Academic Press, New York, N. Y., 1965, p 195 ff.

(12) It is appreciated that the assumptions inherent in this analysis are gross simplifications, *i.e.*, J_t in conformer a *cannot* equal J_t in conformer b and J_g in a *cannot* equal J_g in b or J_g in c on the basis of simple symmetry arguments [K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967)]. However, granted the assumed coupling constants and other approximations [*cf.*, *inter alia*, R. L. Lichter and J. D. Roberts, *J. Org. Chem.*, **35**, 2806 (1970)] we feel that within this series of compounds, although the experimental data cannot unambiguously define the conformations of the compounds in question, the conformer populations are essentially identical.

CHART I



c (Table I) should be the least populated, as is the case for amphetamine.[12a]

Experimental Section

Nmr spectra were recorded at 60 and 90 MHz as 0.5 *M* solutions in the indicated solvents. Coupling constants were determined from calculated spectra (LAOCN3).

(*E*)-2-Methylcinnamic acid (2) was prepared by silver oxide oxidation of 2-methylcinnamaldehyde (Aldrich) in 70% yield: mp 81–83° (lit.[4] mp 81°); nmr ($CDCl_3$) δ 2.04 (CH_3, d, J = 2.0 Hz), 7.59 (vinylic H, q, J = 2.0 Hz).

2,3-Dideuterio-2-methylcinnamic acid (4a and 4b) was prepared by exchanging the acidic proton of 15.0 g (0.093 mol) of **2** in 90 ml of ethyl acetate with three 15-ml portions of D_2O, with subsequent catalytic reduction (200 mg of 5% Pd on carbon) of 2-d_1 in a deuterium atmosphere at 45 psi. Removal of catalyst and solvent afforded 12.3 g (80%) of **4**: mp 35–36°; bp 142° (2 mm)[13] [lit.[14] bp 174–176° (20 mm)]; nmr ($CDCl_3$) δ 1.10 (2-methyl, s), 2.55 (H_b, s).

2,3-Dideuterio-2-methylcinnamamide was prepared by the previously described sequence for the conversion of dihydro-2-methylcinnamic acid to dihydro-2-methylcinnamamide.[15] The product amide exhibited mp 108–110° (lit. mp 108°,[14] 110°[13]); nmr (DMSO-d_6) δ 0.97 (2-methyl, s), 2.44 (H_b, s).

(1*R*,2*R*)- and (1*S*,2*S*)-1,2-Dideuterio-1-phenyl-2-propylamine (5a and 5b) (dideuterioamphetamine) was prepared in a manner analogous to that described for the nondeuterated analog.[15] The product amine exhibited bp 200–201° (lit.[16] bp 205°); nmr ($CDCl_3$) δ 0.97 (2-methyl, s), 2.69 (H_b, s). Amphetamine (Aldrich) had nmr ($CDCl_3$) δ 0.97 (2-methyl, d, J = 6.0 Hz), 2.52 (H_a), 2.69 (H_b), 3.17 (H_x); J_{ab} = −14.29, J_{ax} = 8.31, J_{bx} = 5.84 Hz.

Registry No.—**1**, 300-62-9; **2**, 1895-97-2; **4**, 39949-56-9; **5**, 39949-57-0.

(12a) NOTE ADDED IN PROOF.—The assignments of protons H_A and H_B of amphetamine have recently been made [G. E. Wright, *Tetrahedron Lett.*, 1097 (1973)]; although the assignments are correct by comparison with this work, the claim that the assignments confirm the work of Bailey, *et al.* [K. Bailey, A. W. By, K. C. Graham, and D. Verner, *Can. J. Chem.*, **49**, 3143 (1971)] is incorrect since the assignments of conformer population by Wright are reversed.

(13) I. Shahak, *J. Chem. Soc.*, 3160 (1961).

(14) V. Franzen, *Justus Liebigs Ann. Chem.*, **602**, 199 (1957).

(15) E. S. Wallis and S. C. Nagel, *J. Amer. Chem. Soc.*, **53**, 2787 (1931).

(16) D. H. Hey, *J. Chem. Soc.*, 18 (1930).

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to the Clemson University Basic Research Fund donors.

Preparation of Methyl and Ethyl *N*-Monochlorocarbamates by Disproportionation[1]

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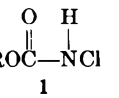
Received February 21, 1973

N-Monochlorocarbamate esters (1) are versatile pseudohalogens. They add predominantly in cis fashion to olefins in the presence of ultraviolet to yield vicinal chlorocarbamates,[3] they react rapidly with thioethers to form iminosulfonium salts,[4] and they form interesting isolable salts on reaction with base.[5,6]



1

(1) Pseudohalogens. XIX. Paper XVIII: *J. Org. Chem.*, **37**, 3004 (1972). Work supported in part by U. S. Public Health Service Grants CA-12227 and CA-07803 of the National Cancer Institute, and the Samuel S. Fels Fund.

(2) Participants in the Chemistry Honors Undergraduate Research Program, Temple University.

(3) K. Schrage, *Tetrahedron Lett.*, 5795 (1966); *Tetrahedron*, **23**, 3033, 3039 (1967).

(4) G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, *Tetrahedron Lett.*, 3543 (1970).

(5) D. Saika and D. Swern, *J. Org. Chem.*, **33**, 4548 (1968).

(6) P. Chabrier, *Ann. Chim. (Paris)*, **17**, 353 (1942), and references therein to older literature.

The usual method of preparation of **1** is reaction of equimolar quantities of chlorine with carbamate esters (**2**).[5-7] It was recognized only recently, however, that the reaction product is a mixture of **1** (major component), *N*,*N*-dichlorocarbamates (**3**) and unreacted **2**.[5] Analysis of reaction products solely for positive halogen is an insufficient criterion of product purity. Assay of composition requires iodometric analysis for positive halogen and determination of acid value (compounds **1** are relatively strong acids), and nmr to determine unreacted **2**. To obtain pure **1** from such mixtures vacuum distillation is required, but it is essential that distillation temperatures be below about 100° as disproportionation of **1** to **2** and **3** occurs at elevated temperatures, a fact not recognized by early investigators. In our earlier work,[5] we isolated ethyl *N*-monochlorocarbamate (**4**), purity >99%, by distillation at 45° (0.2 Torr), but yields are only 40–50% at best.

Earlier investigators had stated that **1** can be prepared in virtually quantitative yield by reaction of equimolar quantities of neat **2** and **3** at room temperature in a disproportionation reaction,[6,8] but details are lacking in the older literature and criteria of purity are not reported. Since pure **3** can be easily prepared in 80–90% yield from **2** and 2 mol of chlorine,[9] we have reinvestigated the disproportionation reaction for the preparation of **4** and methyl *N*-chlorocarbamate (**5**). We report here the explicit experimental details and determination of purity of **1**.

Reaction of equimolar quantities of ethyl *N*,*N*-dichlorocarbamate (**6**) with ethyl carbamate (**7**) at room temperature in the dark for 24 hr (reaction monitored by refractive index and neutralization analysis[5]) gave virtually a quantitative yield of **4**, purity of undistilled product >97%. Increased purity can be obtained by vacuum distillation but considerable reduction in yield is experienced; the crude reaction product is satisfactory for the usual reactions of **4**. Identical results are obtained in the preparation of **5** from methyl *N*,*N*-dichlorocarbamate (**8**) and methyl carbamate (**9**), but the reaction is complete in 3.5–4.5 hr. Because of the high positive halogen content of **8** (*ca.* 50%), its purification by vacuum distillation should be conducted at low pressures in the dark [bp 50–70° (12–20 Torr)] and in all-glass apparatus to avoid overheating and possible vigorous decomposition.

$$\underset{\textbf{6, R = } C_2H_5 \quad \textbf{8, R = } CH_3}{ROCNCl_2} + \underset{\textbf{7, R = } C_2H_5 \quad \textbf{9, R = } CH_3}{ROCNH_2} \longrightarrow \underset{\textbf{4, R = } C_2H_5 \quad \textbf{5, R = } CH_3}{2ROC{-}NCl}$$

Our experience with the disproportionation reaction for the preparation of **4** and **5** suggests that the reaction is of general applicability for the preparation of other homologous esters in high purity.

Experimental Section

Ethyl *N*-Monochlorocarbamate (4).—In a three-neck flask equipped with a thermometer and a calcium sulfate drying tube, **6** (8.17 g, 0.052 mol) (obtained either from Aldrich Chemical Co. or prepared in our laboratory[9]) and **7** (4.56 g, 0.051 mol) were stirred slowly with a Teflon-coated magnetic stirrer at room temperature in the dark. Samples were removed periodically and monitored by change in refractive index and by the combined neutralization and iodometric methods.[5] No exotherm was noted and reaction was complete in about 24 hr: purity 96.7% (iodometric), 98.9% (neutralization); nmr (neat) δ 1.29 (t, 3, CH_3, J = 7 cps), 4.24 (q, 2, CH_2, J = 7 cps), and 7.53 (broad s, 1, NH). A small broad signal at δ 5.7 suggested that the impurity was **7**.

Methyl *N*-Monochlorocarbamate (5).—As described above, **5** was prepared from **8** (14.64 g, 0.100 mol, 98.3% purity) and **9** (7.507 g, 0.100 mol) (Baker Chemical Co.). The reaction mixture became homogeneous within about 20 min. Reaction was usually complete within 3.5–4.5 hr: purity 99.3% (iodometric), 98.3% (neutralization); nmr ($CDCl_3$ with TMS as internal standard) δ 3.80 (s, 3, CH_3O–), 6.98 (broad s, 1, NH,) [nmr (neat) shows same shift for methoxyl protons but δ 7.52 (broad s, 1, NH) for associated (hydrogen bonded) amide proton]; mp 23–24° (lit.[8] 32°).

Compound **8** was prepared from **9** and chlorine as described for the preparation of **6**[9] but special precautions (shields, all-glass apparatus, avoidance of light) should be taken owing to the high positive halogen content.

Registry No.—**4**, 16844-21-6; **5**, 39982-28-0; **6**, 13698-16-3; **7**, 51-79-6; **8**, 16487-46-0; **9**, 598-55-0.

(7) W. Traube and H. Gockel, *Chem. Ber.*, **56B**, 384 (1923).

(8) Fabriques de Produits de Chimie Organique de Laire, French Patent 974,085 (1951).

(9) T. A. Foglia and D. Swern, *J. Org. Chem.*, **31**, 3625 (1966).

Wolff–Kishner Reduction of 8,9-Dehydro-2-adamantanone

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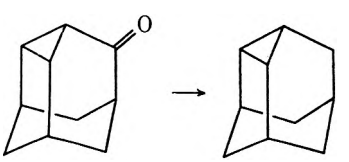
As the cyclopropane ring in 2,4-dehydroadamantane (**1**) can readily be opened by a variety of electrophilic reagents, **1** has proven to be a useful precursor for the synthesis of a variety of 2-substituted and 2,4-disubstituted adamantane derivatives.[1] Three syntheses of **1** have been reported:[2] (1) pyrolysis of the lithium salt of the *p*-tosylhydrazone of adamantanone provides **1** in 65% yield and a 5% yield of adamantane,[3] (2) lithium aluminum hydride reduction of 2,4-diiodoadamantane gives **1** and adamantane in *ca.* 50–55 and 20–25% yields, respectively,[1] and (3) pyrolysis of 2-adamantyl methane- or toluene-*p*-sulfonate affords a mixture (3:2) of **1** and protoadamantene in 95% yield overall.[4] In each case, preparative glpc separation is required to obtain pure **1**.

In principle, **1** should be accessible by the Wolff–Kishner reduction of 8,9-dehydro-2-adamantanone (**2**).



2 **1**

(1) A. C. Udding, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 1345 (1968).

(2) 2,4-Dehydroadamantane has also been detected in the reaction mixture obtained in the deamination of 2-aminoadamantane by the phenyltriazine method: M. L. Sinnott, H. J. Storesund, and M. C. Whiting, *Chem. Commun.*, 1000 (1969).

(3) A. C. Udding, J. Strating, and H. Wynberg, *Chem. Commun.*, 657 (1966).

(4) J. Boyd and K. H. Overton, *J. Chem. Soc., Perkin Trans. 1*, 2533 (1972).

Although ring cleavage has been found to occur in the Wolff–Kishner reduction of one cyclopropyl ketone,[5] a number of strained cyclopropyl ketones have been successfully reduced to the corresponding hydrocarbons by this technique.[6] In contrast to these results, Baldwin and Foglesong have reported that attempts to convert **2** to **1** by Wolff–Kishner reduction were unsuccessful.[7] We have repeated this study and have found that treatment of **2** under the conditions of the normal Huang-Minlon modification of the Wolff–Kishner reduction[8] provides **1** as the only detectable product in 75% yield. In particular, it is to be noted that by glpc analysis neither protoadamantane nor adamantane could be detected in the material isolated from the reaction mixture.

Experimental Section

2,4-Dehydroadamantane (1).—A solution of 1.0 g of potassium hydroxide, 0.75 g of 95% hydrazine, and 188 mg (1.27×10^{-3} mol) of **2**[7] in 3 ml of diethylene glycol was heated with stirring at 110° for 30 min, and then for 3 hr at 180°. During this time, a white solid appeared on the water-cooled condenser. The system was cooled and the material on the condenser was dissolved in cyclohexane,[9] which was then dried over anhydrous magnesium sulfate and concentrated. Analysis by gas chromatography indicated the presence of a single product and no remaining starting material. Chromatography of this material on silica gel with heptane provided 128 mg (75%) of **1** which was identical in its physical (melting point and glpc retention time) and spectral (ir and pmr) properties with an authentic sample of 2,4-dehydroadamantane.[3]

Registry No.—**1**, 10501-16-3; **2**, 10497-56-0.

Acknowledgment.—This work was supported by grants from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Delaware Research Foundation.

(5) S. M. Kupchan, E. Abushanab, K. T. Shamasundar, and A. W. By, *J. Amer. Chem. Soc.*, **89**, 6327 (1967).

(6) For examples see N. A. LeBel and R. N. Liesemer, *J. Amer. Chem. Soc.*, **87**, 4301 (1965); U. Biethan, U. v. Gizycki, and H. Musso, *Tetrahedron Lett.*, 1477 (1965); W. v. E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, 3943 (1967); S. A. Monti, *J. Org. Chem.*, **35**, 380 (1970).

(7) J. E. Baldwin and W. D. Foglesong, *J. Amer. Chem. Soc.*, **90**, 4303 (1968).

(8) R. L. Augustine, Ed., "Reduction Techniques and Applications in Organic Synthesis," Marcel Dekker, New York, N. Y., 1968, pp 171–185, and references cited therein.

(9) Extraction of the pot residue with cyclohexane provided negligible organic material.

4-Isocyanatophthalic Anhydride. A Novel Difunctional Monomer

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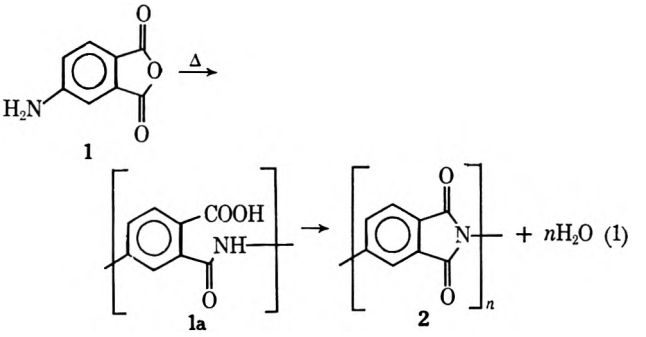
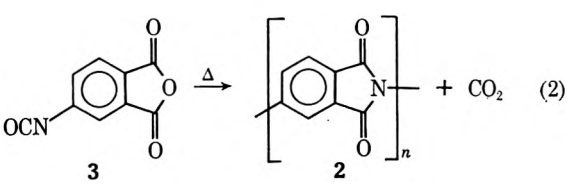
Received February 16, 1973

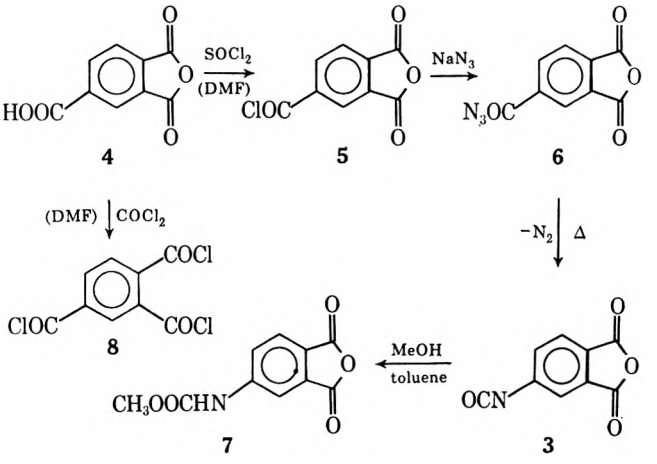
The incorporation of two different polymerizable groups into one molecule capable of undergoing a polycondensation reaction is an interesting concept because only one monomer is required to construct the macromolecule. Stoichiometric problems are eliminated and the purity of the monomers and possible side reactions determine the degree of polymerization achievable. For example, the polyimide **2** was prepared from 4-aminophthalic anhydride **1**[1] (eq 1).



Our interest in isocyanate chemistry prompted us to synthesize 4-isocyanatophthalic anhydride (**3**) a novel monomer having the isocyanato group as well as the anhydride group attached to the benzene ring. It has been previously shown that the reaction of a diisocyanate with a dianhydride produces polyimides with elimination of carbon dioxide.[2] This one-step method (eq 2) has advantages over the amine anhydride route (eq 1) because the complex[3] water elimination step from the intermediate polyamide acid **1a** is not required. The synthesis of **3** (Scheme I)



SCHEME I



started with trimellitic anhydride (**4**) or the corresponding anhydride acid chloride **5**, both readily available raw materials. However, since the commerical **5** required purification, we preferred to prepare the material prior to use and found that treating **4** with thionyl chloride in the presence of catalytic

(1) J. D. Seddon (ICI), British Patent 1,192,001 (1970); it was already observed by M. T. Bogert and R. R. Renshaw, *J. Amer. Chem. Soc.*, **30**, 1135 (1908), that heating of 4-aminophthalic anhydride resulted in loss of water.

(2) W. J. Farrissey, Jr., J. S. Rose, and P. S. Carleton, *J. Appl. Polym. Sci.*, **14**, 1093 (1970).

(3) C. K. Sauers, C. L. Gould, and E. S. Ioannou, *J. Amer. Chem. Soc.*, **94**, 8156 (1972).

amounts of *N,N*-dimethylformamide gave high yields of **5**. This compound was converted to the azide **6** by treatment with NaN_3 in acetone or acetonitrile, and on thermolysis (or photolysis) the isocyanatophthalic anhydride **3**, mp 80–82°, was obtained in high yield.

If carbonyl chloride was used instead of thionyl chloride in the conversion **4** to **5**, the trichloride **8** was formed in high yield. This method of synthesis of **8** is superior to the one described previously.[4]

The anhydride isocyanate **3** reacted selectively on the isocyanate group when treated with 1 equiv of methanol in toluene, giving the carbamate **7** in high yield. Studies to evaluate **3** or the more stable **7** as useful precursors of condensation polymers are underway.

Experimental Section

4-Chloroformylphthalic Anhydride (5).[4]—A suspension of 100 g (0.52 mol) of trimellitic anhydride in 100 g (0.85 mol) of thionyl chloride and 100 mg of *N,N*-dimethylformamide was stirred under reflux (bath temperature 115°) until the gas evolution ceased and a clear yellow solution was formed (2.0–2.5 hr). The excess thionyl chloride was removed under reduced pressure and vacuum distillation of the residue gave 105 g (96%) of **5**, bp 120–124° (0.1 mm), mp 69°.

4-Azidoformylphthalic Anhydride[5] **(6).**—To a solution of 10.2 g (0.048 mol) of freshly distilled 4-chloroformylphthalic anhydride in 60 ml of acetone, 3.25 g (0.05 mol) of sodium azide and 2 drops of triethylamine were added. The suspension was stirred rapidly at room temperature and the progress of the initially exothermic reaction was followed by ir (maximum absorption of the azide band at 2150 cm^{-1} with shoulder at 2200 cm^{-1} which occurred after approximately 2 hr). The precipitated sodium chloride was removed by filtration and the solvent was evaporated under vacuum, care being taken not to exceed a bath temperature of 50–55°.[6] Thus, 10.60 g (97%) of colorless needles of **6** were obtained, mp 100–103°.

Anal. Calcd for $C_9H_3N_3O_4$: C, 49.79; H, 1.39; N, 19.35. Found: C, 49.57; H, 1.32; N, 19.40.

4-Isocyanatophthalic Anhydride[5] **(3).**—To a solution of 31.5 g (0.15 mol) of 4-chloroformylphthalic anhydride in 100 ml of acetone, 11.3 g (0.175 mol) of sodium azide was added. After stirring for 2 hr at room temperature, 100 ml of toluene was added to the suspension, and the reaction flask was immersed in an oil bath and slowly heated to a bath temperature of 115°. During the heating period (1–2 hr) acetone was removed by distillation. Overheating and splashing of concentrated liquid onto hot surfaces of the apparatus has to be avoided because of the danger of explosion. After the evolution of nitrogen ceased the precipitated sodium chloride was removed by filtration, and the filtrate was evaporated under reduced pressure (bath temperature 60°). The crude product, 28.4 g (quantitative), mp 70–75°, can be purified by sublimation to give colorless crystals, mp 80–82°, ir (KBr) 2260 cm^{-1} (NCO).

Anal. Calcd for $C_9H_3NO_4$: C, 57.16: H, 1.60; N, 7.40. Found: C, 57.16; H, 1.49; N, 7.28.

4-Methylcarbamatophthalic Anhydride (7).—A solution of 4.8 g (0.15 mol) of methanol in 30 ml of toluene was added dropwise with stirring to a solution of 28.4 g (0.15 mol) of 4-isocyanatophthalic anhydride in 100 ml of toluene over a period of 15–20 min. The slightly exothermic reaction was controlled at 40–50°, and the reaction product precipitated as a yellow amorphous solid. Filtration and washing with diethyl ether gave 27.5 g (83%) of **7**, mp 150–154° dec.

Anal. Calcd for $C_{10}H_7NO_5$: C, 54.30; H, 3.19; N, 6.33. Found: C, 53.97; H, 3.07; N, 6.03.

1,2,4-Benzenetricarboxylic Acid Trichloride (8).—A suspension of 50 g (0.26 mol) of trimellitic anhydride in 250 ml of benzene containing 100–200 mg of *N,N*-dimethylformamide was heated to 65° and carbonyl chloride was added until a clear yellow solution was obtained (approximately 90 min). Excess carbonyl chloride was removed with nitrogen and vacuum distillation yielded 60.4 g (87%) of **8**, bp 124° (0.1 mm) [lit.[4] bp 143–148° (3 mm)].

Anal. Calcd for $C_9H_3Cl_3O_3$: C, 40.72; H, 1.14; Cl, 40.06. Found: C, 40.51; H, 1.06; Cl, 39.2.

Registry No.—**3**, 40139-36-4; **4**, 552-30-7; **5**, 1204-28-0; **6**, 40139-39-7; **7**, 40139-40-0; **8**, 3867-55-8; sodium azide, 12136-89-9; thionyl chloride, 7719-09-7; carbonyl chloride, 75-44-5.

(4) G. Drechsler and S. Heidenreich, *J. Prakt. Chem.*, **27**, 152 (1965).

(5) *Caution!* All reactions involving azides should be carried out behind safety shields.

(6) Impure samples of azide, obtained by using undistilled acid chloride in the reaction, decomposed sometimes spontaneously during the drying process.

Photochemical Deconjugation as a Synthetic Route to 1,2,3,6-Tetrahydropyridine-4-acetic Acid Esters from $\Delta^{4,\alpha}$-Piperidine-4-acetic Acid Esters[1]

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Received February 5, 1973

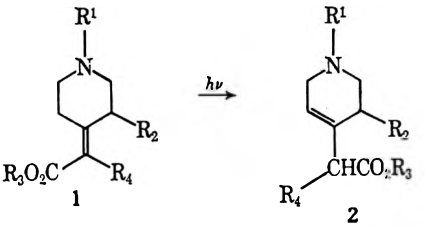
The Wittig reaction employing carbalkoxymethylphosphonates makes esters of $\Delta^{4,\alpha}$-piperidine-4-acetic acids readily available from the corresponding substituted 4-piperidones.[2] These α,β-unsaturated esters can subsequently be converted to the endocyclic isomers by acid- or base-catalyzed equilibration.[2a-f] We report here that photochemical deconjugation[3] constitutes an alternative method for effecting this transformation and that the photochemical method often has the advantage of effecting complete conversion in contrast to the catalytic equilibration procedures.

Ethyl 1-methyl-$\Delta^{4,\alpha}$-piperidine-4-acetate (**1a**) can be prepared in good yield from 1-methyl-4-piperidone.[2b] The compound is isomerized by base or heat to a mixture of **1a** and **2a**. A 4:7 mixture was obtained on isomerization with sodium ethoxide[2f] while a 25:75 mixture was obtained by the thermal method.[2b] The conversion to pure **2a** is 36% in the base-catalyzed method. Irradiation of **1a** in methanol or ethanol effected complete conversion to **2a**, identified by spectral data. The most informative spectral change which accompanies the isomerization is a shift in the carbonyl frequency from 1715 cm^{-1} for **1a** to 1740 cm^{-1} for **2a**. In the nmr spectrum, the singlet at δ 5.62 due to the exocyclic vinyl hydrogen is replaced by a broad unresolved multiplet at δ 5.5. The *N*-benzyl analog **1b** was isomerized to **2b** under similar conditions

(1) Supported by NSF Grant GP-19374 and NCI Grant 12940.

(2) (a) R. J. Sundberg, W. V. Ligon, Jr., and L.-S. Lin, *J. Org. Chem.*, **36**, 2471 (1971); (b) L. D. Quin, J. W. Russell, Jr., R. D. Prince, and H. E. Shook, Jr., *ibid.*, **36**, 1495 (1971); (c) R. J. Sundberg and F. O. Holcombe, Jr., *ibid.*, **34**, 3273 (1969); (d) N. Whittaker, *J. Chem. Soc. C*, 94 (1969); (e) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1461 (1963); (f) R. F. Borne and H. Y. Aboul-Enein, *J. Heterocycl. Chem.*, **9**, 869 (1972); (g) C. Szantay, L. Töke, and P. Kolonits, *J. Org. Chem.*, **31**, 1447 (1966); (h) S. Sugasawa and H. Matsuo, *Chem. Pharm. Bull.*, **8**, 819 (1960); (i) F. O. Holcombe, Ph.D. Thesis, University of Virginia, 1971.

(3) For studies of the synthetic utility of photochemical deconjugation in aliphatic systems see (a) R. R. Rando and W. v. E. Doering, *J. Org. Chem.*, **33**, 1671 (1968). For mechanistic studies see (b) J. R. Scheffer and B. A. Boire, *J. Amer. Chem. Soc.*, **93**, 5490 (1971); (c) M. J. Jorgenson, *ibid.*, **91**, 198 (1969); (d) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968); (e) M. J. Jorgenson and L. Gundel, *ibid.*, 4991 (1968); (f) R. Noyori, H. Inoue, and M. Kato, *J. Amer. Chem. Soc.*, **92**, 6699 (1970); (g) J. K. Crandall and C. F. Mayer, *J. Org. Chem.*, **35**, 3049 (1970); P. J. Kropp and H. J. Krauss, *ibid.*, **32**, 3222 (1967).



	R_1	R_2	R_3	R_4
a	CH_3	H	C_2H_5	H
b	$PhCH_2$	H	C_2H_5	H
c	PhCO	H	C_2H_5	H
d	PhCO	C_2H_5	C_2H_5	H
e	$PhCH_2OCO$	H	CH_3	H
f	$PhCH_2OCO$	C_2H_5	CH_3	H
g	PhCO	H	C_2H_5	C_2H_5

but the reaction was not so clean. Extensive decomposition of product to undefined materials was observed when the photoisomerization was carried beyond 60% completion.

Ethyl 1-benzoyl-$\Delta^{4,a}$-piperidine-4-acetate is partially converted to the isomeric 1,2,3,6-tetrahydropyridine with ethanolic sodium ethoxide and the mixture can be separated by chromatography. We have observed about 75% conversion to **2c** at room temperature. Borne and Aboul-Enein[2f] report a higher **2c**:**1c** ratio by treatment of a Wittig reaction mixture containing **1c** with sodium ethoxide at reflux, but the net conversion to **2c** is lower (39%). Photodeconjugation effects complete conversion to pure endocyclic ester **2c**.

The 3-ethyl derivative **1d** is converted to an equilibrium mixture containing about 45% **2d** by base-catalyzed isomerization.[2c] The photochemical procedure effects complete transformation of **1d**. The spectral properties of the residual material, which consists of a single component according to tlc, establish that it is primarily **2d**. The integration of the vinyl proton region is only about 70% of what is expected. This suggests that the photochemical reaction has resulted in the formation of as much as 30% of the alternative endocyclic ester, ethyl 1-benzoyl-5-ethyl-1,2,3,6-tetrahydropyridine-4-acetate. Although **1d** can be assigned the structure shown with confidence on the basis of the steric factors which govern olefin geometry in the Wittig reaction, it is likely that **1d** is photoequilibrated with the double bond geometric isomer at a rate exceeding the deconjugation reaction.[4]

Methyl 1-carbobenzyloxy-$\Delta^{4,a}$-piperidineacetate is converted cleanly to the endocyclic isomer **2e**. The reaction has been used preparatively and has routinely provided 80–90% yield of pure product on up to 15-g quantities of **1e**.

Photolysis of **1f** leads to complete disappearance and quantitative conversion to isomeric material. As in the case of **1d**, although the product is primarily **2f** it may contain some of the alternative endocyclic isomer. The distilled product analyzes correctly and appears homogeneous to tlc. The integration of the vinyl proton region is only approximately 70% of what is expected. The 1-acylpiperidines **1d** and **1f**, therefore, do not appear to show the very high selectivity for trisubstituted endocyclic olefin which Jorgenson and Patumtevapibal observed in the carbocyclic system, ethyl 2-methylcyclohexylideneacetate.[4]

Base-catalyzed isomerization of the tetrasubstituted olefin **1g** to **2g** in 81% yield has been carried out directly on a Wittig reaction mixture containing **1g**.[2f] Photochemical isomerization was complete and the spectral properties of the crude product were identical with those of a pure sample prepared by a base-catalyzed isomerization.

While our work indicates that the photochemical procedure has some limitations as indicated for **1b**, **1d**, and **1f**, it constitutes a major improvement over base-catalyzed isomerization in other cases studied and would appear to be a useful synthetic route to tetrahydropyridines from 4-piperidones.

Experimental Section

General.—Hanovia mercury lamps (Type S, 200 W or Type L, 450 W) in water-cooled quartz or Vycor immersion wells (25–30°) were used. A Vycor filter sleeve was used with the quartz immersion well. No substantial reaction occurred when compound **1b** was irradiated with the Type S lamp using a Pyrex filter. The solutions were purged with nitrogen for 0.5 hr prior to commencing photolysis and the purge was continued during the photolysis. The photolysis periods cited in the individual experiments represent approximately the minimal time for complete conversion on the scale reported.

Isomerization of 1a.—A solution of **1a** (3.66 g, 2.1 mmol) in methanol (350 ml) was irradiated for 17 hr using the Type L lamp. Evaporation of the solvent left **2a** which was completely free of **1a**, as indicated by the absence of the conjugated CO absorbance. The nmr and infrared spectra of this material were identical with those of an analytically pure sample purified by distillation: bp 65° (0.2 mm); nmr ($CDCl_3$) δ 5.5 (broad s, 1), 4.1 (q, 2), 2.95 (broad, 4), 2.7–2.2 (NCH_3 singlet overlapping multiplets, 7), and 1.21 (t, 3).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.65; H, 9.38; N, 7.56.

The methiodide was prepared by reaction with excess methyl iodide in ether, mp 133–135° after recrystallization from ethanol–ether (lit.[5] mp 134–135°).

Synthesis of 1b[6] and 2b.—Triethyl phosphonoacetate (20.0 g, 84.7 mmol) was added to a solution of sodium ethoxide (1.95 g of sodium metal dissolved in 150 ml of ethanol) and the solution was stirred for 20 min. 1-Benzyl-4-piperidone (10.0 g, 53.0 mmol) was added and the mixture was stirred for 4 hr. Approximately half of the ethanol was removed on a rotary evaporator and the residue was diluted with cold brine (400 ml). The product was isolated by extracting with ether, drying, and evaporating. Two colorless oils were separated by chromatography on silicic acid. The more readily eluted product was the endocyclic isomer **2b** (2.80 g, 20%): ir (neat) 1750 cm^{-1} (CO); nmr ($CDCl_3$) δ 7.30 (s, 5), 5.52 (broad s, 1), 4.14 (q, 2), 3.54 (s, 2), 2.96 (broad, 4), 2.52 (m, 2), 2.20 (broad, 2), 1.22 (t, 3).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.01; H, 8.27; N, 5.46.

The less readily eluted product was the exocyclic isomer **1b** (5.3 g, 39%): ir (neat) 1720 cm^{-1} (CO); nmr ($CDCl_3$) δ 7.30 (s, 5), 5.61 (s, 1), 4.15 (q, 2), 3.50 (s, 2), 3.0 (distorted t, 2), 2.5 (m, 6), 1.25 (t, 3).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.32; H, 8.33; N, 5.61.

Photoisomerization of 1b.—Solutions of pure **1b** (~1 mmol) in methanol (60 ml) were irradiated with the Type S lamp. After 7.5 hr the product mixture (80% yield) was 40% **1b** and 60% **2b** as determined by the relative intensity of the carbonyl absorptions and confirmed by the size of the two vinyl hydrogen signals in the nmr. Continued photolysis led to complete disappearance of exo isomer but much decomposition also occurred

(4) M. J. Jorgenson and S. Patumtevapibal, *Tetrahedron Lett.*, 489 (1970).

(5) S. M. McElvain and R. E. Lyle, Jr., *J. Amer. Chem. Soc.*, **72**, 384 (1950).

(6) Compound **1b** has been prepared previously and characterized as the methiodide, ref 2h.

with eventual disappearance of the nmr signals characteristic of 2b.

Photoisomerization of 1c.—A solution of 1c[2c] (0.50 g) in ethanol (60 ml) was irradiated using a Type L lamp for 5 hr. Evaporation of the solvent left pure 2c having infrared and nmr spectral properties identical with those of previously characterized 2c.[2c]

Photoisomerization of 1d.—Irradiation of 1d (160 mg) in methanol (60 ml) for 3 hr using the Type S lamp resulted in complete disappearance of 1d as shown by tlc. The material obtained by evaporation of the solvent had nmr and ir spectra which were very similar to those of an authentic sample of 2d.[2c] The aromatic:vinyl integration ratio was about 7:1, however.

Preparation of 1e.—A mixture of 1c and 2c (80 g) prepared by the method of Sundberg, Ligon, and Lin[2a] was refluxed for 24 hr with 300 ml of 10% sodium hydroxide solution. The cooled alkaline solution was extracted with ether to remove organic impurities and then made strongly acidic with concentrated hydrochloric acid and extracted with ether to remove benzoic acid. The aqueous layer was made alkaline with concentrated sodium hydroxide and treated at 0° with small portions of benzyl chloroformate with vigorous shaking (total 40 ml). The solution was kept alkaline by addition of small portions of concentrated sodium hydroxide during the acylation. The reaction mixture was extracted with ether and acidified, and then the mixture of exocyclic and endocyclic acids was extracted with chloroform (93% yield). Crystallization from absolute ether gave the exocyclic isomer, 1-carbobenzyloxy-$\Delta^{4,\alpha}$-piperidineacetic acid: mp 127.5–128.5°; nmr ($CDCl_3$) δ 11.35 (s, 1), 7.4 (s, 5), 5.8 (s, 1), 5.2 (s, 2), 3.6 (broad t, 2).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.28; H, 6.30; N, 5.01.

Esterification with diazomethane gave 1e.

Photoisomerization of 1e.—Irradiation of a solution of 1e (8.3 g) in methanol (150 ml) for 22 hr using the Type L lamp gave after evaporation of the solvent 7.8 g of 2e having spectral properties identical with those of an analytical sample prepared by bulb-to-bulb distillation: ir 1750 (ester CO), 1720 cm^{-1} (carbamate CO); nmr ($CDCl_3$) δ 7.35 (s, 5), 5.48 (broad, 1), 5.12 (s, 2), 3.6 (overlapping multiplet and singlet, 5), 2.98 (s, 2) and 2.1 (broad, 2).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.58; H, 6.78; N, 4.84.

For routine preparative work the mixture of exocyclic and endocyclic acids described in the previous experiment was esterified with diazomethane and the resulting mixture of esters was converted to pure 2e by irradiation.

Synthesis of 1f.—A mixture of 1d and 2d was prepared from 1-benzoyl-3-ethyl-4-piperidone as described by Sundberg, Ligon and Lin.[2a] Conversion to 1f was carried out as described for 1e. The analytical sample was purified by chromatography on Florisil: ir (neat) 1720 cm^{-1} (CO, broad, overlapping carbamate and conjugated ester); nmr ($CDCl_3$) δ 7.3 (s, 5), 5.68 (s, 1), 5.11 (s, 2), 3.62 (s, 3), 1.4 (q, 2), and 0.82 (t, 3).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.19; H, 7.45; N, 4.47.

Isomerization of 1f.—A solution of 1f (15.5 g, 0.049 mol) in methanol (500 ml) was irradiated with the Type L lamp for 20 hr. Evaporation of the solvent gave a residue which was eluted from Florisil F-100 (200 g) with 10% ether in benzene. Evaporation of the solvent gave a quantitative yield of material having spectral properties identical with those of the analytical sample, prepared from a center fraction: ir (neat) 1749 (CO) and 1720 cm^{-1} (carbamate CO); nmr ($CDCl_3$) δ 7.4 (s, 5), 5.5 (broad s, ~1), 5.18 (s, 2), 3.68 (s, 3), 3.08 (s, 2), 2.1 (broad q, 2) and 1.0 (m, 2).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.35; H, 7.35; N, 4.34.

Although there were no other indications of the presence of a second component, the vinyl proton integration was about 70% of the expected value, indicating that the product might contain up to 30% of the alternative endocyclic isomer.

Preparation of 1g.—Sodium hydride (2.1 g of 50% mineral oil dispersion) was rinsed with hexane and then covered with anhydrous ether (80 ml). A solution of triethyl 2-phosphonobutyrate[7] (12.6 g) in ether (20 ml) was added slowly. When hydrogen evolution had ceased, a solution prepared by dissolving 1-benzoyl-4-piperidone (10.15 g) in ether (100 ml) and benzene (20 ml) was added. The reaction mixture was then refluxed for 17 hr under nitrogen. The reaction mixture was filtered and the organic filtrate was dried and evaporated. Chromatography gave 1g (10.2 g, 68%). The analytical sample was prepared by bulb-to-bulb distillation: bp 174–175° (0.1 mm); ir (neat) 1725 (ester CO), 1640 cm^{-1} (amide CO); nmr ($CDCl_3$) δ 7.5 (s, 5), 4.25 (q, 2), 3.7 (broad, 4), 2.46 (m, 6), and 1.25 and 1.0 (overlapping t, 6).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.94; H, 7.65; N, 4.47.

Photoisomerization of 1g.—A solution of 1g (100 mg) in ethanol (60 ml) was irradiated for 3.5 hr using the Type S lamp. Evaporation of the solvent left 2g having spectral properties identical with those of the analytical sample prepared by bulb-to-bulb distillation: ir (neat) 1745 (ester CO), 1640 cm^{-1} (amide CO); nmr ($CDCl_3$) δ 7.48 (s, 5), 5.60 (bs, 1), 4.15 (q overlapping m, 4), 3.60 (b, 2), 2.90 (t, 1), 2.20 (b, 2), 1.75 (broadened q, 2), 1.25 (t, 3), 0.90 (t, 3).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.55; H, 7.86; N, 4.50.

Base-Catalyzed Isomerization of 1c.—A solution of 1c (40.0 g) was dissolved in ethanol (200 ml) and treated with a sodium ethoxide solution prepared by dissolving sodium metal (0.75 g) in ethanol. After stirring for 3 hr at room temperature the solution was poured into acidic brine and extracted with ether. The product obtained by drying and evaporation of solvent was shown by nmr to be a 1:2.9 mixture of 1c and 2c (92% yield). Separation and characterization of 1c and 2c have been reported previously.[2c]

Registry No.—1a, 28399-82-8; 1b, 40110-55-2; 1c, 21363-69-9; 1d, 21363-68-8; 1e, 40112-93-4; 1f, 40112-94-5; 1g, 40112-95-6; 2a, 37123-97-0; 2b, 40112-97-8; 2c, 21363-70-2; 2d, 21389-71-9; 2e, 30338-85-3; 2f, 40113-01-7; 2g, 37124-04-2; triethyl phosphonoacetate, 867-13-0; 1-benzyl-4-piperidone, 3612-20-2; 1-carbobenzyloxy-$\Delta^{4,\alpha}$-piperidineacetic acid, 40113-03-9; triethyl 2-phosphonobutyrate, 17145-91-4; 1-benzoyl-4-piperidone, 24686-78-0.

Acknowledgment.—Some of the compounds utilized in this work were originally prepared in our laboratory by Dr. F. O. Holcombe.

(7) B. Ackerman, R. M. Chlodek, and D. Swern, *J. Amer. Chem. Soc.*, **79**, 6524 (1957).

Formamoylation of Some Azo Compounds and the Characterization of Reaction Products

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Received February 12, 1973

The free-radical addition of formamide to olefins has been reported.[1] The reaction proceeds with good yields in the presence of peroxide or ultraviolet radiation (2000–2500 Å).[2] Likewise, the addition of a number of free-radical species to azo compounds has been observed.[3] We wish to report here the first addition of the formamoyl radical to azo compounds.

Formamide adds to 1,1′-azobisformamide (ABFA) in the presence of decomposing benzoyl peroxide (BPO)

(1) (a) D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964); (b) D. Elad, *Chem. Ind. (London)*, 362 (1962); (c) L. Friedman and H. Schechter, *Tetrahedron Lett.*, 238 (1961); *Chem. Abstr.*, **55**, 20934*d* (1961).

(2) The addition also proceeds in sunlight.[1a,b]

(3) (a) A. Jones, E. R. Morris, and J. C. J. Thynne, *J. Phys. Chem.*, **72**, 2677 (1968); (b) D. Mackay, U. F. Marx, and W. A. Waters, *J. Chem. Soc.*, 4793 (1964).

(mole ratio 30:1:0.2, respectively) to give a product identified as trisformamoylhydrazine (1) in 86% yield (Scheme I).

SCHEME I

$$(PhCO_2)_2 \longrightarrow 2R\cdot \quad (1)$$

$$R\cdot + HC(O)NH_2 \longrightarrow RH + \cdot C(O)NH_2 \quad (2)$$

$$\cdot C(O)NH_2 + H_2NCON{=}NCONH_2 \longrightarrow H_2NCONN(CONH_2)_2 \quad (3)$$

$$H_2NCONN(CONH_2)_2 + HCONH_2 \longrightarrow \underset{\mathbf{1}}{H_2NCONHN(CONH_2)_2} + \cdot C(O)NH_2 \quad (4)$$

No attempt was made to optimize conditions, but our results and those of other workers suggest that the chain sequence postulated is short and/or that the initial process (eq 2) leading to formamoyl radical formation proceeds in low yield. Thus, it was observed that at levels of BPO below 5 mol %, formamoylation of ABFA does not occur. That the reaction proceeds *via* a radical course analogous to that suggested for additions to olefins was demonstrated when 83% of the ABFA was recovered unchanged in a control reaction carried out in the absence of BPO. The remaining 17% was accounted for as **1** (~9%), cyanuric acid, and urea, resulting from slight thermal decomposition of ABFA.

The reaction was extended to *N*,*N*,*N*′,*N*′-tetramethylazobisformamide (TMABFA) and gave the corresponding formamoylated product, **2**, in 32% yield. An attempt to add formamide to azobenzene under similar reaction conditions failed to yield any 1:1 adduct (**3**). This observation suggests that for

$\underset{\mathbf{2}}{Me_2NCONHN(CONH_2)CONMe_2}$ $\underset{\mathbf{3}}{PhNHN(CONH_2)Ph}$

addition of formamoyl radical to proceed, the azo function should possess a low electron density, a condition met by the azo compounds ABFA and TMABFA. The structural assignments (**1** and **2**) for the formamoylation products of ABFA and TMABFA, respectively, were based on the following rationale: (1) direct analogy to the process and products (amides) obtained in the formamide–olefin reaction;[1] (2) from reported studies[4] involving the direct examination of the radical produced from formamide and its assigned structure as $\cdot C(O)NH_2$, and (3) from chemical and physical properties of the 1:1 adducts obtained.

Structures **1** and **2**, assigned to the addition products from ABFA and TMABFA upon reaction with formamide, are supported by elemental analyses and molecular-weight determinations. In addition, the mass spectral fragmentation pattern of the 1:1 ABFA–formamide adduct is in agreement with the assigned structure **1**. Although a molecular ion (*m*/*e* 161) was not readily discernible, a peak at *m*/*e* 118 was reasonably intense and possibly represents a charged hydrazobisformamide (biurea) species. Below *m*/*e* 118, the fragmentation pattern of **1** was in general agreement with that of biurea.

The nmr spectrum of **1** in DMSO-d_6 exhibits four singlets (integral ratio 2:2:2:1) between δ 6.0 and 8.0. The lowest field absorption (δ 7.95, 1 H) was assigned to the hydrazo proton. The lone formamoyl group occurs as a sharp singlet at δ 6.11 and the geminal formamoyl groups as broad singlets at δ 6.97 and 7.59. Warming to approximately 40° caused the signals at δ 6.97 and 7.59 to coalesce (δ 7.17, 4 H). The process was completely reversible on cooling.

Formamoyl-substituted hydrazo compounds do not exhibit doubling of the amide proton signals under these conditions.[5] The occurrence of two signals for the geminal formamoyl groups is a consequence of rotational barriers involving the C–N–N bonds,[6] barriers to nitrogen inversion, or possibly both.[7] We have not made a thorough study of the temperature-dependent nmr spectrum of **1**. The relative importance of each of these parameters could not be established unambiguously in **1**.

By comparison, the nmr spectrum of **2** was relatively straightforward. The nmr absorption at δ 8.77 was assigned to the single hydrazo proton and that at 6.60 to the two amide protons. Signals at δ 2.88 and 2.80 were assigned to the protons of each *N*,*N*-dimethylcarbamoyl group.

The chemical and thermal properties of **1** were also briefly investigated and indicate a relatively facile loss of cyanic acid and formation of biurea. Treatment of **1** with aqueous alkali or diethylamine, or refluxing an aqueous solution of **1**, gave quantitative yields of biurea and products attributed to the intermediacy of cyanic acid. Heating **1** in DMSO solution at 115° resulted in the formation of biurea and cyanuric acid as major reaction products. Thermogravimetric analysis of **1** showed an initial weight loss of *ca.* 26% between 225 and 250°, which corresponds to that calculated for cyanic acid.

$$H_2NCONHN(CONH_2)_2 \xrightarrow[\text{see text}]{\Delta} \underset{\text{biurea}}{H_2NCONHNHCONH_2} + \underset{\text{cyanic acid}}{HNCO}$$

$$3HNCO \longrightarrow \underset{\text{cyanuric acid}}{\text{HOC}_3\text{N}_3\text{(OH)}_3}$$

Experimental Section

Nmr spectra were obtained with a Jeolco Model JNM-4H-100 100-MHz spectrometer (TMS internal standard) and the ir spectra on a Perkin-Elmer 451 spectrophotometer. Thermogravimetric analyses (TGA) were determined in dry air at 6°/min, using an American Instrument Co. Thermo-Grav. Analyses were performed by Galbraith Laboratories, Inc., Knoxville 21, Tenn. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Boiling points are uncorrected.

Materials.—1,1′-Azobisformamide (ABFA) (Aldrich Chemical Co.) [λ_{max}^{DMSO} (ϵ_{max}) 262 (1680), 423 (51.1)], azobenzene (Eastman Organic Chemicals), and benzoyl peroxide (Lucidol Division of Wallace and Tiernan) were used as received. Formamide

(4) (a) R. Livingston and H. Zeldes, *J. Chem. Phys.*, **47**, 4173 (1967); (b) H. Bower, J. McRae, and M. C. R. Symons, *J. Chem. Soc. A*, 2400 (1971).

(5) Unpublished results from this laboratory. Note also that the remaining formamoyl group in **1** appears as a sharp singlet.

(6) G. J. Bishop, B. J. Price, and I. O. Sutherland, *Chem. Commun.*, 672 (1967).

(7) M. J. S. Dewar and W. B. Jennings, *J. Amer. Chem. Soc.*, **91**, 3655 (1969); M. J. S. Dewar and W. B. Jennings, *Tetrahedron Lett.*, 339 (1970), and references cited therein.

(Fisher, reagent grade) was dried over magnesium sulfate and distilled *in vacuo;* the fraction of bp 66–67° (1.0 mm) was retained. *N,N,N',N'*-Tetramethylazobisformamide (TMABFA) was prepared by lead tetracetate oxidation of the corresponding hydrazobisformamide suspended in methylene chloride maintained at 20 ± 2°. The crude TMABFA recrystallized from hexane–benzene (5:1, v/v) melted at 111–113° (lit.[8] mp 112–113°).

Formamoylation of ABFA.—To a stirred slurry of ABFA (11.6 g, 100 mmol) in formamide (135 g, 3.0 mol) was added benzoyl peroxide (2.42 g, 10 mmol). The reaction mixture was then heated at 80 ± 2° under an oxygen-free nitrogen atmosphere for 4 hr. Additional peroxide (10 mmol) was then added and the reaction temperature was maintained for 24 hr.

Distillation of the clear, pale orange-amber reaction mixture *in vacuo* [pot temperature 85° (0.1 mm)] left a cream-colored solid residue. The residue was triturated consecutively with portions of alcohol and ether, leaving 13.9 g (81 mmol, 86.4%) of crude trisformamoylhydrazine (1), mp 214–222° dec. The crude cream-colored solid 1 was recrystallized twice from aqueous 75% alcohol and dried *in vacuo* (0.5 mm, 110°) to give an analytical sample melting at 220–225° dec.

Anal. Calcd for $C_3H_7N_5O_3$ (1): C, 22.36; H, 4.38; N, 43.47; mol wt, 161. Found: C, 22.21, 22.37; H, 4.39, 4.44; N, 43.56, 43.59; mol wt, 162 (determined cryoscopically in DMSO).

An ir spectrum (KBr) of 1 showed NH absorptions at 3475 (s), 3410 (shoulder, s), 3390 (s), 3350 (s), 3290 (s), and 3220 (m), a series of absorptions in the carbonyl region at 1695 (vs), 1660 (vs), 1630 (m), 1580 (m), and 1515 (m), and absorptions at 1360 (s), 1090 (w), 1063 (w), and 640 cm^{-1} (m).

The uv spectrum (H_2O) of 1 exhibits no maxima above 200 nm (ϵ_{200} 7000 l. mol^{-1}).

The nmr spectrum (DMSO-d_6) of 1 showed absorptions at δ 6.11 (s, relatively sharp, 2 H), 6.97 (broad s, 2 H), 7.59 (broad s, 2 H), and 7.95 (s, 1 H). Addition of D_2O to the DMSO-d_6 solution of 1 caused greatest diminution in the absorption at δ 7.95.

The mass spectrum of 1 (20 eV, 170°) exhibits the following: *m/e* (rel intensity) 118 (95), 101 (100), 86 m (4), 75 (95), 45 (11), 44 (95), 31 (97), and 18 (32).[9]

Formamoylation of TMABFA.—A stirred solution of TMABFA (7.8 g, 45 mmol) in formamide (135 g, 3.0 mol) containing 2.42 g (10 mmol) of benzoyl peroxide was heated to 80 ± 2° under an oxygen-free nitrogen atmosphere for 4 hr. Additional peroxide (10 mmol) was added and heating was continued for 15 hr.

The clear, pale orange reaction mixture was distilled *in vacuo* (pot <80°, 0.15 mm) and left an orange-amber semisolid residue that was slurried with warm methylene chloride (80 ml) and filtered. The filter cake, crude 1-formamoyl-1,2-bis(*N,N*-dimethylcarbamoyl)hydrazine (2) (3.15 g, 32%), mp 180–185°, was recrystallized twice from absolute alcohol to afford analytically pure 2: mp 183–184.5°; ir (KBr) 3430 (s, NH), 3220 (m), 2930 (w), 1690 (s, shoulder, C=O), 1675 (vs, C=O), 1690 (s, shoulder, C=O), 1365 (m), and 1272 cm^{-1} (w); uv (H_2O) exhibits no maxima above 200 nm (ϵ_{200} 14,600 l. mol^{-1}); nmr (DMSO d_6) δ 2.80 (s, 6 H, CH_3), 6.60 (s, 2 H), and 8.77 (s, 1 H). *Anal.* Calcd for $C_7H_{15}N_5O_3$ (2): C, 38.70; H, 6.96; N, 32.24; mol wt, 217. Found: C, 38.55; H, 7.01; N, 32.44; mol wt, 210 (determined in THF by vapor phase osmometry).

Hydrolysis of Trisformamoylhydrazine (1).—A clear solution of 1 (1.0 g, 6.2 mmol) in 75 mol of water was heated to reflux. After 4.5 hr, the reaction mixture contained some insolubles and ammonia was detected. The reaction mixture was refluxed for an additional 2 hr, cooled, and filtered. The dried filter cake (0.7 g) was identified as biurea (5.9 mmol) by melting point, mixture melting point, and ir. Evaporation of the weakly basic aqueous filtrate left a solid residue (undetermined amount) identified by ir as urea.

Basic Hydrolysis of Trisformamoylhydrazine (1).—To a slurry of 1 (1.0 g, 6.2 mmol) in 50 ml of water was added 5 ml of aqueous 40% sodium hydroxide, causing immediate solution of 1. After several minutes at room temperature, the reaction mixture become turbid and a finely divided solid precipitated. The filtered and dried solid (0.7 g) was identified as biurea (5.9 mmol). An acidulated aqueous solution of benzoyl hydrazide was added to the clear, pale yellow basic filtrate from the main reaction mixture. Upon cooling the mixture, 4-benzoylsemicarbazide precipitated; it was identified by melting point (222–225° dec), mixture melting point, and ir.

Aminolysis of Trisformamoylhydrazine (1).—To a suspension of 1 (1.0 g, 6.2 mol) in water (25 ml) at room temperature was added a solution of diethylamine (2.0 g, 41.0 mmol) in water (*ca.* 15–20 ml). After *ca.* 15 min, a solid precipitated from the turbid reaction mixture. After an additional 30 min at room temperature, the solid was filtered and the filter cake was washed consecutively with alcohol and ether. The dried filter cake (0.7 g) was identified as biurea (6.0 mmol) by melting point and ir.

The aqueous filtrate was evaporated to dryness, and the residual solid was extracted with ether. Concentration of the combined ether extracts gave diethylurea, mp 65–69°, identified by ir and nmr.

Thermolysis of Trisformamoylhydrazine (1).—A solution of 1 (6.5 mmol) in 25 ml of DMSO was heated at 115° for 21 hr. The solvent was removed by distillation *in vacuo* (pot temperature <80°, 0.1 mm). The solid residue was found to contain biurea (5.1 mmol) and cyanuric acid (2.1 mmol), as determined by nmr.

Registry No.—1, 39981-78-7; 2, 40081-62-7; ABFA, 123-77-3; formamide, 75-12-7; TMABFA, 10465-78-8; biurea, 110-21-4; benzoyl hydrazide, 613-94-5; 4-benzoylsemicarbazide, 39981-79-8; diethylamine, 109-89-7; diethylurea, 623-76-7; cyanuric acid, 108-80-5.

Acknowledgment.—The authors wish to express their appreciation to Professor D. Swern, Temple University, for his helpful suggestions, to Professor J. E. Sturm, Lehigh University, for recording the mass spectra, and Mr. A. G. Geigley for recording the nmr spectra.

(8) R. J. Crawford and R. Raap, *J. Org. Chem.*, **28**, 2419 (1963).

(9) The mass spectrum of authentic biurea (obtained from Aldrich Chemical Co., Inc.) exhibits the following fragmentation pattern (20 eV, 210°): *m/e* (rel intensity) 118 (2), 101 (89), 75 (100), 60 (21), 45 (85), 44 (90), 31 (90), 30 (54), 18 (82), and 17 (41).

The Electrocyclodimerization of *N*-Vinylcarbazole

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Received February 13, 1973

Passage of electric current through solutions of *N*-vinylcarbazole (VCZ), for example, with silver perchlorate in nitrobenzene[1] or with zinc bromide in acetone,[2] has been shown to result in polymerization. However, Breitenbach[3] also reported that electroinitiation with Hg^{II} cyanide, in acetonitrile, gave a cyclic dimer. Similarly, photoirradiation in the presence of organic electron acceptors results in the production of polymer or cyclic dimer depending on the acceptor and the solvent. Tada, *et al.*,[4] found that the basic character of the solvent was a critical factor in determining the production of cyclic dimer or polymer. In copolymerization studies with electron-accepting monomers,[5] it was found that as the concentration of the electron-accepting monomer decreased the proportion of cyclodimer product increased. It was con-

(1) J. W. Breitenbach and C. Srna, *Pure Appl. Chem.*, **4**, 245 (1962).

(2) D. C. Phillips, D. H. Davies, and J. D. B. Smith, *Macromolecules*, **5**, 674 (1972).

(3) J. W. Breitenbach, O. F. Olaj, and F. Wehrman, *Monatsh. Chem.*, **95**, 1007 (1964).

(4) K. Tada, Y. Shirota, S. Kusadazashi, and H. Mikawa, *Chem. Commun.*, 1169 (1971).

(5) K. Tada, Y. Shirota, and H. Mikawa, *J. Polym. Sci., Part B*, **10**, 691 (1972).

cluded that cation solvation of a radical cation species was responsible for the cyclodimerization reaction. Ledwith, *et al.*[6] reached similar conclusions when studying the metal salt catalyzed reactions of a number of aromatic enamines. It has been generally accepted that the cyclic dimer, in the *N*-vinylcarbazole system, is *trans*-1,2-dicarbazylcyclobutane (TCB).[2,3]

In this note, we report that the electroinitiated reaction of VCZ, using zinc bromide as electrolyte in acetone solution, can result in either linear polymer or TCB in high yield. The product depends only upon the current density used in the electrolytic cell. The work reported here is largely confined to the current density regions where both products are obtained. The conventional polymerization process has been discussed previously.[2]

Experimental Section

The electrolytic experiments were conducted in a 50-ml darkened reaction flask to avoid the possible occurrence of any extraneous photochemical reactions. The vessel, which was maintained at 25° by means of a jacket through which water flowed, was equipped with stirrer and nitrogen inlet and outlet. The standard electrolytic cell contained two identical platinum foil electrodes (2.0 × 5.0 cm) separated by 4.0 cm. Similar cells modified with porous battery cup separation of anode and cathode compartments were also used. All reactions were performed under conditions of constant current using a dc power supply (Northeast Scientific Corp. Model RI233, 0–233 mA/0–360 V).

The purification of starting materials is reported elsewhere.[2,7] The zinc bromide and *N*-vinylcarbazole monomer were separately dissolved in two equal volumes of acetone contained in darkened vessels. Equal quantities of each solution were mixed just prior to the application of current. After passage of electrolytic current, the products of the reaction were isolated by precipitation into a large excess of absolute methanol. This procedure served to separate the products from monomer, since the monomer is readily soluble in methanol. The crude product was further purified by reprecipitation from toluene solution into excess methanol followed by several methanol washes. Total yield was then determined gravimetrically.

The product was separated into polymer and dimer fractions using gel permeation chromatography, the product being dissolved in toluene and passed through a bank of four Styragel columns at 75° using a flow rate of 1 ml/min. Under these conditions the two peaks were well resolved and the percentage of each product was then determined through calibration of the chromatogram using a known mixture. Some product samples were separated by acetone extraction (the dimer being soluble in acetone) and analyzed gravimetrically. Both techniques gave good correlation.

The cyclic dimer was characterized using a number of techniques. Elemental analysis gave the following results: C, 87.1; H, 5.7; N, 6.9; calcd C, 87.3; H, 5.8; N, 6.8. Nmr analysis, in $CDCl_3$ on a Varian A-60 instrument, gave the results shown in Table I. These data are close to those reported by Ellinger[8] for the dimer.

Mass spectral fragmentation (Perkin-Elmer Model 270) indicated a molecular weight of 386 and confirmed the adjacent position of the carbazole rings by the presence of significant levels of 1,2-dicarbazyl ethylene fragments. The crystalline solid dimer had a melting point of 191–192° (uncorrected) close to that reported by Breitenbach. The polymer was also studied and is discussed in more detail elsewhere.[7] The polymer average molecular weight ranged between 3000 and 20,000 and was independent of the current strength and the zinc bromide concentration. Analysis of the major products for bromine or zinc proved negative. No significant amounts of other products were found.

TABLE I

NMR ANALYSIS OF *trans*-1,2-DICARBAZYLCYCLOBUTANE[a]

Protons	Nmr, τ	Rel intensities, Calcd	Rel intensities, Found
Aromatic (1,8 positions)	1.98 (m)	2	1.8
Aromatic	2.69 (m)	6	5.9
CH cyclobutane ring	3.77 (m)	1	1.0
CH_2 cyclobutane ring	7.25 (m)	2	1.7

[a] TMS as internal reference.

Results and Discussion

The current density was varied while maintaining other variables constant and holding a 5:1 VCZ:$ZnBr_2$ constant mole ratio. The results, presented in Table II, show that as the current density is decreased the corresponding proportion of the dimer is increased. Above 1.0 mA cm^{-2} the reaction produces almost exclusively polymer. Below 0.05 mA cm^{-2} the cyclic dimer, TCB, was produced in high yield.

TABLE II

ELECTROINITIATION OF VCZ–$ZnBr_2$–ACETONE SOLUTIONS[a]

Current density, mA cm^{-2}	Time, hr	Product formation as percentage of initial monomer, TCB	Product formation as percentage of initial monomer, Poly VCZ
4.0	2	0.2	83.5
1.0	2	0.8	66.6
0.20	2	13.0	46.2
0.05	2	13.8	0.1
0.05	8	34.0	0.1
0.05	18	61.3	0.2

[a] VCZ:$ZnBr_2$ = 5:1, VCZ:acetone = 1:40.

Also shown in Table II is the effect of increased time at the lowest current density. Even at extremely long reaction times no significant levels of polymer could be found. Increasing the VCZ monomer concentration, while maintaining the current density, reaction time, and zinc bromide concentration constant, decreased the polymerization rate while increasing the rate of cyclodimerization. For example, using a 10:1 VCZ:$ZnBr_2$ mole ratio and 2 hr of 4.0 mA cm^{-2} current passage gave 24% polymer product and 0.5% dimer. At a current density of 0.05 mA cm^{-2} a similar decrease in polymer yield, accompanied by an increase in TCB formation, was observed. The exponent (α) and the constant (k) in the rate equation $R_n = kI^\alpha + c$ were determined. (c and k are constants and I the electrolytic current density.) R_n is the rate of cyclodimerization (R_c) or the rate of polymerization (R_p). Also determined was the equivalent function for photoirradiation of the same system with 254-nm uv, I being the uv intensity in this case. The experimental conditions for irradiation are similar to those reported elsewhere.[9] The result of irradiation as was expected from the results of Tada, *et al.*[4] The TCB was always the major product and only small amounts of polymer were found. Table III shows the results of irradiation, and Table IV the rate equation determination data.

(6) F. A. Bell, R. A. Crellin, H. Fujii, and A. Ledwith, *Chem. Commun.*, 251 (1969).

(7) D. C. Phillips, J. D. B. Smith, and D. H. Davies, *Makromol. Chem.*, in press.

(8) L. P. Ellinger, J. Feeney, and A. Ledwith, *Monatsh. Chem.*, **96**, 131 (1965).

(9) D. H. Davies, D. C. Phillips, and J. D. B. Smith, *J. Polym. Sci., Part A-1*, **10**, 3253 (1972).

TABLE III

UV IRRADIATION OF VCZ–$ZnBr_2$–ACETONE SOLUTIONS[a]

Intensity of 254-nm uv, $\mu A\ cm^{-2}$	Time, hr	Product formation as percentage of initial monomer— TCB	Poly VCZ
30×10^3	1	8.6	2.4
30×10^3	2	61.5	1.8
30×10^3	5	99.5	0.2
16×10^3	5	73.0	<0.1
10×10^3	5	55.0	<0.1

[a] VCZ:$ZnBr_2$ = 5:1, VCZ:acetone = 40:1, under N_2.

TABLE IV

INTENSITY EXPONENT DATA FOR PHOTO- AND ELECTROINITIATED REACTIONS OF VCZ IN $ZnBr_2$–ACETONE SOLUTIONS[a]

System	k	α
Photodimerization	+0.52	+0.53
Electrodimerization	+1.56	−0.98
Electropolymerization	+1.92	+0.30

[a] VCZ:$ZnBr_2$ = 5:1, VCZ:acetone = 40:1; photoirradiation 254 nm, 5 hr under N_2; electroinitiation, 2 hr, 0.05–4.0 mA cm^{-2}

The intensity exponent for the photodimerization is very close to that obtained by Tazuke[10] (α = 0.56–0.45) in his analysis of a variety of photoinitiated VCZ polymerizations. This confirms the proposal that, in the absence of significant competing reactions, the initiation step for both photodimerization and photopolymerization is the same.

The very different data for the electroinitiated reactions must reflect the competitive processes of polymerization and cyclodimerization. The possibility of other initiation routes, however, cannot be ruled out and this will be discussed in more detail below. It should be noted that the data on the electroinitiated reaction refer only to the low current densities detailed above, *i.e.*, under conditions where both products are obtained. This analysis allows us to conclude tentatively that (a) the chemistry of the $ZnBr_2$–acetone–VCZ system will be similar to that of other VCZ systems since the photoinitiation results are clearly similar to those obtained by other workers on various photo VCZ systems,[4,10] and (b) competition is occurring between the two product routes in low current density electroinitiation, *i.e.*, both products are not formed independently but arise from a common initiation process.

There are four mechanistic possibilities in the electroreaction that could explain the formation of the TCB. These follow. (1) Extraneous photochemical reaction could occur. This is a possibility considering the solvent system and the results of Tada.[4] This likelihood was eliminated by careful exclusion of light in all stages of sample preparation and reaction. Also, the rate dependence on current density, as indicated in Table II, makes this unlikely. (2) Direct chemical catalysis could occur. This is similar to the results of Ledwith[6] using Fe^{3+} and Cd^{4+}. There was no significant reaction in blank solutions of the above compositions which were shielded from the light but through which no current was passed. (3) Cathodic electrolytic reaction could occur. Using the porous battery cup technique the locus of reaction was determined to be the anode. No product, TCB or polymer, could be found at the cathode. (4) Anodic electrolytic reaction could occur. Both products were formed exclusively in the anode region. Some small filaments of product were found at the electrode with the higher current densities. Principally, however, the reaction occurred in the bulk and the product was only isolated upon extraction. Analysis of the reaction product from the anode cup indicated that a similar polymer:TCB product ratio was obtained for comparable single-cell data. The overall reaction rate was somewhat different, presumably because of diffusion rate limitations.

The role of radical cation species as the initiating activity in both VCZ polymerization and cyclodimerization has been proposed.[2,6,10,11] Both photochemical and metal-catalyzed systems involve these intermediates. Complex formation ($VCZ\cdot{}^{+}Fe^{II}X_3^{-}$) was proposed by Ledwith[6] as the initial stage in the latter reaction. As we have proposed previously, for the $ZnBr_2$-catalyzed polymerization of VCZ at high current densities,[2] it is likely that donation from the basic carbazole nitrogen to the zinc salt (Lewis acid) occurs to give a complex. Similar complexes have been isolated for the analogous $ZnBr_2$–vinylimidazole system.[12] It was shown that conjugation of the vinyl unsaturation with the heteroaromatic ring occurs. The evidence for the existence of these complexes is discussed in more detail elsewhere.[7]

The formation of these charge-transfer donor–acceptor (D–A) complexes has been shown by Gaylord[13] to be a very useful method for inducing reaction. Funt[14] has further shown that such D–A complexes are readily susceptible to electrolytic reaction, although the exact nature of the electrode process is not known. The result of this process when applied to our system is the formation of a VCZ radical cation stabilized by a VCZ–metal salt radical anion system. The radical cation ($VCZ\cdot{}^{+}$) results in either polymerization or cyclic dimerization. It is well established that the polymerization is a consequence of the cation function of this species.[2,7] However, if the concentration of neutral VCZ molecules is high enough it is possible that they interact with $VCZ\cdot{}^{+}$ in the fashion proposed by Ledwith for chemical catalysis.[6] The result is radical cyclic dimerization to give TCB, as was found in the chemical catalytic system. This mechanistic path can explain the unusual features of the results detailed above. At low current densities, the concentration of neutral VCZ molecules is high. The reaction path leading to TCB is therefore likely. However, at the higher current densities the concentration of available neutral VCZ molecules is significantly depleted relative to the electrode-produced radical cation. Therefore, the alternative, competitive, cationic polymerization is more likely. Similarly, the higher the VCZ monomer concentration, relative to $ZnBr_2$, the more likely is the process leading to cyclic dimerization, as was found. This mechanism, however, assumes that similar initiating species are produced at the electrode at both extremes of the range

(10) M. Asai, K. Kameoka, Y. Takeda, and S. Tazuke, *J. Polym. Sci., Part B*, **9**, 247 (1971).

(11) N. G. Gaylord, *Polym. Prepr.*, 277 (1969).

(12) S. Tazuke and S. Okamura, *J. Polym. Sci., Part A-1*, **7**, 851 (1969).

(13) N. G. Gaylord and A. Takahashi, *Advan. Chem. Ser.*, **91**, 94 (1969).

(14) B. L. Funt, I. McGregor, and J. Tanner, *J. Polym. Sci., Part B*, **8**, 699 (1970).

of current densities. Albeck, *et al.*,[15] examined the electrode reaction potential, as a function of current density, for lithium acetate–methanol–acrylate systems. They found that changes in current density (0.2–1.6 mA cm^{-2}) could more than double the electrode reaction potential. It is therefore feasible that alternative initiating species (possibly dications) are produced at the different current densities and that product formation is a function of this phenomenon rather than of monomer depletion.

Registry No.—VCZ, 1484-13-5; TCB, 1484-96-4.

(15) M. Albeck, M. Konigsbuch, and J. Relis, *J. Polym. Sci., Part A-1*, **9**, 1375 (1971).

The Interception of Transitory 1-Azirines with Cyclopentadienones during the Thermal Decomposition of Certain Vinyl Azides. Formation of 3*H*-Azepines[1]

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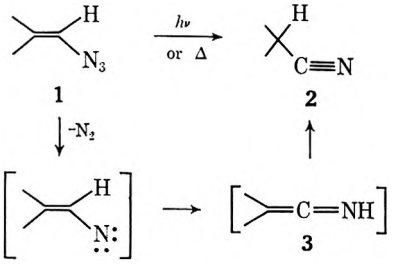
Received March 28, 1973

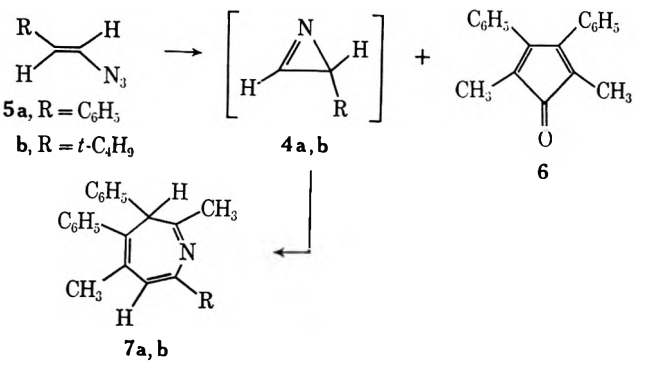
We have recently described the formation[2] of azepines from 1-azirines and cyclopentadienones, and discussed the mechanistic implications.[3] We now demonstrate the effectiveness of cyclopentadienones as a general reaction, to intercept (in a Diels–Alder fashion) 1-azirines possessing only a fleeting existence, formed during the thermolysis of particular vinyl azides.

When terminal vinyl azides **1** are decomposed, frequently the major product is the nitrile **2** believed[4] to be formed *via* the vinyl nitrene and ketenimine **3**.

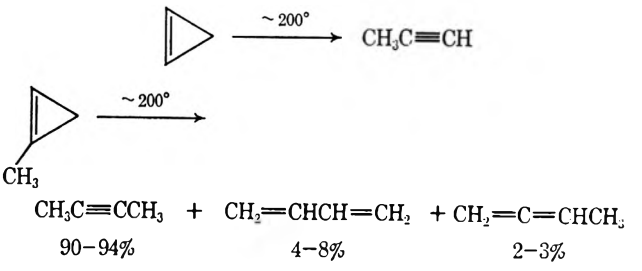


However, spectroscopic and chemical evidence[5] have indicated the presence of 1-azirines **4** in these reactions. Indeed, one such azirine, unsubstituted on carbon 2, has been isolated[6] and found to rearrange to both nitrile and isonitrile.

When the terminal vinyl azides **5a** and **5b** were decomposed in refluxing toluene in the presence of the cyclone **6**, the appropriate 3*H*-azepines **7a** and **7b** were isolated in high yield. It is apparent, therefore, that azirines **4** are formed in the thermal decomposition of **5**

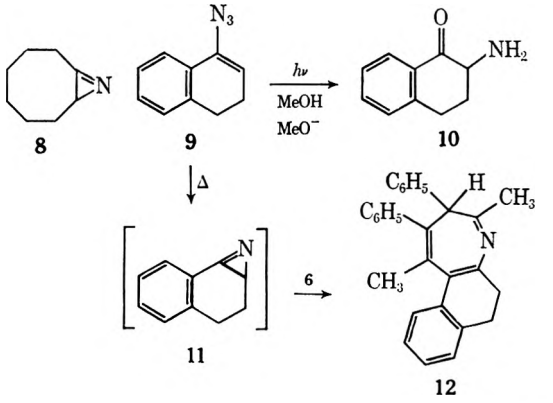


and hence are intermediates in the formation of nitriles and ketenimines. By analogy, cyclopropene rearranges thermally[7] to 1-propyne, and 1-methylcyclopropene affords 2-butyne, butadiene, and methyl allene.



The structures of azepines **7** were inferred from their nmr and mass spectra in analogy to previous cases.[2,3]

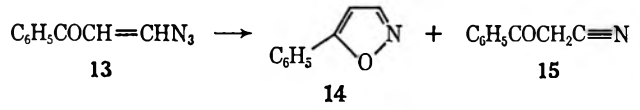
1-Azirines fused to eight-membered rings, for example **8**, have been prepared[8] from the appropriate vinyl azides. However, decomposition of the six-membered ring vinyl azide **9** alone produced polymeric material. Photochemical decomposition of **9** in methanol, in the presence of methoxide, did produce the amino ketone **10**, suggesting the intermediacy of the fused azirine **11**. When **9** was allowed to decompose in refluxing toluene in the presence of the cyclone **6**, the 3*H*-azepine **12** was



formed together with much polymeric material, thus inferring the fused azirine **11** as an intermediate.

The decomposition of β-azidoacrylophenone (**13**) has led[9] to the formation of the isoxazole **14** and benzoylacetonitrile (**15**). We were unable to trap the possible

(1) Cycloadditions. XIII. For previous paper in the series see J. Rasmussen and A. Hassner, *J. Org. Chem.*, **38**, 2114 (1973).
(2) D. J. Anderson and A. Hassner, *J. Amer. Chem. Soc.*, **93**, 4339 (1971).
(3) A. Hassner and D. J. Anderson, *ibid.*, **94**, 8255 (1972).
(4) J. H. Boyer, W. E. Krueger, and G. J. Mikol, *ibid.*, **89**, 5504 (1967).
(5) K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968); A. Hassner and A. B. Levy, *J. Amer. Chem. Soc.*, **93**, 5469 (1971).
(6) W. Bauer and K. Hafner, *Angew. Chem., Int. Ed. Engl.*, **8**, 772 (1969).
(7) R. Srinivasan, *J. Amer. Chem. Soc.*, **91**, 6250 (1969).
(8) A. Hassner and F. W. Fowler, *ibid.*, **90**, 2869 (1968).
(9) S. Sato, *Bull. Chem. Soc. Jap.*, **41**, 2524 (1968).



1-azirine intermediate in this reaction, using the cyclone **6** in refluxing chloroform or benzene. In fact the reaction path of **13** → **14** + **15** was completely unaltered by addition of **6**.

It is noteworthy that the *in situ* generation of the azirines lacking a 2 substituent, from the terminal vinyl azides **5a** and **5b**, produces species with greatly enhanced dienophilic properties when compared to those possessing a 2 substituent.[2,3] Details of this enhanced property will shortly be revealed.

Experimental Section[10]

Reaction of Cyclone 6 and 1-Azido-2-phenylethylene (5a).—The vinyl azide (0.8 g, 5.5 mmol) and the dienone (1.4 g, 5.5 mmol) were heated under reflux in toluene (25 ml) for 2 hr. Removal of the solvent yielded an orange oil, which rapidly solidified (1.30 g, 69%). Recrystallization from ethanol gave colorless needles of **2,5-dimethyl-3,4,7-triphenyl-3*H*-azepine (7a)**: mp 108°; τ ($CDCl_3$) 7.91 (s, 3 H), 7.72 (s, 3 H), 4.59 (s, 1 H), 3.87 (s, 1 H), 2.94–2.45 (m, 15 H); mass spectrum *m/e* (rel intensity) 350 (25), 349 (100), 348 (52), 334 (10), 308 (20), 293 (12), 272 (11), 246 (8), 231 (8), 229 (9), 215 (34), 115 (7) 91 (13).

Anal. Calcd for $C_{26}H_{23}N$: C, 89.4; H, 6.6. Found: C, 89.1; H, 6.8.

Reaction of Cyclone 6 and 1-Azido-2-*tert*-butylethylene (5b).—The vinyl azide (1.25 g, 10 mmol) and the dienone (2.60 g, 10 mmol) were heated under reflux in toluene (25 ml) for 5 hr. Removal of the solvent afforded an orange oil. Chromatography using dichloromethane–pentane (1:4) eluent afforded a pale yellow oil which solidified (2.35 g, 71%) on trituration. Recrystallization from ethanol afforded large, pale yellow crystals of **7-*tert*-butyl-2,5-dimethyl-3,4-diphenyl-3H-azepine (7b)**: mp 97°; nmr ($CDCl_3$) τ 9.14 (s, 9 H), 7.97 (s, 3 H), 7.72 (s, 3 H), 4.74 (s, 1 H), 4.20 (s, 1 H), 2.89 (s, 5 H), 2.65 (s, 5 H); mass spectrum *m/e* (rel intensity) 330 (25), 329 (100), 328 (25), 314 (55), 287 (27), 273 (50), 258 (77), 257 (58), 246 (30), 231 (25), 215 (20), 91 (17).

Anal. Calcd for $C_{24}H_{27}N$: C, 87.5; H, 8.3. Found: C, 87.8; H, 8.2.

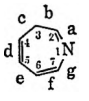
Reaction of Cyclone 6 and 4-Azido-1,2-dihydronaphthalene (9).—The vinyl azide (1.71 g, 10 mmol) and the dienone (2.60 g, 10 mmol) were heated under reflux in toluene (25 ml) for 8 hr. Removal of the solvent and chromatography of the residue (dichloromethane) afforded **2,5-dimethyl-3,4-diphenyl-1,2-dihydronaphtho[3,4-*f*]-3*H*-azepine (12)**[11] (1.2 g, 32%) as golden plates from ethanol: mp 163°; nmr ($CDCl_3$) τ 8.04 (s, 3 H), 7.68 (s, 3 H), 8.35–6.55 (m, 4 H), 4.92 (s, 1 H), 3.15–2.56 (m, 14 H); mass spectrum *m/e* (rel intensity) 376 (32), 375 (100), 374 (44), 360 (12), 284 (60), 178 (10), 115 (7), 91 (17).

Anal. Calcd for $C_{28}H_{25}N$: C, 89.6; H, 6.7. Found: C, 89.8; H, 6.8.

Ethyl acetate–dichloromethane (1:19) eluted unreacted dienone (1.5 g, 58%). Use of a threefold excess of the vinyl azide gave 12 in 45% yield.

(10) All melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrophotometer as KBr pellets. Nmr spectra were recorded with a Varian A-60A spectrometer using tetramethylsilane as an internal standard. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(11) Since the numbering of the azepine system is not completely systematic,[12] the lettering system adopted in this paper follows the numbers shown.



3 H

(12) L. A. Paquette in "Nonbenzenoid Aromatics," Vol. 1, J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, p 249.

Registry No.—**5a**, 16722-99-9; **5b**, 40168-86-3; **6**, 26307-17-5; **7a**, 40168-88-5; **7b**, 40168-89-6; **9**, 16719-58-7; **12**, 40168-91-0.

Acknowledgment.—Support of this work by a grant from NSF is gratefully acknowledged.

Nitrogen Photochemistry. XIII. The Deoxygenation of Aniline and Naphthylamine *N*-Oxides

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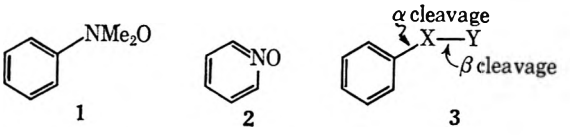
Received September 11, 1972

We are studying various aniline and naphthylamine *N*-oxide derivatives as potential sources of atomic oxygen in the liquid phase since these *N*-oxides are expected not to rearrange in contrast to the well-studied *N*-oxides where the nitrogen is part of the aromatic ring. It is important that a distinction be made between the amine oxide photochemistry described in this article, *e.g.*, of **1**, and that of the aromatic *N*-oxides such as **2**. Only the latter has been extensively studied. The former has a benzene chromophore and the latter a pyridine chromophore. *N*-Oxides such as **2** rearrange and undergo α cleavages on irradiation,[1-5] whereas we now wish to demonstrate that the excited state of **1** leads almost exclusively to β cleavages and, importantly, with little rearrangement. The nomenclature is that defined on structure **3**.[6] This article contains the descriptive work on aniline and naphthylamine *N*-oxide photochemistry.



Previously Jerina, Boyd, and Daly[7] irradiated *N,N*-dimethylaniline *N*-oxide to gain deuterium retention data during the photochemical hydroxylation of 4-deuterioanisole and demonstrated that an undefined oxygen species was transferred to anisole forming *p*-hydroxyanisole. No other products were reported.

With *N,N*-dimethylaniline *N*-oxide, there are two chromophores in the near-uv spectrum. Its uv spectrum is recorded in Figure 1 together with those of benzene and aniline for reference purposes. The 260-nm chromophore of *N,N*-dimethylaniline *N*-oxide is essentially the π,π^* transition of benzene with slight modification for the functional group. This is expected because the parent amine *N*-oxide chromophore,

(1) J. Streith, B. Danner, and C. Sigwalt, *Chem. Commun.*, 979 (1967).
(2) T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, 2213 (1970).
(3) H. Igeta, T. Tsuchiya, M. Yamada, and H. Arai, *Chem. Pharm. Bull.*, **16**, 767 (1968).
(4) T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, 2747 (1969).
(5) M. Ogata and K. Kano, *Chem. Commun.*, 1176 (1967).
(6) V. I. Stenberg and D. R. Dutton, *Tetrahedron*, **28**, 4635 (1972). This article is regarded as part XII of this series.
(7) D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, 457 (1970).

TABLE I
PRODUCTS FROM THE IRRADIATION OF AMINE N-OXIDES

Amine oxide	Conditions	Products[a]
$(CH_3)_3NO \cdot 2H_2O$	Solid, quartz	$(CH_3)_3N$ (9%); $(CH_3)_2NH$ (2%); H_2O;[c] $(CH_3)_2NCHO$
	CH_3OH, quartz	$(CH_3)_3N$ (30%); H_2O[c] (83%)
$(C_2H_5)_3NO \cdot 2H_2O$	Solid, quartz	$(C_2H_5)_3N$ (major); $(C_2H_5)_2NH$ (minor); CH_3CHO (trace)
$C_6H_5N(CH_3)_2O \cdot H_2O$	CH_3OH, Vycor	$C_6H_5N(CH_3)_2$ (55%); $C_6H_5NH(CH_3)$[b] (31%); $2\text{-}(OH)C_6H_5N(CH_3)_2$ (5%); H_2O[c] (73%)
$2\text{-}C_{10}H_7N(CH_3)_2O$	$CH_3CHOHCH_3$, Pyrex	*N,N*-Dimethyl-2-naphthylamine; *N*-methyl-2-naphthylamine
$1\text{-}C_{10}H_7N(CH_3)_2O$	$CH_3CHOHCH_3$, Pyrex	*N,N*-Dimethyl-1-naphtylamine (57%); *N*-methyl-1-naphthylamine[b] (23%); H_2O[c] (58%); CH_3COCH_3 (18%)

[a] The percentage yields are based on converted starting material. [b] Both the monomethyl- and dimethylamines are primary products since irradiation of either *N,N*-dimethylaniline or *N,N*-dimethyl-1-naphthylamine under similar conditions does not give the corresponding monomethylamines. [c] Water was measured quantitatively by injecting an aliquot of the reaction solutions directly into the glpc (Porapak Q column).

as illustrated in the uv spectrum of trimethylamine *N*-oxide in Figure 1, is virtually transparent above 250 nm. With a Vycor filter, incident light, which is directed at the $S_0 \rightarrow S_1$ transition, causes efficient deoxygenation in methanol, Table I. Demethylation also occurs to a significant extent to give monomethylaniline. Altogether, 86% of deoxygenated products are produced together with 73% water. A small yield of the rearrangement product, 2-hydroxy-*N,N*-dimethylaniline, is observed. In the better hydrogen-donor solvent, 2-propanol,[8] little change of products is noted other than the formation of acetone.

The *N,N*-dimethylnaphthylamine *N*-oxides have uv spectra similar in most characteristics to naphthalene rather than parent amine spectra, Figure 1. Their relatively long wavelength absorption bands conveniently allow excitation of $S_0 \rightarrow S_1$ transition in Pyrex glassware. The extinction coefficient at 300 nm of the α isomer is larger than that of the β which makes it the more desirable. The irradiation of *N,N*-dimethyl-1-naphthylamine *N*-oxide in several solvents provides 80–94% total yields of the two amines *N,N*-dimethyl-1-naphthylamine and *N*-methyl-1-naphthylamine, Table I. Again the expelled oxygen atom could only be found in the form of water.

The irradiation of trialkylamine *N*-oxides shows the consequences of n,σ^* excitation of the amine oxide functional group. Trimethyl- and triethylamine *N*-oxides when irradiated as solids in thin films provide the corresponding parent amines as the major products. Minor amounts of the secondary amines are also formed, and dimethylformanide was identified as a secondary product from the irradiation of solid trimethylamine *N*-oxide dihydrate. In methanol solution, the irradiation of trimethylamine *N*-oxide dihydrate produces trimethylamine, dimethylamine, and water. However, the aliphatic *N*-oxides are undesirable as potential sources of atomic oxygen since they have virtually transparent near-uv absorption spectra, Figure 1, and they are very polar compounds which are nearly insoluble in most organic solvents.

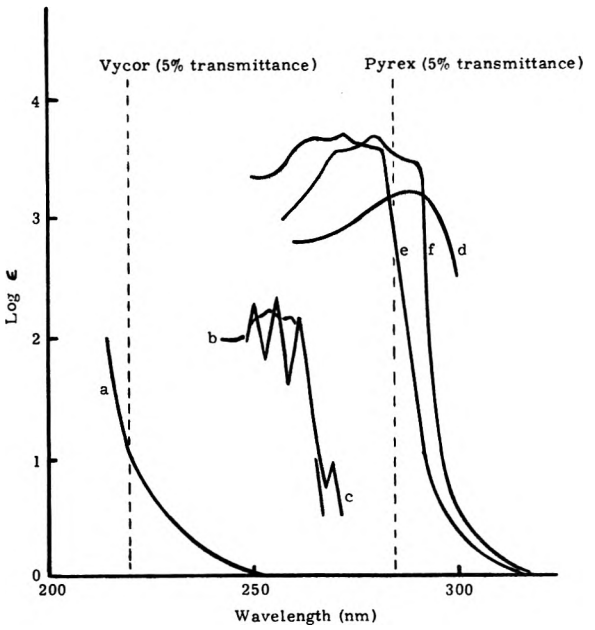


Figure 1.—Ultraviolet spectra of trimethylamine *N*-oxine (a) and *N,N*-dimethylaniline *N*-oxide (b) in 2-propanol; benzene (c) and aniline (d) in isooctane; and *N,N*-dimethyl-2-naphthylamine (e) and *N,N*-dimethyl-1-naphthylamine (f) in 2-propanol.

Experimental Section

Reagents.—Trimethylamine *N*-oxide was purchased from Chemical Procedurement Laboratories, College Point, N. Y. Triethylamine *N*-oxide,[9] *N,N*-dimethylaniline *N*-oxide,[10] and 2-hydroxy-*N,N*-dimethylaniline[11] were prepared by known procedures. The amines were methylated using either dimethyl sulfate[12] or trimethyl phosphate.[13] Methanol was purified by distillation from magnesium. 2-Propanol was treated similarly and distilled a second time after a 2-hr reflux with $NaBH_4$.

Irradiation of Aniline and Naphthylamine *N*-Oxides.—The amine oxide was dissolved in alcohol (typically 0.1 g of oxide in 25 ml). The solution was vacuum degassed and irradiated in a Rayonet photochemical reactor. The 253.7-nm lamps were used for the aniline oxides and the 300-nm ones for the naphthylamine oxides. In 3–6 hr, 50–75% of the starting material reacted. Afterward the solvent was removed by distillation, the products were separated from the amine oxide by washing the residue with ether, and the ether extract was analyzed by glpc using a Carbowax 20M column (10 ft × 0.25 in. on Chromosorb W, 150–230°). Water was determined by direct gspc analysis of the irradiation solution before work-up (10 ft × 0.25 in. Porapak Q, 125°).

Besides their glpc retention times, *N,N*-dimethylaniline, *N*-methylaniline, *o*-hydroxy-*N,N*-dimethylaniline, *N,N*-dimethyl-1-naphthylamine, and *N*-methyl-1-naphthylamine were identified by ir and nmr spectroscopy; *N,N*-dimethyl-2-naphthylamine was identified by its nmr spectrum and mp 40–41°, mmp 40.5–42.5° (lit.[14] 46–47°), and *N*-methyl-2-naphthylamine by its nmr spectrum.

General Procedure for the Preparation of *N,N*-Dimethyl-1-naphthylamine *N*-Oxide and *N,N*-Dimethyl-2-naphthylamine

(8) R. Walsh and S. W. Benson, *J. Amer. Chem. Soc.*, **88**, 3480 (1966).
(9) W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **75**, 1004 (1899).
(10) N. G. Chernova and A. S. Khokhlov, *Zh. Obsch. Khim.*, **30**, 1281 (1960); *Chem. Abstr.*, **55**, 551e (1961).
(11) E. Boyland, D. Manson, and P. Sims, *J. Chem. Soc.*, 3623 (1953).
(12) H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, 1500 (1936).
(13) J. H. Billman, A. Radike, and B. W. Mundy, *J. Amer. Chem. Soc.*, **64**, 2977 (1942).
(14) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, London, 1965, p 1185.

Oxide.—The method of Chernova and Khokhlov[10] was not successful for the preparation of these oxides from the amines in our laboratory. Oxidation of the amines was accomplished by peroxybenzoic acid.[15] A stoichiometric quantity of peroxybenzoic acid in $CHCl_3$ (100 ml of 0.05 *M*) was added dropwise with stirring to a solution of the amine in $CHCl_3$ (0.86 g in 50 ml) at −35°. After 2 hr the solution was warmed to room temperature. After all the peracid had reacted, the $CHCl_3$ was removed under vacuum and the residue washed with ether. An equivalent of 6 *M* HCl was then added to give the amine oxide hydrochloride which could be recrystallized from acetone. The hydrochloride of *N*,*N*-dimethyl-1-naphthylamine *N*-oxide melts at 170° dec and *N*,*N*-dimethyl-2-naphthylamine *N*-oxide hydrochloride melts at 146–148° dec with nmr signals (acetone-d_6–D_2O, 5:1), at δ 9.5–7 (m, 7) and 3.76 [s, $NO(CH_3)_2$, 6]. The amine oxide was obtained using Ag_2O and recrystallized from acetone. *N*,*N*-Dimethyl-2-naphthylamine *N*-oxide had mp 152–155° dec and nmr (acetone-d_6–D_2O, 5:1) δ 9–7 (m, 7) and 3.93 [s, $NO(CH_3)_2$, 6]. *N*,*N*-Dimethyl-1-naphthylamine *N*-oxide rapidly hydrated and gave a variable melting point.

Irradiation of Trimethyl- and Triethylamine *N*-Oxides.—The amine oxide (1 g) was dissolved in methanol and the solvent allowed to evaporate in a rotating, cylindrical vessel leaving a thin film of the oxide. This solid was irradiated in a vacuum with a medium-pressure, mercury-arc lamp in a quartz immersion well until all the amine oxide had disappeared from the surface (1–3 hr). The products, in a cold trap attached the vessel, were analyzed by gspc using a Poropak Q column (10 ft × 0.25 in., 60–120°).

The irradiation solution of trimethylamine *N*-oxide was degassed and irradiated with the medium-pressure lamp in quartz. The products were separated from unreacted amine oxide by bulb-to-bulb distillation and analyzed by glpc. Besides their glpc retention times, trimethylamine was identified by its nmr spectrum, dimethylamine by mp 167–169°, mmp 166–168° (lit.[16] mp 171°) of its hydrochloride salt, water by its melting point and color change with anhydrous copper sulfate, and dimethylformamide by its ir spectrum.

Registry No.—Trimethylamine *N*-oxide, 1184-78-7; triethylamine *N*-oxide, 2687-45-8; *N*,*N*-dimethylaniline *N*-oxide, 874-52-2; 2-hydroxy-*N*,*N*-dimethylaniline, 3743-22-4; 1-*N*,*N*-dimethylnaphthylamine *N*-oxide, 830-70-6; 2-*N*,*N*-dimethylnaphthylamine *N*-oxide, 34418-90-1; *N*,*N*-dimethyl-1-naphthylamine *N*-oxide hydrochloride, 39717-26-5; *N*,*N*-dimethyl-2-naphthylamine *N*-oxide hydrochloride, 39717-27-6; peroxybenzoic acid, 93-59-4.

Acknowledgments.—This investigation was supported by a Public Health Service Research Career Development Award (1-K4-GM 9888: V.I.S.) from the National Institute of General Medical Sciences and a NDEA traineeship (J. E. S.).

(15) J. R. Moyer and N. C. Manley, *J. Org. Chem.*, **29**, 2099 (1964).
(16) R. C. Weast, Ed., "Handbook of Chemistry and Physics," 52nd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1971–1972, p C101.

Triangular Kinetic Schemes. An Elaboration

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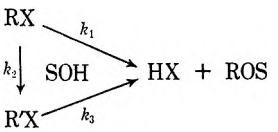
We recently reported[1] the derivation of the analytical equations governing triangular kinetic schemes of the type particularly common to solvolytic processes. Judging by the response to this paper, some amplification of the assertions given there is in order.



(1)

The exact solution[1a] (in closed form) of the differential equations appropriate to eq 1 provides the relationship[2]

$$[HX]_t = [RX]_0\left[1 + \frac{(k_3 - k_1)e^{-(k_1 + k_2)t} - k_2e^{-k_3t}}{k_1 + k_2 - k_3}\right] \quad (2)$$

The instantaneous "first-order" titrimetric rate constant (k_{inst}) can be obtained as follows.

$$\ln\left(\frac{[HX]_\infty}{[HX]_\infty - [HX]_t}\right) = \ln\left[\frac{k_1 + k_2 - k_3}{k_2e^{-k_3t} + (k_1 - k_3)e^{-(k_1+k_2)t}}\right] \quad (3)$$

$$k_{inst} = \frac{d}{dt}\ln\left(\frac{[HX]_\infty}{[HX]_\infty - [HX]_t}\right) \quad (4)$$

$$= \frac{d}{dt}\ln\left[\frac{k_1 + k_2 - k_3}{k_2e^{-k_3t} + (k_1 - k_3)e^{-(k_1+k_2)t}}\right] \quad (5)$$

Extraction of the derivative, then multiplication by $\exp(k_3t)$, leads to

$$k_{inst} = \left[\frac{k_2k_3 + (k_1 - k_3)(k_1 + k_2)e^{Kt}}{k_2 + (k_1 - k_3)e^{Kt}}\right] \equiv \frac{N}{D} \quad (6)$$

where $K = k_3 - k_1 - k_2$

The proof that the sense of curvature of "first-order" plots of titrimetric data ($\ln [HX]_\infty/[HX]_\infty - [HX]_t$ *vs.* time) depends only on the relative magnitudes of k_1 and k_3 can be seen by examining the first derivative of k_{inst}

$$\text{curvature} = \frac{dk_{inst}}{dt} = \frac{D\frac{dN}{dt} - N\frac{dD}{dt}}{D^2} \quad (7)$$

The *sign* of curvature is a function of the numerator in eq 7, which expands to

$$\begin{aligned}\text{sign} &= [k_2 + (k_1 - k_3)e^{Kt}][(k_1 - k_3)(k_1 + k_2)Ke^{Kt}] - \\ &\quad [k_2k_3 + (k_1 - k_3)(k_1 + k_2)e^{Kt}][(k_1 - k_3)Ke^{Kt}] \\ &= k_2(k_1 + k_2 - k_3)K(k_1 - k_3)e^{Kt} \\ &= (k_3 - k_1)K^2k_2e^{Kt} \end{aligned} \quad (8)$$

Since the last three terms are strictly positive, the nature of curvature is determined by $(k_3 - k_1)$; if $k_3 > k_1$, the plot will be concave upward and k_{inst} will increase with time, while if $k_3 < k_1$, the curve will exhibit negative curvature and k_{inst} will fall off with time. Clearly, the *magnitude* of curvature (which can be calculated with eq 7) will depend on the relative magnitudes of all three rate constants. If $k_1 = k_3$, the effect of the k_2 pathway will be titrimetrically unobservable.[1a]

It has on occasion been incorrectly stated that extrapolation of k_{inst} (as defined by eq 4) to $t = 0$ provides a value of $(k_1 + k_2)$, even though Winstein and coworkers have used such graphical extrapolations to ob-

(1) (a) R. S. Macomber, *J. Org. Chem.*, **36**, 2182 (1971). (b) For a description of similar schemes, including those with reversible reactions, see R. A. Alberty and W. G. Miller, *J. Chem. Phys.*, **26**, 1231 (1957).

(2) For the relevant equations when $k_3 = k_1 + k_2$, see footnote 9 of ref 1a.

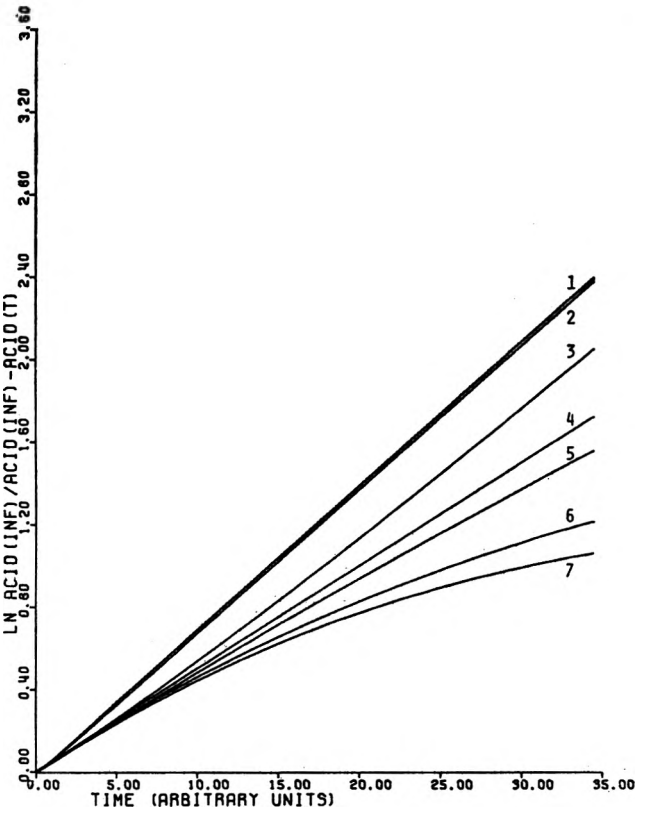


Figure 1.—Titrimetric plots for $k_1 = 0.05$, $k_2 = 0.02$, and $k_3 = 2.0$ (curve 1), 0.7 (2), 0.1 (3), 0.05 (4), 0.035 (5), 0.01 (6), 0.001 (7). Each curve covers *ca.* 4 half-lives.

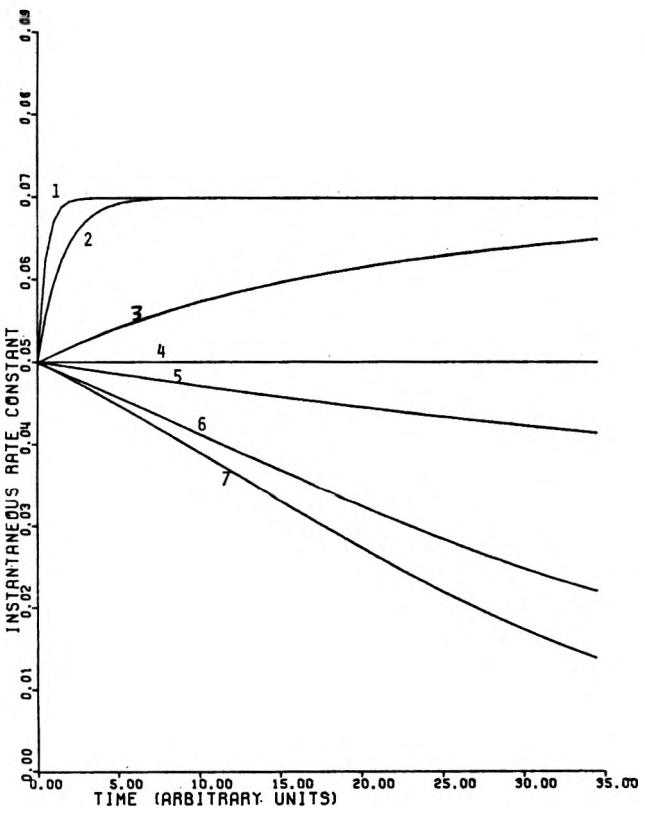


Figure 2.—Plots of k_{inst} *vs.* time for the data in Figure 1.

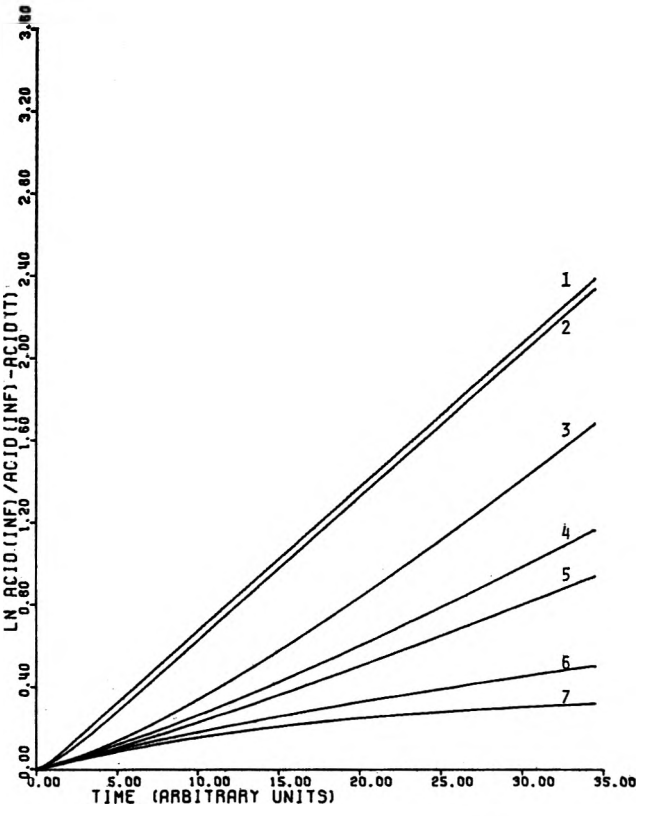


Figure 3.—Titrimetric plots for $k_1 = 0.02$, $k_2 = 0.05$, and $k_3 = 2.0$ (curve 1), 0.7 (2), 0.1 (3), 0.05 (4), 0.035 (5), 0.01 (6), 0.001 (7). Each curve covers *ca.* 4 half-lives.

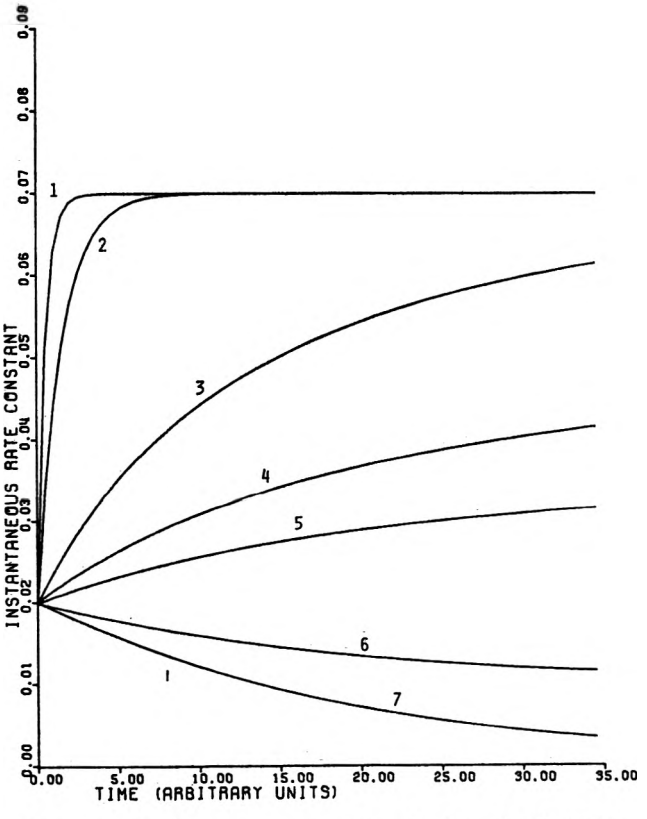


Figure 4.—Plots of k_{inst} *vs.* time for the data in Figure 3.

tain values of k_1.[3] This misconception probably arises from a belief that the early stages of such reactions mimic the situation where $k_3 = 0$, but this is not the case. As can be seen from eq 6 at $t = 0$

$$k_{inst} = k_1 \tag{9}$$

but, as demonstrated below, k_{inst} rapidly increases to $k_1 + k_2$ when $k_3 \gg (k_1 + k_2)$. It *is* true, whether or not $k_3 = 0$, that $d/dt \ln ([RX]_0/[RX]_t) = k_1 + k_2$ at *all* stages of the reaction (and monitoring actual disappearance of RX, *e.g.*, spectrophotometrically, gives $k_1 + k_2$). However, $d/dt \ln [RX]_t$ is only equal to $d/dt ([HX]_\infty - [HX]_t)$ when $k_3 = 0$ or $k_3 \gg k_1 + k_2$.[4] It is also instructive to consider the latter stages of the reaction. If $k_3 > (k_1 + k_2)$, k_{inst} will approach $(k_1 + k_2)$ as $t \rightarrow \infty$, whereas if $k_3 < (k_1 + k_2)$, k_{inst} approaches k_3, regardless of the sense of curvature.

Several further observations with eq 6 are pertinent. As expected,[1a] if $k_3 \gg k_1 + k_2$ (*i.e.*, as $k_3 \rightarrow \infty$), eq 6 becomes

$$k_{inst} = k_1 + k_2 \tag{10}$$

However, although eq 2 reduces to the appropriate form[4] upon substitution of $k_3 = 0$, the same is not true for eq 3–8. For example, while it is easily shown[4] that $k_{inst} = k_1 + k_2$ when $k_3 = 0$, eq 6 does not reduce to that result upon substitution of $k_3 = 0$. This is because the boundary conditions for obtaining eq 3 from 2 ($t \rightarrow \infty$) erase part of the k_3 dependence. An equivalent way of appreciating this is to realize that the equations derived here apply when the infinity titer reflects 100% conversion of starting material to acid. If $k_3 = 0$, the infinity titer will be $k_1/(k_1 + k_2)$ times the 100% infinity titer, and attempts to use this "observed" infinity titer for fitting eq 3–8 will lead to erroneous values for the rate constants. It is always preferable to use the theoretical (100% conversion) infinity titer to obtain the most information from plots of eq 3. When one is dealing with situations where k_3 is known to be negligibly small, the appropriate equations[4] should be generated from eq 2.

Finally, it is useful to examine the effect on titrimetric plots and k_{inst} of variations in k_3. By defining the half-life of the reaction as $0.69/(k_1 + k_2)$, then arbitrarily fixing the values of k_1 and k_2, one can vary k_3 and plot eq 3 and 6 as functions of time. For example, Figure 1 shows titrimetric plots where $k_1 = 0.05$, $k_2 = 0.02$ ($t_{1/2} = 10$ time units), and k_3 varies from 2.0 to 0.001. Figure 2 shows the behavior of k_{inst} over the same interval. A similar pair of plots is shown in Figures 3 and 4, where the values of k_1 and k_2 have been interchanged. These plots summarize the preceding discussion. If $k_3 > 10(k_1 + k_2)$, titrimetric plots will be essentially linear with slope $k_1 + k_2$. In the region $10(k_1 + k_2) > k_3 > k_1$, plots exhibit positive curvature, and k_{inst} approaches the lesser of k_3 or $(k_1 + k_2)$. When $k_3 = k_1$, the plot is again linear, but with slope k_1. Further decrease in k_3 gives rise to negative curvature, and k_{inst} approaches k_3. Again, for experimental fittings of these lines, one must use the theoretical infinity titer (*vide supra*).

An iterative nonlinear least squares Fortran IV program has been written to extract the values of k_1, k_2, and k_3 from experimental titrimetric (or equivalent) data, by obtaining the best fit of eq 3. A listing will be supplied upon request.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemican Society, for support of this work.

(3) See, for example, W. G. Young, S. Winstein, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1958 (1951).

(4) Footnote 7, ref 1a.

See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

CIDNP Evidence for Radical Pair Mechanism in Photo-Fries Rearrangement

Summary: Photolysis of *p*-cresyl *p*-chlorobenzoate (**1**) affords *p'*-chlorobenzoyl-*p*-cresol (**2**) as the major and *p*-cresol (**3**) as the minor product *via* aryloxy–aroyl radical pair intermediates **4**, derived from singlet excited state precursors **1***.

Sir: CIDNP (chemically induced dynamic nuclear polarization) is a powerful diagnostic tool for radical cage reaction,[1] and we wish to communicate our CIDNP evidence for a radical pair mechanism of the photo-Fries rearrangement. A recent review on this reaction[2] reveals still numerous mechanistic uncertainties in regard to whether a concerted or stepwise process is involved and whether the rearrangement products are derived from singlet or triplet precursors, although, quite recently, flash photolysis[3] and gas phase photolysis[4] have demonstrated the involvement of free radicals in the rearrangement of aryl esters. For our model study we selected *p*-cresyl *p*-chlorobenzoate (**1**), a choice dictated by practical considerations for CIDNP detection. Thus, the *p*-cresyl and *p*-chlorobenzoyl moieties would assure rapid conversion, minimal overlap of the aromatic protons, relatively simple nmr spectra, and only ortho rearrangement product, and the *p*-methyl substituent would serve as an effective polarization probe.

Irradiation of a 0.1 *M* CH_2Cl_2 solution of ester **1** in a quartz tube directly in the Varian HA-100D nmr spectrometer with an unfiltered 1000-W mercury arc produced the spectra (sets A, B, and C) in Figure 1. It is evident that the ortho protons of the *p*-cresyl moiety in ester **1** (compare top and center spectra in set A) and in the phenol **2** (compare bottom and center spectra in A) exhibit enhanced absorption, while the ortho protons in phenol **3** (compare spectra in set B) and the *p*-methyl protons in ester **1** (compare top and center spectra in set C) and in phenol **2** (compare bottom and center spectra in set C) display emission. To pronounce the observed CIDNP effects in the starting material, in the top spectra of sets A and C, which refer, respectively, to the ortho protons and the *p*-methyl protons of the *p*-cresyl moiety of **1**, we show as well signal intensities during (broken line) and after (solid line) irradiation. Unfortunately, on careful comparison of the resonances of the *p*-methyl protons with those of authentic products, it was found that in CH_2Cl_2 the δ 2.34 ppm emission (center spectrum in set C) corresponds to superimposed polarizations of the *p*-methyl protons of phenols **2** and **3** (bottom spectrum in set C). For this reason we examined the photolysis of ester **1** in benzene (0.02 *M*) since now the *p*-methyl proton resonances of **1**, **2**, and **3** are all sufficiently separated to permit individual detection (set D). Now the *p*-methyl protons of ester **1** show clearly emission at δ 2.03 ppm (compare top and center spectra in set D), of phenol **2** strong emission at 1.88, and of phenol **3** weak enhanced absorption at 2.05 (compare center and bottom spectra in set D).[5] None of these CIDNP effects could be observed when authentic products were irradiated under similar photolysis conditions as controls.[6] These CIDNP results of the photorearrangement of ester **1** in CH_2Cl_2 and C_6H_6 are summarized in Table I. The same polarization signs were also observed in CCl_4, $CH_3OCH_2CH_2OCH_3$, and CH_3OH, although the proportion of products varied in these solvents.

TABLE I
PHOTO-CIDNP OF *p*-CRESYL *p*-CHLOROBENZOATE (**1**)

Products	Type of protons[a]	CH_2Cl_2[b] $\delta \times 10^6$[d]	CH_2Cl_2[b] r[e]	C_6H_6[c] $\delta \times 10^6$[d]	C_6H_6[c] r[e]
Ester **1**	*p*-Methyl	2.46	E	2.03	E
	o-Cresyl	7.12	A		*f*
		7.20			
Phenol **2**	*p*-Methyl	2.34	E	1.88	E
	o-Cresyl	7.01	A		*f*
		7.05			
		7.10			
Phenol **3**	*p*-Methyl	2.34	*g*	2.05	A
	o-Cresyl	6.74	E		*f*
		6.83			

[a] Assignments were made by comparison of product resonances with authentic samples. [b] Sets A, B, and C in Figure 1. [c] Set D in Figure 1. [d] Relative to TMS and within ±0.01 ppm. [e] Owing to extensive overlapping of the aromatic protons of **1**, **2**, and **3** it was not possible to diagnose a multiplet effect. [f] Aromatic protons are masked by benzene. [g] Obscured because of superposition with *p*-methyl of phenol **2**.

With the help of Kaptein's formula for net polarization[7] and the esr parameters for the related phenoxy and benzoyl radicals,[8] we find perfect agreement between the observed (Table I) and the predicted CIDNP effects if we assume that $\mu < 0$ (singlet precursor) and $\epsilon > 0$ (cage products) for ester **1** and phenol **2** and $\epsilon < 0$ (escape product) for phenol **3**. Thus, our CIDNP data support the radical pair mechanism suggested for the photo-Fries rearrangement.[3,4] However, as shown in Scheme I, photoactivation of ester **1** leads first to the singlet excited state **1*** which subsequently suffers principally carbon–oxygen bond rupture into

(1) H. Fischer, *Top. Curr. Chem.*, **24**, 1 (1971); G. L. Closs, *Spec. Lect. Int. Congr. Pure Appl. Chem., 28th*, **4**, 19 (1971); H. Ward, *Accounts Chem. Res.*, **5**, 18 (1972).

(2) D. Bellus, *Advan. Photochem.*, **8**, 109 (1971).

(3) C. E. Kalmus and D. M. Hercules, *Tetrahedron Lett.*, 1575 (1972).

(4) J. W. Meyer and G. S. Hammond, *J. Amer. Chem. Soc.*, **94**, 2219 (1972).

(5) It was not possible to record the polarizations of the aromatic protons since C_6H_6 masked this region. Even C_6D_6 was not suitable since the aromatic protons of **1**, **2**, and **3** overlapped still more severely than in CH_2Cl_2.

(6) H. D. Becker, *J. Org. Chem.*, **32**, 2140 (1967).

(7) R. Kaptein, *J. Chem. Soc., Chem. Commun.*, 732 (1971).

(8) K. Scheffler and H. B. Stegmann, "Elektronenspinresonanz," Springer Verlag, Berlin, Germany, 1970: g (PhO·) = 2.0047, a(*p*-Me) = +11.95 *G* and a(ortho H) = −6.0 *G*. H. Paul, University of Zürich, personal communication: g(PhCO·) = 2.0006, a(ortho H) ≅ 0 and a(meta H) ≅ +1.2 *G*. In view of the small hyperfine coupling constants of the aromatic protons and overlapping resonances it was difficult to trace the *p*-chlorobenzoyl radical by CIDNP.

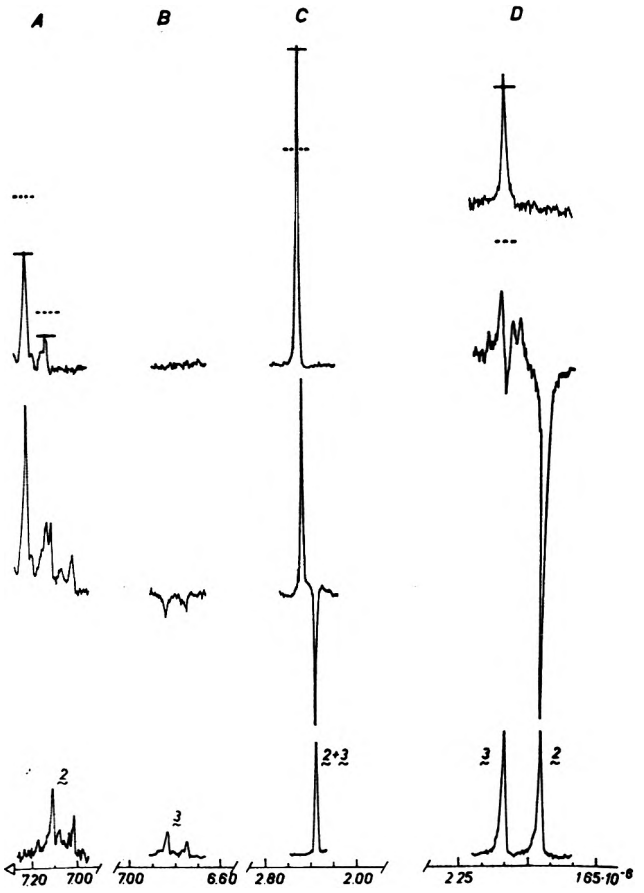


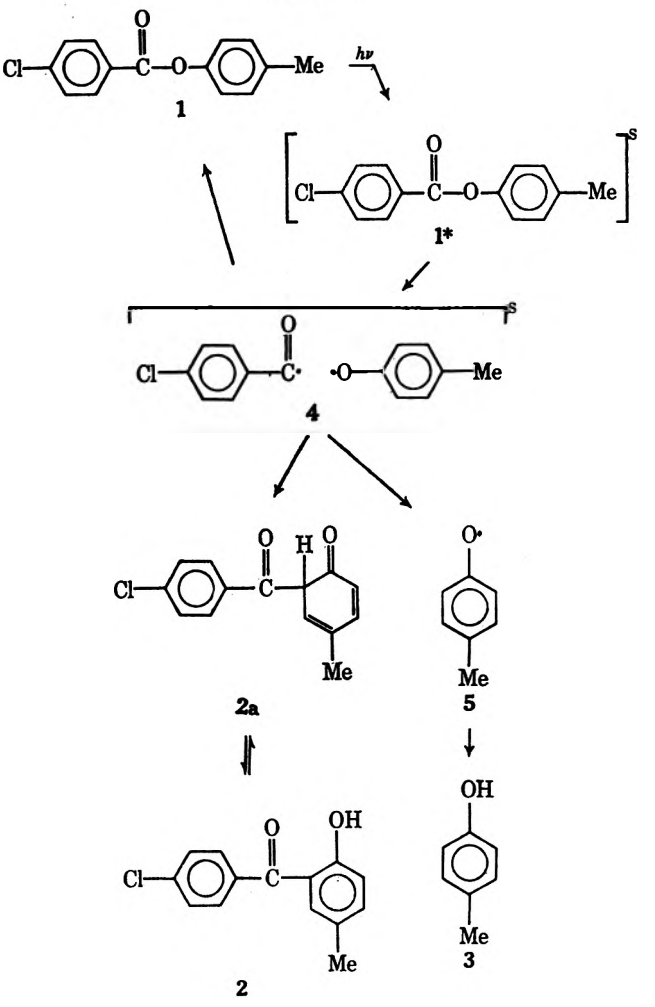
Figure 1.—CIDNP during photolysis of *p*-cresyl *p*-chlorobenzoate (1). Sets A, B, and C are in CH_2Cl_2, set D in C_6H_6. Bars in the top spectra of sets A, C, and D refer to signal intensities of the polarizations in ester 1 during (broken) and after (solid) irradiation. The reference numbers in the bottom spectra of sets A, B, C, and D refer to the proton resonances of authentic *p'*-chlorobenzoyl-*p*-cresol (2) and *p*-cresol (3) products relative to TMS.

the aroyl–aryloxy radical pair **4** prior to intersystem crossing. Cage combination results in ester **1** or phenol **2** *via* its **2a** tautomer, the latter having a lifetime (t) considerably shorter than the relaxation times (T_1) of its polarized protons, *i.e.*, $t \ll T_1$. Some aryloxy radicals **5** escape the cage and on hydrogen abstraction give phenol **3**.

It is unlikely that a concerted pathway[2] is of major importance in the photo-Fries rearrangement of *p*-cresyl *p*-chlorobenzoate (**1**), at least in the solvents used here. For example, measurement[9] of the enhancement factor (V_{exp}) for the *p*-methyl polarization of the rearrangement product **2** gave $V_{exp} = -243 \pm 13$. With the help of Adrian's high field CIDNP treatment,[10] employing a one-proton model and making reasonable assumptions about the time between diffusive pair displacements ($10^{-12} \leqq \tau \leqq 10^{-11}$ sec),[9] the calculated enhancement factor (V_{calcd}) for the formation of **2** entirely from radical pair **4** *via* a singlet reaction is $V_{calcd} = 200 \pm 50$. We anticipate that analogous radical pair mechanisms obtain quite generally for the related photorearrangements of aryl ethers[11] and amides.[12]

(9) M. Lehnig and H. Fischer, *Z. Naturforsch.*, **27a**, 1300 (1972).
(10) F. J. Adrian, *J. Chem. Phys.*, **75**, 3410 (1971).
(11) F. A. Carroll and G. S. Hammond, *J. Amer. Chem. Soc.*, **94**, 7152 (1972).
(12) H. Shizuka and I. Tanaka, *Bull. Chem. Soc. Jap.*, **42**, 909 (1969).

SCHEME I



Acknowledgments.—W. A. expresses his appreciation to the John Simon Guggenheim Memorial Foundation for a fellowship, the University of Zürich for the hospitality offered him during his sabbatical stay, the University of Puerto Rico for a sabbatical leave, and Mr. B. Blank and Dr. G. Laroff for technical advice with the HA-100D nmr spectrometer. J. A. de S. successfully defended this CIDNP application as a research proposition in Oct 1972.

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RECEIVED MARCH 13, 1973

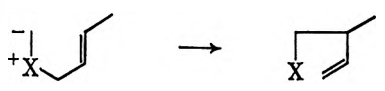
A Stereoselective Trans-Trisubstituted Olefin Synthesis *via* Rearrangement of Allylic Sulfonium Ylides

Summary: The [2,3]-sigmatropic rearrangement of α-substituted methallylsulfonium ylides results in a stereoselective formation of trans-trisubstituted olefins.

Sir: The need for stereoselective methods for olefin synthesis continues as demonstrated by several recent

publications.[1] The synthetic potential of the [2,3]-sigmatropic rearrangement in olefin synthesis has been demonstrated.[2] Recently,[3] α-substituted methallyl aryl sulfoxides have been shown to undergo such a rearrangement to allylic sulfenate esters which can be intercepted by nucleophiles, thus providing a new and useful route to trisubstituted olefins.

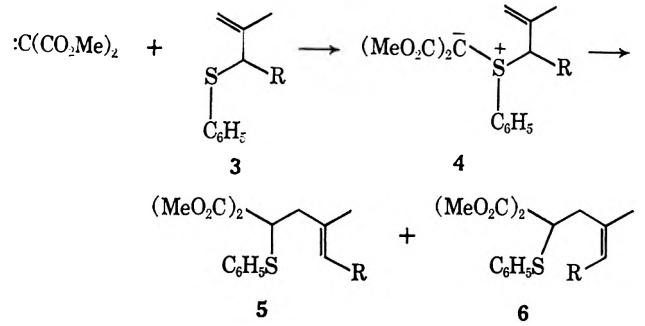
As part of a continuing program aimed at development of the [2,3]-sigmatropic rearrangement for construction of trisubstituted olefinic linkages found in polyisoprenoids, we have examined the stereospecificity which accompanies the [2,3]-sigmatropic rearrangement of α-substituted methallylsulfonium ylides. The [2,3]-sigmatropic rearrangement of ylides and related species (*e.g.*, 1 → 2) represents a well-established reaction[4]



1 2

which has recently received much attention in organic synthesis.[5] Allylic sulfonium ylides have previously been generated[6] by the addition of the appropriate carbene precursor; however, no study demonstrating the stereospecificity of this potential trisubstituted olefin forming reaction has been investigated. We wish to describe here a stereoselective trisubstituted olefin synthesis employing allylic sulfonium ylides of type **4**.

Heating a mixture of methyl diazomalonate (1.1 equiv)[7] and the α-substituted methallyl sulfide **3** (R = *n*-Bu) (prepared by treatment of phenyl methallyl sulfide at −78° in anhydrous THF with *n*-BuLi followed by the addition of *n*-BuI and warming to room temperature) in the presence of a catalytic amount of anhydrous cupric sulfate at 100° for ~15 hr (no solvent) results in a 90:10 mixture (indicated by vpc) of the

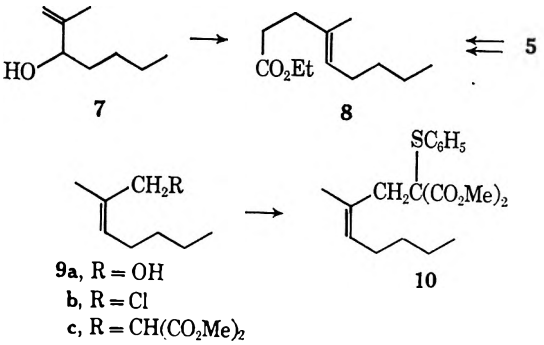


3 4

5 6

trans and cis olefins **5** and **6** (R = *n*-Bu), respectively, in 70% yield after purification.

That the major product **5** (R = *n*-Bu) had the stereochemistry indicated was demonstrated by conversion to **8** [decarboxylation, esterification, followed by desulfurization (W-2 Raney Ni)] which was shown to be identical with a sample prepared by Claisen rearrangement[8] of **7** with ethyl orthoacetate. Confirmation of the cis isomer **6** (R = *n*-Bu) was obtained by direct synthesis from **9a**.[9] Conversion of **9a** to the corresponding chloride **9b**[10] followed by alkylation with dimethyl malonate afforded **9c**. Treatment of the sodio derivative of **9c** in anhydrous THF with benzenesulfenyl chloride produced **10** which was identical with the cis isomer **6** (R = *n*-Bu) obtained from the rearrangement described above.



7 8 5

9a, R = OH
b, R = Cl
c, R = $CH(CO_2Me)_2$

10

Similarly, reaction of bis(carbomethoxy)carbene with sulfide **3** (R = Et) at 100° resulted in an 89:11 mixture of the trans and cis olefins **5** and **6** (R = Et), respectively, in 71% isolated yield.

The present olefin synthesis complements the existing methods of olefin synthesis.[1,3] In addition, it further demonstrates the potential or [2,3]-sigmatropic rearrangements in olefin synthesis.

Acknowledgment.—We wish to acknowledge the National Cancer Institute (Public Health Service Grant CA 13689-02) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(1) For recent reviews see (a) J. Reucroft and P. G. Sammes, *Quart. Rev. (London)*, **25**, 135 (1971); (b) D. J. Faulkner, *Syn.*, 175 (1971).

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(9) **9a** was obtained from a β-oxido ylide reaction [E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 226 (1970)].

(10) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969).

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RECEIVED MARCH 26, 1973

The Addition of Cycloheptatrienylidene to Phenylacetylene. The Possible Intermediacy of a Spiro[2.6]nona-1,4,6,8-tetraene

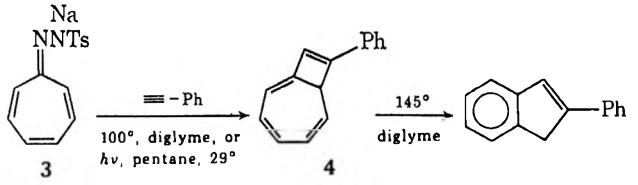
Summary: The addition of cycloheptatrienylidene to phenylacetylene yields 8-phenylbicyclo[5.2.0]nona-1,3,-5,8-tetraene, possibly *via* a spiro[2.6]nona-1,4,6,8-tetraene.

Sir: Recent studies have shown that spiro[2.6]nona-4,6,8-trienes can be conveniently synthesized by addi-

tion of cycloheptatrienylidene (1) to carbon–carbon double bonds. Suitable acceptors include dimethyl fumarate,[1] 1,3-pentadiene,[2] styrene,[3] and ethylene.[4] As a logical extension of this work as well as possible entry into the theoretically interesting[5] spirononatetraene system 2, we have now studied the addition of cycloheptatrienylidene to phenylacetylene.

1 2

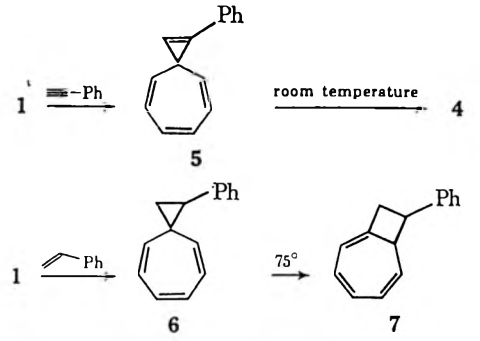
Either thermolysis (100°, diglyme) or photolysis (29°, pentane or THF) of the sodium salt of tropone tosylhydrazone (3)[1] in the presence of excess phenyl-



3 4

acetylene resulted in a $C_{15}H_{12}$ hydrocarbon in 21–25% yield in addition to a trace of heptafulvalene. From its spectral and chemical properties, this material was assigned the structure of 8-phenylbicyclo[5.2.0]nona-1,3,5,8-tetraene (4). The nmr spectrum of 4 ($CDCl_3$) shows a multiplet between 7.6 and 7.2 (5 H, aromatic), a doublet at 6.46 (1.4 Hz, 1 H, H_9), a multiplet between 6.35 and 5.65 (5 H, H_2–H_6), and a narrow multiplet at 4.76 ppm (1 H, H_7). The extent of the conjugation is indicated by the uv spectrum which has maxima (in *n*-pentane) at 370 nm (ε 9000) and 269 (31,000).[6] The ir and mass spectra are in agreement with the proposed structure.[9] When 4 was heated at 140° in diglyme, it was smoothly converted to 2-phenylindene,[10] a conversion that is strong supporting evidence for the assigned structure. Additional evidence for this structure was obtained by generating 1 in the presence of β-deuteriophenylacetylene. The nmr spectrum of the product (4-d_1) showed no resonance at 6.46 ppm. In addition, the line width of the signal at 4.76 ppm was reduced. When 4-d_1 was heated at 145°, 2-phenylindene-d_1 was produced. From the nmr spectrum, it was concluded that the deuterium had equilibrated (presumably as a secondary reaction) between the 1 and 3 positions of the indene.

By comparison with the addition of cycloheptatrienylidene to styrene,[2,3] the primary product of the addition of 1 to phenylacetylene is probably the spirononatetraene, 5.[12] Unstable, even at room temperature,



5 undergoes what is probably a stepwise rearrangement[13] to the tetraene, 4. The instability of 5 relative to 6 is not surprising, since cyclopropenes undergo thermal ring opening much more readily than cyclopropanes.[14] The thermal conversion of 4 to 2-phenylindene is analogous to the rearrangement of 7 to 2-phenylindan.[2]

(1) W. M. Jones and C. L. Ennis, *J. Amer. Chem. Soc.*, **91**, 6391 (1969).

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(3) (a) K. G. Untch, private communication; (b) L. W. Christensen, E. E. Waali, and W. M. Jones, *J. Amer. Chem. Soc.*, **94**, 2118 (1972).

(4) E. E. Waali and W. M. Jones, *Syn. Commun.*, **3**, 49 (1973).

(5) H. E. Simmons and T. Fukunaga, *J. Amer. Chem. Soc.*, **89**, 5208 (1967); R. Hoffmann, A. Imamura, and G. D. Zeiss, *ibid.*, **89**, 5219 (1967); M. J. Goldstein and R. Hoffmann, *ibid.*, **93**, 6193 (1971).

(6) Walborsky and Pendleton[7] reported the uv spectrum of 1-phenyl 1,3,5,7-octatetraene [λ_{max} 365 nm (ε 72,300), 337 (85,000), and 236 (11,000)]. The difference in the maxima and extinction coefficients between 4 and this model compound are expected since 4 has several cis and s-cis bonds and the model compound is all trans.[8]

(7) H. M. Walborsky and J. F. Pendleton, *J. Amer. Chem. Soc.*, **82**, 1405 (1960).

(8) R. M. Silverstein and R. M. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, p 157.

(9) Ir (neat film) ν 3070 (w), 3010 (m), 2850 (w), 1662 (m), 1482 (m), 1446 (m), 759 (s), 703 (s), 692 (s); mass spectrum *m/e* (rel intensity) 192 (100), 106 (45), 105 (41), 86 (50), 84 (73). The tetraene, 4, is sensitive to oxygen. It was reduced over Pt/C with the uptake of 4 equiv of hydrogen. The resulting hydrocarbon was shown to have the formula $C_{15}H_{20}$ by mass spectrometry and satisfactory elemental analysis.

(10) Mp 166–167° (lit.[11] mp 167.5); nmr ($CDCl_3$) 7.7 to 7.1 (m, 10 H, aromatic and olefinic) and 3.79 ppm (narrow m, 2 H, benzylic).

(11) F. Mayer, A. Sieglitz, and W. Ludwig, *Chem. Ber.*, **54**, 1397 (1921).

(12) To date, there has appeared no verified two-step addition of cycloheptatrienylidene (or an isomeric cycloheptatetraene) to a multiple bond.

(13) A concerted, thermal [1,7]-sigmatropic shift is unlikely based on orbital symmetry considerations: R. B. Woodward and R. Hoffmann, "The Conversation of Orbital Symmetry," Verlag Chemie, GmbH, Weinheim Bergstr., 1970.

(14) In view of (1) the large difference in the activation energy for ring openings of cyclopropenes and cyclopropanes (~30 kcal/mol[15]), (2) the probability that the rearrangement of 5 to 4 is stepwise and (3) the facile rearrangement of 6 to 7, it is highly unlikely that 5 will be isolable under ordinary conditions. The question remains open whether replacement of the phenyl group by hydrogen (2, R = H) will increase the energy of activation for the rearrangement sufficiently to permit isolation of the parent spirononatetraene.

(15) (a) R. Srinivasan, *J. Amer. Chem. Soc.*, **91**, 6250 (1969); (b) E. W. Schlag and B. S. Rabinovitch, *ibid.*, **82**, 5996 (1960).

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RECEIVED APRIL 10, 1973

The Reaction of Alkyl- and Aryldichloroboranes with Ethyl Diazoacetate at Low Temperature[1]

Summary: Ethyl diazoacetate reacts readily at low temperatures with aryl- and alkyldichloroboranes to give after protonolysis the corresponding ethyl arylacetates and alkylacetates in yields ranging from quantitative for the aryl to approximately 60% for the alkyl derivatives.

Sir: Trialkylboranes react with a variety of functionally substituted alkyldiazo compounds.[2] How-

(1) Joint publication was decided on after we learned of our related research in this area. The Purdue group investigated the alkyl-, the Alberta group the aryldichloroborane series.

(2) (a) J. Hooz and S. Linke, *J. Amer. Chem. Soc.*, **90**, 5936 (1968); (b) J. Hooz and D. M. Gunn, *Chem. Commun.*, 139 (1969); (c) J. Hooz and S. Linke, *J. Amer. Chem. Soc.*, **90**, 6891 (1968); (d) J. Hooz and G. F. Morrison, *Can. J. Chem.*, **48**, 868 (1970); (e) J. Hooz and D. M. Gunn, *J. Amer. Chem. Soc.*, **91**, 6195 (1969).

ever, reaction is sluggish (and yields poorer) for organoboranes containing bulky alkyl groups. Also, the reaction permits the transfer of only one of three possible alkyl groups. To maximize the synthetic utility of this process, it is clearly desirable to achieve selective alkyl/aryl group migration from a suitable series of readily available "mixed" organoborane derivatives.[3,4]

This problem has partially been overcome by the discovery that dialkylchloroboranes react readily at −78° with ethyl diazoacetate to give the corresponding esters in high yields.[5] Unfortunately, even in these reactions only one of the two available alkyl groups is used.

The accessibility of both alkyldichloroboranes[6] and aryldichloroboranes[7] led to the exploration of their reactions with a typical α-diazocarbonyl derivative, ethyl diazoacetate (eq 1).

$$(Ar)RBCl_2 + N_2CHCOOC_2H_5 \longrightarrow (Ar)RCH_2COOC_2H_5 \quad (1)$$

When ethyl diazoacetate (1 *M* in THF) was added to a solution of phenyldichloroborane (1 *M* in THF, −25°), nitrogen was quantitatively evolved. Protonolysis provided ethyl phenylacetate (92%). Repetition of the reaction in THF with *n*-butyldichloroborane (100% N_2 evolution) gave relatively poor results, 43% ethyl hexanoate and 30% ethyl chloroacetate.[8] Various solvents, including THF, ether, toluene, pentane, and dichloromethane, were investigated at temperatures ranging from −25 to −78°. The best results for the alkyl series, yields of 57–71% of the alkyl ester, were obtained in ether (−62°). When applied to a series of alkyl- and aryldichloroboranes under optimum conditions, all reactions evolved nitrogen (>95%) within 90 min. Table I summarizes the results.

The following procedure for the preparation of ethyl *p*-chlorophenylacetate is representative. A dry 50-ml flask equipped with a magnetic stirring bar and septum inlet is flushed with nitrogen. The flask is cooled to −25° (Dry Ice–carbon tetrachloride–acetone slush bath) and charged with 1.89 g (10 mmol) of *p*-chlorophenyldichloroborane in 10 ml of THF. To this solution is added, dropwise, 1.25 g (11 mmol) of ethyl diazoacetate in 10 ml of THF at such a rate (1 ml/3–5 min) that nitrogen is smoothly evolved (~1.5 hr). At this temperature, 5 ml of water and 5 ml of methanol are added. Finally, the cooling bath is removed. The mixture is poured into saturated aqueous Na_2CO_3 solution (75 ml) and extracted with three 50-ml portions of ether. Distillation of the dried ($MgSO_4$), concentrated residue affords 1.80 g (91%) of ethyl *p*-chlorophenylacetate, bp 106–107 (3.5 mm), mp 31–32° (lit.[9] mp 32°).

TABLE I

REACTION OF ALKYL AND ARYLDICHLOROBORANES WITH ETHYL DIAZOACETATE TO GIVE THE CORRESPONDING ETHYL ALKYL- OR ARYLACETATES

Alkyl- or aryldichloroborane	Procedure[a]	Product	Yield,[b] %	% ethyl chloroacetate[c]
n-Butyl	A	Ethyl hexanoate	57	32
2-Methyl-1-pentyl	A	Ethyl 3-methylheptanoate	61	29
3-Hexyl	A	Ethyl 3-ethylhexanoate	60	26
Cyclopentyl	A	Ethyl cyclopentylacetate	71	22
Cyclohexyl	A	Ethyl cyclohexylacetate	57	26
exo-Norbornyl	A	Ethyl *exo*-norbornylacetate	60	26
Phenyl[d]	A	Ethyl phenylacetate	87	9
Phenyl[d]	B	Ethyl phenylacetate	92	5
Phenyl[d,e]	B	Ethyl phenylacetate	100 (98)	
p-Chlorophenyl[e]	B	Ethyl *p*-chlorophenylacetate	100 (91)	
p-Tolyl[e]	B	Ethyl *p*-tolylacetate	100 (95)	
p-Biphenyl[e]	B	Ethyl *p*-biphenylacetate	100 (91)	

[a] In procedure A each experiment used 5 mmol of ethyl diazoacetate in 5 ml of ether which was added to 5 mmol of alkyldichloroborane in 5 ml of ether at −62°. Procedure B consisted of using THF as solvent at −25° on a 10-mmol scale. Otherwise the procedures were identical. [b] Analysis by glpc. Isolated yields are in parentheses. [c] These yields represent upper limits of chlorine transfer. See ref 8. [d] Commercially available from Aldrich. [e] A 10% excess of ethyl diazoacetate was used.

These results suggest a mechanism involving initial Lewis acid–base coordination to produce the quaternary boron intermediate **1** (eq 2), followed by loss of nitrogen, with either subsequent or concurrent migration of an alkyl (aryl) group (eq 3) or chlorine (eq 4).

$$RBCl_2 + N_2CHCO_2C_2H_5 \rightleftharpoons \underset{\mathbf{1}}{ClB^-(R)(Cl)-CHCO_2C_2H_5\ (N_2^+)} \quad (2)$$

$$\mathbf{1} \longrightarrow \underset{\mathbf{2}}{ClBCHCO_2C_2H_5} + N_2 \quad (3)$$

$$\mathbf{1} \longrightarrow \underset{\mathbf{3}}{ClBCHCO_2C_2H_5} + N_2 \quad (4)$$

(3) Boronic esters [$RB(OR')_2$] prove to be unsatisfactory owing to the decreased electrophilicity of boron in these derivatives. Only 5–20% N_2 evolution occurs when either diethoxy-*n*-butylborane or dimethoxycyclopentylborane is treated with ethyl diazoacetate. Resonance contributions (>B—OR ↔ >B$^-$=$^+$OR) apparently outweigh the inductive effect of alkoxy, and initial coordination (eq 2, OR in place of Cl) is unfavorable. Unpublished results of G. F. Morrison (University of Alberta).

(4) Alkyldichloroboranes react rapidly and in high yield with organic azides to produce the corresponding secondary amines: H. C. Brown, M. M. Midland, and A. B. Levy, *J. Amer. Chem. Soc.*, **95**, 2394 (1973).

(5) H. C. Brown, M. M. Midland, and A. B. Levy, *J. Amer. Chem. Soc.*, **94**, 3662 (1972).

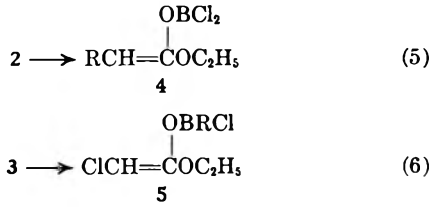
(6) H. C. Brown and N. Ravindran, *J. Amer. Chem. Soc.*, **95**, 2396 (1973).

(7) J. Hooz and J. G. Calzada, *Org. Prep. Proc. Int.*, **4**, 219 (1972).

(8) The ethyl chloroacetate could conceivably arise from the reaction of hydrochloric acid (formed in the hydrolysis of the chloroborane intermediates) with residual diazo ester. However, the fact that nitrogen evolution is essentially complete indicates that residual diazo ester cannot be significant, so that this path can be ruled out as a major source of the chloroacetate. Consequently, we conclude that in this system transfer of chlorine from boron to carbon must occur competitively with the transfer of the alkyl groups.

(9) R. v. Walther and A. Wetzlich, *J. Prakt. Chem.*, **61**, 169 (1900).

Pasto and Wojtkowski[10] have recently isolated several enol borinates and suggest that intermediates such as 2 or 3 exist in the isomeric enol borinate forms 4 or 5. Thus, if this reaction involves an α bora ester, the boron must migrate to oxygen (eq 5 and 6). Such intermediates are rapidly hydrolyzed by water.



Since α-haloboranes rearrange upon addition of a nucleophile,[11] methanolysis of 2 or 3 should give alkyl homologated esters unless protonolysis competes with the rearrangement. In an attempt to increase the yield of alkyl homologation, nucleophiles such as pyridine and triethylamine were added. After transfer, protonolysis should then give the alkyl ester. However, the yields of alkyl ester did not improve, suggesting that the rearrangement to the enol borinates 4 and 5 may be fast and irreversible even at $-62°$. Alternatively, the α transfer must be slow at these temperatures even when catalyzed by good nucleophiles. Attempts to identify definitively the intermediates by nmr were unsuccessful owing to the complicated spectrum of the mixture.

If the reasonable assumption is made that the conversion to the enol borinate is faster than rearrangement, the yields of chloro, alkyl, and aryl esters indicate their relative migratory aptitude. The data in Table I thus suggests the migratory aptitude to be in the order Ar > R > Cl. Such an order for aryl *vs.* alkyl has previously been observed in the rearrangements of α-haloboronates.[12]

In spite of some limitations, this reaction provides a highly useful and operationally simple method for converting alkenes/arenes to their corresponding two-carbon chain-lengthened ethyl esters. Simple procedures have recently become available for the synthesis of the required alkyldichloroboranes[6] and aryldichloroboranes.[7]

We are continuing to explore the use of alkyl and aryldichloroboranes in organic synthesis.

Acknowledgment.—One of us (J. H.) wishes to thank the National Research Council of Canada for financial support. Mr. G. T. Morrison and Dr. R. B. Layton (University of Alberta) conducted the initial exploratory experiments with phenyldichloroborane.

(10) D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970).
(11) H. C. Brown and Y. Yamamoto, *J. Amer. Chem. Soc.*, **93**, 2796 (1971).
(12) D. S. Matteson and R. W. H. Mah, *J. Amer. Chem. Soc.*, **85**, 2599 (1963).
(13) University of Alberta, Postdoctoral Research Fellow, 1970–1972.
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RECEIVED MARCH 20, 1973

α-Halocarbonyl Compounds. II. A Position-Specific Preparation of α-Bromo Ketones by Bromination of Lithium Enolates. A Position-Specific Introduction of α,β-Unsaturation into Unsymmetrical Ketones

Summary: Low-temperature bromination of specifically generated ketone enolates under aprotic conditions produces position-specific α-bromo ketones which can be converted to α,β-unsaturated ketones; no Favorskii rearrangement or other base-catalyzed side reactions and no positional equilibration of bromine are observed.

Sir: Because α-halocarbonyl compounds are useful synthetic intermediates in a number of widely different organic transformations,[1] we have been interested for some time in devising some new efficient methods for their preparation.[2] Common methods for preparing α-halo ketones, in general, provide little position selectivity if both α and α' positions are available for direct halogenation.[1a,3a] The available, generally applicable methods[3] for specific preparation of either α- or α'-halogenated unsymmetrical ketones usually require extensive reaction sequences or produce the desired product in only moderate yield, often still contaminated with significant amounts of isomeric halo ketone. Even the well-known bromination of isomerically specific, neutral enol derivatives[3c,d] of unsymmetrical ketones, *e.g.*, enol acetates, suffers the disadvantage that acidic byproducts may catalyze equilibration of starting material or of product halo ketone. Consequently, both α- and α'-bromo ketones, as well as polybrominated materials, may be observed.

Perhaps the most obvious method for position-specific halogenation of unsymmetrical ketones, the quenching of position-specific enolate anions[4] by halogen, has not received appropriate attention because of the attendant possibility of subsequent reactions (Favorskii rearrangements and/or alkylations and condensations) of the often quite reactive α-halo ketones under strongly basic reaction conditions. However, we wish to report that bromination of lithium enolates at low temperature is as effective a method for preparing specifically α- or α'-

(1) See a–d for examples. (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., pp 459–478. (b) H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **90**, 6218 (1968); **91**, 2147 (1969); **91**, 6852 (1969). (c) T. A. Spencer, R. W. Britton, and D. S. Watt, *ibid.*, **89**, 5727 (1967). (d) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. Fr.*, 366 (1958).

(2) (a) P. L. Stotter and K. A. Hill, "γ-Halotiglates: Ubiquitous Reagents for Natural Products Synthesis," paper delivered before the Second International Symposium on Synthesis in Organic Chemistry, Cambridge, England, July 1971. (b) P. L. Stotter and K. A. Hill, *Tetrahedron Lett.*, 4067 (1972).

(3) (a) Other halogenation methods (direct and indirect) which may, *in certain cases*, provide positional selectivity are also reviewed in ref 1a. (b) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer. Chem. Soc.*, **77**, 5415 (1955). (c) H. Piotrowska, W. Wojnarowski, B. Waegell, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 3511 (1965). (d) We have observed that direct bromination of the less substituted enol silyl ether derived from 2-methylcyclohexanone gives a complex product mixture at $-20°$; more promising results were obtained at $-70°$, but some difficulties were nonetheless encountered in our attempts to separate product bromo ketone from trimethylsilanol and hexamethyldisiloxane on work-up.

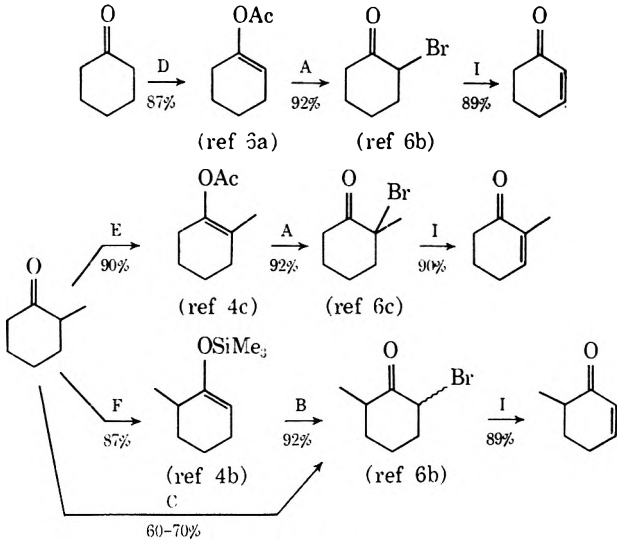
(4) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965), and references cited therein. (b) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969). (c) H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971).

bromo ketones, as has already been reported for preparing the more readily available α-bromo esters.[2a,5]

Position-specific lithium enolates generated in tetrahydrofuran from enol acetates,[4a] enol silyl ethers,[4b] or directly from the ketone (by the kinetic action of lithium diisopropylamide[4c]) were brominated at $-78°$ by rapid addition of 1 equiv of bromine, as a solution in methylene chloride. This cold reaction, which instantaneously decolorized the bromine solution, was stirred for 1 min and then rapidly quenched with excess aqueous sodium bicarbonate. Extraction of the resulting slurry with pentane allowed isolation of the desired α-bromo ketone in good to excellent yield. The crude bromo ketones showed negligible amounts of polybromination or equilibration of bromine to the α' position. We observed no evidence of Favorskii rearrangement or of alkylation or condensation by-products, even in those cases where stronger base than lithium enolate was present (enolate solutions derived from enol acetates by the action of methyllithium contained 1 equiv of lithium *tert*-butoxide). Some representative results for the direct bromination of lithium enolates are described for several unsymmetrical ketones in Schemes I and II.[6]

SCHEME I[a]

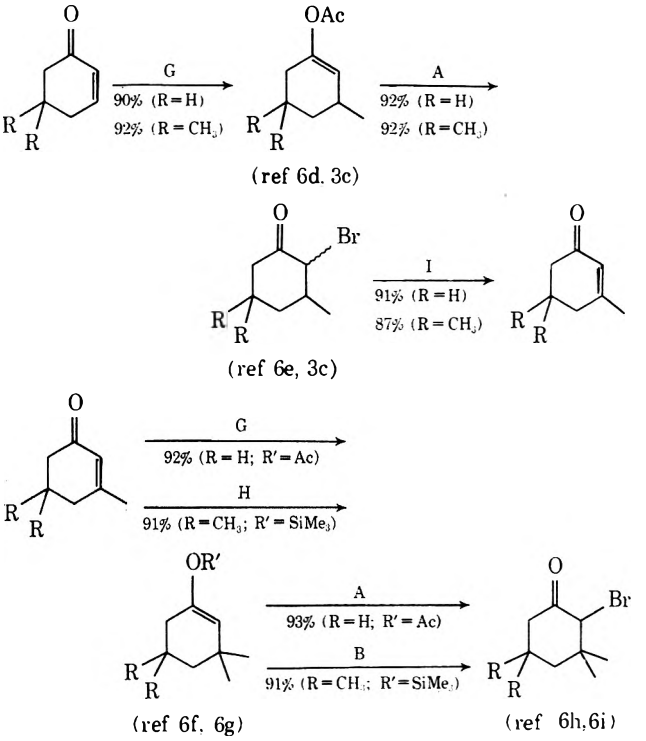
BROMINATION OF ENOLATES DERIVED FROM CYCLOHEXANONE AND 2-METHYLCYCLOHEXANONE



[a] Procedures for generation of lithium enolates and subsequent bromination: (A) enol acetate and 2 equiv of MeLi in THF at room temperature, addition Br_2 in CH_2Cl_2 at $-78°$, quench with aqueous bicarbonate;[4a] (B) enol silyl ether and 1 equiv of MeLi in THF at room temperature, addition Br_2 in CH_2Cl_2 at $-78°$, quench with aqueous bicarbonate;[4b] (C) ketone and 1 equiv of lithium diisopropylamide in THF at room temperature, addition Br_2 in CH_2Cl_2 at $-78°$, quench with aqueous bicarbonate, final work-up with cold dilute sulfuric acid[4c] (product may contain small amounts of α'-brominated isomer depending on contact time with acid). Procedures for preparation of enol derivatives: (D) mixture of ketone, isopropenyl acetate, and catalytic TsOH with distillation of acetone;[5a] (E) mixture of ketone, Ac_2O, and catalytic $HClO_4$ in CCl_4 at room temperature;[4c] (F) ketone and 1 equiv of lithium diisopropylamide in THF at room temperature, quench at 0° with excess $ClSiMe_3$ and Et_3N, bicarbonate then dilute acid work-up; (G) unsaturated ketone and 1.1 equiv of $LiMe_2Cu$ in ether at 0°, quench with excess Ac_2O, partition between aqueous bicarbonate and pentane with cold dilute ammonium hydroxide work-up; (H) unsaturated ketone and 1.1 equiv of $LiMe_2Cu$ in ether at 0°, quench with excess $ClSiMe_3$ and Et_3N, partition between aqueous bicarbonate and pentane with cold dilute acid work-up. Procedure for dehydrobromination: (I) crude α-bromo ketone in DMF added dropwise to excess Li_2CO_3 and LiBr in DMF at $\sim 130°$.[1d]

SCHEME II[a]

BROMINATION OF ENOLATES DERIVED FROM TRAPPED INTERMEDIATES OF CONJUGATE ADDITION TO CYCLOHEXENONES



[a] See Scheme I, footnote *a*.

Note that the yields of α-bromo ketone are extremely high[6] in all cases where no reactive amine is present. Even when a secondary amide base was used to generate the kinetic enolate of 2-methylcyclohexanone and the subsequent bromination carried out in the presence of secondary amine, the yield of α-bromo ketone is superior to those observed with most other methods of preparation. And, finally, the purity of α-bromo ketones prepared by enolate bromination as directly derived from evaporation of the pentane extract is sufficient for use in most synthetic transformations requiring these versatile intermediates.

The enol derivatives[6] used as precursors to α-bromo ketones in Scheme II were derived in high yield by conjugate addition of 1.1 equiv of lithium dimethylcopper in ether at 0° to the appropriate α,β-unsaturated

(5) M. W. Rathke and A. Lindert, *Tetrahedron Lett.*, 3995 (1971).

(6) Yields indicated in Schemes I and II for enol acetates, enol silyl ethers, and enones represent distilled materials in each case. Yields indicated for α-bromo ketones were carefully estimated by nmr examination of samples directly obtained by reduced pressure evaporation of the pentane extracts. Further purification (*e.g.*, distillation or chromatography) often resulted in positional equilibration of bromine as well as destruction of extensive amounts of the unstable bromo ketones. That this method of estimating yields is reasonably accurate was demonstrated by the high-yield conversion of several of these crude α-bromo ketones to known α,β-unsaturated ketones as described in the text. All α-bromo ketones and their precursors were identified by comparison with known samples or by careful correlation of observed spectral data and physical constants with those already reported (see references cited in Schemes I and II): (a) H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949); (b) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965); (c) W. W. Rinne, H. R. Deutsch, M. I. Bowman, and I. B. Joffe, *J. Amer. Chem. Soc.*, **72**, 5759 (1950); (d) L. Bardou, J. Elquero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 297 (1967); (e) C. Djerassi, L. E. Geller, and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 1 (1960); (f) J. Champagne, H. Favre, D. Vocelle, and I. Zbikowski, *Can. J. Chem.*, **42**, 212 (1964); (g) P. F. Hudrlik, Ph.D. Thesis, Columbia University, New York, N. Y., 1968; (h) H. Duerr, G. Ourisson, and B. Waegell, *Chem. Ber.*, **98**, 1858 (1965); (i) B. Waegell, *Bull. Soc. Chim. Fr.*, 855 (1964).

ketone; the resultant enolate mixtures were trapped[7] by addition of excess acetic anhydride or of chlorotrimethylsilane (mixed with triethylamine).

Finally, it should also be noted that this position-specific α bromination of unsymmetrical ketones readily allows the introduction of specific α,β unsaturation *via* direct dehydrobromination[1d] of the crude α-bromo ketone. Accordingly, in 70–75% overall yield, 2-methylcyclohexanone was converted specifically to either methylcyclohexenone shown in Scheme I. Scheme II further demonstrates that similar dehydrobromination of α-bromo ketones derived from conjugate addition completes, in comparable overall yield, a sequence which is, formally, the nucleophilic substitution of alkyl for hydrogen at the β position of α,β-unsaturated ketones. A forthcoming publication will describe in greater detail this β-nucleophilic substitution sequence.

(7) (a) For reports of enol silyl ethers by quenching magnesium enolates (from copper-catalyzed Grignard conjugate additions), see ref 4b and 6g. (b) For reports of enol acetates by quenching magnesium enolates using acetyl chloride, see J. A. Marshall and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **91**, 648 (1969). (c) For a preliminary report of enol acetates by quenching complex lithium–copper enolates (from lithium dialkylcopper conjugate additions) with acetyl chloride, see E. Piers, W. de Waal, and R. W. Britton, *ibid.*, **93**, 5113 (1971).

Acknowledgments.—The authors would like to express their thanks to the Robert A. Welch Foundation (Grant F-345) for supporting the bulk of this research, as well as to Research Corporation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for supporting this work in its initial stages.

(8) Du Pont Predoctoral Fellow, 1969; Robert A. Welch Foundation Predoctoral Fellow, 1970–1972; University of Texas Predoctoral Fellow, 1971.

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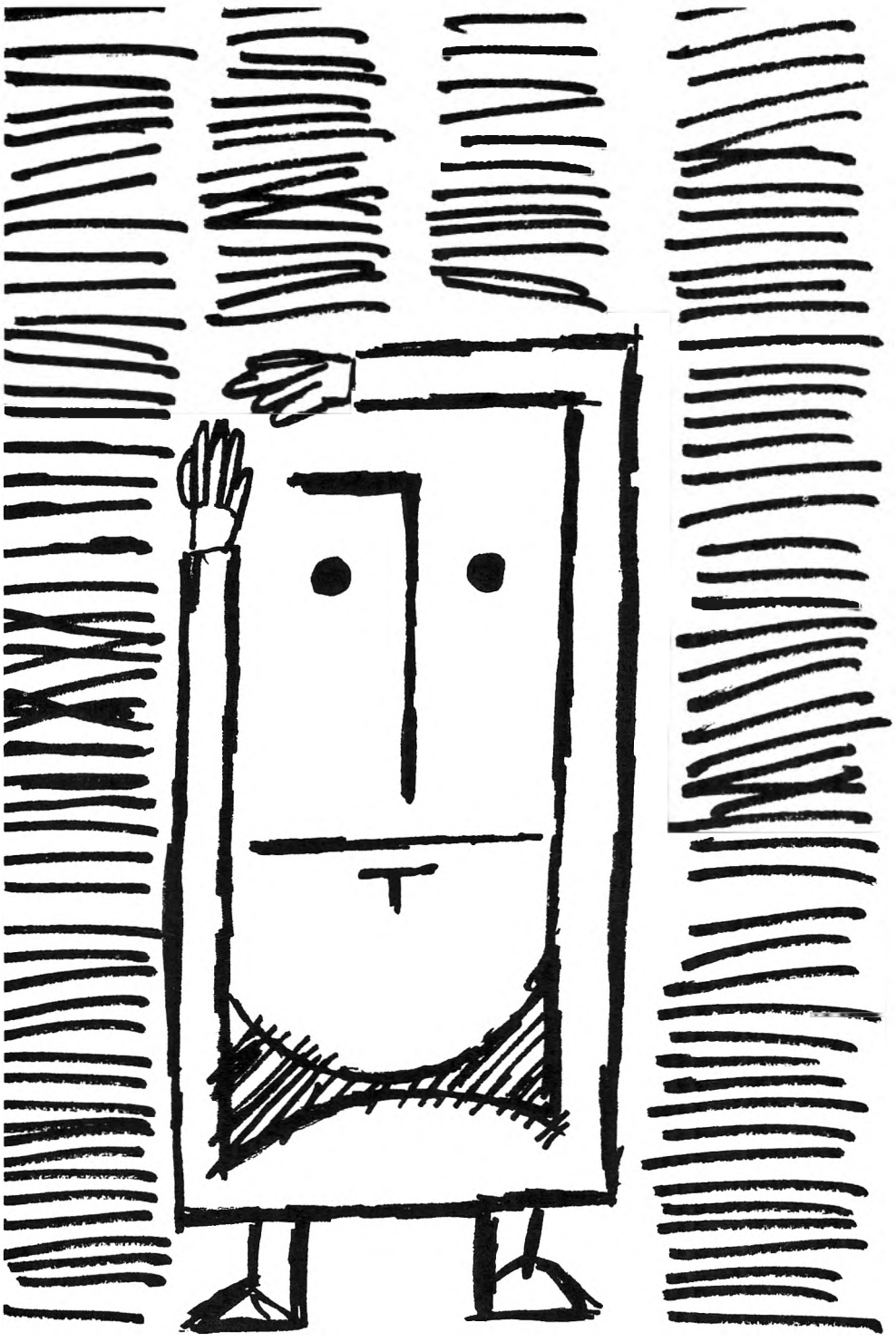

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17,974-4

2-Fluoroethylamine hydrochloride

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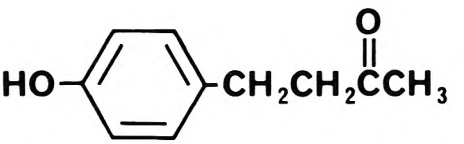
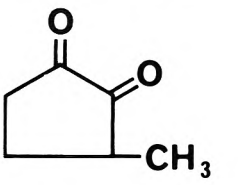


17,851-9

4-*p*-Hydroxyphenyl-2-butanone

Naturally occurring raspberry flavor

50g 9.60 250g 32.00

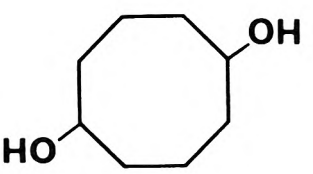


17,850-0

3-Methyl-1,2-cyclopentanedione

"Roasted" odor

50g 11.50 250g 38.00



17,903-5

cis-**Cyclooctanediol**

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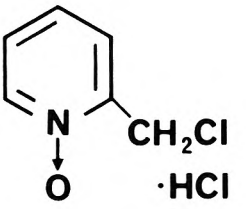
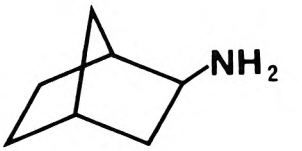


17,769-5

2-Picolyl chloride N-oxide hydrochloride

Protecting group for amino and imino functions.

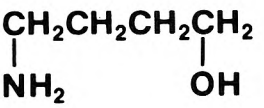
5g 6.50 25g 21.40



17,960-4

exo-**2-Aminonorbornane**

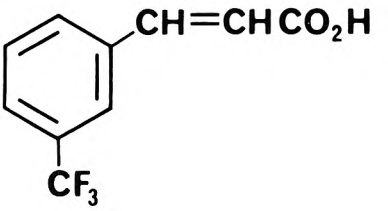
5g 15.00 25g 60.00



17,833-0

4-Amino-1-butanol

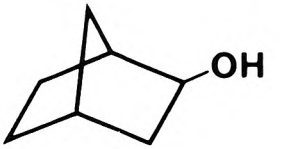
10g 12.00 50g 40.00



17,892-6

m-**Trifluoromethylcinnamic acid**

10g 8.50 50g 29.50



17,959-0

exo-**Norborneol**

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